PROGRESS TOWARDS THE TOTAL SYNTHESIS OF SORANGICIN

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Declaration

I declare that this thesis is the result of my own work and has not, whether in the same or different manner, been presented to this or any university in support of an application for any degree other than that for which I am now a candidate.

I also declare that the work provided in this thesis is the result of my own investigations and where the work of other researcher has been used, this has been fully acknowledged in the thesis.

Kumeneger Debalike Belayneh

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Table of Contents

Contents i
Abstract iv
Zusammenfassung v
List of Abbreviations vi
1. Background 1
1.1 Introduction 2
1.2 Myxobacteria as Producers of Novel Natural Products 3
1.3 Isolation and Structural Determination of Sorangicin 4
1.4 Overview of the Biological Activity of Sorangicin **A** 6
1.5 Review of Prior Progress to the Total Synthesis of Sorangicin 8
1.5.1 Synthetic Efforts by Smith 8
1.5.1.1 Synthesis of the THP Fragment 8
1.5.1.2 Synthesis of the DHP Fragment 11
1.5.1.3 Synthesis of the Bicyclic and Trienoate Fragments 12
1.5.1.4 First Total Synthesis of Sorangicin **A** 14
1.5.2 Synthetic Efforts by Crimmins 17
1.5.3 Synthetic Efforts by Lee 18
2. Objective of Thesis Research 20
2.1 Objective 20
2.2 Synthesis of Fragment **I** and **II** 21
2.3 Synthesis of the Dihydropyran Fragment 24
3. Synthesis of Fragment D 26
3.1 Synthesis of L-hexoses 26
3.1.1 Sharpless's Reiterative Two-Carbon Extension Cycle 26
3.1.2 Modifications to Sharpless's Strategy 27
3.1.3 Hetero-Diels-Alder Reactions 28
3.1.4 Proline Catalyzed Aldol Reactions 28

3.2 Synthesis of L-glucose Fragment 29
3.3 Carbon-Ferrier Rearrangements 31
3.3.1 Modified Carbon-Ferrier Rearrangement 31
3.3.2 Classical Carbon-Ferrier Rearrangement 32
3.4 Oxidative Cleavage of the Terminal Double Bond 34
3.4.1 Sharpless Asymmetric Dihydroxylation 34
3.4.2 Ozonolysis 34
3.5 Protection of the Aldehyde 35
3.5.1 Selective Protection of the Aldehyde 35
3.5.2 Simultaneous Protection and Deprotection 35
3.6 Completion of Fragment **D** 35
3.7 Review of Synthetic Routes Tested 37

4.**Synthesis of Fragment E** 40

4.1 Synthesis of Seebach Auxiliary 40
4.2 Synthesis of (2R)-Methyl-hept-6-en-1-ol 40
4.3 Synthesis of (2*R*)-2-(2-Methylhept-6-en-1-sulfonyl)-1-phenyl-1H-tetrazole 41
4.4 Synthesis of (2*R*)-2-(2-Methylhept-6-en-1-sulfonyl)-benzothiazole 42
4.5 Synthesis of (Hept-6-ene-1-sulfonyl)-benzene 42

5. **Coupling of the Fragments** 43

5.1 Modern Olefination Methods 43
5.1.1 Wittig Olefination 43
5.1.2 Horner-Wadsworth-Emmons Olefination 44
5.1.3 The Horner-Wittig Olefination 45
5.1.4 The Peterson Olefination 45
5.1.5 Classical Julia Olefination 46
5.1.6 Modified Julia Olefination 46
5.2 Previous Efforts to Couple Fragments 47
5.3 Coupling Strategies 48

6. **Summary and Outlook** 53

6.1 Summary 53

6.2 Future Direction 54

7. **Experimental Part** 58

7.1 Materials and Methods 58

8. **List of References** 113

9. **Spectral Data** 117

Abstract

Sorangicin is a macrolide polyether antibiotic which was isolated from *Sorangium Cellulosum*. The structural complexity and exciting biological activity of sorangicin have promoted our effort to develop an efficient and effective synthetic approach to fragments of sorangicin. To date there have been one total synthesis of sorangicin **A** and three partial syntheses reported. In this work a new modern and compact method for synthesizing the C(1)-C(19) fragment of sorangicin **A** has been evaluated and as well as a new approach for synthesizing the L-glucose fragment was developed. The construction of fragment **III** started by synthesizing fragment **D**, fragment **E** and fragment **F**. Fragment **D** was synthesized in twelve steps by starting from ethylene glycol and cis-2-butenediol. The ethylene glycol **170** was selectively protected and oxidized to give TBS-protected aldehyde **18** and subsequent enantioselective aldol reaction using D-proline as catalyst furnished the aldol product **23**. The cis-2-butenediol **173** was converted into the corresponding alkene **22** in three steps. The aldol **23** and TMS-protected alkene **22** underwent Mukaiyama aldol reaction using $MgBr_2 \cdot Et_2O$ and subsequent treatment with HBr/AcOH afforded TBS-protected glucal **25** which underwent carbon-Ferrier rearrangement and oxidized using Sharpless condition to give **31**. The aldehyde **31** was protected, deprotected, underwent Grignard addition and oxidized to afford ketone **180**. Deprotection of methyl ketone **180**, Mitsunobu inversion and finally protection with TBSCl afforded fragment **D**. Fragment **E** was synthesized by starting from D-valine which afforded in three steps Seebach auxiliary **3**. The auxiliary **3** and 6-heptenoic-acid chloride **4** were coupled using n-BuLi and the coupled product **5** was changed in three steps to the corresponding alcohol **7**. Subsequent Mitsunobu reaction condition and oxidation furnished the corresponding sulfones, fragment **E** and benzothiazole sulfone **14**. Fragment **F** was synthesized in three steps from 1,4-butanediol. The synthesis of fragment **III** was tested by coupling fragment **D,** fragment **E** and fragment **F** using modified Julia olefination by employing LiHMDS, KHMDS, NaHMDS, LDA and t-BuLi as bases. Different coupling reaction conditions were evaluated including both premetallate and barbier conditions to couple the fragments.

Zusammenfassung

Sorangicin ist ein Makrolid-Polyether-Antibiotikum das aus *Sorangium cellulosum* isoliert wurde. Die strukturelle Komplexität und interessante biologische Aktivität von Sorangicin haben uns in unseren Bemühungen, einen effizienten und effektiven synthetischen Ansatz für die Fragmente von Sorangicin zu entwickeln, gestärkt. Bisher ist eine Totalsynthese von Sorangicin **A** bekannt und es ist von drei Teilsynthesen berichtet worden. In dieser Arbeit wurde ein neues, modernes und kompaktes Verfahren zur Synthese des C(1)-C(19)-Fragment von Sorangicin **A** getestet, sowie ein neuer Ansatz für die Synthese des L-Glucose-Fragmentes entwickelt. Die Synthese von Fragment **III** baut auf die Synthese von Fragment **D,** Fragment **E** und Fragment **F** auf. Fragment **D** wurde, ausgehend von Ethylenglykol und cis-2-Butendiol in zwölf Stufen in einer Gesamtausbeute von über 25% synthetisiert. Ethylenglykol **170** wurde selektiv geschützt und oxidiert um den geschützten Aldehyd **18** zu erhalten. Die anschließende enantioselektive Aldolreaktion mit D-Prolin als Katalysator lieferte das Aldolprodukt **23**. Aus cis-2-Butendiol **173** wurde in drei Stufen das entsprechend geschützte Alken **22** gebildet. Das Aldolprodukt **23** und das geschützte Alken **22** wurden einer Mukaiyama-Aldolreaktion mit $MgBr_2 \cdot Et_2O$ unterzogen und weiter mit HBr/AcOH behandelt, um das TBS-geschützte Glucal **25** zu erhalten. Um Fragment **D** zu erhalten, wurde das Glucal **25** einer Carbon-Ferrier-Umlagerung und einer Sharpless-Oxidation unterzogen, danach geschützt und wieder entschützt, einer Grignard-Addition unterzogen und schließlich oxidiert. Das so erhaltene Methylketon **180** wurde mittels Entschützung, Mitsunobu-Inversion und abschließendes TBS-Schützung in Fragment **D** überführt. Fragment **E** wurde ausgehend von D-Valin synthetisiert, welches zunächst nach drei Stufen das Seebach-Auxiliar **3** lieferte. Das Auxiliar **3** wurde mit 6-Heptensäurechlorid **4** zum Produkt **5** gekuppelt. Das Kupplungsprodukt **5** wurde über drei Stufen zum entsprechenden Alkohol **7** umgewandelt und über eine anschließende Mitsunobu-Reaktion und Oxidation konnten die entsprechenden Sulfone, Fragment **E** und **14** erhalten werden. Die Synthese von Fragment **III** wurde durch die Kopplung von Fragment **D**, Fragment **E** und Fragment **F** mittels modifizierter Julia-Olefinierung durch den Einsatz von KHMDS, NaHMDS, LDA und t-BuLi als Base getestet. Weiterhin wurde u.a. der Einfluß der Reaktionsführung (Prämetallieg. bzw. Barbierbedingungen) untersucht.

List of Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
AcCl	Acetyl chloride
AcOH	Acetic acid
9-BBN	9-Borabicyclo [3.3.1] nonane
Bn	Benzyl
Bu	Butyl
BPS	t-Butyldiphenylsilyl
Bz	Benzoyl
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
Cbz	Benzyloxycarbonyl
Chx	Cyclohexyl
CSA	Camphorsulfonic acid
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethylazodicarboxylate
DIAD	Diisopropylazodicarboxylate
DET	Diethyl tartrate
DIBAL-H	Diisobutylaluminium hydride
DIPT	Diisopropyl tartrate
DMAP	4-(*N*, *N*-dimethylamino) pyridine
DME	Dimethyl ethoxy
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane

DMPU	Dimethyltetrahydropyrimidinone
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
de	Diastereomeric excess
ee	Enantiomeric excess
Equiv	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
FTIR	Fourier Transform Infrared Spectroscopy
^{1}H NMR	Proton Nuclear Magnetic Resonance
hrs	Hour(s)
H-bonding	Hydrogen bonding
HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum coherence
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectroscopy
i-Bu	Isobutyl (2-methylpropyl)
i-Pr	Isopropyl
IR	Infrared
LiDBB	Lithium 4',4'-ditert-butylbiphenylide

LDA	Lithium diisopropylamide
m-CPBA	3-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeLi	Methyl lithium
MHz	Megahertz
min	Minute(s)
MOM	Methoxymethyl
PMB	*p*-Methoxybenzyl
MS	Mass Spectrometry
MsCl	Methanesulphonyl Chloride
MTPA	2-Methoxy-2-(trifluoromethyl)-2-phenylacetic acid
MTPACl	2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl chloride
NBS	N-Bromosuccinimide
n-BuLi	*n*-Butyl lithium
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Enhancement
OTBS	*tert*-Butyldimethylsilyloxy
OTf	Trifluoromethanesulfonate
PPTS	*p*-Toluenesulfonic acid
Py	Pyridine
RT	Room Temperature
Sat.	Saturated
Sec	Second(s)

TBAF	tetra-Butylammonium fluoride
TBSCl	*tert*-Butyldimethylsilyl chloride
t-BuLi	*tert*-Butyllithium
TEA	Triethylamine
TES	Triethylsilyl
TESOTf	Triethylsilyltriflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl Chloride
TMSCN	Trimethylsilyl Cyanide
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

Chapter 1- Background

Natural products have been major sources of medicine in the last few decades and the development of various screening approaches improved the ease with which natural products can be used in drug discovery. Natural products can be extracted from various resources including plants, marine world, microorganisms, animals, venoms and toxins. Plants have always been a rich source of lead compounds (morphine, cocaine, nicotine). Many of these lead compounds are useful drugs in themselves (morphine) and others have been basis for synthetic drugs (local anesthetics developed from cocaine). Clinically useful drugs which have been recently isolated from plants include anticancer agent paclitaxel (taxol) from yew tree. Microorganisms such as bacteria and fungi have been invaluable for discovering drugs and lead compounds (Sorangicin, Epothilone). Soil and water samples collected have been leading to an impressive arsenal of antibacterial and antagonist agents such as cephalosporin, tetracycline, and amino glycosides. The marine world has been a source of biologically potent chemicals with interesting inflammatory, antiviral, and anticancer activity. Antitumor agents derived from marine sources includes, curacin, discodermolide, and lovastatin. Animals can sometimes be a source of new lead compounds. For example, a series of peptide antibiotics were extracted from skin of the African clawed frog. Epibatidine, potent analgesic, was obtained from the skin extracts of Ecuadorian frog. Venoms and toxins have been used as lead sources in the development of novel drugs such as teprotide, a peptide isolated from venom of the Brazilian viper, was the lead compound for the development of antihypertensive agents cilazapril and captopril.

The reasons for the success of natural products are their great structural diversity and the fact that evolution over millions of years preselected these compounds for interaction and activity. The dominance and pharmaceutical success of natural products is most obvious in the field of antibiotics. This was particularly evident in the areas of cancer and infectious diseases, where over 60% and 75% of these drugs, respectively, were shown to be of natural product origin[1]. Most antibacterial drugs introduced worldwide in the last three decades can be traced to natural products. It is surprising that more than 200 antibacterial drugs which have been launched for human therapy since the invention of sulfonamides by Domagk in 1935[2] belong to a limited number of antibacterial classes. From 11 antibacterial classes introduced for systemic use in humans, 8 are derived from natural products[4].

Despite the overall success of natural products and the fact that antibiotics have saved millions of lives, downsizing or even termination of both natural products and antibiotic research have been observed in large pharmaceutical companies[4] in the last decade. Reasons for the decline of natural products research includes the following: (i) traditional extract-based screening leads to the rediscovery of previously known compounds; (ii) structural complexity of natural products made total synthesis and derivation of them more difficult; (iii) because of supply problems, the time required to develop a natural product from an extract hit to a pharmaceutical drug is long; (iv) focus on combinatorial chemistry to generate huge compound library is needed to fulfill the demand of high-throughput-screening (HTS) technologies.

There are several reasons underlying the urgent need for new antibiotics, firstly, the fact that infectious diseases are still the second major cause of death worldwide[4]. Secondly the emergence and spread of multi-resistant pathogens particularly in the hospital environment as well as constant decrease in the total number of antibacterial agents that have been approved by drug controlling authorities.

1.1 Introduction

Gliding bacteria are a fascinating group of diverse microorganisms which have adapted to environments such as hydrothermal vents, tropical rainforests, marine shores, wastewater, deserts and intestinal tract of man and animals[3]. Due to their ubiquitous occurrence, gliding bacteria play a major role in microbial ecology. Gliding is defined as a slow surface associated translocation of a non-flagellated cell in the direction of its long axis. Bacteria with gliding motility are known from both Gram-positive and Gram-negative genera, crossing the entire spectrum of physiological types. Creeping movement is a consistent trait within the chloroflexi which represents the only phylum consisting exclusively gliding bacteria. However most gliding species originate from cyanobacteria, proteobacteria and bacteroidetes. Based on their physiology gliding bacteria can be roughly divided into two distinct groups. The first group consists of heterotrophic organisms, heterotrophs, which decomposes macromolecular substrates such as proteins and polysaccharides. This group lack genes required for an endogenous production of certain amino acids as a result predation has evolved as a reliable alternative to biosynthesis for this group. It comprises

myxobacteria, lysobacter, herpetosiphon, cytophaga and flavobacterium. The second group, phototrophs and autotrophs, produce complex carbohydrates, fats, and proteins by themselves, exhibit an autotrophic way of life. The group covers cyanobacteria, proteobacteria, thiothrix, achromatium, beggiatoa and thioploca. The autotrophs typically use gliding motility in order to adapt to shifting growth conditions within their natural habitat.

In the last four decades there have been an increase in the interest of research on gliding bacteria due to their great potential as source of potent natural products. Some of the potent natural products include angiolam, antibacterial macrolide agent, which inhibits protein synthesis. Phenalamide, antifungal and anti-HIV polyene agent. Epothilone, a cytotoxic macrolide which inhibits tubulin depolymerization. Myxochromide, a lipopeptide which acts as a pigment. Ripostatin, an antibacterial macrolide agent which inhibits RNA polymerase. Sorangicin, an antibacterial macrolide agent that inhibits RNA polymerase.

1.2 Myxobacteria as Proficient Producers of Novel Natural Products

The myxobacteria are a group of Gram-negative eubacteria belonging to the delta group of proteobacteria. They were originally isolated in 1892 by Roland Thaxter[5] who recognized them as a distinct and unusual group of bacteria. They are common in animal dung and organic-rich soils of neutral or alkaline medium. They are found everywhere, in all climate zones and vegetation belts, but are particularly numerous in semi-arid, warm areas such as Egypt, Northern India, and Southwestern United States. Some of them grow by utilizing cellulose, but many of them feed themselves by secreting antibiotics to kill other bacteria and then produce an enzyme that lyses the cells of their prey. Myxobacteria have the largest genomes known from bacteria and genome of one strain of s*orangium cellulosum,* a cellulose degrader, which has been fully sequenced, is 13.04 Mbp long, about three times the size of the E. coli genome[3]. They are social bacteria with developed communication systems and produce fruiting bodies in starvation conditions. Fruiting bodies usually are 0.1-1mm in size and often can be recognized with the naked eye. Inside the maturing fruiting body, the vegetative cells convert into desiccation resistant myxospores and in this form the bacteria may survive 5-15 years of drought. The vegetative cells of all myxobacteria are aerobic, elongated rods with either rounded or tapered ends. They glide in water film across solid surfaces secreting slime (polysaccharide) tracks in which many cell migrate to produce feathery

extensions at the colony margin. At the onset of nutrient depletion the cells migrate back along the slime tracks, aggregating by chemotaxis, to form large concentrations of cells.

Many compounds from myxobacteria are entirely new, mostly they are polyketides or peptides often with very unusual amino acids and are synthesized by multienzyme complexes[3]. Myxobacteria has been source of many biologically active compounds such as rhizopodin which has a dramatic effect on cell morphology, chondramides which stimulate actin polymerization and stabilize the F-actin. Disorazol and tubulysin can be used as potential anticancer drugs. Epothilone which promotes tubulin polymerization and stabilizes microtubuli. Sorangicin a macrolide polyether antibiotic. The picture below represents a typical colony of myxobacteria (**Figure**. **1**).

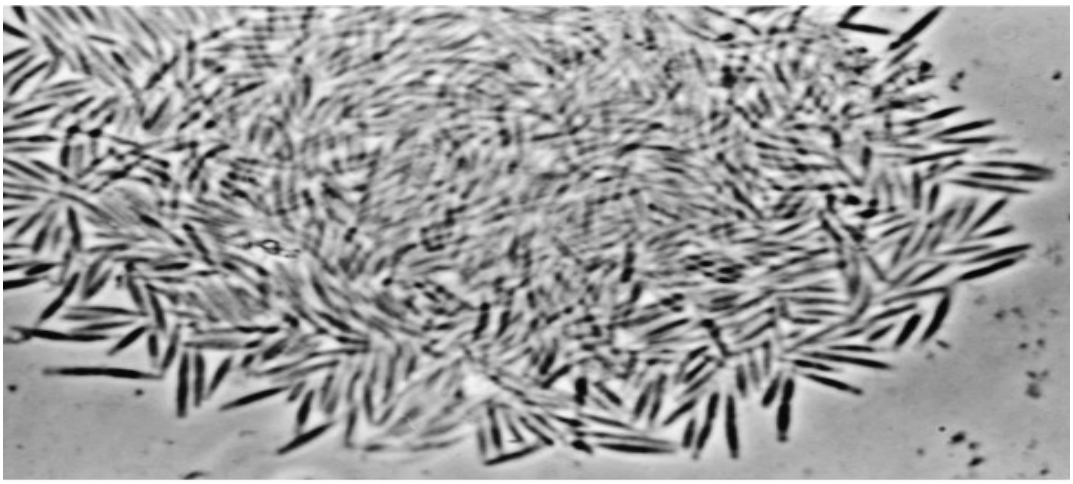


Figure. 1 Vegetative Cell of Myxobacteria Representative of the Suborder Cystobacterineae

1.3 Isolation and Structural Determination of Sorangicin

Sorangicin a macrolide polyether antibiotic which was first isolated in 1985 is a new class of macrolide natural products. The research groups of G. Höfle and H. Reichenbach[6] at the Helmholtz Zentrum fur Infektionsforschung in Braunschweig, Germany, reported the isolation of the novel antibiotic sorangicin from the gliding bacteria *sorangium cellulosum.* Importantly, (+)-sorangicin **A**, the most potent congener, has demonstrated extraordinary antibiotic activity against a broad panel of both Gram-positive and Gram-negative bacteria. Subsequent mechanistic examination revealed that the selective biological response induced

by sorangicin in prokaryotic cells arises from the inhibition of ribonucleic acid polymerase (RNAP). The minimal inhibitory concentration (MIC) values against Gram-negative bacteria range from 2-32 μg/ml and for Gram-positive bacteria the MIC may be less 10 μg/ml. Sorangicin has proved to be effective against experimental staphylococcal infections in rats and the mechanism of action has been shown to be the inhibition of the DNA dependent RNA polymerase in staphylococcus aureus and E. coli. The structure of sorangicin comprises a signature dioxabicyclo[3.2.1]octane skeleton in conjunction with a rare (Z,Z,E)-trienoate linkage, both inscribed within a highly unsaturated 31-membered macrolactone ring containing 15 stereogenic centers. The structure was determined by extensive use of ^{1}H-NMR, ^{13}C NMR, MS and UV data. From the main classes of sorangicin, sorangicin **A** and sorangicin **B**, (**Figure**. **2**) have been studied in more details compared with sorangioside (**Figure**. **2**) and sorangicin **C** (**Figure**. **3)**. Sorangicin **A** has been effective antibiotic against tuberculosis and sorangicin **B** has been effective in treating hepatitis-B-virus.

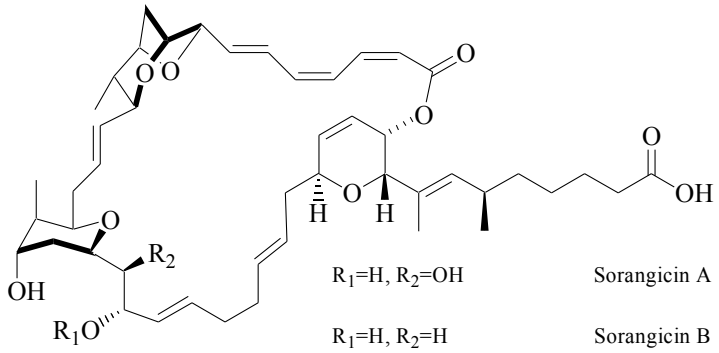


Figure. 2 Classes of Sorangicin, Sorangicin A, Sorangicin B, Sorangioside

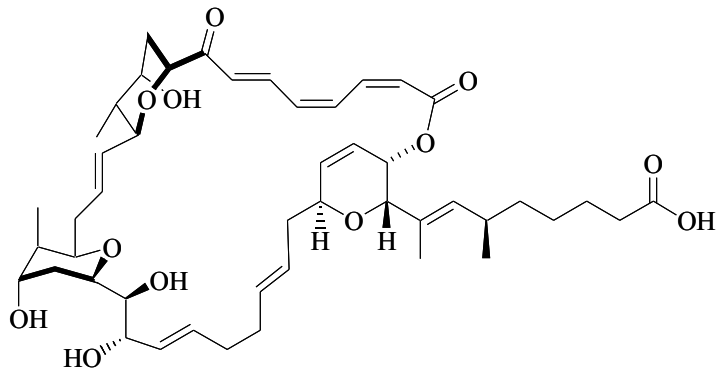


Figure. 3 Sorangicin C

1.4 Overview of the Biological Activity of Sorangicin A

A detailed study[7] into the structural, functional and genetic analysis of sorangicin suggests that sorangicin **A** is very much similar in antibiotic activity, with rifampicin (**Figure**. **4)**, an antibiotic which is commonly used to treat tuberculosis. This study revealed that sorangicin **A** lacks the chemical and structural similarity with rifampicin, nevertheless it binds in the same antibiotic-binding subunit pocket as rifampicin.

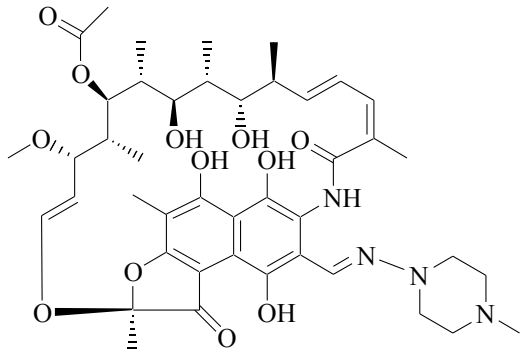


Figure. 4 Rifampicin

The results from sorangicin **A** study[7] confirms that rifampicin and sorangicin **A** binding sites of RNA polymerase (RNAP) largely overlap. However the lack of cross-resistance at all of the tested positions suggests that there are subtle differences in the way the two antibiotics interact with RNAP. Functional analysis further revealed that the two antibiotics inhibit RNAP transcription in the same way, by blocking the synthesis of transcripts no longer than 2–3 nucleotides in length. This is clearly by virtue of occupying the same site, which directly blocks the path of the elongating RNA product within the growing RNA/DNA hybrid. Sorangicin **A** was observed to inhibit transcription initiation, but not elongation, similar to rifampicin. This genetic analysis also indicates that rifampicin is extremely sensitive to mutations expected to change the shape of the antibiotic binding pocket but sorangicin **A** is not. This intrinsic conformational flexibility of sorangicin **A** allows it to adapt to change in the shape of the antibiotic binding pocket and this feature of sorangicin **A** has an important implication in the design of drugs against rapidly mutating targets. The study also suggested that the three hydroxyls (C-21, C-22 and C-25) of sorangicin **A** are very important (**Figure**. **5**) for the antibiotic activity of sorangicin **A**. The two hydroxyls (C-21 and C-22) are critical for transcription inhibition as well as participate in hydrogen bonds when sorangicin interacts with RNAP. Breaking the ring structure of sorangicin, along with other chemical or

stereochemical changes eliminates the antibiotic activity of sorangicin, suggesting that the overall structure of sorangicin is critical for its activity[8]. Sorangicin **A**, the myxobacterium *Sorangium (Polyangium) cellulosum*, strain So ce12, was initially isolated from a soil sample in 1978 from Xcaret[9], Mexico. It has a molecular weight of 806 g/mol, and molecular formula, $C_{47}H_{66}O_{11}$, which was confirmed by negative ion F.A.B mass spectrometry and elemental analysis[10].

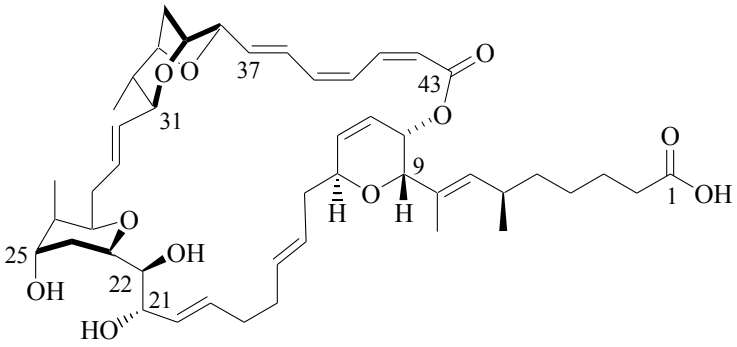


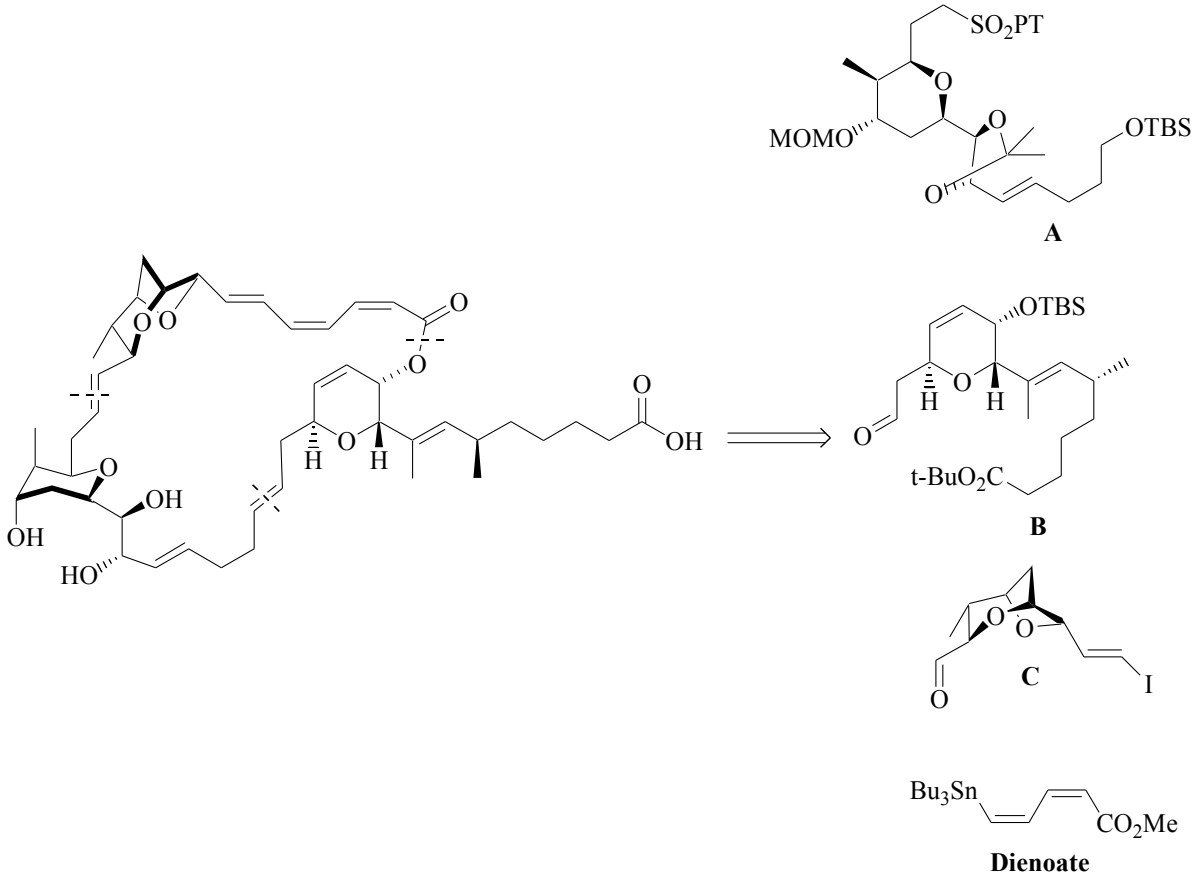
Figure. 5 Biological Activity of Sorangicin A

1.5 Prior Progress to the Total Synthesis of Sorangicin A

1.5.1 Synthetic Efforts by Smith

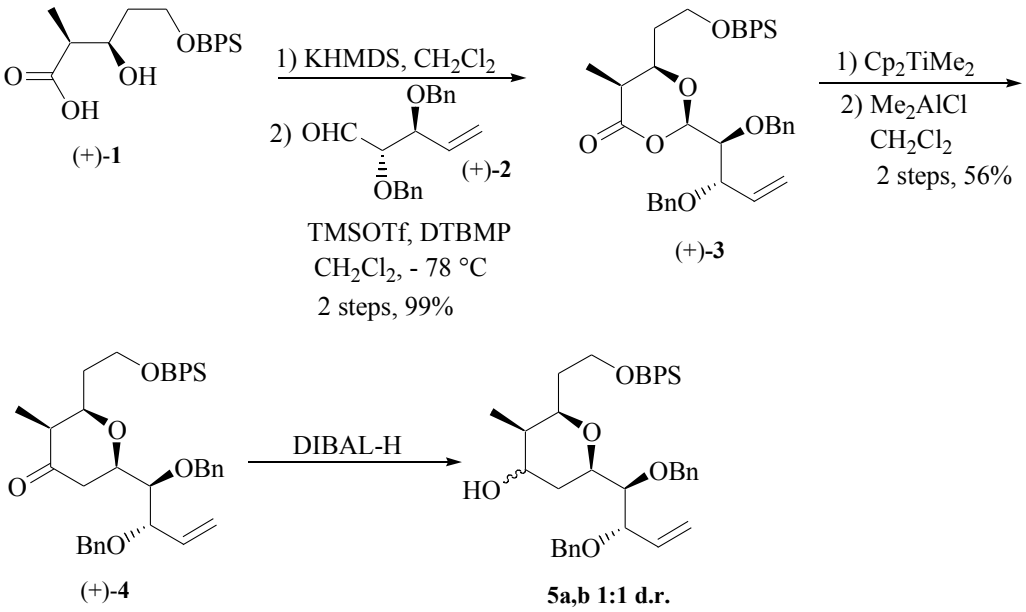
1.5.1.1 Synthesis of the THP Fragment

The Smith work group published the synthesis of the four fragments[11], [12] as well as the first total synthesis of sorangicin **A**[13]. The Smith group developed synthetic route for the synthesis of the bicyclic ether fragment, tetrahydropyran fragment (THP), dihydropyran fragment (DHP), as well as the dienoate moiety.



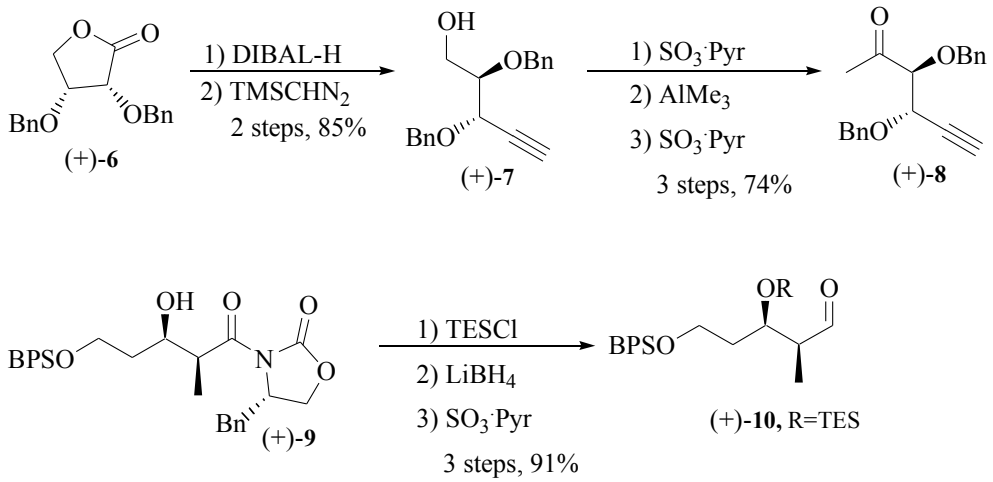
Scheme 1. Smith's Retrosynthesis of Sorangicin A

The synthesis of the THP fragment started by silylaton of the known conjugated β-hydroxy acid (+)-**1** followed by condensation with the aldehyde (+)-**2**, facilitated by TMSOTf to afford the dioxanone (+)-**3** (**Scheme 2**). Petasis-Tebbe methylenation and exposure of the derived enol ether to Me_2AlCl to trigger Petasis-Ferrier rearrangement which provided tetrahydropyranone (+)-**4** in good yield. Reduction of (+)-**4** with DIBAL-H resulted in best mixture (1:1) of C-25 axial and equatorial alcohols **5a**, **5b**.



Scheme 2. Initial THP Synthesis Trial

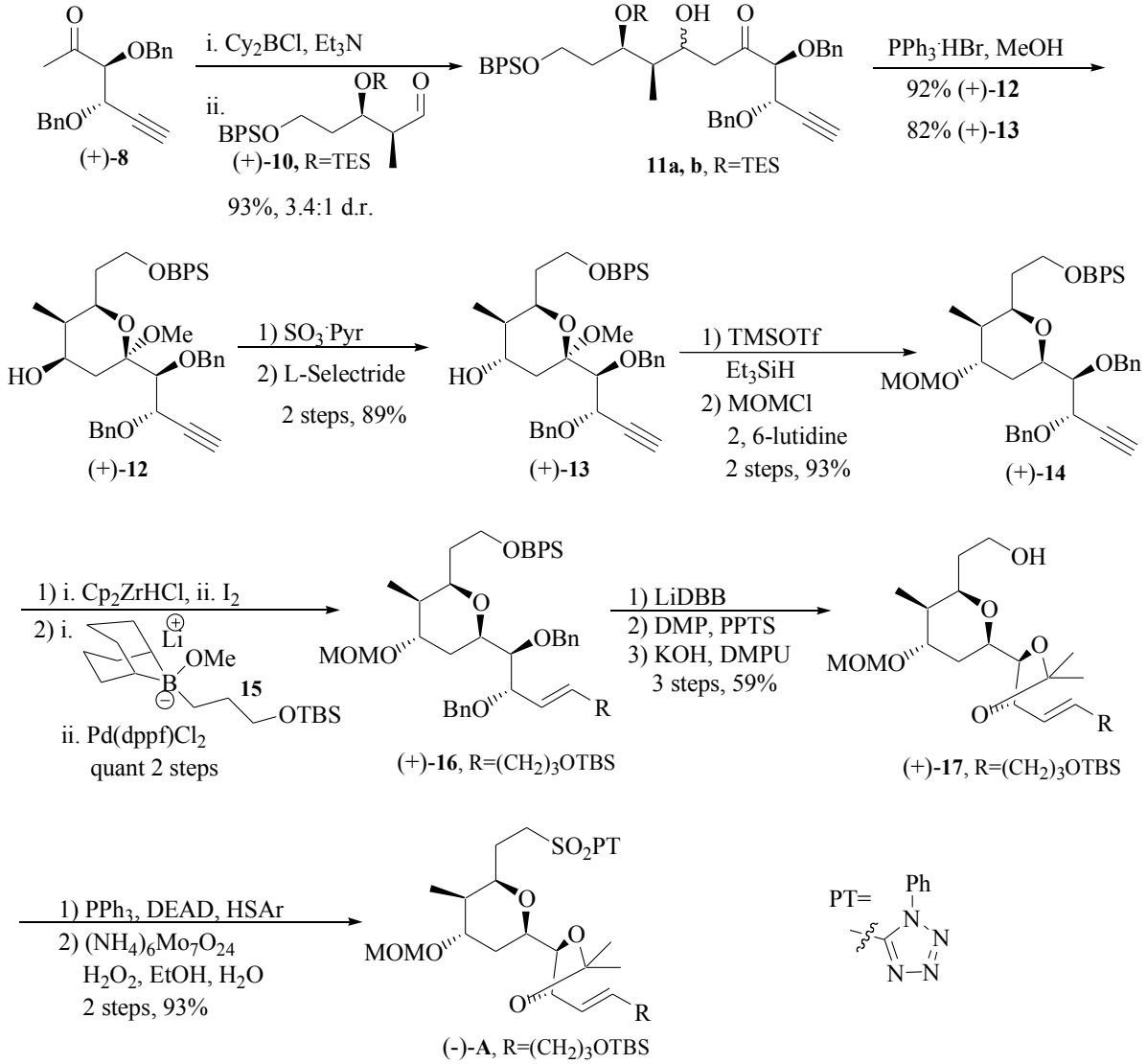
Because of the disappointing reduction result they turned their attention to aldol construction tactic with methyl ketone (+)-**8** and aldehyde (+)-**10**. The construction of ketone (+)-**8** was achieved via DIBAL-H reduction of lactone (+)-**6** and treatment with trimethylsilyldiazomethane provided alcohol (+)-**7**. Compound (+)-**7** underwent oxidation, methyl addition and oxidation consecutively to afford the methyl ketone (+)-**8**.



Scheme 3. THP Synthesis

The treatment of boron enolate derived from (+)-**8** with aldehyde (+)-**10** furnished a separable mixture (3.4:1) of C-25 diastereomers (**Scheme 4**). Removal of the TES group in **11a**, **11b** followed by cyclization and methyl ketal formation furnished mixed methyl ketals

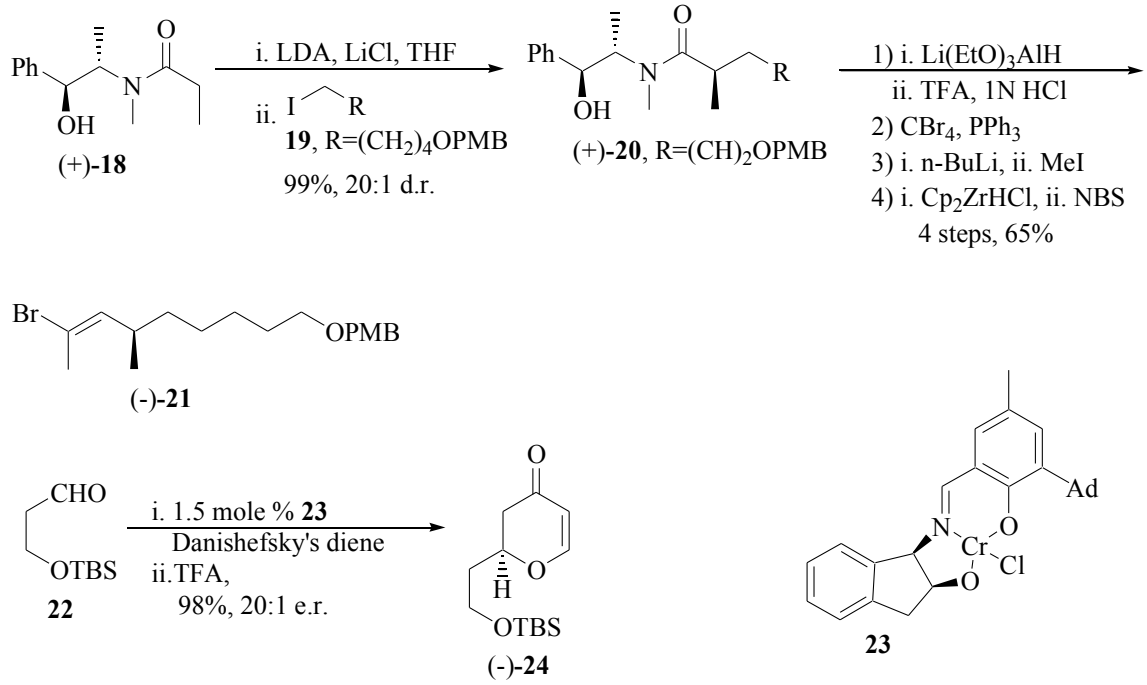
(+)-**12**, (+)-**13** in excellent yield. The minor diastereomer (+)-**12** was completely converted to (+)-**13** via oxidation and reduction. Reduction of methyl ketal (+)-**13** with Et_3SiH promoted by TMSOTf and MOM protection of the hydroxyl afforded tetrahydropyran fragment (+)-**14** as a single diastereomer. Hydrozirconation/iodination followed by Suzuki-Miyaura coupling with alkyl boronate **15** next provided the trans olefin (+)-**16**. Removal of the benzyl group, protection of the diol and selective removal of the tert-butyldiphenylsilyl (BPS) group with hydroxide consecutively led to alcohol (+)-**17**. Thio-ether formation of (+)-**17** via a Mitsunobu reaction and oxidation of the sulfide to sulfone completed construction of fragment **A**. Sulfone (-)-**A** was thus prepared in 17 steps from commercially available starting material, with 17% overall yield.



Scheme 4. Completion of THP Synthesis

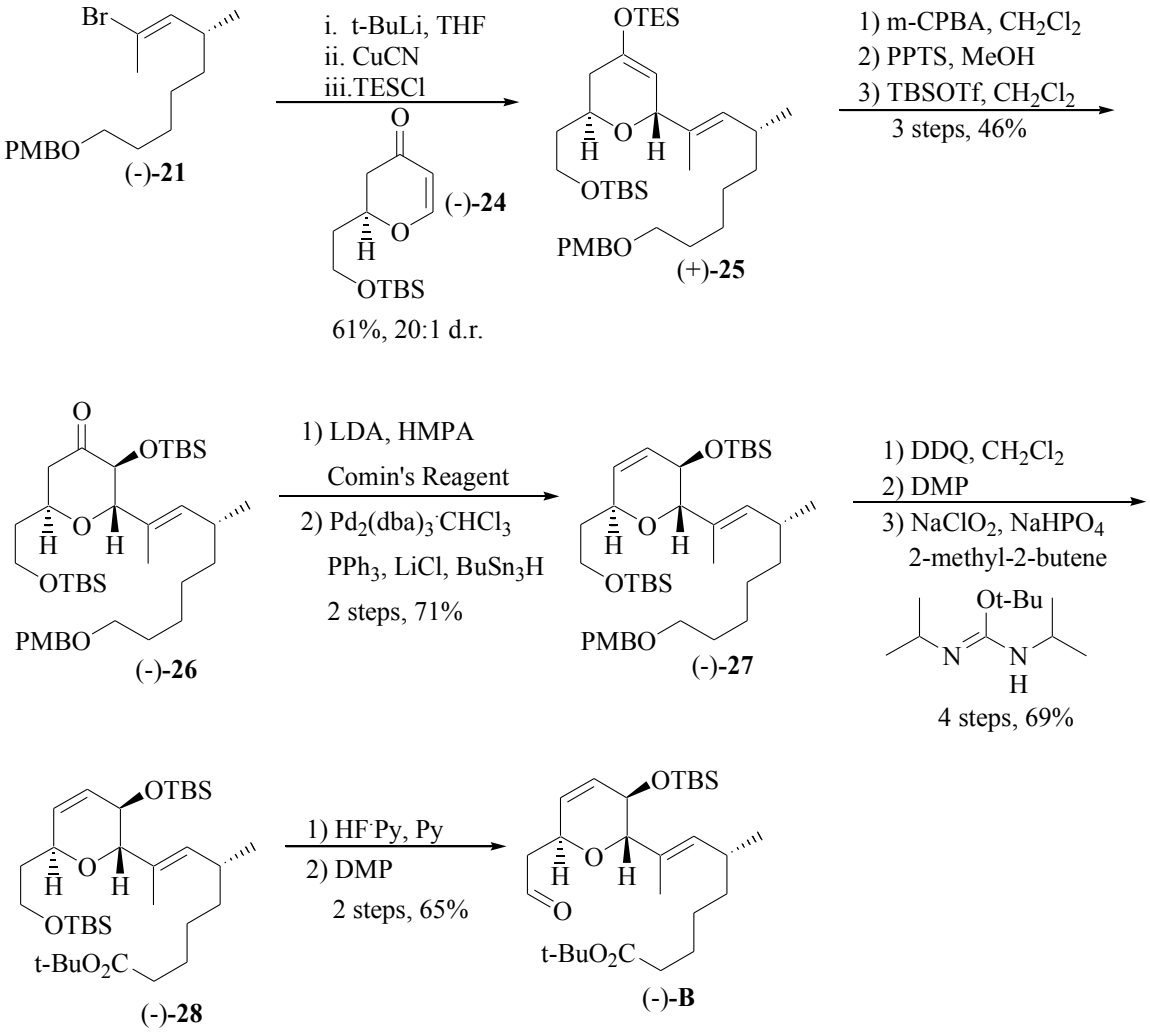
1.5.1.2 Synthesis of the DHP Fragment

The synthesis of the DHP fragment **B** was started with enone **(-)-24** exploiting a conjugate addition/oxygenation sequence. Synthesis of the requisite vinyl bromide (-)-**21** entailed a Myers alkylation between ketone (+)-**18** and iodide **19** to furnish amide (+)-**20**. Reduction of amide (+)-**20** followed by Corey-Fuchs homologation and hydrozirconation/bromination led to vinyl bromide (-)-**21** as a single stereoisomer. Enone (-)-**24** was prepared enantioselectively via cyclocondensation between Danishefsky's diene and aldehyde **22**, catalyzed by chromium complex **23 (Scheme 5)**.



Scheme 5. Synthesis of DHP Fragment

Treatment of the higher order cuprate derived from (-)-**21** with enone (-)-**24** (**Scheme 6**) in the presence of TESCl led to enol ether (+)-**25** as a single diastereomer. Chemo- and stereoselective C-10 oxidation of (+)-**25** employing the Rubottom protocol followed by conversion of the derived O-TES ether to O-TBS ether provided (-)-**26**. Kinetic enolate formation with LDA/HMPA followed in turn by formation of the enol triflate with Comin's reagent [*N*-(5-chloro-2-pyridyl)-triflimide] and palladium catalyzed reduction led to diene (-)-**27**. Removal of the PMB group followed by a two-step oxidation and tert-butyl ester formation furnished (-)-**28**. Finally selective deprotection of the primary TBS group and Dess-Martin oxidation provided the DHP fragment. Overall, the synthesis of (-)-**B** entailed a longest linear sequence of 19 steps with 5% overall yield.

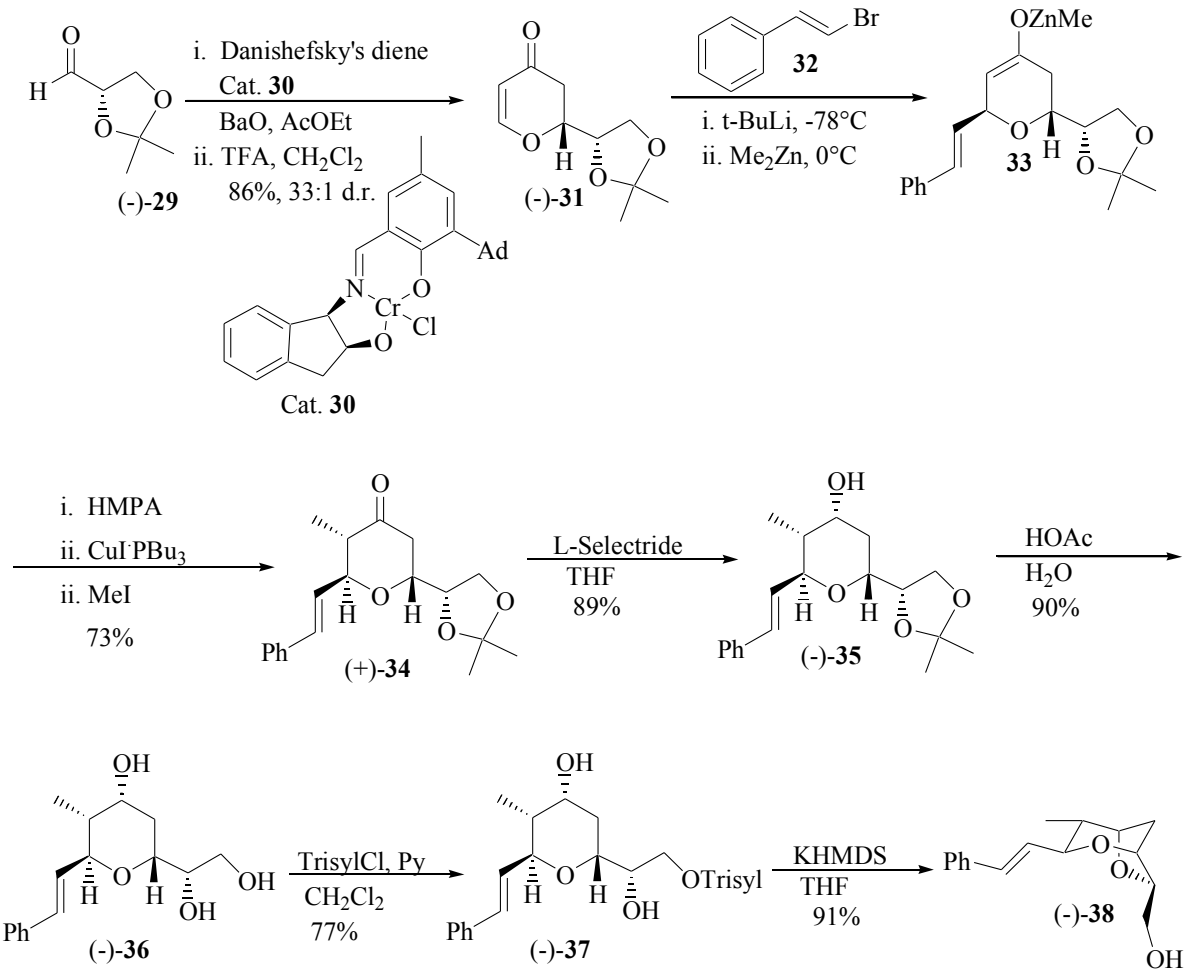


Scheme 6. Completion of DHP Synthesis

1.5.1.3 Synthesis of the Bicyclic and Trienoate Fragments

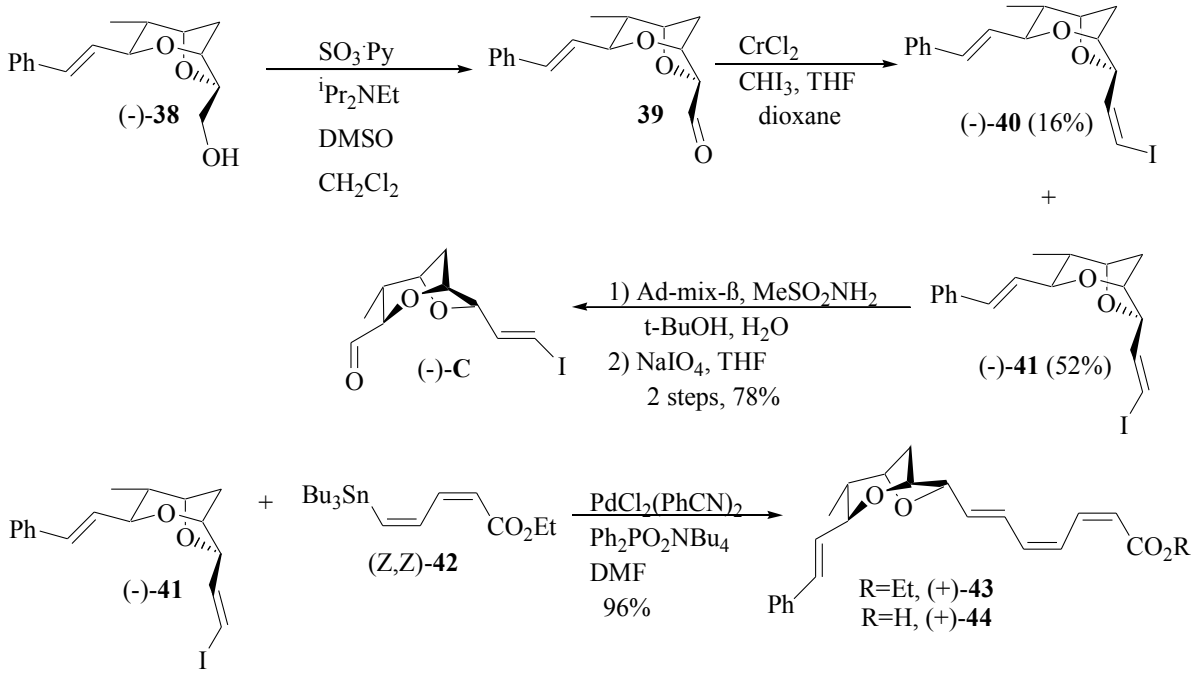
Smith *et al*. reported[11] the synthesis of the (*Z,Z,E*)-trienoate linkage and dioxabicyclo-[3.2.1]octane. Synthesis of dihydropyranone (+)-**34** was affected via an asymmetric Diels-Alder reaction of aldehyde (-)-**29** with Danishefsky's diene catalyzed by Cat. **30** followed by hydrolysis provided enol ether (-)-**31** (**Scheme 7**). The treatment of enol ether (-)-**31** with bromostyrene **32** by applying Noyori three-component coupling protocol involving lithium halogen exchange of bromine with t-BuLi at -78 °C and followed by addition of Me_2Zn warming to 0 °C furnished a mixed zincate **33**. The enolate **33** was treated with HMPA and addition of $CuI{\cdot}PBu_3$ just prior to the addition of methyl iodide provided (+)-**34**. Stereoselective reduction of ketone (+)-**34** resulted in alcohol **(-)-35** and acidic deprotection provided triol (-)-**36**. Treatment of triol (-)-**36** with isopropylbenzenesulfonyl chloride (TrisylCl)

afforded the primary sulfonate (-)-**37**. Exposure of (-)-**37** to KHMDS effected both epoxide formation and subsequent epoxide opening providing the five membered ring bicyclic ether(-)-**38**.



Scheme 7. Bicycles Synthesis

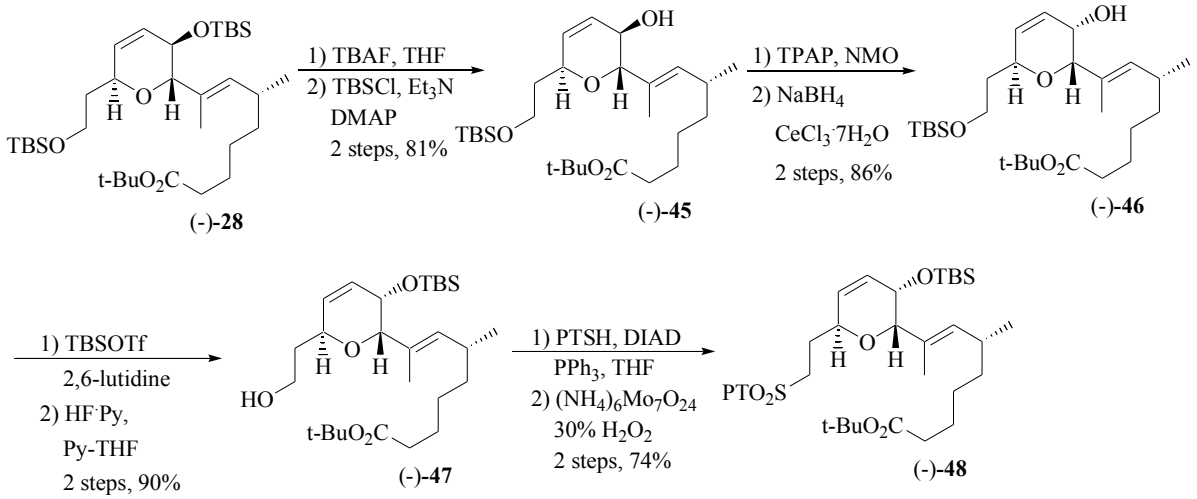
The alcohol (-)-**38** underwent Parikh-Doering oxidation followed by subjection of the crude aldehyde **39** to Takai olefination condition yielding vinyl iodide **(-)-40** (*Z*) and (-)-**41** (*E*) as diastereomeric mixture (**Scheme 8**). Finally selective dihydroxylation of the styrene-olefin (-)-**41** followed by oxidative cleavage provided aldehyde (-)-**C**. The vinyl iodide (-)-**41** was coupled with known vinyl (*Z*,*Z*)-dienoate **42** catalyzed by palladium and subsequent hydrolysis provided the bicyclic-triene carboxylic acid (+)-**44**.



Scheme 8. Synthesis of Bicycles and Trienoate Fragments

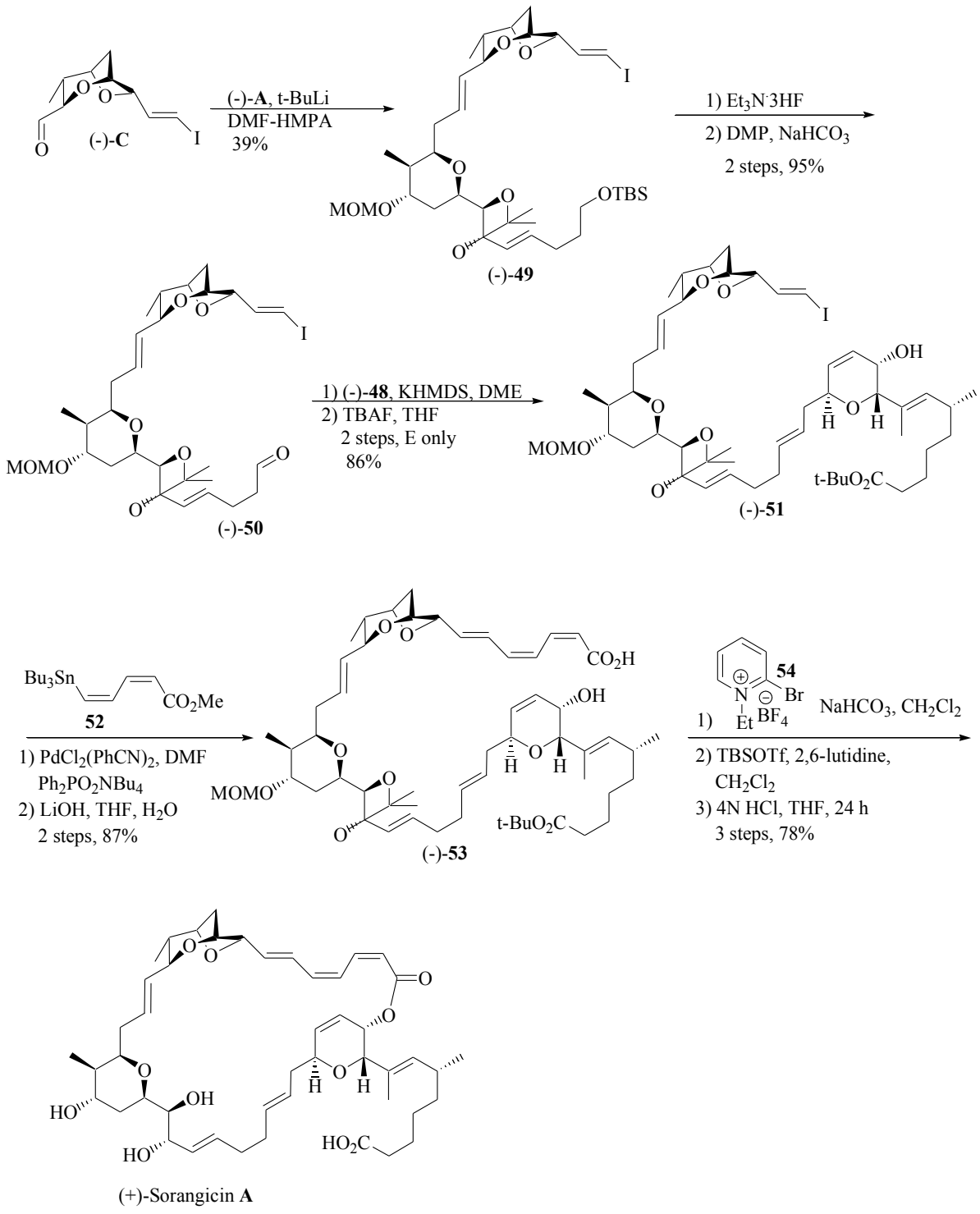
1.5.1.4 First Total Synthesis of Sorangicin **A**

In a very recent paper Smith *et al*. published[13] the first total synthesis of sorangicin **A** involving the coupling of the four fragments, dihydropyran (DHP), tetrahydropyran (THP), the bicycles and Stannyl dienoate fragments. Although the synthesis of the DHP fragment was already reported[12] from the group, the stereochemistry at C-10 of sorangicin **A** required adjustment (**Scheme 9**). Global desilylation of (-)**-28** followed by chemoselective silylation furnished allylic alcohol (-)**-45**. Ley oxidation and Luche reduction generated the desired alcohol (-)**-46**. Protection with TBSOTf and selective deprotection of the primary TBS group with HF·Py/Py-THF resulted in the primary alcohol (-)**-47** and the alcohol was converted in two steps to sulfone (-)**-48**.



Scheme 9. Modification of DHP Synthesis

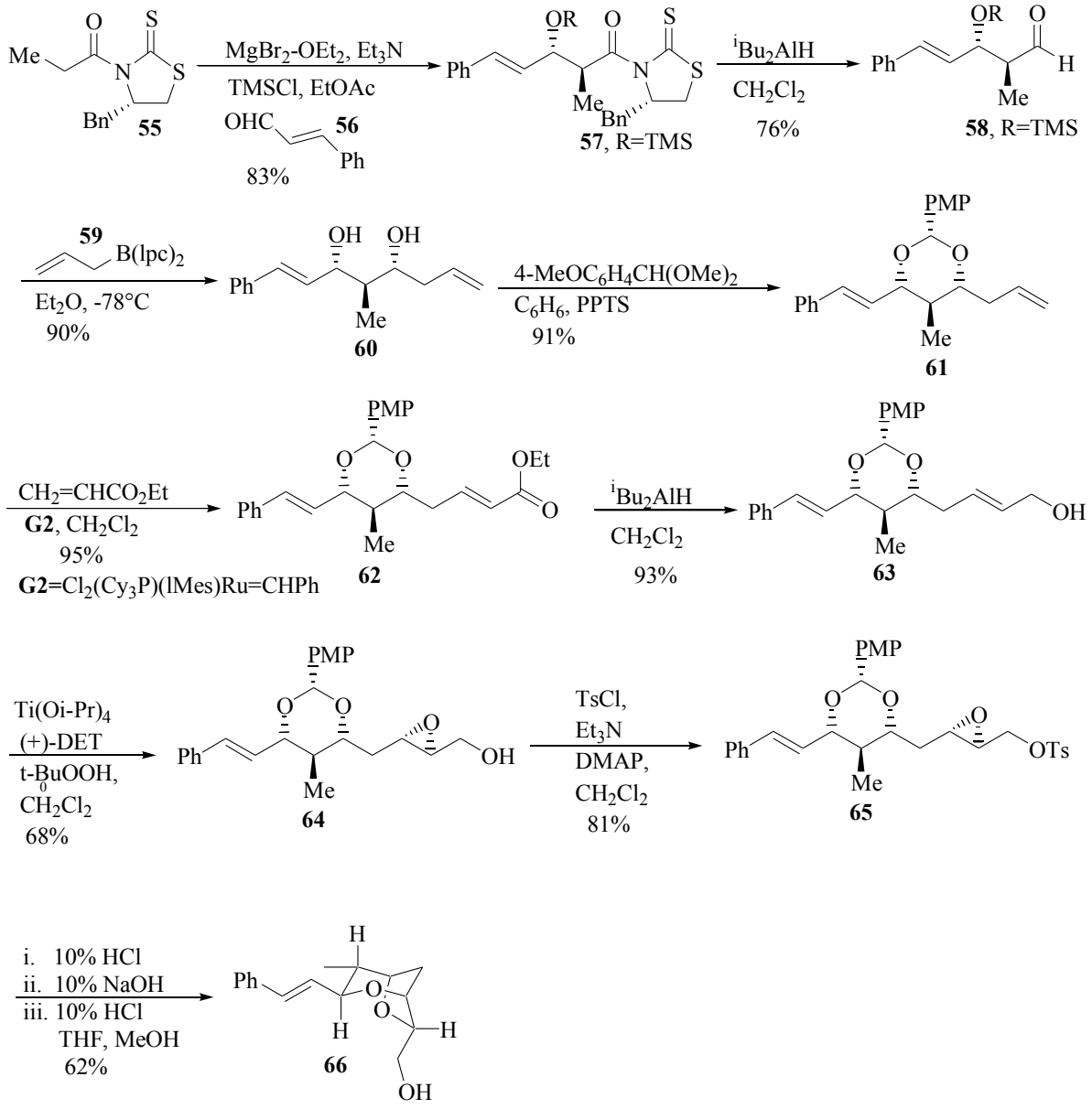
Smith *et al*. started construction of both C(29)-C(30) and C(15)-C(16) trans double bonds via Julia-Kocienski olefination followed by Stille coupling and macrolactonization to complete the overall carbon skeleton. Coupling between (-)-**C** and (-)-**A** using t-BuLi in aprotic solvent (DMF/HMPA) provided iodide (-)-**49** with *E*-configuration (**Scheme 10**). The vinyl iodide (-)-**49** was converted in two steps to the corresponding aldehyde (-)-**50** and subsequent Julia-Kocienski olefination with (-)-**48** under KHMDS/DME condition provided (+)-**51**. The coupling of Stannyl dienoate **52** with (+)-**51** by using excess $Ph_2PO_2NBu_4$ (12 equiv) to suppress the *E/Z* isomerization and subsequent hydrolysis with LiOH in aqueous THF provided (*Z,Z,E*) trienoate (+)-**53**. Treatment of (+)-**53** with TBSOTf (buffered with 2,6-lutidine) transformed the tert-butylester groups to the TBS ether and exposure to 4N HCl in THF at room temperature for 24 h afforded (+)-sorangicin **A** which was identical in all respect (^{1}H, ^{13}C, HRMS, HPLC, LRMS) to an authentic natural samples provided by the laboratory of G. Höfle *et al*.[14].



Scheme 10. First Total Synthesis of Sorangicin A

1.5.2 Synthetic Efforts by Crimmins

Crimmins *et al*. reported[15] the construction of the C(29)-C(37) bicyclic ether by using the epoxy tosylate **65** (**Scheme 11**). The approach was designed around a three-step sequence of epoxide opening, epoxide formation and a second epoxide opening to afford the bicyclic fragment **66** from epoxide **65**.



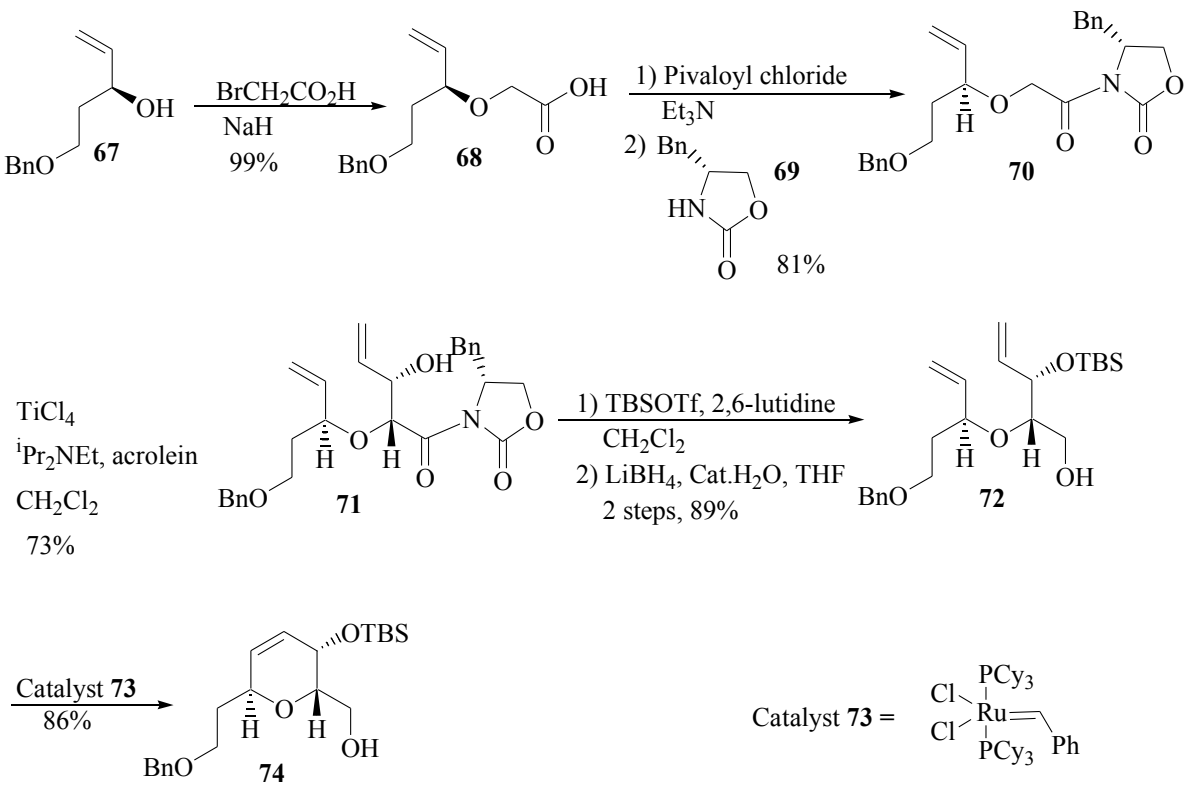
Scheme 11. Crimmins's Bicycles Synthesis

The synthesis of the epoxide **65** was started with the known Evans anti-aldol reaction of *N*-propionylthiazolidinethione **55** and (*E*)-cinnamaldehyde **56**, which delivered the aldol adduct **57**. The chiral auxiliary **57** was reductively removed with *i*-Bu_2AlH and the resultant

aldehyde **58** was immediately subjected to Brown asymmetric allylation to afford the diol **60** which was exposed to PPTS and 4-methoxybenzaldehyde dimethyl acetal to afford the *p*-methoxyphenyl acetal **61**. Treatment of alkene **61** with two equivalent of ethyl acrylate in the presence of Grubb's second generation catalyst **G2** at room temperature provided unsaturated ester **62**. Reduction of ester **62** by exposure to *i*-Bu_2AlH afforded allylic alcohol **63** and subsequent Sharpless asymmetric epoxidation furnished epoxide **64**. Epoxy alcohol **64** was treated with *p*-toluenesulfonyl chloride under basic condition to yield tosylate **65** (**Scheme 11**). Treatment of the epoxide **65** successively by 10% HCl, 10% NaOH and 10% aqueous HCl in THF/MeOH in one-pot synthesis furnished bicyclic ether **66**. Crimmins *et al*. developed a very efficient route to the bicyclic fragment **66** of (+)-sorangicin **A** with only nine steps and proceeds in good overall yield.

1.5.3 Synthetic Efforts by Lee

The Lee laboratory group published[16] synthetic routes for the dihydropyran fragment with out the side chain using ring closing metathesis reaction to form the six membered ring. The synthesis of DHP fragment **74** started with known chiral alcohol **67** and alkylation of **67** with bromoacetic acid in the presence of NaH furnished glycolic acid **68**. Treatment of the glycolic acid **68** with pivaloyl chloride and use of the lithiated oxazolidinone provided **70**. Treatment of the acylated oxazolidinone **70** with acrolein provided the hydroxyl compound 7**1**. TBS-protection of the resulting secondary alcohol **71** and subsequent reductive elimination of the auxiliary afforded the primary alcohol **72**. Olefinic ring closing metathesis reaction in the presence of Grubb's first generation catalyst **73** provided the desired DHP core **74**.

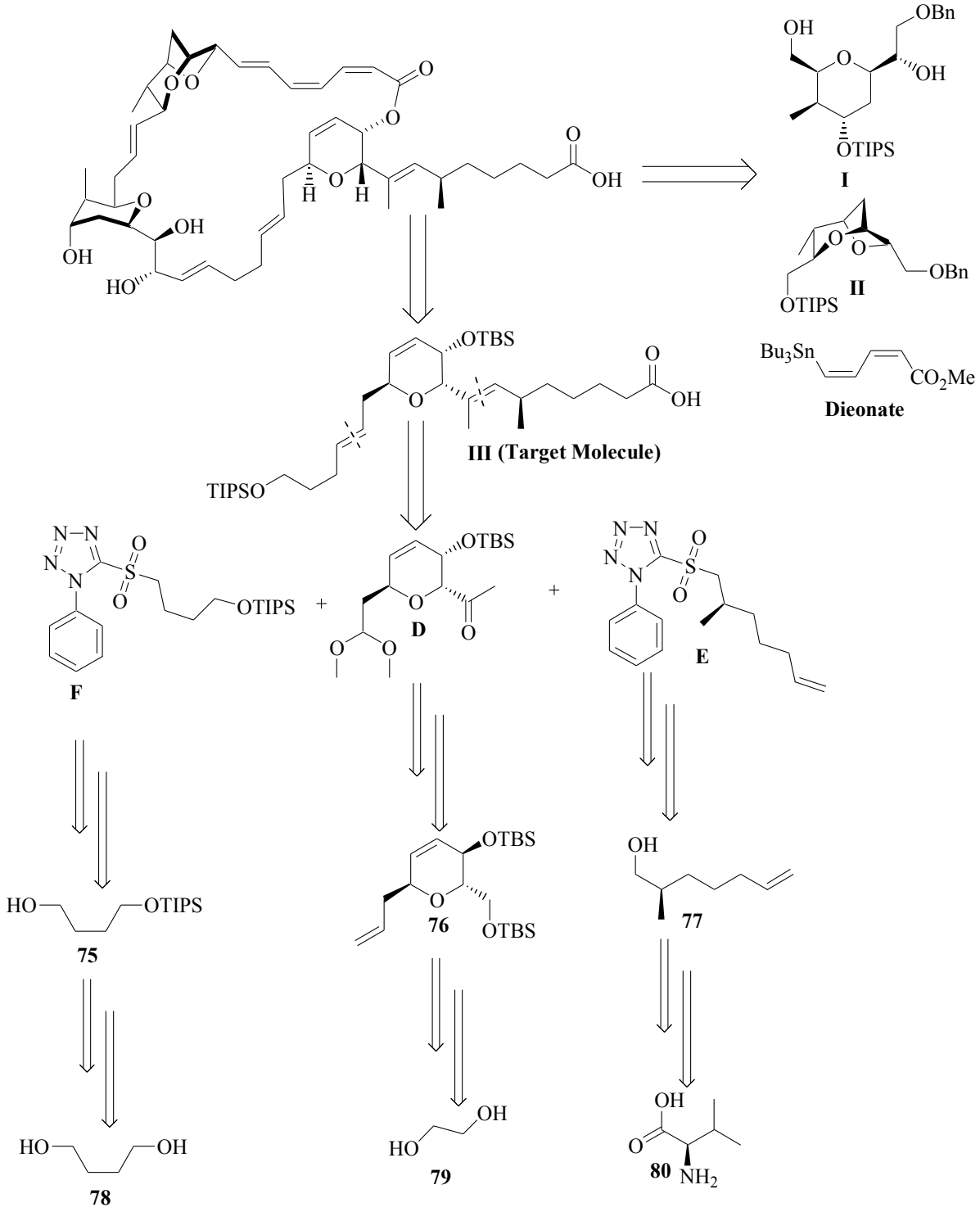


Scheme 12. Lee's DHP Fragment Synthesis

Chapter 2- Objective of Thesis Research

2.1 Objective

The objective of this work was to develop an efficient synthetic route to the C(1)-C(19) fragment of sorangicin with high yield and very good stereoselectivity (**Scheme13**).



Scheme 13. Retrosynthesis of Sorangicin

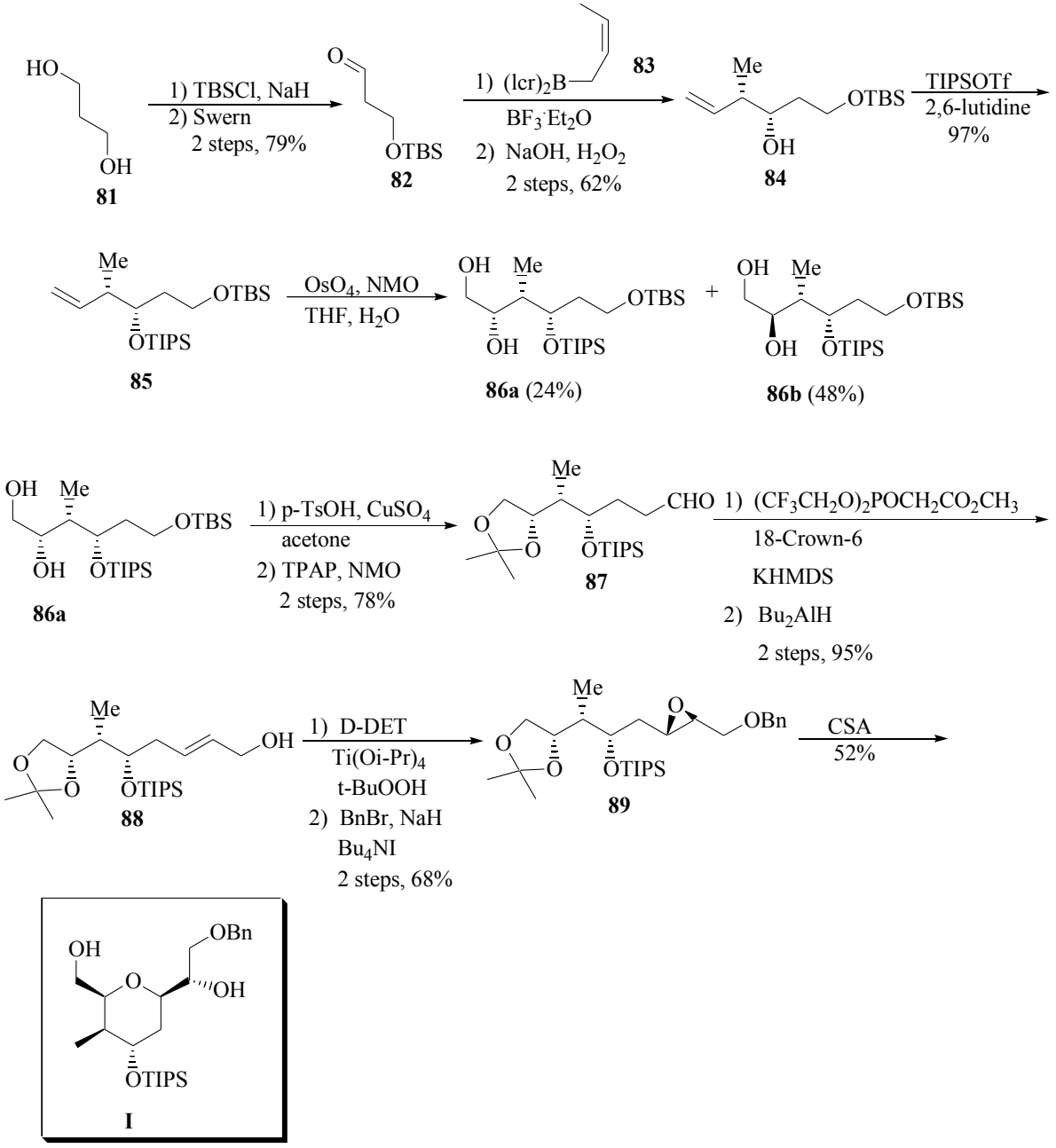
2.2 Synthesis of Fragment I and II

The synthesis of fragment **I** and fragment **II** as well as trials to the synthesis of the dihydropyran fragment were reported[17], [18], [19] from our work group.

The synthesis of fragment **I** and fragment **II** was reported by Claudia Schulz[20]. The synthesis of both tetrahydropyran fragment **I** and bicyclic ether fragment **II** were accessed from one common intermediate.

The synthesis of the fragments started from propanediol **81** which was selectively protected and oxidized to provide TBS-protected aldehyde **82** and subsequent asymmetric Brown crotylation gave homoallylic alcohol **84**. Protection of **84** with TIPSOTf gave terminal olefin **85** (**Scheme 14**). Dihydroxylation of olefin **85** under Sharpless condition gave two diastereomeric diols **86a** and **86b**. The syn,syn-diol **86a** was able to afford the THP fragment **I** while the anti,syn-diol **86b** gave the bicyclic fragment **II**.

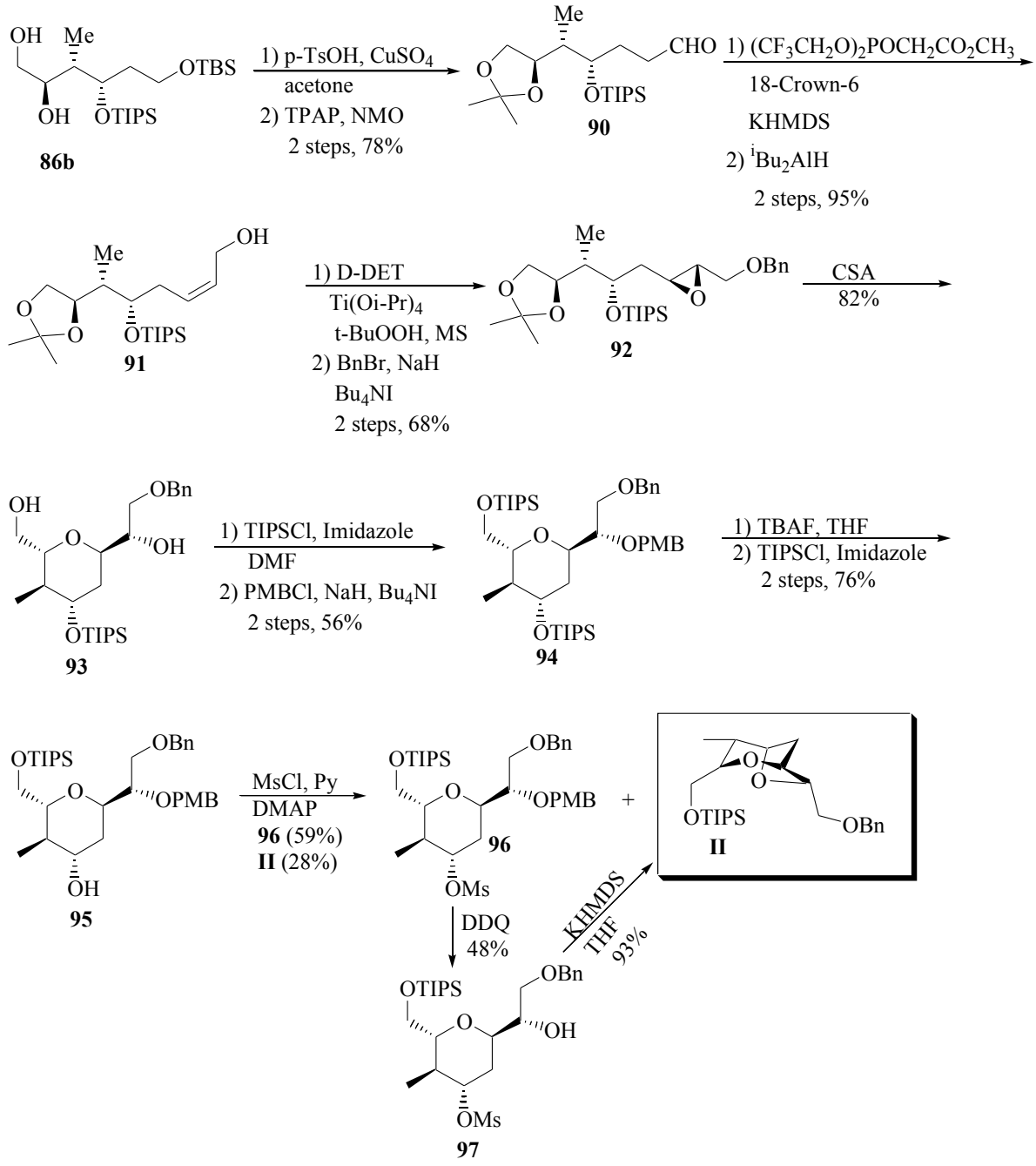
The construction of the THP fragment was continued by protecting diol **86a** and deprotection of the TBS-ether and oxidation of the alcohol provided aldehyde **87**. Selective Horners-Wadsworth-Emmons olefination and 1,2-reduction gave allylic alcohol **88**. Epoxidation of the internal olefin followed by protection of the alcohol with BnBr provided the epoxide **89** and subsequent acidic deprotection promoted the exo-cyclization to afford the THP fragment **I**.



Scheme 14. Synthesis of Fragment I

For synthesizing the bicyclic fragment **II** the anti,syn-diol **86b** was used. Protecting diol **86b** and deprotection of the TBS-ether and subsequent oxidation of the alcohol gave aldehyde **90**. Selective Horners-Wadsworth-Emmons olefination and 1,2-reduction provided allylic alcohol **91**. Epoxidation of the internal olefin followed by protection of the alcohol provided epoxide **92** and subsequent acidic deprotection promoted the Exo-cyclization to afford diol **93**. Protecting group manipulations prior to ultimate sulfonylation furnished mesylate **96**

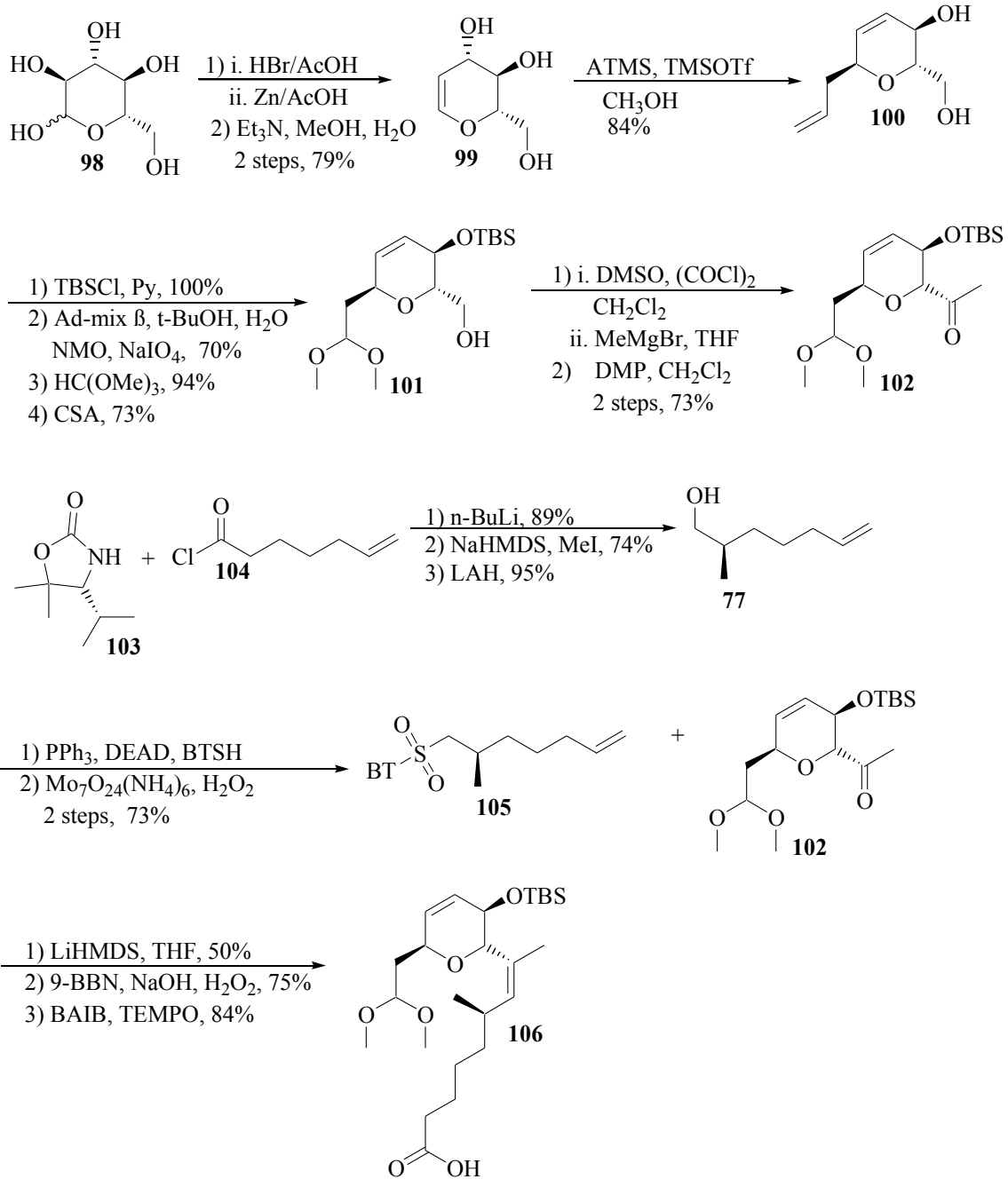
and fragment **II**. Selective cleavage of the PMB functionality of mesylate **96** with DDQ furnished alcohol **97** which was exposed to KHMDS to afford fragment **II**.



Scheme 15. Synthesis of Fragment II

2.3 Synthesis of the Dihydropyran Fragment

The trial to the synthesis of the dihydropyran fragment was reported from our work group by Olga Krug[21]. The synthesis of the DHP subunit started with known conversion of glucose **98** to tri-O-acetyl glucal which was reduced by basic methanol solution to afford glucal **99** (**Scheme 16**). Subjection of the glucal to TMSOTf followed by the addition of allyltrimethylsilane (ATMS) afforded diol **100**. The diols were protected with TBSCl and underwent Sharpless dihydroxylation, oxidative cleavage of the diols with $NaIO_4$ as well as subsequent deprotection and protection afforded alcohol **101**. Compound **101** underwent swern oxidation, Grignard addition and DMP oxidation to afford methyl ketone **102**. The synthesis of the side chain fragment started by coupling the known Seebach auxiliary **103** with 6-heptenoyl chloride **104**. Subsequent alkylation with MeI and reductive removal of the auxiliary with LAH resulted in alcohol **77**. Treatment of **77** with Mitsunobu condition and subsequent oxidation gave the desired sulfone **105**. The methyl ketone **102** and sulfone **105** were coupled using Julia-Kocienski olefination condition to afford in three steps the *Z*-isomer acid **106**.



Scheme 16. DHP fragment Synthesis trial

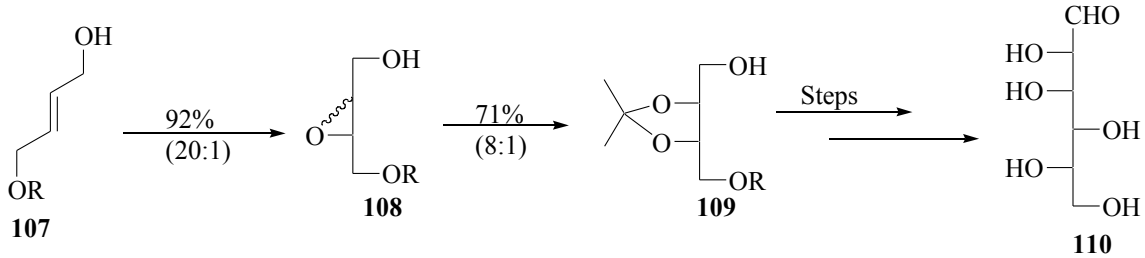
Chapter 3- Synthesis of Fragment D

3.1 Synthesis of L-hexoses

The synthesis of L-hexoses has been an interest for organic chemists for the past few decades. Many organic chemists have been trying to develop methods for synthesizing hexoses. The synthesis of L-hexoses involves the construction of four stereocenters with five similar hydroxyl groups. The hexoses are stereoisomers having a concatenation of four contiguous hydroxy-bearing carbogenic centers. Their enantio-controlled synthesis therefore requires a procedure leading to eight pairs of stereoisomers in enantio-and diastereo-controlled manner.

3.1.1 Sharpless's Reiterative Two Carbon Extension Cycle

Sharpless *et al*.[22] described a systematic, stereoselective synthesis of all eight L-hexoses by a synthetic methodology developed in their laboratories for the preparation of polyhydroxylated natural products. Their strategy is based on the reiterative two-carbon extension cycle (**Scheme 17**). It consists of four steps, (i) conversion of an aldehyde into its corresponding *E*-allylic alcohol, (ii) asymmetric epoxidation (AE) with titanium tetraisopropoxide, t-butylhydroperoxide, and (+) or (-) diethyl tartrate, (iii) treatment of the epoxy alcohol with benzenethiolate anion in a basic medium, (iv) oxidation and Pummerer reaction of the sulfide followed by the net hydrolysis of the resulting gem-acetoxysulfide with or without inversion of the carbon center. The synthesis of the hexoses was accomplished in 14 synthetic steps and most of the reaction proceeding in a very good regio- and stereoselectivity.



107

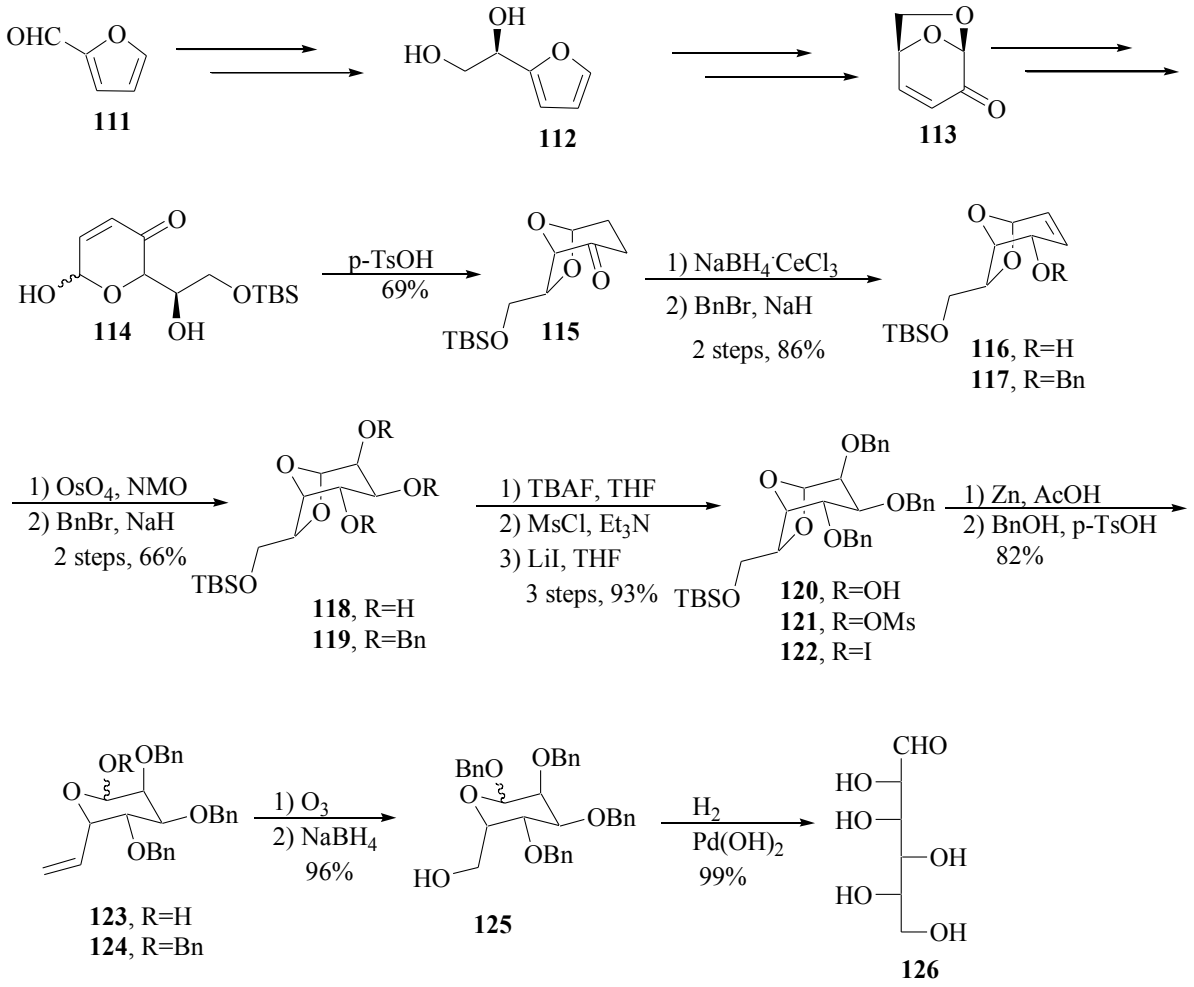
R=CH(Ph)$_2$

108 **109** **110**

Scheme 17. Sharpless's Synthesis of Hexoses

3.1.2 Modifications to Sharpless's Strategy

Ogasawara *et al*.[23] reported an alternative to Sharpless route which required reiteration of two-carbon elongation and asymmetric epoxidation. They described a new strategy capable of producing all stereoisomers of L-hexoses from a single starting material employing an asymmetric chiral induction step (**Scheme 18**).



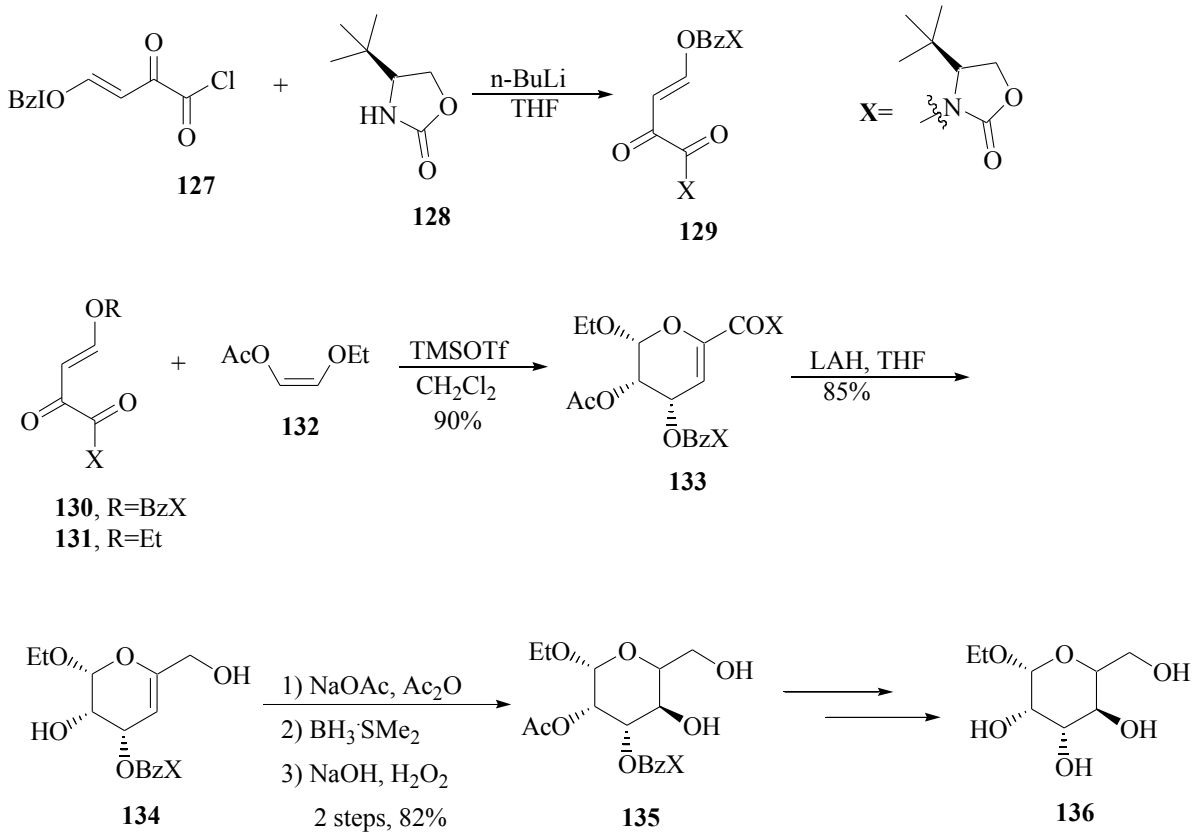
Scheme 18. Ogasawara's Synthesis of L-Hexoses

Their strategy involves the utilization of the levo-glucosenone-type intermediate **113**. The intermediate **113** have an extra hydroxymethyl functionality to control the regioselective cleavage of the bicyclic system as well as to discriminate the two terminal functionalities of the substrate. With respect to the construction of the four contiguous hydroxy-bearing centers, as the key intermediate **115** possesses fixed oxygen functionality fated to be one of the four contiguous hydroxyl functionalities which planned to install the three remaining

hydroxyl function by modification of the enone functionality. The most salient feature of the strategy is the use of the key intermediate **115** in two ways, namely the acetal carbon and the C-2 of the glycol carbons are placed at either the C-1 formyl functionality or the C-6 hydroxymethyl functionality of the target hexoses so as to produce the isomeric and/or the enantiomeric hexoses from the same precursor.

3.1.3 Hetero-Diels-Alder Reaction

Tietze et al.[24] reported the synthesis of sugars using hetero Diels-Alder reactions. The hetero Diels-Alder reactions of **130** with **132** was carried out using TMSOTf or Me_2AlCl which has provided in a very good yield and with high endo-selectivity **133**. The dihydropyran **133** was converted into carbohydrates in five step reaction sequences in a very good yield and high stereoselectivity (**Scheme 19**).

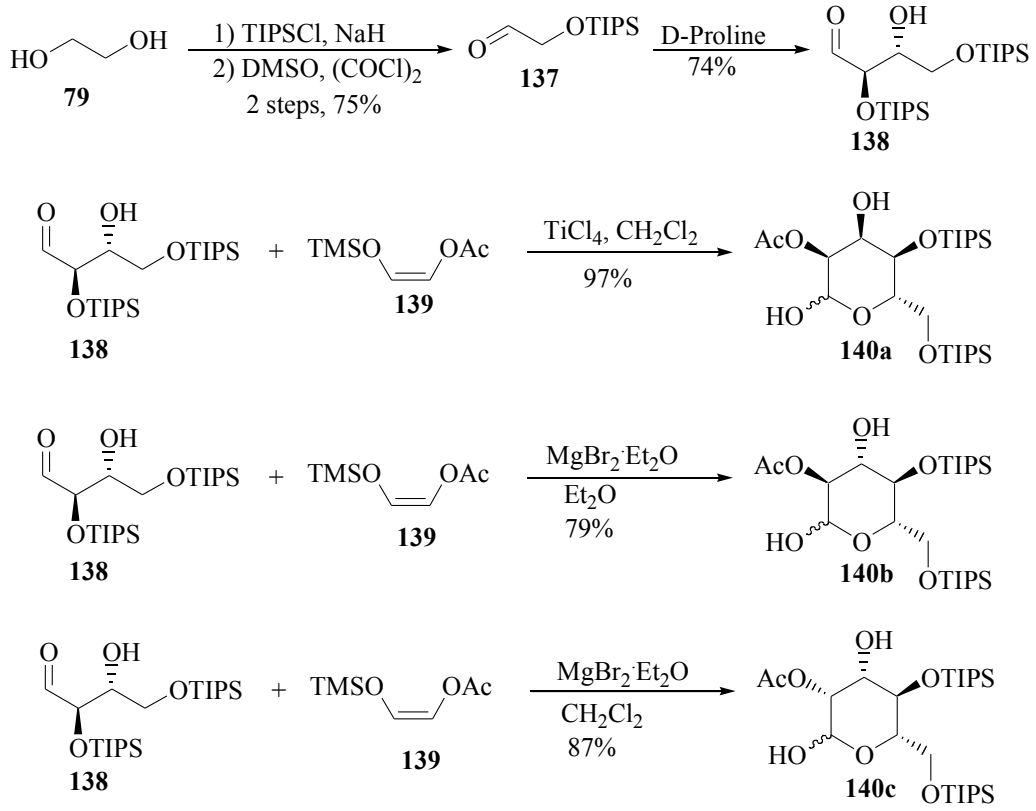


Scheme 19. Tietze's Synthesis of L-Hexoses

3.1.4 Proline Catalyzed Aldol Reaction

MacMillan *et al*.[25] reported a synthetic route based on aldol coupling of aldehydes in only two synthetic steps. The first step is a stereoselective dimerization of α-oxyaldehydes cataly-

zed by D-proline which was then followed by a tandem Mukaiyama aldol addition- cyclization step catalyzed by a Lewis acid. The initial step requires that the α-oxyaldehyde **137** participate both as a nucleophile and an electrophile, whereas the product **138** must be inert for further aldol reactions. Mukaiyama aldol reaction of oxy-enolsilane **139** with TIPS- protected β-oxyaldehyde **138** in the presence of a Lewis acid afforded the cyclization products, carbohydrate ring system (**Scheme 20**). Exposure of the β-oxyaldehyde **138** and enolsilane **139** to $TiCl_4$ in CH_2Cl_2 affords high selectivity for allose **140a** with a 97% yield and 19:1 selectivity. The use of $MgBr_2{\cdot}OEt_2$ in solvents such as Et_2O, toluene or pentane shows preference for glucose **140b** with 8:1-10:1 selectivity. Using optimized condition, a 79% yield and a 10:1 preference for glucose in Et_2O was obtained, whereas using $MgBr_2{\cdot}OEt_2$ in CH_2Cl_2 resulted in 87% yield and 19:1 selectivity for mannose **140c**.

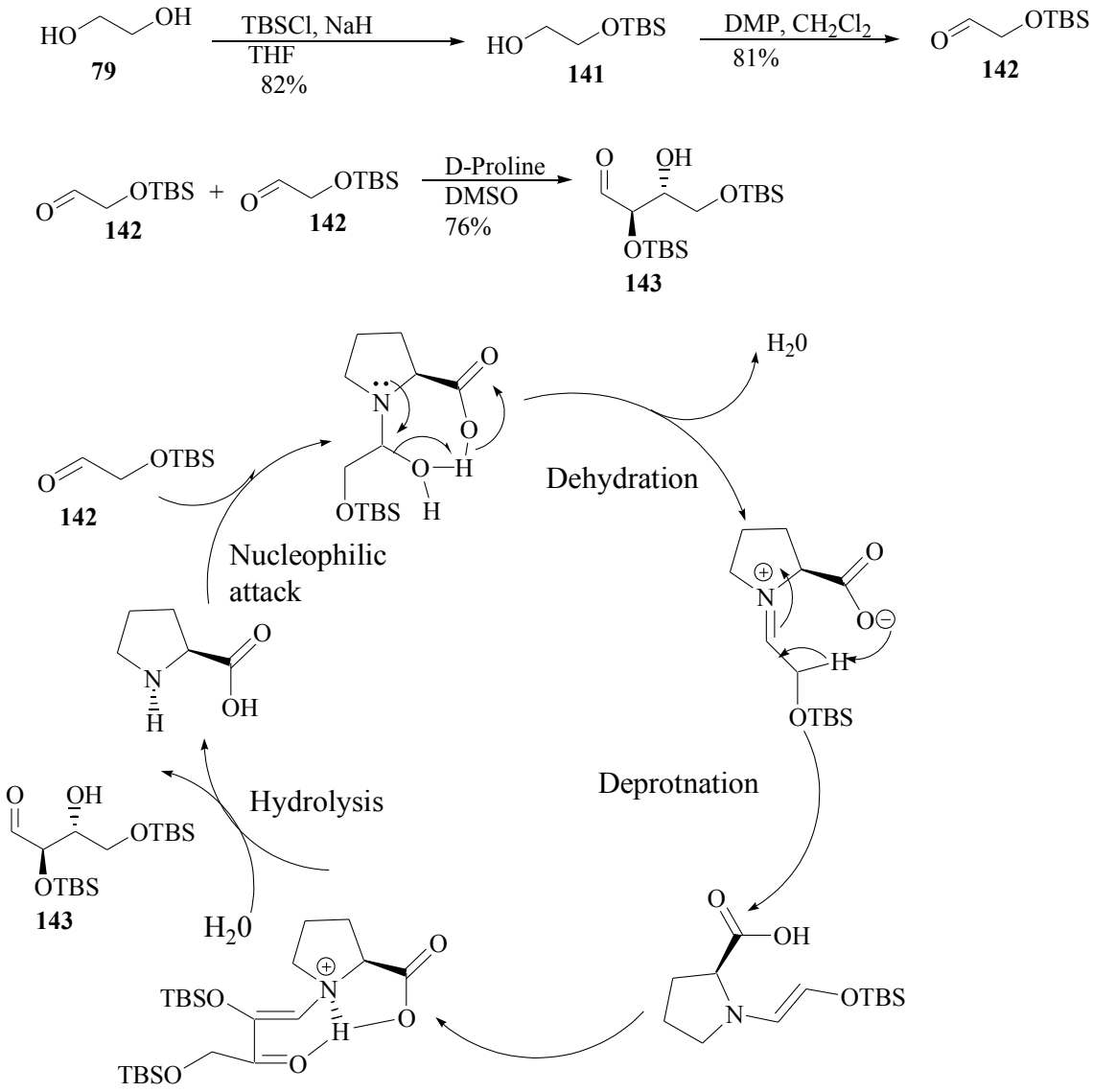


Scheme 20. MacMillan's Synthesis of Hexose

3.2 Synthesis of L-glucose Fragment

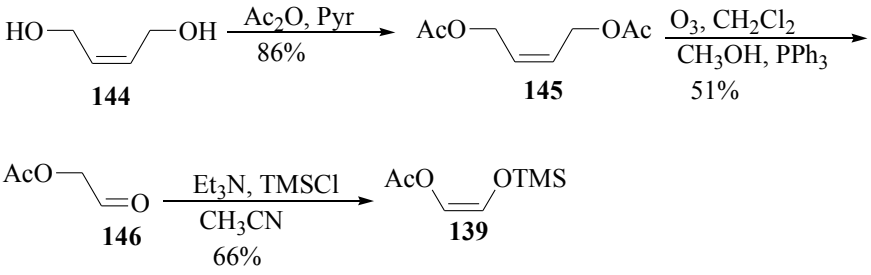
The synthesis of L-glucose fragment started using commercially available ethylene glycol **79**, was selectively protected with TBSCl/NaH conditions to afford TBS-protected alcohol **141** in 82% yield. Compound **141** was selectively oxidized using DMP/CH_2Cl_2 condition to provide aldehyde **142** in 81% yield[25].

The aldehyde **142**, was used both as nucleophile and electrophile, underwent dimerization using D-proline/DMSO condition to afford TBS-protected β-oxyaldehyde **143** in 76% (syn:anti, 1:3.4) yield (**Scheme 21**).



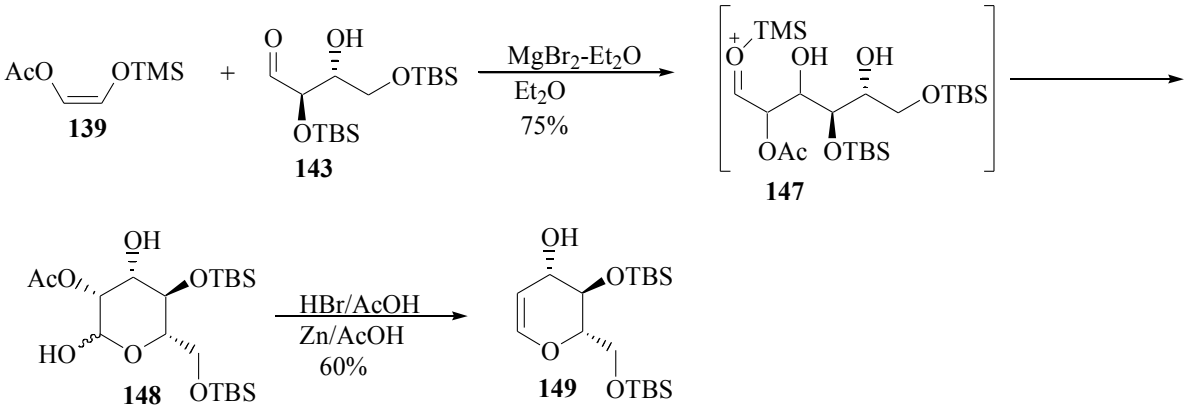
Scheme 21. Synthesis of Oxyaldehyde

The synthesis of oxy-enolsilane **139** started from commercially available cis-2-butenediol **144** which was acylated using Ac_2O/Py condition[28] to afford the acylated alkene **145** in 86% yield. The alkene **145** was oxidized with ozone to give the corresponding aldehyde **146** in 51% yield and subsequent selective protection of **146** with TMSCl/Et_3N/CH_3CN condition[29] provided the *Z*-isomer oxy-enolsilane **139** in 66% yield and very good selectivity (**Scheme 22**).



Scheme 22. Synthesis of Oxy-enolsilane

TBS-protected β-oxyaldehyde **143** underwent Mukaiyama aldol reaction with oxy-enolsilane **139** using $MgBr_2{\cdot}Et_2O/Et_2O$ as a promoter to afford the intermediate oxocarbenium product **147** which rapidly cyclized to afford the hexose fragment **148** in 75% yield. The treatment of **148** with HBr/AcOH followed by Zn/AcOH furnished the TBS-protected glucal **149** in 60% yield[30] (**Scheme 23**).

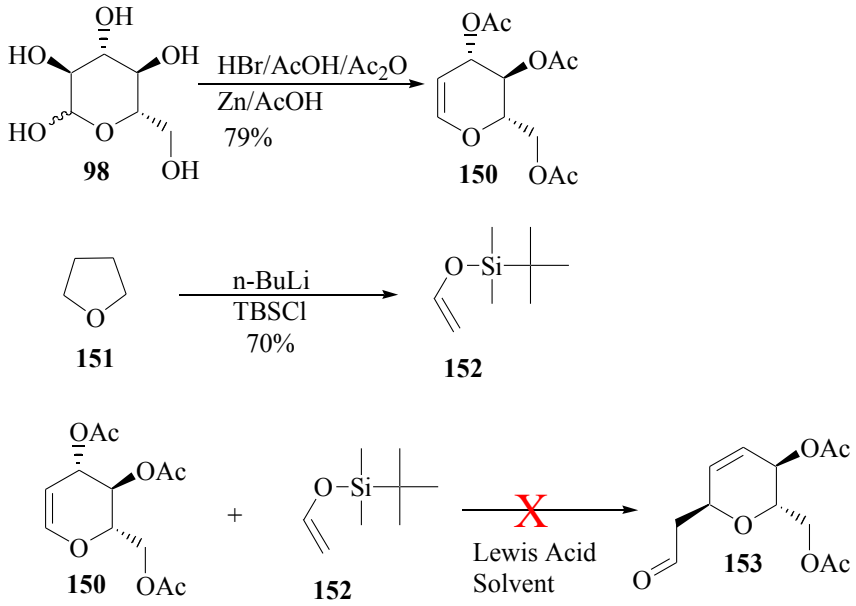


Scheme 23. Synthesis of L-glucose Fragment

3.3 Carbon-Ferrier Rearrangement

3.3.1 Modified Carbon Ferrier Rearrangements

A modified version of carbon Ferrier rearrangement was tested using tri-O-acetyl-L-glucal **150** with silyl-vinyl-ether **152**. The L-glucal **150** was synthesized in a single step from L-glucose **98** using Ac_2O/HBr/AcOH condition and after 24 h the solution was treated with Zn/AcOH to afford the tri-O-acetyl-L-glucal **150** in 79% yield. The silyl-vinyl-ether **150** was synthesized in a single step by treating THF **151** with n-BuLi and subsequent addition of TBSCl provided **152** in 70% yield (**Scheme 24**).



Scheme 24. Modified Ferrier Reaction Trials

The modified Ferrier reaction of **150** with **152** was tested in a temperature ranging from -35 °C to 25 °C as well as using different combination of Lewis acids and solvents (**Table 1**).

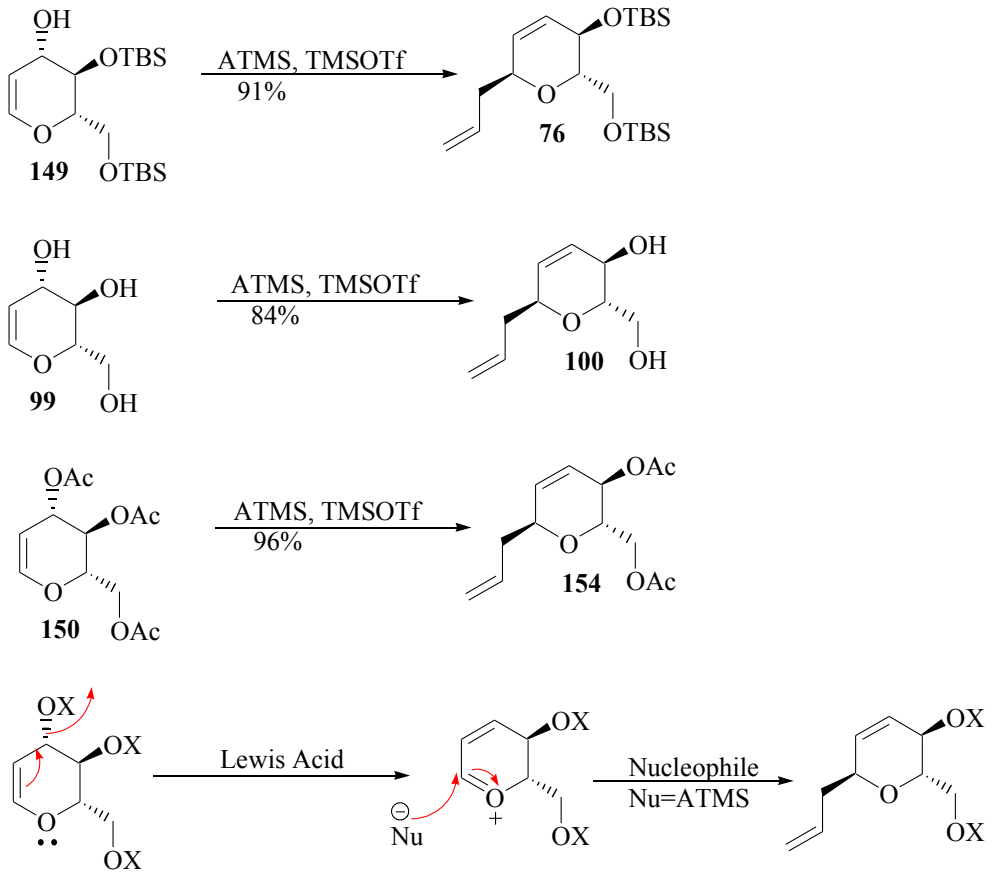
Lewis Acid	**Solvent**	**Results**
$TiCl_2(OCH(CH_3)_2)_2$	CH_2Cl_2	No Reaction
TMSOTf	CH_2Cl_2	No Reaction
$BF_3 \cdot OEt_2$	CH_2Cl_2	No Reaction
$LiClO_4$	EtOAc	No Reaction

Table 1. Modified Ferrier Reaction Results

3.3.2 Classical Carbon Ferrier Rearrangements

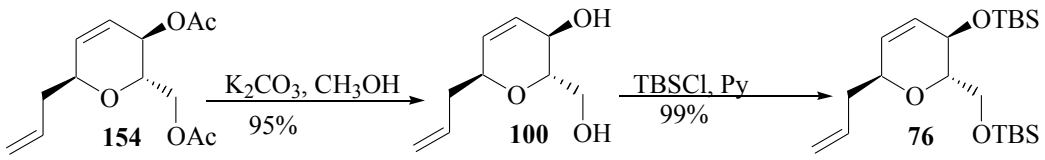
After testing the modified Ferrier reaction, our attention turned towards using the classical Ferrier reaction conditions by employing different precursors. Treatment of the TBS protected alcohol **149** with ATMS/TMSOTF furnished alkene **76** in 2 h, 91% yield and a very good selectivity as well as it shortened the overall synthetic route for the DHP fragment synthesis. L-glucal **99** was treated with ATMS/TMSOTf to afford diol **100** in 84% yield[21]. Despite the good yield, the synthesis of the L-glucal needed improvement as a result we tested

the tri-O-acetyl-L-glucal **150**. The treatment of **150** with ATMS/TMSOTf afforded the di-acetal alkene **154** in 96% and in a very good selectivity in 30 minutes[32] (**Scheme 25**).



Scheme 25. Classical Ferrier Reactions

The diacetal alkene **154** was used for the next step with out any cleaning and reduction of **154** with K_2CO_3/CH_3OH afforded diol **100** in less than 1 h in 95% yield and it was used for the next step without any purification. Global silylation of **100** with TBSCl/Py afforded alkene **76** in 99% yield (**Scheme 26**).

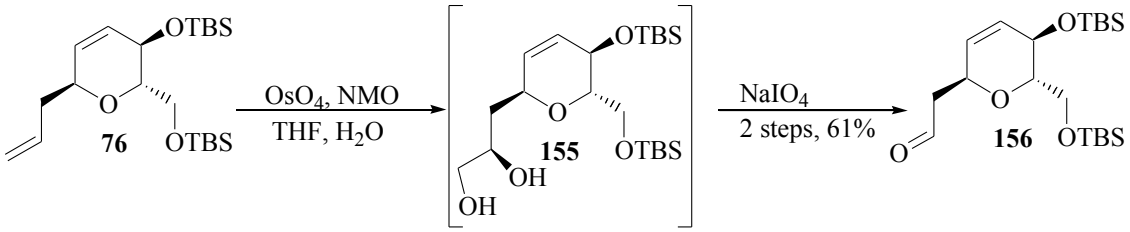


Scheme 26. Protection of the diols

3.4 Oxidative Cleavage of the Terminal Double Bond

3.4.1 Sharpless Asymmetric Dihydroxylation

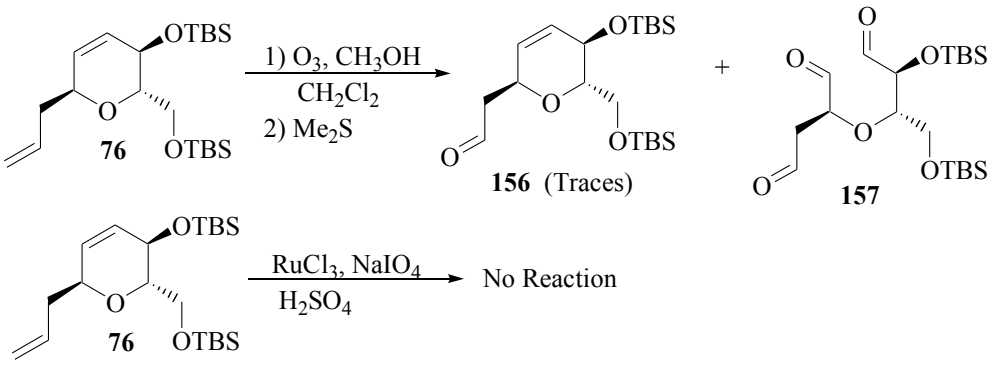
The TBS-protected alkene **76** was oxidized using Sharpless reaction condition[33]. Initial trial of oxidation using AD-mix-β in combination with t-BuOH/H_2O (10:1) afforded the intermediate product *cis*-diol **155** after 24 h of stirring. Oxidative cleavage of the diol with $NaIO_4$ afforded the aldehyde **156** in a cumulative yield of 40%. Being discouraged by long reaction time, we employed[34] the use of catalytic amount of OsO_4/NMO in combination with THF/H_2O (1:1) which resulted in more clean intermediate *cis*-diol **155** in less than 5 h. Oxidative cleavage of diol **155** with $NaIO_4$ afforded aldehyde **156** with a cumulative yield of 61% (**Scheme 2**7).



Scheme 27. Sharpless's Hydroxylation of the Terminal Alkenes

3.4.2 Ozonolysis

In addition to Sharpless dihydroxylation method we tested ozonolysis as well as $RuCl_3/NaIO_4/H_2SO_4$ oxidation conditions[35]. Analysis of NMR spectra showed that the use of ozone resulted not only in the oxidation of the terminal double bond but it also resulted in the oxidation of the double bond on the ring. The use of the Ruthenium catalyzed oxidation did not work (**Scheme 28**).

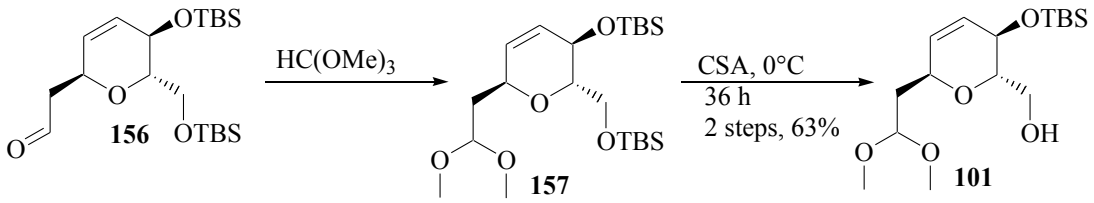


Scheme 28. Oxidation of the Terminal Alkenes

3.5 Protection of the Aldehyde

3.5.1 Selective Protection of the Aldehyde

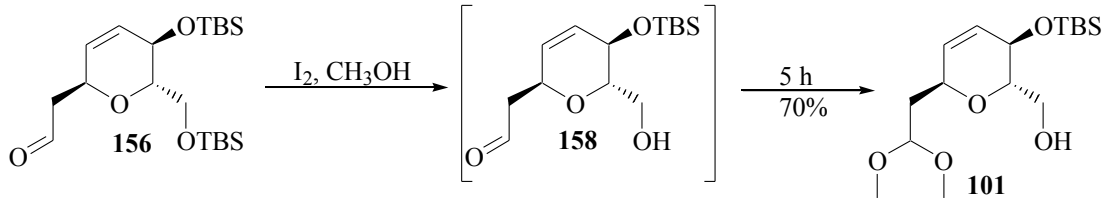
The treatment of aldehyde **156** with $HC(OMe)_3$ gave the protected alkene **157** which was subjected[36] to Camphorsulfonic acid (CSA) to afford alcohol **101** in a reaction time of 36 h and cumulative yield of 63% (**Scheme 29**).



Scheme 29. Selective Protection of the Aldehyde

3.5.2 Simultaneous Protection and Deprotection

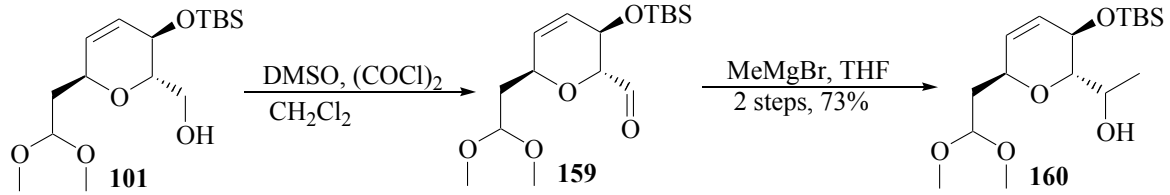
After trying the two step protection and deprotection of aldehyde **156** with $HC(OMe)_3$/CSA and being discouraged by long reaction time, we turned our attention to simultaneous protection and deprotection using molecular iodine in methanol solution[38]. The treatment of aldehyde **156** with CH_3OH/I_2 proceeded with deprotection of the primary TBS group providing the intermediate aldol **158** followed by protection of the aldehyde which afforded the alcohol **101** in less than 5 h. This reaction gave a satisfactory yield of 70%, as well as proceeded with high selectivity in deprotecting the primary TBS exclusively (**Scheme 30**).



Scheme 30. Simultaneous Protection and Deprotection

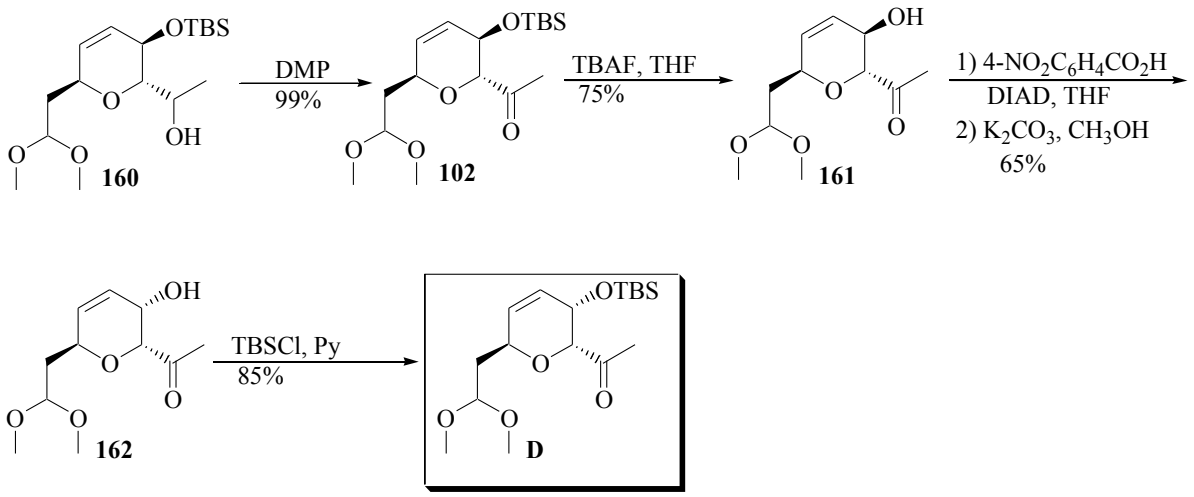
3.6 Completion of Fragment **D**

The alcohol **101** underwent Swern[39] oxidation using DMSO/$(COCl)_2$ condition to afford the intermediate aldehyde **159** which was treated with MeMgBr/THF to afford methyl alcohol **170** with a cumulative yield of 73% (**Scheme 31**). As an alternative to Swern condition, Dess-Martin oxidation[41] of **101** afforded the intermediate aldehyde **159** in 95% yield.



Scheme 31. Grignard Reaction

The methyl alcohol **160** was oxidized with Dess-Martin periodinane to afford the methyl ketone fragment **102** in 99% yield in less than 5 h. Because the stereochemistry at C-10 of sorangicin **A** was not right[13], classical Mitsunobu inversion reaction condition was employed[43]. Deprotection of **102** with TBAF/THF afforded hydroxymethyl ketone **161** in 75% yield. The alcohol **161** was treated with PPh_3/DIAD/PNBA stirred overnight and reduced with K_2CO_3/CH_3OH condition to afford the right configured hydroxy-methyl ketone **162** in 65% cumulative yield. Protection of **162** with TBSCl/Py condition afforded fragment **D** in 85% yield (**Scheme 32**).

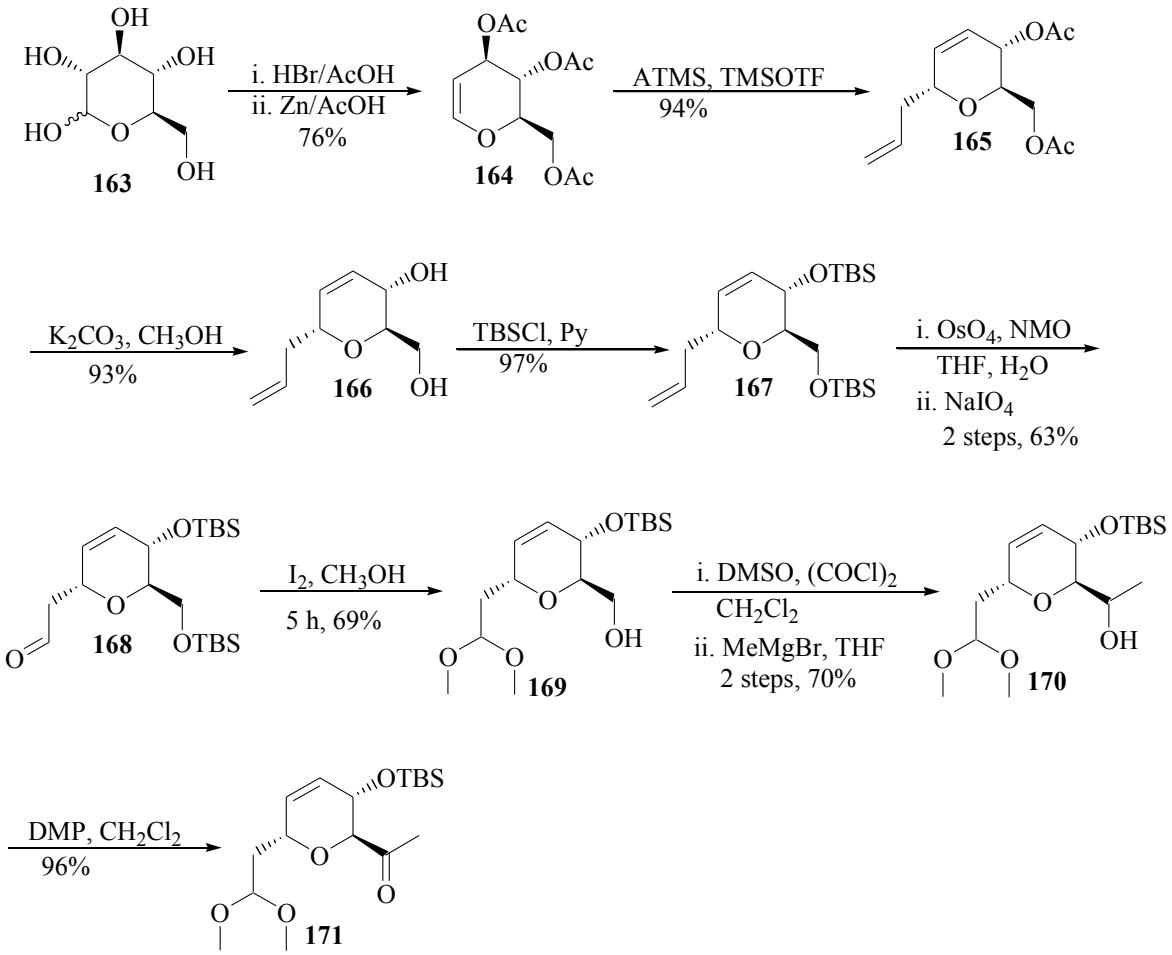


Scheme 32. Completion of Fragment D

3.7 Review of Synthetic Routes Tested

In developing a synthetic route for fragment **D** a number of routes as well as different precursors were evaluated. In these synthetic routes we tested D-glucose, L-glucose and ethylene glycol/cis-2-butenediol as a starting material.

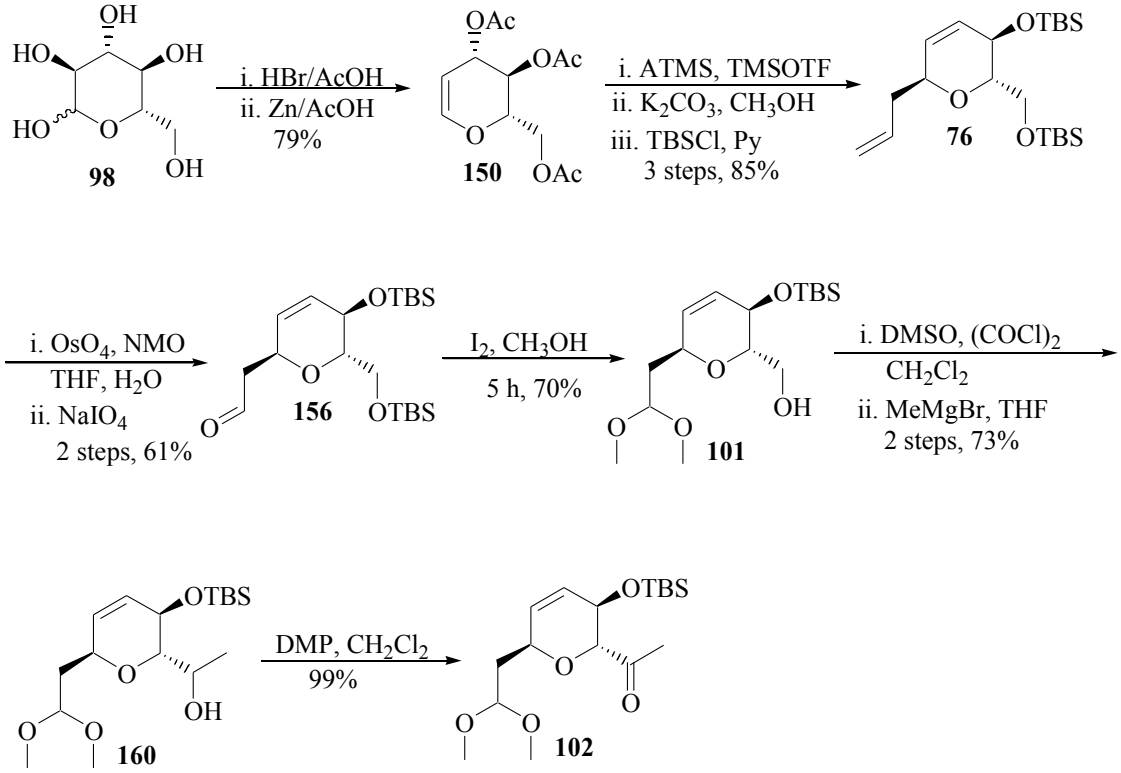
In our initial attempt D-glucose was used to test different reactions as well as develop new synthetic route for the DHP fragment synthesis as it is the cheaper isomer to test reactions. It was possible to change D-glucose **163** to the corresponding methyl ketone **171** in 8 reaction steps with an overall yield of more than 20% (**Scheme 33**).



Scheme 33. D-glucose Synthetic Route

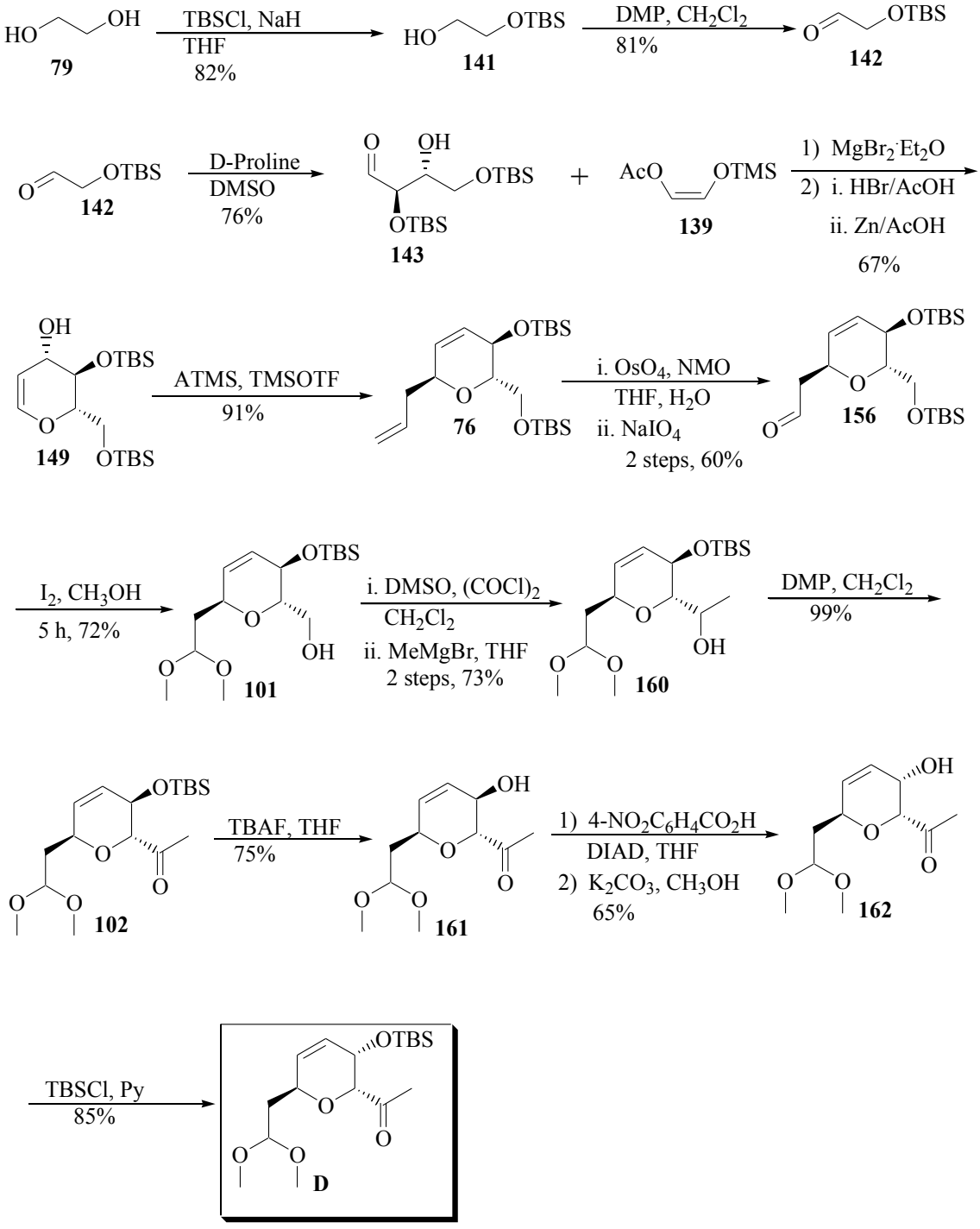
After testing the reactions using D-glucose we modified the synthetic route using L-glucose. By taking into account the fact that many of the reaction steps produced clean products in our initial testing using D-glucose, we proceeded with out any purification in many synthetic steps using L-glucose **98**. It was possible to transform the L-glucose to methyl ketone **102** in

less than 6 reaction steps with an overall yield 25% and very good selectivity (**Scheme 34**).



Scheme 34. L-glucose Synthetic Route

In our third synthetic route tested, methyl ketone fragment **D** was synthesized by starting from ethylene glycol/cis-2-butenediol in 12 reaction steps with an overall yield of more than 17%. In this synthetic route it was possible to get the right stereochemistry at C-10 of soran-gicin **A** as it has been discussed in the earlier part of this thesis **(Scheme 35)**.

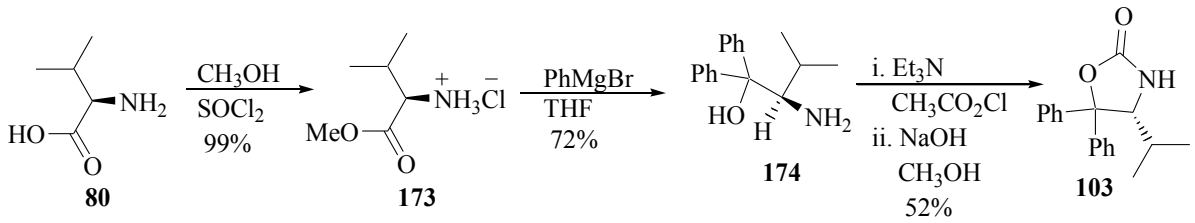


Scheme 35. Ethylene Glycol Synthetic Route

Chapter 4- Synthesis of Fragment E

4.1 Synthesis of Seebach Auxiliary

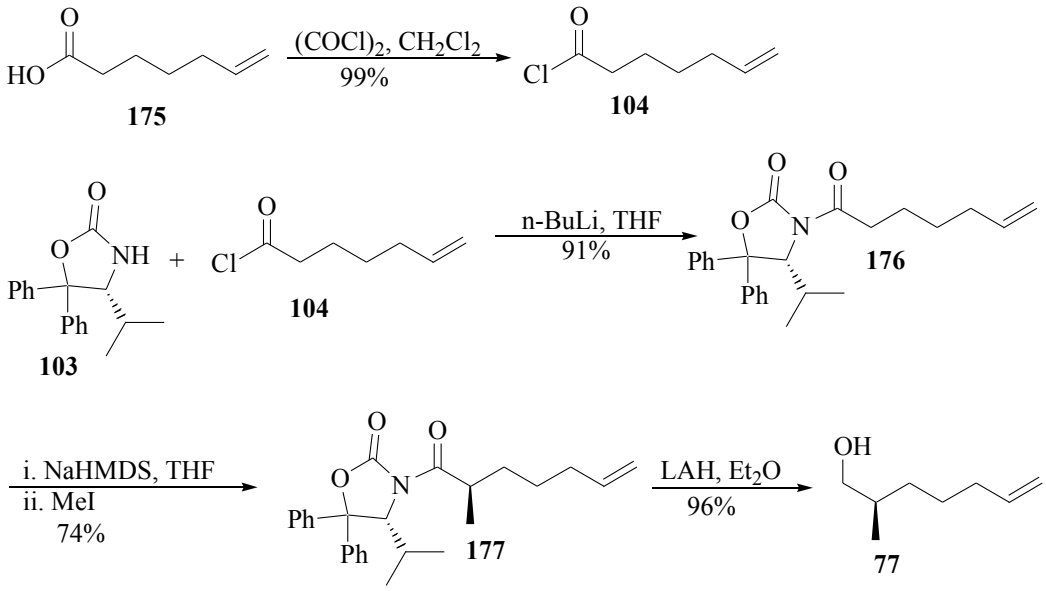
The synthesis of the side chain fragment **E** started by synthesizing Seebach auxiliary **103** to insert the proper stereochemistry on the side chain fragment[44]. The Seebach auxiliary was synthesized by starting from D-valine **80** which was treated with thionyl chloride to afford the hydrochloride methyl ester **173** in 99% yield. The methyl ester hydrochloride **173** underwent Grignard addition reaction using PhMgBr to afford the diphenyl alcohol **174** in 72% yield. Compound **174** was treated with acetyl chloride and triethylamine to afford the Seebach auxiliary **103** in 52% yield (**Scheme 36**).



Scheme 36. Seebach Auxiliary Synthesis

4.2 Synthesis of (2R)-Methyl-hept-6-en-1-ol

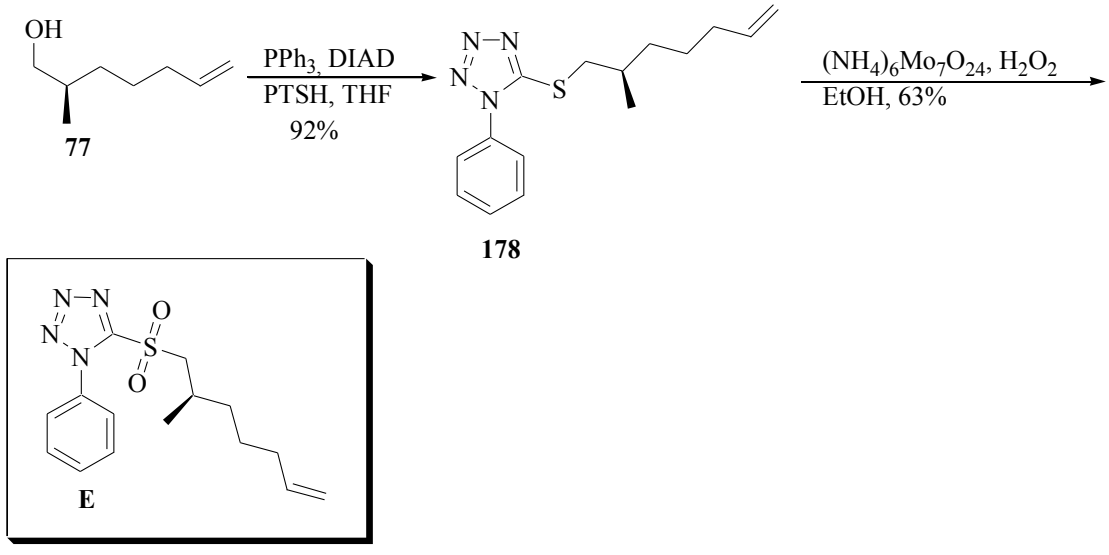
The commercially available 6-heptenoic acid **175** was used as a starting material[21] in the synthesis of alcohol **77**. The acid **175** was converted into a more reacting substance using oxalyl chloride to afford acyl-chloride **104** in 99% yield (**Scheme 37**). The acid chloride **104** was coupled with Seebach auxiliary **103** in the presence of n-BuLi to afford the corresponding diphenyl oxazolidinone **176** in 91% yield. The oxazolidinone **176** was treated with NaHMDS and underwent alkylation with MeI in high diasteroselectivity to afford the methyl-diphenyl oxazolidinone **177**. Reductive removal of the Seebach auxiliary from **177** using LAH furnished methyl-hept-6-en-1-ol **77**.



Scheme 37. Synthesis of (2R)-Methyl-hept-6-en-1-ol

4.3 Synthesis of (2R)-2-(2-Methylhept-6-en-1-sulfonyl)-1-phenyl-1H-tetrazole

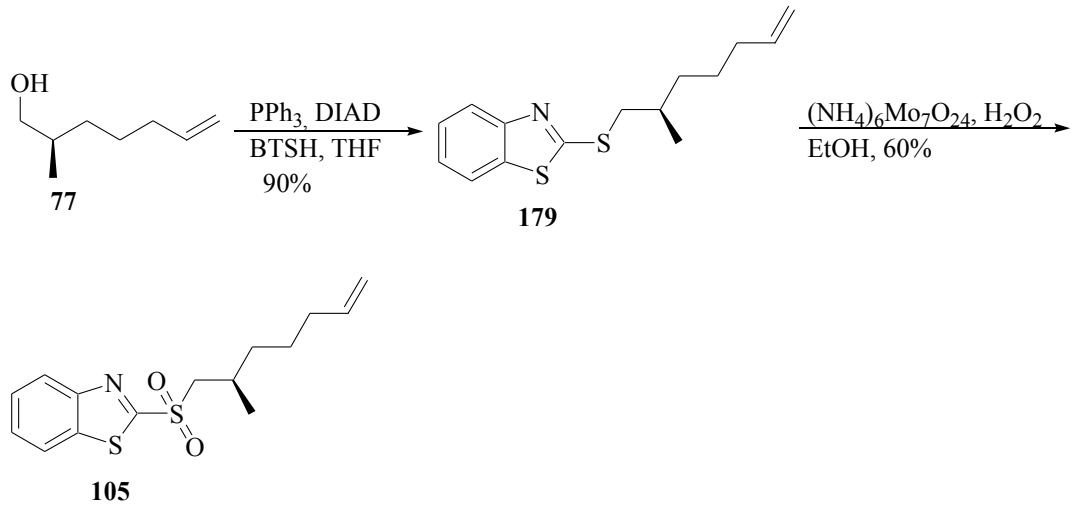
The modified Julia olefination[53] precursor fragment **E** synthesis was started by using the alcohol **77** which was converted to thiol **178** by employing the classical Mitsunobu reaction condition, PPh_3/ DIAD/PTSH, in 92% yield. Sulfide **178** was converted to the corresponding sulfone fragment **E** in 63% yield using $(NH_4)_6Mo_7O_{24}/H_2O_2$ reaction condition (**Scheme 38**).



Scheme 38. Synthesis of Fragment E

4.4 Synthesis of (2R)-2-(2-Methylhept-6-en-1-sulfonyl)-Benzothiazole

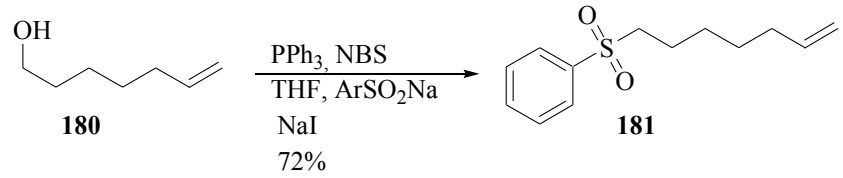
The synthesis of benzothiazole **105** began with alcohol **77** which was converted to the corresponding thiol **179** using classical Mitsunobu reaction condition, PPh_3/DIAD/BTSH, in 90% yield. Compound **179** was oxidized to the corresponding sulfone using $(NH_4)_6Mo_7O_{24}/H_2O_2$ condition to afford sulfone **105** in 60% which was used as a precursor for the modified Julia olefination[49] (**Scheme 39**).



Scheme 39. BT Sulfone Synthesis

4.5 Synthesis of (Hept-6-ene-1-sulfonyl)-benzene

In addition to synthesizing the precursors for modified Julia olefination we devised a new method for synthesizing the precursor for classical Julia olefination using one pot synthesis (**Scheme 40**). Treatment of hept-6-en-1-ol **180** with NBS/PPh_3/THF and subsequent addition of $ArSO_2Na$/NaI delivered phenyl sulfone **181** in 4 h with 72% yield[56]. The sulfone **8** can be used as a precursor in testing the classical Julia olefination.

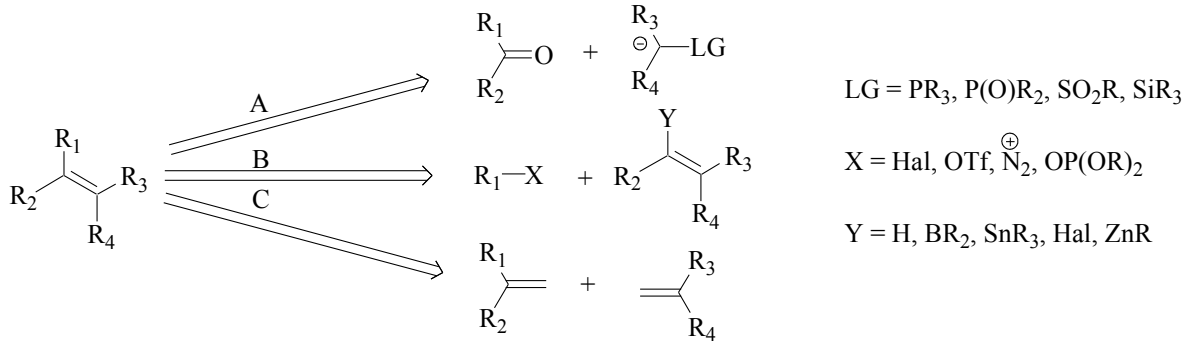


Scheme 40. Classical Julia Precursor Synthesis

5 Coupling of the Fragments

5.1 Modern Olefination Methods

The coupling of fragments by olefination dates back to first olefination of carbonyl compounds by Georg Wittig back[65] in 1950 and he was awarded the Nobel prize for his pioneer work in 1960. The olefination reaction has been an indispensable strategic tool in total synthesis as well in the construction of complex structure natural products for the last six decades. There are couple of strategies developed in the last four decades that allow synthesis of alkene with broad structural variety and functional group tolerance. The reaction of the carbanion being stabilized by leaving group (LG) that acts at the same time as good leaving group with aldehydes or ketones. Depending on the type of leaving group these transformation are known as Wittig reaction[66] (LG = PR_3), Horner-Wittig[67] (LG = $P(O)Ph_2$, Horner-Wadsworth-Emmons[68] (LG = $P(O)(OR)_2$), Julia olefination[69] (LG = SO_2R) or Peterson olefination[70] (LG = SiR_3). In addition to these olefination methods, reactions were developed with direct or cross coupling of alkenes which includes Heck reaction[71] (Y = H) or with alkenyl metal Stille reaction[72] (Y = SnR_3) or Negishi reaction[73] (Y = ZnR) by using appropriate activated alkyl subustrate (**Scheme 41**). The discovery of robust and readily availiable catalyst by Schrock[74] and Grubbs[75] made it also possible for synthesizing olefins through metathesis reactions.

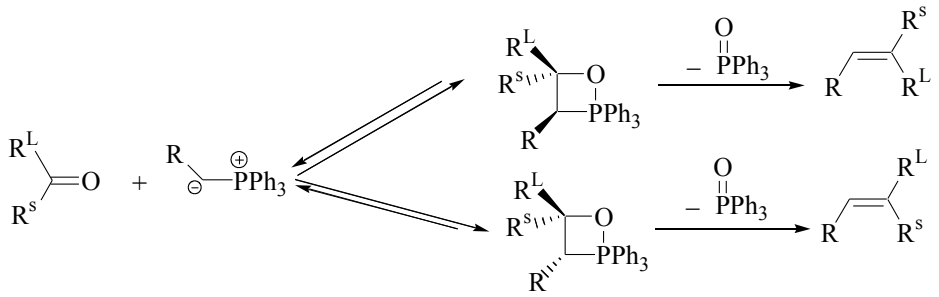


Scheme 41. Olefination Methods

5.1.1 Wittig Olefination

The Wittig reaction is one of the most reliable reaction for the synthesis of alkene. It involves the use of phosphonium ylides which dates back to 1980s. Olefination occurs with complete regioseletivity where the carbonyl group of the substrate is replaced by alkene.

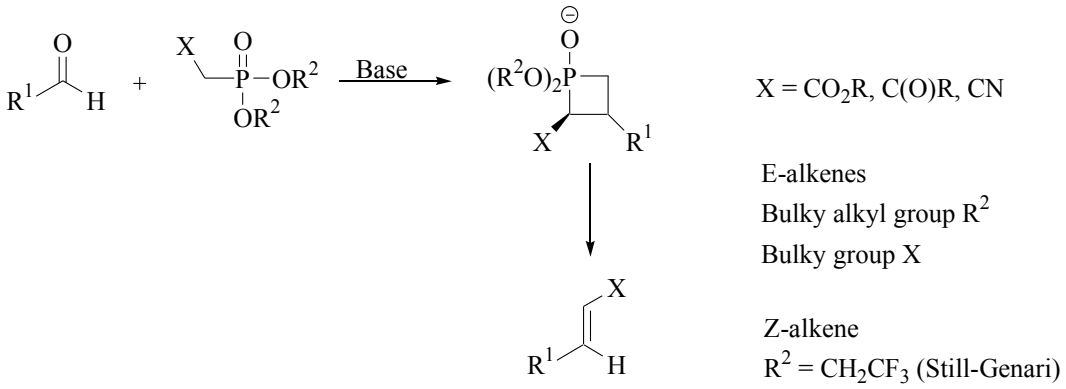
The currently accepted mechanism for Wittig olefination is through the formation of an intermediate phosphaoxetanes which stereospecifically collapse to give Z-or E-alkenes.



Scheme 42. Wittig Olefination

5.1.2 Horner-Wadsworth-Emmons Olefination

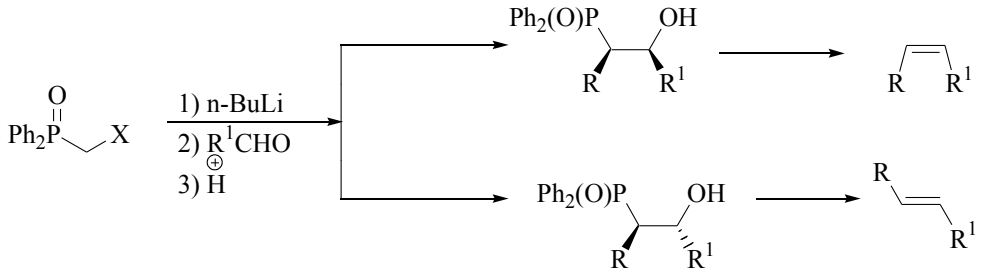
An alternative to Wittig reaction was developed by Horner-Wadsworth-Emmons by using phosphonate instead of phosphonium ylides. The distinct difference between the two ylides is that the carbanion obtained upon deprotonation of the phosphonate are generally more reactive than phosphonium ylides so they need to be stabilized by electron withdrawing substituent in order to give useful ylides in a subsequent reaction with either aldehyde or ketone. The stereoselectivity of HWE reaction can be controlled by steric and electronic properties of the alcohol group R^2 in the phosphonate. A significant advantage of the HWE procedure is that the phosphorous by-product, the phosphoric acid salt, is water soluble and can be easily removed by aqueous work up unlike the Wittig olefination.



Scheme 43. Horner-Wadsworth-Emmons Olefination

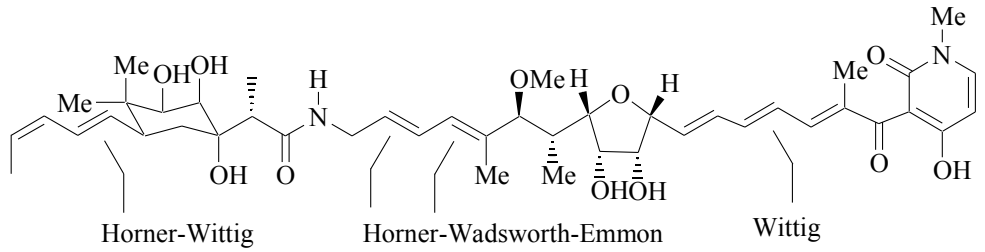
5.1.3 The Horner-Wittig Olefination

Phosphine oxide is another class of phosphor ylide which can be used for carbonyl olefination for a reaction that is commonly referred as Horner-Wittig reaction. The mechanism is similar to Wittig and HWE but the important difference is the ability to separate hydroxy phosphine oxides when lithium bases and low temperature are employed.



Scheme 44. Horner-Wittig Olefination

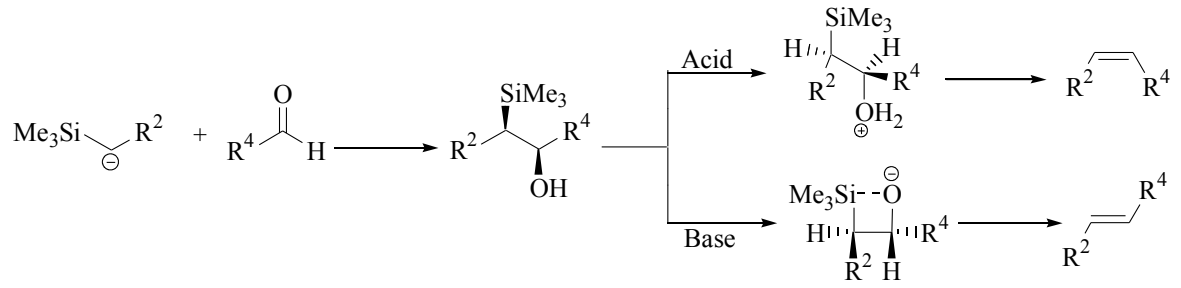
There are numerous examples of Wittig type of olefination in a natural product synthesis. A particular impressive example is the synthesis of the antibiotic aurodox by K. C. Nicolaou group[76].



Scheme 45. Wittig Type Olefination Reactions

5.1.4 The Peterson Olefination

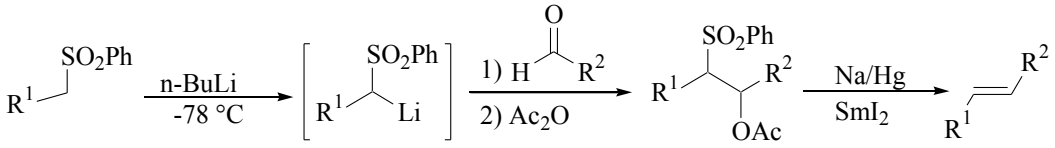
Peterson olefination concept is similar to that of Wittig olefination, but it is quite different in scope and limitation are alkenylations that proceed through β-hydroxysilane. It involves alkene formation from carbanions stabilized by trialkylsilyl groups. In this olefination an α-silylated carbanion is added to a carbonyl compound to give rise to two diastereomeric β-hydroxysilane which can be isolated and transformed separately to alkene. Alkene formation from the β-hydroxysilane can occur by two different mechanisms depending on whether acidic or basic condition are employed.



Scheme 46. Peterson Olefination

5.1.5 Classical Julia Olefination

The classical Julia[59] (Julia-Lythgoe) olefination was developed 40 years ago by Marc Julia and Jean-Marc Paris and it makes use of phenylsulfones. It has a high stereo-selectivity for trans-olefins, but the classical Julia olefination proceeds with four different synthetic operations[60], metallation of a phenylsulfone, addition of the metallate to an aldehyde, acylation of the resulting β-alkoxysulfone and reductive elimination of the β-acyloxysulfone with a single electron donor to afford alkene products.

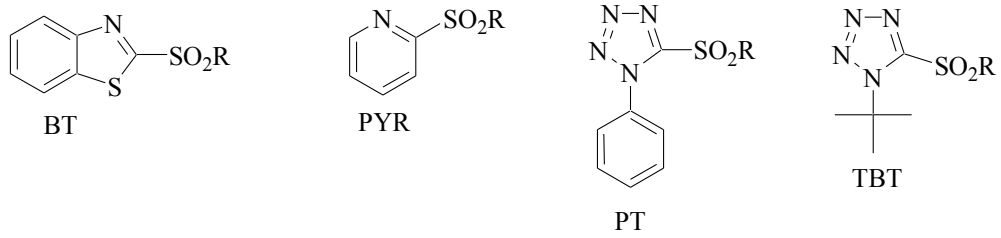


Scheme 47. Classical Julia Olefination

It has been reported[60] that isolation of the intermediate products is very essential to get a good yield from classical Julia olefination reactions unlike modified Julia olefination which proceeds only in a single reaction step.

5.1.6 Modified Julia Olefination

The modified Julia[49] (Julia-Kocienski) olefination was developed by Sylvestre Julia *et al*. and it makes use of hetero-arylsulfones. The selectivity of modified Julia olefination is affected by many factors including base, hetero-arylsulfone and structure of the substrate. The choice of hetero-arylsulfone affects selectivity as well as stereochemical outcome of the reaction. The different sulfone sources developed so far include benzothiazole (BT) , pyridin (PYR), phenyltetrazole (PT), tert-butyltetrazole (TBT).

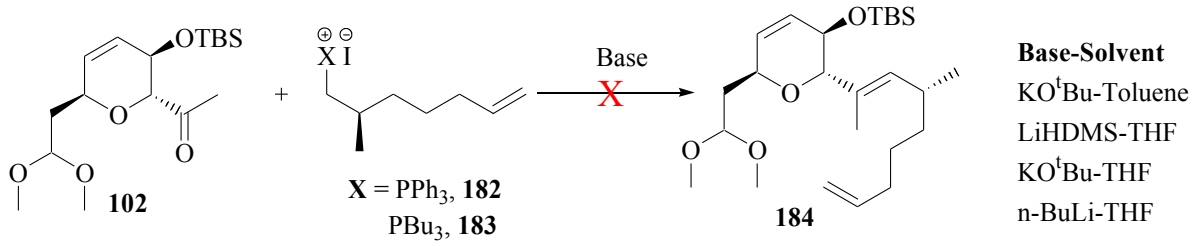


Scheme 48. Modified Julia Sulfone Sources

The stereochemical outcome of the BT-variant of modified Julia olefination is substrate controlled but it can also be influenced by controlling reaction conditions to synthesize the desired E:Z ratio of the product olefin. Generally PYR-sulfone give lower yields of trans-olefin products compared with BT-sulfones despite the stability of PYR-sulfone metallate. The PT-sulfone provides an alternative to the BT-sulfone and it has a higher level of trans-selectivity in the absence of biasing electronic or steric factors. Replacement of the phenyl moiety on the tetrazole ring in PT-sulfone improves the sulfone metallate stability, thus the bulk tert-butyl group in TBT-sulfone promotes high selectivity for cis-olefins.

5.2 Previous Efforts to Couple Fragments

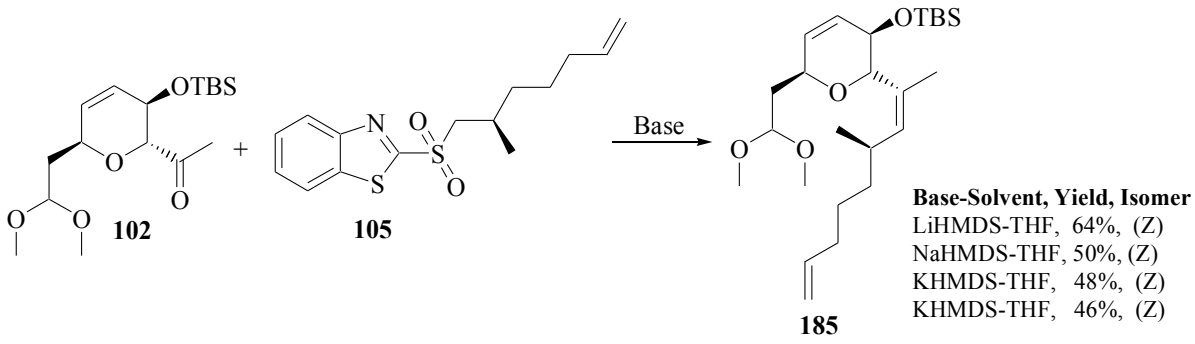
The coupling of the fragments started by taking into consideration the different modern olefination methods discussed in the previous section as well as earlier trials to couple fragments from our group[21]. There were efforts from our group to couple the dihydropyran fragment **102** and the side chain fragments **182, 183** using a Wittig type of reaction. The reactions were tested by employing different bases and solvents but none of the reaction tested resulted in triene **184** (**Scheme 49**).



Scheme 49. Wittig Coupling Trials

Due to discouraging result from Wittig reaction there were other attempts from our group[21] to couple the fragments by using modified Julia olefination employing BT-sulfone **105**. Despite different combination of solvents and bases the reaction resulted only in *Z*-isomer

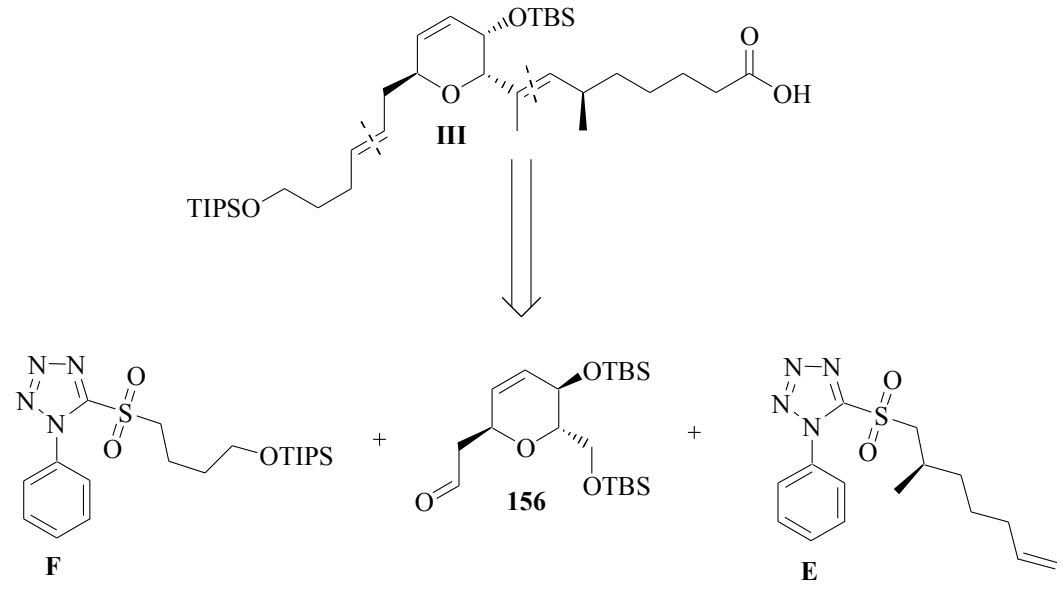
triene **185** (**Scheme 50**).



Scheme 50. Modified Julia Coupling Trials

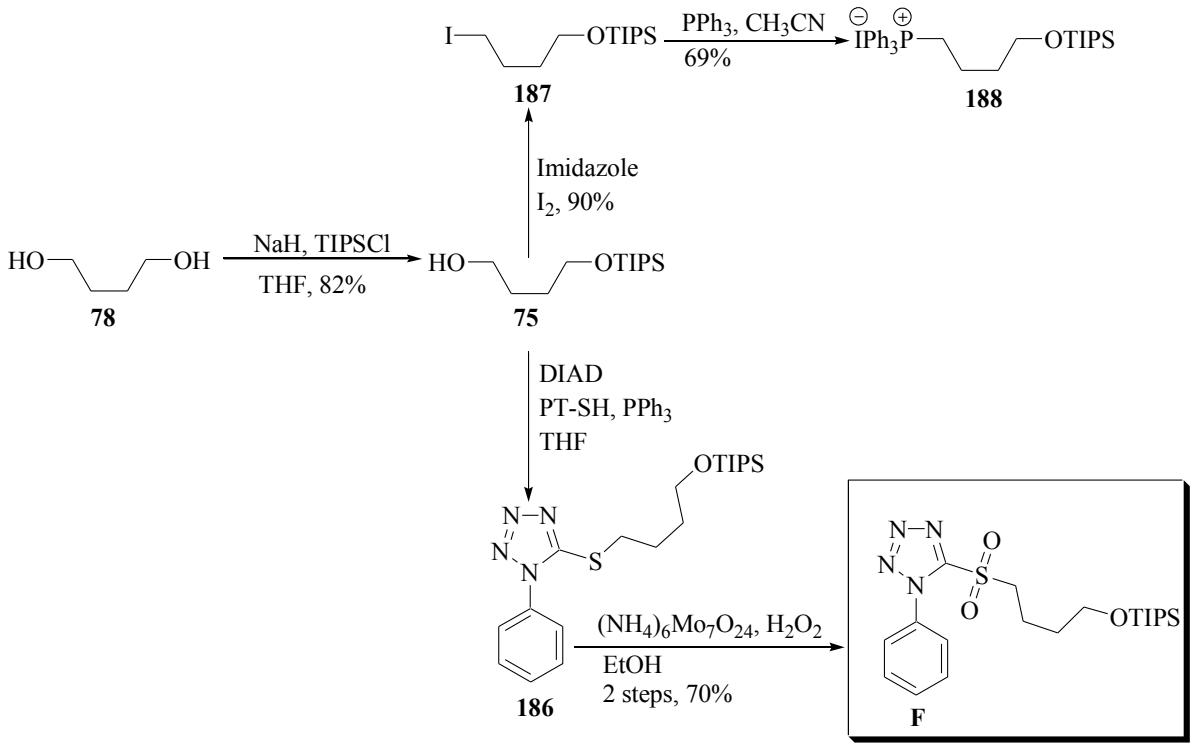
5.3 Coupling Strategies

The construction of the C(1)-C(19) fragment started by synthesizing the three precursors, TIPS-protected phenyltetrazole sulfone **F**, methyl ketone **D** and the modified Julia olefination precursor **E**. As a synthetic strategy we pursued to use modified Julia olefination conditions to construct C(7)-C(8) and C(15)-C(16) double bonds. We envisioned the first coupling reaction between the sulfone fragment **F** and aldehyde **156** followed by deprotection, Grignard addition, oxidation, inversion and finally a second modified Julia olefination with sulfone fragment **E** to complete the synthesis of our target molecule **III** (**Scheme 51**). We have pursued to couple the fragments using different coupling methods and reaction conditions.



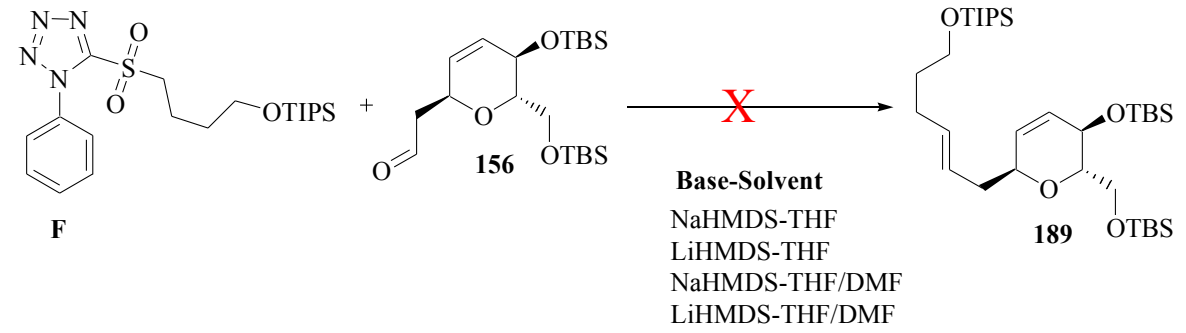
Scheme 51. Retrosynthesis of Target Molecule

The TIPS-protected phenyltetrazole sulfone fragment **F** and the phosphonium salt **188** were synthesized in three steps from 1,4-butanediol **78**. Selective protection of the diol **78** with NaH/TIPSCl afforded TIPS-protected alcohol **75** in 82% which was converted into the corresponding sulfone, fragment **F**, or phosphonium salt **188** in two synthetic steps. Mitsunobu condition reaction of **75** followed by oxidation with $(NH_4)_6Mo_7O_{24}/H_2O_2$ condition provided fragment **F** with a cumulative yield of 70% for two steps. Treatment of **75** with I_2/Imidazole condition afforded iodide **187** in 90% which was subjected to PPh_3/CH_3CN to afford phosphonium salt **188** in 69% (**Scheme 52**).



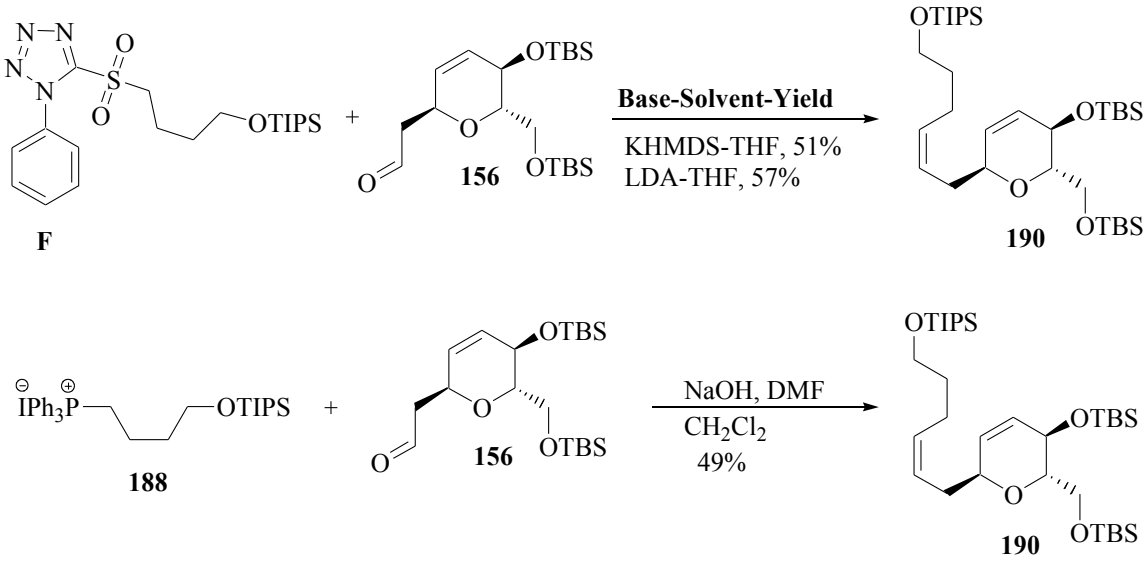
Scheme 52. Synthesis of Fragment F

In our initial attempt we pursued to couple fragment **E** with aldehyde **156** by using modified Julia olefination under barbier reaction conditions. The coupling reactions were tested by employing different combination of bases and solvents but none of the reactions tested resulted in diene **189** (**Scheme 53**).



Scheme 53. Initial coupling trials I

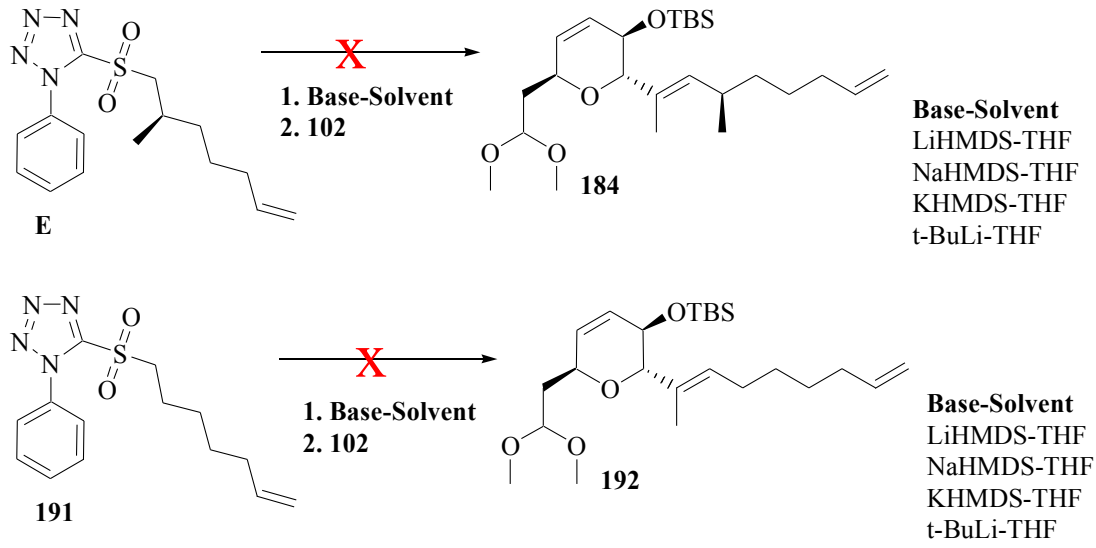
After being discouraged by our initial attempts to couple the fragments using LiHMDS and NaHMDS we further tested the Julia olefination using KHMDS and LDA as well as the Wittig olefination which have resulted in the formation of the diene **190**. First attempts to couple the fragment **F** with aldehyde **156** using KHMDS and LDA as bases resulted only in Z-isomer with 51% and 57% yields respectively. Further attempt to couple the phosphonium salt **188** with aldehyde **156** by employing Wittig reaction condition resulted also in Z-isomer diene **190** in 49% yield (**Scheme 54**).



Scheme 54. Initial coupling trials II

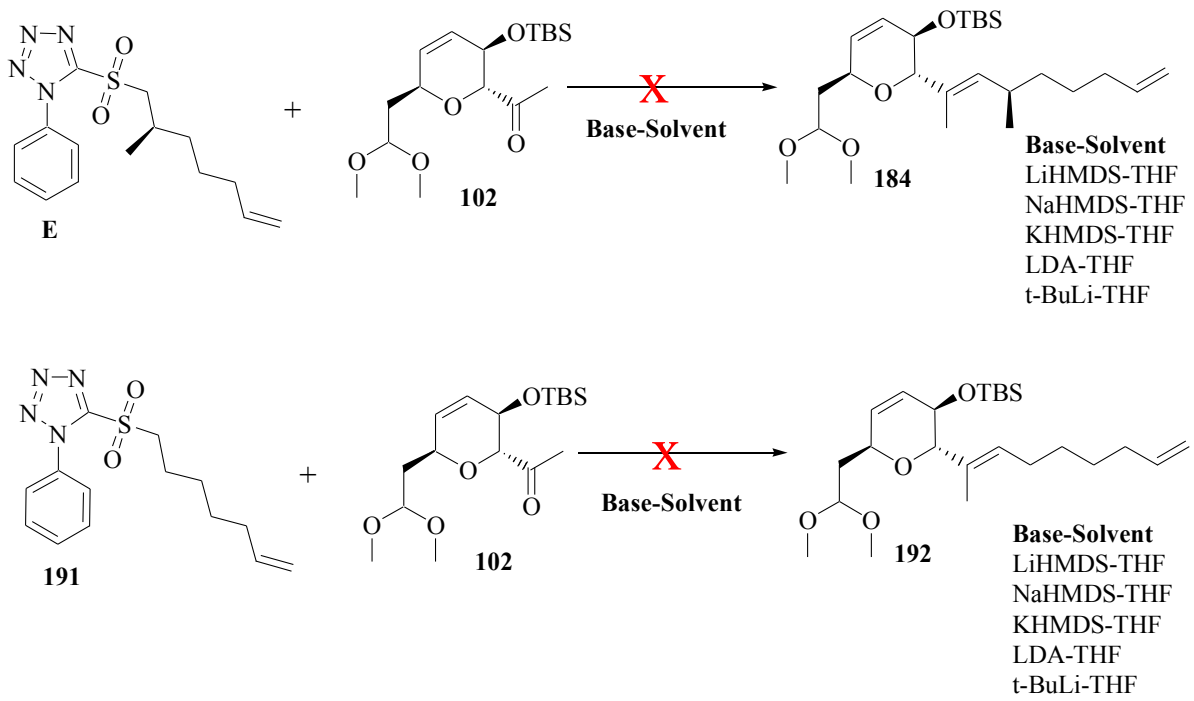
After testing the initial coupling, we proceeded to evaluate different methods to couple the dihydropyran fragment **102** with the side chain fragment **E**. As it has been reported by Blakemore[60] phenyltetrazole sulfone and benzothiazole sulfone gives predominantly trans-olefins compared with the other sulfone sources developed so far. As a result coupling reactions were tested using sufone **191** or fragment **E** as well as benzothiazole sulfone **105**.

In addition to the type of sulfone source used, the order of addition of the substrates have been found to influence the outcome of the reaction as a result we tested both premetallate and barbier reaction conditions. Initially we tested premetallate condition, where the sulfone **191** or fragment **E** and the base are added together to form the premetallate, followed by the addition of the methyl ketone **102** subsequently to the reaction mixture. Different combination of bases and solvents were employed, but none of the reactions tested afforded triene **184** or **192** (**Scheme 55**).



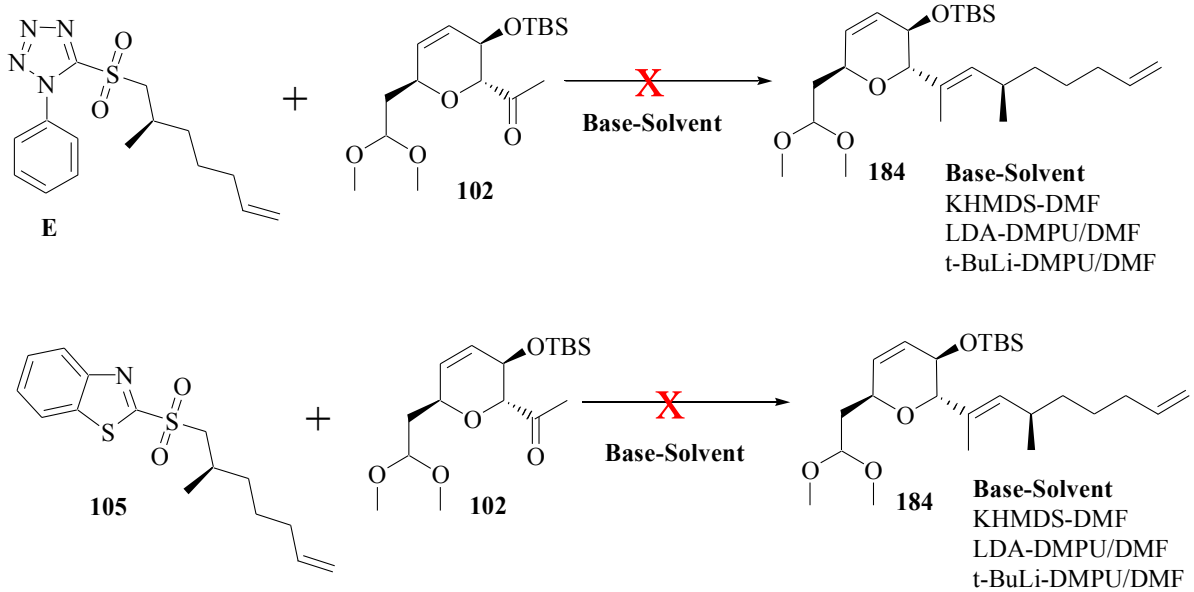
Scheme 55. Premetallate Conditions

After testing the premetallate condition, we further pursued to evaluate the barbier condition where the base was added to the mixture of the sulfone **191** or fragment **E** and methyl ketone **102** which allows the metallate to react directly to the ketone reducing self-condensation of the sulfone. Different combination of bases and solvents were evaluated, but none of the tested reactions resulted in triene **184** or **192** (**Scheme 56**).



Scheme 56. Barbier Conditions

In further attempt to couple the fragments, modfied Julia olefination reactions were tested by using a more polar aprotic solvent, DMPU, in combination with DMF by employing different bases and using barbier olefination condition. The phenyltetrazole sulfone, fragment **E**, and benzothiazole sulfone **105** were used as a Julia olefination precursors. Despite the different combination of solvents and bases, NMR analysis revealed the presence of the coupling partners fragment **E** or **105** and **102** substantially (**Scheme 57**).



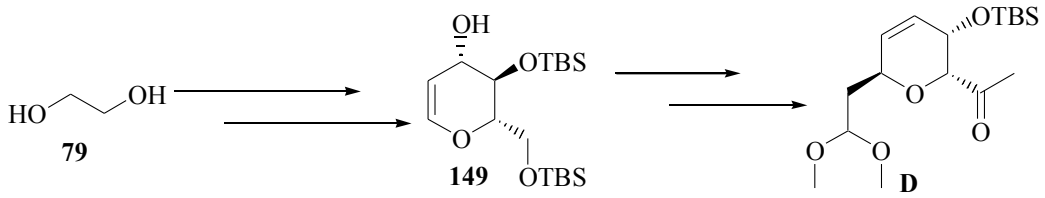
Scheme 57. Coupling trials with DMPU

6. Summary and Outlook

6.1 Summary

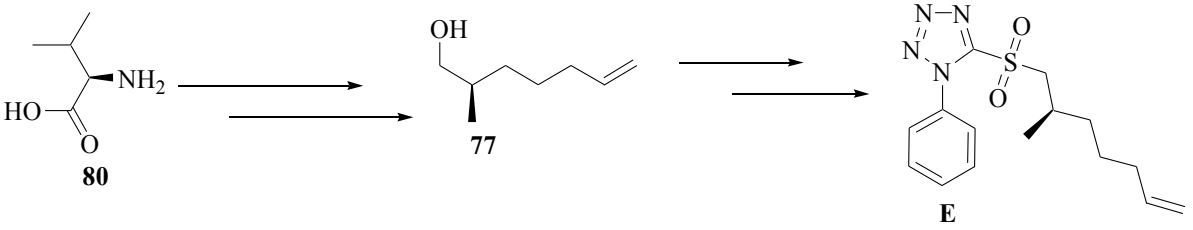
This work focused on the synthesis of C(1)-C(19) fragment of sorangicin **A** as well as developing highly-selective and good yield synthetic routes for the synthesis of precursor fragments.

In the first part, we have evaluated different synthetic routes for the synthesis of fragment **D** by starting from L-glucose. We have improved the synthetic route reported[21] from our group by reducing the reaction steps as well developing new reaction steps which are highly selective, proceed with very good yield and which resulted in more clean products. But the use of L-glucose as starting material was not feasible as a gram of L-glucose costs nearly 100 Euro as a result we have developed a new synthetic route for synthesizing fragment **D** by starting from a commercially available cheap starting material, ethylene glycol **79** and cis-2-butenediol **144**. It was possible to synthesize fragment **D** in less than 12 steps with an overall yield of more than 17%.



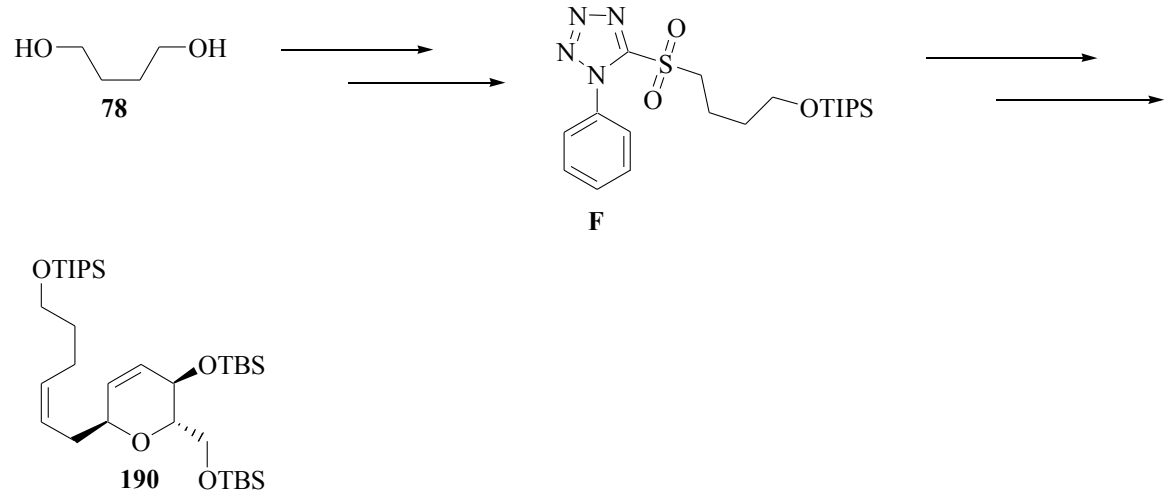
Scheme 58. Synthesis of Fragment D

In the second part we have developed efficient synthetic route for synthesizing fragment **E** by starting from D-valine **80** as well as employing reagents which are less toxic. The synthesis of Julia olefination precursors **191**, fragment **E** and **105** were achieved in less than eight reaction steps and in an overall yield of more than 25%. In addition a new approach has been developed for synthesizing the precursor for classical Julia olefination.



Scheme 59. Synthesis of Fragment E

In the final part of this work we tested different reaction conditions to couple fragment **D**, fragment **E** and fragment **F**. A new synthetic route approach was developed for the construction of C(15)-C(16) double bond as well as a new approach has been developed for synthesizing the C(8)-C(19) fragments of sorangicin (**Scheme 60**).



Scheme 60. Coupling Trials

6.2 Future Direction

In the overall synthesis of the C(1)-C(19) fragment of sorangicin **A** there are still rooms for improvements as well as to develop new synthetic routes to couple the fragments.

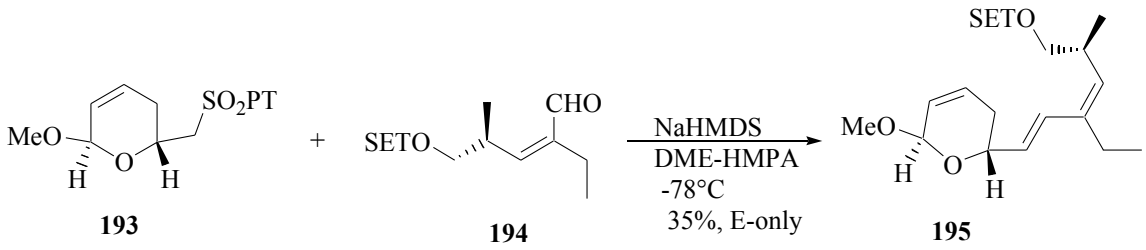
In synthesizing fragment **D,** the route for synthesizing the L-glucose fragment can be further improved by employing substrates possessing the right protecting group and stereochemistry which can undergo olefin metathesis[16] to afford the DHP fragment with the right stereochemistry at C-10 of sorangicin **A**.

In synthesizing fragment **E**, heptenoic acid in combination with Seebach auxiliary were used as a starting material, it would be very reasonable to produce the intermediate alcohol **77** by starting from very cheap starting material as heptenoic acid is relatively expensive.

In coupling the fragments by employing Julia olefination the following adjustments can be made in the future which could improve the coupling of the fragments as well as for the reaction to proceed with better selection for the trans-isomer.

A. Introduction of strong polar aprotic solvents such as HMPA

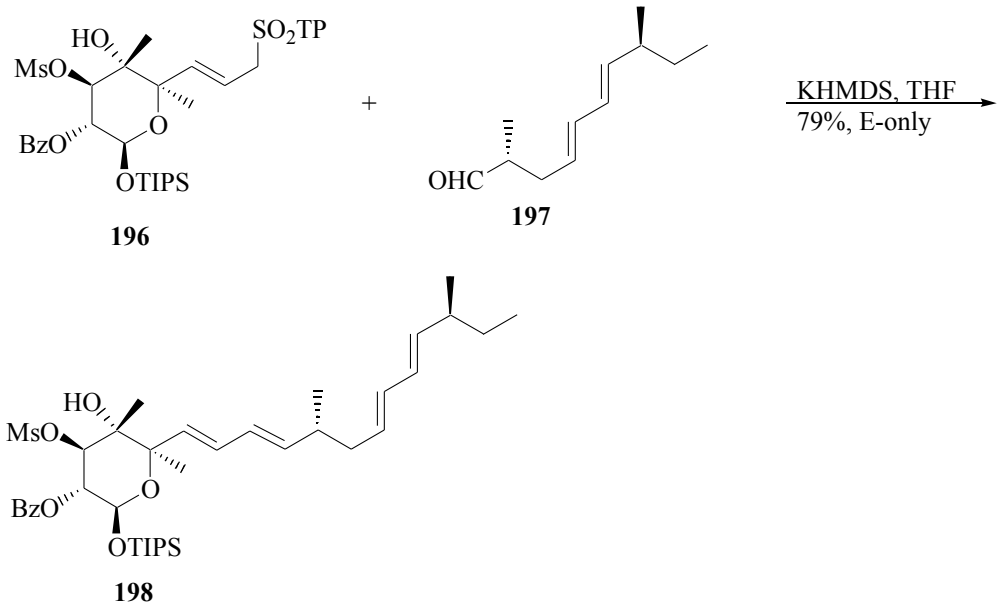
The use of polar aprotic solvent such as HMPA in combination with THF, DME or DMF has been found[60] to improve the rate of coupling of the substrates as well as provides a higher selectivity for the trans-isomer.



Scheme 61. Julia Olefination using aprotic solvents

B. Using DHP Fragment as Julia Olefination precursor

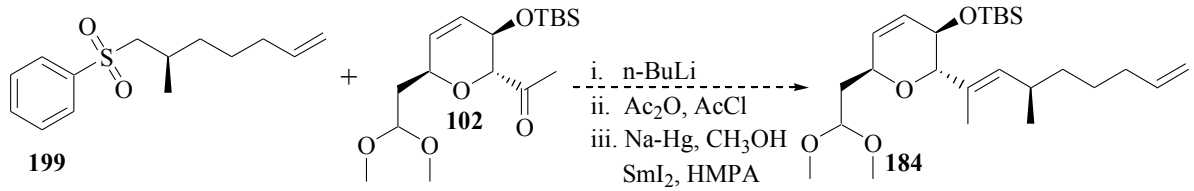
The use of DHP or THP fragment as Julia olefination precursor instead of a side chain fragment has resulted [13], [60] in a better coupling results as well as gives higher selectivity for the trans-isomer. Thus it could be possible to couple the fragments by synthesizing the aldehyde from the side chain fragment and the sulfone from the L-glucose fragment.



Scheme 62. DHP Fragment as Julia precursor

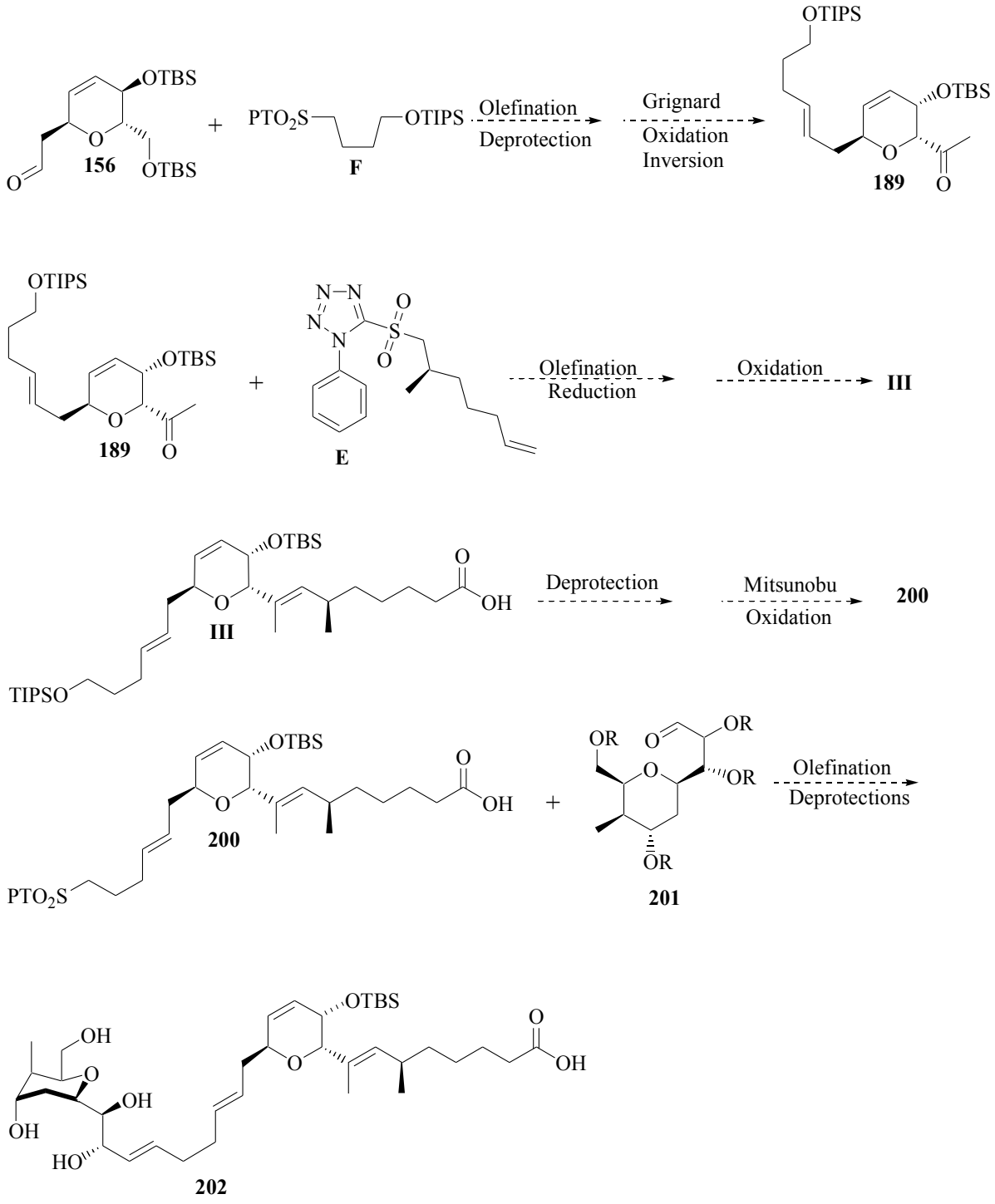
C. Employing Classical Julia Olefination

It would be also possible to use the classical Julia olefination by using the phenyl-sulfone **199** and methyl-ketone **200** as a last alternative to couple the fragments as classical Julia olefination is known to give predominantly trans-isomer[59] despite the need for four distinct synthetic operation.



Scheme 63. Classical Julia Olefination.

Based on the different synthetic route tested and experiments done in this work, the synthesis of C(1)-C(28) fragments of sorangicin **A** can be easily achieved by using a simple operation of protection, deprotection and olefination (**Scheme 66**). Olefination of aldehyde **156** with the phenyltetrazole sulfone fragment **F** could afford diene **189** in four steps. The diene **189** will be coupled with the side chain fragment **E** to give in three steps the triene fragment **III**. Deprotection of the TIPS group in fragment **III** followed by subsequent Mitsunobu reaction and oxidation will afford the sulfone **200**. Metathesis or olefination between sulfone **200** and aldehyde **201** and subsequent deprotection manipulations could afford, **202**, the C(1)-C(28) fragment of sorangicin **A**.



Scheme 64. Classical Julia Olefination.

7. Experimental Part

7.1 Materials and Methods

All reactions involving air-sensitive compounds were carried out under nitrogen by using oven-dried (90 °C) or flame dried glasses.

The commercially available chemicals products were used without further purification or when appropriate were distilled before use.

Tetrahydrofuran (THF) and diethyl ether were distilled with sodium/benzophenone and dichloromethane (DCM) was distilled with calcium hydride absolutely under nitrogen before use and reaction solvents were purified according to standard methods or dried over molecular sieves before use.

Preparative Column Chromatography

Chromatographic purification of products (flash chromatography) was performed on E. Merck Silica Gel 60 (230-400 mesh) using a forced flow of eluant at 0.3-0.5 bar.

Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure, unless otherwise stated.

Yields refer to chromatographically purified and spectroscopically pure compounds.

Nomenclature

The compounds are named essentially according to IUPAC rules. The evaluation of the spectroscopic data used in quantifying the carbon centers was for reasons of clarity, and synthetic sequence is maintained.

Analysis

For analytical thin-layer chromatography, TLC Cards PolyGram SIL G/UV254 with fluorescent indicator of the company Macherey & Nagel were used. The detection was carried out by irradiation with UV light (254 nm) and by immersing the developing TLC cards in vanillin, cerium (IV)-sulfate/phosphormolybdium acid or $KMnO_4$ reagent followed by heating.

^{1}H-NMR spectra were measured with Bruker using $CDCl_3$ as a solvent. The chemical shifts are given in (δ, ppm), coupling constants (J, Hz) specified. For the signal-multiplicity the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublets, dt = double triplets, ddd = doublet of a doublets etc.

^{13}C-NMR spectra were measured with Bruker using $CDCl_3$ as a solvent. To determine the signal-multiplicity DEPT-135-were used. The signal-multiplicities are as follows. q= CH_3 groups, t = CH_2 groups, d = CH-group, s = quaternary C-atoms.

Signal assignment is partly based on comparative data and analyzed using ^{1}H, ^{1}H-COSY, ^{1}H, ^{13}C-coupling experiments and NOESY experiments.

Mass Spectra was measured with a Finnigan SSQ 7000 mass spectrometer. The relative intensities are in [%] relative to the Base peak (100%) indicated. Ionization method was used with CH_4 as a reactant gas.

High Resolution Mass Spectrometry (HRMS) were measured with a Finnigan MAT 95 mass spectrometer after escan methods.

IR Spectra were measured with a Perkin-Elmer FT-IR-2000-spectrometer. The spectra of liquids were measured as a thin film on KBr discs with an IR microscope. The position of the absorption bands are indicated in wave numbers ν [cm-1]. The relative band intensities are abbreviated as follows: w = weak, m = medium, s = strong, b = broad signal.

UV / VIS Spectra were measured with a Perkin-Elmer Lambda 19 spectrometer.

Specific Rotation values were measured with a Perkin-Elmer 341-polarimeter. The specific rotation value (α) is given in (10^{2} deg kg^{-1} m^{-2}) at 25 °C and the concentration.

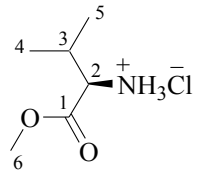
Coloring agents for Thin-Layer Chromatography

a) Vanillin Reagent:- Dissolve 8.6 g of vanillin in 200 ml of ethanol and add slowly 2.5 ml of sulfuric acid

b) Cerium (IV)-Sulfate/Phosphomolybdic acid: - Slowly add 16 ml of concentrated sulfuric acid to 5 g of Phosphomolybdic acid in 200 ml of water and 2 g of cerium (IV)-sulfate.

c) Potassium Permanganate:- Slowly add 5 ml of 5% caustic soda to a mixture of 3 g $KMnO_4$ and 20 g K_2CO_3 in 300 ml water.

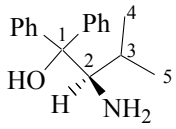
D-Valine-hydrochloride-methylester (173)



D-valine (10 g, 85.4 mmol) was dissolved in methanol (100 ml), cooled to 0 °C and thionyl chloride (15 g, 126 mmol) was added dropwise over a period of 30 minutes[44]. The reaction mixture was warmed up to room temperature, stirred for 24 h and volatiles were removed in vacuo to afford a white crystalline product **173** (14.3 g, 85 mmol, 99%).

General Data:	$C_6H_{14}ClNO_2$, M = 167.63 g/mol, white solid;
	R_f = 0.1 (100% EtOAc); UV (+); Vanillin (-);
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 4.82 (s, H-6, 3H); 3.88 (d, 4.7 Hz, H-2, 1H);
	2.40 (m, H-3, 1H); 1.08 (d, 5.7 Hz, H-4, 3H);
	1.07 (d, 5.4 Hz, H-5, 3H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 172.48 (C-1), 60.54 (C-2), 55.58 (C-6), 31.44
	(C-3), 19.47 (C-4), 19.20 (C-5);
MS (EI)	167.1 (5%), 149.1 (36%), 131.2 (28%), 88.1 (85%)
	74.0 (16%), 72.1 (100%), 55.1 (100%);
IR (Cap. Film)	3431 (br), 2968 (s), 1942 (s), 1586 (s), 1437 (s),
	1334 (s), 1294 (s);
HRMS	$C_6H_{14}ClNO_2$
	Calcd: 167.070
	Found: 167.075

2-Amino-3-methyl-1,1-diphenyl-butane-1-ol (174)

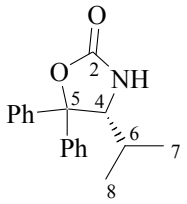


To a freshly prepared solution of PhMgBr (45 g, 248 mmol) in abs. Et_2O (150 ml) compound **173** (14.3 g, 85.3 mmol) was added dropwise[44]. The reaction mixture was stirred at room temperature for 30 minutes and further refluxed for 24 h. The reaction was cooled to room temperature quenched by adding ice cold water and treated with HCl (1N) and EtOAc (110 ml) consecutively. The reaction mixture was brought to pH=5 by using ammonia solution and the water phase was extracted with Et_2O (3 x 50 ml). Methanol (5 ml) was added to the solution and the combined organic layer was dried over $MgSO_4$. The volatiles were concentrated in vacuo to afford the alcohol **174** (15.7 g, 61.5 mmol, 72%).

General Data:	$C_{17}H_{21}NO$, M = 255.35 g/mol, yellowish solid; R_f = 0.53 (100% EtOAc); UV (+); Vanillin (-);
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 7.62-7.12 (m, Ph, 10H); 3.83 (m, H-2, 1H); 2.5 (m, H-3, 1H); 0.92 (d, 7.0 Hz, H-4, 3H); 0.89 (d, 7.0 Hz, H-5, 3H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 147. 85 (Ph), 144.80 (Ph), 128.33 (Ph), 127.95 (Ph), 126.52 (Ph), 126.19 (Ph), 125.82 (Ph), 125.3 (Ph), 79.64 (C-1), 60.11 (C-2), 27.75 (C-3), 22.91 (C-4), 16.05 (C-5);
MS (EI)	255.3 (15%), 238.3 (28%), 212.2 (24%), 195.2 (68%), 183.2 (64%), 165.2 (68%), 105.1 (92%), 72.2 (100%), 55.1(82%);

IR (Cap. Film) 3900 (m), 3817(s), 2964 (s), 1739 (s), 1661 (s)
1595 (s), 1490 (s), 704 (s), 639 (s);

4(R)-Isopropyl-5, 5-diphenyl-oxazolidin-2-one (103)



To a solution of alcohol **174** (3.15 g, 12.35 mmol) in abs. CH_2Cl_2 (63 ml) and Et_3N (1.9 ml, 13.6 mmol) cooled to -25 °C was added acetyl chloride (1.9 ml, 24.7 mmol)[44]. The reaction was warmed up to room temperature and was stirred for 24 h. The reaction mixture was treated with HCl (1N) and the volatiles were removed in vacuo. The remaining solution was treated with 1N NaOH in CH_3OH (150 ml) and was refluxed for 9 h. The reaction was diluted with water, cooled to 0 °C and the solid residue was washed with H_2O, Et_2O (1ml/mmol) and pentane consecutively to afford auxiliary **103** (1.8 g, 6.4 mmol, 52%).

General Data: $C_{18}H_{19}NO_2$, M = 281.35 g/mol, White solid;
R_f = 0.55 (100% EtOAc); UV (+); Vanillin (-);

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 7.56-7.54 (m, 2H, Ph); 7.40-7.27 (m, 8H, Ph)
6.17 (br, 1H, NH); 4.36 (d, 3.6 Hz, H-4, 1H);
1.90-1.86 (m, H-6, 1H); 0.90 (d, 7.0 Hz, H-8, 3H)
0.70 (d, 6.8 Hz, H-7, 3H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 158.47 (C-2), 143.84 (Ph), 139.10 (Ph), 128.51
(Ph), 128.19 (Ph), 128.06 (Ph), 127.67 (Ph), 126.28
(Ph), 125.66 (Ph), 89.32 (C-5), 65.77 (C-4), 29.54

(C-6), 20.82 (C-8), 15.56 (C-7);

MS (EI) 281.3 (8%), 261.3 (4%), 238.2 (3%), 194.3 (20%), 183.2 (100%), 165.2 (16%), 105.1 (24%), 77.1 (8%);

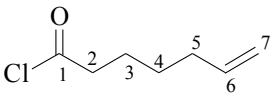
IR (Cap. Film) 3294 (s), 2982 (s), 1765 (s), 1745 (s), 1468 (s), 1452 (s), 1393 (s), 1316 (s), 1252 (s), 708 (s);

HRMS $C_{18}H_{19}NO_2$

Calcd: 281.140

Found: 281.142

Hept-6-enoylchloride (104)



To a solution of 6-heptenoic acid **175** (2.6 g, 20.3 mmol) in CH_2Cl_2 (10 ml) was added oxalyl chloride (5.15 g, 40.6 mmol) and the reaction was stirred for 1 h at room temperature and refluxed at 40 °C for 1 h[21]. Volatiles were removed in vacuo to afford the acid chloride **104** (2.97 g, 20.2 mmol, 99%).

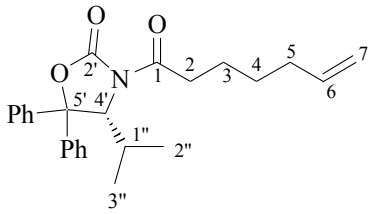
General Data: $C_7H_{11}ClO$, M = 146.62 g/mol, colorless oil;

R_f = 0.64 (100% EtOAc); Vanillin: blue, UV (-);

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 5.86-5.66 (m, H-6, 1H), 5.06-4.92 (m, H-7, 2H); 2.88 (m, H-2, 2H); 2.55-2.01 (m, H-5, 2H); 1.52-1.36 (m, H-3, H-4, 4H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 173.64 (C-1), 137.75 (C-6), 115.12 (C-7), 46.87 (C-2), 33.05 (C-5), 27.52 (C-3), 24.41 (C-4);

3'-Hept-6-enoyl-4'(R)-isopropyl-5',5'-diphenyl-oxazolidin-2'-one (176)



To a solution of the auxiliary **103** (856 mg, 3.0 mmol) in THF (5 ml) cooled to 0 °C was added n-BuLi (2.22 ml, 3.45 mmol, 1.6 M in Hexane). To the resulting clear solution was added acid chloride **104** (558 mg, 3.81 mmol) in one portion[21]. The reaction was stirred for 24 h and quenched with saturated aqueous $NaHCO_3$ and the water phase was extracted with Et_2O (4 x 25 ml). The organic phase was washed successively with HCl (1M), NaOH (1M) and saturated aqueous NaCl. The organic phase was dried over Na_2SO_4 and volatiles were removed in vacuo and residue was purified by flash chromatography with Pentane:Ether (5:1) to afford **176** (1.07 g, 2.73 mmol, 91%).

General Data: $C_{25}H_{29}NO_3$, M = 391.50 g/mol, yellowish oil;

R_f = 0.69 (100% EtOAc); UV (+);

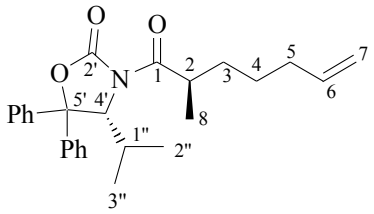
$[\alpha]^{20}$ = +179.0° (c = 1.30 $CHCl_3$); Vanillin: rose;

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 7.49-7.25 (m, Ph, 10H); 5.79 (m, H-6, 1H); 5.37 (d, 3.4 Hz, H-4', 1H); 4.99 (m, H-7, 2H); 2.91-2.72 (ddd, 16 Hz, 8.2 Hz, 6.7 Hz, H-2, 2H); 2.07-1.93 (m, H-5, H-1", 3H); 1.66-1.28 (m, H-3, H-4, 4H); 0.88 (d, 7.0 Hz, H-3", 3H); 0.77 (d, 6.8 Hz, H-2", 3H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 173.05 (C-1), 153.03 (C-2'), 142.37 (Ph), 138.39 (C-6), 138.17 (Ph), 128.86 (Ph), 128.54 (Ph), 128.35 (Ph), 127.91 (Ph), 125.91 (Ph), 125.60 (Ph), 114.58 (C-7), 89.33 (C-5'), 64.49

	(C-4'), 34.95 (C-2), 33.35 (C-5), 29.83 (C-3), 28.12 (C-1''), 24.07 (C-4), 21.75 (C-3''), 16.40 (C-2'');
MS (EI)	391.5 (100%), 355.3 (28%), 348.4 (68%), 169.3 (60%), 143.3 (100%), 85.2 (69), 57.1 (24);
IR (Cap. Film)	3064 (br), 2968 (s), 2934 (s), 2877 (br), 1785 (s), 1706 (s), 1450 (s), 1364 (s), 1318 (s), 1210 (s), 1175 (s), 761 (s), 704 (s);
HRMS	$C_{25}H_{29}NO_3$ Calcd: 391.214 Found: 391.215

(2R,4'R)-Isopropyl-3'-(2-methyl-hept-6-enoyl)-5',5'-diphenyl-oxazolidin-2'-one (177)



To a solution of **176** (2.0 g, 5.11 mmol) in THF (27 ml) cooled to -78 °C was added NaHMDS (6.01 ml, 6.01 mmol, 1.0 M in THF). After stirring it for 1 h, CH_3I (1.0 g, 7.05 mmol) was added and the reaction was allowed to warm up slowly to room temperature and was stirred for 24 h[21]. The reaction was quenched with saturated aqueous NH_4Cl and the water phase was extracted with Et_2O (4 x 50 ml) and the combined organic phase was dried over $MgSO_4$. The volatiles were removed in vacuo and the residue was purified by flash chromatography with Pentane:Ether (10:1) to afford **177** (1.52 g, 3.75 mmol, 74%).

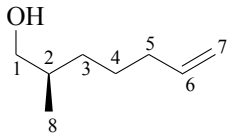
General Data:	$C_{26}H_{31}NO_3$, M = 405.53 g/mol, yellowish oil; R_f = 0.70 (100% EtOAc); UV (+); Vanillin: rose; $[\alpha]^{20}$ = +139.1° (c = 1.05 $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 7.58-7.22 (m, Ph, 10H); 5.61-5.51 (m, H-6, 1H); 5.38 (d, 3.5 Hz, H-4', 1H); 4.86-4.81 (m, H-7, 2H); 3.66 (m, H-2, 1H); 2.01 (m, H-1'', 1H); 1.78-1.72 (m, H-5, 2H); 1.56-1.41 (m, H-3, 2H); 1.20 (d, 6.8 Hz, H-8, 3H); 1.07-1.05 (m, H-4, 2H); 0.87 (d, 7.0 Hz, H-2''); 0.77 (d, 6.7 Hz, H-3'', 3H);
^{13}C-NMR(100MHz, $CDCl_3$, δ_{ppm})	δ = 176.75 (C-1), 152.88 (C-2'), 142.31 (Ph), 138.19 (C-6), 137.96 (Ph), 128.70 (Ph), 128.43 (Ph), 128.37 (Ph), 127.91 (Ph), 125.86 (Ph), 125.56 (Ph), 114.34 (C-7), 89.12 (C-5'), 64.55 (C-4'), 36.98 (C-2), 33.37 (C-5), 32.70 (C-3), 29.62 (C-1''), 25.75 (C-4), 21.57 (C-8), 17.84 (C-3''), 16.29 (C-2'');
MS (EI)	405.2 (5%), 337.2 (21%), 238.1 (13%), 220.1 (50%), 125.1 (48), 97.1 (46%), 77.0 (100%), 55.0 (79%);
IR (Cap. Film)	3392 (b), 2968 (s), 2935 (s), 1786 (s), 1703 (s), 1451 (s), 1385 (s), 1363 (s), 1317 (m), 1210 (m), 761 (s), 705 (s);

HRMS $C_{26}H_{31}NO_3$

Calcd: 405.230

Found: 405.227

(2R)-Methyl-hept-6-en-1-ol (77)



To a 0 °C cooled solution of **177** (1.55 g, 3.71 mmol) in Et_2O (25 ml), was added LAH (1.15 g, 30.23 mmol). The reaction was refluxed for 2 h and then cooled to room temperature and quenched with water[21]. The reaction was filtered over celite and extracted with Et_2O (8 x 50 ml). The volatiles were removed in vacuo and the residue was purified by flash chromatography with Pentane:Ether (3:1) to afford alcohol **77** (0.45 g, 3.52 mmol, 96%).

General Data: $C_8H_{16}O$, M = 128.21 g/mol, colorless liquid;

$[\alpha]^{20}$ = + 19.1 (c = 1.00$CHCl_3$); UV(-);

R_f = 0.5 (100% EtOAc); Vanillin: Violet;

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) δ = 5.79-5.76 (m, H-6, 1H); 5.03-4.93 (m, H-7, 2H); 3.41 (m, H-1, 2H); 2.07-2.03 (m, H-5, 2H); 1.65-1.42 (m, H-2, H-3, H-4, 5H); 1.02 (d, 6.6 Hz, H-8, 3H);

^{13}C-NMR (100MHz, $CDCl_3$, δ ppm) δ = 138.91 (C-7), 114.39 (C-6), 68.31 (C-1), 35.66 (C-2), 34.11 (C-5), 32.60 (C-3), 26.29 (C-4), 16.52 (C-8);

MS (EI)**:** 130.1 (8%), 128.1 (15%), 110 (9%), 97 (12%) 81.1 (44%), 71.1 (28%), 69.1 (34%), 67.1 (35),

56.1 (33%), 55.0 (100%), 43.1 (20%);

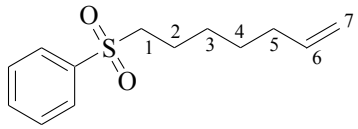
IR (Cap. Film)**:** 3351 (b), 2931 (s), 2879 (s), 1644 (s), 1468 (s), 1379 (s), 1039 (s), 910 (s);

HRMS $C_8H_{16}O$

Calcd: 128.120

Found: 128.109

(Hept-6-en-1-sulfonyl)-benzene (181)



To a stirred solution of the hept-6-en-1-ol **180** (50 mg, 0.39 mmol) and PPh_3 (419 mg, 1.6 mmol) in THF (5 ml) under N_2 was added NBS (315 mg, 1.6 mmol) in small portion over 15 minutes and the reaction was stirred further for 30 minutes[56]. To the reaction was added $ArSO_2Na$ (360 mg, 2.0 mmol) and NaI (15 mg, 0.1 mmol) in three portions over 10 minutes and was stirred for 4 h. The reaction was diluted with EtOAc (10 ml) and 3% aqueous solution $Na_2S_2O_3$ (10 ml). The organic phase was separated and the aqueous phase was extracted with EtOAc (4 x 50 ml) and the organic phase was successively washed with H_2O, brine and dried over Na_2SO_4. The volatiles were removed in vacuo and the residue was purified by flash chromatography with Hexane:EtOAc (9:1) to afford sulfone **181** (70.6 mg, 0.28 mmol, 72%).

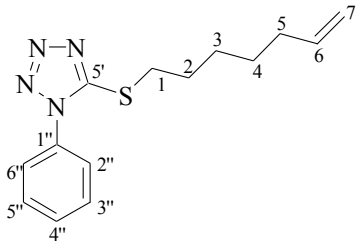
General Data: $C_{13}H_{18}O_2S$, M = 238.35 g/mol, yellowish oil;

R_f= 0.61 (100% EtOAc); UV (+); Vanillin: blue;

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 7.92-7.89 (m, Ph, 2H); 7.72-7.55 (m, Ph, 3H); 5.79 (m, H-6, 1H); 4.98-4.91 (m, H-7, 2H); 3.49-3.10 (m, H-1, 2H); 2.07-1.93 (m, H-5, 2H); 1.76-

	1.51 (m, H-2, 2H); 1.38-1.20 (m, H-3, H-4, 4H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 144.73 (Ph), 138.61 (C-7), 132.01 (Ph),128.9 (Ph), 125.22 (Ph), 114.49 (C-6), 64.66 (C-1), 33.50 (C-5), 29.51 (C-2), 28.31 (C-3), 25.15 (C-4);
MS (EI)	238.1 (5%), 218.0 (15%), 143 (38%), 125 (35%), 97.1 (45%), 77.1 (25%), 55.0 (100%);
IR (Cap. Film)	3469 (br), 3065 (s), 2930 (m), 2857 (s), 1959 (s) 1640 (s), 1462 (s), 1383 (s), 1306 (s), 1135 (s) 753 (s), 698 (s), 595 (s), 564 (s), 536 (s).
HRMS	$C_{13}H_{18}O_2S$ Calcld: 238.100 Found: 238.103

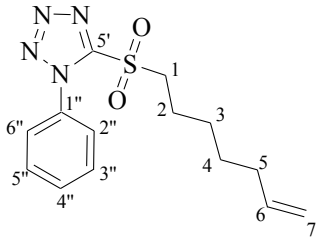
5'-(Hept-6-enylsulfanyl)-1'-phenyl-1H-tetrazole (203)



A solution of the hept-6-en-1-ol (31 mg, 0.27 mmol), 1-phenyl-1H-tetrazole-5-thiol (28 mg, 0.44 mmol) and PPh_3 (114 mg, 0.44 mmol) in THF (2.5 ml) was cooled to 0 °C. After 45 minutes of stirring DIAD (88 mg, 0.44 mmol, 86 µl) was added, reaction was allowed to warm up to room temperature and stirred for 4 h. The volatiles were removed in vacuo and the residue was dissolved in Et_2O (20 ml) and was kept for 4 h at -20 °C. The precipitated $OPPh_3$ was removed by filtration and Et_2O was removed in vacuo. The residue was purified by flash chromatography with Pentane:Ether (10:1) to afford **203** (61 mg, 0.22 mmol, 82%).

General Data:	$C_{14}H_{18}SN_4$, M = 274.39 g/mol, yellowish oil; R_f = 0.56 (Pe/Et_2O 10:1); UV (+); Vanillin: blue;
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm)	δ = 7.51-7.27 (m, H-2", H-3", H-4", H-5", H-6", 5H); 5.79 (ddt, 6.7 Hz, 10.2 Hz, 17.0 Hz, 1H, H-6) 5.01-4.92 (m, H-7, 2H); 3.39 (dd, 14.8 Hz, 7.4 Hz H-1, 2H); 2.08-2.03 (m, H-5, 2H); 1.87-1.77 (m, H-2, 2H); 1.55-1.40 (m, H-4, H-3, 4H);
^{13}C-NMR (100MHz, $CDCl_3$, δ ppm)	δ = 154.38 (C-5"), 138.44 (C-6), 133.68 (C-1"), 129.99 (C-2", C-6"), 129.69 (C-4"), 123.77 (C-3", C-5"), 114.56 (C-7), 33.40 (C-1), 33.20 (C-5), 28.86 (C-2), 28.15 (C-3), 27.96 (C-4);
MS (EI)	274.1 (5%), 241.1 (55%), 227.1 (10%), 213 (12%), 199.1 (15%), 165 (100%), 104 (100%);
IR (Cap. Film)	1959 (s), 1885 (s), 1809 (s), 1641 (s), 1596 (s), 1498 (s), 1462 (s), 1342 (br), 1153 (s), 1077 (m), 914 (s), 726 (s), 544 (s).
HRMS	$C_{14}H_{18}SN_4$ Calcld: 274.130 Found: 274.141

5'-(Hept-6-ene-1-sulfonyl)-1'-phenyl-1H-tetrazole (191)



The prepared sulfide **203** (29 mg, 0.11 mmol) was dissolved in EtOH (3.2 ml), cooled to 0 °C and a premixed, bright yellow solution of $(NH_4)_6Mo_7O_{24}$ (5.12 mg, 0.022 mmol) in 35% aqueous solution of H_2O_2 (5.34 ml, 5.5 mmol) was added slowly over 5 minutes. The reaction was allowed to warm up to room temperature and stirred for 6 h. A mixture of EtOAc:H_2O (1:1) (10 ml) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 ml) and the combined organic layer was washed with H_2O (5 ml), brine (50 ml), and dried over $MgSO_4$. The solvents were removed in vacuo and the residue was purified by flash chromatography with Pentane:Ether (10:1) to afford sulfone **191** (48 mg, 0.029 mmol, 65%).

General Data: $C_{14}H_{18}N_4O_2S$, M = 306.38 g/mol, yellowish oil;

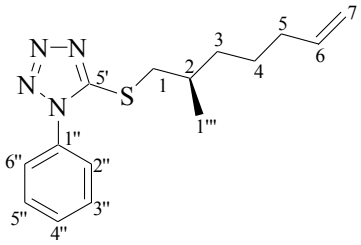
R_f= 0.50 (Pe/Et_2O, 10:1); UV (+); Vanillin: blue;

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 7.61-7.52 (m, H-2", H-3", H-4", H-5", H-6", 5H); 5.79 (ddt, 6.7 Hz,10.2 Hz, 17.0 Hz, H-6, 1H); 5.02-4.95 (m, H-7, 2H); 3.75-3.72 (dd, 16.1 Hz, 7.2 Hz, H-1, 2H); 2.08 (d, 8.1 Hz, H-5, 2H); 1.98-1.94 (m, H-2, 2H); 1.53-1.44 (m, H-4, H-3, 4H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 153.42 (C-5'), 138.04 (C-6), 132.99 (C-1"), 131.43 (C-2", C-6"), 129.68 (C-4"), 125.02 (C-3", C-5"), 114.97 (C-7), 55.88 (C-1), 33.17 (C-5), 29.65 (C-2), 28.03 (C-3), 27.47 (C-4);

MS (EI)	307.1 (5%), 277.1 (55%), 258.1 (10%), 213 (12%), 163.1 (15%), 118.1 (100%), 91.0 (18%), 77.0 (18%), 55.0 (65%);
IR (Cap. Film)	3462 (br), 3075 (s), 2928 (m), 2858 (s), 2486 (s), 1959 (s), 1885 (s), 1809 (s), 1641 (s), 1596 (s), 1498 (s), 1462 (s), 1342 (br), 1153 (s), 1077 (m), 914 (s), 726 (s), 544 (s);
HRMS	$C_{14}H_{18}N_4O_2S$ Calcld: 306.120 Found: 306.115

5'-(2(R)-Methyl-hept-6-enylsulfanyl)-1'-phenyl-1H-tetrazole (178)

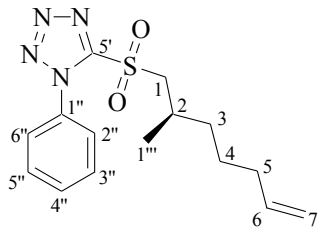


A solution of the alcohol **77** (31 mg, 0.24 mmol), 1-phenyl-1H-tetrazole-5-thiol (28 mg, 0.44 mmol) and PPh_3 (114 mg, 0.44 mmol) in THF (2.5 ml) was cooled to 0 °C. After 45 minutes of stirring DIAD (88 mg, 0.44 mmol, 0.086 ml) was added and reaction was allowed to warm up to room temperature and stirred for 4 h. The volatiles were removed in vacuo and the residue was dissolved in Et_2O (20 ml) and was kept for 4 h at -20 °C. The precipitated $OPPh_3$ was removed by filtration and Et_2O was removed in vacuo. The residue was purified by flash chromatography with Pentane:Ether (10:1) to afford sulfide **178** (61 mg, 0.22 mmol, 92%).

General Data:	$C_{15}H_{20}SN_4$, M = 288.41 g/mol, yellowish oil; R_f = 0.85 (100% EtOAc); Vanillin: blue;

	$[\alpha]^{20} = -3.1°$ (c = 1.03 $CHCl_3$); UV (+);
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 7.60-7.51 (m, H-2", H-3", H-4", H-5", H-6", 5H); 5.79 (ddt, 6.8 Hz, 10.4 Hz, 17.1 Hz H-6, 1H); 5.01-4.95 (m, H-7, 2H); 3.48-3.23 (dd, 12.6 Hz, 7.5Hz, H-1, 2H); 2.06 (dd, 13.2 Hz, 6.5 Hz, H-5, 2H); 1.99 (d, 6.5 Hz, H-2, 1H); 1.55-1.19 (m, H-3, H-4, 4H); 1.04 (d, 6.7 Hz, H-1'", 3H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 154.69 (C-5'), 138.54 (C-6), 133.72 (C-1"), 130.04 (C-2", C-6"), 129.74 (C-4"), 123.86 (C-3", C-5"), 114.63 (C-7), 40.42 (C-1), 35.28 (C-3), 33.73 (C-5), 32.80 (C-2), 26.05 (C-4), 19.06 (C-1'");
MS (EI)	288.1 (8%), 255.1 (52%), 227.1 (6%), 179.2 (96%), 150.2 (52%), 143.1 (60%), 118.2 (100%), 101 (45%), 91.1 (28%), 77.1 (40%) 69 (36%), 55.1 (58%);
IR (Cap. Film)	2963 (b), 2935 (s), 2858 (b), 1591 (b), 1499 (s), 1463 (b), 1414 (s), 1389 (s), 1246 (s), (s), 1089 (s), 1077 (s), 968 (b), 761 (s);
HRMS	$C_{15}H_{20}SN_4$ Calcld: 288.140 Found: 288.141

5'-(2(R)-Methyl-hept-6-ene-1-sulfonyl)-1'-phenyl-1H-tetrazole (E)



The sulfide **178** (29 mg, 0.11 mmol) was dissolved in EtOH (3.2 ml), cooled to 0 °C and a premixed bright yellow solution of $(NH_4)_6Mo_7O_{24}$ (5.12 mg, 0.022 mmol) in 35% aqueous solution of H_2O_2 (5.34 ml, 5.5 mmol) was added slowly over 5 minutes. The reaction was allowed to warm up to room temperature and stirred for 6 h. A mixture of EtOAc:H_2O (1:1) (10 ml) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 ml) and the combined organic layer was washed with H_2O (5 ml), brine (50 ml), and dried over $MgSO_4$. The volatiles were removed in vacuo and the residue was purified by flash chromatography with Pentane:Ether (10:1) to afford sulfone **E** (22 mg, 0.069 mmol, 69%).

General Data

$C_{15}H_{20}N_4O_2S$, M = 320.41 g/mol, yellowish oil;

R_f = 0.73 (Pentane: Ether, 1:1);

$[\alpha]^{20}$ = +17.1° (c = 1.0 $CHCl_3$); UV (+);

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})

δ = 7.69-7.58 (m, H-2", H-3", H-4", H-5", H-6", 5H); 5.78 (ddt, 6.8 Hz, 10.6 Hz, 17.1 Hz, H-6, 1H) 5.00-4.95 (m, H-7, 2H); 3.84-3.56 (dd, 12.6 Hz, 7.5 Hz, H-1, 1H); 2.06 (d, 7.6 Hz, H-5, 2H); 1.99-1.93 (m, H-2, 1H); 1.58-1.38 (m, H-4, H-3, 4H); 1.25 (d, 7.0 Hz, H-1'", 3H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})

δ = 154.07 (C-5'), 138.14 (C-6), 133.08 (C-1"), 131.45 (C-2", C-6"), 129.68 (C-4"), 125.05 (C-3", C-5"), 114.97 (C-7), 61.82 (C-1), 35.94 (C-3),

33.45 (C-5), 28.1 (C-2), 25.58 (C-4), 19.70 (C-1'");

MS (EI) 320 (5%), 309 (6%), 279 (5%), 268 (15%), 241.1 (50%), 231.1 (16%), 227.1 (55%), 199.1 (55%), 173 (8%), 118.0 (100%), 91.1 (6%), 77.1 (25%), 55.0 (35%);

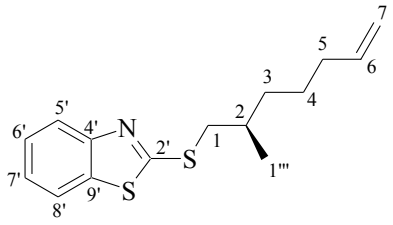
IR (Cap. Film) 3463 (b), 2931 (s), 2859 (b), 1737 (s), 1641 (s), 1498 (s), 1462 (s), 1373 (s), 1243 (b), 1153 (s), 1047 (s), 1016 (s), 916 (s), 764 (s), 521 (s);

HRMS $C_{15}H_{20}N_4O_2S$

Calcld: 320.130

Found: 320.131

2'-(2(R)-Methylhept-6-enylsulfanyl)-Benzothiazole (179)



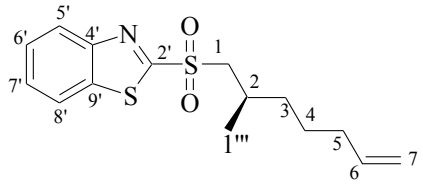
A solution of the alcohol **77** (93 mg, 0.72 mmol), benzothiazole-thiol (84 mg, 1.32 mmol) and PPh_3 (198.3 mg, 0.76 mmol) in THF (7.5 ml) was cooled to 0 °C and DIAD (264 mg, 1.32 mmol, 0.25 ml) was added after 45 minutes[21]. The reaction was allowed to warm up to room temperature and stirred for 4 h. The volatiles were removed in vacuo and the residue was dissolved in Et_2O (20 ml) and was kept for 4 h at -20 °C. The precipitated $OPPh_3$ was removed by filtration and Et_2O was removed in vacuo. The residue was purified by flash chromatography with Pentane:Ether (10:1) to afford sulfide **179** (180 mg, 0.65 mmol, 90%).

General Data: $C_{15}H_{19}NS_2$, M = 277.10 g/mol, colourless oil;

R_f = 0.69 (100%EtOAc); Vanillin: blue;

	$[\alpha]^{20}$ = - 49.5° (c = 1.03 $CHCl_3$), UV (+);
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 7.78 (d, 7.6 Hz, H-5', 1H); 7.65 (d, 8.0 Hz H-8', 1H); 7.31-7.27 (m, H-6', H-7', 2H); 1.1 Hz, H-7', 1H); 5.75 (m, H-6, 1H); 5.02-4.85 (dd, 17.0 Hz, 10.0 Hz, H-7, 2H); 3.41-3.19 (dd, 12.0 Hz, 5.7 Hz, H-1, 2H); 2.06 (d, 6.9 Hz, H-5, 2H); 1.99-1.89 (m, H-2, 1H); 1.62-1.25 (m, H-4, H-3, 4H); 0.99 (m, H-1''', 3H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 167.54 (C-2'), 153.27 (C-4'), 138.75 (C-6) 135.10 (C-9'), 125.91 (C-8'), 124.02 (C-5'), 121.36 (C-6'), 120.82 (C-7'), 114.52 (C-7), 40.56 (C-1), 35.46 (C-3), 33.75 (C-5), 33.08 (C-2), 26.20 (C-4), 19.29 (C-1''');
MS (EI)	277.1 (90%), 262.1 (20%), 223.1 (28%), 167.1 (100%), 166.1 (50%), 77.1 (100%);
IR (Cap. Film)	2928 (b), 1458 (s), 1428 (s), 996 (s), 755 (s), 726 (b);
HRMS	$C_{15}H_{19}NS_2$ Calcld: 277.100 Found: 277.097

2'-(2(R)-Methylhept-6-en-1-sulfonyl)-Benzothiazole (105)



The sulfide **179** (40 mg, 0.15 mmol) was dissolved in EtOH (4.4 ml), cooled to 0°C and a premixed bright yellow solution of $(NH_4)_6Mo_7O_{24}$ (7.15 mg, 0.03 mmol) in 35% aqueous solution of H_2O_2 (6.69 ml, 6.89 mmol) was added slowly over 5 minutes[21]. The reaction was allowed to warm up to room temperature and stirred for 6 h. A mixture of EtOAc:H_2O (1:1) (10 ml) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 ml) and the combined organic layer was washed with H_2O (5 ml), brine (50 ml), and dried over $MgSO_4$. The solvents were removed in vacuo and the residue was purified with flash chromatography with Pentane:Ether (10:1) to afford sulfone **105** (29 mg, 0.094 mmol, 63%).

General Data: $C_{15}H_{19}NO_2S_2$, M = 309.45 g/mol; yellowish oil; R_f = 0.61 (Pentane: Ether, 1:1); Vanillin: blue; $[\alpha]^{20}$ = -7.2° (c = 1.03 $CHCl_3$); UV (+);

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 8.21 (d, 7.9 Hz, 1H, H-5'); 8.02 (dd, 8.1 Hz 1.5 Hz, H-8', 1H); 7.62-7.57 (m, H-6', H-7', 2H); 5.73 (ddt, 10.0 Hz, 17.0 Hz, 6.7 Hz, H-6, 1H); 4.93-4.87 (m, H-7, 2H); 3.56-3.35 (dd, 4.0 Hz 8 Hz, H-1, 1H); 2.32-2.24 (m, H-2, 1H);2.00-1.95 (m, H-5, 2H); 1.6-1.23 (m, H-3, H-4, 4H); 1.14 (m, H-1''', 3H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 166.61 (C-2'), 152.57 (C-4'), 138.13 (C-6), 136.61 (C-9'), 127.91 (C-8'), 127.55 (C-5'), 125.28 (C-6'), 122.27 (C-7'), 114.70 (C-7),

60.62 (C-1), 35.90 (C-3), 33.36 (C-5), 28.33 (C-2), 25.47 (C-4), 19.73 (C-1'");

MS (EI) 310.1 (43%), 295.1 (95%), 268.1 (100%), 188.0 (90%), 135.0 (100%), 55.0 (55%);

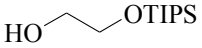
IR (Cap. Film) 3452 (s), 3069 (s), 2931 (s), 1738 (s), 1640 (s), 1473 (s), 1325 (s), 1148 (s), 763 (s), 631 (s);

HRMS $C_{15}H_{19}NO_2S_2$

Calcld: 309.090

Found: 309.085

2-Triisopropylsilanyloxy-ethanol (204)



Ethylene glycol **79** (1.00 g, 15.6 mmol) was added dropwise to NaH (624 mg, 60% in mineral oil, 15.6 mmol) suspended in THF (30 ml). After 1 h vigorous stirring, TIPSCl (3.34 ml, 46.8 mmol) was added in a single portion and the solution was further stirred for 3.5 h at room temperature[25]. The reaction was acidified with saturated aqueous NH_4Cl (250 ml) and extracted with EtOAc (3 x 75 ml). The organic layer was successively washed with 10% aqueous $NaHCO_3$ (100 ml), brine (100 ml) and dried over Na_2SO_4. The volatiles were concentrated in vacuo and the residue was purified by flash chromatography with Pentane:Ether (2:1) to afford TIPS-protected alcohol **204** (2.80 g, 12.8 mmol, 80%).

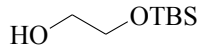
General Data: $C_{11}H_{26}O_2Si$, M = 218.41 g/mol, colorless oil;

R_f = 0.58 (100% EtOAc); UV (-); Vanillin: blue;

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) δ = 3.70 (m, H-1, 2H); 3.57 (m, H-2, 2H); 2.72 (s, OH, 1H); 1.12,0.98 (m, OTIPS, 21H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 64.24 (C-1), 63.48 (C-2), 17.68 (OTIPS), 11.73 (OTIPS);
MS (EI)	218.1 (11%), 157.3 (100%), 115.2 (45%), 103.2 (20%), 87.2 (20%), 75.1 (19%), 59.1 (16%);
IR (Cap. film)	3351 (b), 2944 (s), 2893 (s), 2868 (s), 1464 (s), 1384 (s), 1368 (s), 1249 (s), 1120 (s), 1060 (s), 937 (s), 681 (s);
HRMS	$C_{11}H_{26}O_2Si$ Calcld: 218.170 Found: 218.172

2-(*tert*-Butyldimethylsilanyloxy)-ethanol (141)

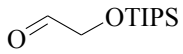


Ethylene glycol **79** (3.00 g, 46.8 mmol) was added dropwise to NaH (1.87 g, 60% in mineral oil, 46.8 mmol) suspended in THF (90 ml). After 1 h vigorous stirring, TBSCl (7.02 g, 46.8 mmol) was added in a single portion and the solution was further stirred for 3.5 h at room temperature. The reaction was acidified with saturated aqueous NH_4Cl (250 ml) and extracted with EtOAc (5 x 150 ml). The organic layer was successively washed with 10% aqueous $NaHCO_3$ (300 ml), brine (300 ml) and dried over Na_2SO_4. The volatiles were concentrated in vacuo and was purified by flash chromatography with Pentane:Ether (2:1) to afford TBS-protected alcohol **141** (7.0 g, 39.7 mmol, 85%).

General Data:	$C_8H_{20}O_2Si$, M = 176.33 g/mol, colorless oil; R_f = 0.56 (100% EtOAc); UV (-); Vanillin: dark blue;
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 3.66 (m, H-1, 2H); 3.58 (m, H-2, 2H);

	2.57 (br, OH, 1H); 0.85 (s, OTBS**,** 9H); 0.03 (s, OTBS, 6H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 64.12 (C-1), 63.52 (C-2), 25.79 (OTBS), 18.22 (OTBS), -5.47 (OTBS);
MS (EI)	176.1 (5%), 161.1 (35%), 147.1 (100%), 119.0 (8%), 89.0 (20%), 75.0 (19%), 59.0 (16%);
IR (Cap. film)	3402 (b), 2955 (s), 2931 (s), 2886 (s), 1473 (s), 1464 (s), 1390 (s), 1060 (s), 664 (s);
HRMS	$C_8H_{20}O_2Si$ Calcld: 176.120 Found: 176.123

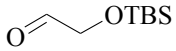
2-Triisopropylsilanyloxy-acetaldehyde (137)



Oxalyl chloride (2.16 ml, 24.8 mmol) was added dropwise to -78 °C cooled solution of DMSO (3.52 ml, 49.5 mmol) and Et_3N (8.63 ml, 61.9 mmol) dissolved in CH_2Cl_2 (115 ml). After stirring for 5 minutes, **204** (2.73 g, 12.4 mmol) was added via cannula as a solution in CH_2Cl_2 (10 ml). After 30 minutes, the reaction was allowed to warm to 0 °C over the course of 1 h and CH_2Cl_2 (75 ml) was added to the reaction mixture[25]. The reaction mixture was successively washed with saturated aqueous NH_4Cl (100 ml), 10% aqueous $NaHCO_3$ (100 ml), brine (100 ml) and dried over Na_2SO_4. The volatiles were concentrated in vacuo and the oily residue was purified by flash chromatography with Pentane:Ether (2:1) to afford the aldehyde **137** (2.31 g, 10.6 mmol, 86%).

General Data:	$C_{11}H_{24}O_2Si$, M = 216.39 g/mol, colorless oil;
	R_f = 0.65 (100% EtOAc);
	UV (-); Vanillin: dark brown;
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 9.74 (m, H-1, 1H); 4.26 (m, H-2, 2H);
	1.25,1.08 (m, OTIPS, 21H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 203.02 (C-1), 69.70 (C-2), 17.81 (OTIPS),
	11.88 (OTIPS);
MS (EI)	217.3 (5%), 175.3 (38%), 131.2 (85.1%),
	103.1 (100%), 75.1 (35%), 65.1 (20%);
IR (Cap. film)	3651 (s), 3314 (s), 2944 (s), 2893 (s), 2867(s)
	1464 (s), 1384 (s), 1368 (s), 883 (s) 788 (s);
HRMS	$C_{11}H_{24}O_2Si$
	Calcld: 216.150
	Found: 216.161

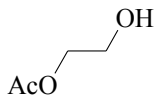
2-(*tert*-Butyldimethylsilanyloxy)-acetaldehyde (142)



Oxalyl chloride (0.42 ml 4.96 mmol) was added dropwise to -78 °C cooled solution of DMSO (0.65 ml, 9.9 mmol) and Et_3N (1.6 ml, 12.39 mmol) dissolved in CH_2Cl_2 (27 ml). After stirring it for 5 minutes compound **141** (0.5 g, 2.48 mmol) was added via cannula as a solution in CH_2Cl_2 (5 ml). After 30 minutes, the reaction was allowed to warm to 0 °C over the course of 1h. Then, CH_2Cl_2 (75 ml) was added and the reaction mixture was successively washed with saturated aqueous NH_4Cl (100 ml), 10% aqueous $NaHCO_3$ (100 ml), brine (100 ml) and dried over Na_2SO_4. The volatiles were concentrated in vacuo and the oily residue was purified by flash chromatography with Pentane:Ether (2:1) to afford the aldehyde **142** (0.35 g, 2.0 mmol, 81%).

General Data:	$C_8H_{18}O_2Si$, M = 174.31 g/mol, colorless oil;
	R_f = 0.68 (100% EtOAc);
	UV (-); Vanillin: brown;
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 9.65 (m, H-1, 1H); 4.17 (m, H-2, 2H);
	0.89 (s, OTBS, 9H); 0.06 (s, OTBS, 6H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 202.03 (C-1), 69.51 (C-2), 25.77 (OTBS),
	18.32 (OTBS), -5.54 (OTBS);
MS (EI)	175.1 (5%), 159.1 (12%), 133.0 (28%),
	117.0 (69%), 75.1 (100%);
IR (Cap. film)	3469 (b), 2955 (s), 2887 (s), 1764 (s), 1739
	(s), 1464 (s), 1389 (s), 1256 (s), 1150 (s),
	837 (s), 664 (s);
HRMS	$C_8H_{18}O_2Si$
	Calcld: 174.110
	Found: 174.120

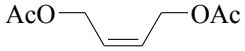
Acetic acid 2-hydroxy-ethyl ester (205)



Trimethyl-orthoacetate (2.98 ml, 23.4 mmol) was added to a room temperature stirring solution of ethylene glycol **79** (1.00 g, 15.6 mmol), PPTS (148 mg, 0.78 mmol) and CH_2Cl_2 (150 ml)[25]. After stirring it for 6 minutes, distilled water (422 µl) was added in a single portion and the mixture was stirred further for additional 6 minutes. The volatiles were removed in vacuo and the residue was purified by flash chromatography with Hexane:Ether (9:1) to afford alcohol **205** (1.50 g, 14.4 mmol, 93%).

General Data:	$C_4H_8O_3$, M = 104.10 g/mol, colorless oil;
	R_f = 0.45 (100% EtOAc)
	Vanillin: yellow; UV(-);
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 3.89 (m, H-1, 2H); 3.78 (s, OH, 1H);
	3.51 (m, H-2, 2H); 1.81 (s, OAc-CH_3,
	3H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 171.0 (**C**OCH_3), 65.3 (C-1), 59.7
	(C-2), 20.1 (CO**C**H_3);
MS (EI)	104.1 (19%), 91.0 (76%), 87.0 (100%),
	77.0 (63%), 57 (25%);
IR (Cap.film)	3439 (s), 2955 (s), 1738 (s), 1442 (s),
	1380 (s), 1247 (b), 1083 (s), 1047 (s),
	885 (s), 607 (s);
HRMS	$C_4H_8O_3$
	Calcld:104.050
	Found:104.048

Acetic acid 4-acetoxy-but-2-enyl ester (145)

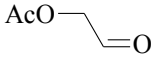


To a solution of cis-2-butene-1,4-diol **144** (1.0 g, 11.4 mmol) in pyridine (5 ml) was added Ac_2O (6.4 ml, 34.2 mmol). The mixture was stirred at room temperature for 1 h and was then extracted with EtOAc (3 x 50 ml). The organic phase was successively washed with 1N HCl (5 x 25 ml), brine (25 ml) and was dried over Na_2SO_4. Volatiles were concentrated in vacuo and the residue was purified by flash chromatography with Pentane:EtOAc (20:1) to

afford the diacylated alkene **145** (1.68 g, 9.8 mmol, 86%).

General Data:	$C_8H_{12}O_4$, M = 172.18 g/mol, colorless oil;
	R_f = 0.65 (100% EtOAc);
	Vanillin: Violet; UV (-);
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 5.5 (m, H-2, H-3, 2H); 4.5 (m, H-1,
	H-4, 4H); 1.84 (s, $COCH_3$, 6H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 170.16 (**C**OCH_3), 127.55 (C-2, C-3),
	59.37 (C-1, C-4), 20.16 (CO**C**H_3);
MS (EI)	172 (85%), 142 (46%), 87 (100%), 70
	(100%), 43 (100%);
IR (Cap. film)	3462 (s), 3036 (s), 2945 (s), 2464 (s),
	2062 (s), 1742 (s), 1439 (s), 1374 (s),
	1227 (b), 1033 (s), 967 (s), 890 (s), 840
	(s), 731 (s), 635 (s), 607 (s);
HRMS	$C_8H_{12}O_4$
	Calcld: 172.070
	Found: 172.074

Acetic acid 2-oxo-ethyl ester (146)



The protected alkene **145** (1.00 g, 19.2 mmol) was dissolved in CH_2Cl_2 (15 ml), CH_3OH (5 ml) and cooled to -78 °C. Ozone was run into the reaction and the color turned to blue in

just 10 minutes. The reaction mixture was treated with PPh_3 (2.5 g, 8.4 mmol) and the volatiles were concentrated in vacuo. The residue was purified by flash chromatography with Pentane:Ether (1:1) to afford the aldehyde **146** (0.98 g, 9.6 mmol, 51%).

General Data: $C_4H_6O_3$, M = 102.09 g/mol, colorless oil;

R_f = 0.53 (100% EtOAc);

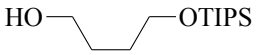
Vanillin: Dark brown, UV (-);

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 9.53 (m, H-2, 1H); 4.66 (m, H-1, 2H); 2.18 (s, $COCH_3$, 3H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 195.6 (C-2), 170.6 (**C**OCH_3), 68.9 (C-1), 20.7 (CO**C**H_3);

IR (Cap. film) 2953 (s), 1739 (s), 1725 (s), 1677 (s), 1436 (s), 1377 (s), 1234 (s), 1042 (s);

4-Triisopropylsilanyloxy-butan-1-ol (75)



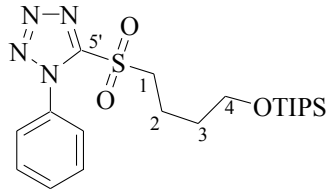
To a solution of NaH (1.9 g, 60% in mineral oil, 46.8 mmol) suspended in THF (90 ml) was added dropwise 1,4-butanediol **78** (4.2 g, 46.8 mmol). After 1 h vigorous stirring, TIPSCl (10.02 ml, 140.4 mmol) was added in a single portion and the solution was stirred further for 3.5 h at room temperature. The reaction was acidified with saturated aqueous NH_4Cl (250 ml) and extracted with EtOAc (3 x 75 ml). The organic layer was successively washed with 10% aqueous $NaHCO_3$ (100 ml), brine (100 ml) and dried over Na_2SO_4. The volatiles were concentrated in vacuo and the residue was purified by flash chromatography with Pentane:Ether (2:1) to afford TIPS-protected alcohol **75** (9.5 g, 38.4 mmol, 82%).

General Data: $C_{13}H_{30}O_2Si$, M = 246. 46 g/mol, colourless liquid;

R_f = 0.74 (100% EtOAc); UV (+); Vanillin (-);

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 3.70 (m, H-1, 2H); 3.60 (m, H-4, 2H); 3.0 (s, OH, 1H); 1.60 (m, H-2, H-3, 4H); 1.63,0.98 (m, OTIPS, 21H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 63.49 (C-1), 62.56 (C-4), 30.52 (C-3), 29.91 (C-2), 17.87 (OTIPS), 11.87 (OTIPS);
MS (EI)	246.2 (25%), 203.2 (46%), 143.1 (100%), 131.1 (78%), 119.1 (100%), 103.1 (100%), 75.0 (35%);
IR (Cap. Film)	3339 (b), 2943 (m), 2867 (s), 2727 (b), 1464 (s), 1384 (s), 1367 (s), 1248 (s), 951 (s), 681 (s);
HRMS	$C_{13}H_{30}O_2Si$ Calcld: 246.200 Found: 246.201

1'-Phenyl-5'-(4-Triisopropylsilanyloxy-butane-1-sulfonyl)-1H-tetrazole (F)



A solution of the alcohol **75** (2 g, 8.11 mmol), PT-SH (1.52 g, 8.51 mmol) and PPh_3 (2.24 g, 8.51 mmol, 1.05 equiv.) in THF (81 ml) was cooled to 0 °C and DIAD (1.93 ml, 9.6 mmol, 1.2 equiv) was added after 45 minutes of stirring. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Volatiles were removed under reduced pressure and the crude reaction mixture was dissolved in Et_2O (72 ml) and kept for 4 h at -20°C. The precipitated $OPPh_3$ was removed by filtration and volatiles were removed under reduced pressure. The residue was dissolved in EtOH (40 ml) and cooled to 0 °C and a premixed bright yellow solution of $(NH_4)_6Mo_7O_{24}$ (372.5 mg, 1.62 mmol) in 35% aqueous solution of

H_2O_2 (78.6 ml 80.0 mmol) was added slowly over 5 minutes. The reaction mixture was allowed to warm up to room temperature and stirred for 6 h. A mixture of EtOAc:H_2O (100 ml) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3x150 ml) and the combined organic phase was washed with H_2O (50 ml), brine (50 ml), dried over $MgSO_4$. The solvents were evaporated in vacuo and crude product was purified by flash chromatography with EtOAc:MeOH (100:0→25:1) to afford sulfone fragment **F** (2.5 g, 5.7 mmol, 70 %).

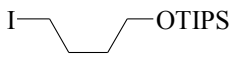
General Data: $C_{20}H_{34}N_4O_3SSi$, M = 438.66 g/mol, white solid;
R_f = 0.79 (Pentane: Ether, 1:1);
UV (+); Vanillin (-);

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 7.58-7.43 (m, aromatic CH, 5H), 3.80 (m, H-4 2H); 3.73 (m, H-1, 2H); 2.04 (m, H-2, 2H); 1.70 (m, H-3, 2H); 1.21,1.02 (m, OTIPS, 21H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 153.32 (C-5'), 132.95, 131.23, 129.51, 124.97 (aromatic CH), 62.26 (C-4), 55.80 (C-1), 30.93 (C-3), 18.76 (C-2), 17.87 (OTIPS), 11.87 (OTIPS);

IR (Cap. Film) 3468 (b), 2893 (s), 2867 (b), 1711 (s), 1463 (s), 1366 (s), 1344 (s), 1256 (s), 1151 (b), 1108 (s), 1073 (s), 1014 (s), 918 (s), 761 (s), 668 (s);

(4-Iodo-butoxy)-triisopropyl-silane (187)

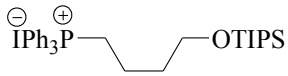


To a 0 °C cooled solution of PPh_3 (3.07 g, 11.7 mmol) in CH_2Cl_2 (50 ml) was added imidazole (810 mg, 11.7 mmol) and I_2 (2.96 g, 11.7 mmol). The reaction was stirred for 10

minutes at 0°C and alcohol **75** (1.91 g, 7.8 mmol) was added to the reaction mixture. The reaction was stirred for another 30 minutes with the same temperature and volatiles were concentrated in vacuo. The residue was purified by flash chromatography with Pentane:Ether (10:1) to afford **187** (2.5 g, 7.01 mmol, 89.9 %).

General Data:	$C_{13}H_{29}IOSi$, M = 356.36 g/mol, colourless liquid;
	R_f = 0.69 (Pentane: Ether, 1:1);
	UV (+); Vanillin (-);
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 3.71 (m, H-1, 2H); 3.20 (m, H-4, 2H); 1.93 (m, H-2, 2H); 1.62 (m, H-3, 2H); 1.25,1.04 (m, OTIPS, 21H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 62.07 (C-1), 33.61 (C-2), 30.19 (C-3), 17.95 (OTIPS), 11.88 (OTIPS), 6.52 (C-4);
MS (EI)	356.1 (5%), 313.0 (14%), 241.0 (40%), 228.9 (100%), 212.9 (28%), 115.1 (18%), 75 (11%);
IR (Cap. Film)	2942 (m), 2866 (s), 2726 (m), 1463 (s), 1383 (s), 1367 (s), 1292 (s), 957 (s), 681 (s);
HRMS	$C_{13}H_{29}IO_2Si$
	Calcld: 356.100
	Found: 356.105

Triphenyl-(4-triisopropylsilanyloxy-butyl)-phosphonium iodide (188)

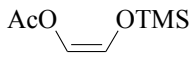


Iodide **187** (1 g, 2.8 mmol) and PPh_3 (810 mg, 11.7 mmol) was dissolved in CH_3CN (33.5

ml) and the reaction was stirred at room temperature for 24 h. Solvents were removed in vacuo and the residue was cleaned by flash chromatography with Pentane:Ether (100:1) to afford **188** (1.2 g, 1.94 mmol, 69%).

General Data:	$C_{31}H_{44}IOPSi$, M = 618.14 g/mol, white solid;
	R_f = 0.72 (Pentane: Ether, 1:1);
	UV (+); Vanillin (-);
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 7.41-7.28 (m, Ph, 15H); 3.85 (m, H-1, 2H);
	3.27 (m, H-4, 2H); 2.03 (m, H-2, 2H); 1.71 (m
	H-3, 2H); 1.37,1.16 (m, OTIPS, 21H);
^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 136.86-128.10 (Ph, 18C); 61.85 (C-1), 33.32
	(C-2), 29.89 (C-3), 17.75 (OTIPS), 11.61 (OTIPS)
	6.92 (C-4);
MS (EI)	618.2 (5%), 491.3 (14%), 241.0 (40%), 228.9
	(100%), 212.9 (28%), 115.1 (18%), 75 (11%);
IR (Cap. Film)	3834 (m), 3339 (s), 2891 (m), 2922 (s), 2863 (s),
	2220 (s), 1586 (s), 1462 (s), 1435 (s), 1110 (s),
	997 (s), 881 (s), 741 (s), 500 (s), 690 (s);
HRMS	$C_{31}H_{44}IOPSi$
	Exact Mass: 618.190
	Found: 618.205

(Z)-Acetic acid 2-trimethylsilanyloxy-vinyl ester (139)



To a room temperature solution of TMSCl (3.95 ml, 24.4 mmol), Et_3N (5.1 ml, 36.5 mmol), and CH_3CN (11 ml) was added aldehyde **146** (1.35 g, 6.1 mmol) dissolved in CH_3CN (1.5 ml). In less than 5 minutes, the solution becomes a hot white suspension that turned into a rust colored suspension with in 15 minutes. The reaction was stirred for 2 h and volatiles were removed in vacuum and the residue was extracted with Et_2O (3 x 50 ml). The volatiles were concentrated in vacuo to afford TMS-protected alkene **139** (0.69 g, 4.0 mmol, 66%, *E*:*Z*, 1:7.5).

General Data: $C_7H_{14}O_3Si$, M = 174.27 g/mol, colorless oil;

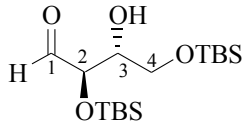
R_f = 0.67 (100% EtOAc)

UV (-); Vanillin: brown;

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 6.55 (d, 3.5 Hz, H-1, 1H); 5.59 (d, 3.3 Hz, H-2, 1H); 1.94 (s, $COCH_3$, 3H); 0.03 (s, OTMS, 9H);

^{13}C-NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 169.8 (**C**OCH_3), 127.3 (C-1), 120.4 (C-2), 20.9 (CO**C**H_3), -0.24 (OTMS);

(2*R*,3*R*)-2,4-Bis-(tert-butyl-dimethyl-silanyloxy)-3-hydroxy-butanal (143)

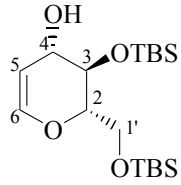


D-proline (38.2 mg, 0.33 mmol) was added to a room temperature mixture of aldehyde **142** (1.45 g, 8.33 mmol) dissolved in DMSO (13.3 ml). After 28 h, the solution was diluted with EtOAc (150 ml) and successively washed with water (100 ml), brine (100 ml), and dried over Na_2SO_4. The volatiles were concentrated in vacuo and the residue was purified by flash

chromatography with Pentane:THF (49:1) to afford yellowish oily liquid as diasteromers **143** (2.18 g, 6.3 mmol, 76%, syn:anti, 1:3.4).

General Data:	$C_{16}H_{36}O_4Si_2$, M = 348.63 g/mol, yellowish oil;
	R_f = 0.55 (100% EtOAc);
	UV(-); Vanillin: brown;
^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 9.64 (d, 1.65 Hz, H-1, 1H); 4.10 (m, H-2, 1H); 3.90 (m, H-3, 1H); 3.70 (m, H-4, 2H); 2.44 (s, OH, 1H); 0.92 (s, OTBS, 9H); 0.89 (s, OTBS, 9H), 0.08,0.06 (s, OTBS, 12H);
^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 201.85 (C-1), 78.31 (C-2), 72.91 (C-3), 62.30 (C-4), 25.81,25.70 (OSiC(**C**H_3)$_3$), 18.2 (OSi**C**(CH_3)$_3$), -4.58,-4.66 (OSi(**C**H_3)$_2$);
MS (EI)	349.1 (43%), 319.2 (95%), 301.1 (25%), 273.1 (35%), 231.1 (100%), 117.1 (100%), 73.0 (72);
IR (Cap. Film)	3437 (b), 2930 (s), 2886 (s), 2859 (s), 2251 1740 (s), 1701 (s), 1390 (s), 1255 (b), 837 (s) 779 (s), 671 (s);
HRMS	$C_{16}H_{36}O_4Si_2$
	Calcld: 348.220
	Found: 348.216

3-(tert-Butyl-dimethyl-silanyloxy)-2-(tert-butyl-dimethylsilanyloxymethyl) -3,4-dihydro-2H-pyran-4-ol (149)

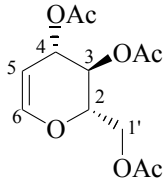


The aldol **143** (100 mg, 0.23 mmol) was added as a solution in Et_2O (2.3 ml) to a mixture of $MgBr_2 \cdot Et_2O$ (129 mg, 0.65 mmol) in Et_2O (2.3 ml) which was cooled to –20 °C. After 30 minutes at -20 °C, **139** (85 µl, 0.92 mmol) was added[25]. The suspension was stirred at -20 °C for 2 h, and then allowed to warm to +4 °C over the course of 4 h. After stirring for an additional 24 h at +4 °C, the reaction was acidified by the addition of 100 ml saturated aqueous NH_4Cl and extracted with EtOAc (2 x 50 ml). The organic layer was washed with brine (100 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was poured to a solution of THF:TFA:H_2O (5 ml, (7:2:1)) at 0 °C and stirred for 30 minutes before being basified with 10% $NaHCO_3$ (50 ml), extracted with EtOAc (100 ml), dried over Na_2SO_4. The volatiles were concentrated in vacuo to afford suspension **148** (85 mg, 0.17 mmol). Compound **148** was dissolved in Ac_2O (1.80 mg, 0.07 mmol) and HBr (100 mg, 33% solution in AcOH) was added in small portion. After 1 h the solution was treated with HBr (740 mg, 33% solution in AcOH). After 24 h stirring the reaction mixture was treated with NaOAc (300 mg) and the resulting solution was immediately added in portions to an aqueous suspension of $CuSO_4 \cdot 5H_2O$ (13 mg), Zinc (1.02 g) in H_2O (5 ml) and AcOH (7.5 ml) containing $NaOAc \cdot 3H_2O$ (1.25 g). The mixture was vigorously stirred at room temperature for 2 h and inorganic solid was filtered off and successively washed with EtOAc (3.5 ml) and H_2O (5 ml). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 ml), brine (2.5 ml) and dried over Na_2SO_4. The solvents were evaporated in vacuo to afford **149** (43 mg, 0.11 mmol, 60%).

General Data	$C_{18}H_{38}O_4Si_2$ M = 374.66 g/mol, colorless syrup;
	R_f = 0.65 (100 % EtOAc);
	UV(-); Vanillin: dark brown;
^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 6.27 (d, 7.4 Hz, H-6, 1H), 4.62 (d, 8.5 Hz,

	H-5, 1H), 4.22-3.75 (m, H-2, H-3, H-4, H-1', 5H), 2.64 (s, OH, 1H), 0.90,0.86 (s, $OSiC(CH_3)_3$ 18H); 0.11,0.08 (s, $OSi(CH_3)_2$, 12H);
^{13}C NMR (100MHz, $CDCl_3$, δ ppm)	δ = 143.29 (C-6), 103.43 (C-5), 77.96 (C-2), 70.93 (C-3), 69.86 (C-4), 63.11 (C-1'), 25.92, 25.82 ($OSiC(\mathbf{C}H_3)_3$); 18.39, 18.12 ($OSi\mathbf{C}(CH_3)_3$) -3.60 ($OSi(\mathbf{C}H_3)_2$); -4.47 ($OSi\mathbf{C}H_3$); -4.50 ($OSi\mathbf{C}H_3$);
IR (Cap. Film)	3468 (b), 3070 (s), 2986 (s), 2930 (s), 2858 (s) 1651 (s), 1463 (s), 1390 (s), 1257 (s), 837 (s) 779 (s), 669 (s);

(2*S*,3*R*,4*S*) Acetic acid 3,4-diacetoxy-3,4-dihydro-2H-pyran-2-yl-methyl ester (150)

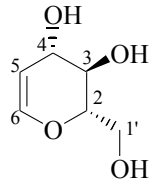


To a magnetically stirred suspension of L-glucose **98** (1.0 g, 5.37 mmol) in Ac_2O (3.61 g, 0.7 mmol), was added HBr (1.0 g, 33% solution in AcOH) in small portion while maintaining the reaction to room temperature with the help of water bath[21]. After 1 h the clear solution was treated with the remaining HBr (7.4 g, 33% solution in AcOH) and the resulting solution was stirred overnight at room temperature. Anhydrous NaOAc (3.0 g) was added to neutralize the excess HBr and the resulting solution was immediately added in portions to an aqueous suspension of $CuSO_4 \cdot 5H_2O$ (260 mg) and zinc (10.2 g) in water (100 ml) and acetic acid (150 ml) containing $NaOAc \cdot 3H_2O$ (12.5 g). The mixture was vigorously stirred at room temperature for 2 h. The inorganic solid was filtered off and washed with EtOAc (70 ml) and water (100 ml). The organic layer was washed with saturated $NaHCO_3$

(100 ml) and brine (50 ml) and dried over Na_2SO_4. The solvents were evaporated in vacuo to afford tri-O-acetyl L-glucal **150** (1.4 g, 5.15 mmol, 96%).

General Data	$C_{12}H_{16}O_7$, M = 272.25 g/mol, colorless syrup;
	R_f = 0.54 (CH_2Cl_2/EtOAc, 1:1);
	UV(-); Vanillin: brown;
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)	δ = 6.38 (d, 8.3 Hz, H-6, 1H), 5.25-5.10 (m, H-5, H-4, 2H), 4.3 (m, H-3, 1H), 4.75 (m, H-2, 1H), 4.20-4.00 (m, H-1', 2H), 2.00 (s, $COCH_3$, 9H);
^{13}C NMR (100MHz, $CDCl_3$, δ ppm)	δ = 170.31 (**C**OCH_3), 170.14 (**C**OCH_3), 169.32 (**C**OCH_3), 145.40 (C-6), 98.75 (C-5), 73.68 (C-3), 67.19 (C-2), 66.91 (C-4), 61.10 (C-1'), 20.70,20.51,20.08 (CO**C**H_3);
MS (EI)	272.1 (5%), 202.1 (5%), 152.1 (25%), 139.1 (70%), 110 (64%), 97 (100%);
IR (Cap. Film)	3456 (b), 2960 (s), 1748 (m), 1649 (s), 1372 (s), 1228 (s), 1045 (s);
HRMS	$C_{12}H_{16}O_7$
	Calcld: 272.090
	Found: 272.089

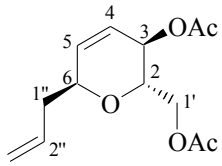
(2*S*,3*R*,4*S*)-2-Hydroxymethyl-3,4-dihydro-2*H*-pyran-3,4-diol (99)



A mixture of the solvents $CH_3OH/H_2O/Et_3N$ (10 ml, 4:5:1) was added to tri-O-acetyl L-glucal **150** (0.7 g, 2.75 mmol). The reaction was stirred for 4 h and solvents were evaporated in vacuo to afford L-glucal **99** as syrup (0.37 g, 2.53 mmol, 91%).

General Data:	$C_6H_{10}O_4$, M = 146.14g/mol, colourless syrup;
	R_f = 0.22 (CH_2Cl_2/ EtOAc, 1:1);
	Vanillin: brown; UV(-);
^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 6.33 (d, 6.0 Hz, H-6, 1H); 4.75 (m, H-5, 1H); 4.30 (m, H-2, 1H); 3.98-3.77 (m, H-3, H-4, H-1', 4H), 2.0 (s, OH, 3H);
^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 143.99 (C-6), 103.16 (C-5), 78.06 (C-3), 70.41 (C-2), 69.84 (C-4), 61.64 (C-1');
MS (EI)	146.2 (5%), 101.2 (40%), 86.2 (100%), 73.1 (12%), 58.1 (48%);
HRMS	$C_6H_{10}O_4$ Calcld: 146.061 Found: 146.050

(*2S,3R,6S*)-3-Acetoxy-2-acethoxymethyl-6-allyl-3,6-dihydro-2*H*-pyran (154)



To a solution of tri-O-acetyl L-glucal **150** (2.72 g, 10 mmol) in dry CH_3CN (40 ml) was added ATMS (1.91 ml, 12 mmol) at 0 °C followed by TMSOTf (1.93 ml, 10 mmol). After stirring it for 30 minutes, the reaction was quenched with saturated aqueous $NaHCO_3$ and the phases were separated. The organic phase was washed with brine and the aqueous layer was extracted with EtOAc (4 x 50 ml). The combined organic layer was dried over $MgSO_4$ and volatiles were concentrated in vacuo to afford clear brownish syrup **154** (2.30 g, 9.06 mmol, 91%). It was used for the next step directly.

General Data: $C_{13}H_{18}O_5$, M = 254.28 g/mol; brownish syrup; R_f = 0.58 (Pentane: Ether, 1:1); Vanillin: blue; $[\alpha]^{20}$ = -61.3° (c = 1.8 $CHCl_3$); UV (-);

^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 5.93 (ddd, 10.3 Hz, 2.4 Hz, 1.6 Hz, H-4 1H); 5.84 (dddd, 17.3 Hz, 7.0 Hz, 7.0 Hz, 3.0 Hz, H-2", 1H); 5.80 (ddd, 10.3 Hz, 2.7 Hz, 1.9 Hz, H-5, 1H); 5.14-5.11 (m, H-3", 2H), 4.28- 4.20 (dddd, 7.8 Hz, 7.8 Hz, 4.1 Hz, 1.6 Hz, H-1', 2H); 4.15 (dd, 11.9 Hz, 3.5 Hz, H-3, 1H); 3.96 (dd, 6.5 Hz, 5.0 Hz, H-6, 1H); 3.47 (ddt, 14.6 Hz, 7.8 Hz, 6.8 Hz, H-2, 1H); 2.32 (ddt, 14.3 Hz, 7.0 Hz, 5.9 Hz, 1.1 Hz, H-1", 2H), 2.09 (s, $COCH_3$, 6H);

^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 170.82 (**C**OCH_3), 170.42 (**C**OCH_3),

133.98 (C-2''), 132.82 (C-4), 123.71 (C-5), 117.59 (C-3''), 71.35 (C-3), 69.78 (C-2), (C-6), 62.87 (C-1'), 37.87 (C-1''), 21.06 (**C**$COCH_3$), 20.08 (**C**$COCH_3$);

MS (EI) 253.1 (5%), 213.1 (68%), 153.0 (24%), 111.0 (100%), 94 (12%), 63 (20%);

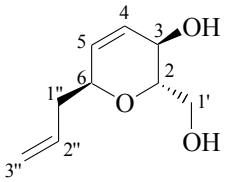
IR (Cap. film) 3460 (b), 2937 (s), 1732 (s), 1644 (s), 1435 (s), 1231 (m), 1048 (m), 1031 (m), 915 (s);

HRMS $C_{13}H_{18}O_5$

Calcld: 254.120

Found: 254.116

(2*S*,3*R*,6*S*)-6-Allyl-2-hydroxymethyl-3,6-dihydro-2*H*-pyran-3-ol (100)



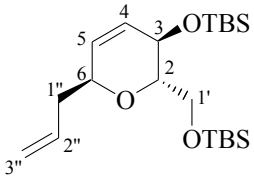
To a solution of the diacetate **154** (3.0 g, 11.8 mmol) in CH_3OH (40 ml) was added K_2CO_3 (6.9 g, 50 mmol) at room temperature. After stirring it for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and CH_3OH was removed in vacuo. The aqueous layer was extracted with EtOAc (7 x 25 ml). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give the diol **100** (1.9 g, 11.1 mmol, 95%). It was used for the next step directly.

General Data: $C_9H_{14}O_3$, M = 170.21, yellowish oil;

R_f = 0.30 (Pe/EtOAc, 1:1); Vanillin: dark blue

	$[\alpha]^{20} = +23.8°$ (c = 0.94 $CHCl_3$); UV(-);
^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 5.85-5.79 (m, H-2", H-4, H-5, 3H); 5.14-5.10 (m, H-3", 2H); 4.25-4.23 (m, H-3, 1H); 4.10 (d, 7.6 Hz, H-6, 1H); 3.83 (dd, 10.9 Hz, 4.2 Hz, H-1', 1H); 3.78 (dd, 11.5 Hz, 4.2 Hz, H-1', 1H); 3.55 (ddt, 7.9 Hz, 5.9 Hz, 4.3 Hz, H-2, 1H); 2.50 (br, OH, 2H); 2.33 (ddt, 13.8 Hz, 6.8 Hz, 6.0 Hz, H-1", 1H); 2.30 (ddt, 13.8 Hz, 6.8 Hz, H-1", 1H);
^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 134.45 (C-2"), 130.58 (C-4), 128.61 (C-5) 117.60 (C-3"), 73.27 (C-2), 72.05 (C-6), 64.06 (C-3), 62.91 (C-1'), 37.83 (C-1");
MS (EI)	170.2 (15%), 169,2 (100%), 129.1 (100%), 111.1 (38%), 85.0 (64%), 55.0 (28%);
IR (Cap. Film)	3438 (b), 2930 (s), 1732(s), 1644 (s), 1384(s) 1257 (s), 918 (s), 729 (s), 578 (s);
HRMS	$C_9H_{14}O_3$ Calcd: 170.090 Found: 170.092

(2S,3R,6S)-6-Allyl-3-(*tert*-butyldimethylsilanyloxy)-2-(*tert*-butyldimethyl-silanyloxymethyl)-3,6-dihydro-2H-pyran (76)



The diol **100** (800 mg, 4.7 mmol) was dissolved in pyridine (10 ml, 12.6 mmol). The reaction was cooled to 0 °C and TBSCl (1.74 g, 11.5 mmol) was added to the reaction slowly[21]. The reaction was allowed to warm up to room temperature and stirred for another 12 h. It was quenched with 5% aqueous $NaHCO_3$ (11.2 ml) and was extracted with Et_2O (3 x 50 ml). The combined organic phase was dried over $MgSO_4$ and volatiles were removed in vacuo. The residue was purified by flash chromatography with Pentane:Ether (100:1) to afford TBS- protected alkene **76** (1.85 g, 4.64 mmol, 99%).

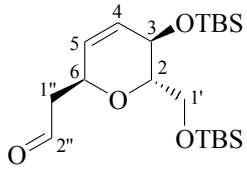
General Data: $C_{21}H_{42}O_3Si_2$, M = 398.73 g/mol, colorless oil; R_f = 0.85 (100% EtOAc); Vanillin: dark blue; $[\alpha]^{20}$ = - 28.9° (c = 0.98 $CHCl_3$); UV(-);

^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 5.81 (dd, 17.0 Hz, 7.1 Hz, H-2", 1H); 5.64 (m, H-4, H-5, 2H) 5.05-4.98 (m, H-3", 2H); 4.12 (m, H-3, 1H); 4.00-3.99 (m, H-6, 1H); 1H); 3.79,3.63 (d, 11.0 Hz, H-1', 2H); 3.38 (ddt, 2.5 Hz, 6.0 Hz, 8.1 Hz, H-2, 1H); 2.47, 2.27 (m, H-1", 2H); 0.84 (s, OTBS, 18H); 0.03 (s, OTBS, 6H); 0.02 (s, OTBS, 6H);

^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 134.01 (C-2"), 129.69 (C-4), 128.67 (C-5), 115.90 (C-3"), 73.41 (C-2), 71.37 (C-6), 63.02 (C-3), 62.18 (C-1'), 37.78 (C-1"), 24.86

	(OSiC(**C**H_3)$_3$), 24.79 (OSiC(**C**H_3)$_3$), 17.31 (OSi**C**(CH$_3$)$_3$), 17.08 (OSi**C**(CH$_3$)$_3$), -5.26 (OSi**C**H$_3$), -5.77 (OSi**C**H$_3$), -6.12 (OSi**C**H$_3$); -6.30 (OSi**C**H$_3$);
MS (EI)	398.1 (15%), 383.2 (20%), 357.2 (9%), 341.1 (44%), 117.0 (100%), 73.1 (95%), 59 (20%);
IR (Cap. Film)	3864 (s), 3468 (s), 2956 (s), 2930 (s), 2886 (b), 2858 (s), 1473 (s), 1463 (s), 1255 (s), 1093 (s), 1020 (s), 878 (s), 837 (s), 777 (s);
HRMS	$C_{21}H_{42}O_3Si_2$, Calcd: 398.270 Found: 398.267

(2S,3R,6S)-5-(tert-Butyldimethylsilanyloxy)-6-(tert-butyldimethyl-silanyloxymethyl)-5,6-dihydro-2H-pyran-2''-yl-acetaldehyde (156)



To a stirred solution of alkene **76** (220 mg, 0.58 mmol) in 50% THF/H_2O (10 ml) solution was added NMO (81.6 mg, 0.70 mmol) and OsO_4 (0.25 ml, 2.5% in t-BuOH) at 0 °C and the reaction was stirred vigorously at room temperature for 5 h. The reaction was quenched with 1M $Na_2S_2O_3$, extracted with EtOAc (3 x 50 ml) and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purified by flash chromatography with Hexane:EtOAc (4:1 to 1:2) to give the intermediate diol **155** (173 mg). To a solution of the intermediate diol **155** (173 mg, 0.40 mmol) in THF (10 ml) was added a suspension of $NaIO_4$ (288 mg, 1.62 mmol) in H_20 (2 ml) at 0 °C. The mixture was stirred for 3.5 h, extracted with EtOAc (4 x 25

ml) and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purified by flash chromatography with Pentane:EtOAc (4:1) to afford aldehyde **156** (140 mg, 0.35 mmol, 61%).

General Data:	$C_{20}H_{40}O_4Si_2$, M = 400.70 g/mol, yellowish oil; R_f = 0.63 (100% EtOAc); Vanillin:dark blue; $[\alpha]^{20}$ = -43.7° (c = 0.85 $CHCl_3$); UV (-);
^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 9.80 (dd, 2.3 Hz, 2.1 Hz, H-2", 1H); 5.77 (dd, 8.5 Hz, 1.8 Hz, H-4, 1H); 5.69 (dd, 8.5Hz 1.6 Hz, H-5, 1H); 4.73 (m, H-6, 1H); 4.10 (m H-3, 1H); 3.81 (dd, 11.1 Hz, 2.7 Hz, H-1',1H); 3.69 (ddt, 2.7 Hz, 5.6 Hz, 11.1 Hz, H-1', 1H); 3.41 (m, H-2, 1H); 2.56-2.52 (m, H-1", 2H); 0.89,0.88 (s, $OSiC(CH_3)_3$, 18H); 0.08,0.03 (s, $OSi(CH_3)_2$, 12H);
^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 200.75 (C-2"), 130.71 (C-5), 128.52 (C-4), 74.64 (C-2), 68.01 (C-6), 63.43 (C -3), 62.71 (C-1'), 46.75 (C-1"), 25.90 ($OSiC(\mathbf{C}H_3)_3$), 25.74 ($OSiC(\mathbf{C}H_3)_3$), 18.37 ($OSi\mathbf{C}(CH_3)_3$); 18.00 ($OSi\mathbf{C}(CH_3)_3$), -4.32 ($OSi\mathbf{C}H_3$), -4.82 ($OSi\mathbf{C}H_3$), -5.01 ($OSi\mathbf{C}H_3$), -5.34 ($OSi\mathbf{C}H_3$);
MS (EI)	401.2 (2%), 369.2 (26%), 355.2 (100%), 345.1 (26%), 315.2 (31%), 272.1 (20%), 180.1 (24%), 169.1 (11%), 75.0 (48%), 61 (100%);

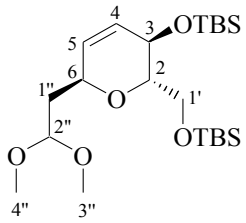
IR (Cap. Film) 3432 (br), 3039 (s), 2930 (s), 2858 (m), 2179 (s), 1726 (s), 1544 (s), 1463 (s), 1375 (s), 1361 (s), 1254 (s), 1087 (s), 939 (s), 881 (s), 838 (s), 778 (s), 724 (s), 670 (s);

HRMS $C_{20}H_{40}O_4Si_2$

Calcd: 400.246

Found: 400.247

(2S,3R,6S)-3-(*tert*-Butyldimethylsilanyloxy)-2-(*tert*-butyldimethyl-silanyloxymethyl)-6-(2'',2''-dimethoxyethyl)-3,6-dihydro-2H-pyran (157)



To a solution of the aldehyde **156** (90 mg, 0.23 mmol) in abs. CH_2Cl_2 (2 ml) was added PPTS (1.0 mg) and $CH(OCH_3)_3$ (167 mg). The reaction was stirred for 2 h at room temperature and volatiles were removed in vacuo. The residue was purified by flash chromatography with Pentane:EtOAc (20:1) to afford **206** (67 mg, 0.15 mmol, 63%).

General Data: $C_{22}H_{46}O_5Si_2$, M = 446.78 g/mol, yellowish oil;

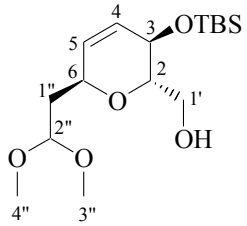
R_f = 0.69 (100% EtOAc); Vanillin: blue; UV (-);

$[\alpha]^{20}$ = - 43.4 (c = 1.16 $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) δ = 5.70-5.68 (m, H-4, H-5, 2H); 4.56 (m, H-2'', 1H); 4.35 (d, 10.5 Hz, H-3, 1H); 4.12 (m, H-6, 1H)); 3.81-3.65 (m, H-1', 2H); 3.36 (s, H-3'', 3H); 3.33 (s, H-4'', 3H); 2.04 (m, H-1'', 2H); 0.89 (s,

	$OSiC(CH_3)_3$, 18H); 0.10,0.09 (s, $OSi(CH_3)_2$, 12H);
^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 130.15 (C-5), 129.45 (C-4), 102.52 (C-2''), 72.77 (C-2), 69.89 (C-3), 64.20 (C-1'), 62.56 (C-6), 53.53 (C-3''), 52.80 (C-4''), 35.58 (C-1''), 25.94 ($OSiC(\mathbf{C}H_3)_3$), 25.74 ($OSiC(\mathbf{C}H_3)_3$), 18.39 ($OSi\mathbf{C}(CH_3)_3$), 18.02 ($OSi\mathbf{C}(CH_3)_3$), -4.82 ($OSi\mathbf{C}H_3$), -4.90 ($OSi\mathbf{C}H_3$), -5.33 ($OSi(CH_3)_2$);
MS (EI)	446.3 (16%), 431.2 (28%), 389.2 (6%), 357.2 (100%), 184.9 (17%), 88.9 (15%), 74.9 (100%);
IR (Cap. Film)	2959 (s), 2937 (s), 2886 (s), 2852 (s), 1474 (s), 1464 (s), 1119 (s), 1089 (s), 883 (m), 775 (s);
HRMS	$C_{22}H_{46}O_5Si_2$ Calcd: 446.288 Found: 446.290

(2S,3R,6S)-3-(*tert*-Butyldimethylsilanyloxy)-6-(2'',2''-dimethoxy-ethyl)-3,6-dihydro-2H-pyranyl)-methanol (101)



To a solution of aldehyde **156** (200 mg, 0.5 mmol) in CH_3OH (6.7 ml) was added I_2 (0.2 mmol, 15 mg) and was stirred for 5 h. The reaction was diluted with Et_2O (10 ml) and

successively washed with 5% $Na_2S_2O_3$ (5 ml), saturated aqueous $NaHCO_3$ (5 ml) and dried over Na_2SO_4. The volatiles were evaporated in vacuo and purified by flash chromatography with Pentane:EtOAc (5:1) to afford the alcohol **101** (119 mg, 0.35 mmol, 70%).

General Data:	$C_{16}H_{32}O_5Si$, M = 332.51 g/mol; yellowish oil; R_f = 0.57 (100% EtOAc); Vanillin: dark blue; $[\alpha]^{20}$ = -57.7 (c = 1.05 $CHCl_3$); UV(-);
^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm})	δ = 5.72-5.67 (m, H-4, H-5, 2H); 4.56 (dd, 3.7 Hz, 7.1 Hz, H-2", 1H); 4.35 (m, H-3, 1H); 4.12 (m, H-6, 1H); 3.80 (dd, 11.3 Hz, 2.7 Hz, H-1', 1H); 3.63 (dd, 11.4 Hz, 5.7 Hz, H-1', 1H); 3.42 (m, H-2, 1H); 3.35 (s, H-3", 3H); 3.31 (s, H-4", 3H); 2.03-1.73 (m, H-1", 2H); 0.88 (s, $OSiC(CH_3)_3$, 9H); 0.09,0.08 (s, $OSi(CH_3)_2$, 6H);
^{13}C NMR(100MHz, $CDCl_3$, δ_{ppm})	δ = 130.14 (C-5), 129.44 (C-4), 102.50 (C-2"), 72.77 (C-2), 69.86 (C-6), 64.18 (C-3), 62.53 (C-1'), 53.50 (C-3"), 52.78 (C-4"), 35.57 (C-1") 25.72 ($OSiC(\mathbf{C}H_3)_3$), 17.96 ($OSi\mathbf{C}(CH_3)_3$), -4.32 ($OSi\mathbf{C}H_3$), - 4.88 ($OSi\mathbf{C}H_3$);
MS (EI)	332.2 (5%), 317.2 (25%), 315.2 (35%), 301.2 (15%), 281.1 (100%), 243.2 (15%), 117.1 (12%), 89.1 (6%), 75.1 (100%);
IR (Cap. Film)	3470 (b), 2956 (s), 2930 (s), 2858 (s), 1739(s)

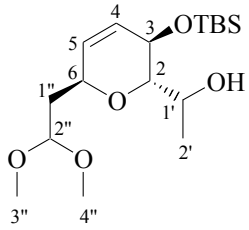
1472 (s), 1464 (s), 1388 (s), 1258 (s), 1086 (s), 1011 (s), 882 (s), 838 (s);

HRMS $C_{16}H_{32}O_5Si$

Calcd: 332.201

Found: 332.202

(2S,3R,6S,1'S)-1'-[3-*tert*-Butyldimethylsilanyloxy-6-(2'',2''dimethoxy-ethyl)-3,6-dihydro-2*H*-pyranyl]-ethanol (160)



A solution of oxalyl chloride (60 mg, 0.47 mmol) in THF (0.15 ml) was cooled to -78 °C and DMSO (58.5 mg, 0.75 mmol) was added dropwise. After 1 h alcohol **101** (60 mg, 0.18 mmol) was added to the mixture and the reaction was warmed to -30 °C and stirred for 2 h. The reaction was quenched with Et_3N (90 mg, 0.92 mmol) warmed to 0 °C and CH_3MgBr (0.1 ml, 3.0 M in THF) was added. After stirring for 24 h the reaction was quenched with freshly prepared saturated aqueous NH_4Cl (1.25 ml) and stirred for 1 h. The mixture was extracted with Et_2O (3 x 25 ml), the combined organic phase was dried over Na_2SO_4 and volatiles were concentrated in vacuo. The residue was purified by flash chromatography with Pentane:Ether (4:1) to afford **160** as yellowish oil (44.5 mg, 0.13 mmol, 73%).

General Data: $C_{17}H_{34}O_5Si$, M = 346.53 g/mol, yellowish oil;

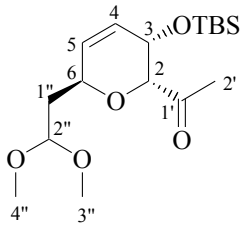
R_f = 0.59 (100% EtOAc); Vanillin: dark blue;

$[\alpha]^{20}$ = -63.4 (c = 1.60 $CHCl_3$), UV(-);

^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 5.74 (m, H-4, 1H); 5.66 (m, H-5, 1H); 4.57 (dd, 8.1 Hz, 3.2 Hz, H-2'', 1H); 4.36 (m, H-3,

	1H); 4.29 (dd, 3.9 Hz, 1.9 Hz, H-6, 1H); 3.99 (m, H-1', 1H); 3.38 (s, H-4", 3H); 3.32 (s, H-3", 3H); 3.13 (dd, 8.1 Hz,1.8 Hz, H-2, 1H); 2.04 (s OH, 1H); 1.93,1.75 (ddt, 14.3 Hz, 3.6 Hz, 8.1 Hz, H-1", 2H); 1.29 (d, 6.7 Hz, H-2', 3H); 0.90 (s, $OSiC(CH_3)_3$, 9H); 0.12 (s, $OSi(CH_3)_2$, 6H);
^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 130.45 (C-5), 129.16 (C-4), 102.39 (C-2"), 75.06 (C-2), 69.89 (C-6), 65.24 (C-1'), 64.01 (C-3), 53.87 (C-3"), 52.69 (C-4"), 35.83 (C-1"), 25.79 ($OSiC(\mathbf{C}H_3)_3$), 20.55 (C-2'), 18.01 ($OSi\mathbf{C}(CH_3)_3$); -4.26 ($OSi\mathbf{C}H_3$); - 4.78 ($OSi\mathbf{C}H_3$);
MS (EI)	346.1 (5%), 257.2 (25%), 213.2 (35%), 199.2 (15%), 185.1 (65%), 159.9 (15%), 117.1 (12%) 89.1 (6%), 75.1 (100%);
IR (Cap. Film)	3470 (b), 2956 (s), 2930 (s), 2896 (s), 2858(s) 1388 (s), 1191 (s), 1087 (s), 882 (s), 777 (s);
HRMS	$C_{17}H_{34}O_5Si$, Calcd: 346.222 Found: 346.228

(2S,3S,6S)-1'-[3-*tert*-Butyldimethylsilanyloxy-6-(2'',2''-dimethoxyethyl)-3,6-dihydro-2*H*-pyranyl]-ethanone (D)



To compound **102** (23 mg, 0.1 mmol) in THF (5 ml), was added 4-nitrobenzoic acid (36.4 mg, 0.2 mmol) and PPh_3 (50.4 mg, 0.2 mmol). After 30 minutes DIAD (44 mg, 0.22 mmol) was added dropwise at a rate such that the temperature of the reaction mixture was maintained below 10 °C. The solution was stirred at room temperature overnight and subsequently at 40 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with Et_2O (15 ml), and washed with saturated aqueous $NaHCO_3$ (10 ml). The aqueous layer was extracted with Et_2O (100 ml) and combined organic layer was dried over Na_2SO_4 and volatiles were removed with vacuo. The residue was dissolved in CH_3OH (3 ml) and K_2CO_3 (30 mg, 0.22 mmol) was added at room temperature. After stirring it for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and CH_3OH was removed in vacuo. The aqueous layer was extracted with EtOAc (7 x 25 ml) and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give alcohol **162** (15 mg, 0.065 mmol, 65%). Compound **162** was dissolved in pyridine (2.5 ml) and was treated with TBSCl (32.6 mg, 3 mmol) and stirred further for 12 h. The reaction was quenched with 5% aqueous $NaHCO_3$ (11.2 ml) and was extracted with Et_2O (3 x 50 ml). The organic phase was dried over $MgSO_4$ and volatiles were removed in vacuo. The residue was purified by flash chromatography with Pentane:Ether (10:1) to afford **D** (19 mg, 0.055 mmol, 85%).

General Data: $C_{17}H_{32}O_5Si$, M = 344.52 g/mol, yellowish oil;

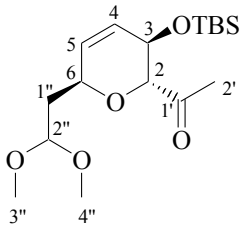
R_f = 0.62 (100% EtOAc); Vanillin: blue;

^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 5.81-5.78 (m, H-4, H-5, 2H); 4.57 (dd, 7.8 Hz, 3.6 Hz, H-2", 1H); 4.37-4.33 (dd, 3.9 Hz, 1.8 Hz, H-2, H-6, 2H); 3.95 (m, H-3, 1H); 3.36 (s, H-4", 3H); 3.34 (s, H-3", 3H); 2.27 (s,

H-2', 3H); 1.93,1.76 (ddt, 3.6 Hz, 8.2 Hz, 8.1 Hz, H-1", 2H); 0.86 (s, $OSiC(CH_3)_3$, 9H); 0.05 0.03 (s, $OSi(CH_3)_2$, 6H);

^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm}) δ = 206.50 (C-1'), 129.74 (C-5), 127.71 (C-4), 102.10 (C-2"), 78.91 (C-2), 69.58 (C-6), 64.18 (C-3), 53.78 (C-3"), 52.72 (C-4"), 36.56 (C-1") 27.72 (C-2'), 25.78 ($OSiC(\mathbf{C}H_3)_3$), 18.03 ($OSi\mathbf{C}(CH_3)_3$), - 4.44 ($OSi\mathbf{C}H_3$), -4.78 ($OSi\mathbf{C}H_3$);

(2S,3R,6S)-1'-[3-*tert*-Butyldimethylsilanyloxy-6-(2'',2''-dimethoxyethyl)-3,6-dihydro-2*H*-pyranyl]-ethanone (102)



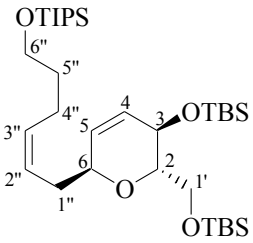
To a solution of the alcohol **160** (102 mg, 0.3 mmol) in CH_2Cl_2 (2 ml), DMP (140 mg, 0.33 mmol, 15% in CH_2Cl_2) was added and the reaction mixture was stirred for 4 h at room temperature. The volatiles were removed in vacuo and the crude product was purified by flash chromatography directly with Pentane:Et_2O (1:1) to afford the Ketone **102** (96.2 mg, 0.28 mmol, 94%).

General Data: $C_{17}H_{32}O_5Si$, M = 344.52 g/mol, yellowish oil; R_f = 0.63 (100% EtOAc); Vanillin: dark blue; $[\alpha]^{20}$ = -51.4 (c = 1.60 $CHCl_3$); UV(-);

^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 5.76-5.68 (m, H-4, H-5, 2H); 4.59 (dd, 7.8

	Hz, 3.7 Hz, H-2", 1H); 4.36-4.34 (dd, 4.1 Hz, 2.0 Hz, H-2, H-6, 2H); 3.95 (m, H-3, 1H); 3.37 (s, H-4", 3H); 3.32 (s, H-3", 3H); 2.26 (s, H-2', 3H); 1.95,1.78 (ddt, 3.6 Hz, 8.1 Hz, 8.1 Hz, H-1", 2H); 0.89 (s, $OSiC(CH_3)_3$, 9H); 0.08 0.05 (s, $OSi(CH_3)_2$, 6H);
^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 206.49 (C-1'), 129.73 (C-5), 128.72 (C-4) 102.09 (C-2"), 78.90 (C-3), 69.57 (C-6), 64.16 (C-2), 53.77 (C-4"), 52.71 (C-3"), 36.54 (C-1") 27.71 (C-2'), 25.77 ($OSiC(\mathbf{C}H_3)_3$), 18.02 ($OSi\mathbf{C}(CH_3)_3$), - 4.45 ($OSi\mathbf{C}H_3$), -4.80 ($OSi\mathbf{C}H_3$);
MS (EI)	343.9 (2%), 288.3 (5%), 257.1 (25%), 255.2 (34%), 230.9 (5%), 197.1 (80%), 155.2 (40%) 89.1 (20%), 75 (100%);
IR (Cap. Film)	2957 (s), 2930 (s), 2858 (s), 1739 (s),1472 (s), 1464 (s), 1362 (s), 1258 (s), 1191 (s), 778 (s);
HRMS	$C_{17}H_{32}O_5Si$ Calcld: 344.200 Found: 344.202

3-(tert-Butyl-dimethyl-silanyloxy)-2-(tert-butyl-dimethylsilanyloxy-methyl)-6-(6-triisopropylsilanyloxy-hex-2''-enyl)-3,6-dihydro-2H-pyran (190)



To a stirred solution of fragment **F** (21 mg, 0.05 mmol, 1.17equiv.) in THF (5 ml), cooled to -78 °C was added LDA (0.02 ml, 2M in THF) dropwise. The reaction was stirred at the same temperature for 10 minutes, the bright yellow mixture was treated with aldehyde **156** (20 mg, 0.12 mmol) dissolved in THF (1.0 ml) and stirred for 3 h during this time the reaction is slowly warmed to room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with Et_2O (3 x 25 ml). The combined organic phase was dried over $MgSO_4$ and volatiles were removed in vacuo. The residue was purified with flash chromatography by using Pentane:Ether (10:1) to afford **190** (16.8 mg, 0.03 mmol, 57%).

General Data: $C_{31}H_{64}O_4Si_3$, M = 585.09 g/mol, white solid;
R_f = 0.91 (100% EtOAc); Vanillin: brown;
$[\alpha]^{20}$ = +81.7 (c = 1.0 $CHCl_3$); UV(-);

^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm}) δ = 5.74-5.71 (m, H-4, H-5, 2H), 5.52-5.51 (m, H-2", H-3", 2H); 4.08 (m, H-3, 1H); 3.83-3.73 (m, H-4", H-1', 4H); 3.66 (m, H-6, 1H); 3.49 (ddt, 2.5 Hz, 6.0 Hz, 8.1 Hz, 1H, H-2); 2.17-1.96 (m, H-1", H-5", 4H); 1.59 (m, H-1", H-4", 2H); 1.39,1.16 (m, OTIPS, 21H); 0.89 (s, OTBS, 18H), 0.09,0.06 (s, OTBS, 12H);

^{13}C NMR (100MHz, $CDCl_3$, δ_{ppm})	δ = 132.58 (C-3''), 129.94 (C-5), 129.46 (C-4), 126.36 (C-2''), 74.42 (C-2), 72.88 (C-6), 64.11 63.23 (C-6''), 62.89 (C-1'), 36.64 (C-4''), 29.70 29.70 (C-1''), 25.97 (OSiC(**C**H_3)$_3$), 25.75 (OSiC(**C**H_3)$_3$), 18.44 (OSi**C**(CH_3)$_3$), 18.02 (OTIPS), 11.98 (OTIPS), -4.25 (OSi(**C**H_3)$_2$), -4.75 (OSi(**C**H_3)$_2$);
MS (EI)	555.8 (12%), 554.8 (25%), 436.8 (8%), 356.9 (100%), 224.9 (15%), 157.0 (32%), 116.2 (98%) 81.0 (52%), 73.0 (100%);
IR (Cap. Film)	3434 (b), 3036 (s), 2929 (s), 2859 (s), 2738 (s), 2032 (s), 1734 (s), 1689 (s), 1626 (s), 1530 (s), 1463 (s), 1361 (s), 1254 (s), 1095 (s), 882 (s), 837 (s), 777 (s), 680 (s);
HRMS	$C_{30}H_{61}O_4Si_3$ Calcld (M+ -$CH(CH_3)_2$): 569.390 Found: 569.388

8 References

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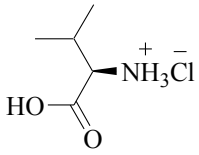
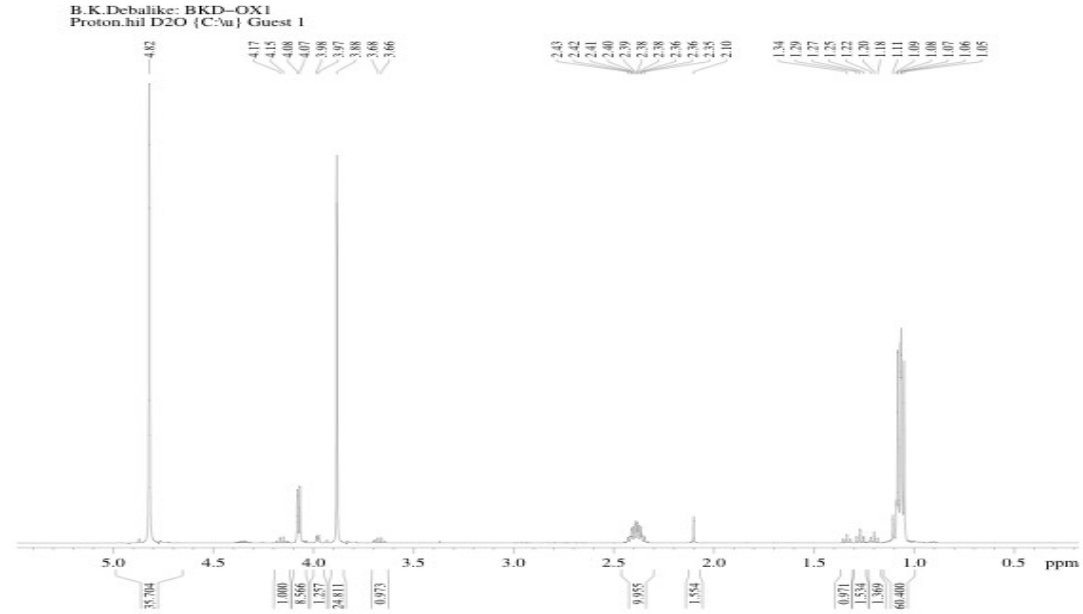
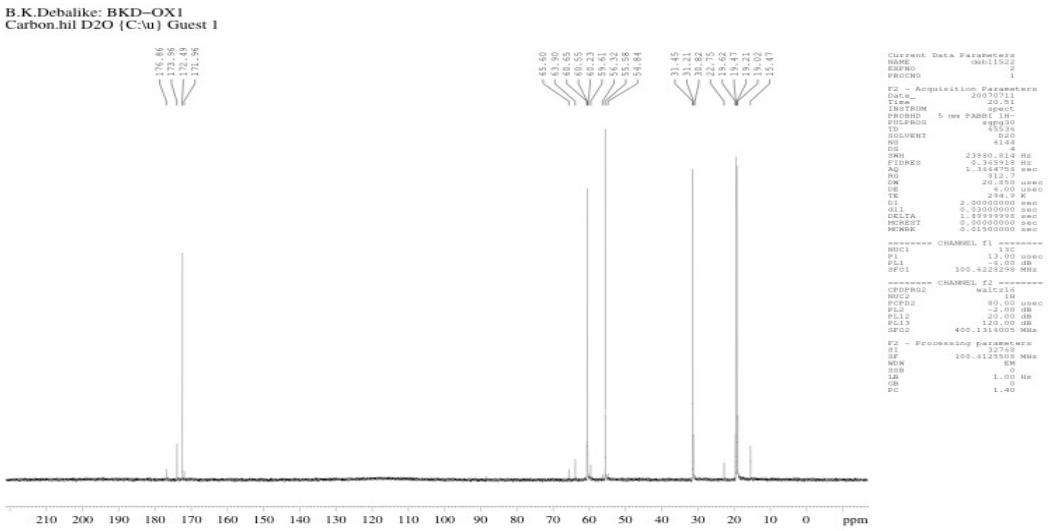
9 Spectral Data

D-Valine-hydrochloride-methylester







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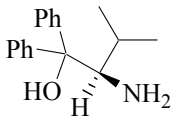
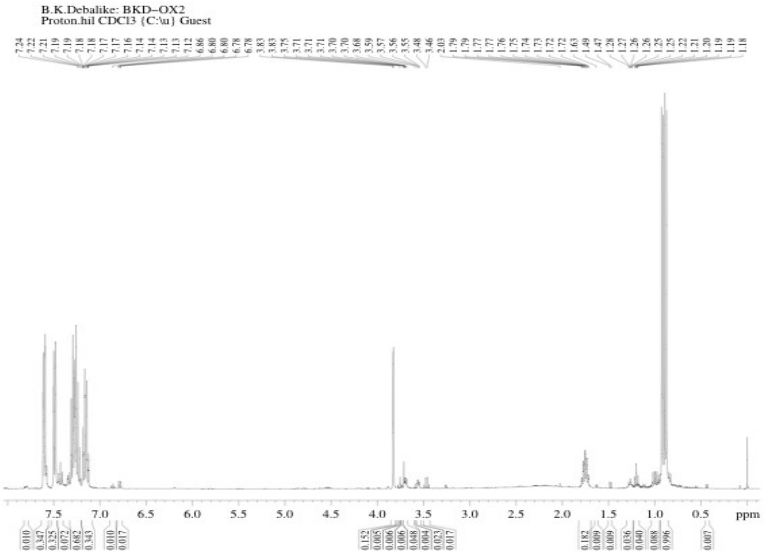
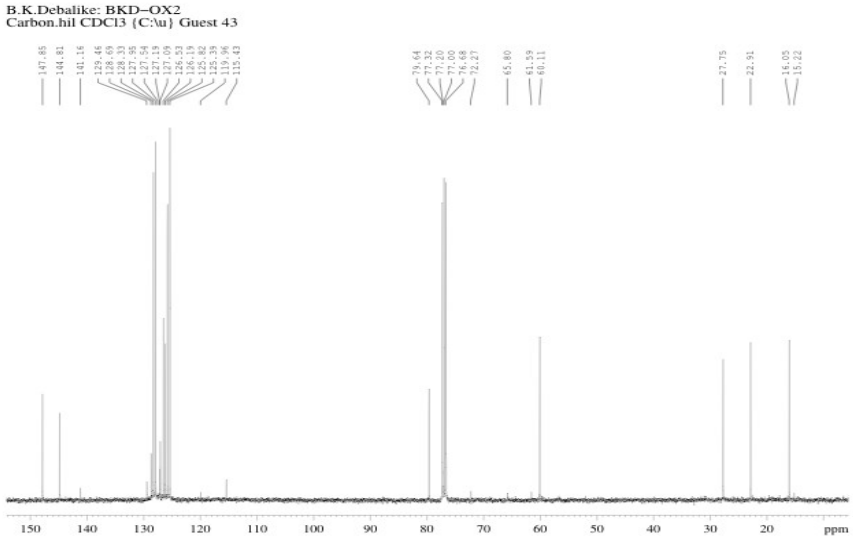
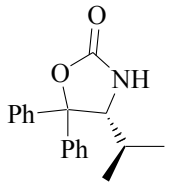
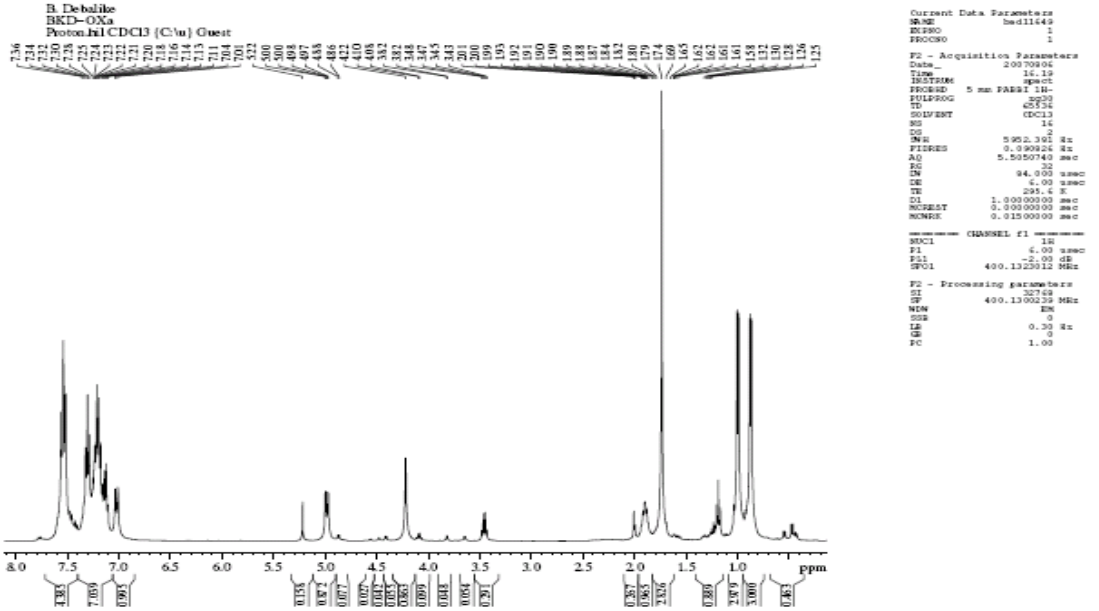


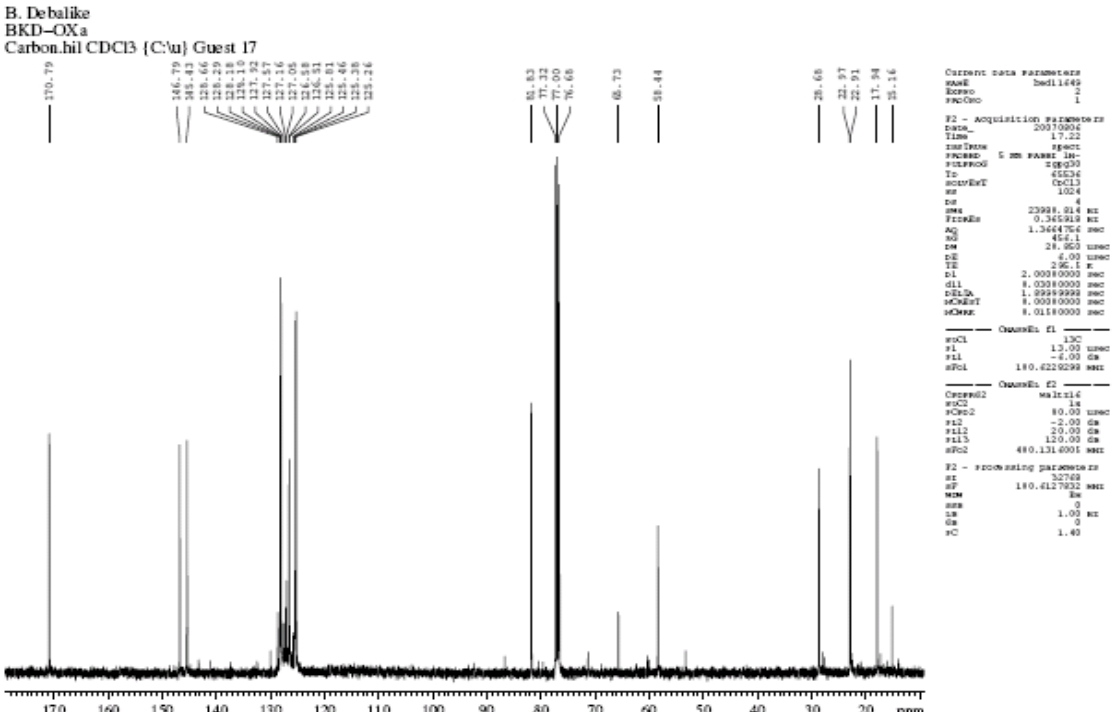




4(R) –Isopropyl-5, 5-diphenyl-oxazolidin-2-on







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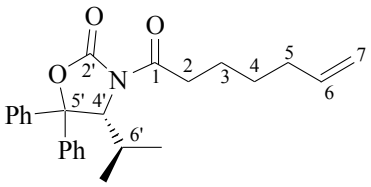

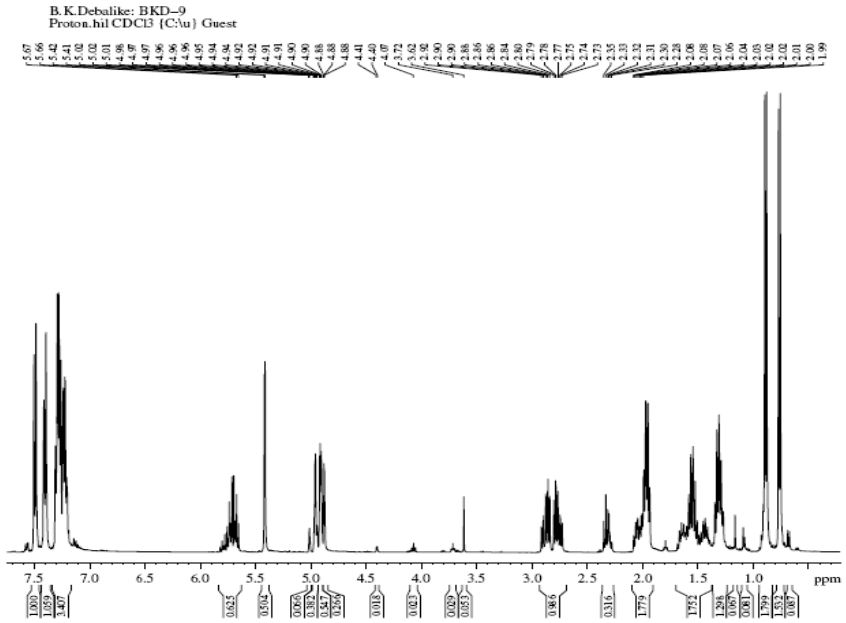


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FIDRES             0.090826 Hz
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DE                     6.50 usec
TE                    295.4 K
D1                 1.00000000 sec
MCREST             0.00000000 sec
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PL1                   -2.00 dB
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B.K.Debalike: BKD--9
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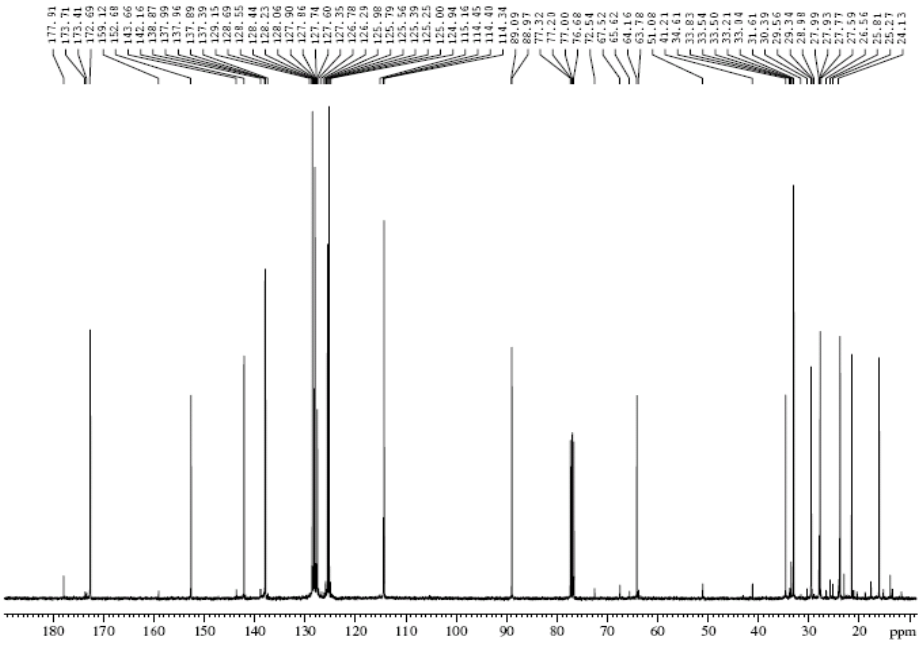


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SFO1           100.6228298 MHz

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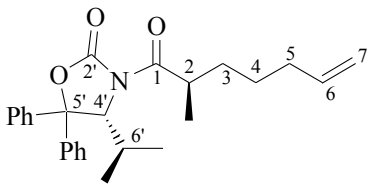
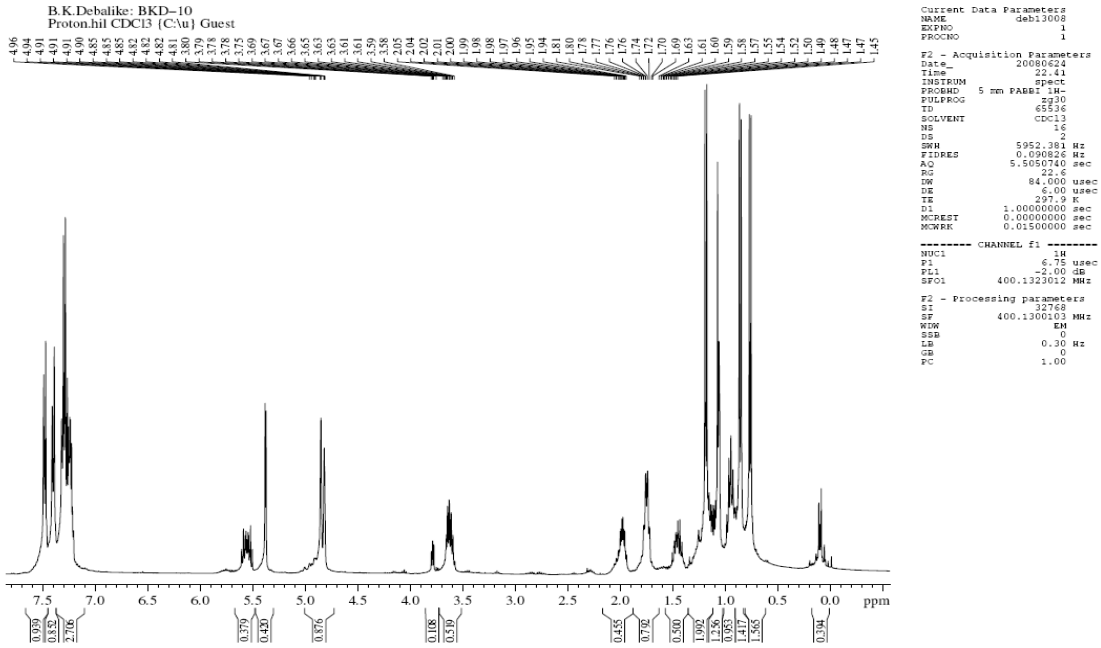
(2R, 4'R)-Isopropyl-3-(2-methyl-hept-6-enoyl)-5,5-diphenyl-oxazolidin-2-on



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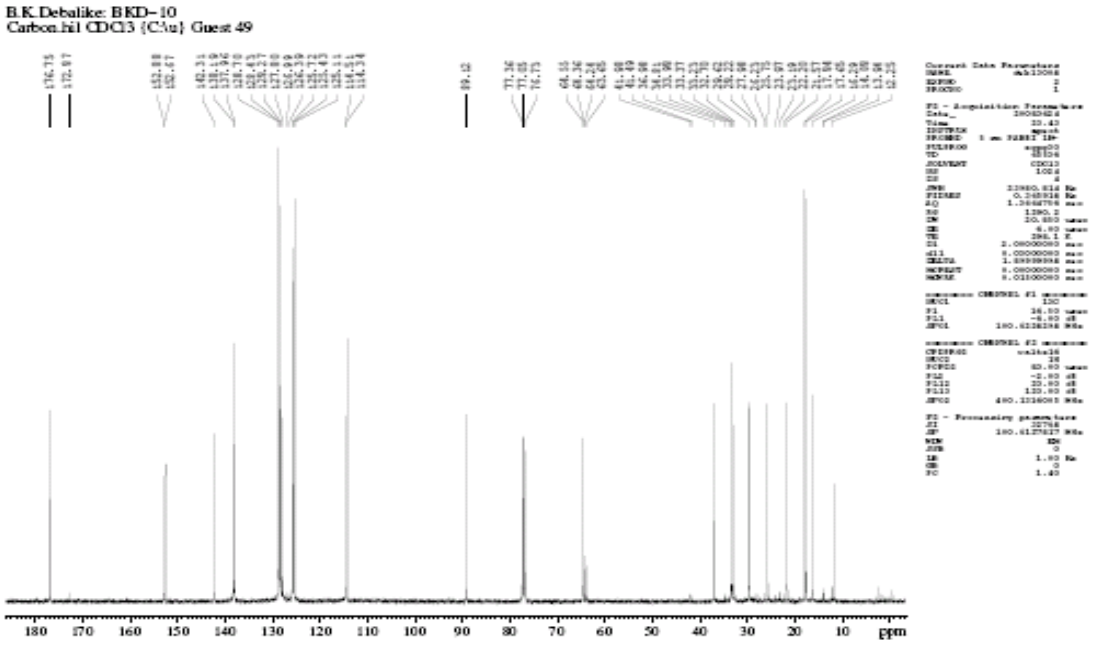

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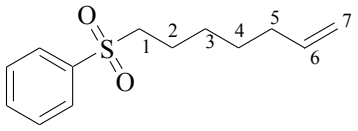

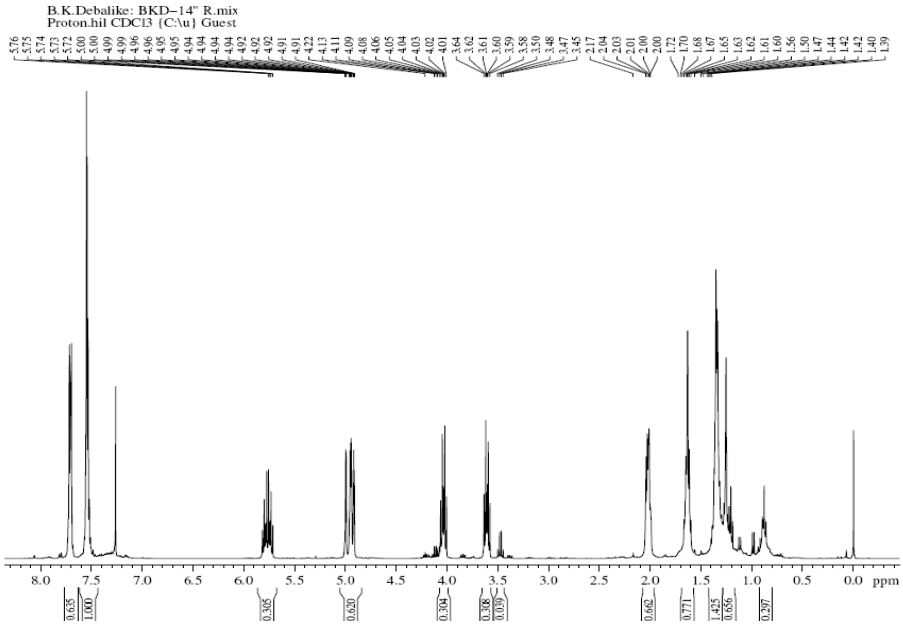


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======== CHANNEL f1 ========
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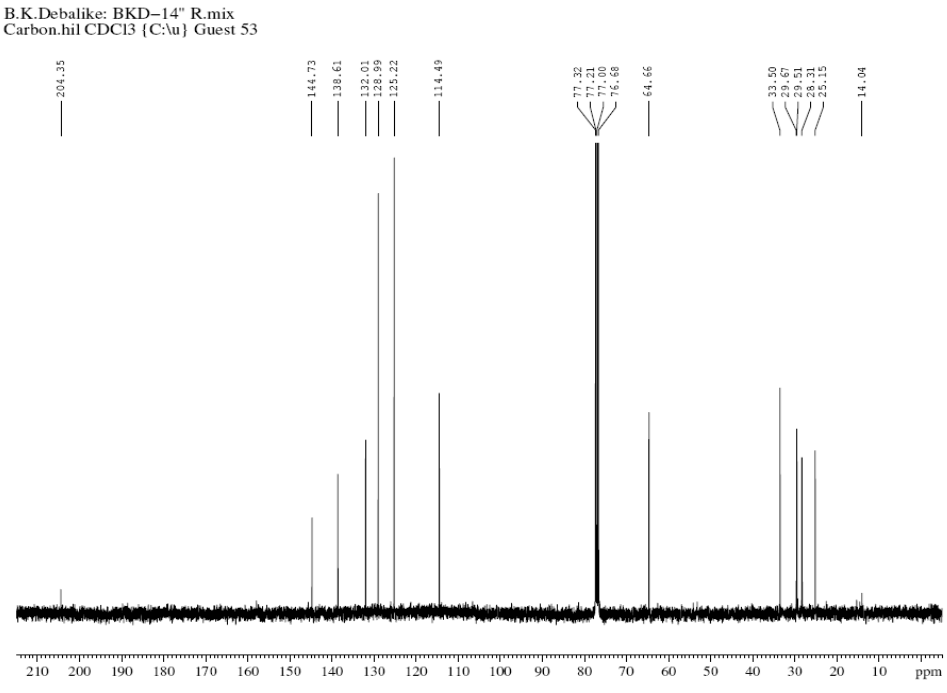


```
Current Data Parameters
NAME                  deb14658
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20090302
Time                 22.34
INSTRUM              spect
PROBHD    5 mm PABBI 1H-
PULPROG              zgpg30
TD                  65536
SOLVENT              CDCl3
NS                    1024
DS                       4
SWH              32258.064 Hz
FIDRES            0.492219 Hz
AQ                1.0158581 sec
RG                   322.5
DW                  15.500 usec
DE                   6.00 usec
TE                  294.7 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                   16.50 usec
PL1                  -6.00 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -2.00 dB
PL12                 20.00 dB
PL13                120.00 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF            100.6127731 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
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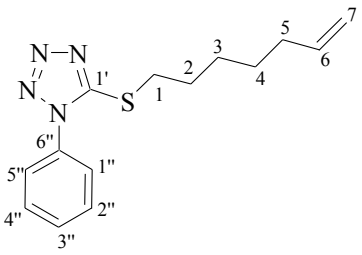
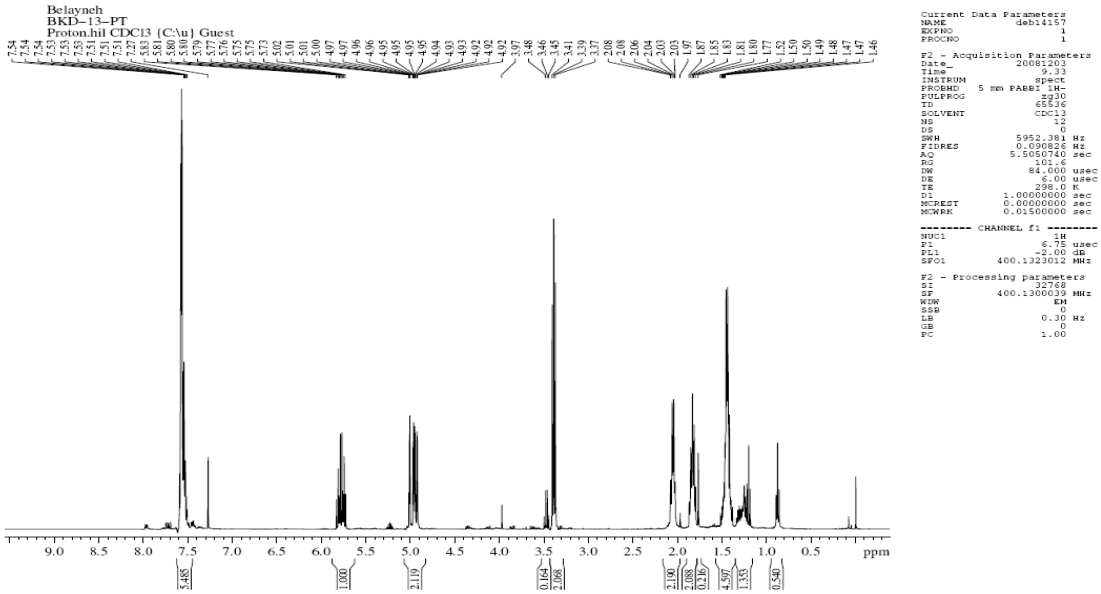
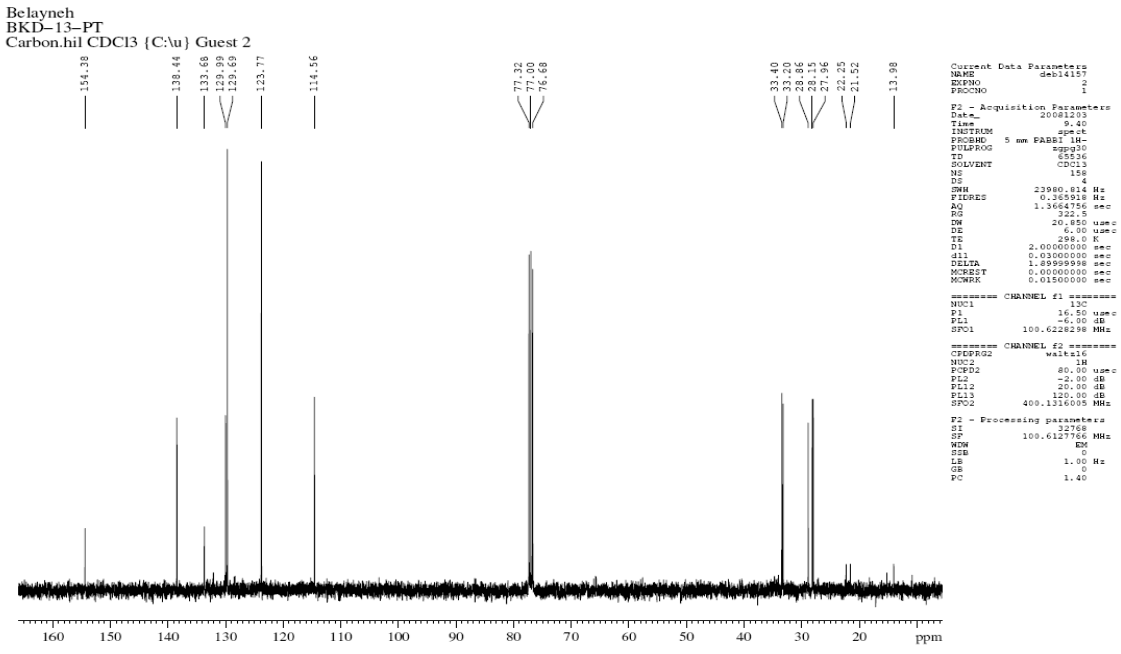
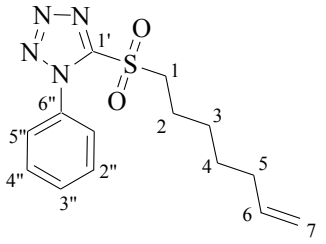
5-Hept-6-enylsulfanyl-1-phenyl-1H-tetrazole

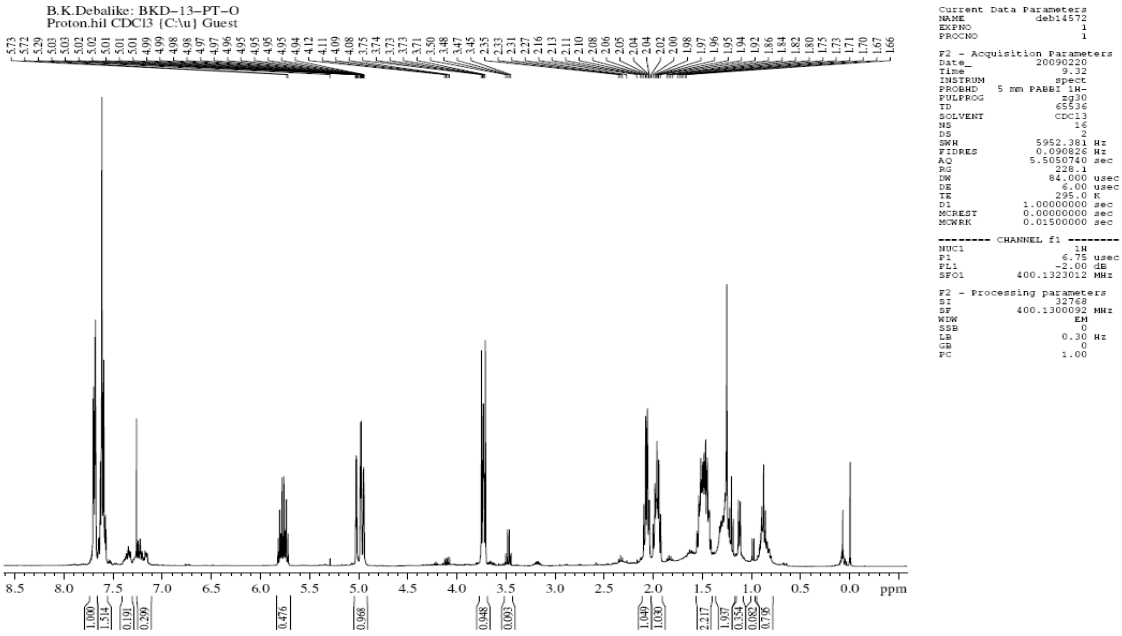






5-(Hept-6-ene-1-sulfonyl)-1-phenyl-1H-tetrazole






```
Current Data Parameters
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EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20090220
Time                    9.32
INSTRUM                 spect
PROBHD    5 mm PABBI 1H-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                5952.381 Hz
FIDRES             0.090826 Hz
AQ                 5.5050740 sec
RG                     228.1
DW                  84.000 usec
DE                   6.00 usec
TE                   295.0 K
D1                 1.00000000 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

-------- CHANNEL f1 --------
NUC1                       1H
P1                       6.75 usec
PL1                     -2.00 dB
SFO1           400.1323012 MHz

F2 - Processing parameters
SI                       32768
SF             400.1300092 MHz
WDW                         EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00
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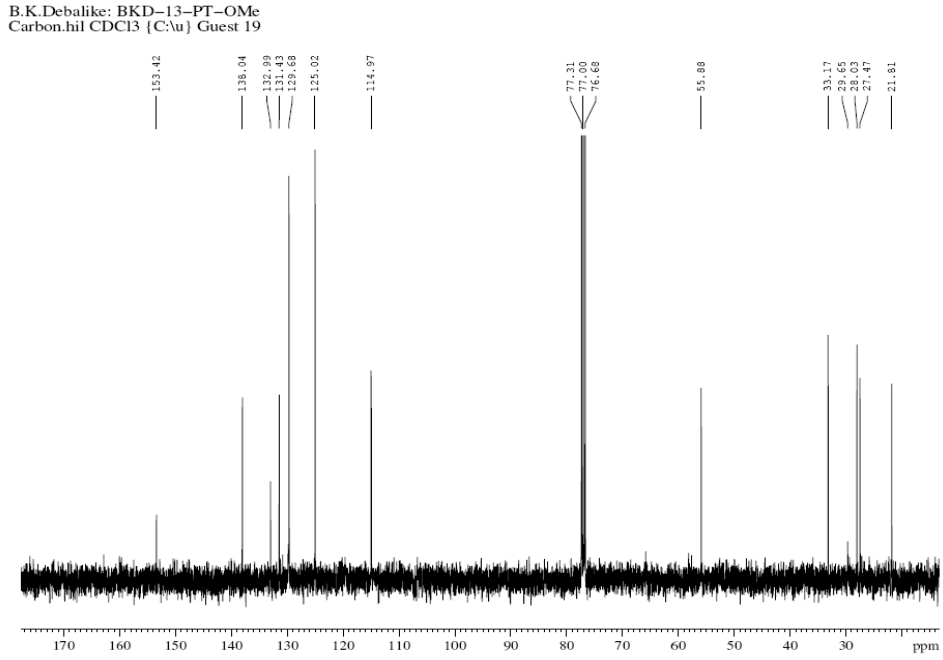
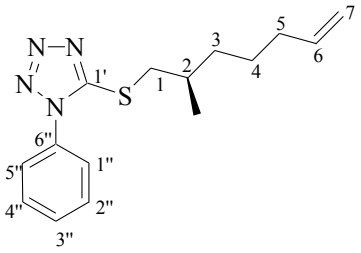
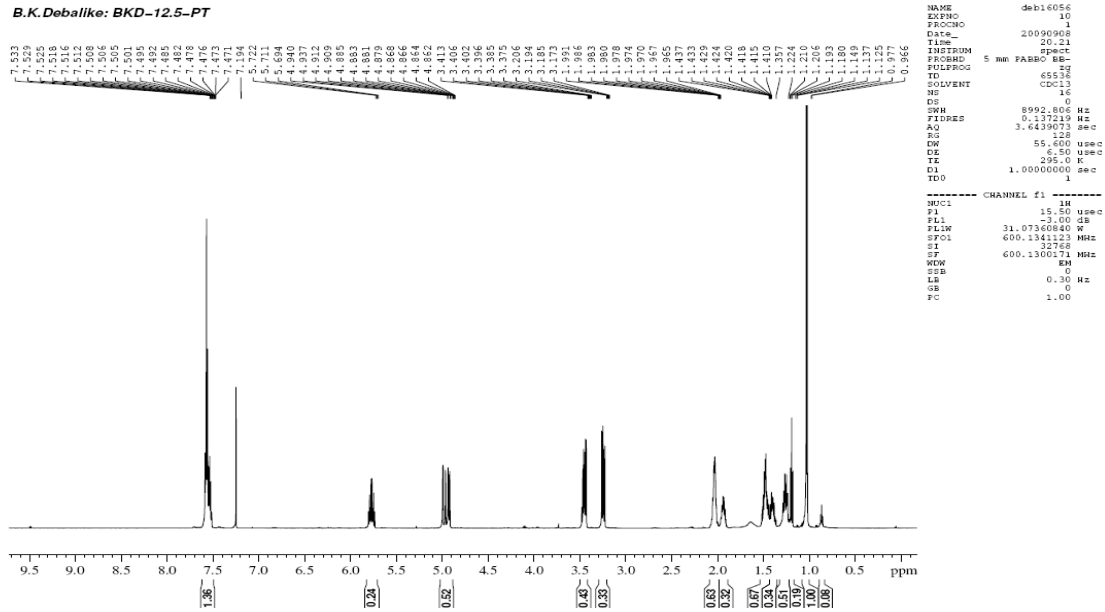
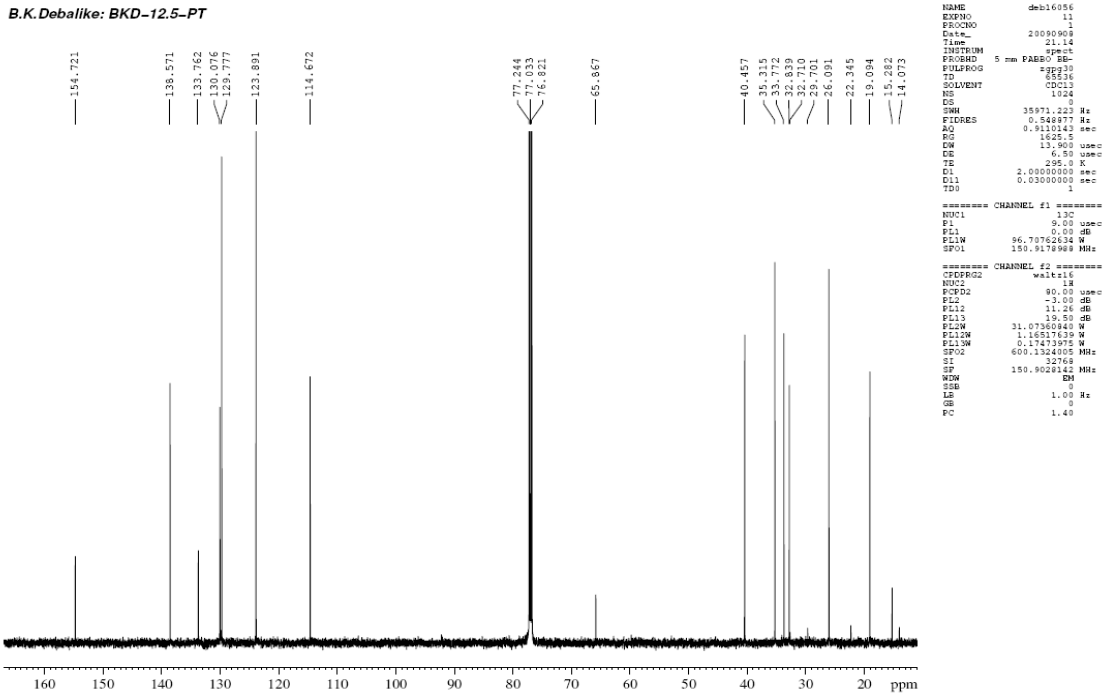



```
Current Data Parameters
NAME                  deb14572
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20090220
Time                    9.36
INSTRUM                 spect
PROBHD    5 mm PABBI 1H-
PULPROG                 zgpg30
TD                     65536
SOLVENT                CDCl3
NS                       249
DS                         4
SWH               23980.814 Hz
FIDRES             0.365918 Hz
AQ                 1.3664756 sec
RG                       512
DW                  20.850 usec
DE                   6.00 usec
TE                   295.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
DELTA              1.89999998 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                      16.50 usec
PL1                      -6.00 dB
SFO1           100.6226298 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   80.00 usec
PL2                      -2.00 dB
PL12                     20.00 dB
PL13                    120.00 dB
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                       32768
SF             100.6127744 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
```

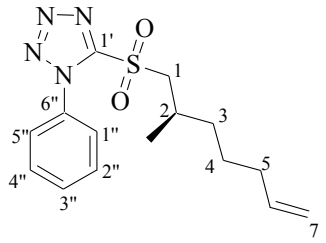
5-(1-Methyl-hept-6-enylsulfanyl)-1-phenyl-1H-tetrazole

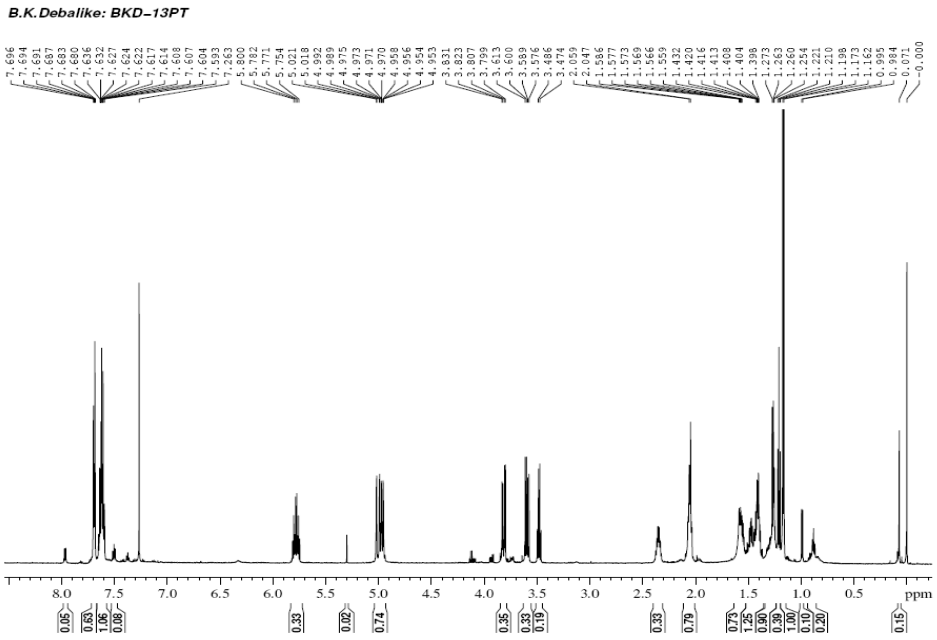


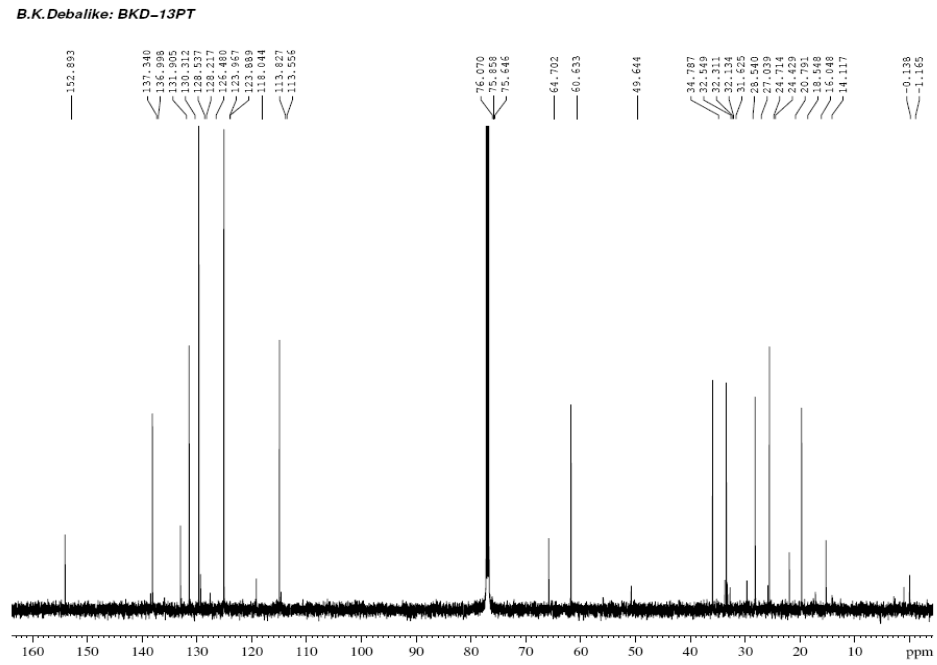




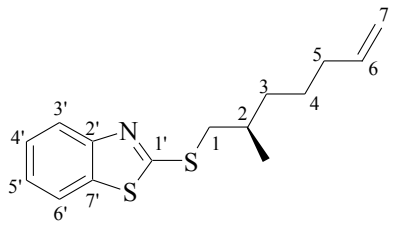
5-(Oct-7-ene-2-sulfonyl)-1-phenyl-1H-tetrazole

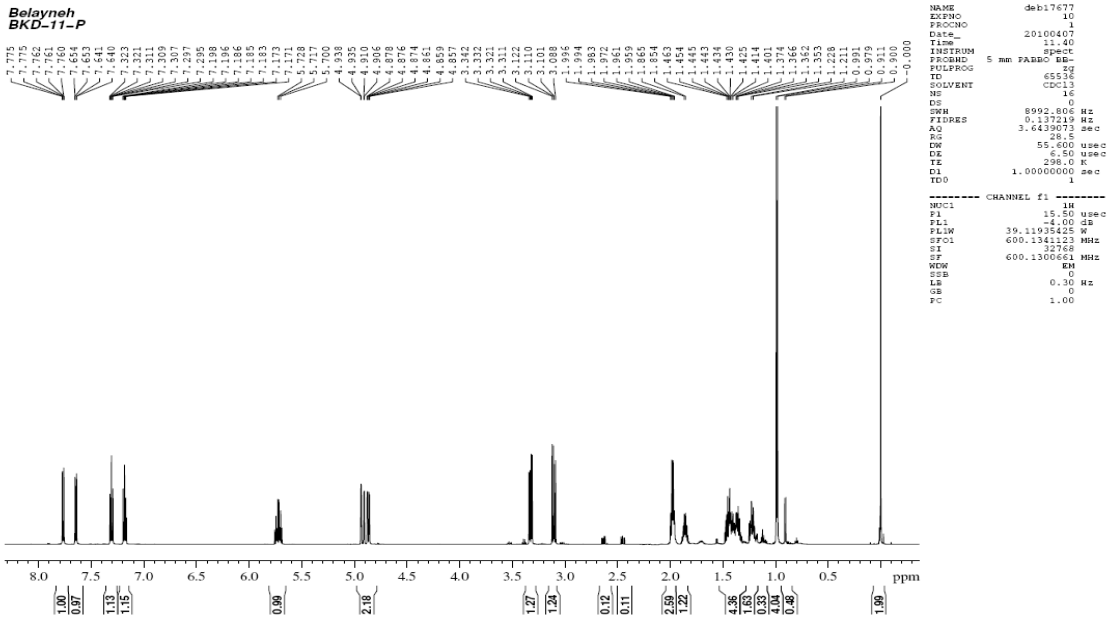


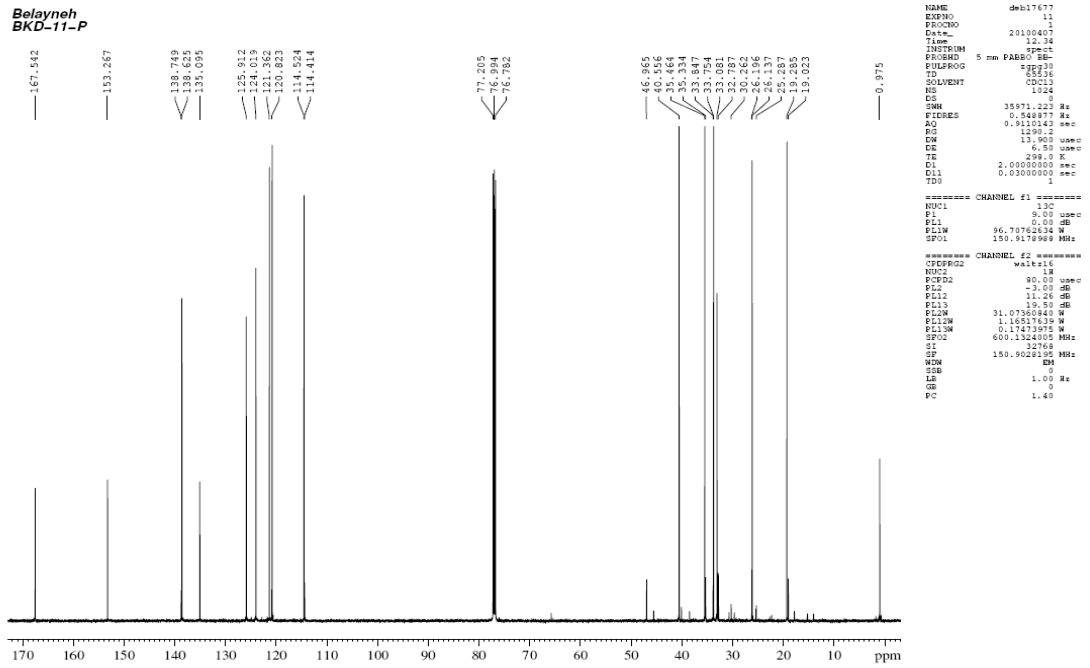




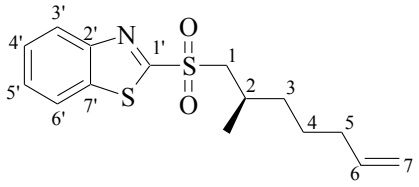
(2*R*)-2-(2-Methylhept-6-enylsulfanyl)-Benzothiazol

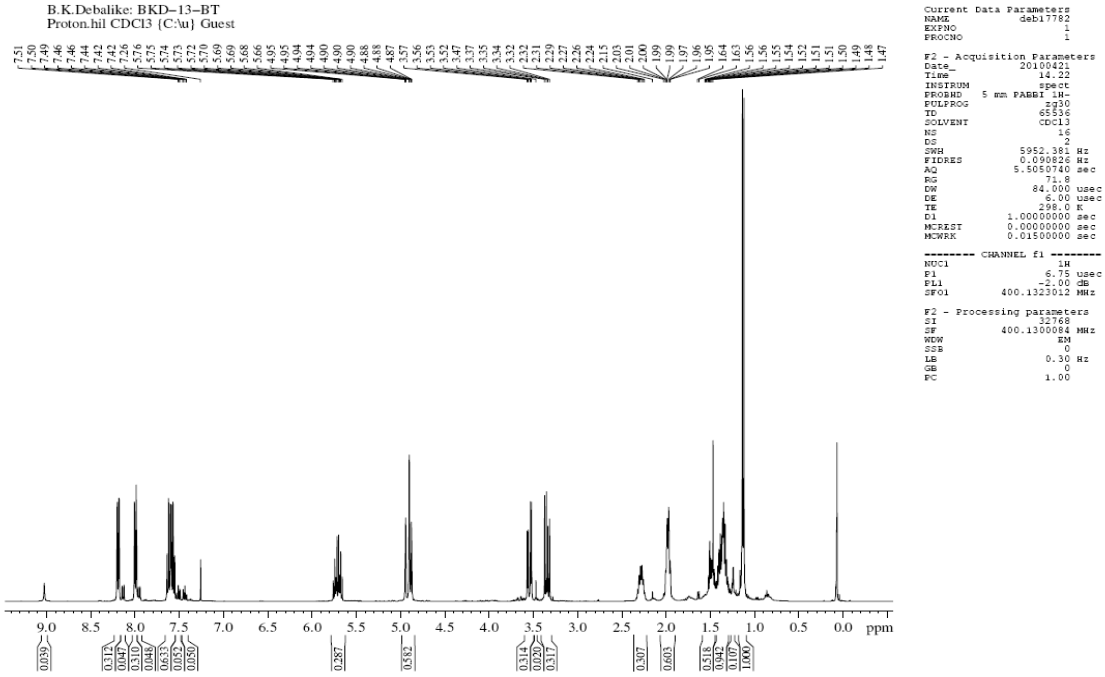


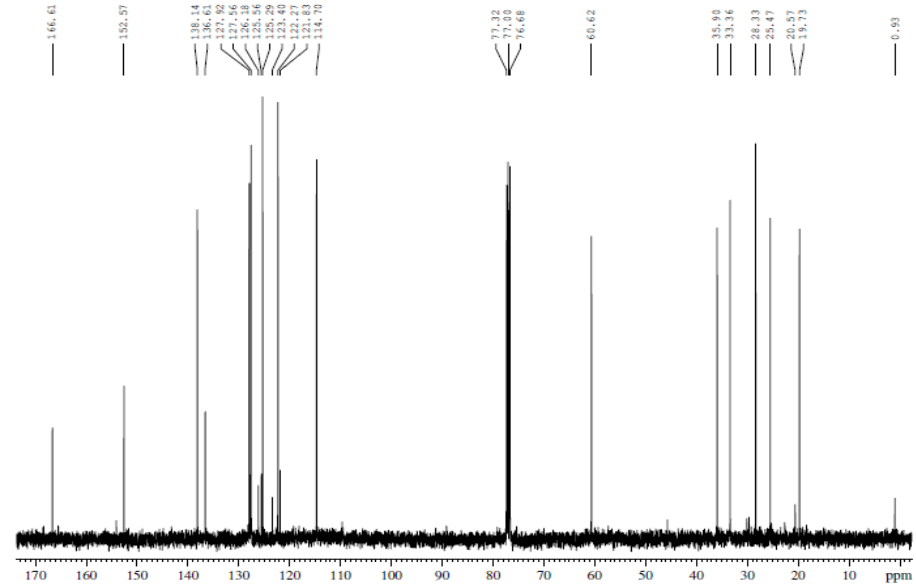




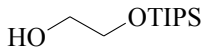
(2*R*)-2-(2-Methylhept-6-en-1-sulfonyl)-Benzothiazol

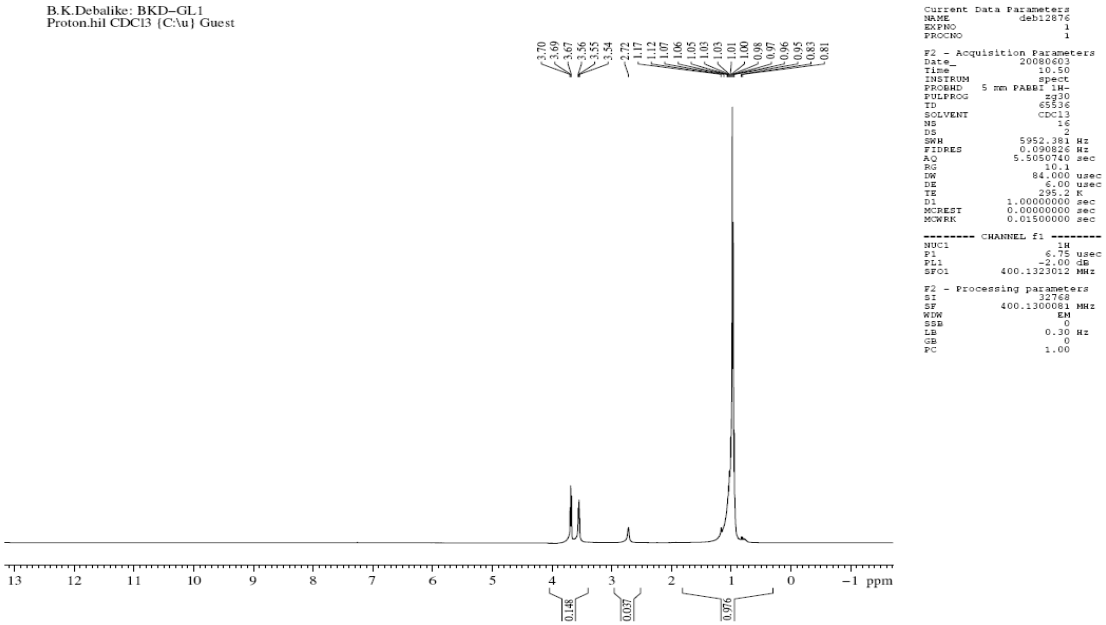


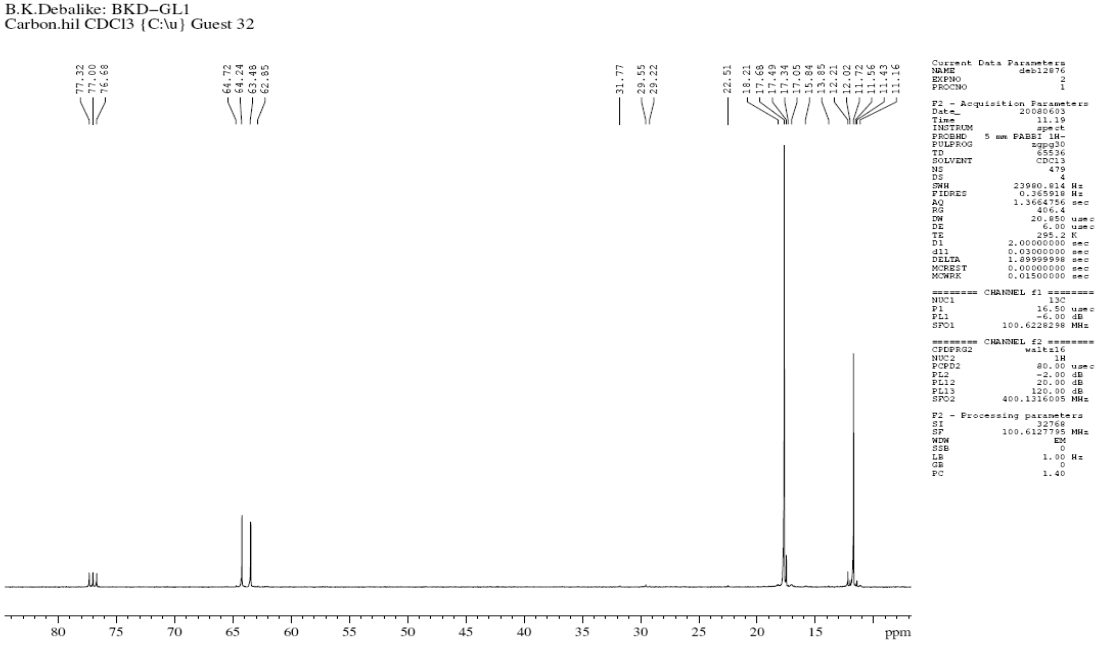




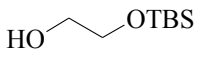
2-Triisopropylsilanyloxy Ethanol

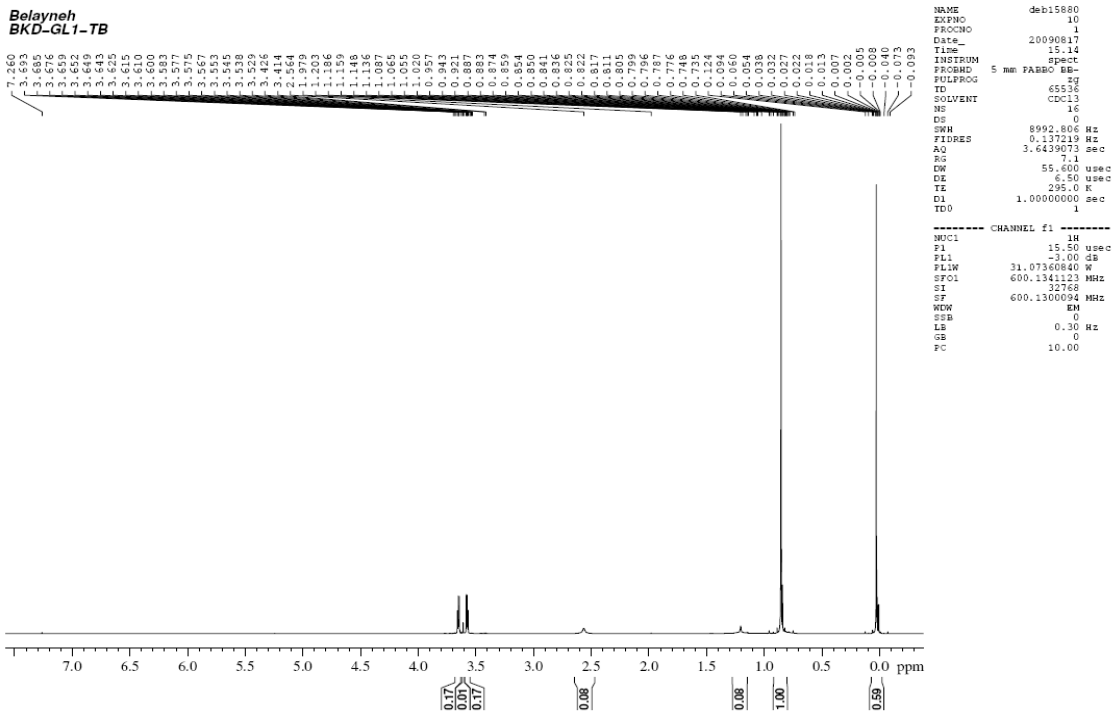


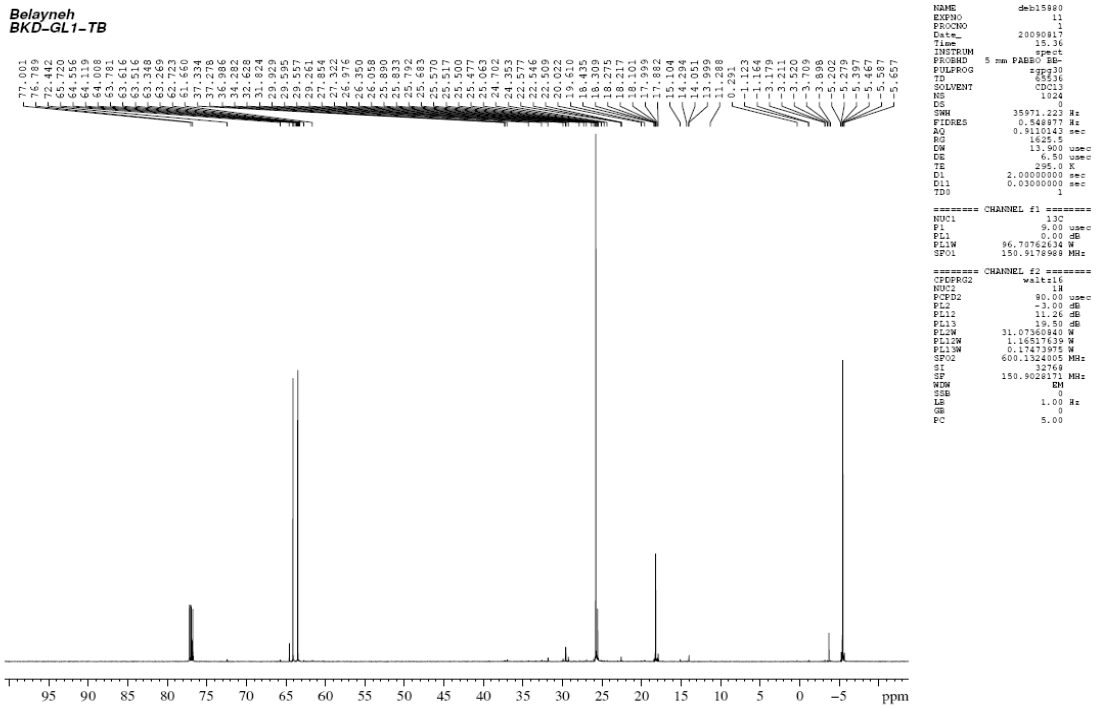




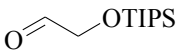
2-(*tert*-Butyldimethylsilyloxy) Ethanol

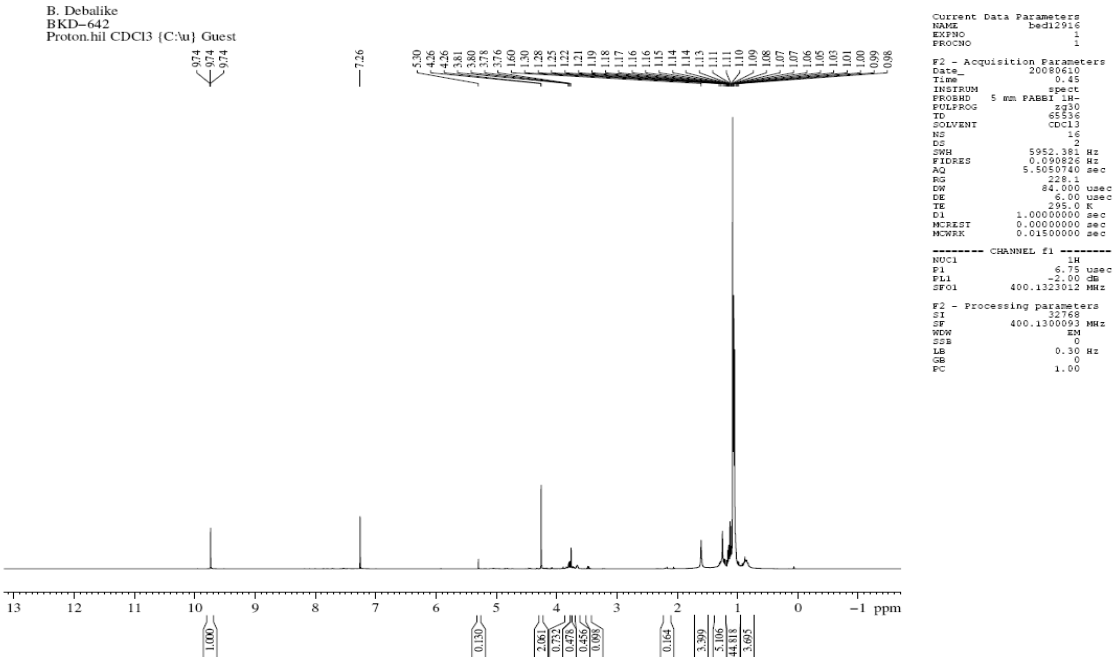


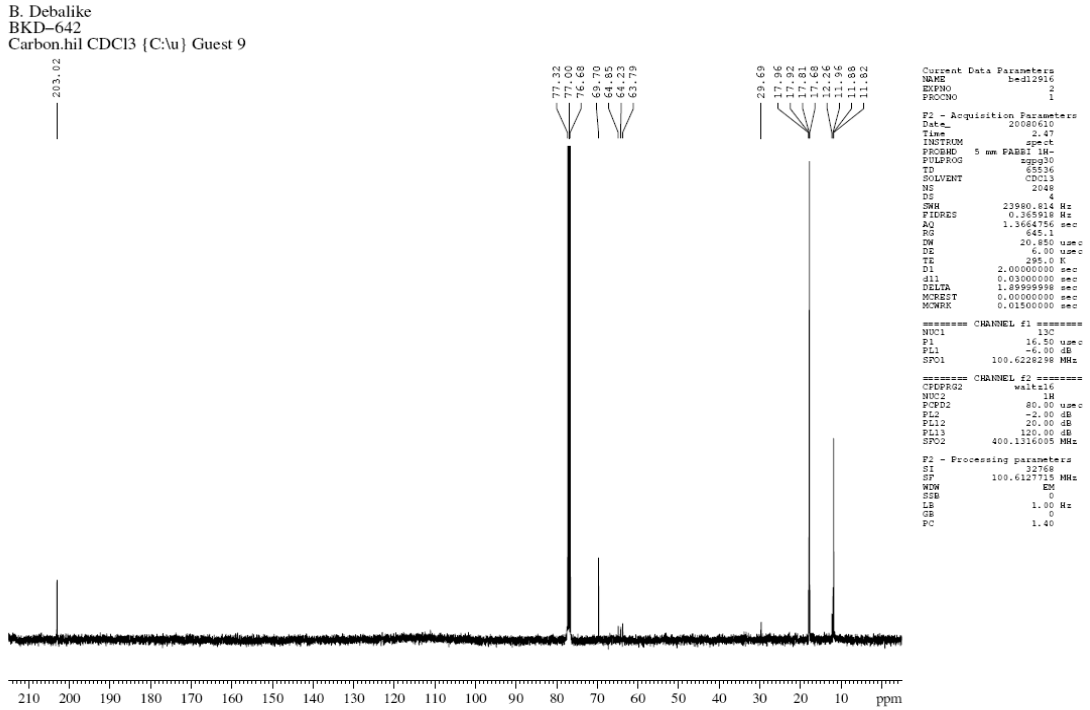




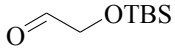
2-(Triisopropylsilyloxy) acetaldehyde

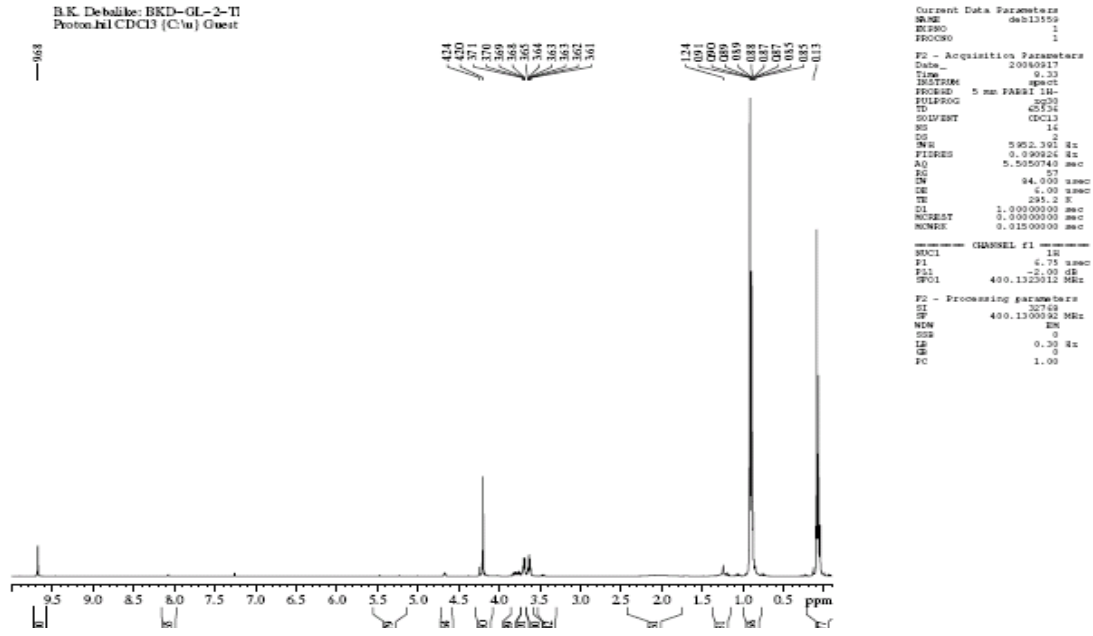


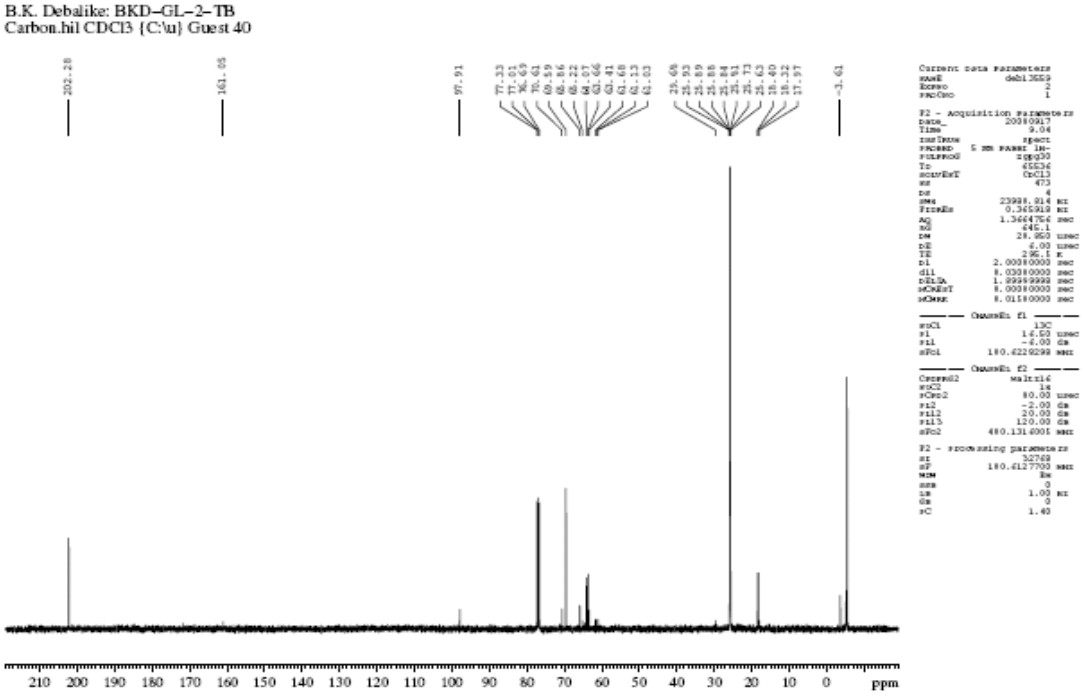




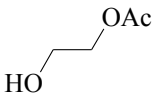
2-(*tert*-Butyldimethylsilyloxy) Acetaldehyde

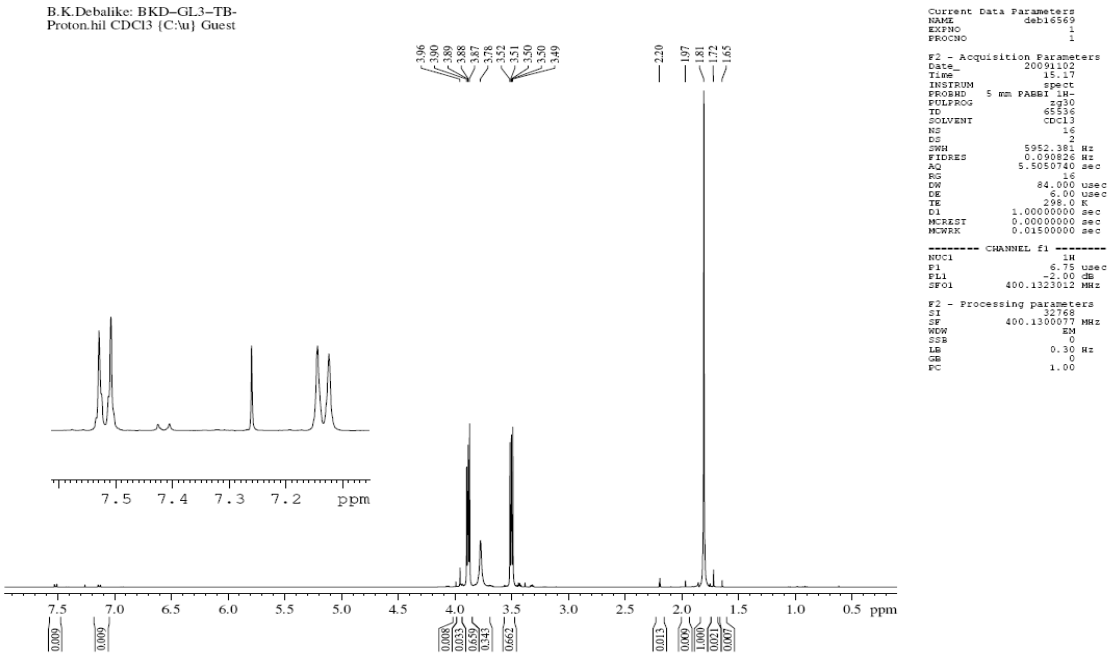


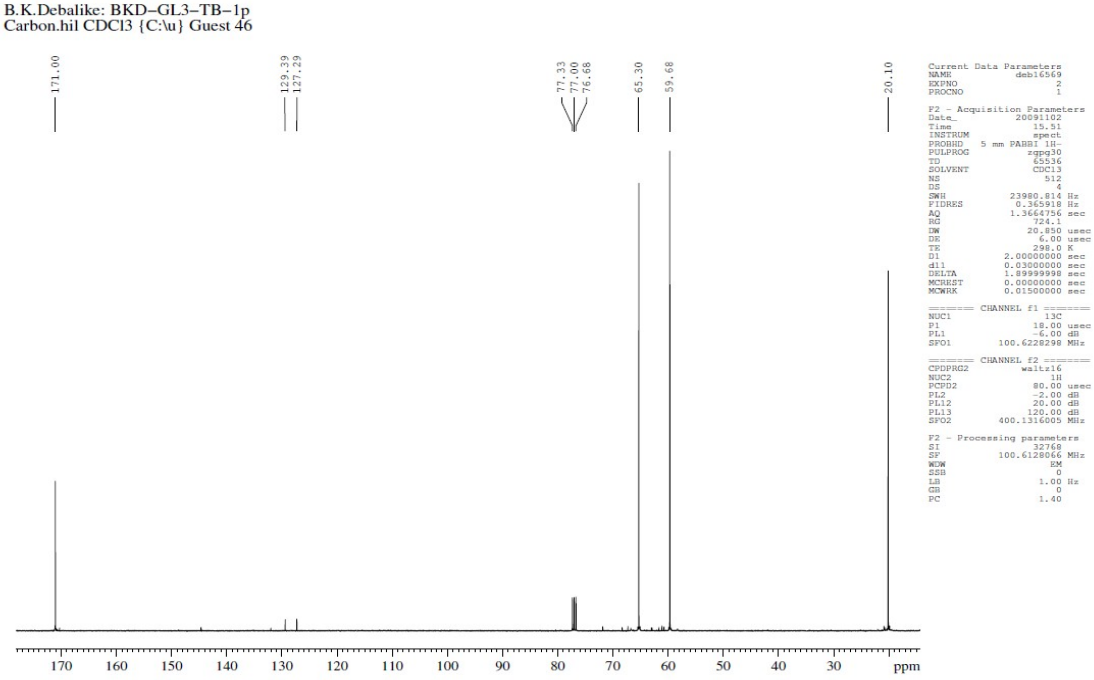




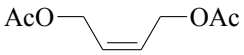
Acetic acid 2-hydroxy-ethyl ester

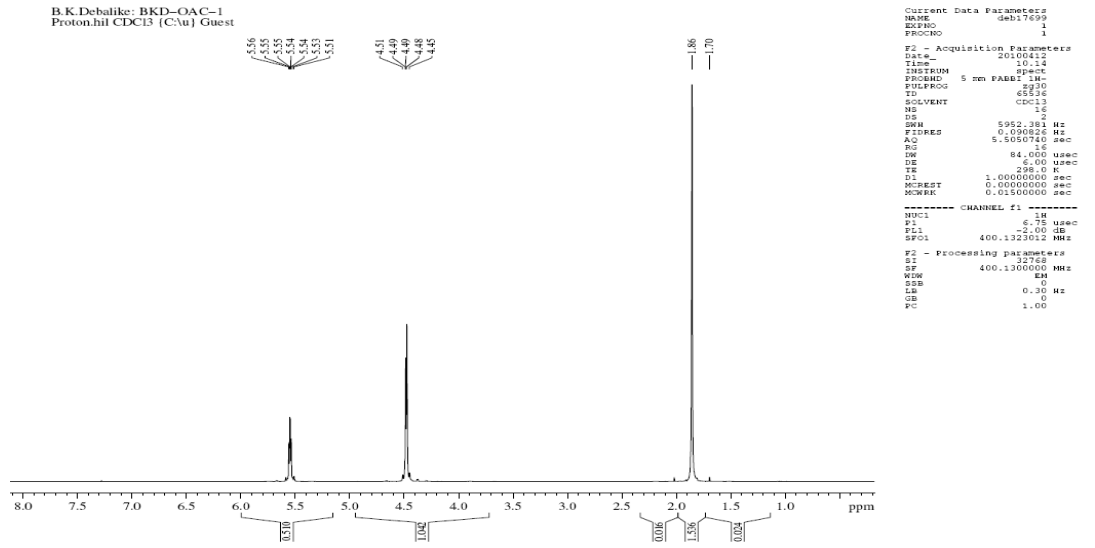


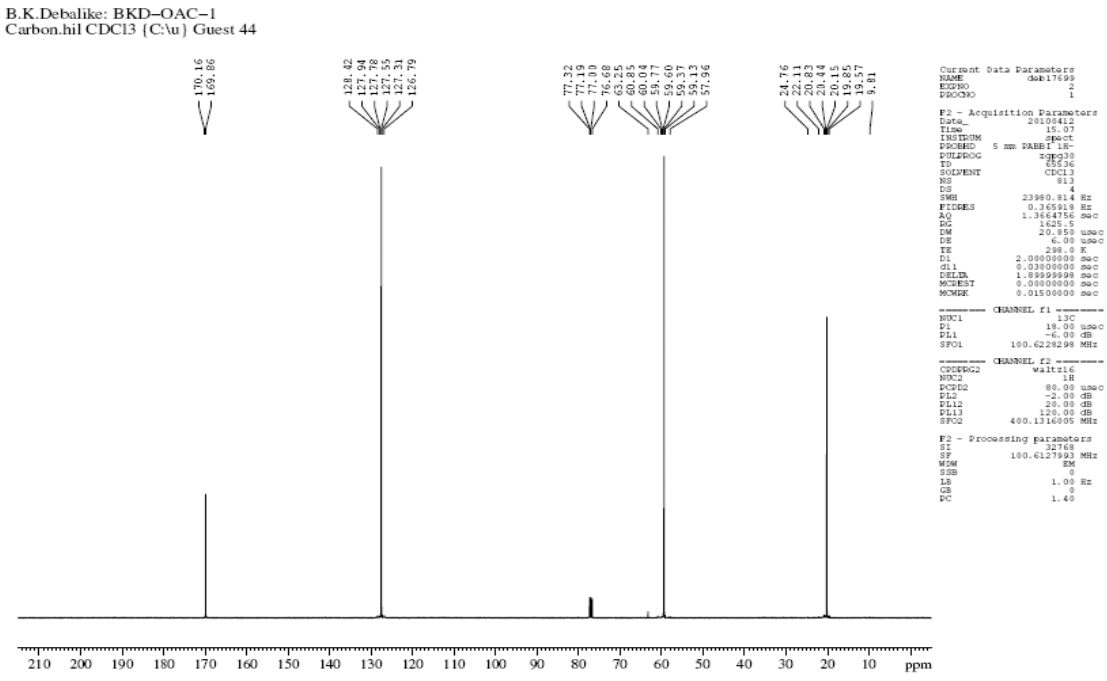




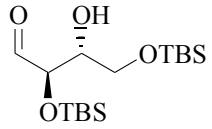
Acetic acid 4-acetoxy-but-2-enyl ester

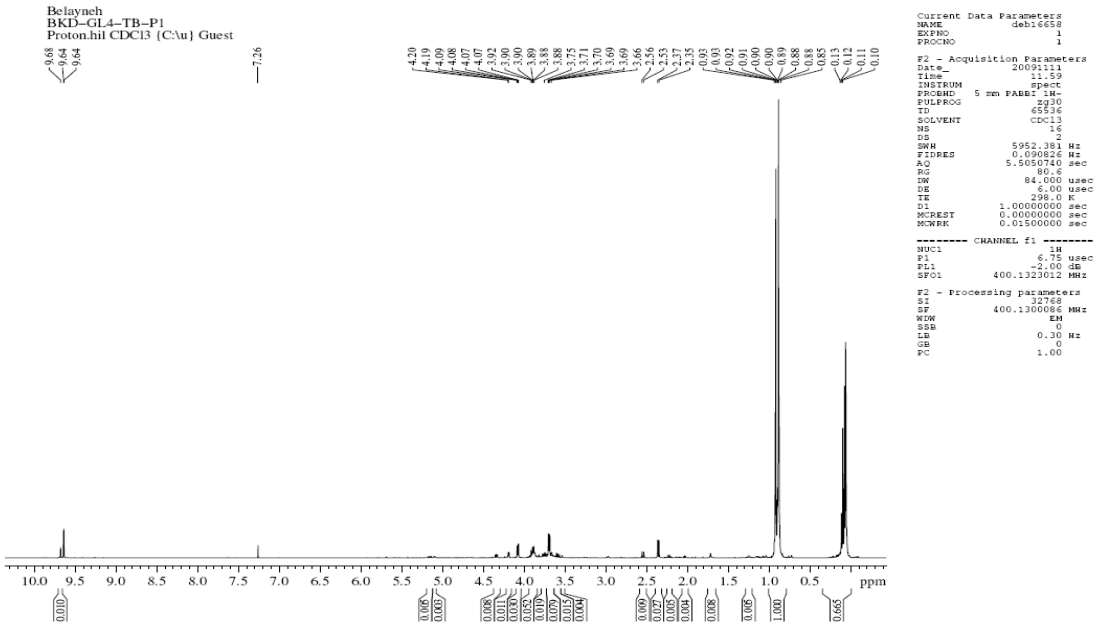


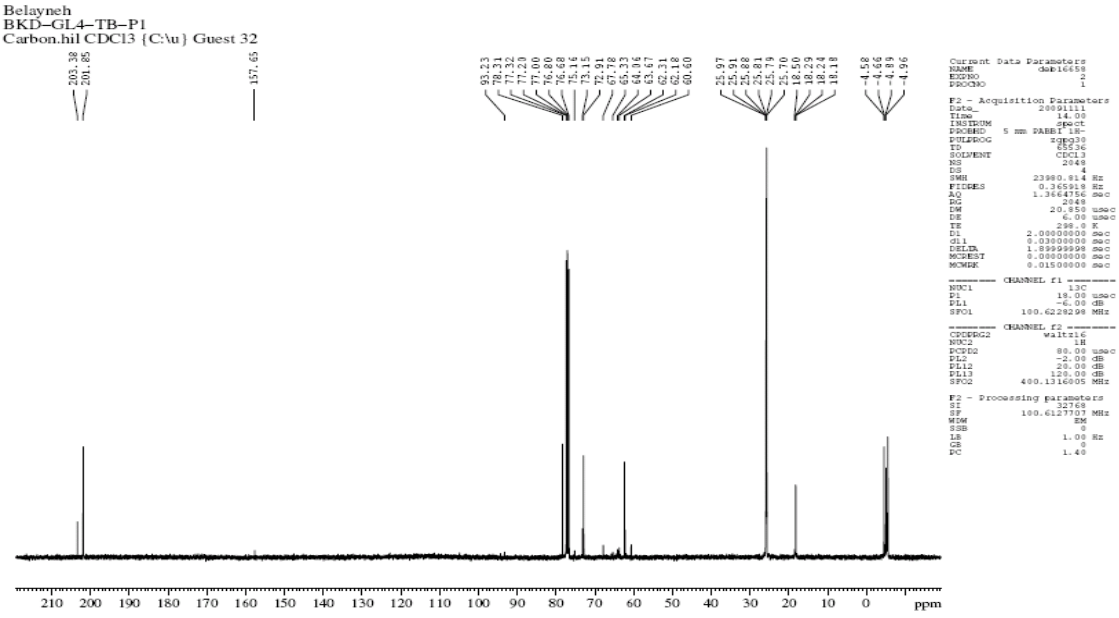




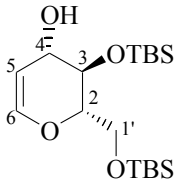
(2*S*,3*S*)-2,4-bis(*tert*-Butyldimethylsilyloxy)-3-hydroxybutanal

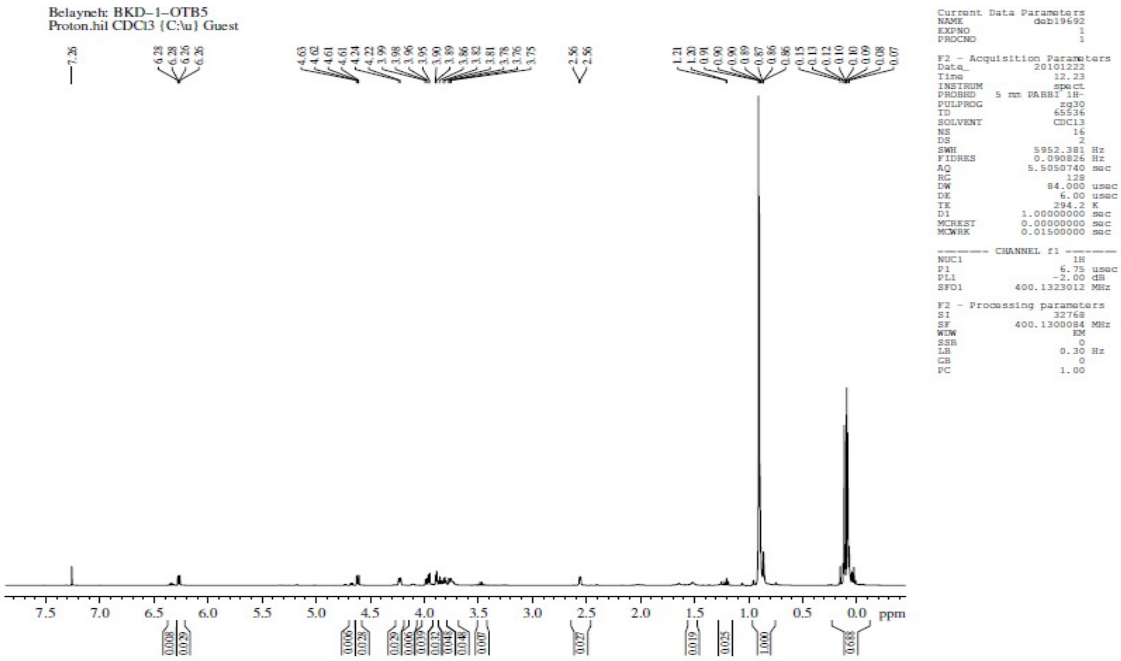


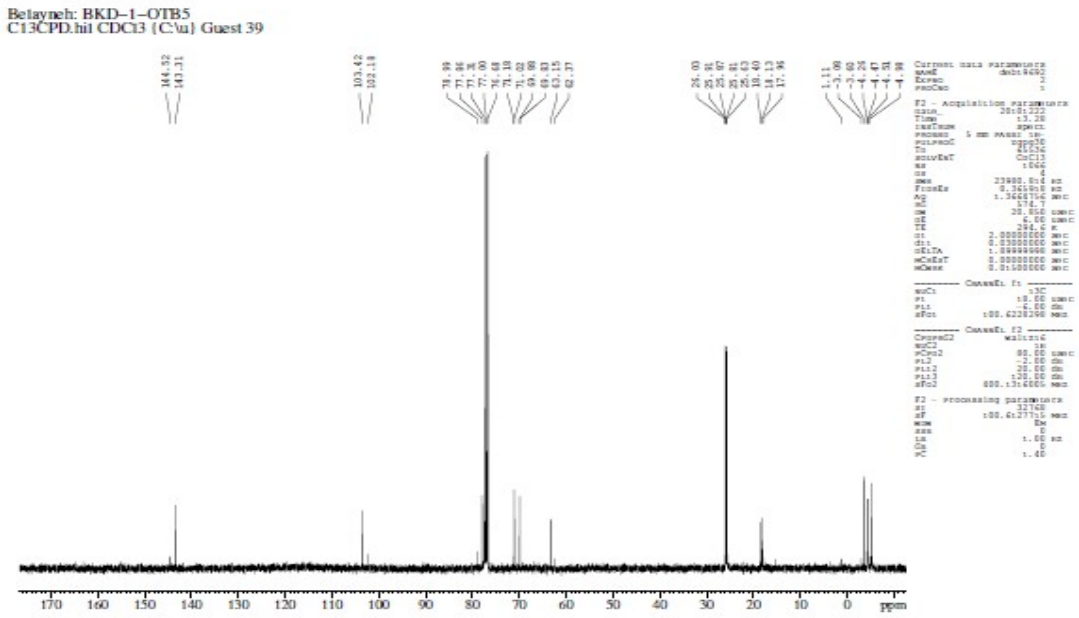




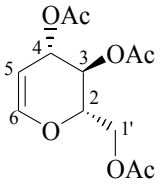
3-(tert-Butyl-dimethyl-silanyloxy)-2-(tert-butyl-dimethyl-silanyloxymethyl)-3,4-dihydro-2H-pyran-4-ol

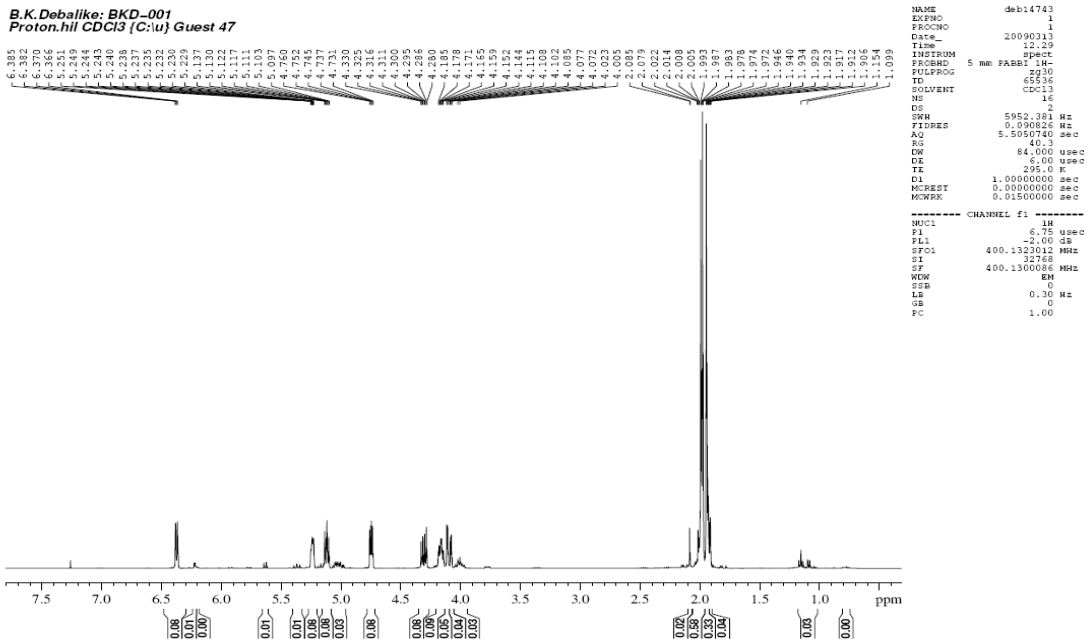


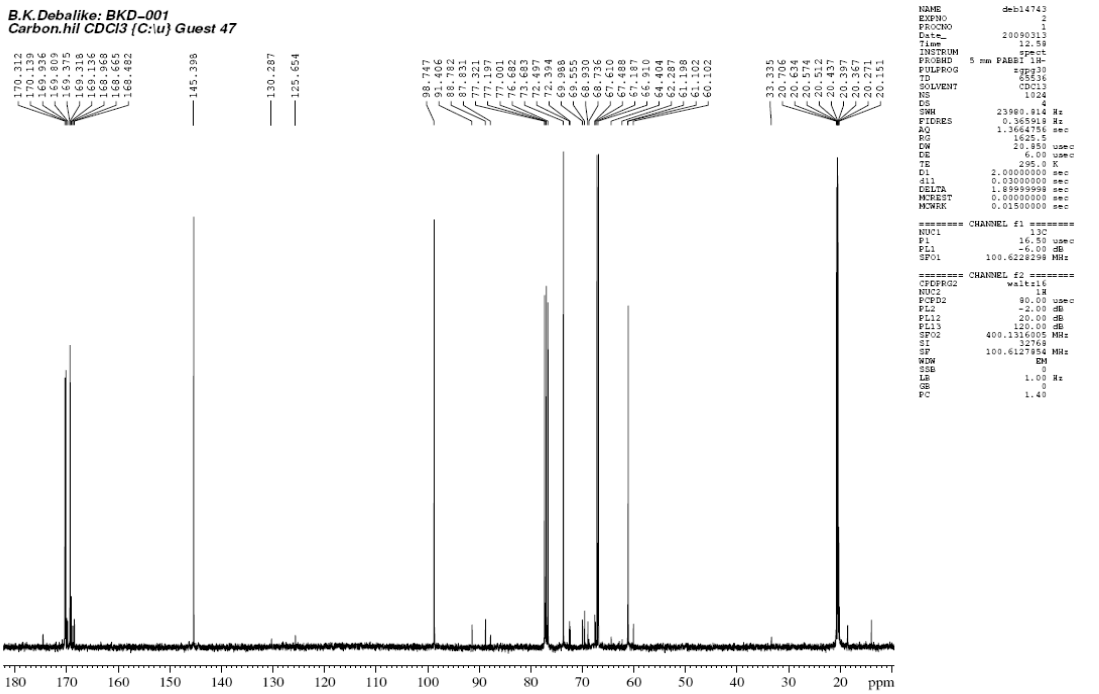




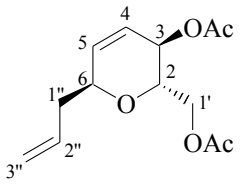
Acetic acid 3-acetoxy-2-acetoxymethyl-3,4-dihydro-2H-pyran-4-yl ester

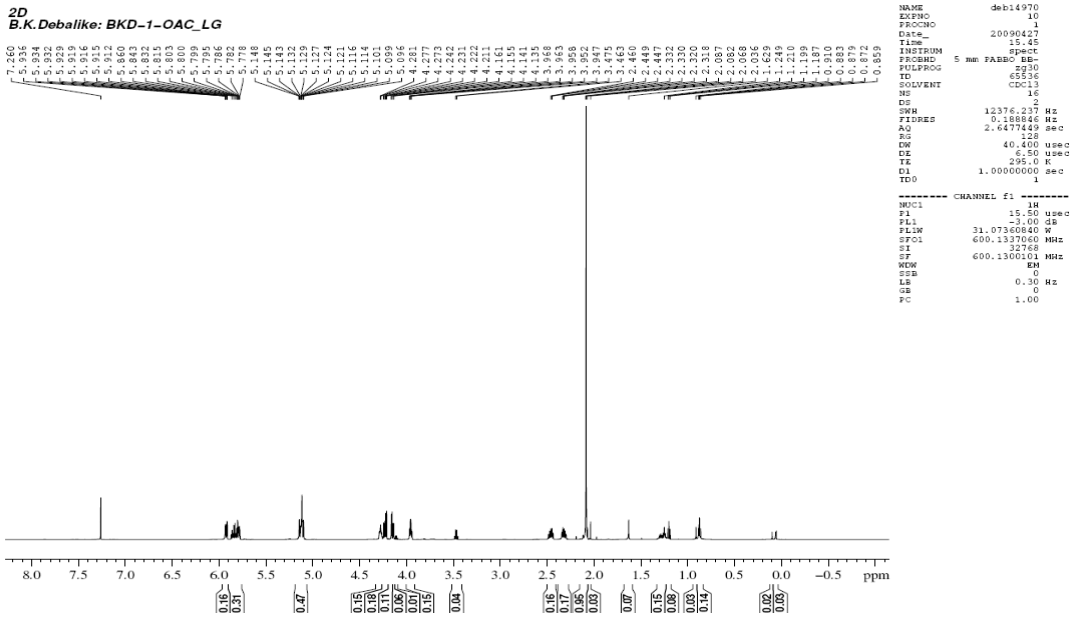


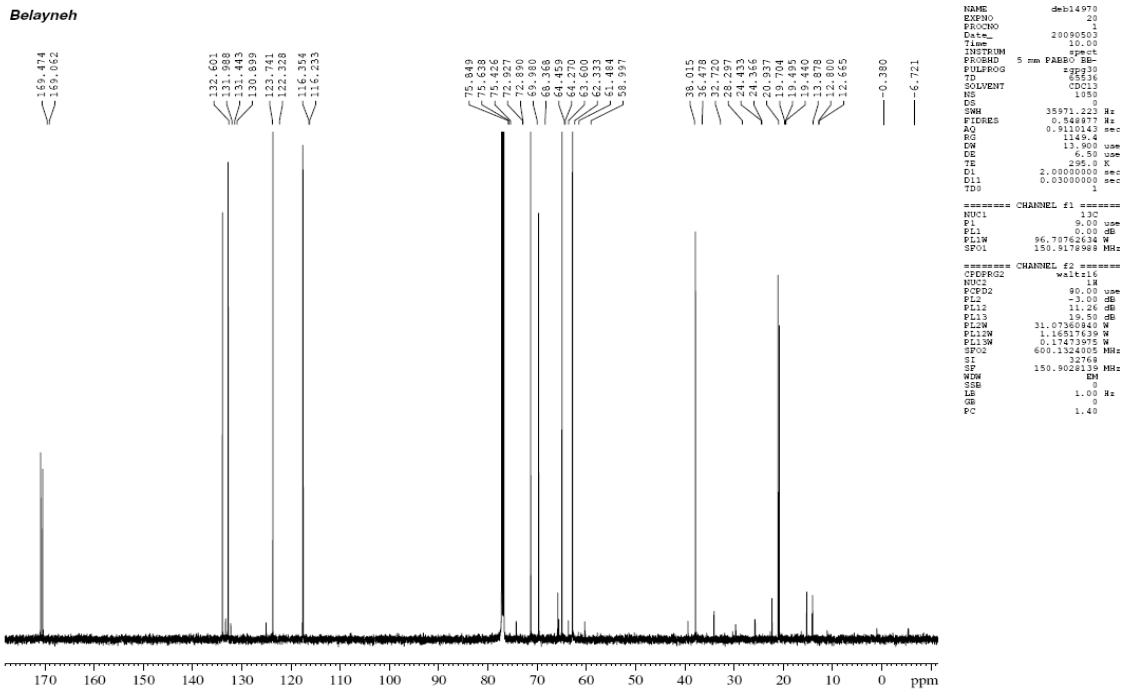




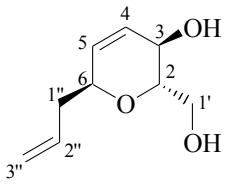
(*2S,3R,6S*)-3-Acethoxy-2-acethoxymethyl-6-allyl-3,6-dihydro-2*H*-pyran

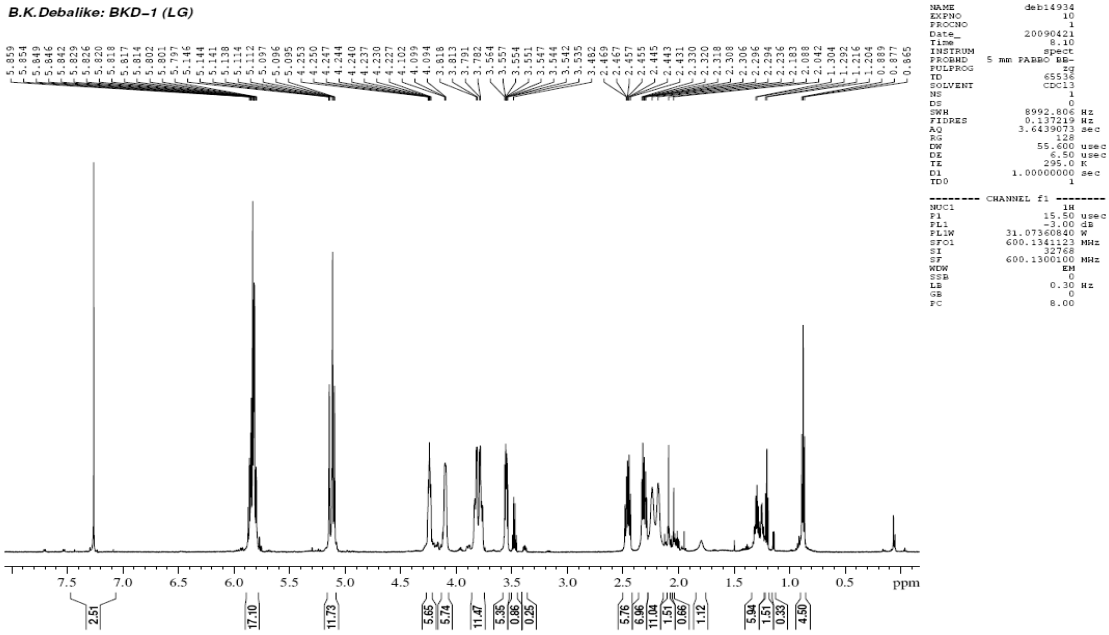




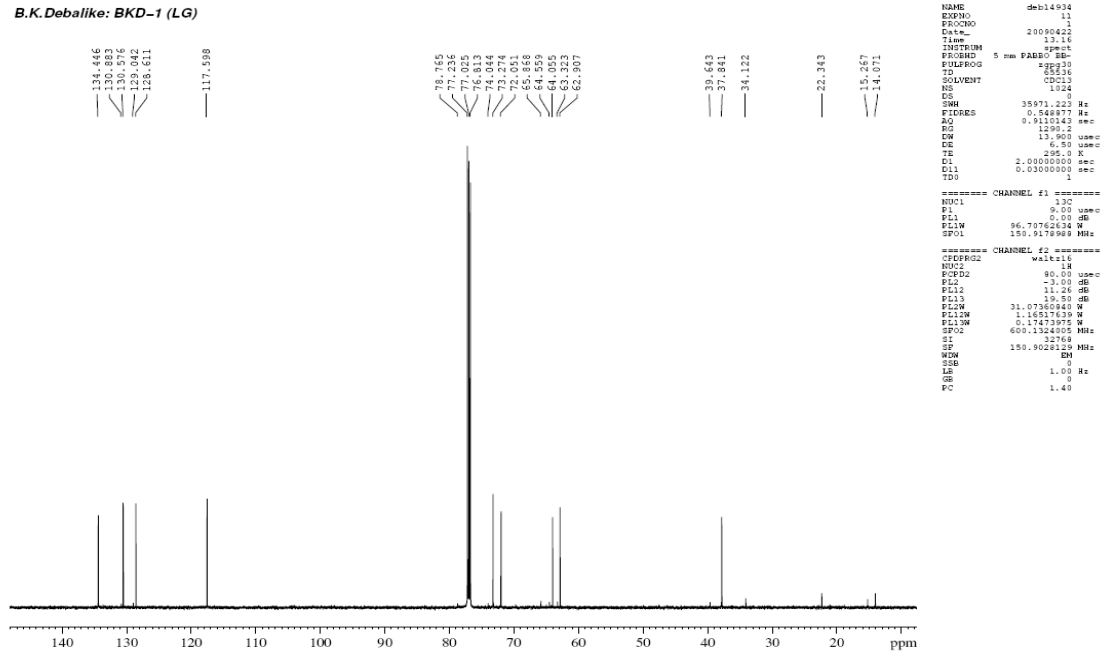


(2*S*,3*R, 6S*)-6-Allyl-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-ol



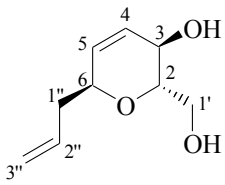


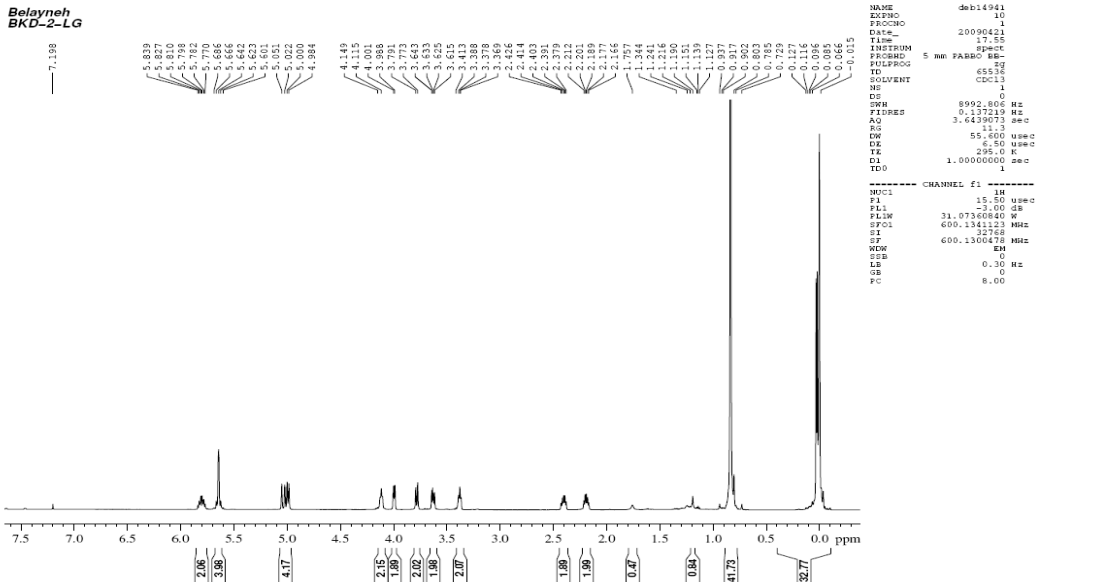

```
NAME              deb14934
EXPNO                   10
PROCNO                   1
Date_             20090421
Time                 8.10
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG                 zg
TD                   65536
SOLVENT              CDCl3
NS                       1
DS                       0
SWH              8992.806 Hz
FIDRES           0.137219 Hz
AQ               3.6439073 sec
RG                     128
DW                55.600 usec
DE                 6.50 usec
TE                295.0 K
D1               1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   1H
P1                 15.50 usec
PL1                -3.00 dB
PL1W         31.07360840 W
SFO1         600.1341123 MHz
SI                   32768
SF           600.1300100 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                 8.00
```

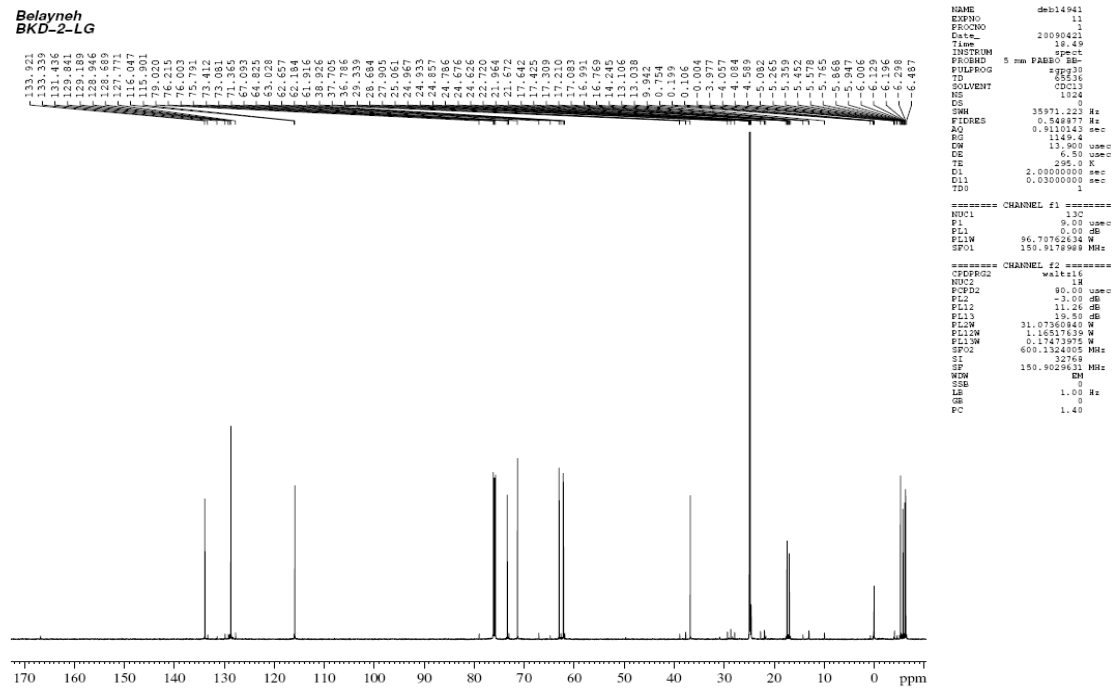



```
NAME              deb14934
EXPNO                   11
PROCNO                   1
Date_             20090422
Time                13.16
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1024
DS                       0
SWH              35971.223 Hz
FIDRES           0.548877 Hz
AQ               0.9120143 sec
RG                  1290.2
DW                13.900 usec
DE                 6.50 usec
TE                295.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                  9.00 usec
PL1                 0.00 dB
PL1W         96.70762634 W
SFO1         150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                   1H
PCPD2              90.00 usec
PL2                -3.00 dB
PL12               11.26 dB
PL13               19.50 dB
PL2W         31.07360840 W
PL12W        1.16517639 W
PL13W        0.17473975 W
SFO2         600.1324005 MHz
SI                   32768
SF           150.9028129 MHz
WDW                    EM
SSB                     0
LB                 1.00 Hz
GB                      0
PC                 1.40
```

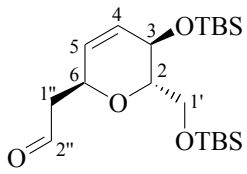
(2S,3R,6S)–6-Allyl-3-*tert*-butyldimethylsilanyloxy-2-*tert*-butyldimethyl-silanyloxymethyl-3,6-dihydro-2H-pyran

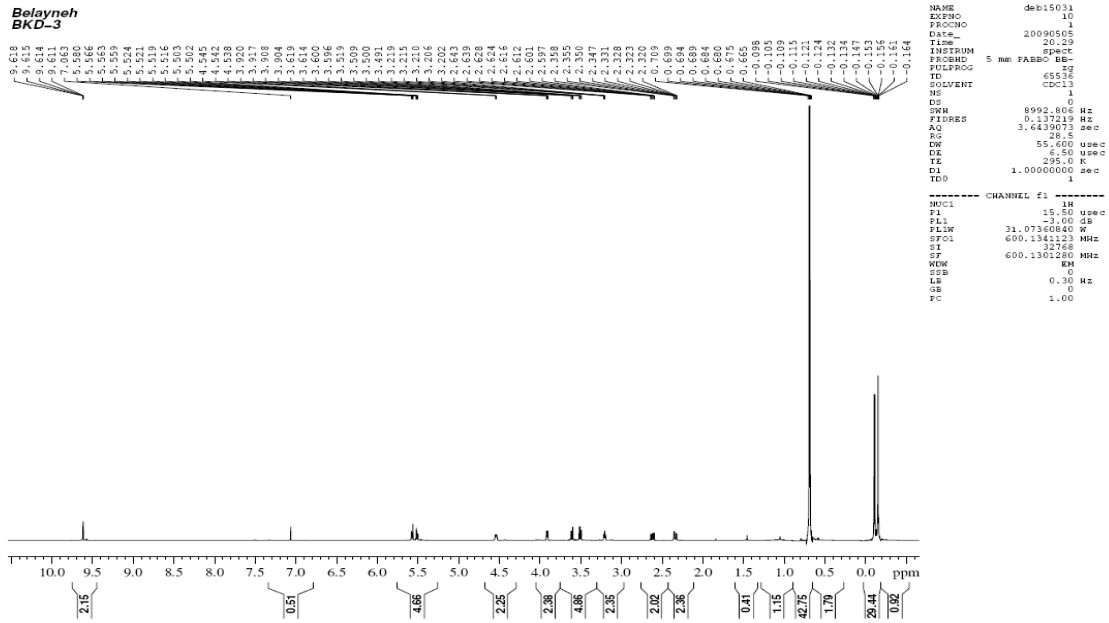


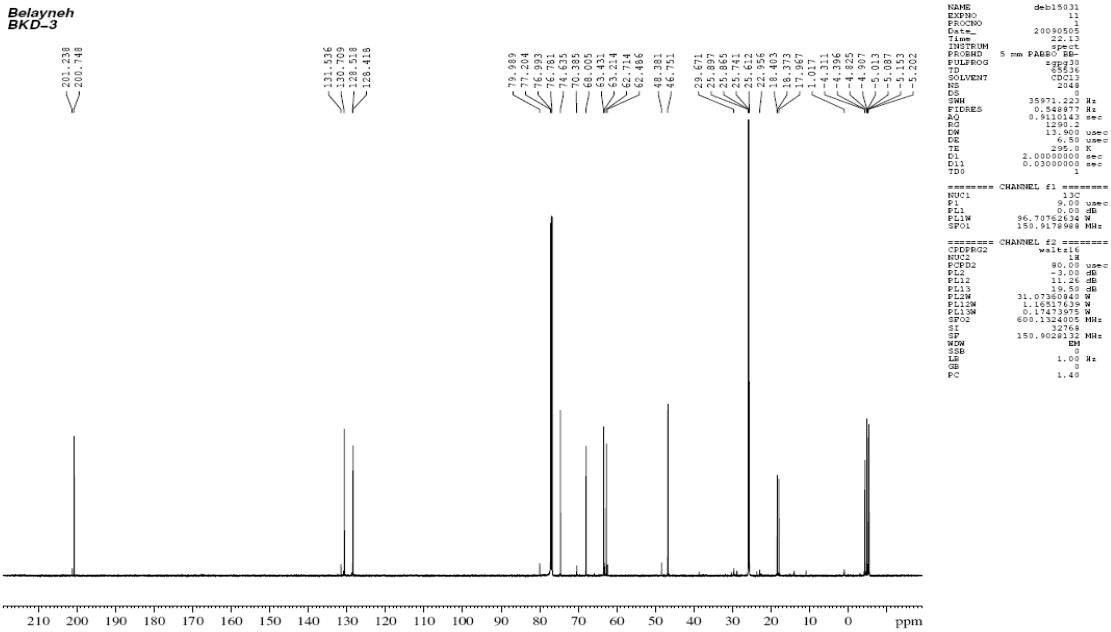




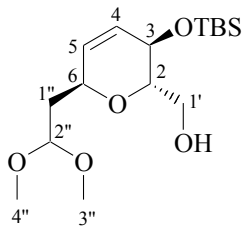
(2S,3R,6S)-5-ter-Butyldimethylsilanyloxy-6-tert-butyldimethyl-silanyloxymethyl-5,6-dihydro-2H-pyran-2-yl-acetaldehyde

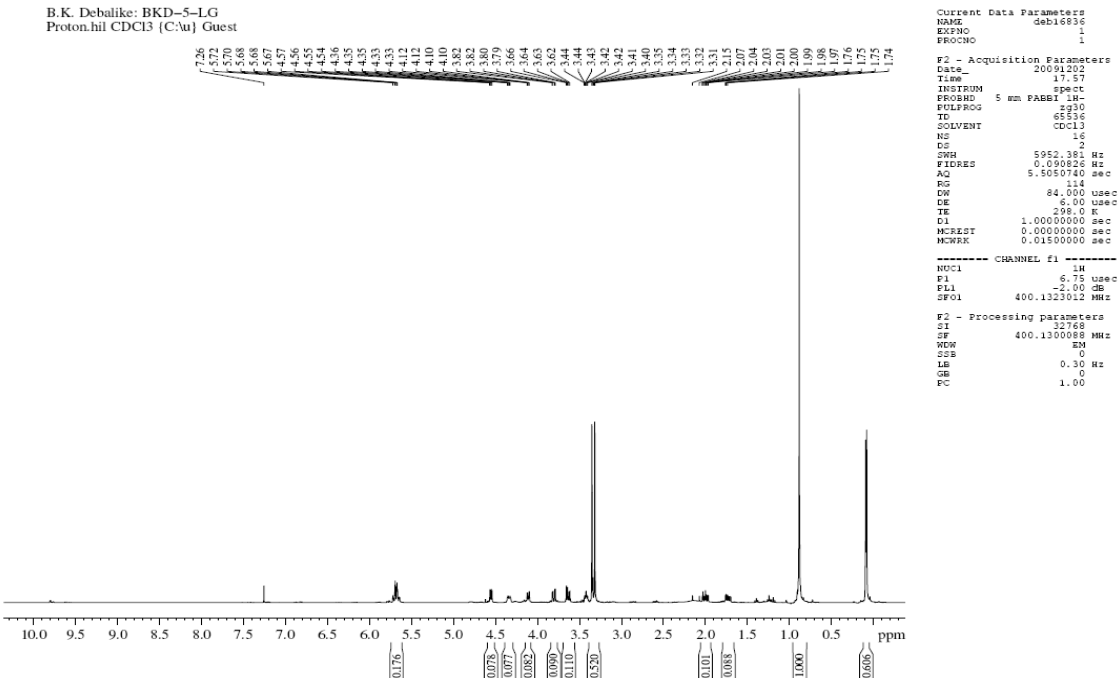


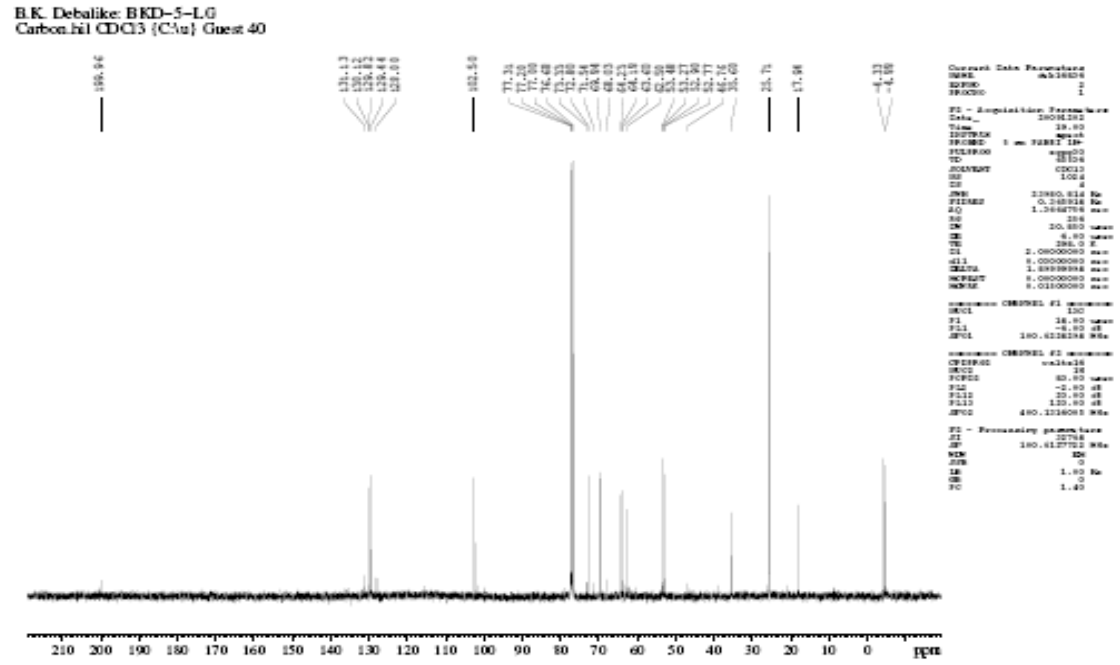




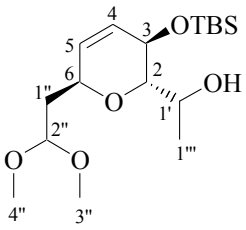
(2S,3R,6S)-*tert*-Butyldimethylsilanyloxy-6-(2,2-dimethoxy-ethyl)-3,6-dihydro-2H-pyranyl)-methanol

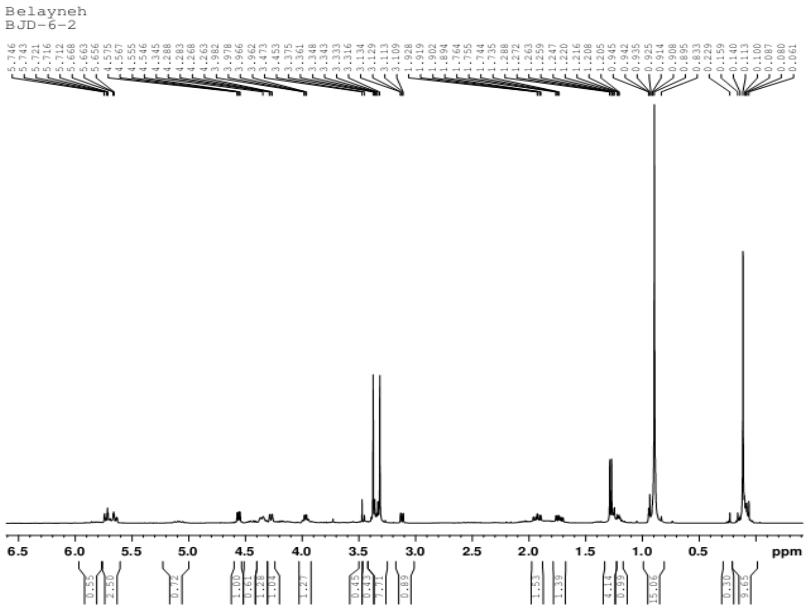




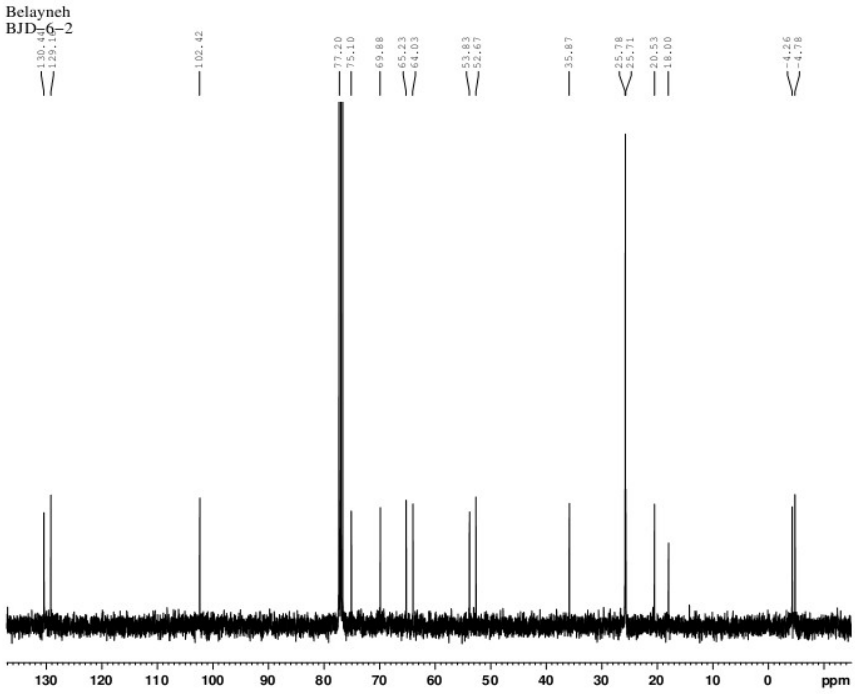


(2S,3R,6S)-1-3-*tert*-Butyldimethylsilanyloxy-6-(2,2-dimethoxyethyl)-3,6-dihydro-2*H*-pyranyl)-ethanol



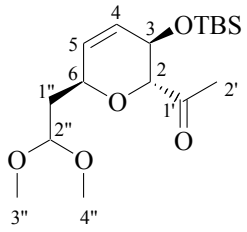


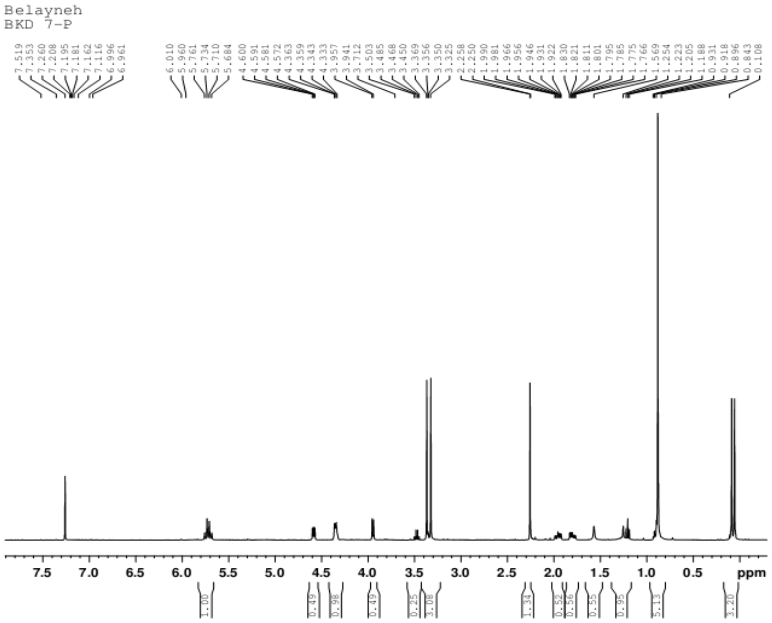

```
Current Data Parameters
NAME                 deb22868
EXPNO                       3
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120302
Time                   12.19
INSTRUM                spect
PROBHD    5 mm PABBO BB/
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                     79.21
DW                    60.800 usec
DE                     6.50 usec
TE                    300.0 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      1H
P1                     15.00 usec
PLW1           10.00000000 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                    65536
SF               400.1300096 MHz
WDW                      EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```



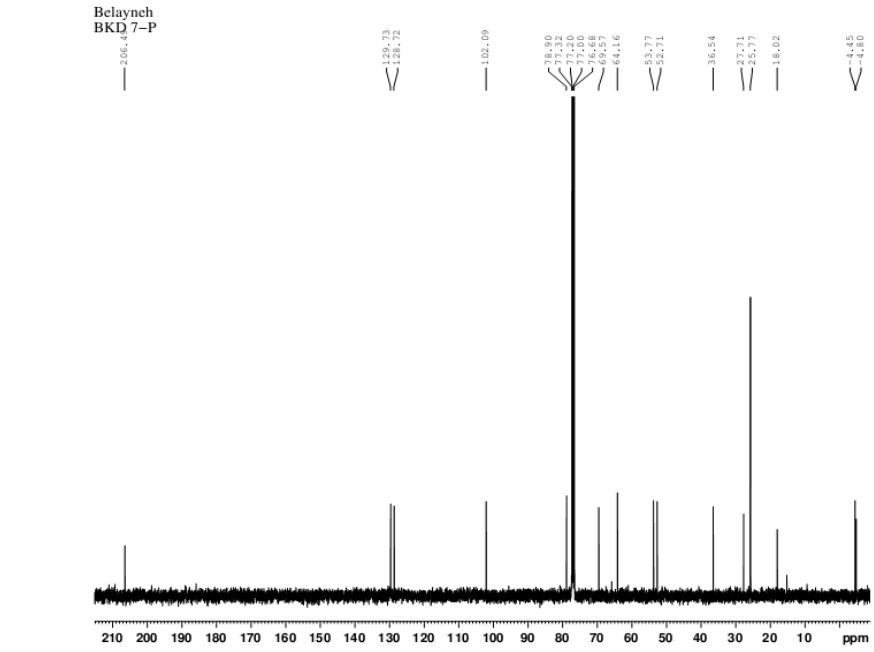

```
Current Data Parameters
NAME                 deb22868
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120302
Time                   12.08
INSTRUM                spect
PROBHD    5 mm PABBO BB/
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      100
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                   20.800 usec
DE                     6.50 usec
TE                    300.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                     13C
P1                     10.00 usec
PLW1           38.00000000 W
SFO1           100.6228293 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                  90.00 usec
PLW2           10.00000000 W
PLW12           0.27778000 W
PLW13           0.22499999 W
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF               100.6127706 MHz
WDW                      EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

(2S,3R,6S)-1-3-*tert*-Butyldimethylsilanyloxy-6-(2,2-dimethoxyethyl)-3,6-dihydro-2*H*-pyranyl-ethanon






```
Current Data Parameters
NAME                 deb22888
EXPNO                      20
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120306
Time                    8.05
INSTRUM                spect
PROBHD   5 mm PABBO BB/
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                    179.58
DW                    60.800 usec
DE                     6.50 usec
TE                    300.0 K
D1                 1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      1H
P1                    15.00 usec
PLW1           10.00000000 W
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                    65536
SF             400.1300097 MHz
WDW                      EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```




```
Current Data Parameters
NAME                 deb22888
EXPNO                      21
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120306
Time                    8.35
INSTRUM                spect
PROBHD   5 mm PABBO BB/
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      498
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                    20.800 usec
DE                     6.50 usec
TE                    299.6 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     13C
P1                    10.00 usec
PLW1           38.00000000 W
SFO1          100.6228293 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                      1H
PCPD2                 90.00 usec
PLW2           10.00000000 W
PLW12           0.27778000 W
PLW13           0.22499999 W
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF             100.6127699 MHz
WDW                      EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

Curriculm Vitae

Personal Data

Name	Kumeneger D. Belayneh
Date of Birth	16.12.1976
Place of Birth	Addis Ababa, Ethiopia
Family Status	Married

Education and Training

1991-1994	Yekatit 12 Secondary High School, Addis Ababa, Ethiopia
1995-1999	Addis Ababa University (AAU), Addis Ababa, Ethiopia B.Sc. in Chemistry
1999-2002	Addis Ababa University (AAU), Addis Ababa, Ethiopia Management and Accounting Basic Training
2001-2002	Addis Ababa University (Virtual University), Ethiopia Basic Computer Course
2002-2004	University of Magdeburg, Germany, 2004 M.Sc. in Quality, Safety and Environment
2004-2005	University of Halle, Germany Doctoral training in Organic Chemistry
2006-2012	University of Magdeburg, Germany Ph.D. in Organic Chemistry

Professional experience

1999-2002	MIDROC-ELICO, Addis Ababa, Ethiopia Head of Retaning and dyeing, Foreman Chemist
2005-2010	University of Magdeburg, Germany Department of Chemistry, Scientific co-worker (Part-time)

Award received

01.04.06-31.12.06	University of Magdeburg, Germany Pro-3 Scholarship
01.07.07-30.06.09	University of Magdeburg, Germany Sachsen-Anhalt-Scholarship
01.07.09-31.12.09	University of Magdeburg, Germany DAAD Scholarship for Doctoral students

Professional membership

Chemical Society of Ethiopia (CSE), Member.

Magdeburg International Ph.D. Students (MIPS), Member.