SYNTHETIC STUDIES TOWARD MYCOLACTONES, EUPOMATILONE-6 AND SOME NOVEL COMPOUNDS

Submitted by

Joseph Cherian

To

University of Pune

For
The Degree of Doctor of Philosophy
(In Chemistry)

Division of Organic Chemistry: Technology
National Chemical Laboratory
Pune-411008
India

September 2003

DECLARATION

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

Date: (Joseph Cherian)

Organic Chemistry: Technology

National Chemical Laboratory

Pune-411 008.

NATIONAL CHEMICAL LABORATORY

Dr. Homi Bhabha Road, PUNE - 411 008 INDIA.

Dr. M. K. Gurjar
Deputy Director & Head
Division of Organic Chemistry: Technology

Telephone and Fax: + 91-20-5893614
+ 91-20-5882456
E-mail: gurjar@dalton.ncl.res.in
Website: http://www.ncl-india.org

CERTIFICATE

The research work presented in this thesis entitled **"*Synthetic studies toward Mycolactones, Eupomatilone-6 and some novel compounds*"** has been carried out under my supervision and is bonafide work of **Mr. Joseph Cherian**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-8 **(Dr. M. K. Gurjar)**

Date: (Research Guide)

Acknowledgements

It gives me immense pleasure to express my deep sense of gratitude to my teacher and research guide Dr. M. K. Gurjar FNASc, Deputy Director and Head of Organic Chemistry: Technology Division, National Chemical Laboratory, Pune for his inspiring guidance and constant encouragement. It would have been impossible to accomplish this work, without his able guidance and unabated perseverance in the quest for success.

I am thankful to Dr. R. A. Joshi, Dr. C. V. Ramana, Dr. M. N. Deshmukh and Mr. I. Shivakumar for timely help and discussion. The help of Dr. P. Rajamohan is gratefully acknowledged.

It is indeed a pleasure to thank for all that I have learned with Dr. Hotha Srinivas, Dr. A. M. S. Murugaiah,Dr. K. K. Reddy and Dr. Arindam Talukdar while working with them.

The warm and friendly attitude of my colleagues at NCL, Pune helped to have cheerful atmosphere in the laboratory. I extend my deep sense gratitude towards them. Also I whole-heartedly thank NCL GJ Hostelites especially the group of mallu's who made the life memorable and pleasant.

I extend my thanks to technical staff of NCL for their assistance. Thanks to DNCL for providing facilities and CSIR New Delhi for financial support.

Whatever I am and whatever I will be in future is because of the goodwill and unstinted support that I have received from my parents, wife and brothers. Their kind cooperation helped me in pursuing the PhD and no words are enough to acknowledge them. Their constant encouragement, sacrifice and support made me achieve the goal.

Joseph Cherian

General Remarks

- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Proton magnetic resonance spectra were recorded on AC-200 MHz, MSL-300 MHz and Bruker-500 MHz spectrometer using tetra methyl silane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C Nuclear magnetic spectra were recorded on AC-50 MHz, MSL-75 MHz and Bruker-125 MHz spectrometer.
- Mass spectra were recorded on a Finnigan Mat 1210 spectrometer at 70 eV using a direct inlet system.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV, I_2 and anisaldehyde in ethanol as development reagents.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry.
- Silica gel (60-120) used for column chromatography was purchased from ACME Chemical Company, Bombay, India.

ABREVIATIONS

Ac	- Acetyl
AcOH	- Acetic acid
Ac_2O	- Acetic anhydride
BF_3:OEt_2	- Borontrifluoride diethyletherate
BINAP	- 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	- Benzyl
BnBr	- Benzyl bromide
BnCl	- Benzyl chloride
Bu_3SnH	-Tributyltinhydride
CAN	- Ammonium cerium(IV) nitrate
DBU	- 1,8-Diazabicyclo [5.4.0]undec-7-ene
DCC	- Dicyclohexylcarbodiimide
DIBAL-H	- Diisobutylaluminium hydride
DIPEA	- Diisopropylethylamine
DMAP	- *N, N'*-Dimethylaminopyridine
DMDO	-Dimethyldioxirane
DME	-Dimethoxyethane
DMF	- *N, N'*-Dimethylformamide
DMP	- 2,2-Dimethoxypropane
DMSO	- Dimethyl sulfoxide
Et	- Ethyl
EtOAc	- Ethyl acetate
EtOEt, Et_2O	-Diethylether
EtOH	- Ethanol
Im	- Imidazole
LDA	- Lithiumdiisopropylamide
MeOH	- Methanol
MEMCl	-Methoxyethoxymethylchloride
MTPA	-α-Methoxy-α-trifluoromethylphenylacetic acid
NaOMe	- Sodium methoxide

NBS	- *N*-Bromosuccinimide
Pd/C	- Palladium on carbon
PDC	- Pyridiniumdichromate
PMB	- *para*-Methoxy benzyl
PPTS	-pyridinium-*para*-toluenesulphonate
*p*TSA	- *para*-Toluenesulfonic acid
Py	- Pyridine
TBAF	- Tetrabutylammonium fluoride
TBDMS-Cl	- *tert*-Butyldimethylchlorosilane
TBDPS-Cl	- *tert*-Butyldiphenylchlorosilane
TEA	- Triethyl amine
THF	- Tetrahydrofuran
TsCl	-*p*-Toluenesulphonylchloride

Contents

	Page No.
Abstract	i
Chapter-I: Synthetic Studies Toward C_1-C_{16} Section of Mycolactones A and B	
Introduction	1
Present Work	13
Experimental	26
References	34
Chapter-II: Stereoselective Synthesis of Eupomatilone-6	
Introduction	37
Present Work	47
Experimental	63
References	75
Chapter-III:	
General Introduction	78
Section I: Synthesis of [4,4`]-Spiro-proline Derivative	
Introduction	83
Present Work	89
Experimental	96
References	102
Section II: Synthesis of Bicyclic Ethers by Ring Closing Metathesis	
Introduction	105
Present Work	110
Experimental	116
References	124
Publications	126

Introduction

Buruli ulcer, known as 'modern leprosy' is an emerging ulcerative skin disease caused by *Mycobacterium ulcerans*. It is the third most common mycobacterial disease in humans after tuberculosis (*Mycobacterium tuberculosis*) and leprosy (*Mycobacterium leprae*) and is the most poorly understood of these three diseases.[1] Unlike the other two, however, *Mycobacterium ulcerans* generally does not live inside the cells of its host, but dwells in the material surrounding cells. It was first detected in 1948 among farmers in Australia. However, Sir Albert Cook described cases as early as 1897 in Uganda. Most patients are women and children who live in rural areas near rivers or wet lands.

Buruli ulcer is also known as Searles ulcer, Kumusi ulcer and Bairns ulcer, but more precisely, *M. ulcerans* infection. The name Buruli ulcer originated from the Buruli district of Uganda where the first large number of the diseases was recorded. Buruli ulcer is found in marshy parts of the tropical and subtropical regions of Africa, Asia, Latin America and the western Pacific. In many areas, *M. ulcerans* infection has occurred only after significant environmental disturbance like flooding, human migration, deforestation and man made topographic modifications such as dams and resorts. The sources of *M. ulcerans* in nature are becoming clearer from epidemiological data and from molecular biologic findings. Because all major endemic foci are in wetlands of tropical or subtropical countries, environmental factors must play an essential role in the survival of the etiologic agent.

Transmission

Although the exact mode of transmission is not known, trauma seems to be the most likely means by which *mycobacterium ulcerans* is introduced. Recently inoculation of mycobacterium ulcerans bacteria into the skin by aquatic insects has also been proposed as a possible mode of transmission. Transmission from person-to-person or by aerosol spread has not been proven.

Pathogenesis and Pathology

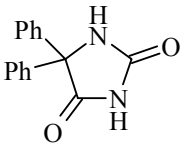
The disease often starts as a painless swelling in the skin. A nodule develops beneath the skin's surface teeming with mycobacteria. Unlike other mycobacteria, *M. Ulcerans* produces a toxin which destroys tissue and suppresses the immune system. One important feature of buruli ulcer is the minimally painful nature of the disease.[2,3] After inoculation into

the skin, *M. Ulcerans* proliferates and elaborates a toxin[2] that causes necrosis of the dermis, panniculus and deep fascia. Early lesions are closed, but as the necrosis spreads, the overlying dermis and epidermis eventually ulcerate, with undermined edges and a necrotic slough in the base of the ulcer. Histopathologic sections reveal a contiguous coagulation necrosis of the deep dermis and panniculus, with destruction of nerves, appendages, and blood vessels. Clumps of extracellular acid-fast bacilli are plentiful and are frequently limited to the base of the ulcer and adjacent necrotic subcutaneous tissue. Bone is sometimes involved, and specific osteomyelitis is well known. Histologically there may be local and regional lymphadenitis with invasion by *M. Ulcerans*. In active lesions, inflammatory cells are conspicuously few, presumably as a result of the immunosuppressive activity of the toxin. With healing, there is a granulomatous response, and the ulcerated area is eventually replaced by a depressed scar. HIV infection does not seem to predispose to Buruli ulcer nor render infection with *M. ulcerans* more aggressive. Death due to Buruli ulcer is rare.

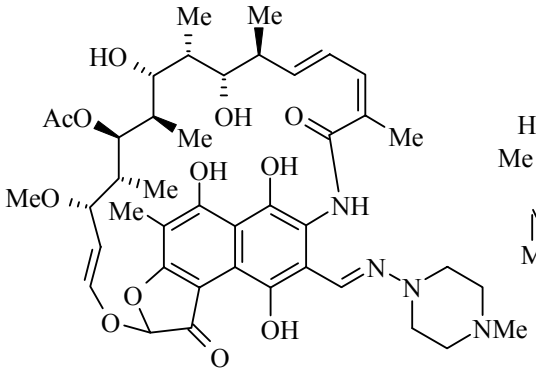
Disruption of the normal immune response to a bacterial infection is a hallmark of buruli ulcer. When tissue starts to die from an infection, white blood cells (neutrophils) normally rush in, generating the pus typical of many wounds. In buruli ulcer, however, neutrophils rarely enter the dying tissue, giving the ulcer a clean look.

Treatment and Immunization

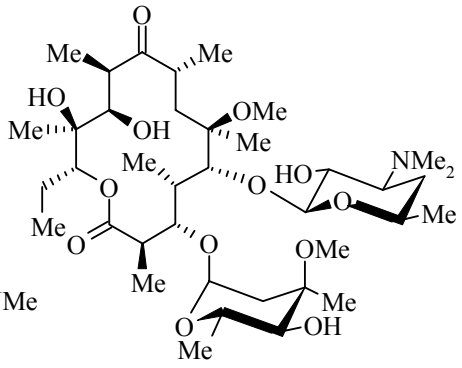
Treatment options for Buruli ulcer are surgery, topical preparations, and



Penytoin (1)



Rifampicin (2)

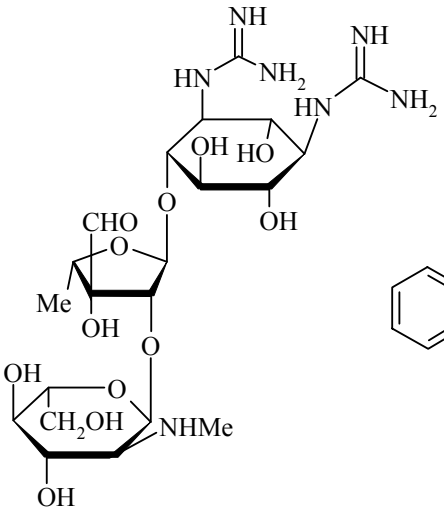


Clarithromycin (3)

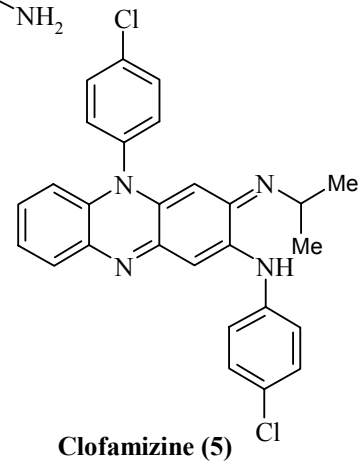
antimycobacterials. Surgery is currently the treatment of choice. The removal of nodules at an early stage through simple excision and suturing results in a cure. For large ulcers, the

only effective treatment is wide surgical excision followed by skin grafting later when the wound is clean.

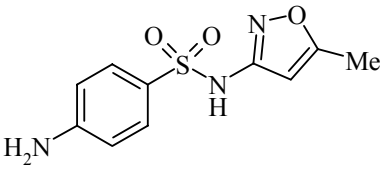
Topical treatment with phenytoin (**1**), a drug used in treating epilepsy, has been suggested and used by some clinicians. Its mechanism of action in treating ulcers is not known. It is believed to promote healing without the scar formation often associated with Buruli ulcer. Topical heat application to ulcers is also believed to be of benefit since the optimal temperature for *Mycobacterium ulcerans* growth is 31 to 33 ^{o}C. Application of heat



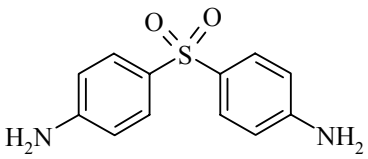
Streptomycin (4)



Clofamizine (5)



Cotrimoxazole (6)



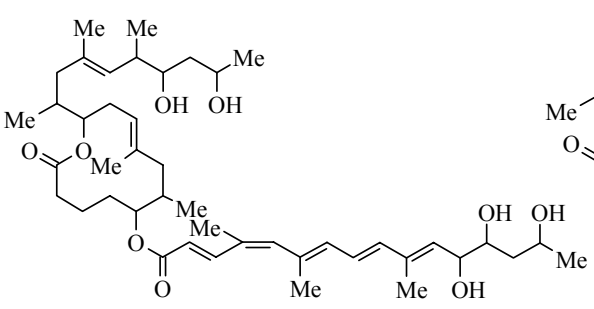
Dapsone (7)

greater than the optimum growth temperature of *Mycobacterium ulcerans* results in poor growth. The efficacy of both topical phenytoin and topical heat need further evaluation. Antimycobacterials are antibiotics effective against mycobacteria and are used routinely for the treatment of mycobacterial infections such as tuberculosis and leprosy. There have been reports of their use for treating Buruli ulcer. These include rifampicin (**2**), clarithromycin (**3**), streptomycin (**4**), clofamizine (**5**), cotrimoxazole (**6**) and dapsone (**7**). The current role of antimycobacterials in treating Buruli ulcer is said to be limited. The poor response to antibiotics has been attributed to the reduced penetration of antimycobacterials into dead (necrotic) tissue, which characterize buruli ulcers. Despite all this, it is still believed that antimycobacterials in the right combination for the appropriate duration may reduce healing time for ulcers, as well as reducing recurrences. They could also be beneficial in the stage of the disease that precedes ulcer formation. The effect of antimycobacterials on Buruli ulcer needs to be evaluated. Bacille Calmette Guerin (BCG) vaccine is found to have a protective effect for Buruli Ulcer. Though it is not given routinely for preventing buruli ulcer, it is

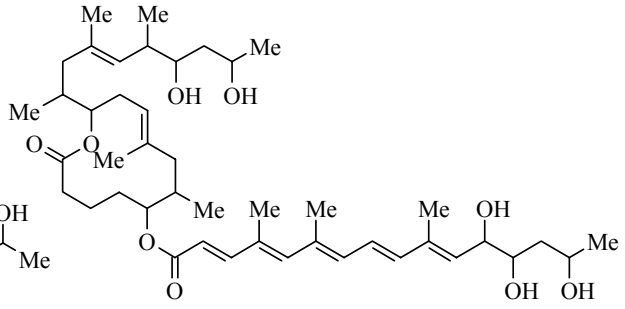
currently being encouraged in infants as a means of preventing Buruli ulcer. It has been suggested that administration of multiple doses of BCG to high-risk populations could prevent Buruli ulcer since its protective effect for buruli ulcer is short lasting.

Toxin

A curious feature of Buruli ulcer pathology is that organisms lie in a necrotic focus with the necrosis extending some distance from the site of bacterial colonization. This observation led to the hypothesis that *M. ulcerans* secreted a toxin.[2,4] After several unsuccessful attempts,[5,6] polyketide-derived macrolides, named mycolactones A and B (**8** & **9**), which are in a dynamic equilibrium with each other, were purified from *M. ulcerans*.[7] Mycolactones are also present in sterile filtrate, though in lesser quantities than that associated with intact bacterium. Based on two-dimensional NMR spectral analysis and mass spectral datas, the macrolides were assigned the basic skeleton as shown in figure. They contain a polyketide derived 12-membered macrolide, to which two side chains are attached.



Mycolactone A (8)



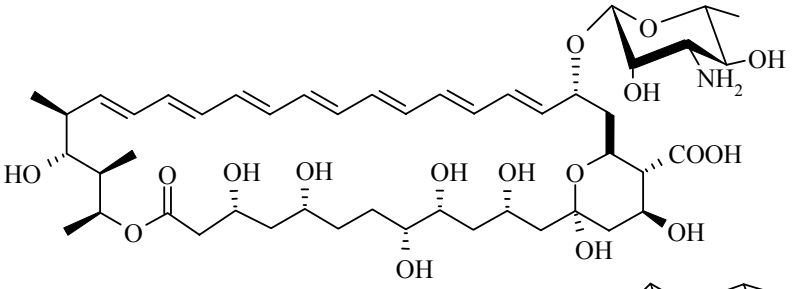
Mycolactone B (9)

Mycolactone is the first toxin isolated from Mycobacteria species as well as the first complex polyketide isolated from a pathogenic mycobacteria species.[8] The discovery that *M. Ulcerans* toxin is a polyketide is highly significant. Polyketides are produced as secondary metabolites from a number of soil bacteria in the order Actinomycetales.[9] They are magic molecules with remarkable biological activity including immunosuppressive (FK 406), antibiotic (erythromycin), cytostatic (bafilomycin), antihelmethic (ivermectin) and antifungal (amphotericin). Mycolactone appears to act as both an immunosuppresant and a cytostatin. It is speculated that mycolactone protects *M. ulcerans* from predatory eukaryotes in its natural habitat.[10] Although polyketides are not in themselves usually immunogenic, they can be made

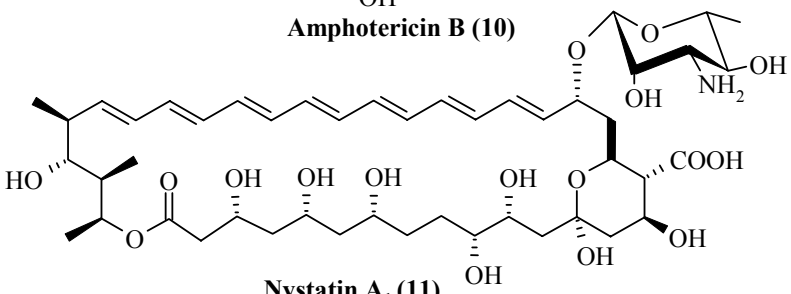
so. Thus mycolactone may prove to have a value either in the treatment or prevention of Buruli ulcer.

Polyene natural products - an overview

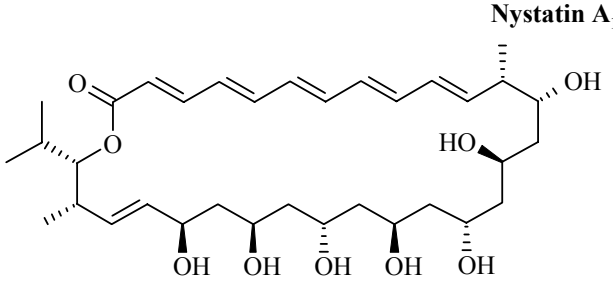
Natural products containing conjugated alkenyl units represent a large and structurally diverse group of compounds.[11] Particularly significant are those possessing biological activity, including the eicosanoids (the arachidonic acid derivatives such as the leukotrienes and lipoxins), the retenoids and the polyene macrolides — a large group comprising over 200 members.[12]



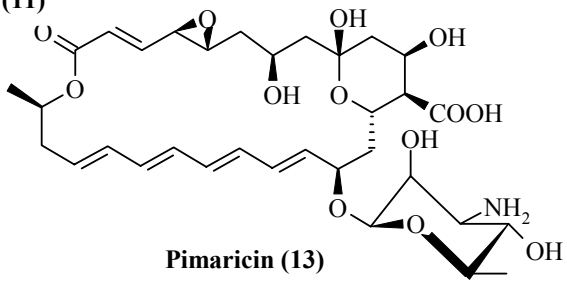
Amphotericin B (10)



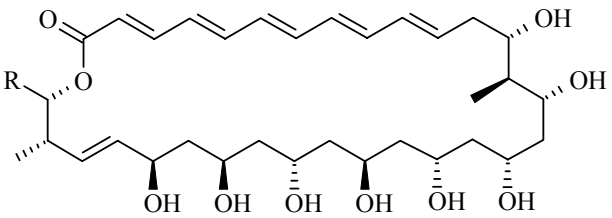
Nystatin A_1 (11)



Roxaticin (12)



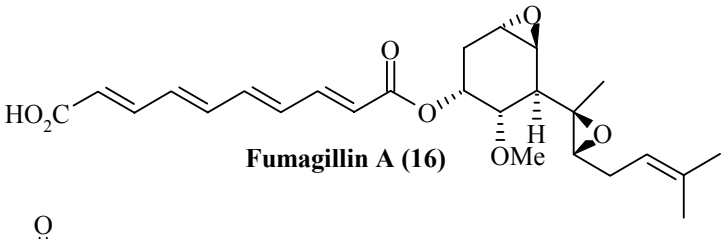
Pimaricin (13)



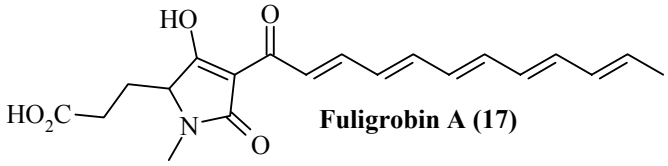
R = *i*-Pr Mycoticin A (14)
R = *s*-Bu Mycoticin B (15)

The most important sub-category of polyene natural products is macrolides derived from bacteria. Structurally, they are very large macrocyclic lactones with 22-44 membered rings commonplace. The polyenic section incorporates between 4 and 8 conjugate double bonds. Some of the clinically important polyene macrolides produced by bacteria include amphotericin B (**10**), nystatin A_1 (**11**), roxaticin (**12**), pimaricin (**13**) and Mycoticin A and B (**14 & 15**).

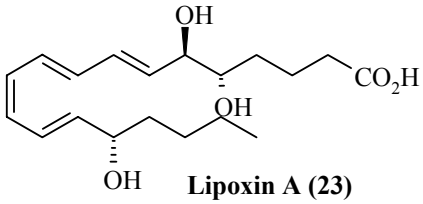
Other sources of polyene natural products include i) fungi [eg. Fumagillin (**16)**]; ii) slime-moulds [eg. Fuligrobin A (**17**)] and plant sources [deoxyphorbol ester derivative (**18**)]; iii) marine organisms [eg. Keronopsins (**19**)] and iv) animals [eg. Lipoxin A (**20**)].



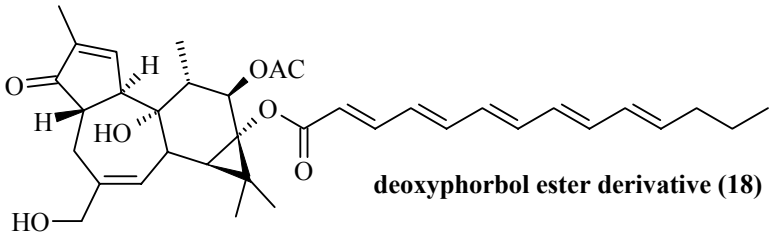
Fumagillin A (16)



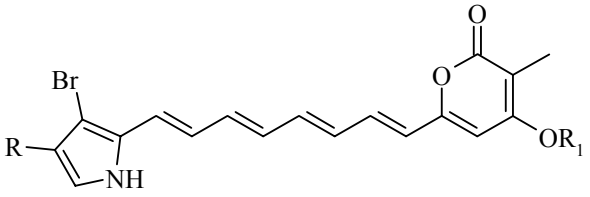
Fuligrobin A (17)



Lipoxin A (23)



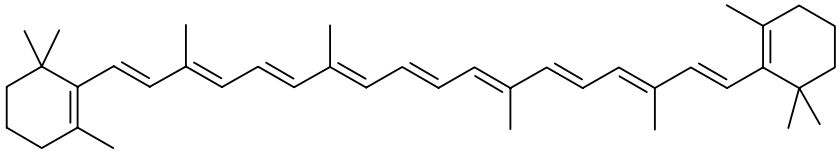
deoxyphorbol ester derivative (18)



R	R_1	**Keronopsin**
SO_3Na	H	A_1 **19**
SO_3Na	Br	A_2 **20**
H	H	B_1 **21**
H	Br	B_2 **22**

If one considers that i) the isolation of β-carotene (**24**) which has been called the classical compound of polyene chemistry[13] dates back to 1831; ii) the structure of β-carotene was established in 1930;[14] iii) the total synthesis of β-carotene was first published in 1950[15] and more interestingly also in 2001[16] (other than dozens of publications over the years[13]), it is

certainly true that the chemistry of polyconjugated compounds is one of the most attractive and intensely researched areas of organic chemistry. Furthermore, more than 600 carotenoids have been isolated from nature from which approximately one third has already been synthesized.



β-carotene (24)

The interest in the isolation and the synthesis of the polyconjugated compounds arose from the curiosity and necessity to learn more about nature. Although this is still a very important factor, recent and current interest in this area is pointing more and more in the direction of material sciences with the promising results that polyenes can be used as molecular wires in molecular electronics. On the one hand, a desire to prepare natural products, not only carotenoids or other terpenes but also polyconjugated bioactive macrolides or at least systems that can mimic biological oligomers and polymers and on the other hand the wish to construct ultra-fast, ultra-dense and molecular sized computational systems,[17] the interest of the researchers on polyconjugated compounds keeps growing and diversifying and will remain like that for many years to come.

Synthesis of polyenes-general strategies

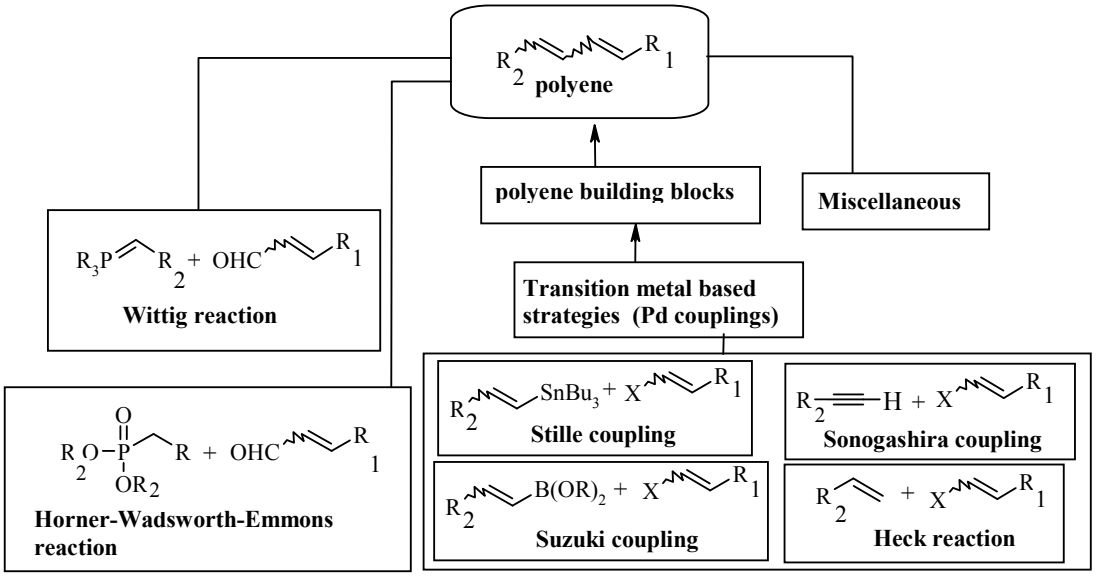


Fig. 1 Most common strategies used in polyene synthesis.

The principal requirements for polyene synthesis are:

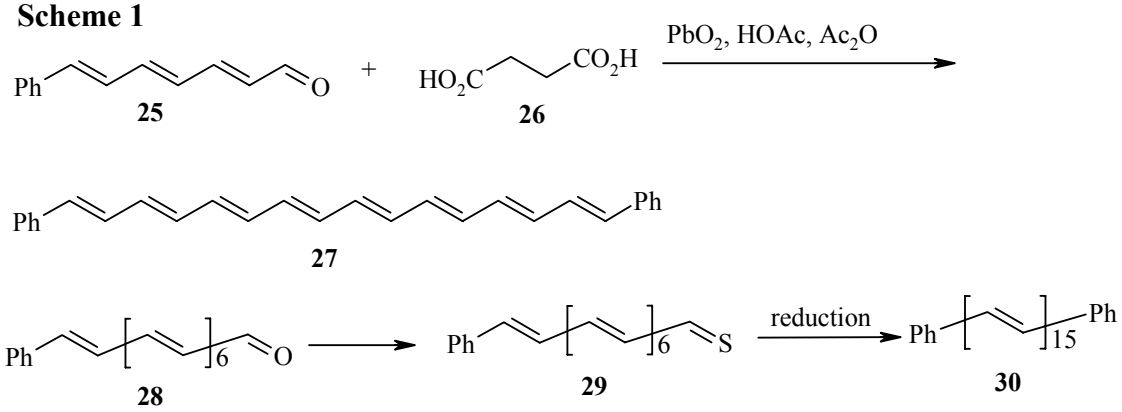
i) a reliable olefination procedure that produces alkenes in high geometric purity;

ii) a procedure that allows ready access to either isomer, whilst at the same time being mild and functional group tolerant.

The general methods taken to date to access polyenes are outlined in fig. 1.

It is possible to illustrate the most important developments in the synthesis of natural or unnatural polyenes by just looking at the numerous studies published on a single compound which was referred previously as being the classic of its kind, namely β-carotene **24**. However, this statement would be overlooking the fact that Kuhn had synthesized α,ω-diphenyl substituted polyene systems containing up to 15 double bonds in 1937 already. In his

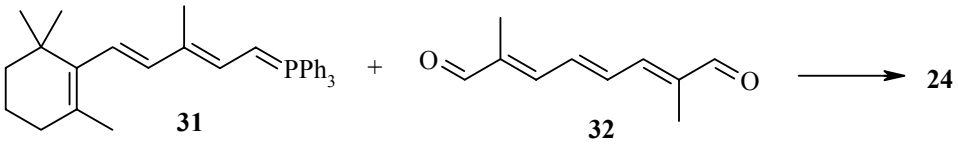
Scheme 1



approach, Kuhn and co-workers prepared the polyenes up to 8 double bonds by condensing two molecules of 7-phenyl-hepta-2,4,6-trienal with succinic acid in acetic acid-acetic anhydride in the presence of lead oxide (Scheme 1). For the synthesis of **30** containing 15 double bonds, the necessary aldehyde **28** was first converted into the thio derivative **29** with H_2S, which then was desulfurized by the use of piperidine or other amines or metals to give the dimerization product **30**.[18]

The discovery of the carbon-carbon double bond forming reaction between a carbonyl compound and a phosphorane by Wittig and co-workers in 1953 can definitely be referred as the most important development in the preparation of polyconjugated compounds.[19] Wittig reported the synthesis of β-carotene **24** in 1956 by using the reaction later named after him. Reaction of 2 equivalents of the phosphorane **31** with the dialdehyde **32** readily gave **24** (Scheme 2).

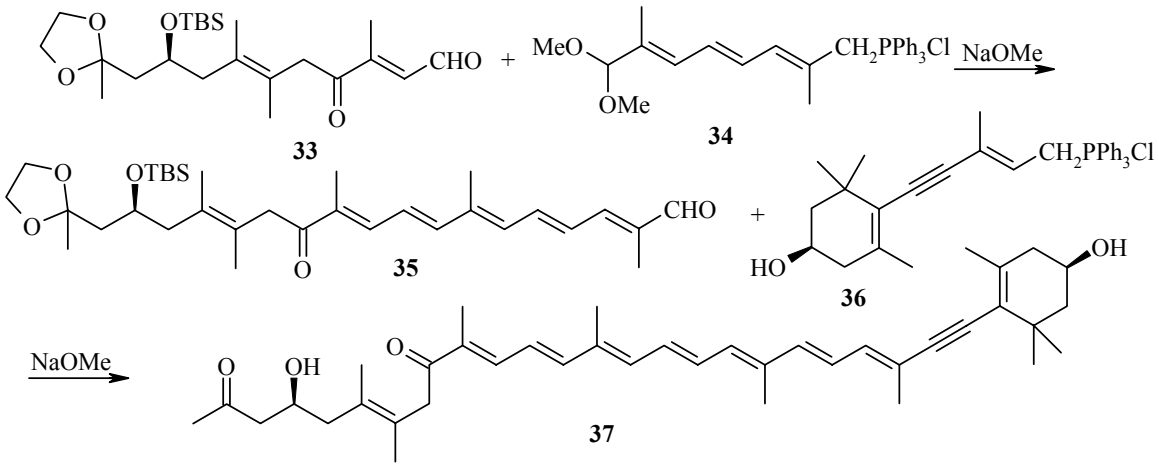
Scheme 2



Wittig reaction has proved historically to be the reaction of choice for the formation of alkenes. The synthetic power inherent with these kinds of coupling and homologation reactions has spurred research into optimizing, modifying or supplanting[20] these methods with others that operate under different reactions conditions,[21] can be prepared from alternative starting materials[22] or that enhance stereochemical control.[23]

Tode's group in the first synthesis of marine carotenoiod crassostreaxanthin B (**37**) employed Wittig reaction (Scheme 3).[24] The synthesis involved a sequence of Wittig

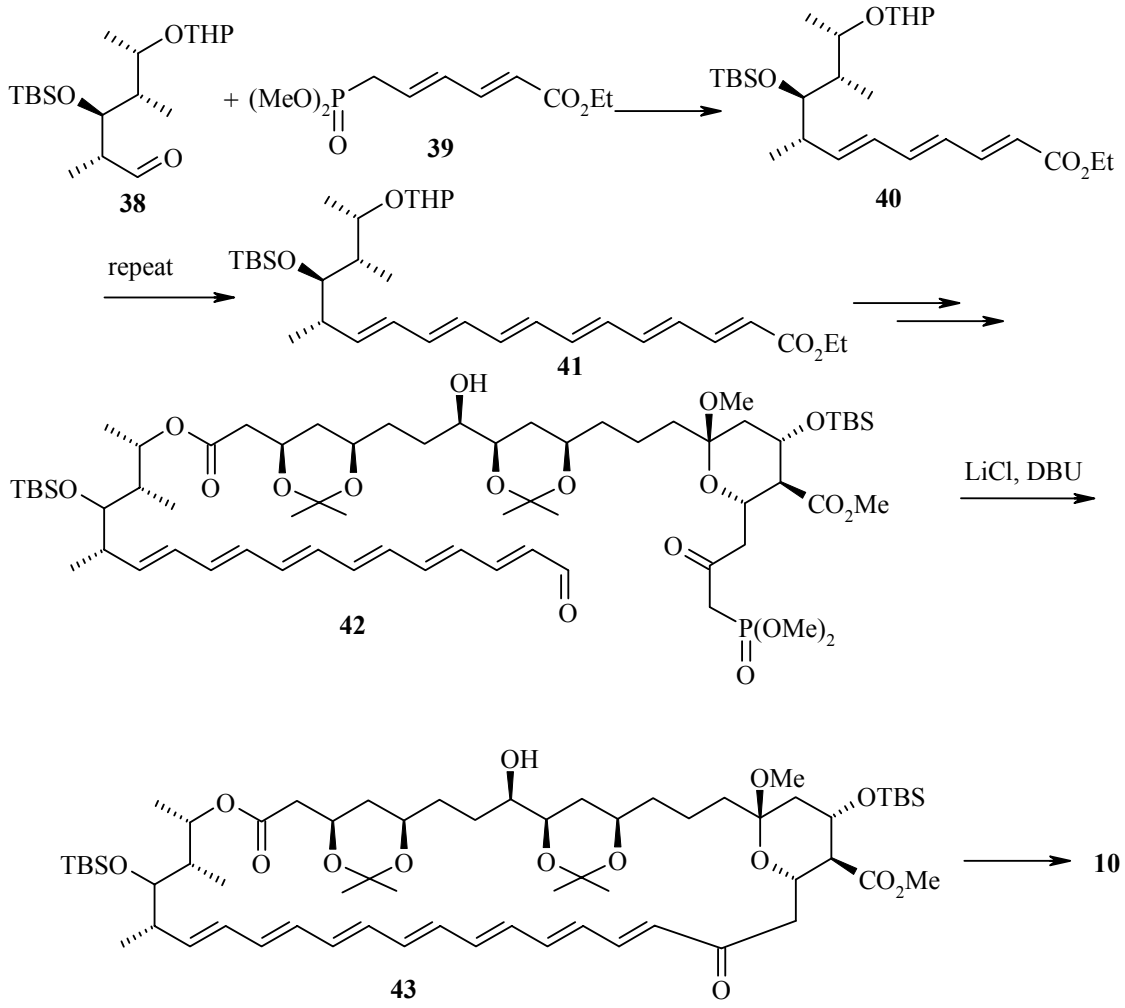
Scheme 3



reactions, the first one being between Wittig salt **34** and aldehyde **33** in presence of 1 M NaOMe to produce aldehyde **35** after acid catalyzed removal of the acetal protection. The aldehyde **35** when treated with phosphorane generated from **36** using NaOMe followed by the removal of ketal protection and TBS ether resulted in the formation of **37**.

However, Wittig reaction with phosphoranes suffers largely from the mixture of isomers formed and purification problems due to the by-product phosphine oxide. The closely related Horner-Wadsworth-Emmons (H. W. E.) procedure[25] using dialkyl phosphonates is increasingly used in all areas of natural product synthesis, particularly due to more selectivity. A prominent example is Nicoloau and co-worker's total synthesis of amphotericin B (**10**) (Scheme 4).[26]

Scheme 4



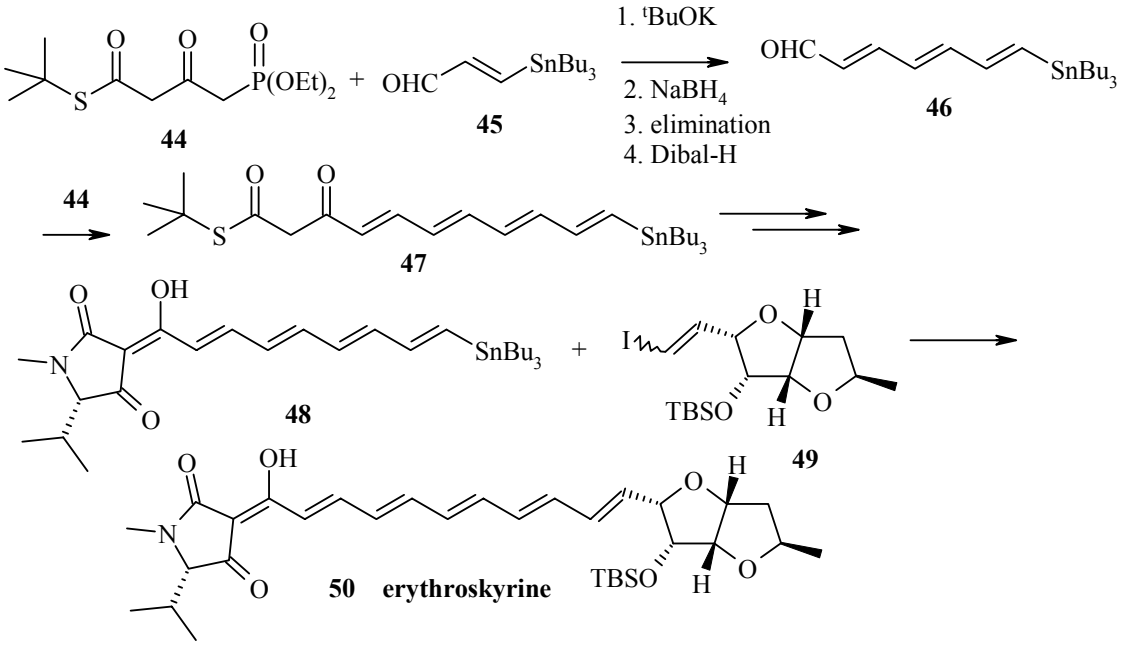
Several variants of Wittig and H. W. E reactions to enhance selectivity towards a particular geometrical isomer are known in the literature.[27]

Transition metal based strategies

Other than Wittig reaction, the most important reactions for formation of C-C double bond, which are often used in polyene chemistry are those involving transition metals. Representative of these strategies are the palladium cross coupling reactions, allowing single bond formation between two sp^2 centers with excellent stereoselectivity and often under mild conditions. The Stille reaction[28] involves coupling of a vinyl stannane and vinyl halide and proceeds with retention of configuration of the latter. A combination of H. W. E and Stille coupling lead to the synthesis of erythroskyrine by Ley *et al* (Scheme 5).[29] Coupling of the phosphonate **44** with β-tributylstannyl aldehyde **45**, reduction of the keto functionality, elimination and DIBAL-H mediated reduction afforded the aldehyde **46**. Coupling with the

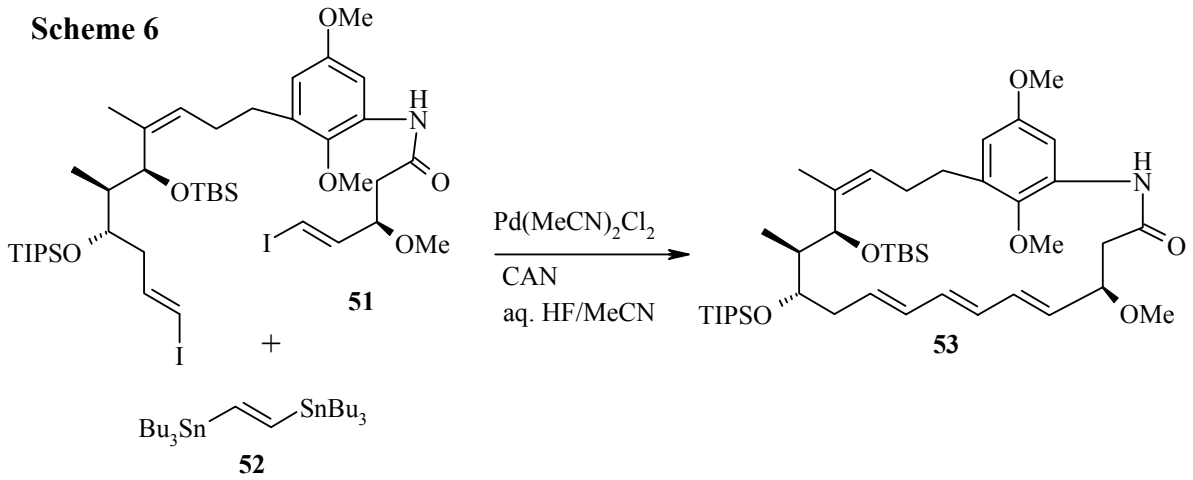
phosphonate **44** gave the stannyl derivative **47**, which was converted to the stannane **48**. Stille coupling with the vinyl iodide **49** gave **50**.

Scheme 5



Panek and Masses' synthesis of mycotrienol[30] also exploits Stille reaction (Scheme 6). The vinyl iodide **51** was coupled with the *bis*-stannyl derivative **52** in presence of

Scheme 6

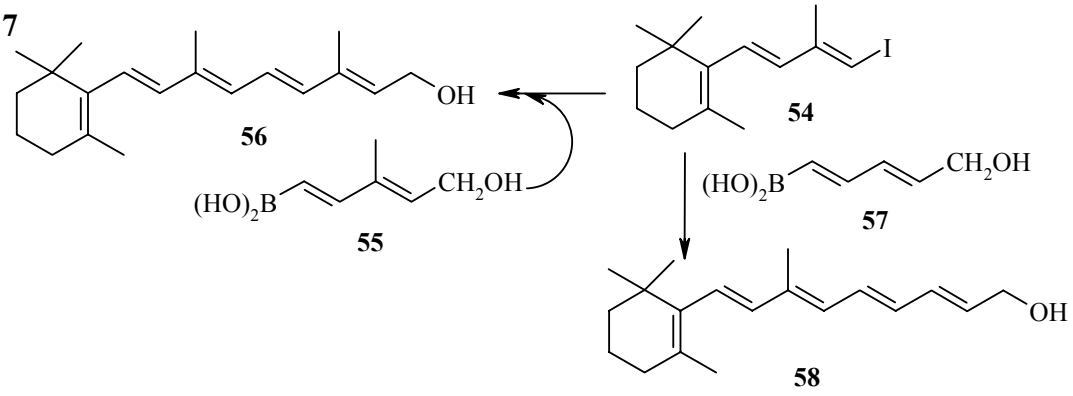


$Pd(MeCN)_2Cl_2$ to afford **53**.

Like Stille coupling reaction, the closely related Suzuki reaction[31] using alkenylboronic acid has found utility in polyene synthesis. Suzuki reaction can operate under extremely mild conditions making it an ideal way to synthesize potentially unstable polyenes. De Lera's group have achieved a highly stereoselective retenoid synthesis *via* thalium

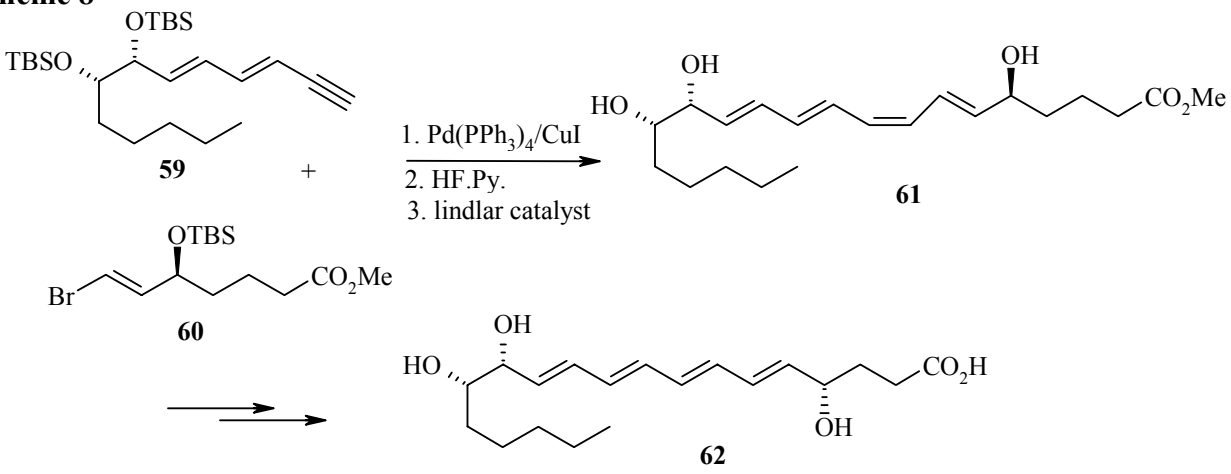
accelerated Suzuki coupling reaction.[32] Thus coupling of boronic acids **55** and **57** with the vinylic iodide derivative **54** resulted in the formation of **56** and **58** respectively with total retention of geometries of coupling partners (Scheme 7).

Scheme 7



Heck reaction has found little utility in polyene synthesis mainly due to the reason that it often leads to a mixture of isomers, unlike Stille coupling in which the stereochemical integrity of the coupling partners is retained. [33] However, the alkyne variant of Heck reaction known as Sonagashira coupling has found numerous applications. This method was applied

Scheme 8

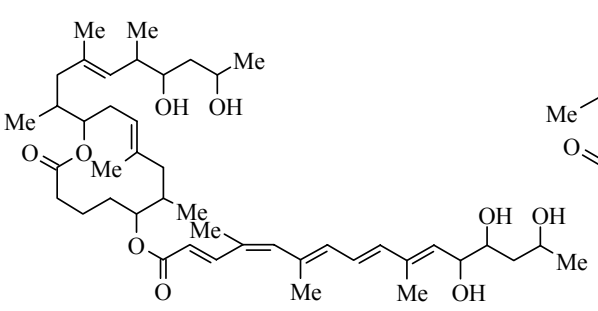


to synthesize all *trans*-lipoxin B (**62**). Thus, coupling of the alkyne **59** with vinylic bromide **60** in presence of Pd(0) and CuI resulted in the formation of **61** which was subsequently isomerised to all *trans* **62** (Scheme 8).[34]

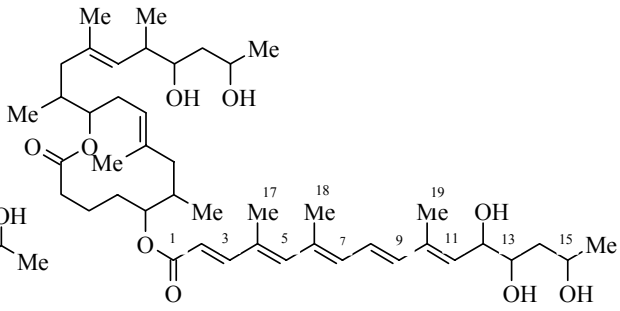
Several other methods including those using Pd, Zn and Zr catalysed couplings have been reported in the recent literature.[16, 35]

Present Work

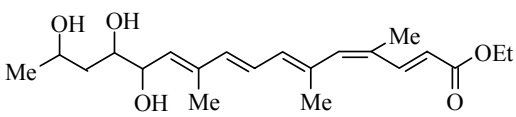
Most pathogenic bacteria produce toxins that are important in disease. However, none has been identified for *Mycobacterium tuberculosis* or *Mycobacterium leprae*. The only Mycobacterial pathogen for which there is any evidence of toxin production is *Mycobacterium ulcerans*, the causative pathogen of Buruli Ulcer. Although Buruli Ulcer is little known outside the tropics, it recently has been recognized as an emerging infection in Western Africa. Despite several attempts, no compound responsible for the cytopathic effect of this organism has been identified till 1999 when Small *et al* identified the toxin and found it to be a polyketide. Polyketides are lipid-like molecules that, although relatively small compared with protein toxin, have potent biological activities. To reflect its mycobacterial source and chemical structure the toxin isolated from *Mycobacterium Ulcerans* has been named as Mycolactones A and B. Mycolactones are the first toxin isolated from *Mycobacteria* species as well as the first complex polyketide produced by a human pathogen.



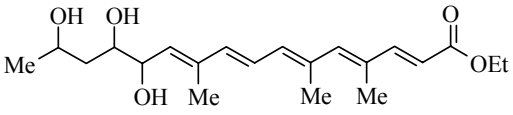
Mycolactone A (8)



Mycolactone B (9)



63



64

The role of mycolactones as a virulence determinant may have implications far beyond those for buruli ulcer. A major surprise from the Mycobacterium tuberculosis genome project was the discovery that the genome contains a larger number of polyketide synthesis geneses, although no polyketide have been isolated form *M. tuberculosis*. This family of potent compounds could play a major role in both the tissue destruction and immunological modulation characteristic of diseases such as leprosy and tuberculosis. Further, because most pathogenic mycobacteria are intracellular pathogens, it is possible that

they play an important role in intracellular survival. Complex polyketides such as mycolactones may represent the first of newly discovered class of virulence compounds.

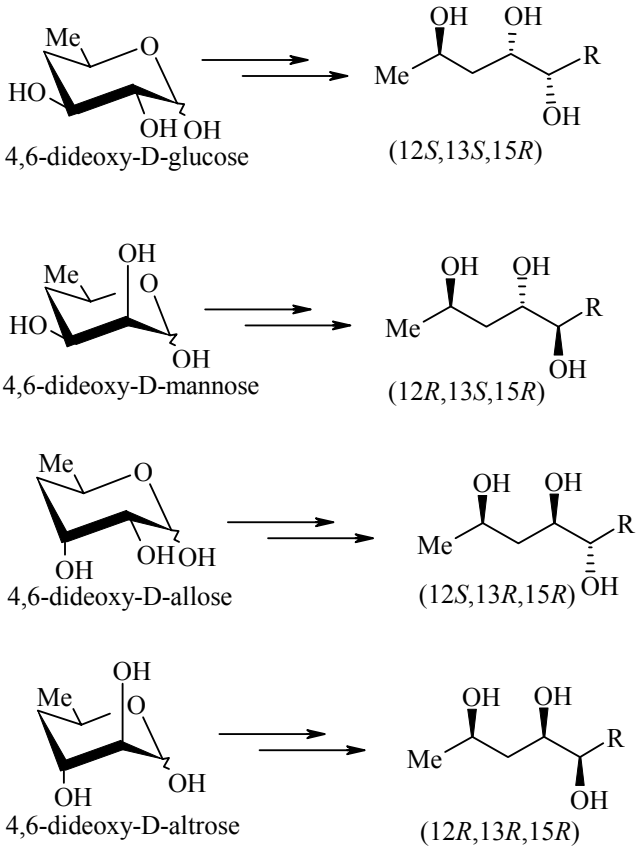
Mycolactones contain a 12-membered lactone core with two side chains attached to it. Among the two side chains, one is a unique polyene fatty acid fragment. Mycolactones A and B differ in the stereochemistry at the C-4 double bond of this polyene fragment (**63** & **64**) and are in a dynamic equilibrium with each other in a 3:2 ratio.

The difficulty in isolating the toxin from *M. ulcerans* and its biological importance inspired us to embark on a programme aimed at its chemical synthesis. The structural elucidation of toxins by chemical synthesis is imperative not only for understanding the molecular basis of mechanism of action, but also for designing proper counter measures such as detection and determination of exact therapeutic methods. In an effort to design a versatile approach towards Mycolactones A and B, we first embarked upon the synthesis of C-1-C-16 segment.

Retro synthetic analysis and strategy

The general strategy for the construction of C-1 – C-16 fragment (**64**) of mycolactones is based on the retro synthetic analysis outlined in Scheme 9. The relative or absolute stereochemical assignments of chiral carbons at C-12, C-13 and C-15 were not known when we initiated the synthetic studies. Therefore, it was desirable to design a synthetic strategy, which can provide all the stereochemical combination for C-12, C-13 and C-15 centers. The most obvious choice was the chiralpool strategy using carbohydrate as starting precursors. A close examination revealed that the centers at C-12, C-13 and C-15 of **63** and **64** could be correlated to C-2, C-3 and C-5 of 4,6-dideoxyhexoses. Hence, 4,6-dideoxy-D-glucose would lead to (12*S*,13*S*,15*R*) configuration whereas 4,6-dideoxy-D-mannose, 4,6-dideoxy-D-allose and 4,6-dideoxy-D-altrose would lead to (12*R*,13*S*,15*R*), (12*S*,13*R*,15*R*) and (12*R*,13*R*,15*R*) configuration respectively. This strategy could be used to make the four diastereomers of **63** and **64**.

With regards to the installation of polyene side chain, it was possible to carryout the job with stepwise formation of double bonds. The alternate approach, which in our opinion more realistic was to build C-8 phosphonate (**95**) separately and then, add to C-8 aldehyde

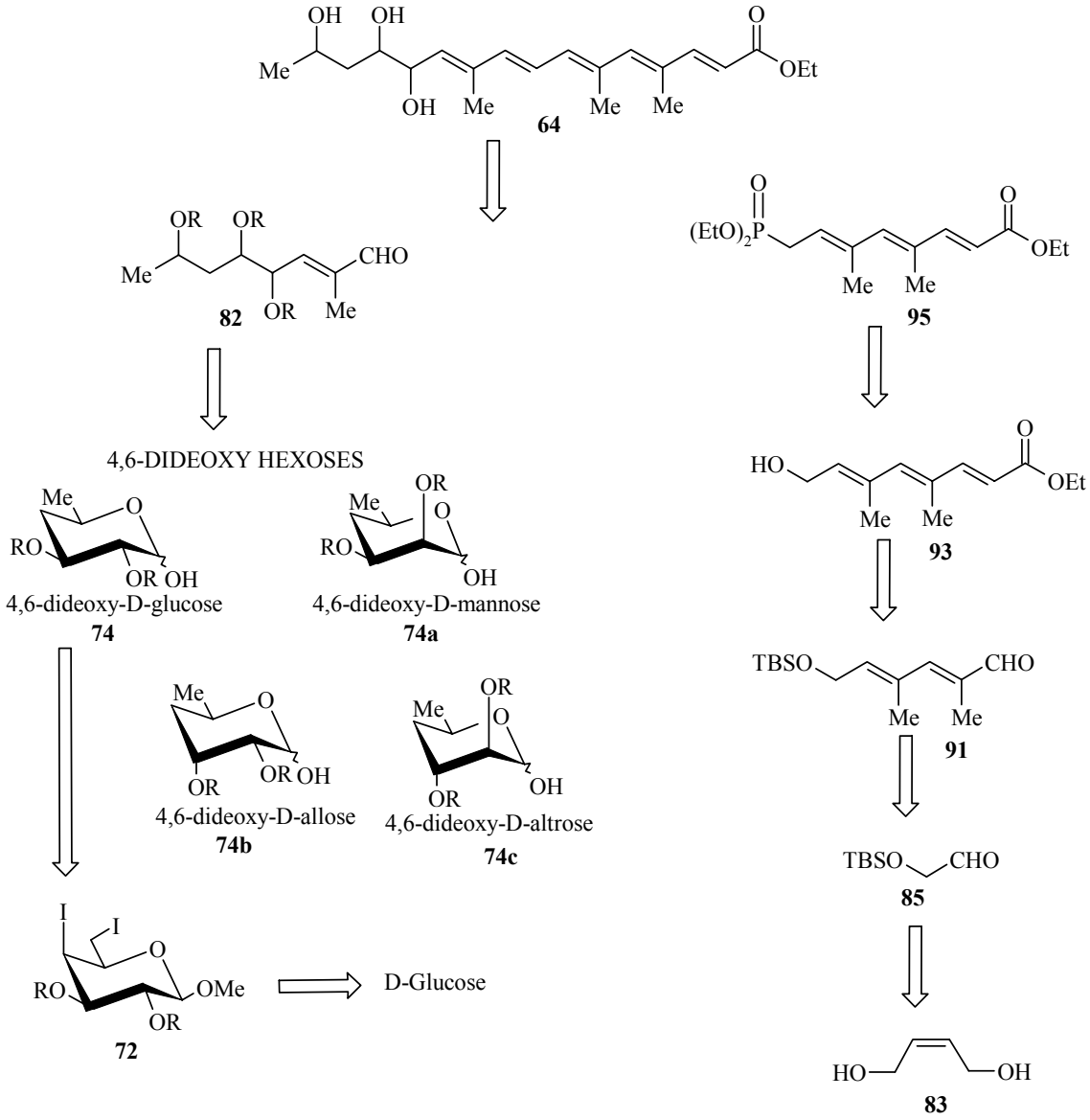


(**82**). We envisaged that **64** could be obtained by Horner-Wadsworth-Emmons reaction between phosphonate **95** and aldehyde **82**. As the mycolactones differ only in the stereochemistry of the double bond at C-4 and are in equilibrium, we expected that **63** would accompany **64**.

The aldehyde **82** and its diastereomers could be obtained from suitably protected 4,6-dideoxy hexose derivatives **74**, **74a**, **74b** and **74c**. The opening of the pyranose ring, selective oxidation of the primary hydroxyl group, Wittig homologation with $Ph_3P{=}C(Me)CO_2Et$ and selective reduction of **74**, **74a**, **74b** and **74c** should lead to the aldehyde **82**. Hydrodehalogenation of the corresponding di-halohexose derivatives would lead to the 4,6-dideoxy hexoses **74**, **74a**, **74b** and **74c**. We envisaged that Garegg's protocol for iodination of a suitably protected hexose derivative, for e.g., methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside which is readily available from D-glucose, would pave a way to the desired diiodo derivative **72**. Benzyl was chosen as the protecting group of choice mainly because of its tolerability to stringent conditions. The other diastereomers of the aldehyde **82** could be prepared in a similar manner from the corresponding sugars.

Phosphonate **95** could be obtained from the alcohol **93** *via* conversion to the bromo derivative and Arbuzov reaction using triethylphosphite. The alcohol in turn can be prepared from the aldehyde **91** by Wittig homologation followed by silyl ether deprotection. A close examination revealed that the aldehyde **91** could be realized from the aldehyde **85** by following an iterative approach involving Wittig homologation, reduction and oxidation sequence. A retro-ozonolysis reaction resulted in the observation that **85** would be accessible from the readily available *cis*-2-butene-1,4-diol (**83**).

Scheme 9

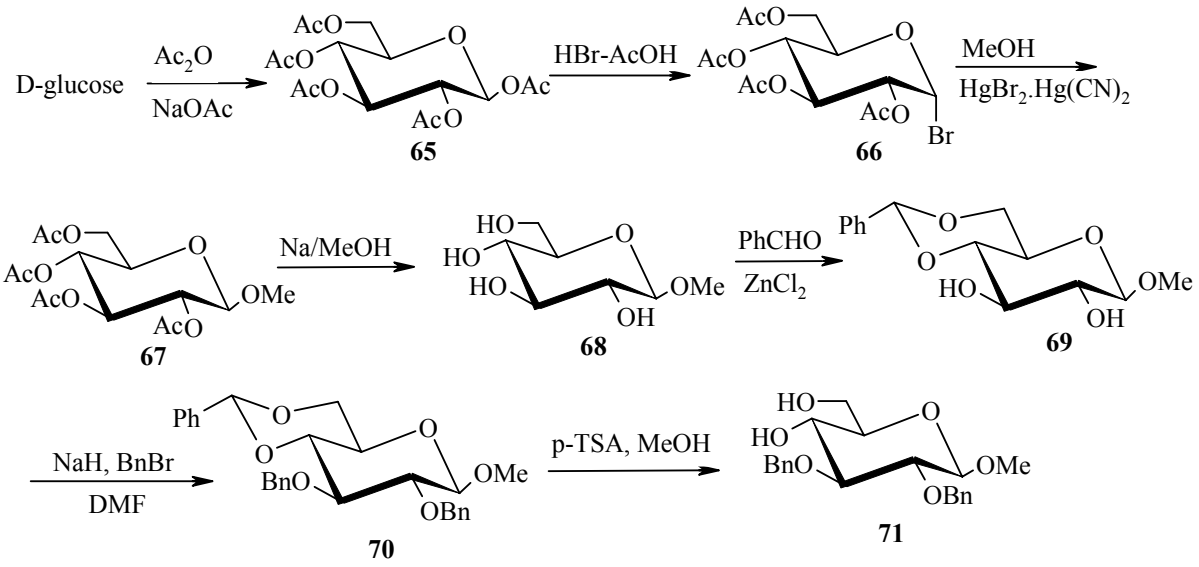


The execution of this general strategy is discussed below.

Synthesis of intermediate (12*S*,13*S*,15*R*) C-9─C-16 fragment (82).

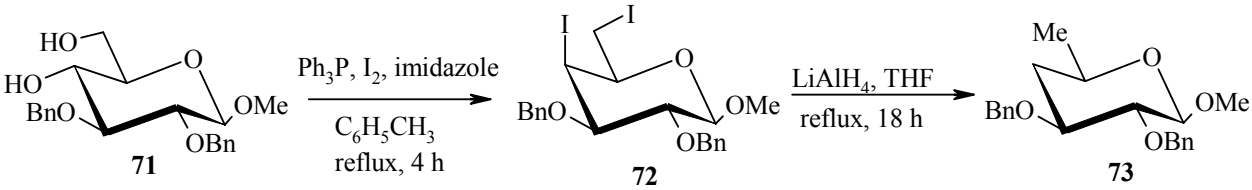
D-Glucose was first converted into the pentaacetate derivative (**65**) by reacting with acetic anhydride – NaOAc combination. Subsequent reaction with HBr-AcOH provided 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**66**).[36] Treatment of **66** with MeOH in presence of $HgBr_2.Hg(CN)_2$ followed by Zémplen deacetylation[37] gave methyl-β-D-glucopyranoside (**68**). Transformation of **68** into the corresponding 4,6-*O*-benzylidene derivative (**69**) was accomplished by using PhCHO-$ZnCl_2$ (Scheme 10).[38] Subsequent benzylation of the free hydroxyl groups on C-2 and C-3 with NaH and BnBr according to the literature procedure[39] afforded the 2,3-di-*O*-benzylated product (**70**). Acid catalysed hydrolysis of the 4,6-benzylidene group with *p*-TSA in MeOH afforded the diol **71** as a white solid.[39] The ^1H and ^{13}C NMR spectra were in agreement with the assigned structure.

Scheme 10



Deoxygenation at C-4 and C-6 were planned in a two-step sequence, with first formation of the dihalo derivative[40] followed by hydrodehalogenation[41] (Scheme 11). Thus, the diol (**71**) was treated according to Garegg's protocol[42] with PPh_3, iodine and imidazole in refluxing toluene for 4 h to afford the 4,6-dideoxy-4-6-diiodo derivative (**72**). The ^1H, ^{13}C NMR spectra and elemental analysis supported the structure **12**. In the ^1H NMR spectrum of **72**, the diastereotopic C-6 protons appeared as a double doublet at δ 3.43 (J = 6.6, 10.2 Hz) and δ 3.23 (J = 6.8, 10.2 Hz), whereas C-4 proton appeared as a double doublet at δ 4.70 (J = 1.0, 4.5 Hz). In the ^{13}C NMR spectra of **72**, C-4 and C-6 appeared at δ 40.0 and 8.3

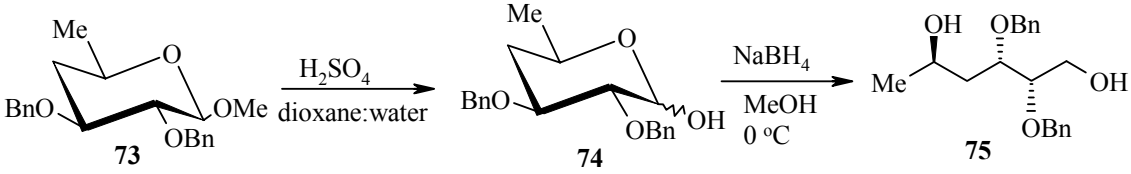
Scheme 11



respectively. Hydrodehalogenation with $LiAlH_4$ in THF under reflux condition[41] for 18-20 h gave the corresponding 4,6-dideoxy product **73**. The ^1H NMR spectrum showed the characteristic doublet due to the methyl group at δ 1.21 (J = 6.3 Hz) while C-4 methylene protons appeared at δ 1.43 and 2.04 as two multiplets. In the ^{13}C NMR spectra of **73**, the C-4 and C-6 carbons appeared at δ 39.0 and 20.7 respectively.

Hydrolysis of the methyl glycoside bond in presence of H_2SO_4 in dioxane-water under reflux conditions afforded a mixture of α and β-hexose derivatives, which were reduced with

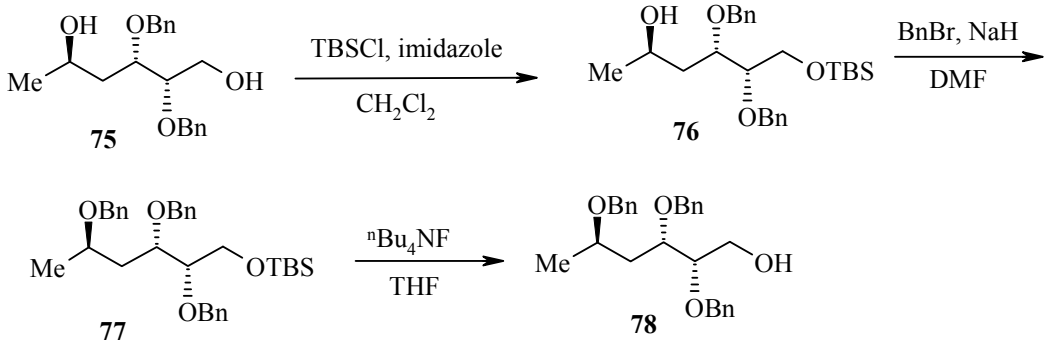
Scheme 12



$NaBH_4$ in MeOH[43] at 0 °C to afford the straight chain diol **75** (Scheme 12).

The primary hydroxyl group of **75** was protected as its silyl ether[44] (**76**) with TBSCl and imidazole in CH_2Cl_2 (Scheme 13). Subsequently, the secondary hydroxyl group was protected as its benzyl ether (**77**) using NaH and BnBr in DMF at 0 °C. The cleavage of the silyl ether[44] group with TBAF in THF afforded the tribenzyloxyhexanol derivative **78** in

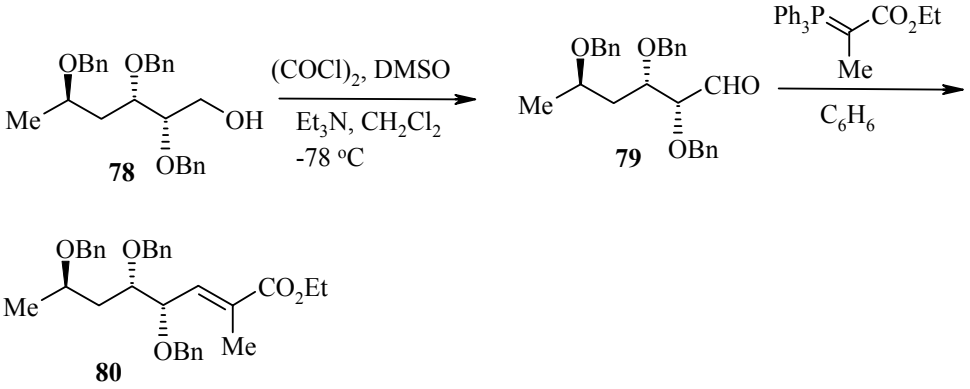
Scheme 13



which the free hydroxyl group at a terminal carbon is suitable for dramatization of polyene structure. The ^{1}H and ^{13}C NMR spectra and elemental analysis were in agreement with the assigned structure.

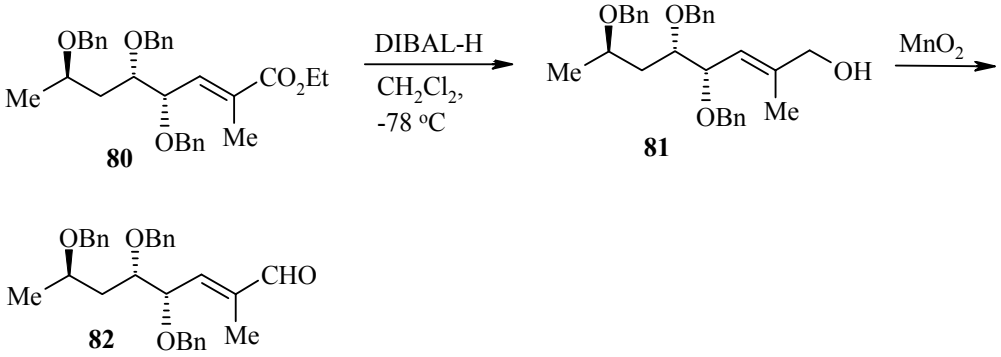
The next stage in the synthetic plan was to obtain the C-8 unsaturated aldehyde (**82**). Thus, compound **78** was oxidized to the aldehyde derivative **79** under Swern oxidation[45] conditions using $(COCl)_2$, DMSO and Et_3N in CH_2Cl_2 at –78 ^{o}C (Scheme 14). As a precautionary measure taken against possible decomposition of **79**, it was immediately

Scheme 14



subjected to the next olefination reaction. Thus, **79** and $Ph_3P{=}C(Me)CO_2Et$ were refluxed in benzene. Under these Wittig reaction conditions, exclusive formation of *E*-isomer (**80**) was observed in 80 % yield. ^{1}H, ^{13}C NMR spectra and elemental analysis suggested the structure to be **80**. The olefinic proton appeared as a doublet at δ 6.70 (J = 10.0 Hz). The methyl protons of the carboxylate ester appeared as a triplet at δ 1.35 (J = 6.6 Hz). The absolute stereochemical assignment of *E*-isomer could not be definitely ascertained at this stage but based on literature data,[27] we believe that *E*-isomer has been formed. The correct stereochemical assignment to prove *E*-isomer (**80**) has been done at a later stage of synthesis by using NOESY studies. Attempted selective reduction of the ester to the corresponding aldehyde derivative **82** using 1 eq. of DIBAL-H at –78 ^{o}C resulted in the formation of two compounds *viz.* the aldehyde **82** and alcohol **81**. Adopting a two-step sequence solved the problem. Thus, reduction of **80** with DIBAL-H –78 ^{o}C gave the alcohol **81** (Scheme 15). The structure of **81** was confirmed by its ^{1}H and ^{13}C NMR spectra.

Scheme 15

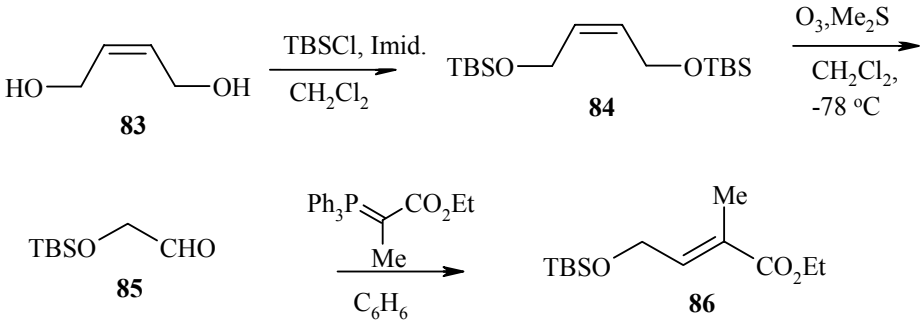


Oxidation of the allylic alcohol **81** to the aldehyde **82** using activated MnO_2 in $CHCl_3$ at room temperature[46] occurred smoothly. The ^1H NMR spectrum of **82** showed the characteristic resonance due to the aldehyde group downfield at δ 9.40 as a singlet.

Synthesis of Phosphonate (95)

The next synthetic target was the phosphonate derivative **95**, for which the aldehyde **85** was identified as the starting material. *Cis*-2-butene-1,4-diol (**83**) was protected as di-TBS ether (**84**) and then subjected to oxidative cleavage of olefin with ozone (Scheme 16).[47] This protocol gave the aldehyde **85** which was subjected to two-carbon homologation by Wittig

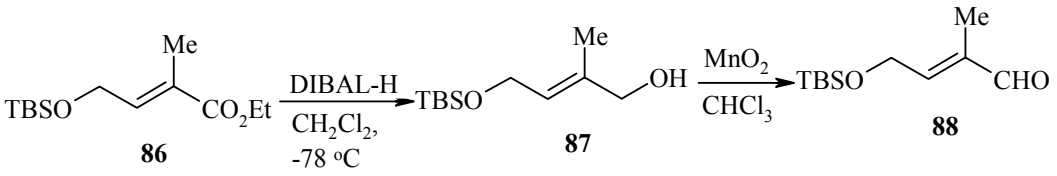
Scheme 16



reaction with the ylide $Ph_3P{=}C(Me)CO_2Et$ in benzene under reflux to provide[47] the (*E*)–α, β-unsaturated ester **86** (Scheme 16). In the ^1H NMR spectrum of **86**, the olefinic proton appeared as a triplet at δ 6.75 (J = 5.8 Hz) while the vinylic methyl group resonated at δ 1.81 as a singlet.

Reduction of **86** to the corresponding allylic alcohol **87** was carried out with DIBAL-H at –78 °C (Scheme 17). Disappearance of signals due to the ethyl ester in the ^1H NMR spectrum clearly indicated the transformation. The methylene protons of C-1 appeared at δ 3.97 as a singlet.

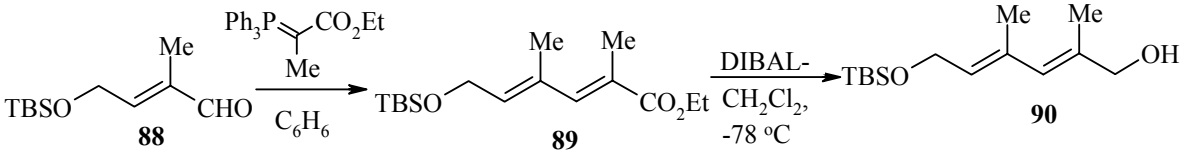
Scheme 17



Oxidation of the allylic alcohol present in **87** was carried out using MnO_2[46] in $CHCl_3$ at room temperature to afford the aldehyde **88** whose ^1H NMR spectrum revealed the characteristic signal of aldehyde proton at δ 9.40. As expected, a downfield shift of the olefinic proton of **88** compared to **87** was observed in the ^1H NMR spectrum.

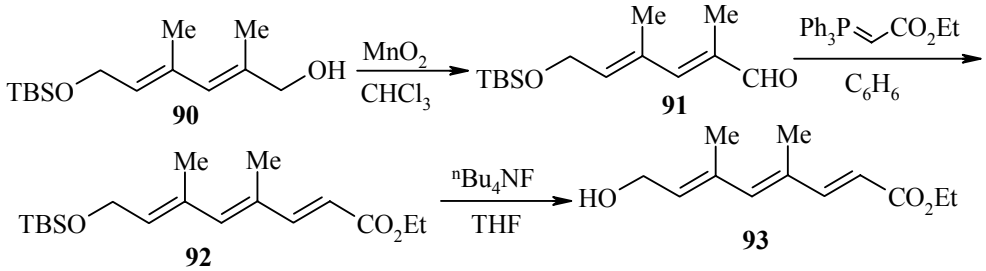
Wittig reaction of the aldehyde **88** with $Ph_3P{=}C(Me)CO_2Et$ in benzene under reflux gave the diene **89** in 84 % yield (Scheme 18). In the ^1H NMR spectrum, the C-3 and C-5 olefinic protons appeared at δ 7.05 (singlet) and 5.66 (triplet, J = 5.8 Hz) whereas the vinylic methyls appeared as singlets at δ 1.99 and 1.89. The ester group in **89** was reduced to alcohol **90** with DIBAL-H. The ^1H and ^{13}C NMR spectra were in support of the structure **90**.

Scheme 18



The alcohol **90** was oxidized to the aldehyde **91** using MnO_2 and immediately subjected to Wittig reaction with $Ph_3P{=}CHCO_2Et$ in refluxing benzene to yield the triene **92** (Scheme 19). In the ^1H NMR spectrum of **92**, the C-2 and C-3 protons appeared as doublets

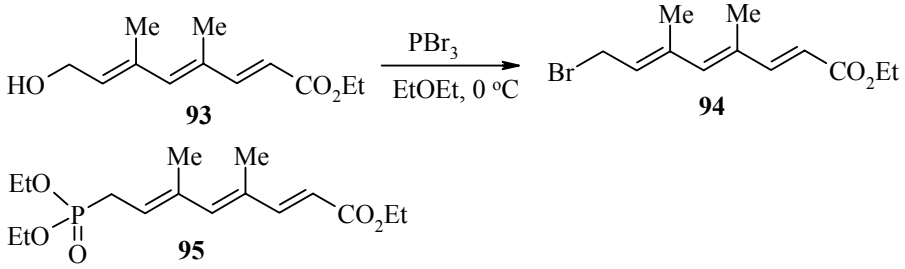
Scheme 19



at δ 7.24 (J = 15.6 Hz) and δ 5.75 (J = 15.6 Hz). The coupling constants were characteristic of *trans* isomer. The C-5 proton appeared as a singlet at δ 6.15 and C-6 proton appeared at δ 5.52 as a triplet (J = 5.8 Hz). In the ^{13}C NMR spectrum of **92**, the carbonyl carbon appeared at δ 166.6. Removal of silyl ether in **92** was effected with TBAF to afford the allyl alcohol **93**.

Conversion of alcohol **93** to the corresponding bromo derivative **94** with TPP/CBr_4[48] resulted in the formation of unidentified products. However, the conversion was achieved with PBr_3 in diethyl ether at 0 °C (Scheme 20).[49] Michaelis-Arbuzov reaction of the resulting bromo derivative **94** with $P(OEt)_3$ at 90 °C afforded[50] the phosphonate **95** whose structure was confirmed by ^{1}H, ^{13}C NMR spectra and elemental analysis. In the ^{1}H NMR spectrum of **95**,

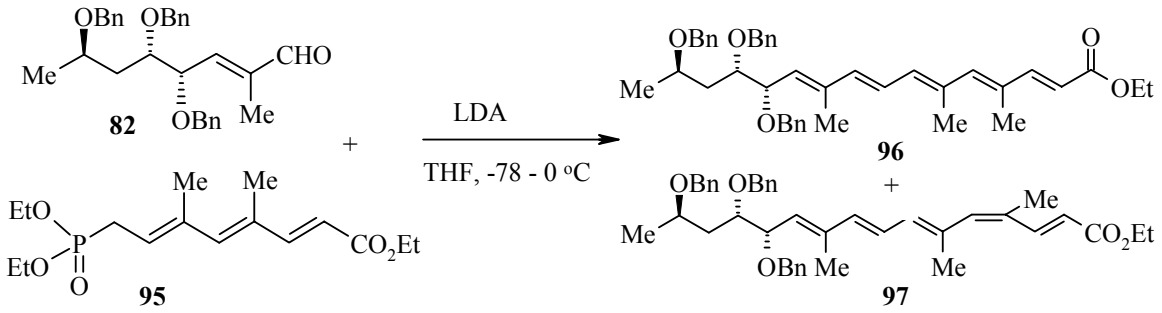
Scheme 20



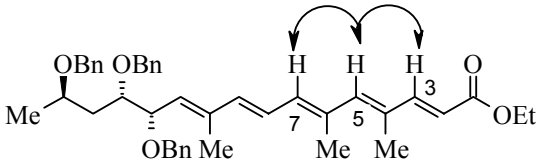
the active methylene protons appeared as a doublet of doublet at δ 2.66 (J = 7.8 Hz). The methylene protons of the $P(OEt)_2$ group appeared as a multiplet at 4.10 ppm while the methyl protons appeared at 1.26 ppm as a multiplet. All the other resonances were in agreement with the assigned structure **95**.

Finally, the two key intermediates **82** and **95** were subjected to Horner-Wadsworth-Emmons reaction conditions at –78 °C using LDA as base (Scheme 21). ^{1}H NMR spectrum of the product indicated the presence of two compounds, although TLC showed only one spot. It was finally attributed to *cis* and *trans* isomers, after comparing the NMR spectrum with that of natural product.[7] Baseline separation of the isomers was finally achieved using HPLC analysis (Chiralcel OD, 5 % Isopropanol in hexanes). However, re-examination of the pure fractions of each isomer under the same conditions showed that the *cis* isomer is contaminated with the 12 % of *trans* isomer and vice-versa, proving that a dynamic equilibrium exists between the two. This was indeed proved by NMR experiments, which showed very similar data with those reported for natural product. For instance, the ^{1}H NMR spectrum of the *trans* isomer (**96**) showed characteristic doublets at δ 7.40 (J = 16.0 Hz) and δ

Scheme 21



6.29 (J = 10.6 Hz) for H-3 and H-7 respectively. The corresponding signals in the *cis* isomer (**97**) appeared at δ 7.96 (J = 15.5 Hz) and δ 6.15 (J = 11.1 Hz). These values correspond well with those reported for natural products. In the ^{13}C-NMR spectrum of **96**, C-3 was observed at δ 150.0 and for compound **97**, at 142.5 ppm. The 2D-NOESY studies were also carried out for **96** and **97** (fig. 2). Interestingly, H-5 of the *cis* isomer **97**, which appeared at δ 6.27 showed NOE with 17-CH_3 and 18-CH_3 as expected. The NOE of H-3 (δ 7.96) with H-7 (δ 6.15) and H-5 were observed. However, in the *trans* isomer **96**, the NOE of H-5 (δ 6.39) with both H-3 (δ 7.40) and H-7 (δ 6.29) suggested the *E*-configuration at C-4. The lack of NOEs between H-3 (δ 7.40) and H-7 (δ 6.29) were also noticed.



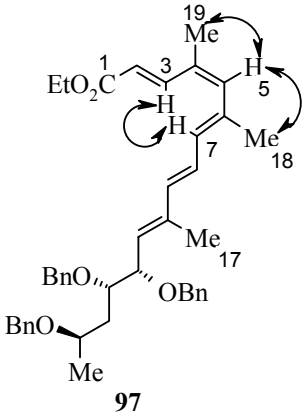
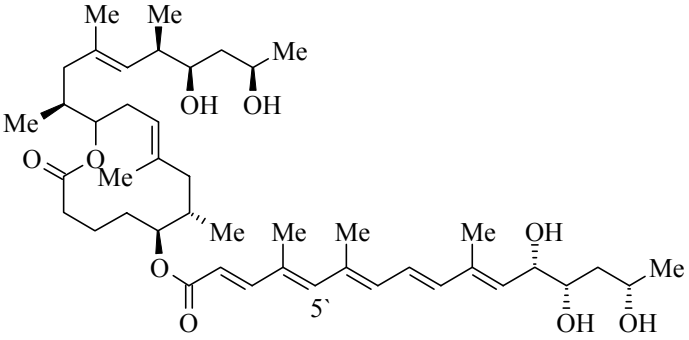


Fig. 2 NOE studies of 96 and 97

Thus a versatile synthetic strategy towards the C-1-C-16 fragment of mycolactones A and B has been achieved which could lead to the easy access of its diastereomers as well.

Post work

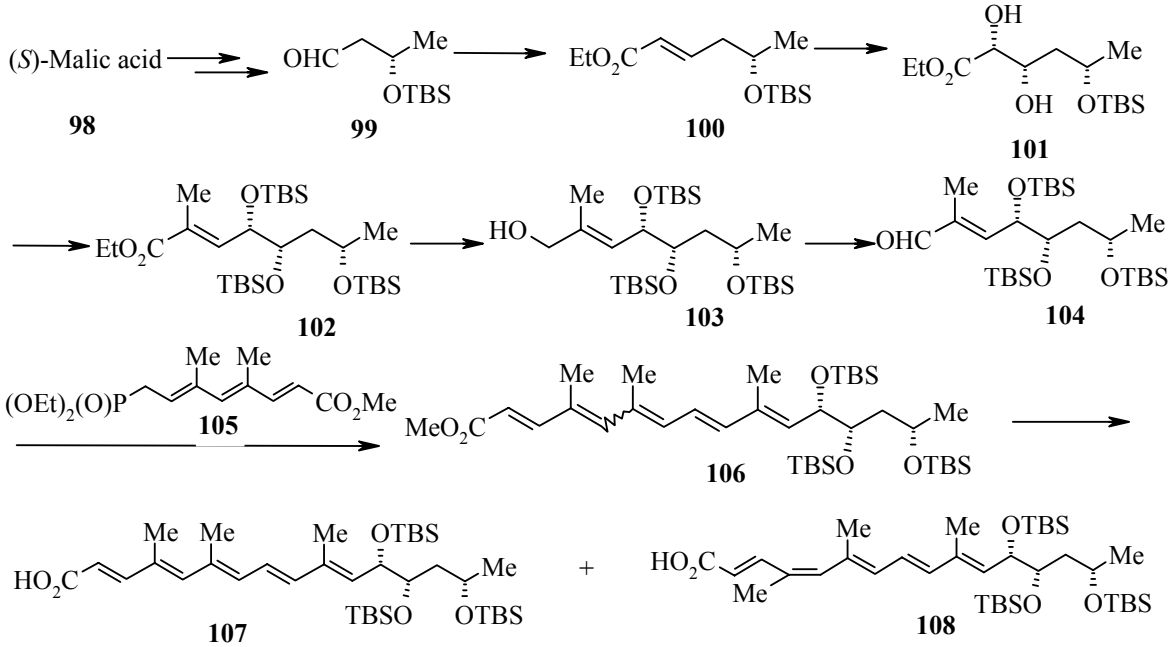
In 2001, Kishi *et al* reported[51] the absolute configuration of the mycolactones A and B through a detailed study including NMR database approach, preparation of model compounds and a new concept including universal NMR database in chiral solvents.



(*Z*-4,`5`) - Mycolactone-A (8); (*E*-4,`5`) -Mycolactone-B(9)

Kishi *et al* also achieved the first total synthesis[51] of mycolactones in which the fatty acid side chain C-1 – C-16 fragment was synthesized from (*S*)-malic acid as depicted in Scheme 22. The aldehyde **99**, prepared from *S*-malic acid **98** was subjected to Wittig

Scheme 22



homologation and Sharpless asymmetric dihydroxylation to obtain the diol derivative **101**. The diol **101** was converted to the allylic alcohol **103** by employing Wittig reaction and reduction. Oxidation of the allylic alcohol **103** provided the aldehyde **104** whose reaction

with the phosphonate **105** gave **106** as an inseparable mixture of isomers. However, hydrolysis of the ester to the corresponding carboxylic acid resulted in separation of the isomers **107** and **108** by silica gel column chromatography.

Experimental

Methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside (71)

A mixture of **70**[21] (7.0 g, 15.1 mmol) and *p*-TSA (0.1 g) in MeOH (50 mL) were stirred at rt for 1 h. Solvent was removed *in vacuo* and the residue extracted with EtOAc, washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel chromatography with light petroleum:EtOAc (3:2) as an elutent to afford diol **71** (5.0 g, 90 %).

$[\alpha]_D$ = -15.3 (*c* 1.0 in $CHCl_3$); lit.[22] –13.3 (*c* 2.3 in $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.22 (br s, 1 H), 2.51 (br s, 1 H), 3.28-3.52 (m, 4 H), 3.58 (s, 3 H), 3.67-3.92 (m, 2 H), 4.36 (d, 1 H, *J* = 7.3 Hz), 4.68 (d, 1 H, *J* = 11.7 Hz), 4.70 (d, 1 H, *J* = 11.3 Hz), 4.93 (d, 1 H, *J* = 11.3 Hz), 4.96 (d, 1 H, *J* = 11.3 Hz), 7.33 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$) δ 57.1, 62.0, 70.0, 74.5, 74.9, 75.0, 81.8, 83.8, 104.7, 127.7-128.3, 138.3, 138.5.

Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.38; H, 6.95. Found: C, 67.21; H, 6.77 %.

Methyl 4,6-dideoxy-4,6-diiodo-2,3-di-*O*-benzyl-β-D-galactopyranoside (72)

A mixture of compound **71** (5.0 g, 13.4 mmol), Ph_3P (14.0 g, 53.6 mmol), iodine (13.5 g, 53.6 mmol) and imidazole (3.6 g, 53.6 mmol) in toluene (100 mL) were refluxed for 4 h and cooled to 0 ^oC. Saturated aq. $NaHCO_3$ solution was added, and the organic layer separated, washed with water, aq. sodium thiosulphate, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography with light petroleum:EtOAc (4:1) as an eluent to afford **72** (6.6 g, 83 %).

$[\alpha]_D$ = +69.6 (*c* 0.8, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83 (dt, 1 H, *J* = 1.0, 6.6 Hz), 2.96 (dd, 1 H, *J* = 4.5, 9.0 Hz), 3.23 (dd, 1 H, *J* = 6.6, 10.2 Hz), 3.43 (dd, 1 H, *J* = 6.6, 10.2 Hz), 3.58 (s, 3 H), 3.65 (dd, 1 H, 7.9, 9.0 Hz), 4.33 (d, 1 H, *J* = 7.9 Hz), 4.57 (d, 1 H, *J* = 10.9 Hz), 4.70 (dd, 1 H, *J* = 1.0, 4.5 Hz), 4.75 (d, 2 H, *J* = 10.4 Hz), 4.82 (d, 1 H, *J* = 10.9 Hz), 7.33 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$) δ 8.3, 40.0, 57.3, 71.3, 73.1, 75.2, 78.5, 80.1, 104.8, 127.6-128.4, 137.4, 138.4.

Anal. Calcd. for $C_{21}H_{24}O_4I_2$: C, 42.42; H, 4.04. Found: C, 42.53; H, 4.27 %.

Methyl 2,3-di-*O*-benzyl-4,6-dideoxy-β-D-*xylo*hexopyranoside (73)

To a solution of compound **72** (6.0 g, 10.0 mmol) in THF (50 mL) at 0 ^{o}C was added $LiAlH_4$ (0.57 g, 15.0 mmol) over a period of 10 min. After refluxing the resulting slurry for 24 h, the reaction mixture was quenched by the addition of EtOAc (15 mL) followed by 10 % aq. NaOH solution at 0 ^{o}C. The resulting suspension was filtered, the filtrate concentrated and the residue was purified by silica gel column chromatography (EtOAc:light petroleum 1:9) to afford **73** (2.5 g, 74 %).

$[\alpha]_D$ = -32.3 (*c* 0.8 in $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (d, 3 H, *J* = 6.3 Hz), 1.48-1.58 (m, 1 H), 2.01-2.07 (m, 1 H), 3.37-3.49 (m, 1H), 3.41 (s, 3 H), 3.81-3.96 (m, 2 H), 4.48-4.93 (m, 5 H), 7.32-7.39 (m, 10 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.7, 39.1, 55.8, 71.3, 72.9, 75.2, 78.3, 80.4, 104.7, 127.6-128.4, 137.3, 138.5.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.68; H, 7.60. Found: C, 73.47; H, 7.39 %.

(2*S*,3*S*,5*R*)-2,3-*Bis*-benzyloxyhexan-1,5-diol (75).

Compound **73** (3.5 g, 10.2 mmol) and conc. H_2SO_4 (1 mL) in 2:1 dioxane-water (20 mL) were heated on a boiling water bath for 12 h. The reaction mixture was neutralized with solid $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to afford **74** (2.0 g) which was dissolved in methanol (10 mL) and $NaBH_4$ (0.5 g, 13.0 mmol) was added at 0 ^{o}C. After 0.5 h, excess of $NaBH_4$ was decomposed with acetic acid, solvent removed and solution extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The crude product was purified on silica gel with light petroleum-EtOAc (7:3) as an eluent to give **75** (1.82 g, 54 %). $[\alpha]_D$ –30.2^{o} (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz): δ 1.20 (d, 3 H, *J* = 6.6 Hz), 1.65 (m, 2 H), 2.30 (br s, 2H), 3.50-4.0 (m, 5 H), 4.65 (m, 4 H), 7.25 (m, 10 H);

^{13}C NMR (50 MHz): δ 24.0, 39.5, 61.2, 64.3, 72.5, 73.0, 76.2, 80.8, 127.48-128.2, 138.2.

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.72; H, 7.87. Found: C, 72.83; H, 7.79 %.

(2*S*,3*S*,5*R*)-2,5-*Bis*-benzyloxy-1-(-^{t}butyldimethylsilyloxy)-hexan-3-ol (76)

A solution of **75** (1.1 g, 3.3 mmol), imidazole (0.25 g, 3.6 mmol) and TBSCl (0.55 g, 3.6 mmol) in CH_2Cl_2 (10 mL) under nitrogen was stirred at rt for 2 h. It was washed with water,

dried (Na_2SO_4) and evaporated. The residue was purified on silica gel by column chromatography eluting with EtOAc:light petroleum (1:4) to afford **76** (1.26 g, 85 %);

$[\alpha]_D$ -36.7 (*c* 1.3, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01 (s, 6 H), 0.92 (s, 9 H), 1.18 (d, 3 H, *J* = 6.5 Hz), 1.63 (t, 2 H, *J* = 6.3 Hz), 2.38 (br s, 1 H), 3.60-3.98 (m, 5 H), 4.60 (ABq, 2 H, *J* = 12.0 Hz), 4.73 (ABq, 2 H, *J* = 12.0 Hz), 7.38 (m, 10 H).

Anal. Calcd. for $C_{26}H_{40}O_4Si$: C, 70.23; H, 9.07. Found: C, 70.18; H, 9.37 %.

(2*S*,3*S*,5*R*)-2,3,5-*Tris*-benzyloxyhexan-1-ol (78)

To a solution of **76** (1.3 g, 2.9 mmol) in DMF (10 mL) was added NaH (60 % dispersion in mineral oil, 0.14 g, 3.5 mmol). After 15 min, benzyl bromide (0.4 mL, 3.4 mmol) was introduced and the reaction mixture further stirred for 2 h at rt. Water was added to the reaction, extracted with Et_2O, washed with water and dried (Na_2SO_4). Solvent was evaporated and the residue purified by silica gel column chromatography (ethyl acetate : light petroleum 1:10) to afford **77**. It (1.2 g, 2.2 mmol) was taken in THF (10 mL) and 1 M solution of Bu_4NF in THF (3 mL, 3.0 mmol) was added. After 30 min., solvent was evaporated and the residue purified on silica gel with light petroleum-EtOAc (9:1) as an eluent to give **78** (0.94 g, 76 %).

$[\alpha]_D$ –49.6^o (*c* 0.7, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (d, 3H, *J* = 6.6 Hz), 1.50-1.65 (m, 2 H), 2.40 (br s, 1 H), 3.60-3.75 (m, 4 H), 3.80-4.0 (m, 1 H), 4.20-4.40 (m, 2 H), 4.55-4.70 (m, 4 H), 7.26 (m, 15 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.9, 38.2, 61.4, 71.3, 72.3, 72.7, 75.2, 79.9, 127.2-128.8, 138.4, 138.9.

MS (m/z): 420 (M^+).

Anal. Calcd. for $C_{27}H_{32}O_4$: C, 77.11; H, 7.67. Found: C, 77.37; H, 7.83 %.

Ethyl (2*E*,4*S*,5*S*,7*R*)-4,5,7-*tris*-benzyloxy-2-methyl-oct-2-enoate (80)

To a stirred solution of DMSO (1.0 mL, 14.1 mmol) and oxalyl chloride (0.6 mL, 7.2 mmol) in CH_2Cl_2 (10 mL) at –78 ^{o}C, compound **78** (1.5 g, 3.6 mmol) in CH_2Cl_2 (2 mL) was added. After 1 h at –78 ^{o}C, Et_3N (3.1 mL, 21.6 mmol) was added and the reaction mixture warmed to rt, extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated. The resulting aldehyde **79** (1.4 g, 3.5 mmol) and Ph_3P=C(Me)COOEt (2.6 g, 7.0 mmol) in benzene (15 mL)

were heated under reflux for 3 h. Solvent evaporated and residue was purified on silica gel with light petroleum-EtOAc (20:1) as an eluent to afford **80** (1.35 g, 80 %).

$[\alpha]_D$ –37.5° (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (d, 3 H, *J* = 6.6 Hz), 1.30 (t, 3 H, *J* = 6.6 Hz), 1.50-1.80 (m, 2 H), 1.85 (s, 3 H), 3.75 (m, 1 H), 3.90 (m, 1 H), 4.25 (m, 4 H), 4.36 (d, 2 H, *J* = 13.3 Hz), 4.56 (d, 1 H, *J* = 13.3 Hz), 4.73 (d, 1 H, *J* = 13.3 Hz), 6.70 (d, 1 H, *J* = 10.0 Hz), 7.25 (m, 15 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.1, 14.0, 19.7, 38.9, 60.4, 69.8, 70.6, 71.1, 73.6, 77.8, 127.2-128.0, 131.5, 138.4, 138.7, 138.8, 166.9.

Anal. Calcd. for $C_{32}H_{38}O_5$: C, 76.49; H, 7.56. Found: C, 76.86; H, 7.69 %.

(2*E*,4*S*,5*S*,7*R*)-4,5,7-*Tris*-benzyloxy-2-methyl-oct-2-en-1-ol (81)

To a solution of **80** (0.12 g, 0.24 mmol) in CH_2Cl_2 (10 mL) was added DIBAL-H (1 M solution in toluene, 0.5 mL, 0.5 mmol) at –78 °C. After 30 min at –78 °C the reaction mixture was quenched by adding saturated aq. solution of sodium potassium tartrate, extracted with CH_2Cl_2, washed with water and dried (Na_2SO_4). Evaporation of the solvent followed by silica gel chromatography light petroleum-EtOAc (5:1) as eluents afforded **81** (0.10 g, 94 %).

$[\alpha]_D$ –36.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (d, 3 H, *J* = 6.4 Hz), 1.61 (m, 2 H), 1.65 (s, 3 H), 1.90 (br s, 1 H), 3.77 (m, 2 H), 4.0 (s, 2 H), 4.19 (m, 1 H), 4.25-4.8 (m, 6 H), 5.40 (d, 1 H, *J* = 9.7 Hz), 7.25 (m, 15 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 19.8, 39.3, 67.6, 70.1, 71.5, 73.3, 77.8, 78.3, 122.6, 127.6-128.1, 138.8, 140.5.

Anal. Calcd. for $C_{30}H_{36}O_4$: C, 78.26; H, 7.82. Found: C, 78.51; H, 7.61 %.

(2*E*,4*S*,5*S*,7*R*)-4,5,7-*Tris*-benzyloxy-2-methyl-oct-2-enal (82)

Compound **81** (0.2 g, 0.43 mmol) and freshly prepared MnO_2 (0.2 g, 2.3 mmol) in $CHCl_3$ (5 mL) was stirred at rt for 3 h, filtered and concentrated to afford the aldehyde **82** (0.19 g, 93 %) which was used as such for the next reaction.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (d, 3 H, *J* = 6.1 Hz), 1.65 (s, 3 H), 1.5-1.80 (m, 2 H), 4.19 (d, 1 H, *J* = 11.5 Hz), 4.25-4.75 (m, 6 H), 6.40 (d, 1 H, *J* = 7.7 Hz), 7.24 (m, 15 H), 9.45 (s, 1 H).

Ethyl (2*E*)-4-^{t}butyldimethylsilyloxy-2-methyl-but-2-enoate (86)

Ozone was bubbled through a solution of **84** (5.0 g, 15.7 mmol) in CH_2Cl_2 (150 mL) at –78 ^oC for 15 min and quenched by adding dimethyl sulfide (2 mL). After stirring at –78 ^oC for 8 h, the solvent was removed and the residue dissolved in C_6H_6 (100 mL). Ph_3P=C(Me)COOEt (21.3 g, 58.8 mmol) was added and the mixture refluxed for 12 h. Removal of the solvent followed by purification of the residue on silica gel by eluting with EtOAc:light petroleum (1:9) afforded **86** (3.2 g, 80 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 6 H), 0.91 (s, 9 H), 1.31 (t, 3 H, *J* = 7.3 Hz), 1.81 (s, 3 H), 4.20 (q, 2 H, *J* = 7.3 Hz), 4.35 (d, 2 H, *J* = 5.8 Hz), 6.75 (t, 1 H, *J* = 5.8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.5, 13.5, 14.0, 17.9, 25.4, 59.7, 60.1, 132.3, 134.8, 168.0.

Anal. Calcd. for $C_{13}H_{26}O_3Si$: C, 60.46; H, 10.07. Found: C, 60.58; H, 10.32 %.

(2*E*)-4-(^{t}Butyldimethylsilyloxy)-2-methyl-but-2-en-1-ol (87)

To a solution of **86** (3.0 g, 11.6 mmol) in CH_2Cl_2 (25 mL) at –78 ^oC was added DIBAL-H (2 M solution in toluene, 29.0 mmol, 14.5 mL). After stirring at –78^o C for 1 h, excess DIBAL was quenched by the addition of saturated aq. sodium potassium tartrate. The solid formed was filtered, filtrate concentrated and the residue was purified on silica gel by eluting with EtOAc:light petroleum (1:4) to afford **87** (2.3 g, 92 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.65 (s, 3 H), 2.32 (br s, 1 H), 3.97 (s, 2H), 4.21 (d, 2 H, *J* = 6.3 Hz), 5.53 (t, 1 H, *J* = 6.3 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.5, 13.3, 18.0, 25.6, 59.5, 67.2, 124.3, 135.9.

Anal. Calcd. for $C_{11}H_{24}O_2Si$: C, 61.11; H, 11.11. Found: C, 60.88; H, 10.83 %.

(2*E*)-4-(^{t}Butyldimethylsilyloxy)-2-methyl-but-2-enal (88)

A slurry of **87** (2.0 g, 9.3 mmol) and freshly prepared MnO_2 (4.0 g, 46.0 mmol) in $CHCl_3$ (20 mL) were stirred at rt for 4 h and filtered. The filtrate was concentrated to afford the aldehyde **88** (1.88 g, 95 %), which was used as such for the next reaction.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6 H), 0.85 (s, 9 H), 2.18 (s, 3 H), 4.49 (d, 2 H, *J* = 5.5 Hz), 6.51 (t, 1 H, *J* = 5.5 Hz), 9.48 (s, 1 H).

Ethyl (2*E*,4*E*)-6-^{t}butyldimethylsilyloxy-2,4-dimethyl-hex-2,4-dienoate (89)

The aldehyde **88** (1.9 g, 8.9 mmol) was subjected to Wittig reaction with Ph_3P=C(Me)COOEt (6.0 g, 16.8 mmol) in refluxing benzene for 3 h and worked up as before and purified on silica gel by eluting with light petroleum:EtOAc (9:1) to give **89** (2.0 g, 76 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.30 (t, 3 H, *J* = 7.3 Hz), 1.89 (s, 3 H), 1.99 (s, 3 H), 4.20 (q, 2 H, *J* = 7.3, 14.6 Hz), 4.30 (d, 2 H, *J* = 5,8 Hz), 5.66 (t, 1 H, *J* = 5.8 Hz), 7.05, (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.5, 13.6, 14.0, 16.3, 18.0, 25.6, 59.9, 60.2, 126.0, 132.0, 134.4, 141.5, 168.0.

Anal. Calcd. for $C_{16}H_{30}O_3Si$: C, 64.43; H, 10.06. Found C, 64.08; H, 10.25 %.

6-(^{t}Butyldimethylsilyloxy)- (2*E*,4*E*)-2,4-dimethyl-hexa-2,4-dien-1-ol (90)

Compound **89** (2.0 g, 6.7 mmol) was reduced with DIBAL (2 M solution in toluene, 7.7 mL, 15.4 mmol) and worked up as described before to give **90** (1.6 g, 87 %) after purification on silica gel by eluting with light petroleum:EtOAc (1:4).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (s, 6 H), 0.91 (s, 9 H), 1.74 (s, 3 H), 1.81 (s, 3 H), 4.03 (s, 2 H), 4.25 (d, 2 H, *J* = Hz), 5.43 (t, 1 H, *J* = Hz), 5.86 (s, 1 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.4, 14.9, 16.8, 18.0, 25.6, 59.9, 68.2, 127.7, 129.0, 132.8, 135.2.

Anal. Calcd. for $C_{14}H_{28}O_2Si$: C, 65.62; H, 10.94. Found C, 65.28; H, 10.73 %.

Ethyl (2*E*,4*E*,6*E*)-8-^{t}butyldimethylsilyloxy-4,6-dimethyl-oct-2,4,6-trienoate (92)

Oxidation of the alcohol **90** (1.6 g, 6.2 mmol) was carried out as mentioned earlier with MnO_2 (2.6 g, 29.8 mmol) to afford aldehyde **91** (1.5 g) which was treated immediately with Ph_3P=CHCOOEt (3.9 g, 11.2 mmol) in refluxing C_6H_6, worked up as described earlier and purified on silica gel by eluting with light petroleum:EtOAc (9:1) to give **92** (1.6 g, 80 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01 (s, 6 H), 0.82 (s, 9 H), 1.21 (t, 3 H, *J* = 6.8 Hz), 1.73 (s, 3 H), 1.87 (s, 3 H), 4.10 (q, 2 H, *J* = 6.8, 13.6 Hz), 4.22 (d, 2 H, *J* = 5.8 Hz), 5.52 (t, 1 H, *J*= 5.8 Hz), 5.75 (d, 1 H, *J*= 15.6 Hz), 6.15 (s, 1 H), 7.24 (d, 1 H, *J* = 15.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.5, 13.3, 14.0, 16.6, 17.9, 25.5, 59.6, 59.8, 116.7, 131.9, 132.4, 133.4, 141.9, 149.7, 166.6.

Anal. Calcd. for $C_{18}H_{32}O_3Si$: C, 66.66; H, 9.88. Found: C, 66.54; H, 9.97 %.

Ethyl (2*E*,4*E*,6*E*)-4,6-dimethyl-8-hydroxy-oct-2,4,6-trienoate (93)

A solution of **92** (0.3 g, 0.92 mmol) and 1 M solution of Bu_4NF (1.4 mL, 1.4 mmol) in THF (2 mL) was stirred at rt for 1 h and evaporated. The residue was purified on silica gel with light petroleum-EtOAc (7:3) as eluent to give **93** (0.18 g, 93 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, 3 H, *J* = 7.3 Hz), 1.85 (s, 3 H), 1.95 (s, 3 H), 4.21 (q, 2 H, *J* = 7.3, 14.6 Hz), 4.28 (d, 2 H, *J* = 6.8 Hz), 5.68 (t, 1 H, *J* = 6.8 Hz), 5.82 (d, 1 H, *J* = 15.6 Hz), 6.24 (s, 1 H), 7.31 (d, 1 H, *J* = 15.6 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.3, 14.1, 16.5, 59.7, 68.1, 116.7, 131.8, 132.6, 133.4, 141.7, 149.9, 166.6.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.23; H, 8.61 %.

Ethyl (2*E*,4*E*,6*E*)-8-diethoxyphosphinyl-4,6-dimethyl-oct-2,4,6-trienoate (95)

A solution of **93** (0.6 g, 2.9 mmol) and PBr_3 (0.1 mL, 1.1 mmol) in diethylether (5 mL) was stirred at 0 ^oC for 4 h. The reaction mixture was quenched by the addition of saturated aqueous solution of KBr and layers are separated. The aqueous layer was extracted with diethylether. The combined organic layer was washed with water, dried (Na_2SO_4) and evaporated. The resulting product **94** and triethyl phosphite (0.4 mL, 2.3 mmol) were heated at 90 ^oC for 6 h and chromatographed on silica gel with light petroleum-EtOAc (2:3) as eluent to give **95** (0.6 g, 63 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (m, 9 H), 1.80 (d, 3 H, *J* = 4.5 Hz), 1.90 (s, 3 H), 2.65 (dd, 2 H, *J* = 8.6, 22.8 Hz), 4.10 (m, 6 H), 5.40 (q, 1 H, *J* = 8.6, 14.3 Hz), 5.80 (d, 1 H, *J* = 16.9 Hz), 6.20 (s, 1 H), 7.25 (d, 1 H, *J* = 16.9 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 14.1, 16.2, 16.6, 26.8, 59.8, 61.6, 116.9, 121.6, 132.2, 136.2, 141.8, 149.7, 166.8.

Anal. Calcd. for $C_{16}H_{27}O_5P$: C, 58.18; H, 8.18. Found: C, 58.43, H, 8.26 %.

Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*R*)-12,13,15-*tris*-benzyloxy-4,6,10-trimethylhexadeca-pent-2,4,6,8,10-enoate (96) and Ethyl (2*E*,4*Z*,6*E*,8*E*,10*E*,12*S*,13*S*,15*R*)-12,13,15-*tris*-benzyloxy-4,6,10-trimethyl-hexadecapent-2,4,6,8,10-enoate (97)

To the freshly prepared solution of LDA (1.0 mmol, prepared by adding 0.5 mL (1.0 mmol) of 2 M n-BuLi to a solution of 0.1 mL (1.1 mmol) of diisopropylamine in dry THF at 0 ^oC and stirring at the same temperature for 15 min.) at –78 ^oC was added phosphonate **95** (0.40 g, 1.2 mmol). After 30 min. at –78 ^oC, aldehyde **82** (0.28 g, 0.62 mmol) was added. The reaction mixture was allowed to attain 0 ^oC over a period of 1 h, quenched with saturated NH_4Cl solution and the layers separated. The aqueous layer was extracted with $CHCl_3$, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel with light petroleum-EtOAc (9:1) as an eluent to afford the mixture of diastereomers (**96** and

97) (0.25 g, 65 %). The chiral HPLC separation on Chiralcel OD column with 5 % isopropanol in hexane as an eluent, (UV = 254 nm, flow rate = 1 mL/min) gave the all trans ***E*** isomer (**96**) (retention time = 12.5 min).

$[\alpha]_D$ +57.0 (*c* 0.8, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (d, 3 H, *J* = 6.1 Hz), 1.34 (t, 3 H, *J* = 7.1 Hz), 1.55 (ddd, 1 H, *J* = 2.5, 9.2, 13.3 Hz), 1.72 (ddd, 1 H, *J* = 2.5, 9.2, 13.3 Hz), 1.84 (d, 3 H, *J* = 0.5 Hz), 3.79 (m, 1 H), 3.88 (m, 1 H), 4.25 (q, 2 H, *J* = 7.1 Hz), 4.27 (d, 1 H, *J* = 10.9 Hz), 4.34 (dd, 1 H, *J* = 6.5, 9.8 Hz), 4.40 (d, 1 H, *J* = 10.9 Hz), 4.43 (d, 1 H, *J* = 10.6 Hz), 5.90 (d, 1 H, *J* = 16.0 Hz), 6.29 (d, 1 H, *J* = 10.6 Hz), 6.39 (s, 1 H), 6.42 (d, 1 H, *J* = 16.0 Hz), 6.56 (dd, 1 H, *J* = 10.6, 16.0 Hz), 7.30 (m, 15 H), 7.40 (d, 1 H, *J* = 16.0 Hz);

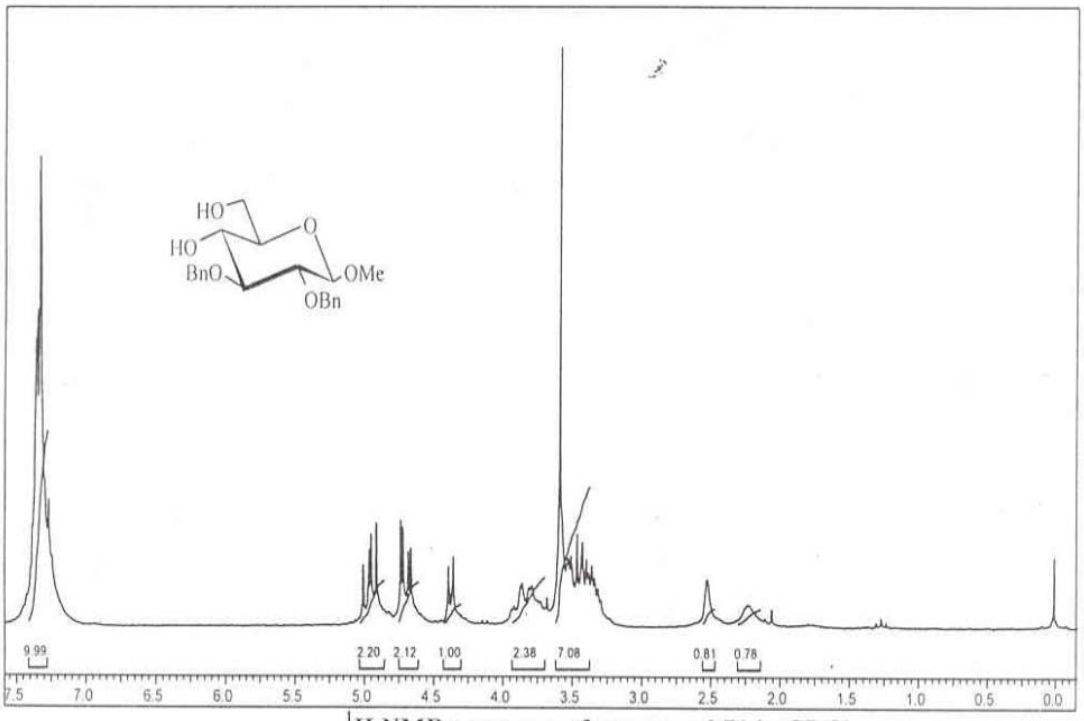
^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 13.9, 14.1, 16.6, 19.6, 39.3, 54.9, 69.9, 70.0, 71.1, 73.9, 78.3, 78.4, 116.1, 124.2, 127.2-128.0, 131.0, 134.4, 138.6-138.7, 143.2, 150.0, 167.3. Anal.Calcd. for $C_{42}H_{50}O_5$: C, 79.49; H, 7.88 %. Found: C, 79.11; H, 7.71 %.

The second fraction eluted was the 4-***Z*** isomer (**97**) (retention time = 19.4 min).

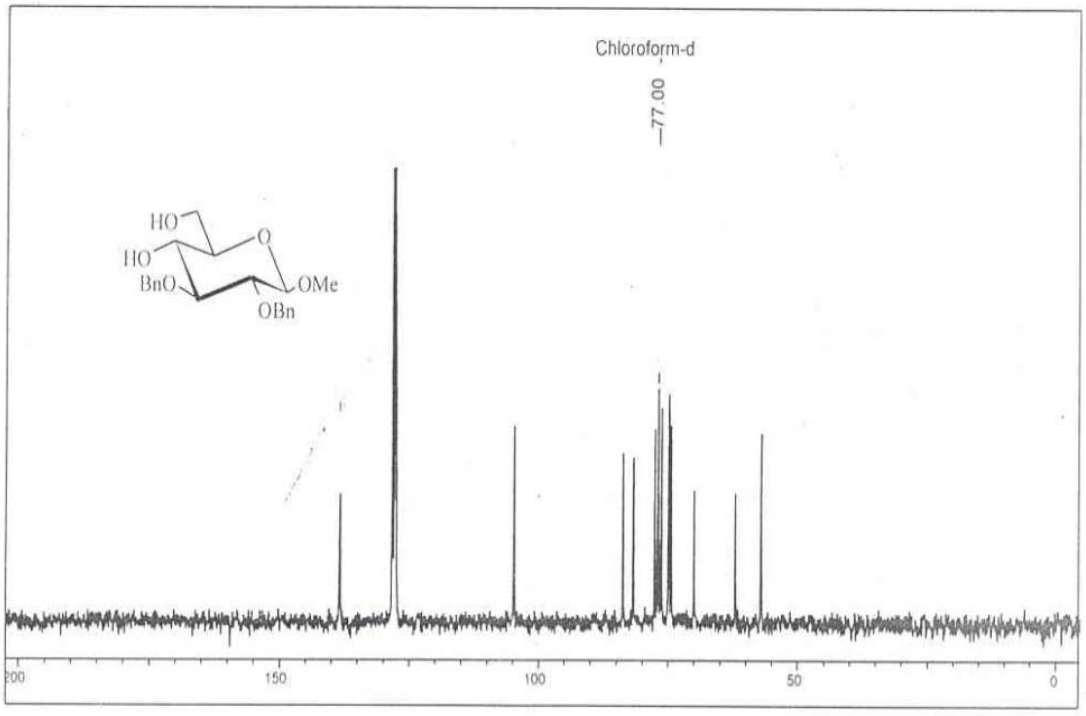
$[\alpha]_D$ +55.4 (*c* 0.7, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (d, 3 H, *J* = 6.0 Hz), 1.32 (t, 3 H, *J* = 7.1 Hz), 1.55 (ddd, 1 H, *J* = 2.5, 10.1, 13.2 Hz), 1.73 (ddd, 1 H, *J* = 2.0, 10.1, 13.2 Hz), 1.83 (d, 3 H, *J* = 0.5 Hz), 1.98 (d, 3 H, *J* = 0.5 Hz), 2.04 (s, 3 H), 3.79 (m, 1 H), 3.89 (m, 1 H), 4.20 (q, 2 H, *J* = 7.1 Hz), 4.27 (d, 1 H, *J* = 10.1 Hz), 4.33 (dd, 1 H, *J* = 6.7, 10.1 Hz), 4.40 (d, 1 H, *J* = 11.3 Hz), 4.44 (d, 1 H, *J* = 10.7 Hz), 4.57 (d, 1 H, *J* = 10.7 Hz), 4.62 (d, 1 H, *J* = 11.3 Hz), 4.84 (d, 1 H, *J* = 10.7 Hz), 5.55 (d, 1 H, *J* = 11.1 Hz), 5.95 (d, 1 H, *J* = 15.5 Hz), 6.15 (d, 1 H, *J* = 11.1 Hz), 6.27 (s, 1 H), 6.40 (dd, 1 H, *J* = 11.1, 15.5 Hz), 7.30 (m, 15 H), 7.96 (d, 1 H, *J* = 15.5 Hz);

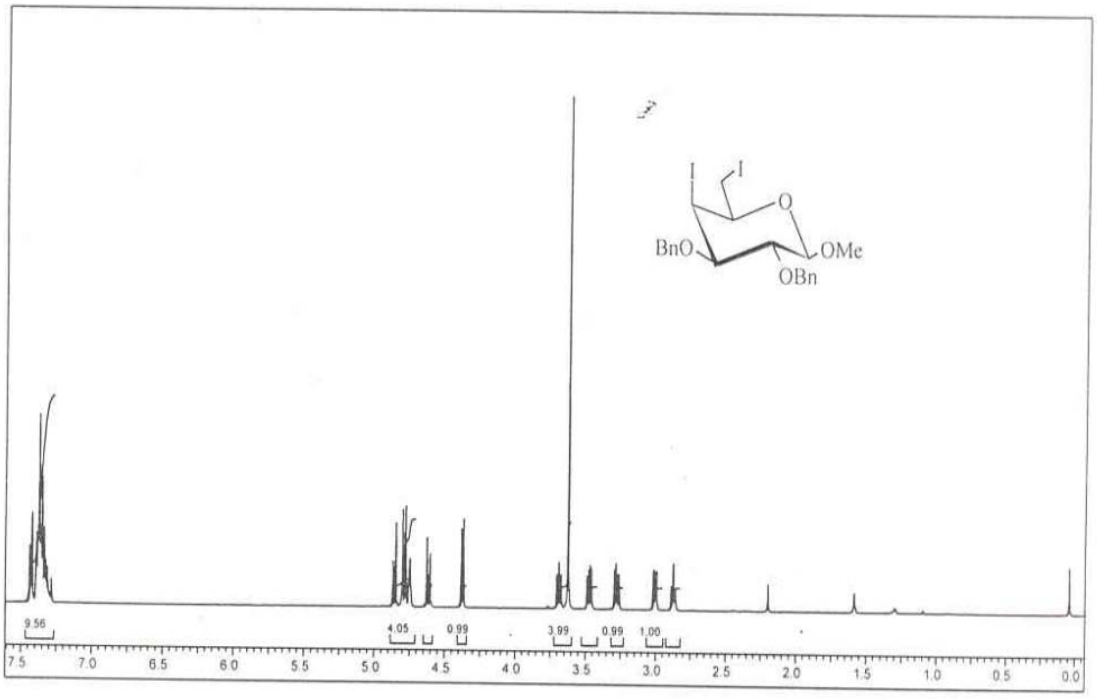
^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 14.0, 17.2, 19.6, 20.7, 39.3, 59.9, 69.9, 70.0, 71.2, 73.8, 78.3, 78.4, 118.2, 124.3, 127.1-127.9, 130.7, 133.6, 138.1-138.8, 140.9, 142.5, 167.2. Anal.Calcd. for $C_{42}H_{50}O_5$: C, 79.49; H, 7.88. Found: C, 79.28; H, 8.01 %.



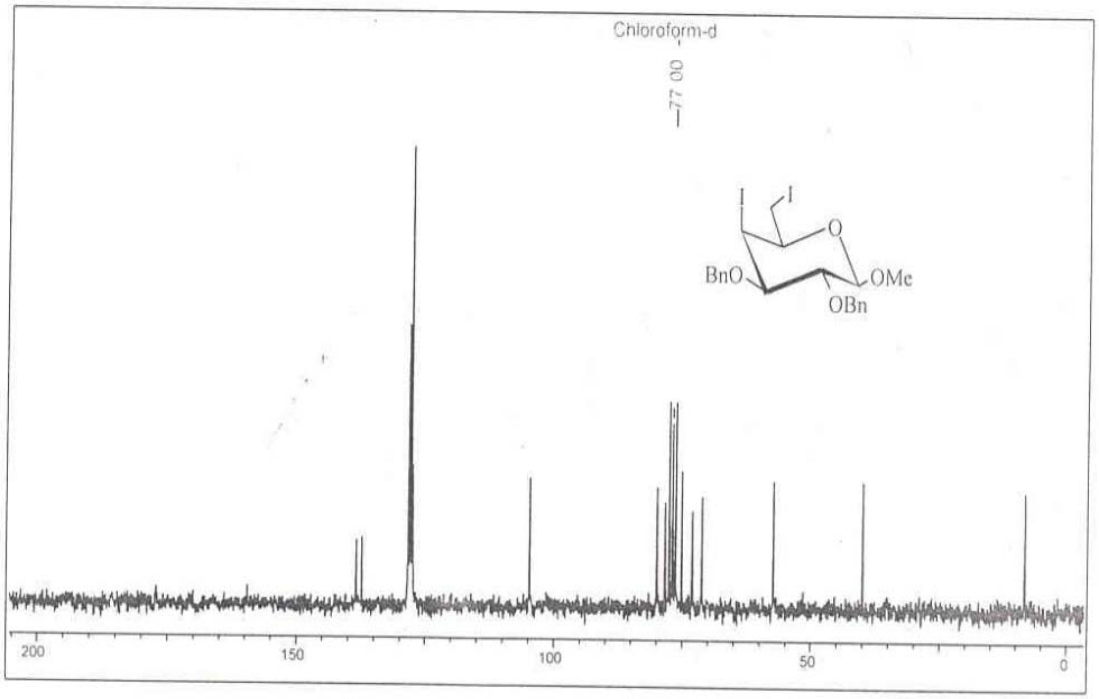
^{1}H NMR spectrum of compound 71 in $CDCl_3$



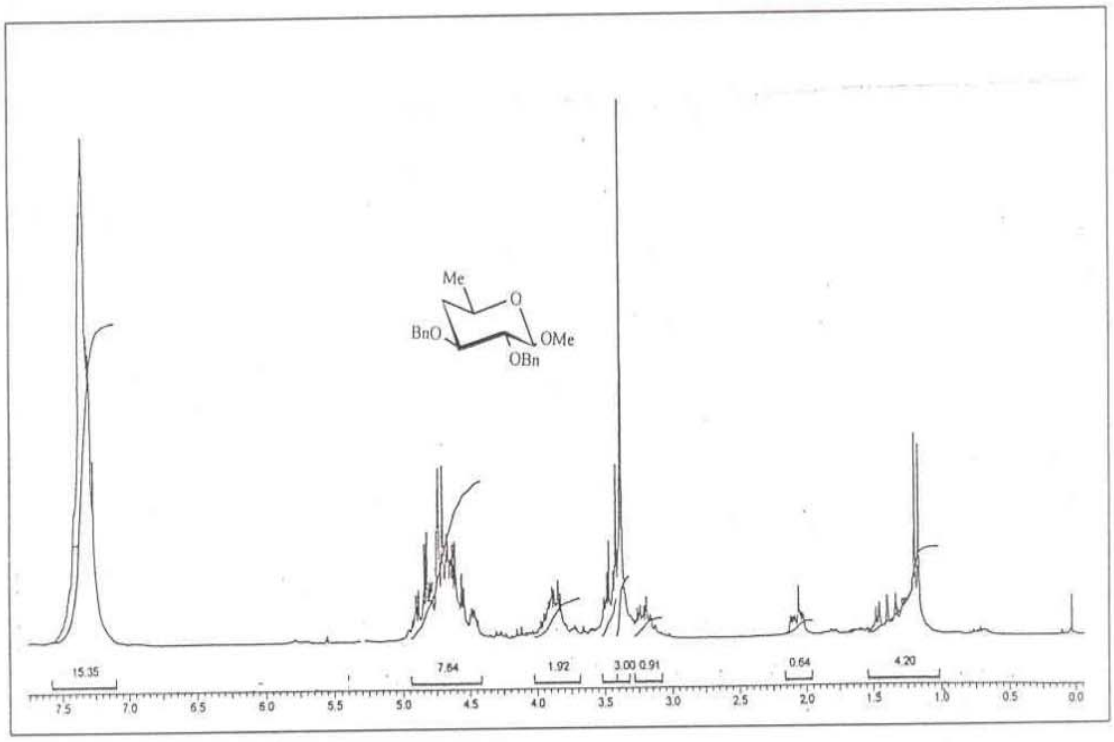
^{13}C NMR spectrum of compound 71 in $CDCl_3$



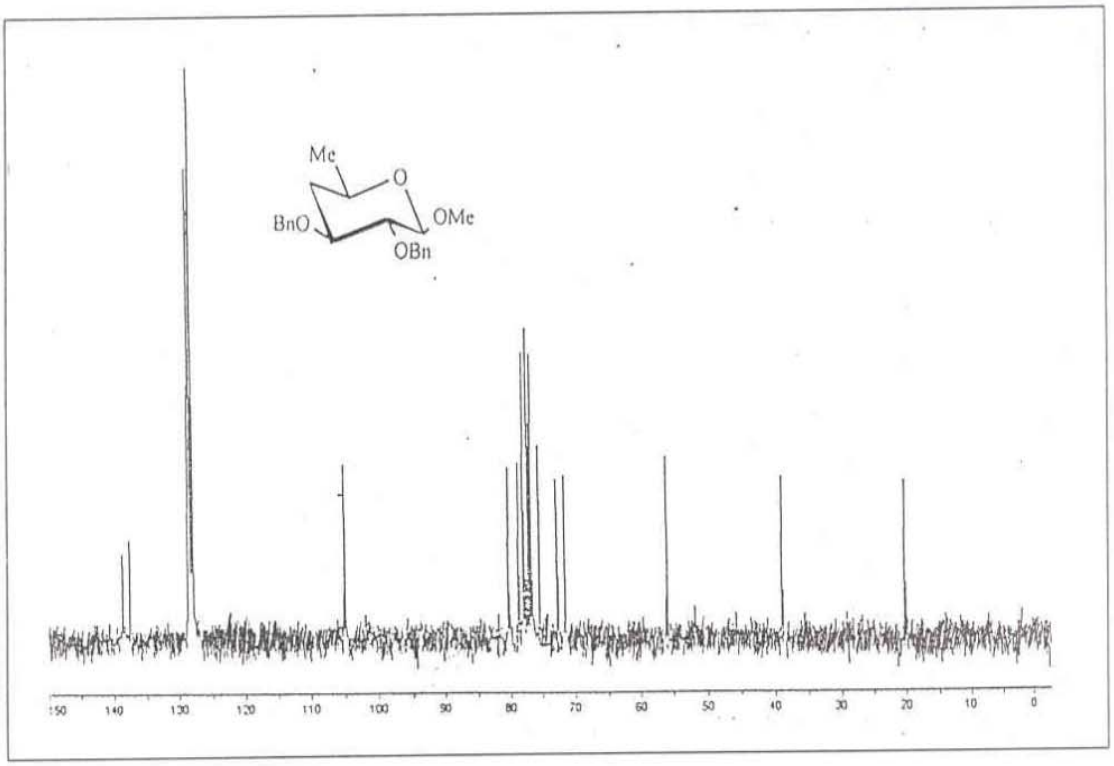
^{1}H NMR spectrum of compound 72 in $CDCl_3$



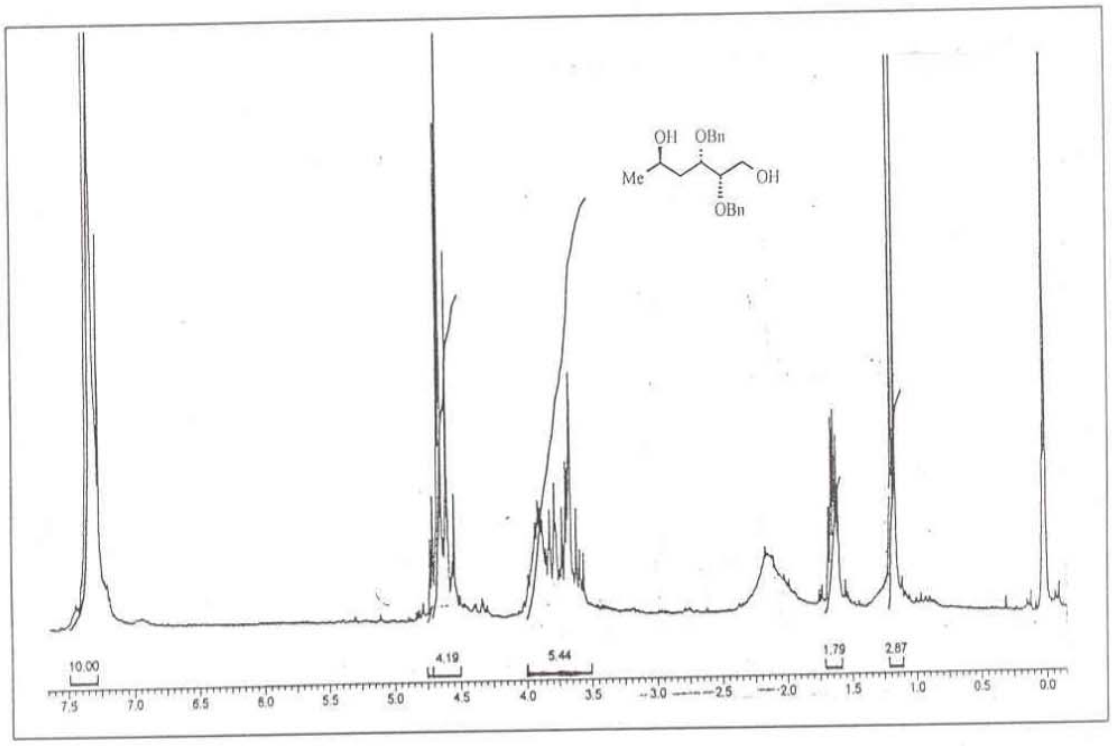
^{13}C NMR spectrum of compound 72 in $CDCl_3$



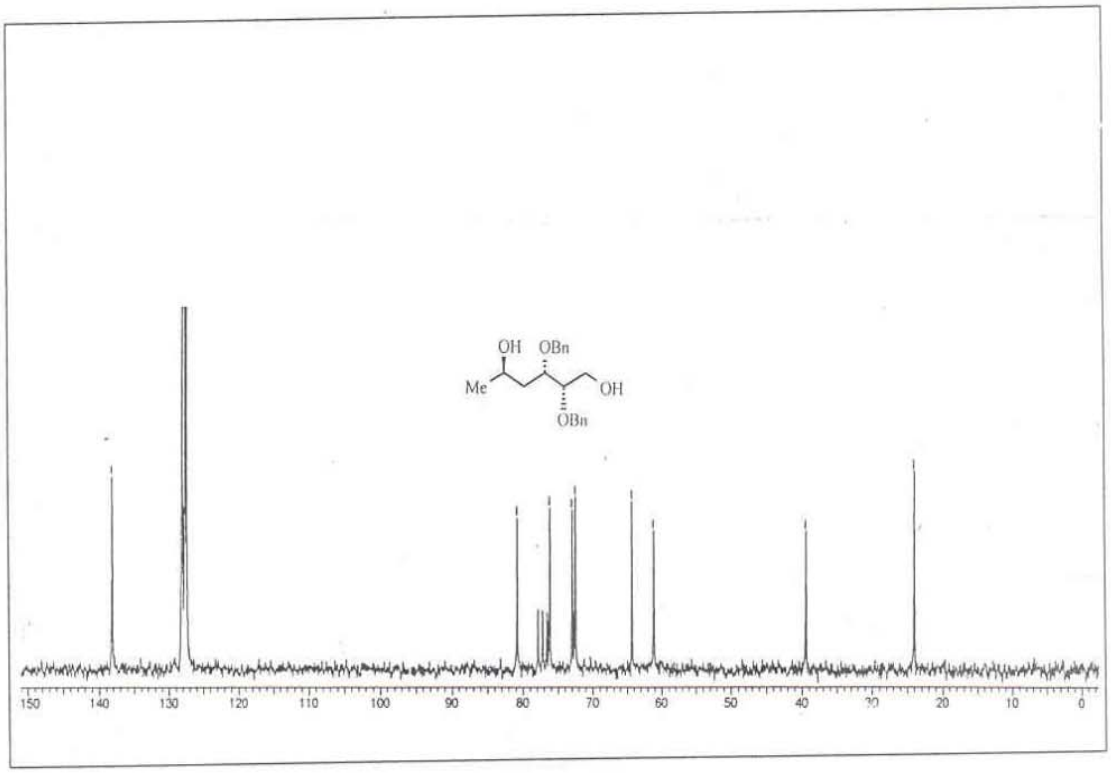
^{1}H NMR spectrum of compound 73 in $CDCl_3$



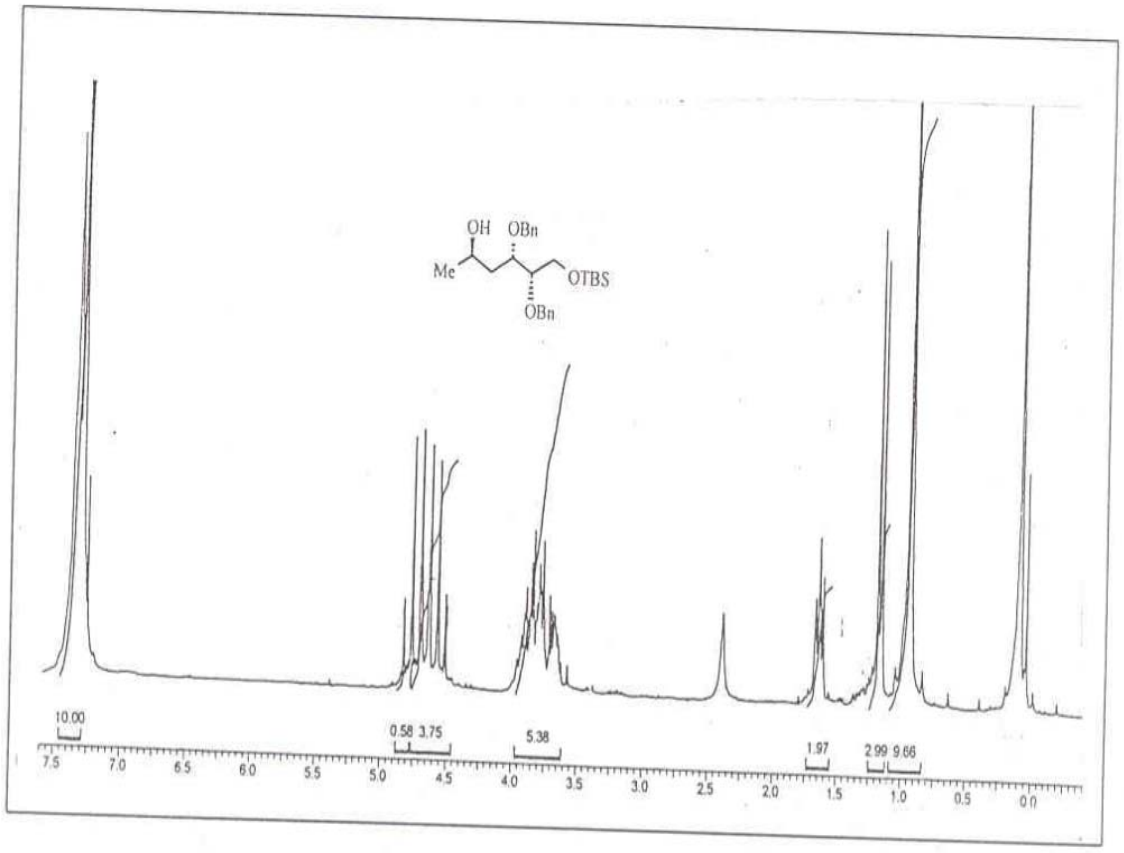
^{13}C NMR spectrum of compound 73 in $CDCl_3$



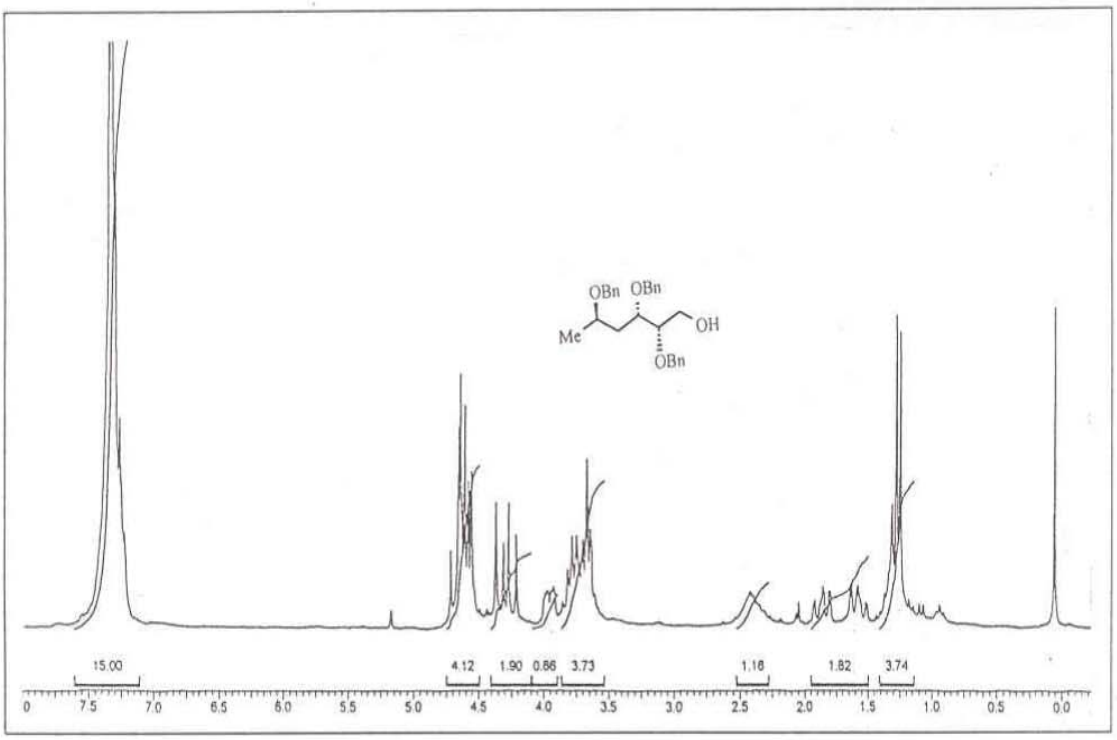
^{1}H NMR spectrum of compound 75 in $CDCl_3$



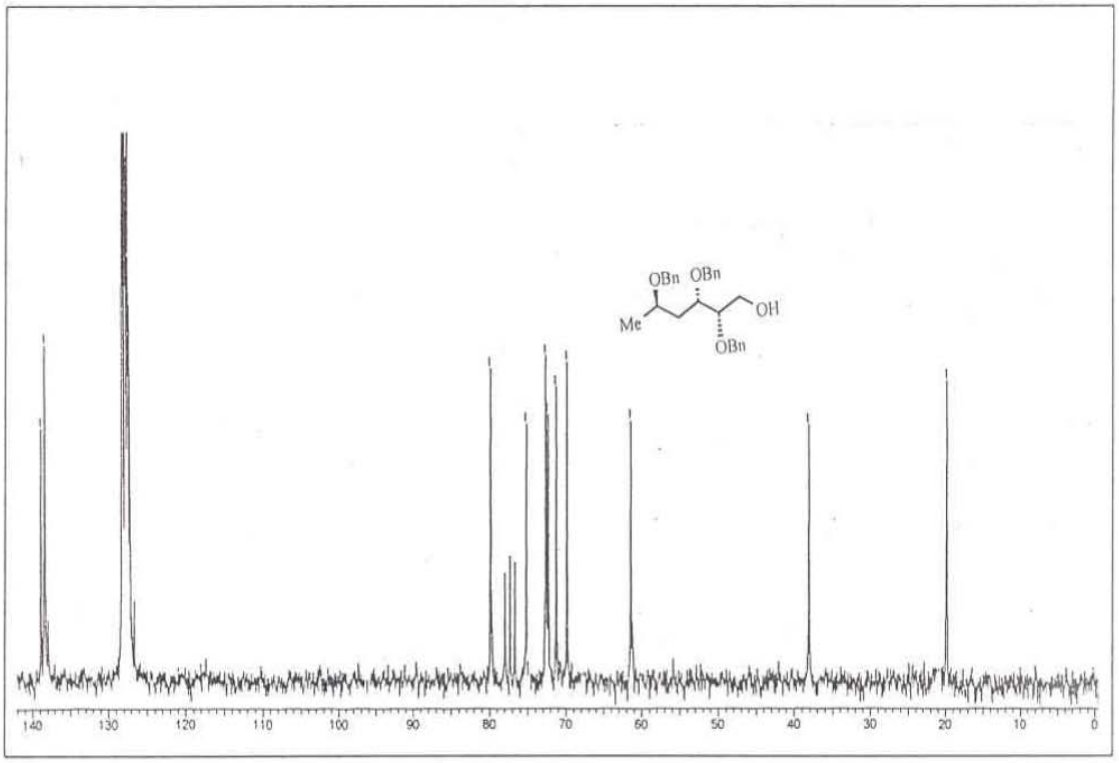
^{13}C NMR spectrum of compound 75 in $CDCl_3$



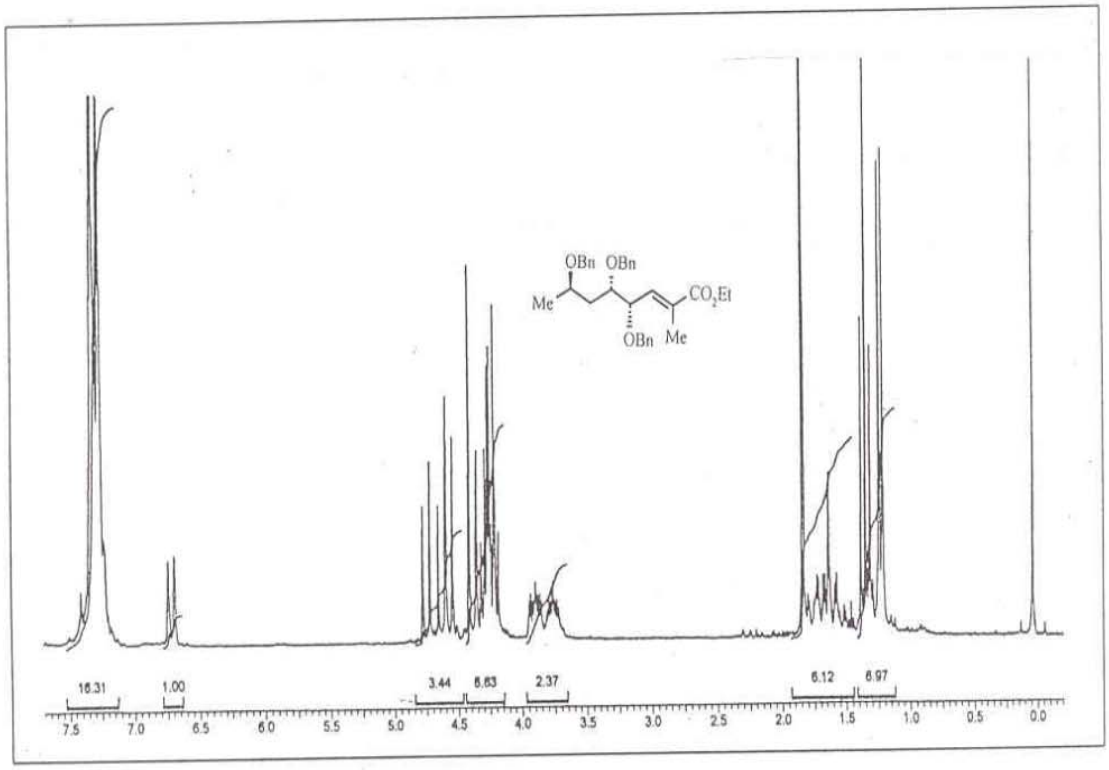
^{1}H NMR spectrum of compound 76 in $CDCl_3$



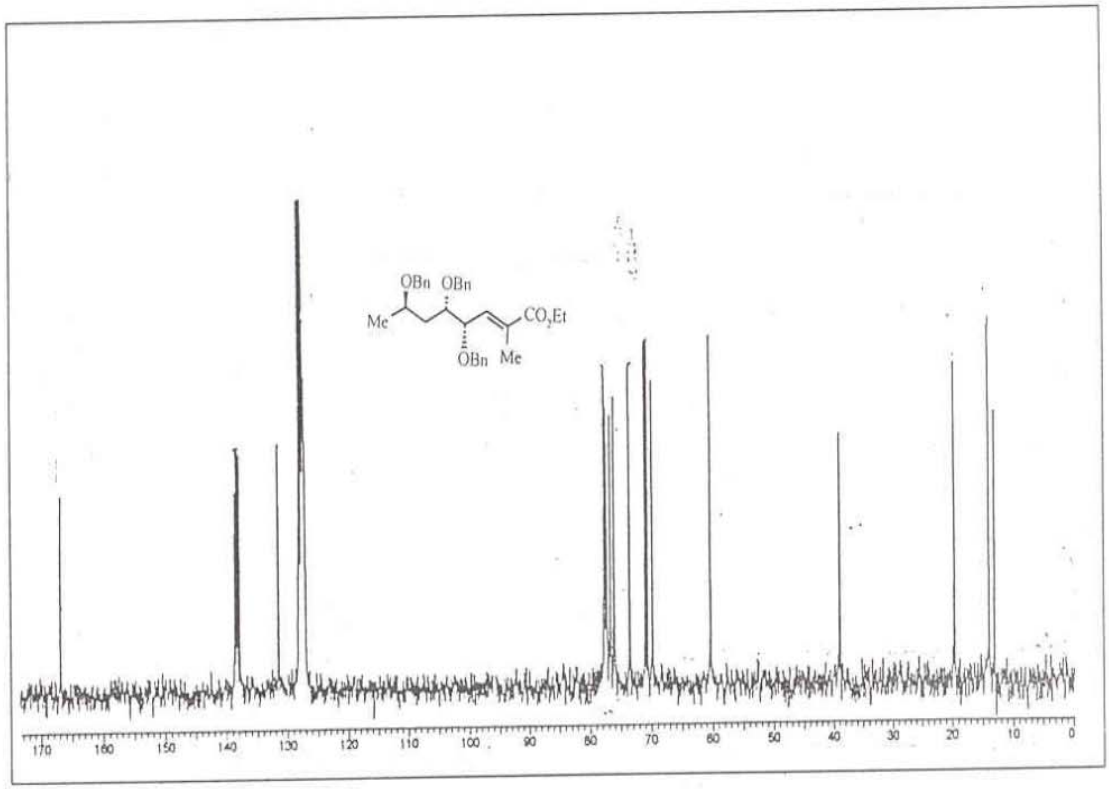
^{1}H NMR spectrum of compound 78 in $CDCl_3$



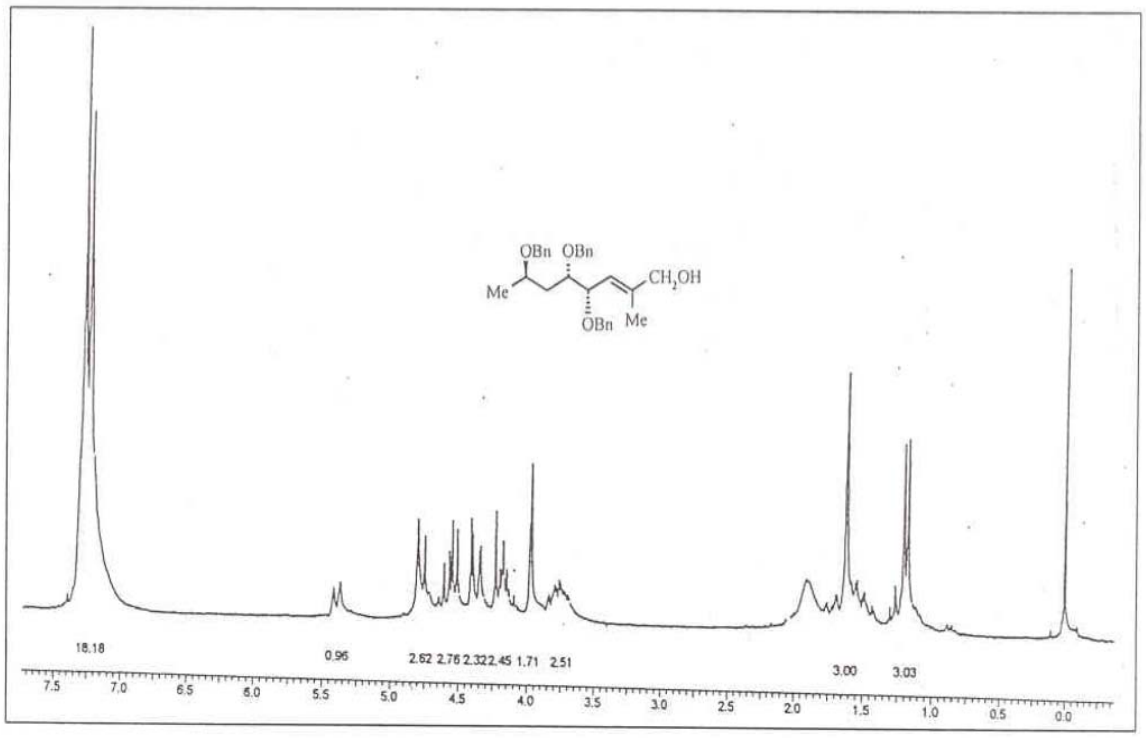
^{13}C NMR spectrum of compound 78 in $CDCl_3$



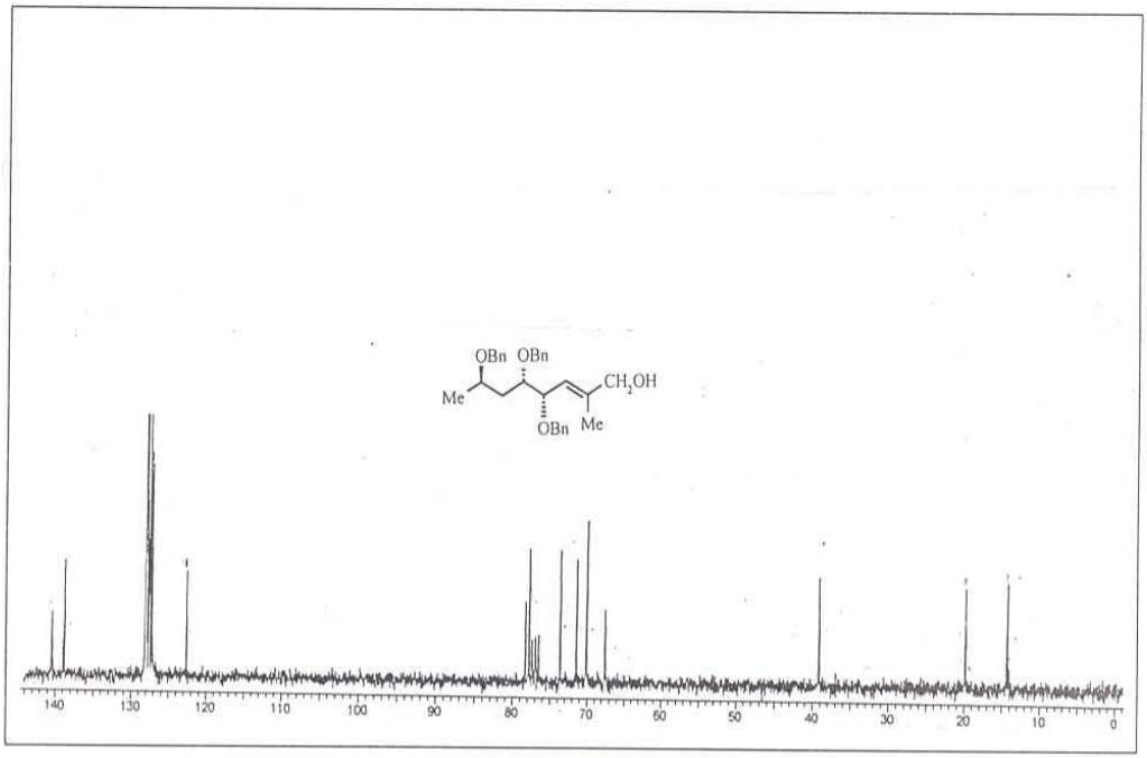
^{1}H NMR spectrum of compound 80 in $CDCl_3$



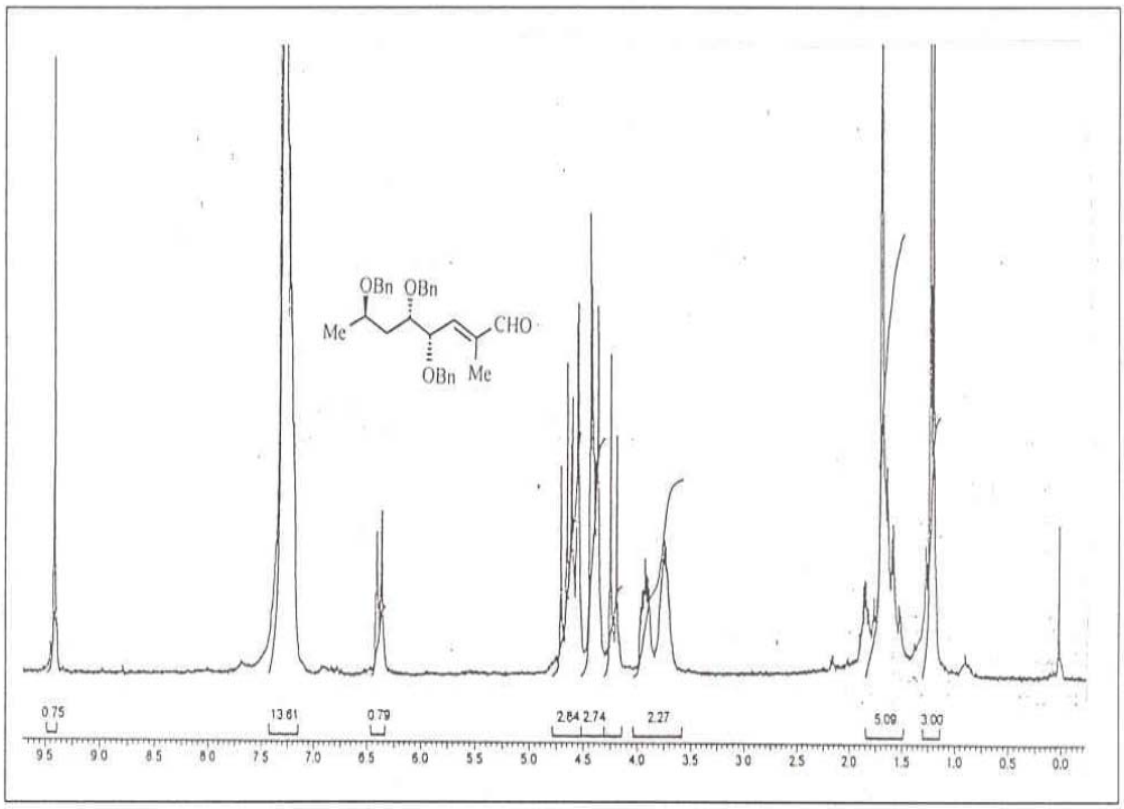
^{13}C NMR spectrum of compound 80 in $CDCl_3$



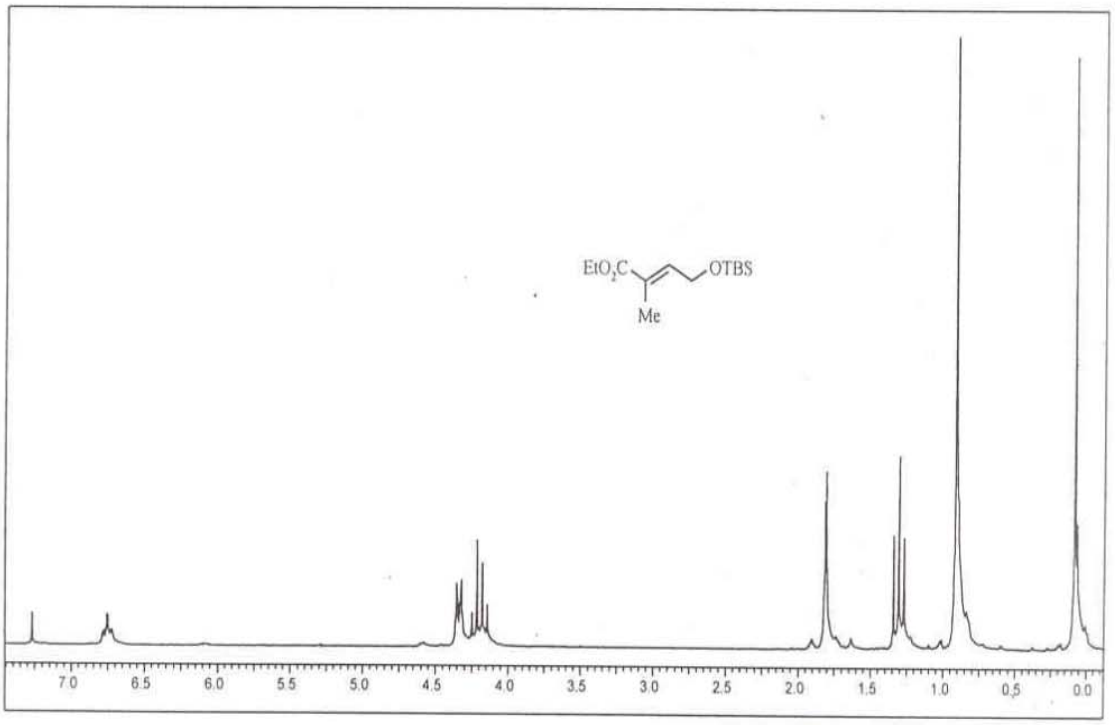
^{1}H NMR spectrum of compound 81 in $CDCl_3$



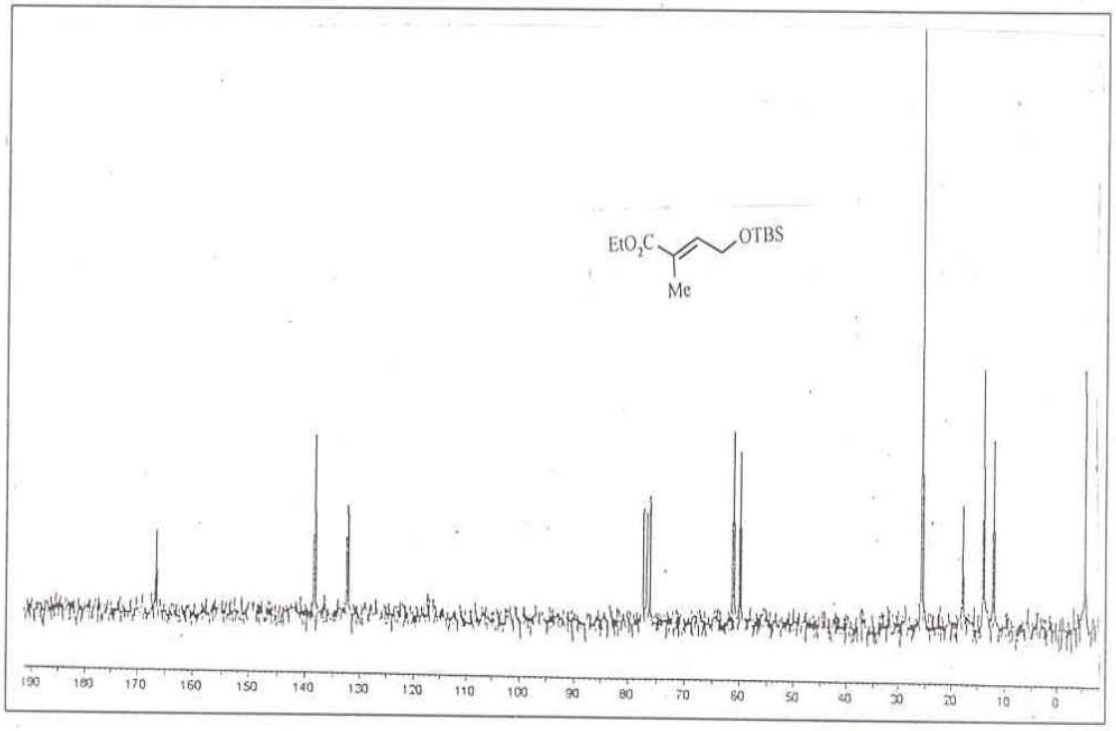
^{13}C NMR spectrum of compound 81 in $CDCl_3$



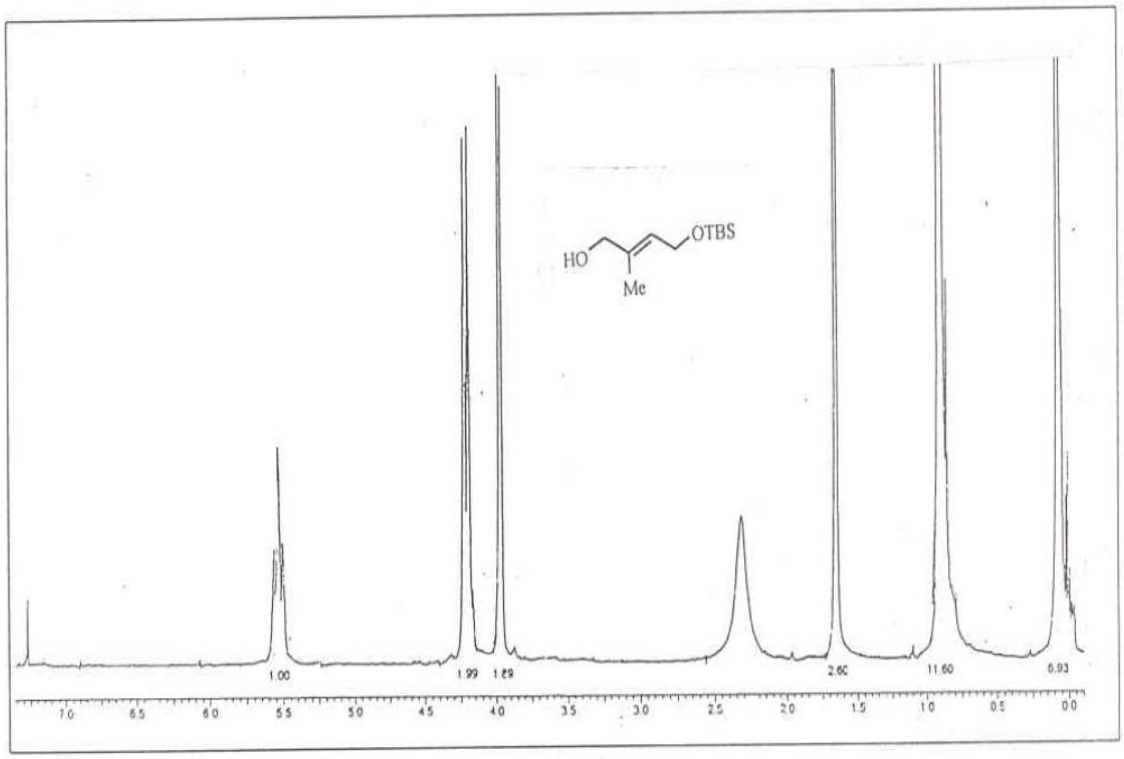
^{1}H NMR spectrum of compound 82 in $CDCl_3$



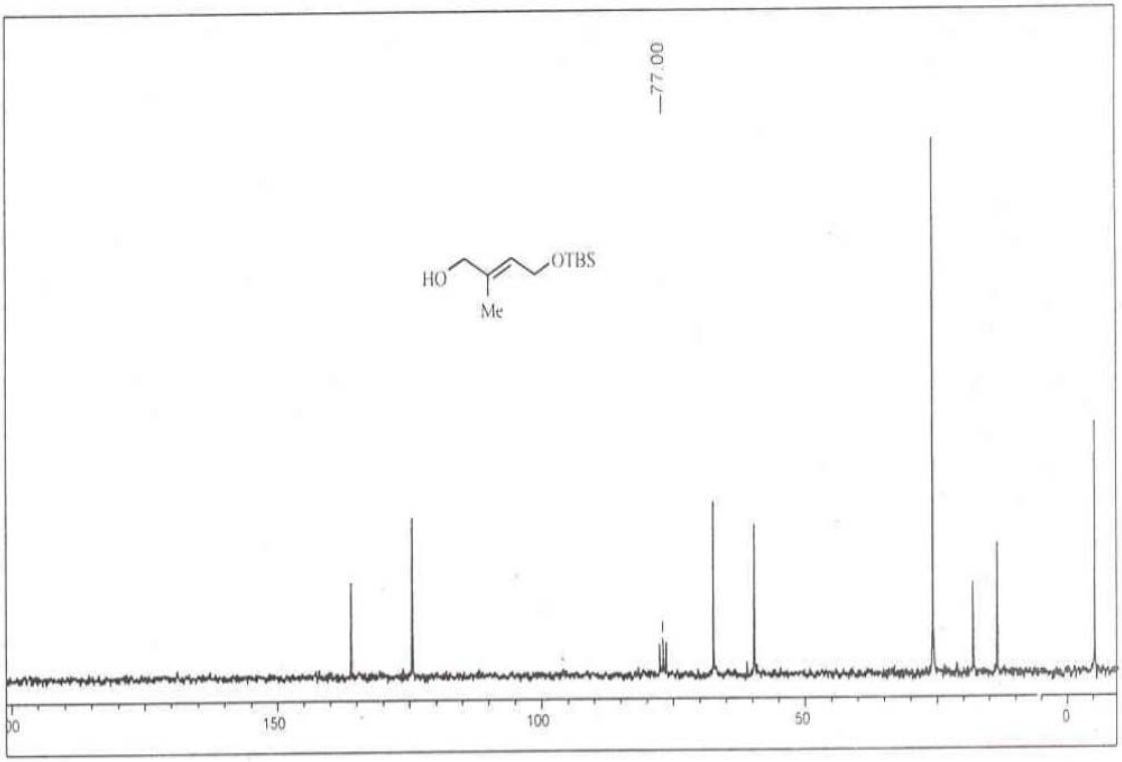
^{1}H NMR spectrum of compound 86 in $CDCl_3$



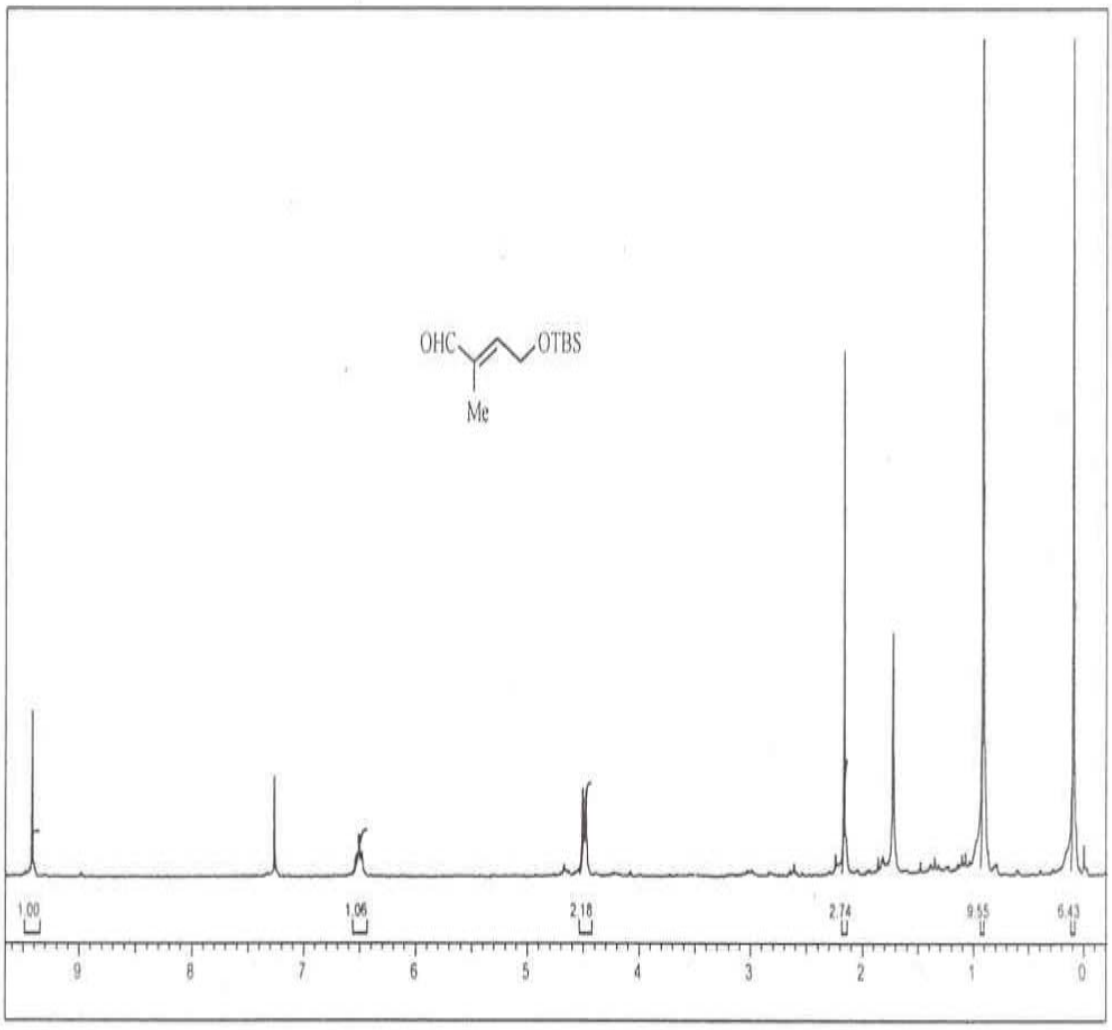
^{13}C NMR spectrum of compound 86 in $CDCl_3$



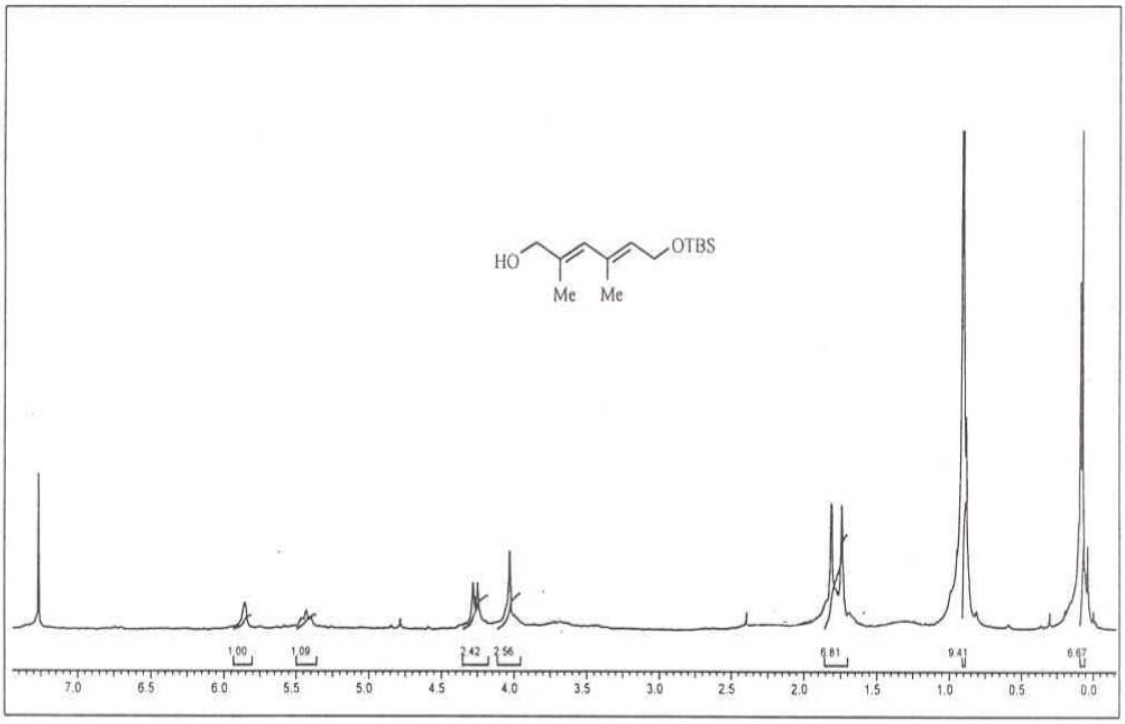
^{1}H NMR spectrum of compound 87 in $CDCl_3$



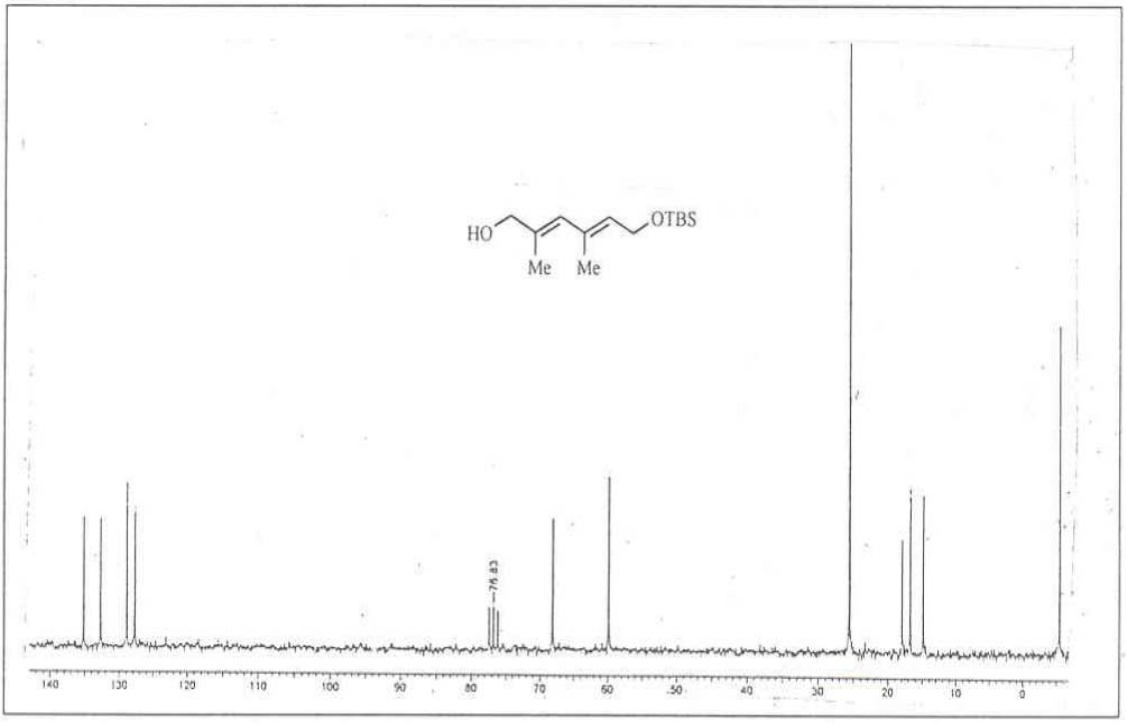
^{13}C NMR spectrum of compound 87 in $CDCl_3$



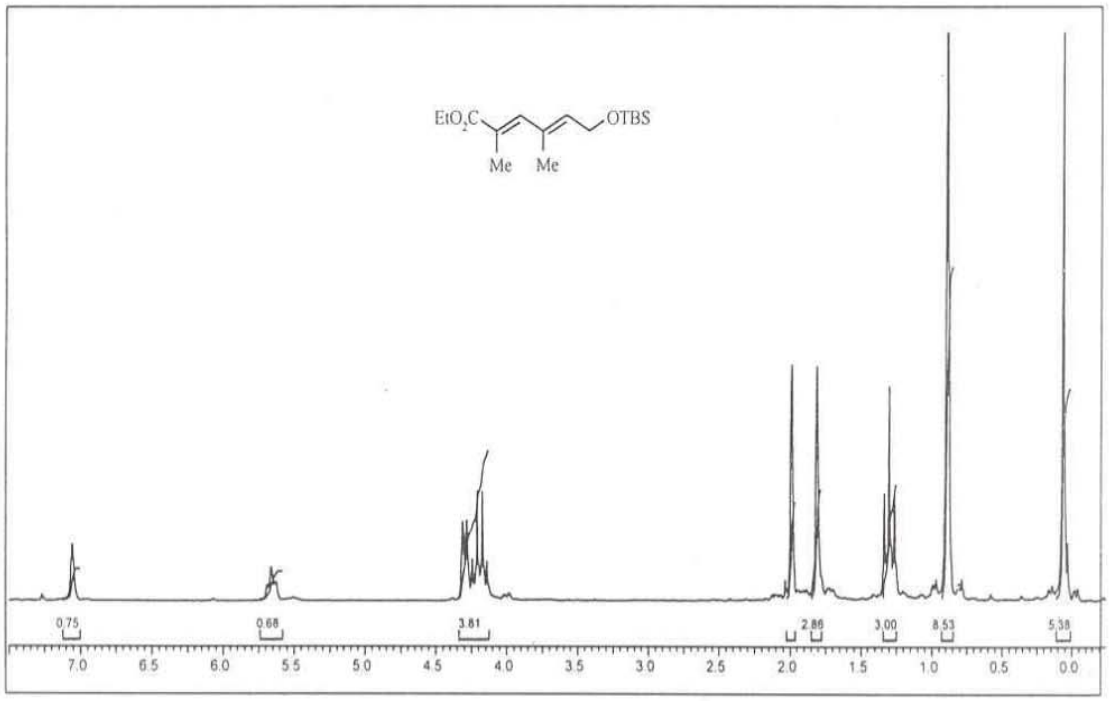
^{1}H NMR spectrum of compound 88 in $CDCl_3$



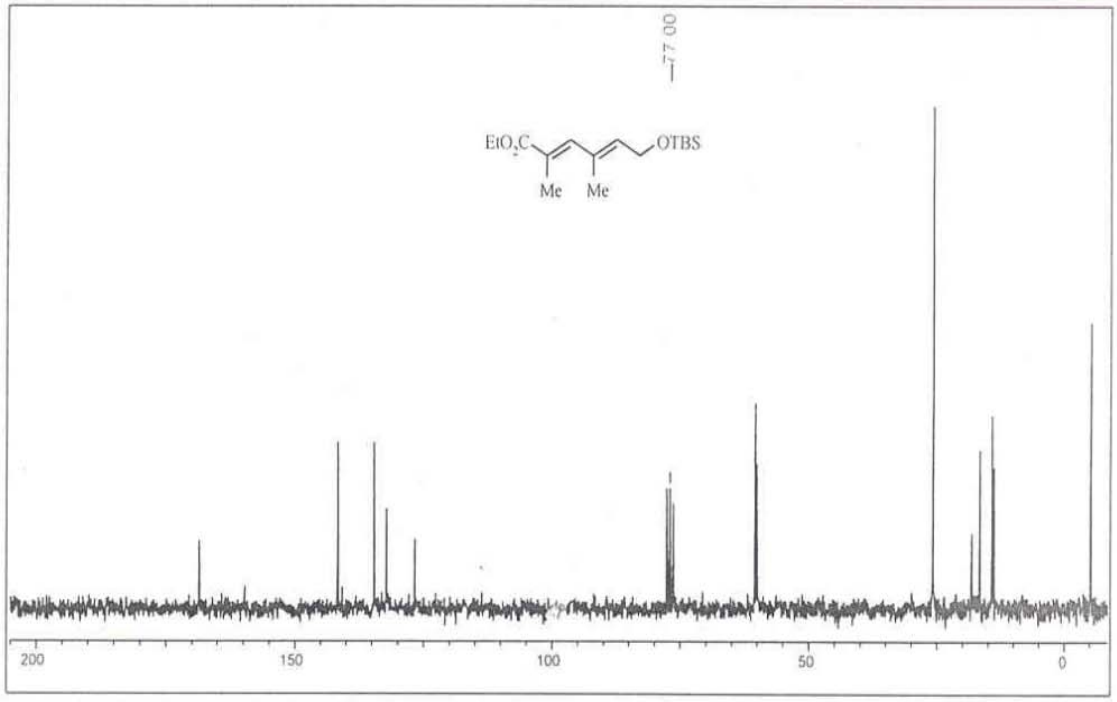
^{1}H NMR spectrum of compound 90 in $CDCl_3$



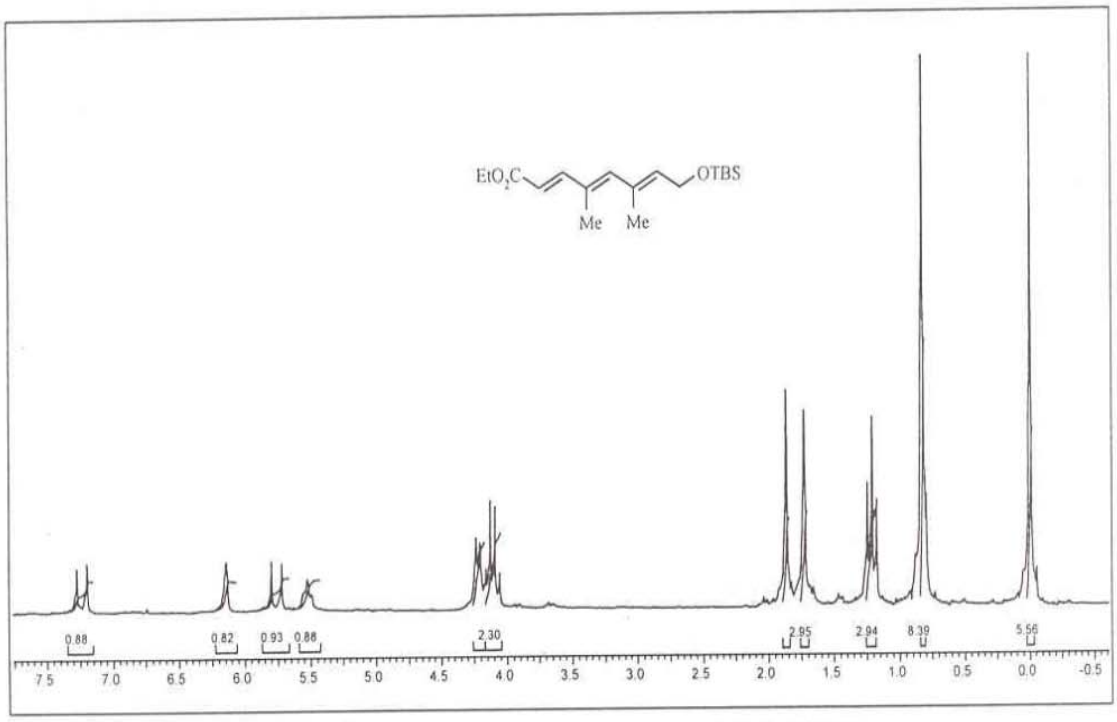
^{13}C NMR spectrum of compound 90 in $CDCl_3$



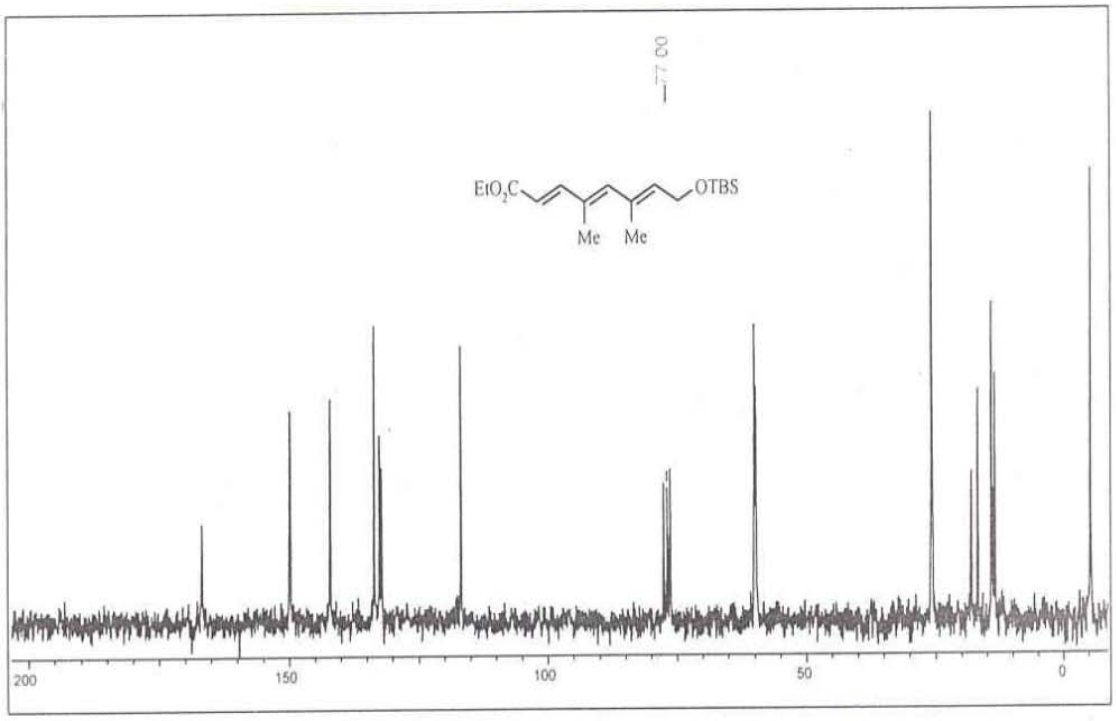
^{1}H NMR spectrum of compound 89 in $CDCl_3$



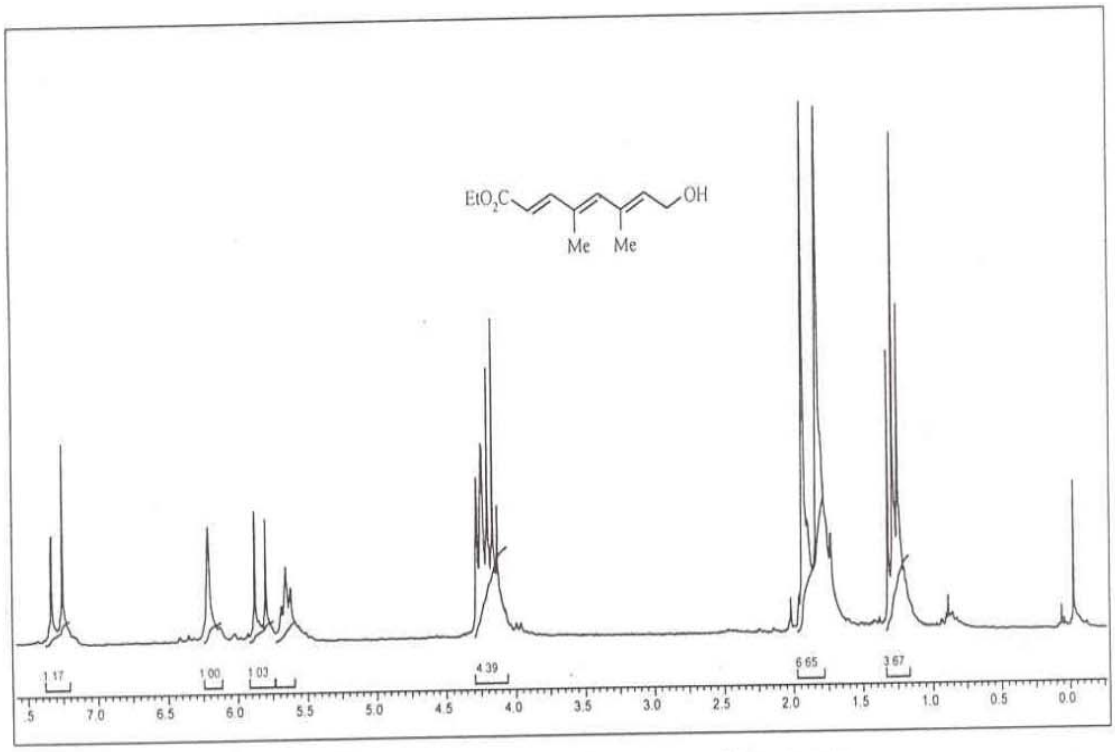
^{13}C NMR spectrum of compound 89 in $CDCl_3$



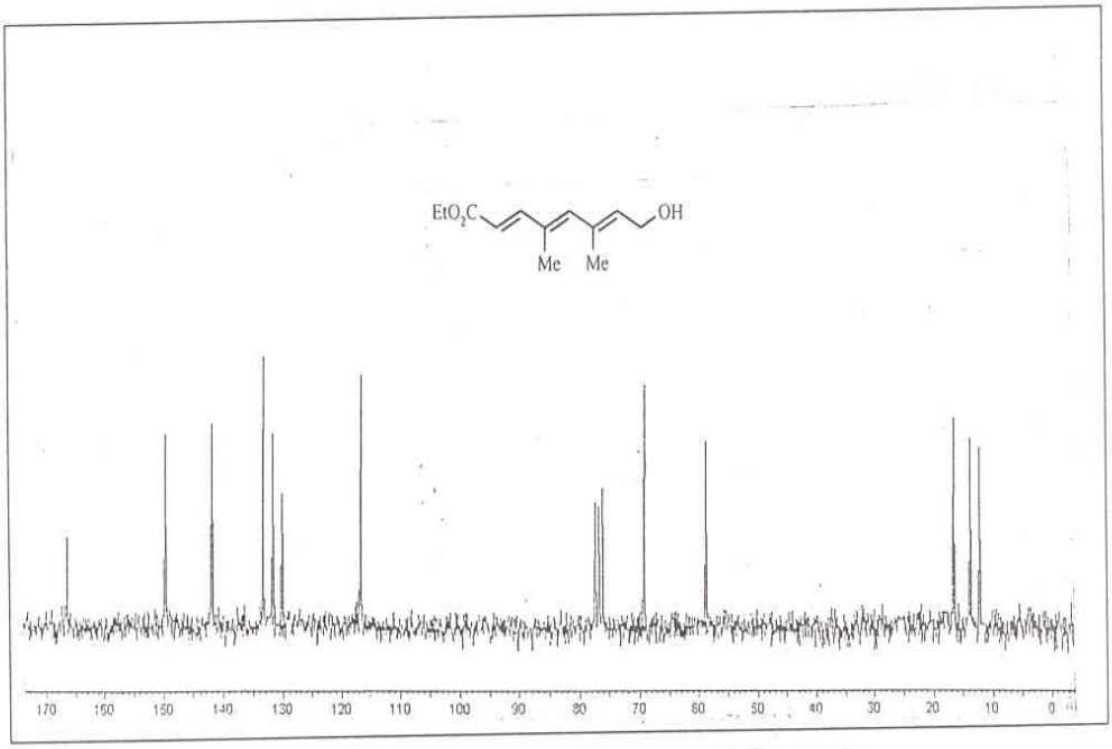
^{1}H NMR spectrum of compound 92 in $CDCl_3$



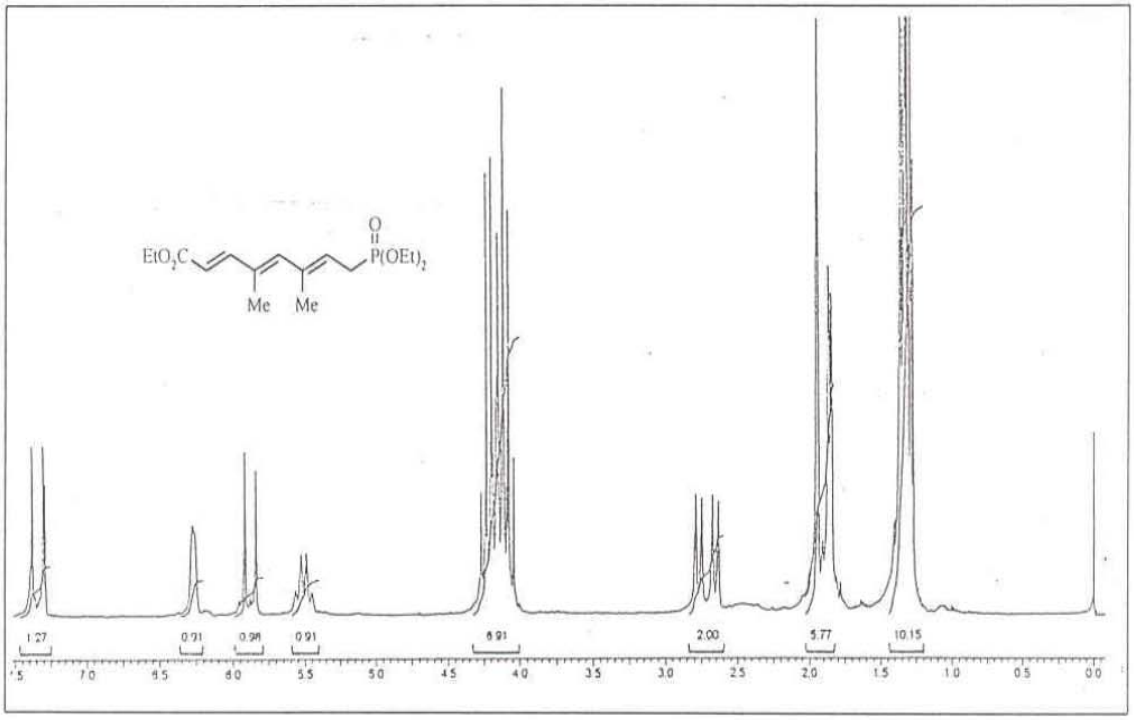
^{13}C NMR spectrum of compound 92 in $CDCl_3$



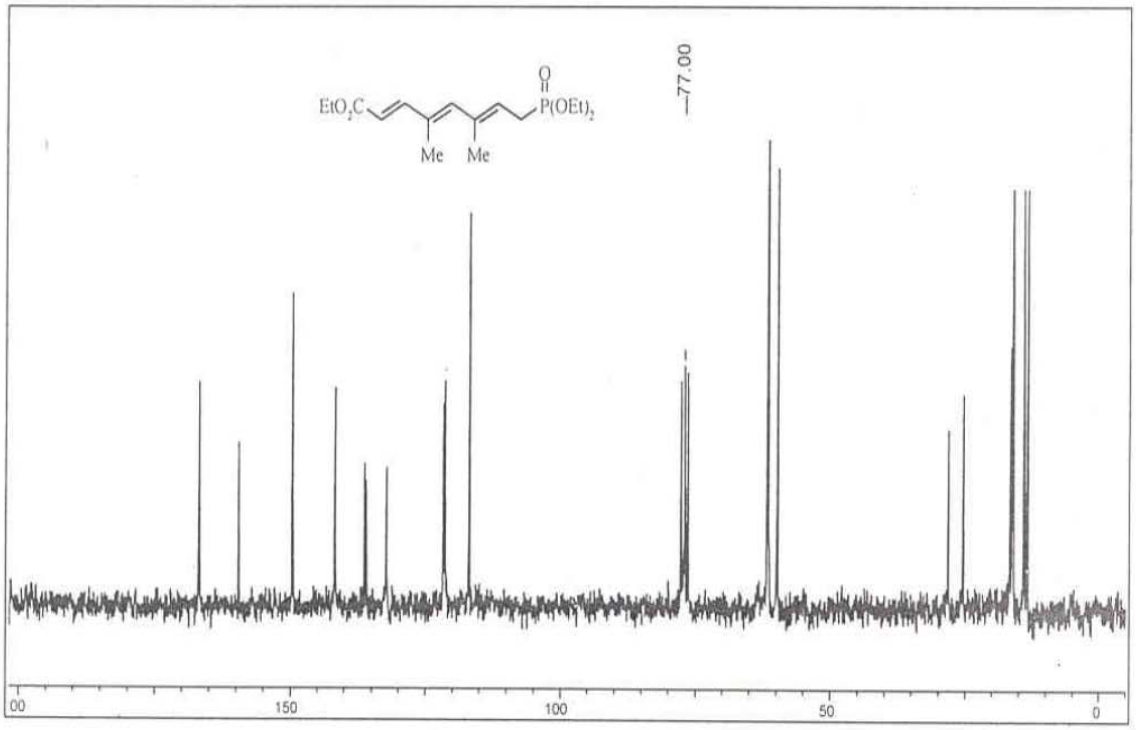
^{1}H NMR spectrum of compound 93 in $CDCl_3$



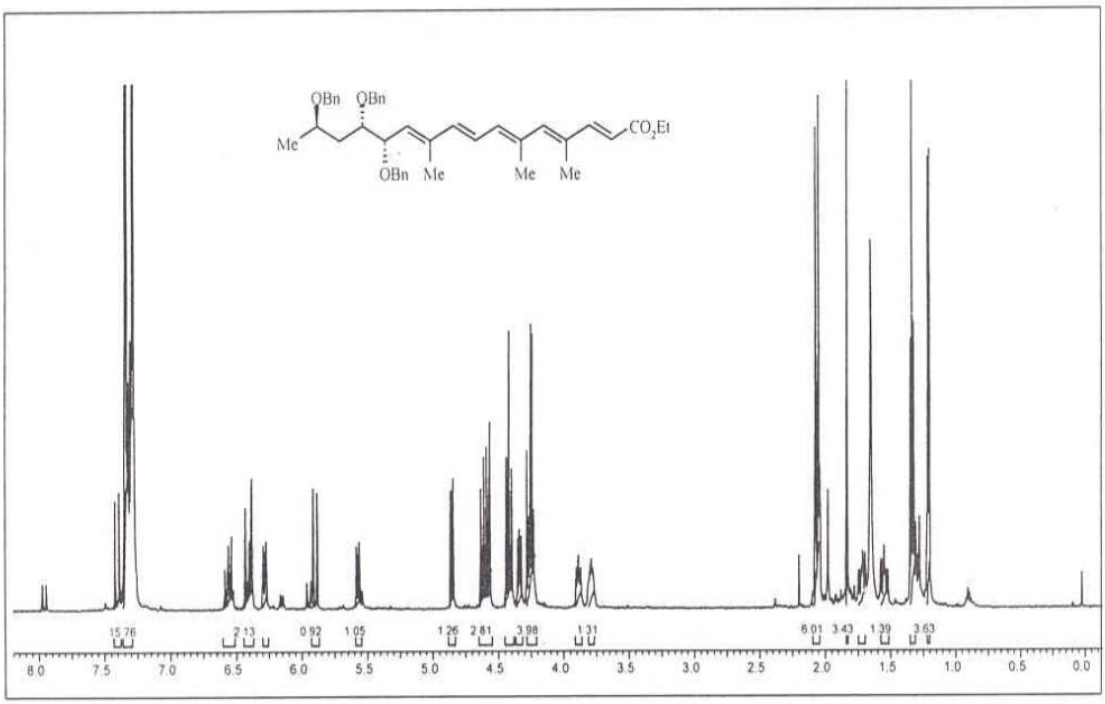
^{13}C NMR spectrum of compound 93 in $CDCl_3$



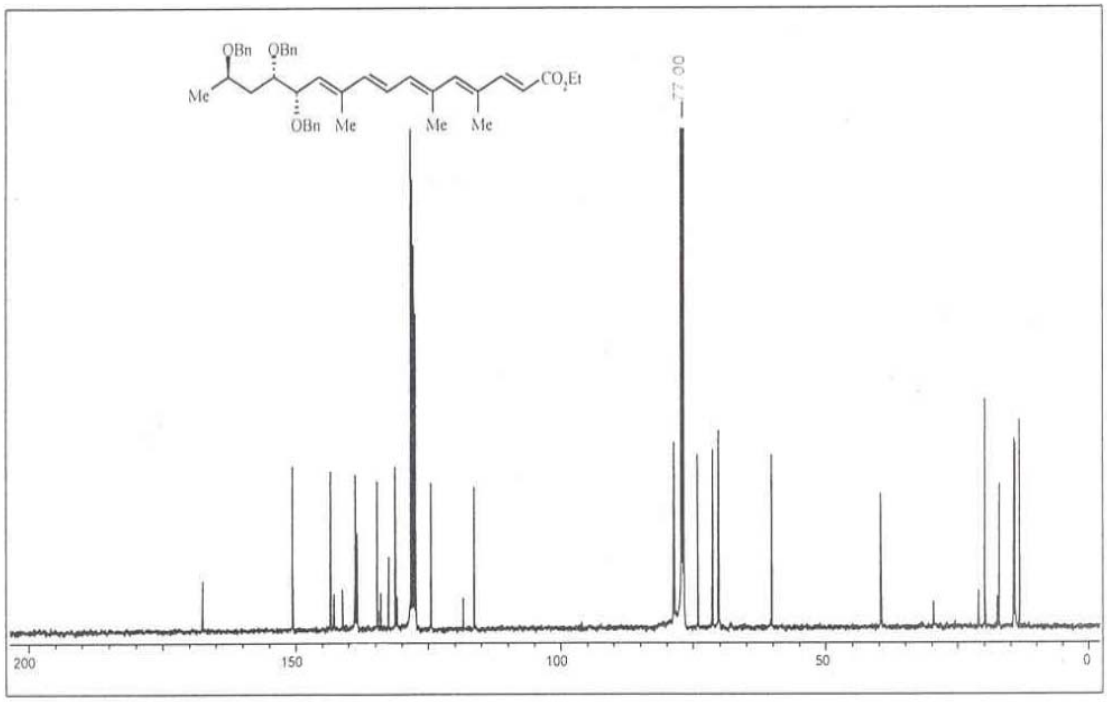
^{1}H NMR spectrum of compound 95 in $CDCl_3$



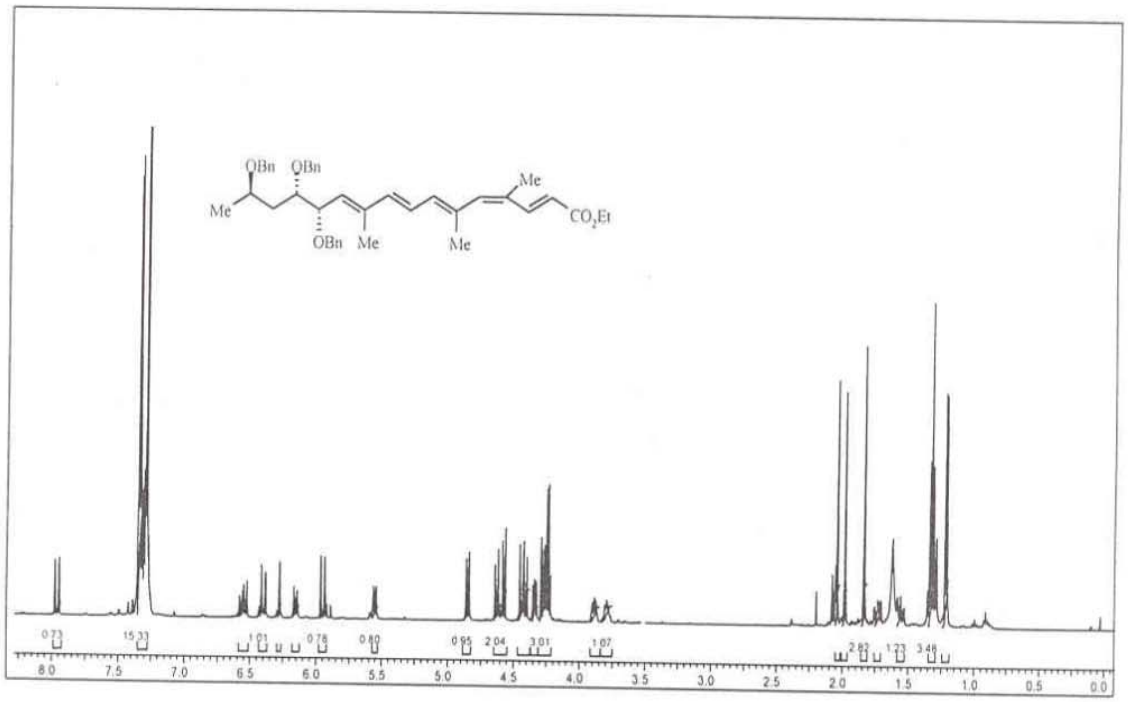
^{13}C NMR spectrum of compound 95 in $CDCl_3$



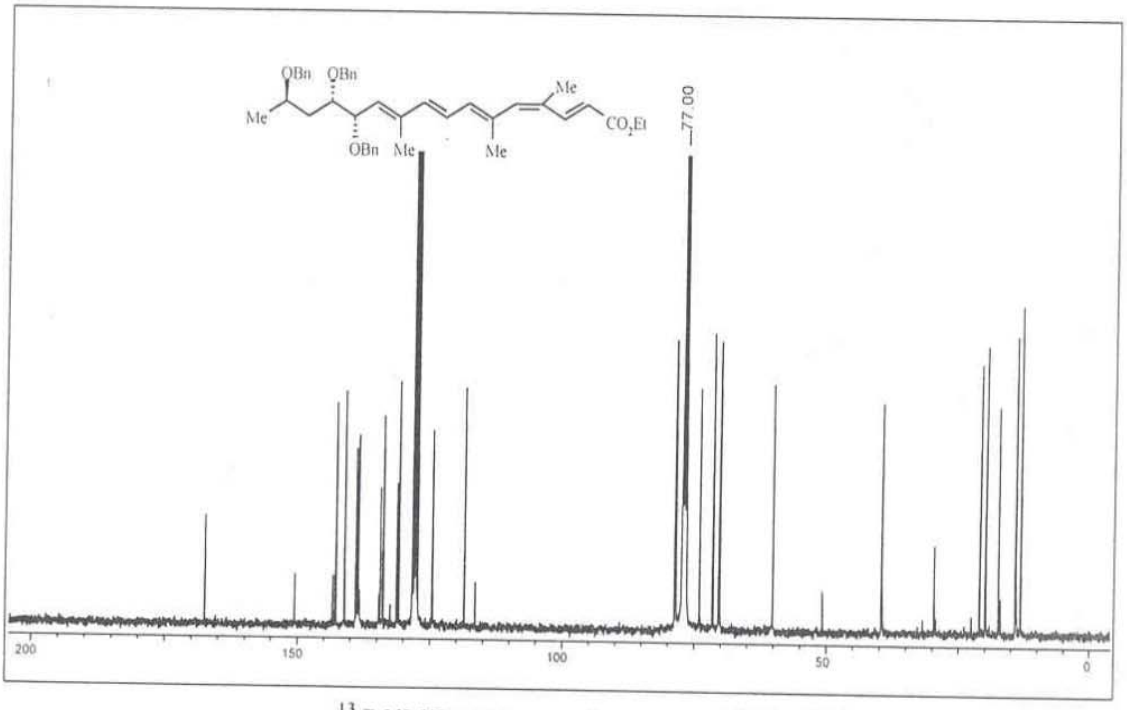
^{1}H NMR spectrum of compound 96 in $CDCl_3$



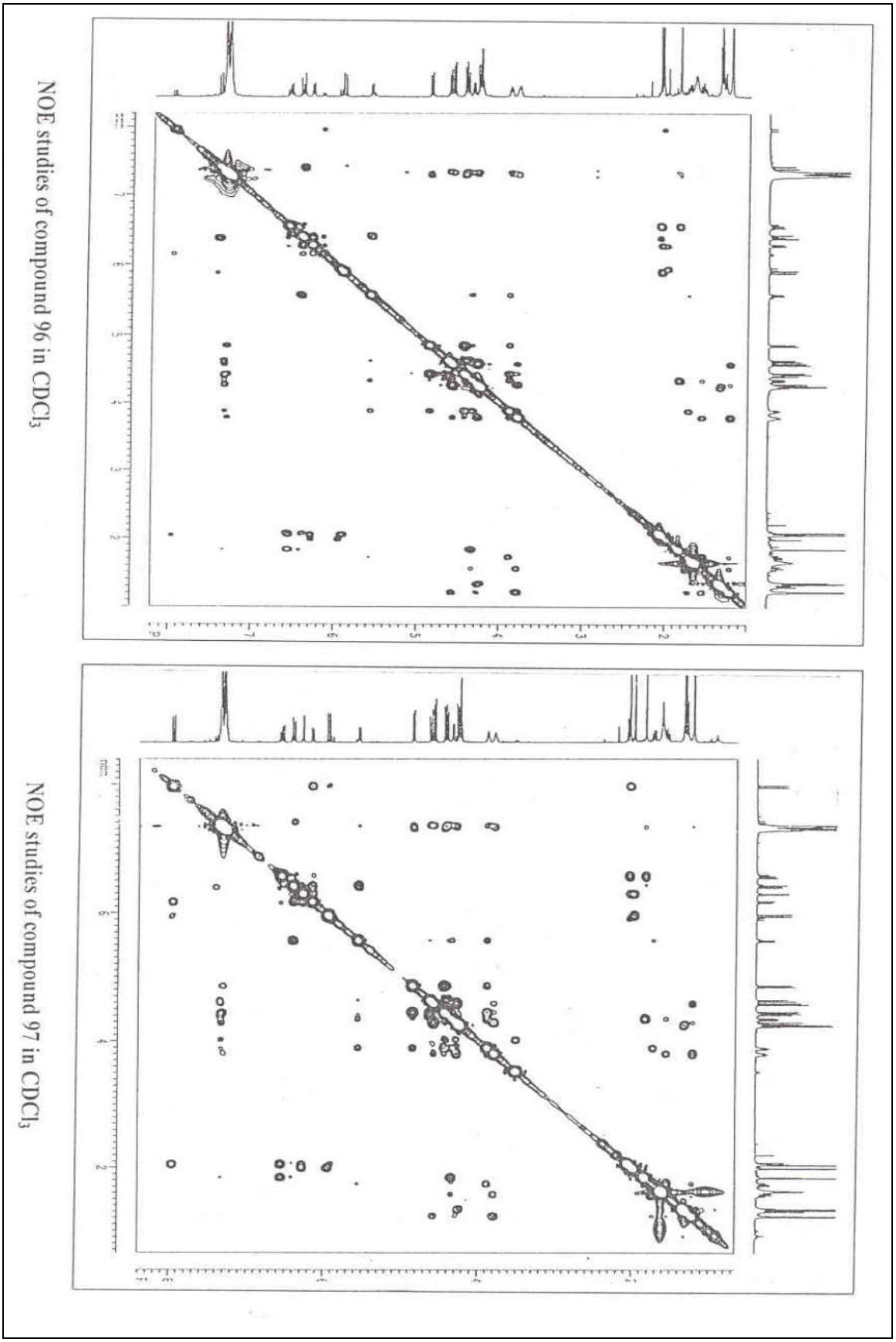
^{13}C NMR spectrum of compound 96 in $CDCl_3$



^{1}H NMR spectrum of compound 97 in $CDCl_3$



^{13}C NMR spectrum of compound 97 in $CDCl_3$



NOE studies of compound 96 in $CDCl_3$

NOE studies of compound 97 in $CDCl_3$

References

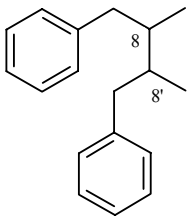
1. *WHO report on Buruli Ulcer*, **2000**, edited by Asiedu, K.; Scherpbier, R.; Ravigilone, M.
2. Connor, D. H.; Lunn, F. H. *Arch. Pathol.* **1966**,*81*, 183.
3. Hayman, J. *J. Clin. Pathol.* **1993**, *46*, 5.
4. Read, J. K. *Infect. Immun.* **1974**, *9*, 1114.
5. Krieg, R. E.; Hockmeyer, W. T.; Connor, D. H. *Arch. Dermatol.* **1974**, *110*, 783.
6. W. T. Hockmeyer, W. T.; Kreig, R. E.; Reich, M.; Johnson, R. D. *Infect. Immun.* **1978**, *21*, 124.
7. George, K. M.; Chatterjee, D.; Gunawardana, G.; Welty, D.; Hayman, J.; Lee, R.; Small, P. L. C. *Science*, **1999**, *283*, 854; Gunawardana, G.; Chatterjee, D.; George, K. M.; Brennan, P.; Whittern, D.; Small, P. L. C.; *J. Am. Chem. Soc.,* **1999**, *121,* 6092.
8. Hudson, A. T.; Campbell I. M.; Bentley, R. *Biochemistry* **1970**, *9*, 3988.
9. Labro, M. *Int. J. Antimicrob. Agents* **1998**, *10*, 11; Hopwood D. A.; Sherman, D. H.; *Annu. Rev. Genet.* **1990**, *24*, 37; Katz, L.; Donadio, S. *Annu. Rev. Microbiol.* **1993***,47*, 875; Maplestone, R. A.; Stone, M. J.; Williams, D. H. *Gene* **1992,** *115,* 151.
10. Ross, B. C. *et al., Appl. Environ. Microbiol.* **63**, 4135 (1997); Cole, S. *et al., Nature* **1998**, *393*, 537.
11. Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1,* **2002**, 999.
12. Rychnovsky, S. D. *Chem.. Rev.*, **1995**, *95*, 2021.
13. Hopf, F. *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim, **2000**.
14. Isler, O. *Carotenoids*, Birkhauser Verlag, Basel, **1971**.
15. Karrer, P.; Eugster, C. H. *Helv. Chim. Acta*, **1950**, *33*, 1172.
16. Zeng, F.; Negishi, E. *Org. Lett.*, **2001**, *3*, 719.
17. Pearson, D. L. *J. Org. Chem.*, **1997**, *62*, 1376.
18. Kuhn, R. *Angew. Chem.*, **1937**, *50*, 703.
19. Wittig, G.; Geissler, G. *Justus Leibigs Ann. Chem.*, **1953**, *580*, 44.
20. Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.*, **2002**, *41*, 3171.
21. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Massamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.*, **1994**, *25*, 2183.

22. For examples with diazoesters, see: Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem. Int. Ed. Engl.*, **2001**, *40*, 2887; Herrman, W. A.; Wang, M. *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1641.
23. Still, W. C.; Gennari, C. *Tetrahedron Lett.*, **1993**, *24*, 4405; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *Tetrahedron Lett.*, **1999**, *40*, 1269.
24. Tode, C.; Yamano, Y.; Ito, M. *J. Chem. Soc. Perkin Trans. 1*, **1999**, 1625.
25. Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.*, **1961**, *83*, 1733.
26. Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.*, **1988**, *110*, 4696.
27. Marynoff, B. E.; Reitz, A. B. *Chem. Rev.,* **1989**, *89*, 863; Horner, L.; Hoffmann, H.; Wipel, H. C.; Klahre, G. *Chem. Ber.*, **1959**, *92*, 2499.; Clayden, J.; Warren, S. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 241.; Buss, A. D.; Warren, S. *J. Chem. Soc., Perkin Trans.1*, **1985**, 2307.; Boutagy, J.; Thomas, R. *Chem. Rev.*, **1974**, *74*, 87.; Wadsworth, W. A. *Org. React.*, **1977**, 25, 73; Stork, G.; Zhao, K. *Tetrahedron Lett.*, **1989**, *30*, 2173; Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.,***2000**, *65,* 4745 and references cited therein.
28. Stille, J. K. *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 508.
29. Dixon, D. J.; Ley, S. V.; Gracza, T.; Szolesanyi, P. *J. Chem. Soc. Perkin Trans. 1*, **1999**, *8*, 839.
30. Panek, J. S.; Masse, C. E. *J. Org. Chem.*, **1997**, *62*, 8290.
31. Suzuki, A.; Miyaura, N. *Chem. Rev.*, **1995**, *95*, 2457.
32. Alvarez, R.; Dominguez, B.; de Lera, A. R. *Tetrahedron*, **1999**, *55*, 13779.
33. Remuiñán, M. J.; Pattenden, G. *Tetrahedron Lett.,* **2000**, *41*, 7367; *Synlett* **2000**, *11*, 1661.
34. Nicolaou, K. C.; Webber, S. E. *Synthesis*, **1986**, 453.
35. Torrado, A.; Iglesias, B.; Lopez, S.; de Lera, A. A. *Tetrahedron*, **1995**, *51*, 2435; Kasatkin, A.; Whitby, R. J. *J. Am. Chem. Soc.*, **1999**, *121*, 7039; Crousse, B.; Alami, M.; Linstrumelle, G. *Tetrahedron*, **1995**, *36*, 4245; Crousse, B.; Mloadenova, M.; Ducept, P.; Alami, M.; Linstrumelle, G. *Tetrahedron*, **1999**, *55*, 4353; Sirakawa, E.; Yoshida, H.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.*, **1999**, *121*, 4290 and references cited therein.

36. *Methods in Carbohydrate Chemistry*, Vol. II, 211, Academic Press Inc., New York, 1963.
37. McAuliffe, J. C.; Hindsgaul, O. *J. Org. Chem*. **1997**, *62*, 1234.
38. Bollenback, G. N. in *Methods in Carbohydrate Chem*., Vol II, *84*, 326, Academic Press Inc., New York, 1963.
39. Dennison, J. C.; McGilvary, D. I. *J. Chem.Soc.*, **1951**, 1616.
40. Szarek, W.; Zamojski, A.; Gibson, A. R.; Vyas, D, M.; Jones, J. K. N. *Can. J. Chem.*, **1976**, *54*, 3783.
41. Krishnamurthy, S.; Brown, H. C. *J. Org. Chem*., **1982**, *47*, 276; Florent, J.-C.; Monneret, C. in *Glycoscience-Chemistry and chemical biology*, Vol. II, p. 231, Springer-Verlag, **2001**.
42. Garegg, P. J.; Samuelsson, B. *J. Chem. Soc. Perk.Trans.1*, **1980**, 2866.
43. Krishnamurthy, S.; Brown, H. C.*Tetrahedron,* **1979**, *35*, 567.
44. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.*, **1972**, *94*, 6190.
45. Omura, K.; Swern, D. *Tetrahedron*, **1978**, *34*, 1651; Tidwell, T. T. *Org. React.*, **1990**, *39*; For modifications of Swern oxidation, see: Luca, L. D.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem*., **2001**, *66*, 7907 and references cited therein.
46. Harfenist, M.; A. Bavley, A.; Lazier, W. A. *J. Org. Chem*., **1954**, *19*, 1608; For the preparation of MnO_2, see: Fatiadi, A.J. *Synthesis*, **1976**, 65 and 133.
47. Nicolaou, K. C. *et al, J. Am. Chem. Soc.*, **1995**, *117*, 634.
48. Weiss, R. G.; Snyder, E. I. *J. Org. Chem.*, **1971**, *36*, 403; *Synth. Commun.,* **1994**, *24*, 1117.
49. Mori, K. *Tetrahedron*, **1974**, *30*, 3807; Mori, K., Tominaga, M.; Matsui, M. *Tetrahedron*, **1975**, *31*, 1846; Axelrod, E.; Milne, G. M.; Tamelen, E. E. V. *J. Am. Chem. Soc.*, **1970**, 2139; Schoning, K.-U.; Wittenberg, R.; Kirschning, A. *Synlett*, **1999**, 1624.
50. Michaelis, A.; Kaehne, R. *Ber.* **1898**, *31*, 1048; Arbuzov, A. E. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687; Kinoshita, M.; Takami, H.; Taniguchi, M.; Tamai, T. *Bull. Chem. Soc. Jpn.,* **1987**, *60*, 2156.
51. Benowitz, A. B.; Fidanze, S.; Small, P. L. C.; Kishi, Y. *J. Am. Chem. Soc.*, **2001**, *123*, 5128; Fidanze, S.; Song, F.; Benowitz, A.; Kishi, Y. *Org. Lett.*, **2002**, *4*, 647.

Introduction

Lignans are dimers of phenylpropanoid (C_6-C_3) units linked by the central carbons of their side chains C_8-$C_{8'}$ (**1**). Naturally occurring dimers that exhibit linkages other than this C_8-$C_{8'}$ type linkage are known as neolignans and are more limited in number and phylogenetic distribution.[1-4] Lignans are fairly widespread throughout the plant kingdom and



Dimeric phenylpropenoid structure showing the 8-8' linkage

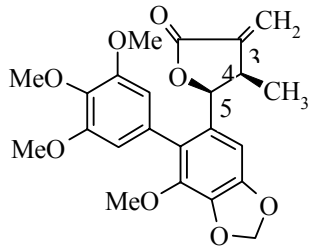
Fig. 1

have been documented in species belonging to up to seventy plant families.[5]They have been identified in pterydophytes, gymnosperms and angiosperms. Their functions and ubiquitous distribution evidences their role in plant evolution, as the structure of lignans increases in complexity with the evolution of gymnosperms and angiosperms. They have been considered one of the earliest forms of defense to evolve in vascular plants. Lignans occur in all parts of plants such as heartwood, roots, leaves, flowers, fruit and even seeds as well as secreted products. They are secondary plant metabolites biosynthetically derived form the shikimate pathway. They play an important part in the defense mechanism of many plant species against pathogens and predators. Another significant role of lignans in certain species is in heartwood formation, since they affect color, durability and texture of the resulting wood. Various roles in chemical defense such as fungicidal, bactericidal and insecticidal have been demonstrated for these secondary metabolites.

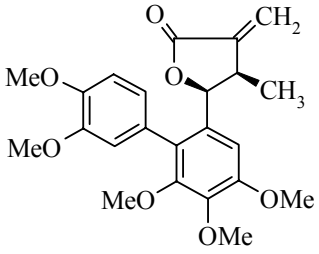
Biological activity of lignans have been studied in detail[3-4] and a vast variety of lignans possessing antitumor, anti-HIV, antiviral, ability to influence nucleic acid metabolism, inhibition of enzyme, cathartic, allergenicity, piscicidal, toxicity to mammals, antimocrobial, fungistatic and germination inhibitory activity have been discovered. [6-7] Lignans those possess antitumor activity is having these common features: i) a five membered lactone ring; ii) a 3,4,5-trimethoxyphenyl group; iii) a methylenedioxy group and iv) two substituted phenyl groups separated by a four-carbon chain. Relatively few lignans have been recorded as allelopathic agents.

Eupomatilones

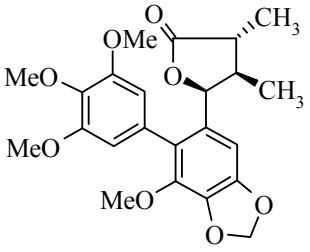
The Australian shrub *Eupomatia Bennettii* F. Muell is a source[8] of rich variety of lignans like eupomatenoids, eupodienones, eupobennettin, bennettinone and eupomatilones. The Eupomatilones are a family of seven degraded lignans. Their relative stereochemistry has been assigned to be as in fig.2 (**1-7**) based on NOE studies. The eupomatilones are unusual among the lignan family in that the C_α-phenyl linkage in one of the phenylpropanoid unit has been cleaved. All members of the family possess C_4-C_5 cis stereochemistry in the



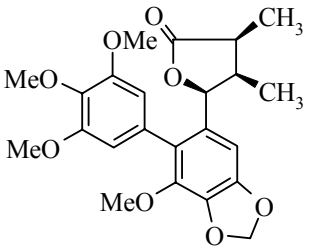
Eupomatilone-1 (**1**)



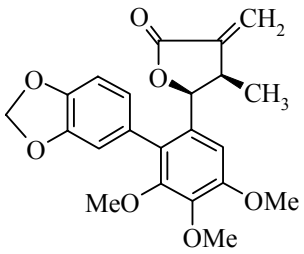
Eupomatilone-2 (**2**)



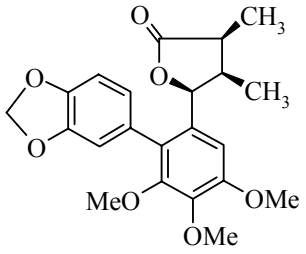
Eupomatilone-3 (**3**)



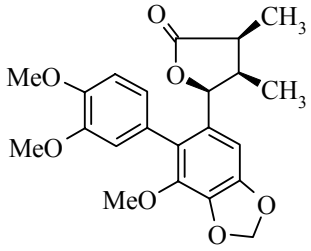
Eupomatilone-4 (**4**)



Eupomatilone-5 (**5**, 1:1 mixture of atropisomers)



Eupomatilone-6 (**6**, 1:1 mixture of atropisomers)

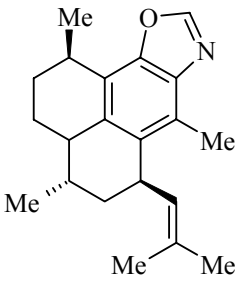


Eupomatilone-7 (**7**, 1:1 mixture of atropisomers)

Fig. 2

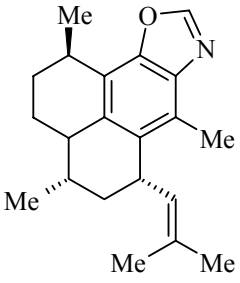
butyrolactone ring. They also possess a biaryl system with a γ-lactone ring attached to one of the aryl rings. Eupomatilones 4, 6 and 7 are having the methyl groups on the butyrolactone ring *cis* to each other. Eupomatilones 5, 6 and 7 exhibited atropisomerism.

Synthesis has played a major role in natural product chemistry. Until the evolution of spectroscopic methods, independent synthesis of a compound was thought to give the ultimate proof for the proposed structure. The proponents of X-ray crystallography and spectroscopy have often claimed that with the advent of these powerful techniques, the need for synthesis abolished. Even a quick look at the recent literature shows, however, that no matter how sophisticate are the instrumental methods used, there is still the ambiguity of experimental error and even today structures elucidated through instrumental means are revised as a result

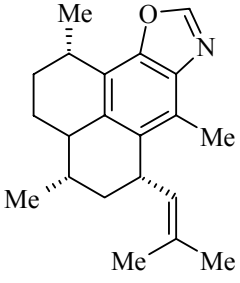


8

Proposed structure



9

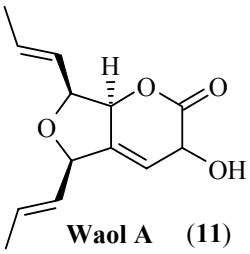


10

probable structure

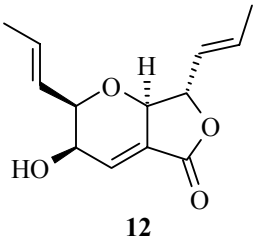
of synthesis. This is increasingly true as the level of complexity of compounds increases. For eg., spectral data of pseudopteroxazole (proposed structure **8**) did not match either its synthetic version or its analogue (**9**). Corey et al suggested that the natural product might be having structure **10**.[9]

Similarly, Snider *et al* has found that the assigned structure of Waol A **11** to be revised as **12**.[10]



Waol A (11)

Proposed structure



12

revised structure

The biaryl is the central building block in a vary large number of natural products of differing structures, biological activity and biosynthetic origin, including for example polyketides, terpenes, lignans, coumarins, flavonoids, tannins, peptides and alkaloids.[11-12] Because of their interesting properties - not only as pharmacologically active natural products,

but also as chiral reagents[13] and crown ethers[14] as chiral host molecules for inclusion compounds,[15] as the basis of chiral phases for chromatography,[16] as inflexible spacers between two halves of a molecule[17-18] or also as the basis of chiral liquid crystals[19] - natural and unnatural biaryls constitute attractive synthetic goals.

In many of the natural or synthetic biaryls bulky ortho substituents next to the biaryl axis lead to hindrance of free rotation around the biaryl axis and thus existence of stable atropisomerism. Some times only three ortho substituents are present while in some extreme cases only two ortho substituents may suffice. The stereochemistry around the biaryl axis is as important as any other chiral center in showing the biological acitivity and pharmacological properties. In nature, most of the sterically hindered biaryls are available in both atropisomeric states although in differing quantities.

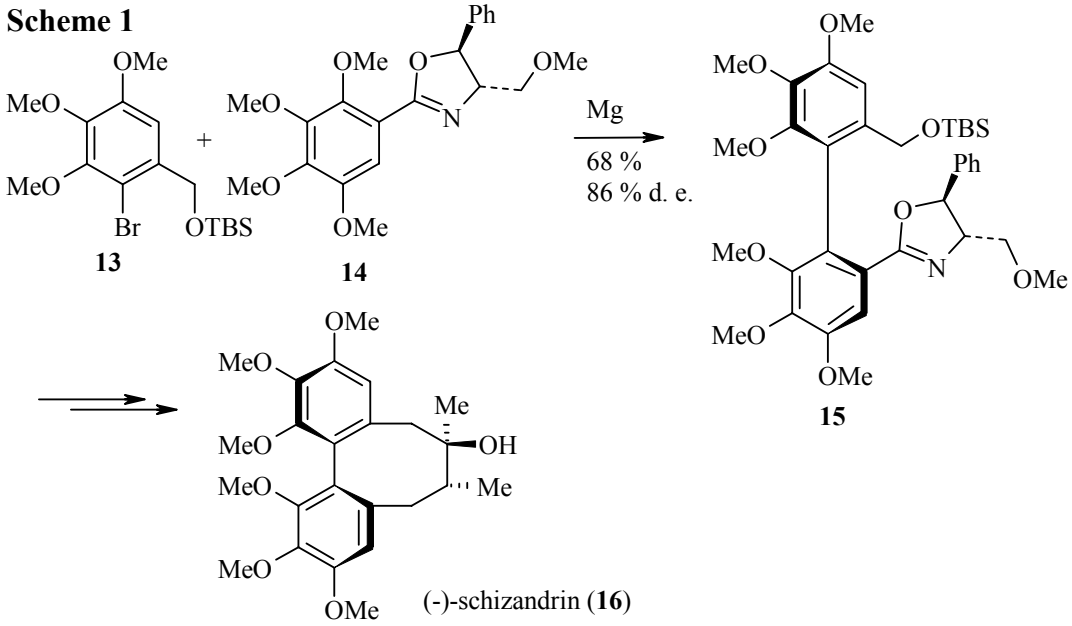
Several efficient methods are available for the synthesis of atropisomerically pure biaryl compounds. The commonly used methods will be discussed briefly here.

Atrop-selective biaryl synthesis

Meyer's oxazoline approach

Meyers elaborated a method based on an aromatic nucleophilic substitution using a

Scheme 1



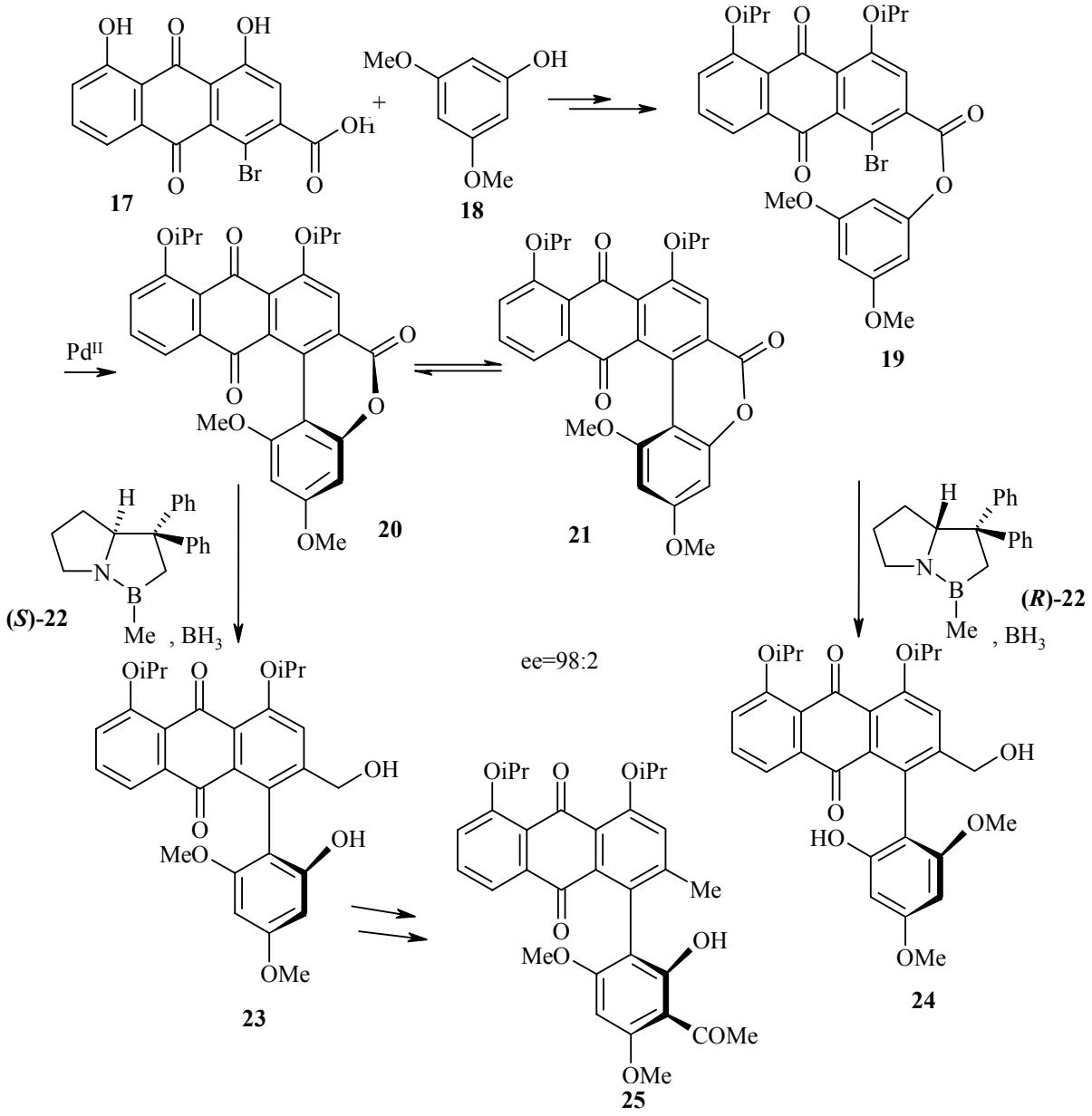
chiral oxazoline auxiliary.[20] The oxazoline moiety readily promotes displacement of ortho-methoxy and fluoro group by strong nucleophiles, generally Grignard reagents. The method works well for biaryls bearing three ortho substituents. Lignan (-)-schizandrin (**16**) was

prepared by atrop-diastereoselective crossed biaryl coupling using grignard generated from **13** and chiral oxazoline **14**[21] (Scheme 1).

Bringmann's lactone approach

Bringmann prepared a wide range of natural biaryl compounds such as (+)-knipholone (**25**) *via* the "lactone method"[22] consisting of the atropselective ring cleavage of configurationally unstable lactone bridged biaryls. This method offers the advantage of controlling the axial chirality using catalytic chiral reagents. In their synthesis[23] of (+)-

Scheme 2

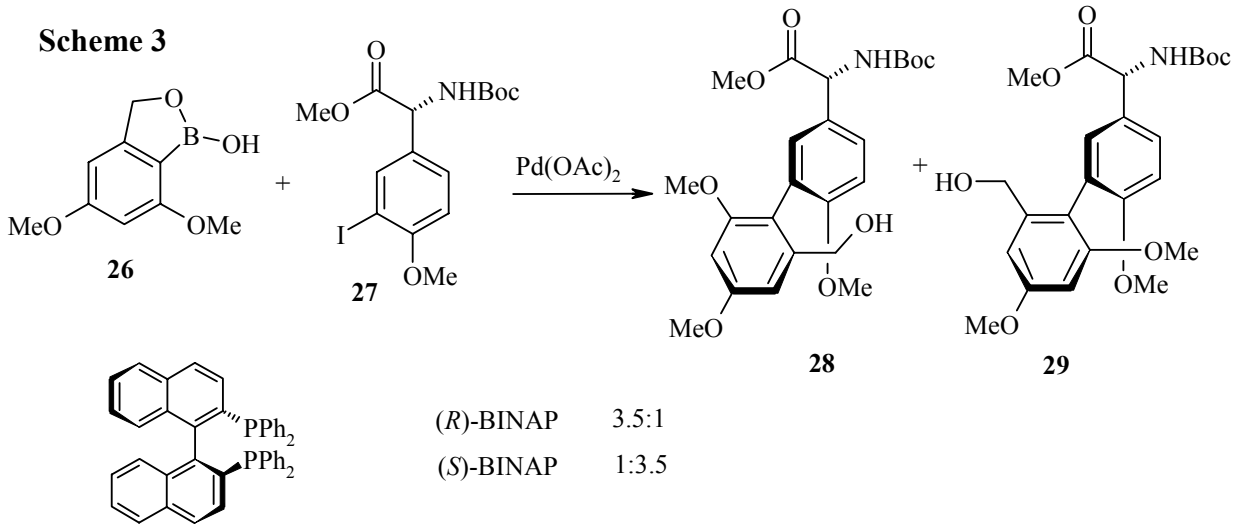


knipholone (Scheme 2), carboxylic acid **17** and 3,5-dimethoxyphenol **18** were coupled to form the ester bridge. Pd-catalyzed intramolecular coupling produced the key intermediate lactone **19**. The most significant function of the ester bridge is that it dramatically lowers the rotational isomerisation barrier at the axis so that in contrast to the corresponding open biaryls, six membered biaryl lactones of type **20** are still configurationally unstable and exists as racemic mixtures of rapidly interconverting atropo-enantiomerns **20** and **21**. Out of this racemic mixture, one form can be cleaved with high stereoselectivity by a number of chiral nucleophiles. By use of the other nucleophilic enantiomer, the other isomeric product can be obtained. Thus cleavage of **20** with (*S*)-**22** gave **23** while (*R*)-**22** gave the enantiomer **24**.

Using chiral catalysts

The use of aryl reactants incorporating a chiral auxiliary as a control element for inducing atropisomer selectivity can however, be limited by their commercial availability as well as by limitation to a particular biaryl substitution pattern. Stereoselective aryl couplings have also been reported using aromatic systems that themselves do not incorporate chiral control elements through the use of chiral catalysts or reagents.

Scheme 3

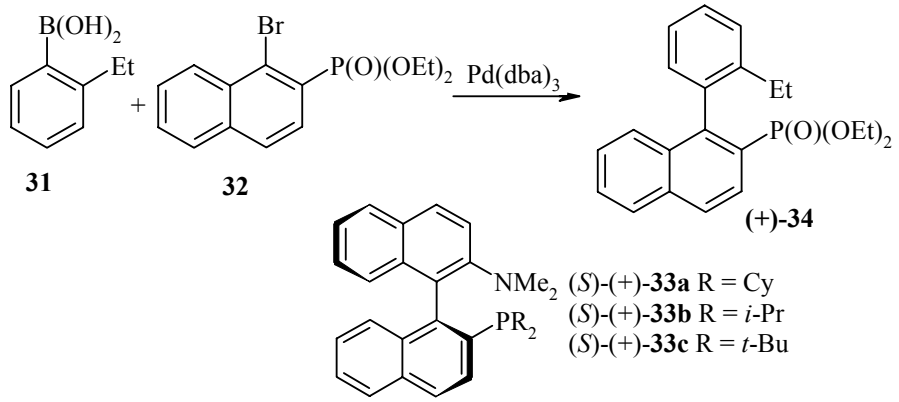


(*R*)-(+)-BINAP (**30**)

Atropo-enantioselective Suzuki coupling reactions are now carried out, mainly using binaphthyl ligands and ferrocenyl ligands. Nicolaou *et al* reported an atropo-diastereoselective Suzuki cross coupling reaction using chiral ligands for the synthesis of biaryl **28** (Scheme 3) in their total synthesis of vancomycin.[24] A variety of chiral and achiral ligands were screened and they found that while achiral ligands lead to no selectivity, among

chiral ligands, only BINAP ligands gave good selectivity. Atropselectivity was reversed upon switching the chirality of the ligand. When the reaction was conducted in toluene (at 90 ^{o}C), atropisomerisation was observed. However in THF (at 60 ^{o}C), no isomerisation was detected.

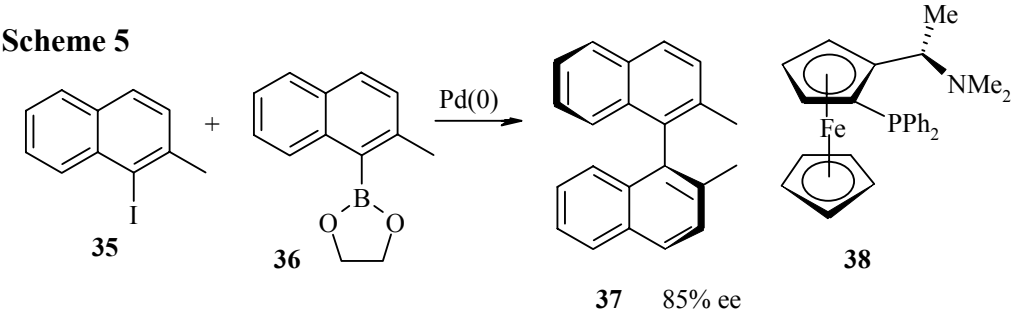
Scheme 4



Ligands **33a-c** was used by Buchwald[25] to obtain ee values upto 92 % in their synthesis of the biaryl (+)-**34** (Scheme 4).

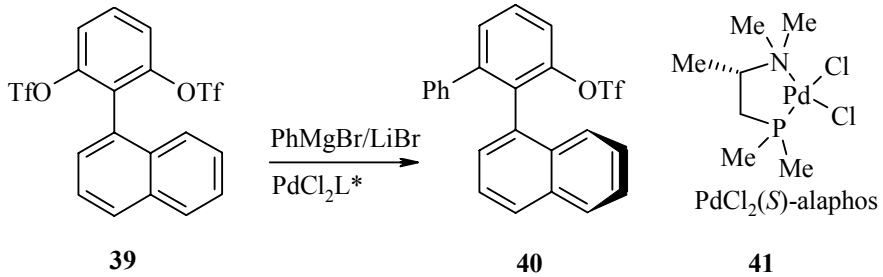
Cammidge reported[26] an atropselective Suzuki coupling with the ferrocenyl ligand **38** with ee upto 85 % (Scheme 5).

Scheme 5



Asymmetric cross coupling of achiral biaryl ditriflates like **39** with aryl grignard reagents in presence of LiBr and palladium complex $PdCl_2$[(S)-alaphos] (**41**) gave axially chiral monoarylated products **40** with high ee (Scheme 6). [27]

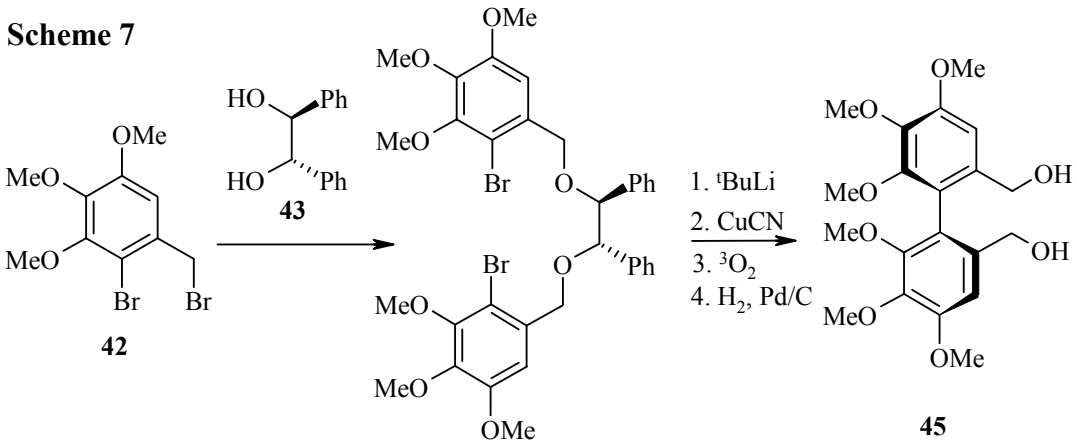
Scheme 6



Other methods

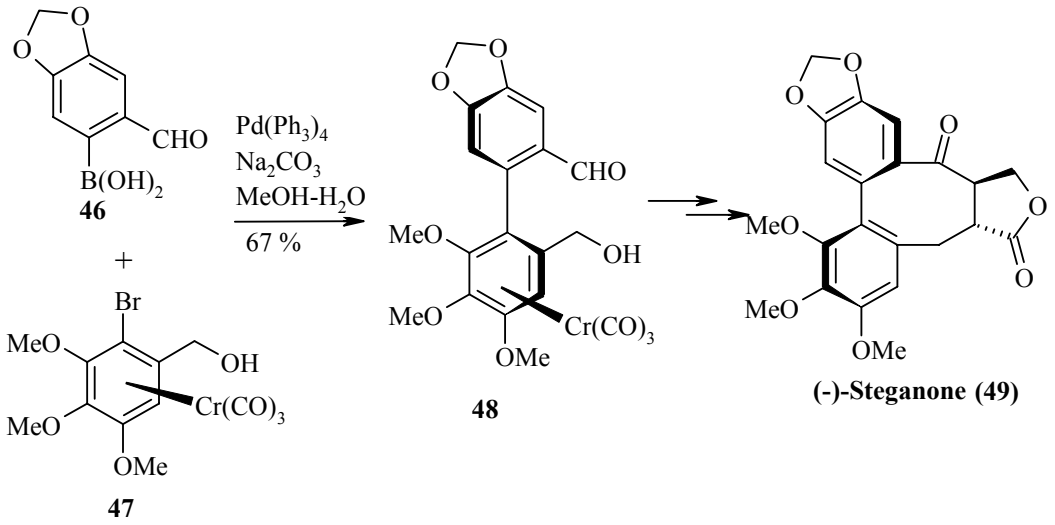
Cyanocuprate mediated intramolecular biaryl coupling has been reported by Lipshutsz *et* al (Scheme 7).[28] The key to controlling the directionality of these couplings lies in the proper choice of the tether, which must: i) join the individual aryl subunits efficiently; ii) allow for cuprate generation and exert 100% stereocontrol in the reductive elimination step;

Scheme 7



and iii) undergo facile and high yield removal. The tethered product **44** was prepared from **42** using tether *S*,*S*-stilbene diol (**43**). Converting **44** to the diarylcuprate, oxidation with molecular oxygen followed by hydrogenation afforded optically pure **45**.

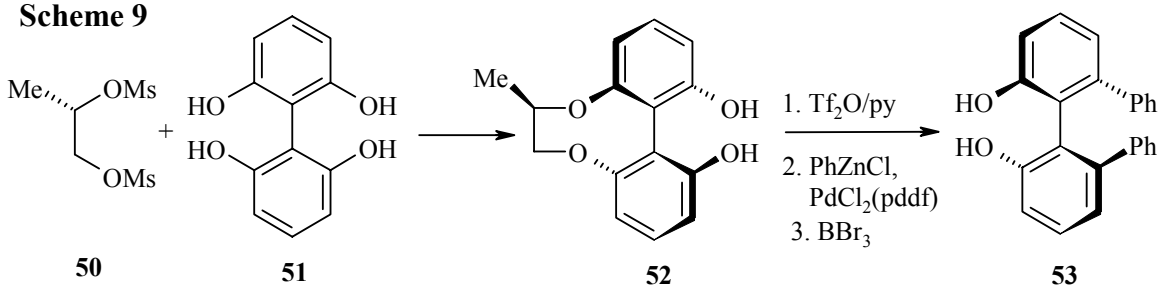
Scheme 8



Natural product (-)-steganone (**49**) has been synthesized using an atropselective Suzuki coupling between the achiral boronic acid **46** and the chiral arene chromium complex **47**, to yield the desired atropisomer **48** (Scheme 8).[29]

6,6'-disubstituted biphenyldiols like **53** has been synthesized (Scheme 9) by asymmetrically desymetrizing the achiral biaryl **51** using (*S*)-*bis*-mesylate **50** giving biaryl **52** as a single enantiomer.[30] The free hydroxyls are then converted into trifaltes and replaced by

Scheme 9

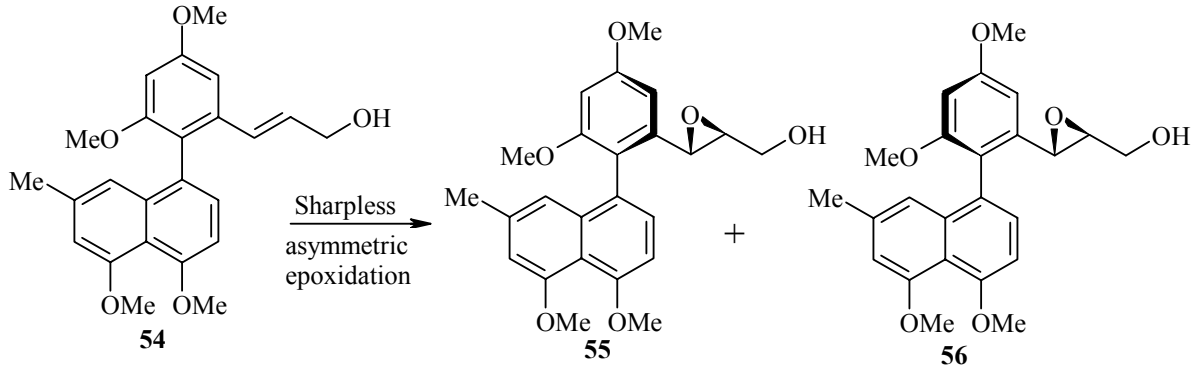


50 **51** **52** **53**

alkyl or aryl group using Negishi reaction with organozinc. Lewis acid promoted cleavage of the bis-ether bond then gives 6,6'-disubstituted biphenyl diols enantioselectively.

Rama Rao *et al* achieved the resolution of biaryls via Sharpless asymmetric

Scheme10



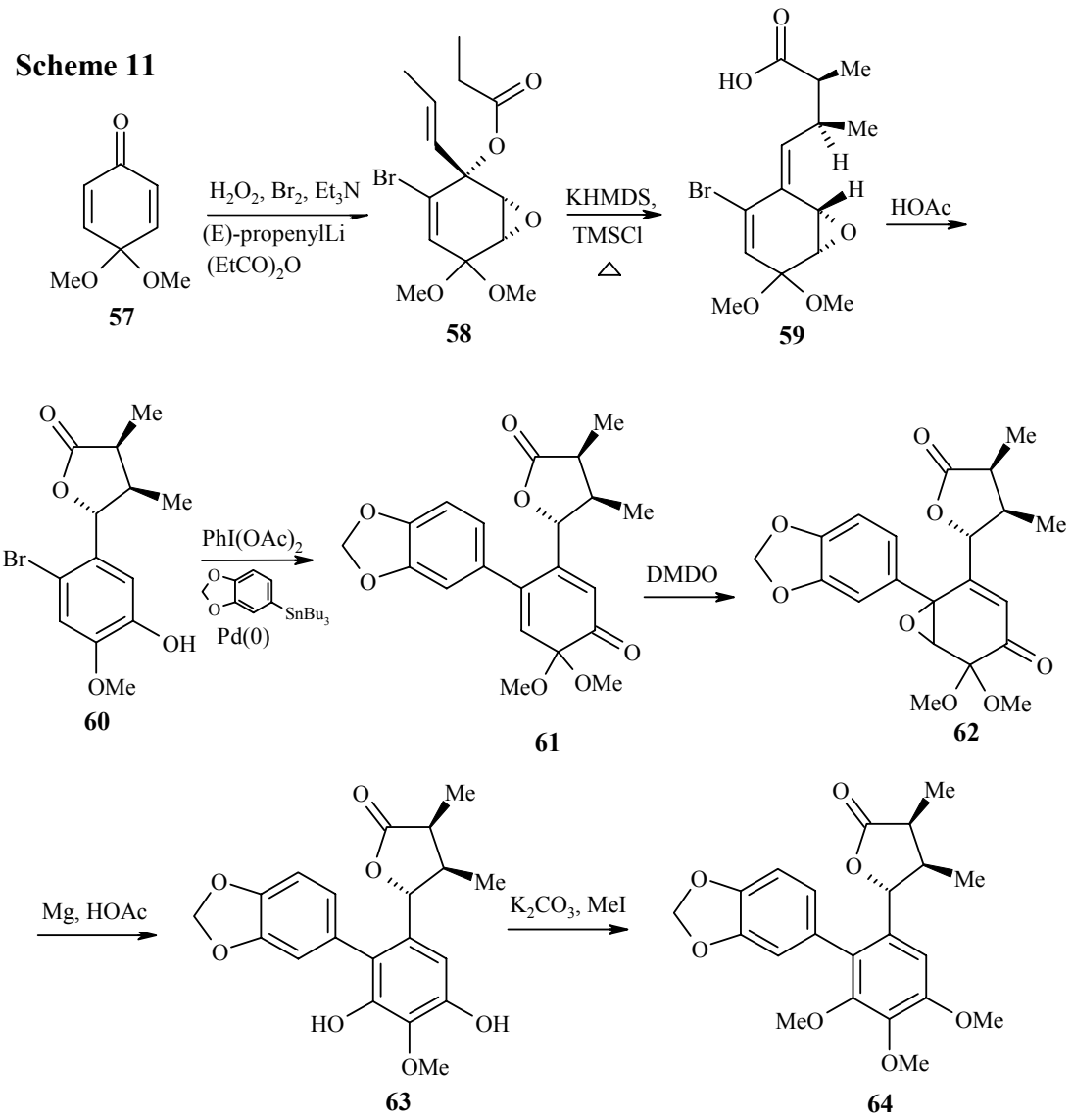
54 **55** **56**

epoxidation (Scheme 10).[31] Racemic biaryl allylic alcohols when subjected to Sharpless asymmetric epoxidation gave rise to mixture of atropisomers which were easily separated by chromatography.

Past Work McIntosh *et al* reported the synthesis of 5-*epi*-eupomatilone-6 (**64**) *via* Ireland-Claisen rearrangement as the key step (Scheme 11).[32] The synthesis involved conversion of the *p*-quinone monoketal **57** to the bromo epoxide followed by the addition of (*E*)-propenyl lithium and *insitu* esterficiation to afford **58** as a single stereoisomer. **58** was converted to **59** by Ireland-Claisen rearrangement. S_N2' lactonization and *insitu* aromatization by heating the acid **59** in HOAc afforded **60**. Oxidation of phenol **60** using $PhI(OAc)_2$ and Stille coupling with piperonyl tributylstannane gave **61**. Regioselective epoxidation of **61** using DMDO and reductive ring opening of the epoxide produced biaryl **62** which existed as non-separable 1:1

mixture of atropisomers. Finally, 5-*epi*-eupomatilone-6 (**64**) was obtained by methylation of

Scheme 11

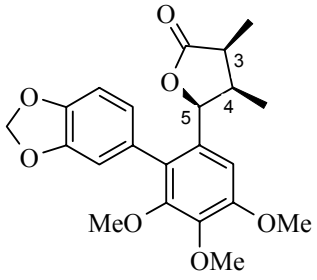


the phenolic hydroxyl group.

Present Work

Lignans are a widely distributed class of dimeric phenyl propanoid derivatives, many of which have strong antimicrobial, antiviral or antifeedant activity and thus play important roles in plant defense. They possess a variety of pharmacological actions in man, though the most interesting of these are subtle and not easily studied. At the ecological level, there is evidence that lignans play a role in plant-fungus, plant-plant and plant-insect interactions. At the molecular level, on the other hand, some are known to bind to the tubulin of microtubules to interrupt nucleotide transport and DNA synthesis and to be specific inhibitors of certain enzymes.

The Australian shrubs *Eupomatia bennettii* F.Muell is the source of a variety of lignans such as eupodienones, eupobennettin, bennettinone and seven closely related substances termed eupomatilones. Extensive spectroscopic studies have established that Eupomatilones are degraded lignans, each having a biphenyl system with a γ-lactone ring attached to one of the aryl rings and they exhibit atropisomerism. Eupomatilone-6 (**27**) is particular among the seven eupomatilones in that all the three substituents on the lactone moiety are *syn* to each other. The relative stereochemistry of eupomatilone-6 is depicted in fig. 1. It exists as a 1:1 mixture of atropisomers.



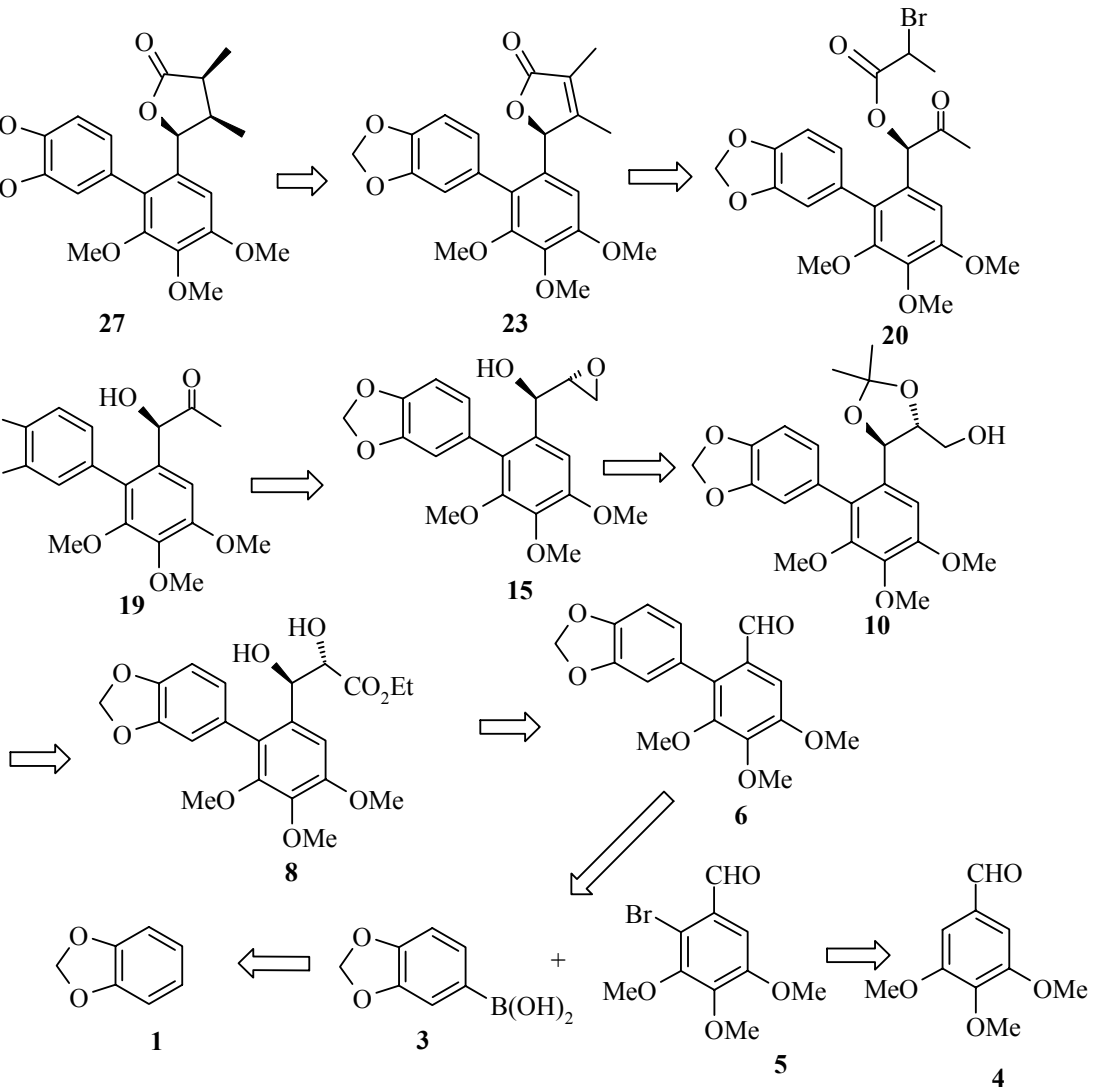
6

Synthesis has played a major role in natural product chemistry. Until the evolution of spectroscopic methods, independent synthesis of a compound was thought to give the ultimate proof for the proposed structure. The proponents of X-ray crystallography and spectroscopy have often claimed that with the advent of these powerful techniques, the need for synthesis abolished. Even a quick look at the recent literature shows, however, that no matter how

sophisticate are the instrumental methods used, there is still the ambiguity of experimental error and even today structures elucidated through instrumental means are revised as a result of synthesis. This is increasingly true as the level of complexity of compounds increases. The field of synthetic method development is highly advanced at present. The single most important effort in synthetic method development at present is devoted to asymmetric synthesis.

Separation of biaryl atropisomers *via* Sharpless asymmetric epoxidation had been reported from our group. This and the structural diversity compared to other eupomatilones prompted us to attempt the synthesis of eupomatilone-6. We planned to examine the use of

Scheme 12

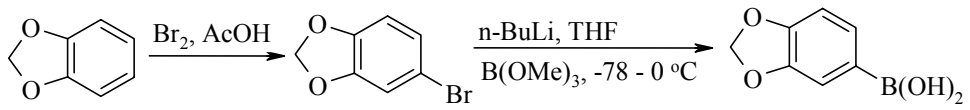


Sharpless asymmetric dihydroxylation for the separation of atropisomers and designed a route involving Sharpless AD towards the synthesis of **27**. Our synthetic plan is based on the retrosynthetic analysis as depicted in Scheme 12.

We envisaged that hydrogenation of the α,β-unsaturated lactone **23** would furnish **27**. A retrosynthetic scission of C-3 - C-4 double bond lead to the α-bromo ester **20**. An intramolecular Reformatsky reaction and elimination would lead to **23**. The ester **20** could be easily made from the α-hydroxyketone **19**, which in turn can be made from the epoxide **15**. A careful observation revealed that the epoxide **15** would be readily obtained from the primary alcohol **10** which could be made from the biaryl aldehyde **6** through two-carbon Wittig homologation and Sharpless asymmetric dihydroxylation **8**, at which stage the atropisomers could be separable. We chose Suzuki coupling reaction to make the biaryl aldehyde **6** between the readily accessible boronic acid **3** and bromo aldehyde **5**.

The retrosynthetic analysis identified the starting materials as 1,3-methylene dioxybenzene and 3,4,5-trimethoxybenzaldehyde. Bromination of **65** was carried out as per the reported procedure (Scheme 13) using bromine in acetic acid. Boronic acid **67** was prepared according to the literature procedure by generating the lithiated aryl species with *n*-BuLi and quenching with trimethylborate.

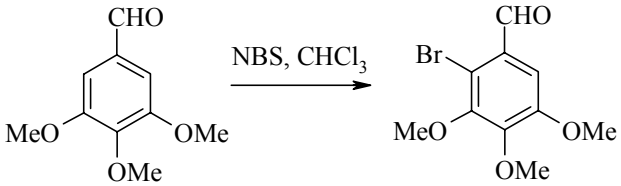
Scheme 13



65 **66** **67**

2-Bromo-3,4,5-trimethoxybenzaldehyde (**69**) was prepared as per the literature procedure (Scheme 14).

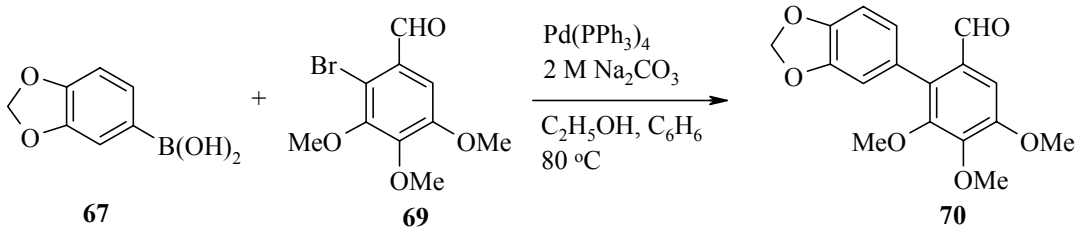
Scheme 14



68 **69**

Suzuki coupling reaction between **67** and **69** in presence of Pd(0) proceeded smoothly to afford the biaryl aldehyde **70** in 79 % yield (Scheme 15). In the ^{1}H NMR spectrum of **70**, the methylene protons of dioxolane ring resonated as a singlet at δ 6.00 while the aldehyde proton

Scheme 15

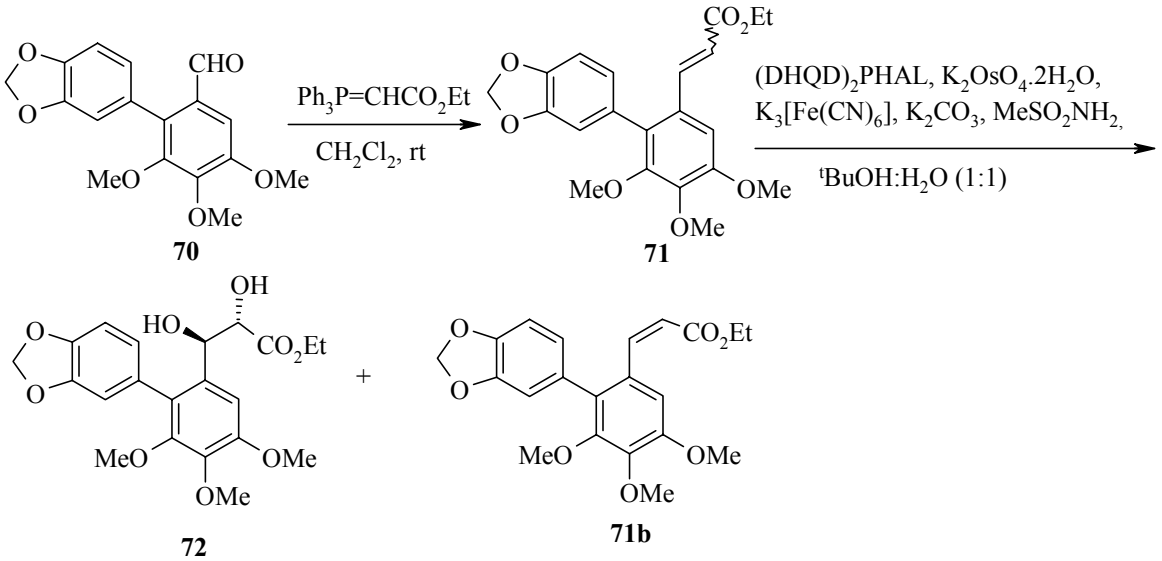


67 **69** **70**

appeared at δ 9.50. All the other resonances were in agreement with the assigned structure.

Having **70** in hand, the next task was two carbon Wittig homologation. Thus, treatment of **70** with ethoxycarbonylmethylene triphenylphosphorane in CH_2Cl_2 afforded **71** as an inseparable mixture of *cis* and *trans* isomers in the ratio 15:85 (Scheme 16). Varying the reaction conditions did not alter the ratio. In the ^{1}H NMR spectrum of **71**, the olefinic protons of the *trans* isomer appeared at δ 6.26 and δ 7.48 as doublets (J = 16.2 Hz) where as those of *cis* isomer appeared at δ 5.80 and δ 6.61 as doublets (J = 12.2 Hz). Since the efforts to separate the mixture by column chromatography

Scheme 16



70 **71** **72** **71b**

failed, we decided to proceed further with the mixture. Sharpless asymmetric dihydroxylation was carried out using ligand $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$ and $K_2OsO_4.2H_2O$ in $^tBuOH:H_2O$ (1:1) at 0 ^oC for 18 h. To our satisfaction, the *cis* isomer (**71b**) remained unreacted and was isolated by column chromatography as a solid. This can be explained by the enhanced reactivity of the *trans* isomer towards asymmetric dihydroxylation compared to the *cis*. [The ee was checked at a later stage]. In the ^1H NMR spectrum of the diol **72**, the benzylic proton appeared at δ 4.86 as a doublet (J = 7.3 Hz). The presence of atropisomers was confirmed by the presence of another doublet at δ 4.84 (J = 7.3 Hz). However, silica gel column chromatographic separation of the atropisomers was not successful. Attempted separation of the atropisomers at this stage using HPLC (chiral HPLC using chiralcel OD, chiralpak, cyclobond, chrompack ultron and chiral amaylose columns) also met with failures, chromatograms indicating the presence of single compound. This also proves the excellent ee obtained in the dihydroxylation step.

A short account of Sharpless asymmetric dihydroxylation (AD)

The stereospecific cis-dihydroxylation of olefins achieved by OsO_4 is one of the most valued transformations for introducing functionality into organic molecules. Initially the AD using derivatives of cinchona alkaloids was performed under stoichiometric conditions. Lateron, with the advent of: i) use of two phase conditions with $K_3Fe(CN)_6$ as reoxidant; ii) $MeSO_2NH_2$ for rate acceleration and iii) second generation ligands (phthalazine and diphenylpyrimidine, with two independent cinchona alkaloid units) by Sharpless et al., catalytic AD came into focus. The enantioselectivity in the AD reaction is due to the enzyme-like binding pocket present in the dimeric cinchona alkaloid ligands. The Cinchona alkaloid backbone is ideally suited for providing high ligand acceleration and enantioselectivity. The reaction rates are influenced by the nature of O-9 substituent of the Cinchona alkaloid. The rate enhancement is caused by a stabilization of the transition state due to aromatic stacking interactions. Although this kind of stabilizations is operative even in monomeric first generation ligand, it is most effective in the dimeric second-generation ligands due to the presence of a binding pocket. Thus the almost perfect match between the phthalazine ligands and aromatic olefins with respect to rates and enantioselectivities can be readily explained by an especially good transition state stabilization resulting from offset-parallel interactions between the aromatic

substituent of the olefin and the phthalazine floor of the ligand, as well as favorable edge-to-face interactions with the bystander methoxyquinoline ring.

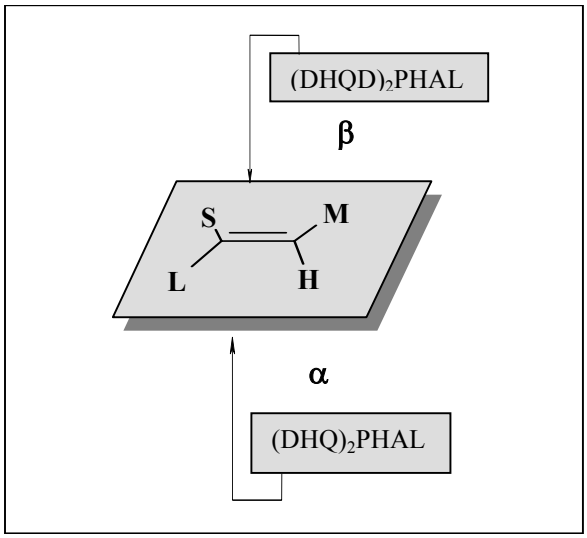
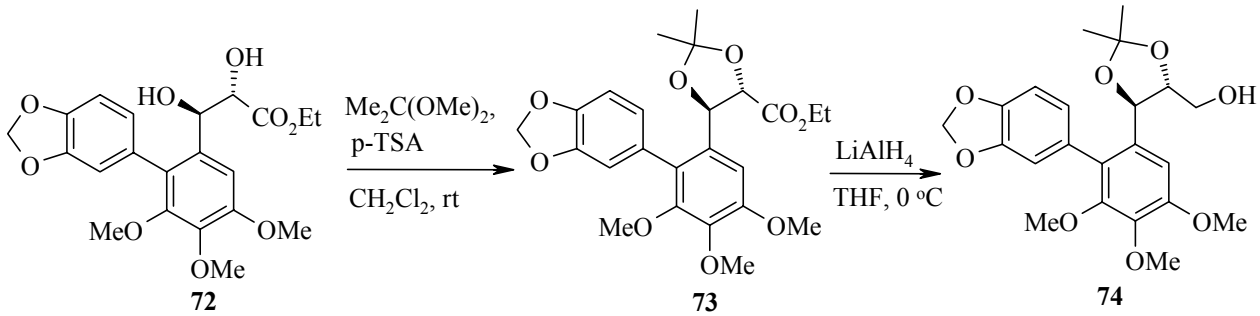


Fig. 2 ***Mnemonic diagram*** *(S = small group, L = large group, M = medium group, H = proton).*

The above observations have led to a revised mnemonic device for predicting the enantiofacial selectivity in the reaction. An olefin positioned accordingly will be attacked either from the top face (β face) in the case of dihdroquinidine derivatives or from the bottom face (α face) in the case of dihydroquinine derived ligands.

Having met with failure in separating the atropisomers, we planned to proceed with the mixture. Thus, reaction of the diol **72** with 1,2-dimethoxypropane in CH_2Cl_2 in presence of catalytic *p*-TSA gave the ketal **73** (Scheme 17). The structure of **73** was confirmed by ^1H

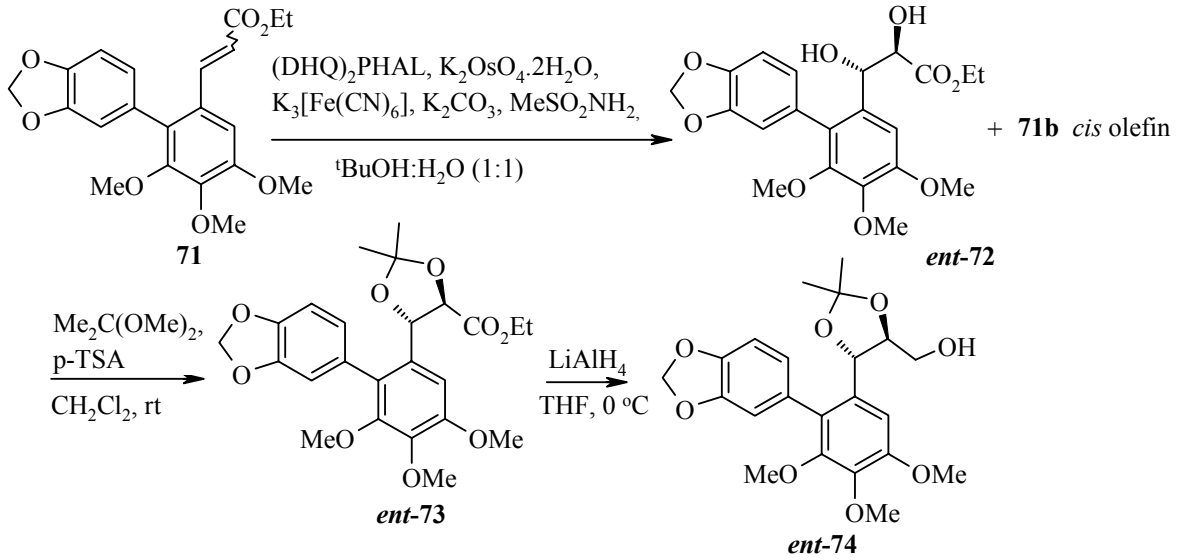
Scheme 17



and ^{13}C NMR spectra. Reduction of the carboxylate ester group was achieved with $LiAlH_4$ in THF at 0 ^oC, to afford the primary alcohol **74**. Disappearance of the ester peak in the ^1H and ^{13}C NMR spectra confirmed the transformation. It has to be mentioned that column chromatographic and HPLC efforts to separate atropisomers at the above stages (compounds **73** and **74**) were not successful.

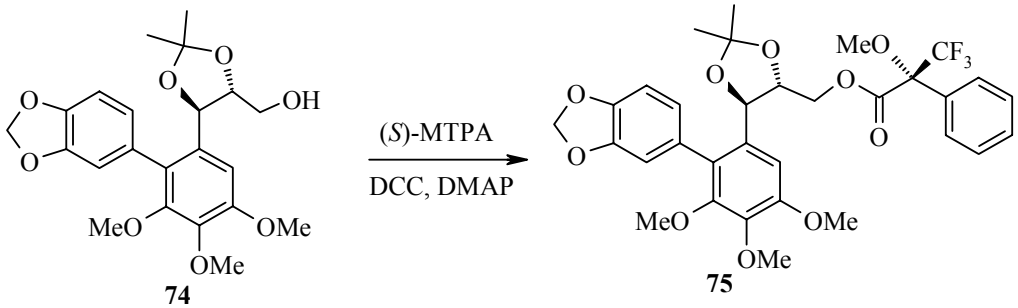
At this stage, we decided to examine the enantiomeric excess by preparing Mosher ester of **74**. Towards this, the enantiomer ***ent*-74** was also prepared following the same sequence of reactions, using $(DHQ)_2PHAL$ as ligand at the asymmetric dihydroxylation step (Scheme 18).

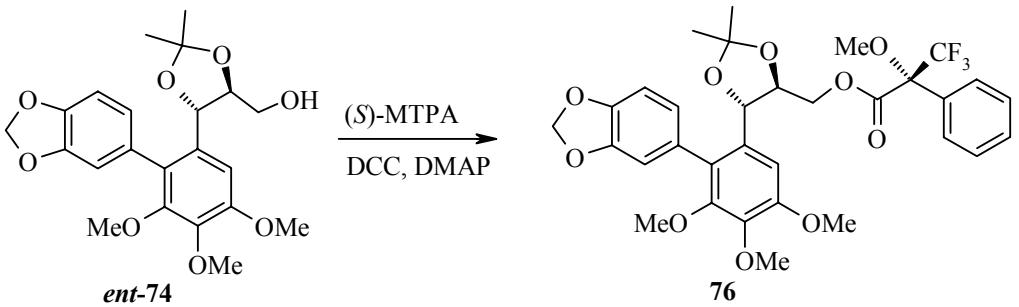
Scheme 18



Esterification of **74** and ***ent*-74** with (*S*)-(-) Mosher acid to the corresponding esters **75** and **76** respectively was accomplished in the conventional manner using DCC and DMAP in CH_2Cl_2 (Scheme 19). Chiral HPLC (Chiralcel OD) analysis of **75** and **76** indicated >99% ee for the preferred isomer **11**.

Scheme 19

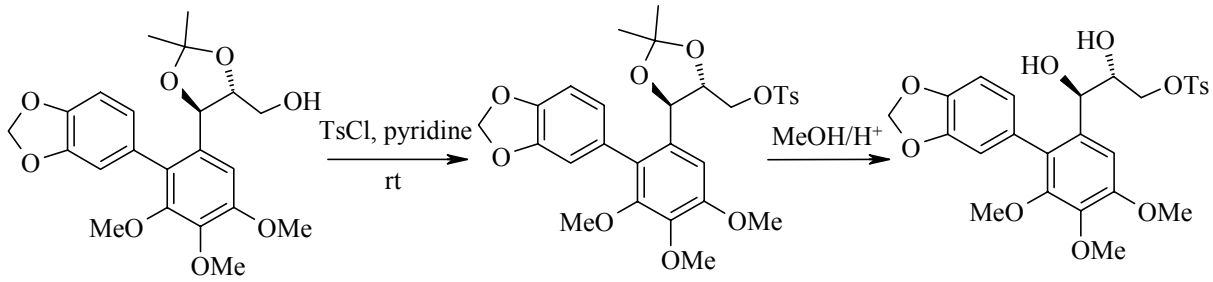




ent-**74** **76**

The primary alcohol **74** was activated as its *p*-toluenesulphonate ester **77** using TsCl in pyridine (Scheme 20). In the ^{1}H NMR spectra of **77**, the characteristic resonances for the aromatic ring protons of tosyl group were observed at δ 7.31 and 7.68 (doublets, J = 8.3 Hz).

Scheme 20

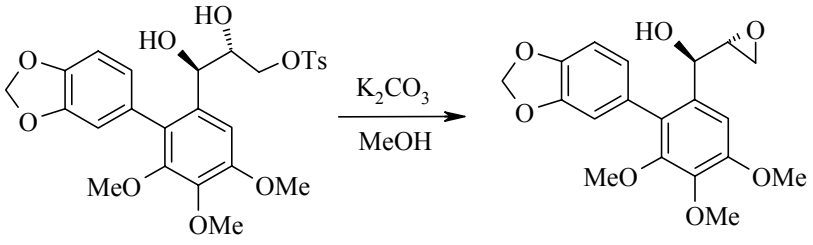


74 **77** **78**

Singlets at δ2.45 and 2.46 (both atropisomers) were attributed to the aromatic methyl group. All the other resonances were in conformity with the structure. Acid mediated hydrolysis of the ketal **77** with *p*-TSA in MeOH afforded the diol **78**.

Next stage in our synthetic plan was to produce the epoxide ring closure *via* intramolecular substitution of sulphonate ester with alkoxide ion. Thus, compound **78** was treated with K_2CO_3 in MeOH to provide the terminal epoxide **79** in 75 % yield (Scheme 21).

Scheme 21

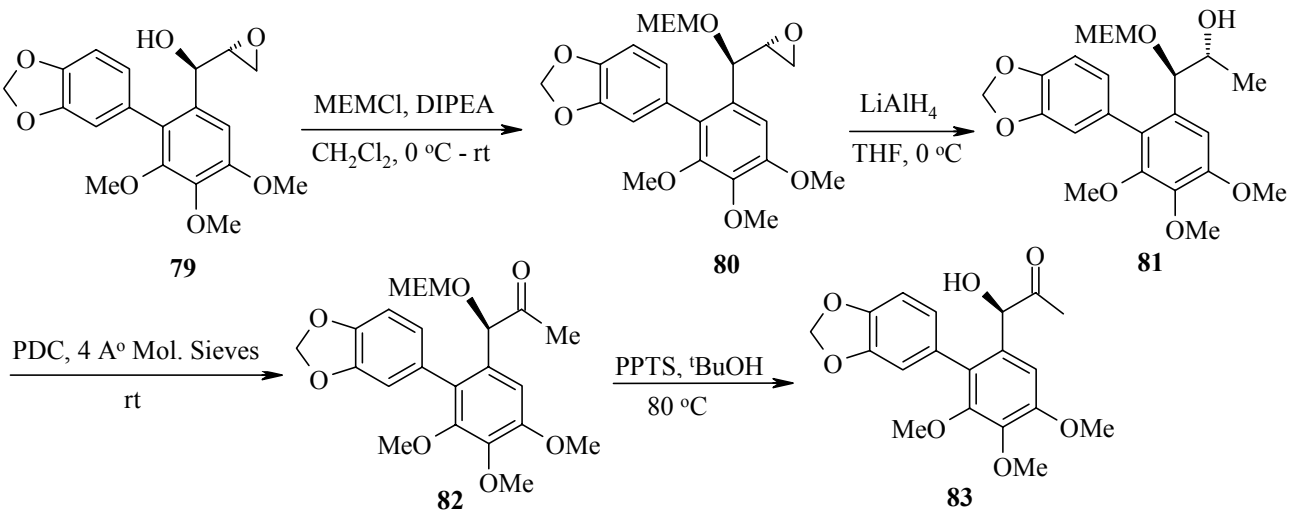


78 **79**

The ^{1}H, ^{13}C NMR spectra and elemental analysis confirmed the structure of **79**. For example, in the ^{1}H NMR spectrum, the epoxide protons resonated at δ 2.38, 2.70, 3.08 as multiplets. The benzylic proton was observed at δ 4.37 and 4.41 as doublets (of both atropisomers, J = 7.9 Hz).

The hydroxyl group of **79** was protected as its MEM ether (**80**) using MEMCl and DIPEA in CH_2Cl_2 (Scheme 22). The ^{1}H and ^{13}C NMR spectra and elemental analysis were in support of the structure **80**. The next critical reaction in our synthetic plan was opening of the

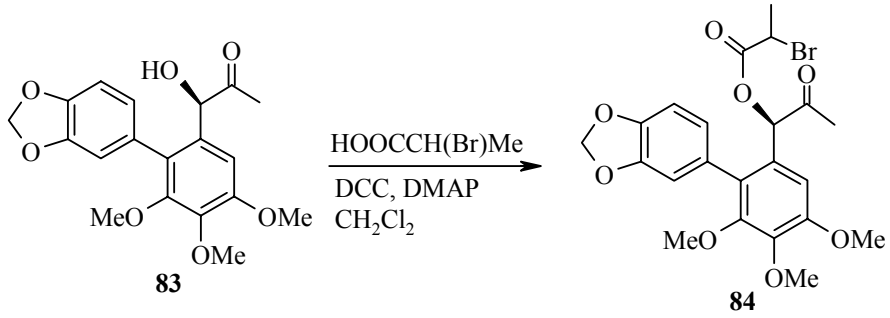
Scheme 22



epoxide to obtain the secondary alcohol **81**. Gratifyingly, treatment of **80** with $LiAlH_4$ at 0 ^{o}C in THF resulted in the exclusive formation **81** in 94 % yield. The ^{1}H NMR spectrum clearly showed disappearance of the signals due to epoxide functionality. A doublet at δ 0.84 (J = 6.3 Hz) accounted for the terminal methyl group. All the other resonances were in support for **81**. ^{13}C NMR spectrum and elemental analaysis further confirmed structure of **81**. Oxidation of **81** to the corresponding keto derivative **82** was accomplished with PDC in presence of 4A^{o} molecular sieves powder in CH_2Cl_2. A downfield shift of signal due to the methyl group as a singlet (δ 1.96, 1.97, both atropisomers) and the disappearance of the C-2 homobenzylic proton signal were in favor of the transformation. In the ^{13}C NMR spectrum, the cabonyl carbon of the keto group appeared at δ 204.7. Deprotection of the MEM ether was carried out with PPTS in ^{t}BuOH at 80 ^{o}C to afford the α–hydroxyketone **83**. The spectral and combustion data confirmed the transformation.

Esterification of **83** with 2-bromo-propionic acid in presence of DCC/DMAP afforded the required precursor **84** for Reformatsky reaction as a mixture of diastereomers (Scheme 23). The downfield shift of the C-3 benzylic proton to appear at δ 5.84 in the ^{1}H NMR spectrum of **84** confirmed the transformation.

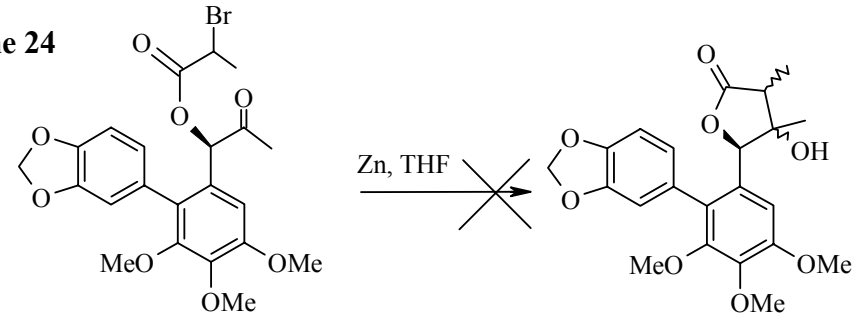
Scheme 23



83 **84**

Attempted Reformatsky reaction of **84** with activated Zn in THF proved to be a failure in our hands, leading to complex mixture of products (Scheme 24). Change in the reaction conditions (using Reike Zn, 0 ^{o}C, rt, and reflux) also produced the same results.

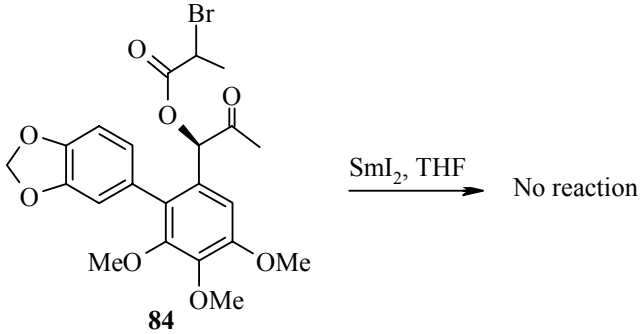
Scheme 24



84 **85**

Intramolecular Reformatsky reaction of **84** using SmI_2 was also not successful (Scheme 25) leaving the starting material **84** unchanged.

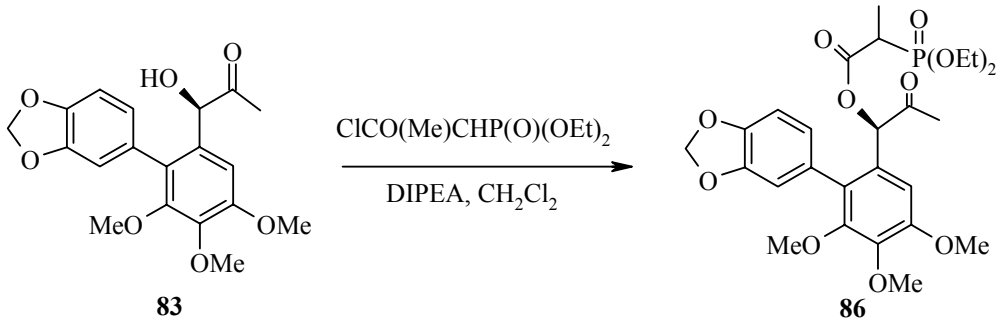
Scheme 25



84

Owing to the failure encountered in intramolecular Reformatsky reaction, we planned to adopt a different strategy. Considering intramolecular Horner-Wadsworth-Emmons

Scheme 26

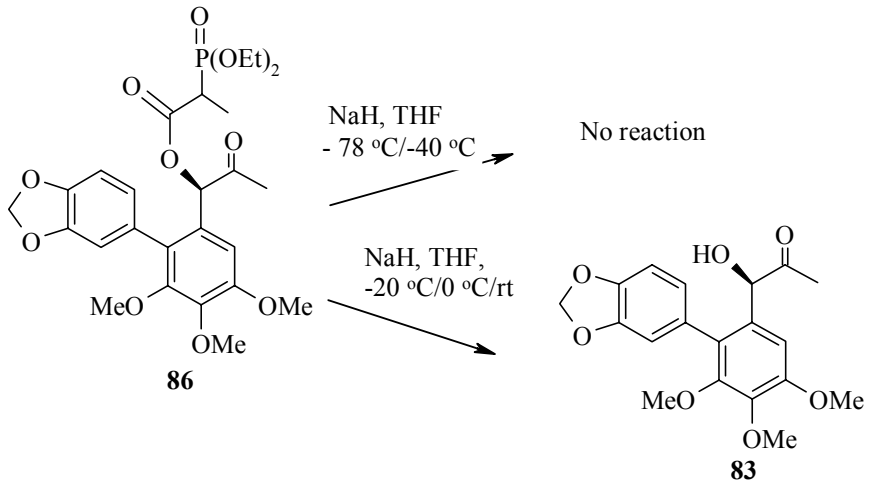


83 **86**

reaction for constructing the lactone, next, we attempted to synthesize phosphonate **86**. Towards this goal, conventional coupling of **83** with 2-(diethoxy-phosphoryl)propionic acid using DCC and DMAP in CH_2Cl_2 to obtain phosphonate **86** turned out as a slow reaction and gave poor yield. However, treatment of the α-hydroxyketone **83** with the corresponding acid chloride in presence of DIPEA in CH_2Cl_2 proceeded well to afford phosphonate **86** as a mixture of diastereomers (Scheme 26). To eliminate/minimize epimerization probability, the reaction was carried out at 0 ^oC using 1.1 eq. of DIPEA. The ^1H NMR spectrum of **86** showed the downfield shift of the benzylic proton, resonating at δ 5.84 while the other resonances were in accordance with the structure.

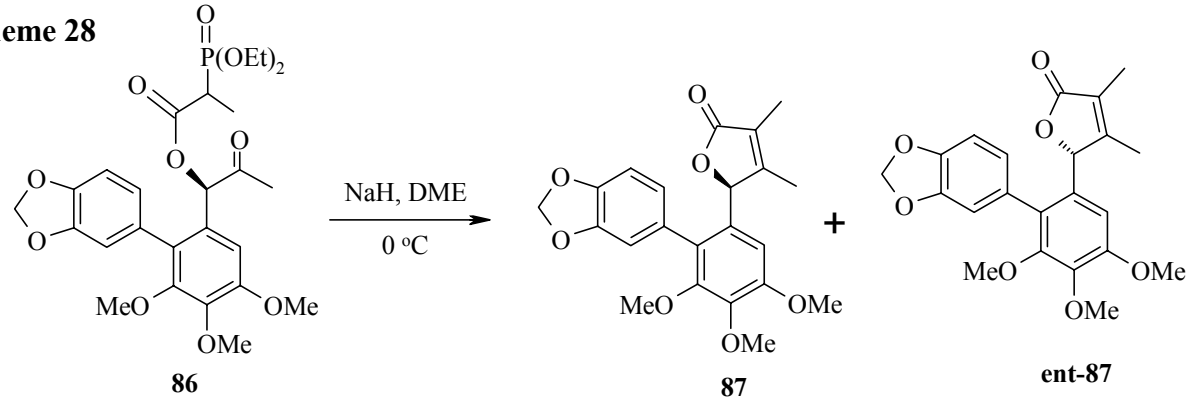
Our next goal was the intramolecular Wittig reaction of **86**. Treatment of **86** with NaH in THF at –78 ^oC or –40 ^oC did not afford any product (Scheme 27). At higher temperature (-20 ^oC, 0 ^oC and rt), in presence of NaH in THF, deacylation was observed. However, the transformation was achieved by carrying out the reaction in DME using NaH at 0 ^oC, resulting in the formation of lactone **87** (Scheme 28). In the ^1H NMR spectrum of **87**, the vinylic methyls resonated at δ 1.74 and 1.85, while they appeared at δ 8.4 and 12.2 in the

Scheme 27



^{13}C NMR spectrum. The carbonyl carbon of lactone resonated at δ 174.2. IR showed absorption at 1752 cm^{-1}, characteristic of α,β- unsaturated lactone. At this stage, the enantiomeric purity of the lactone **87** was determined. Towards this goal, (±)–**87** was prepared from (±)-**83** in the same manner (Scheme 29). Treatment of the biaryl aldehyde **70** with 2-propenylmagnesiumbromide prepared *insitu* from 2-bromopropene and magnesium

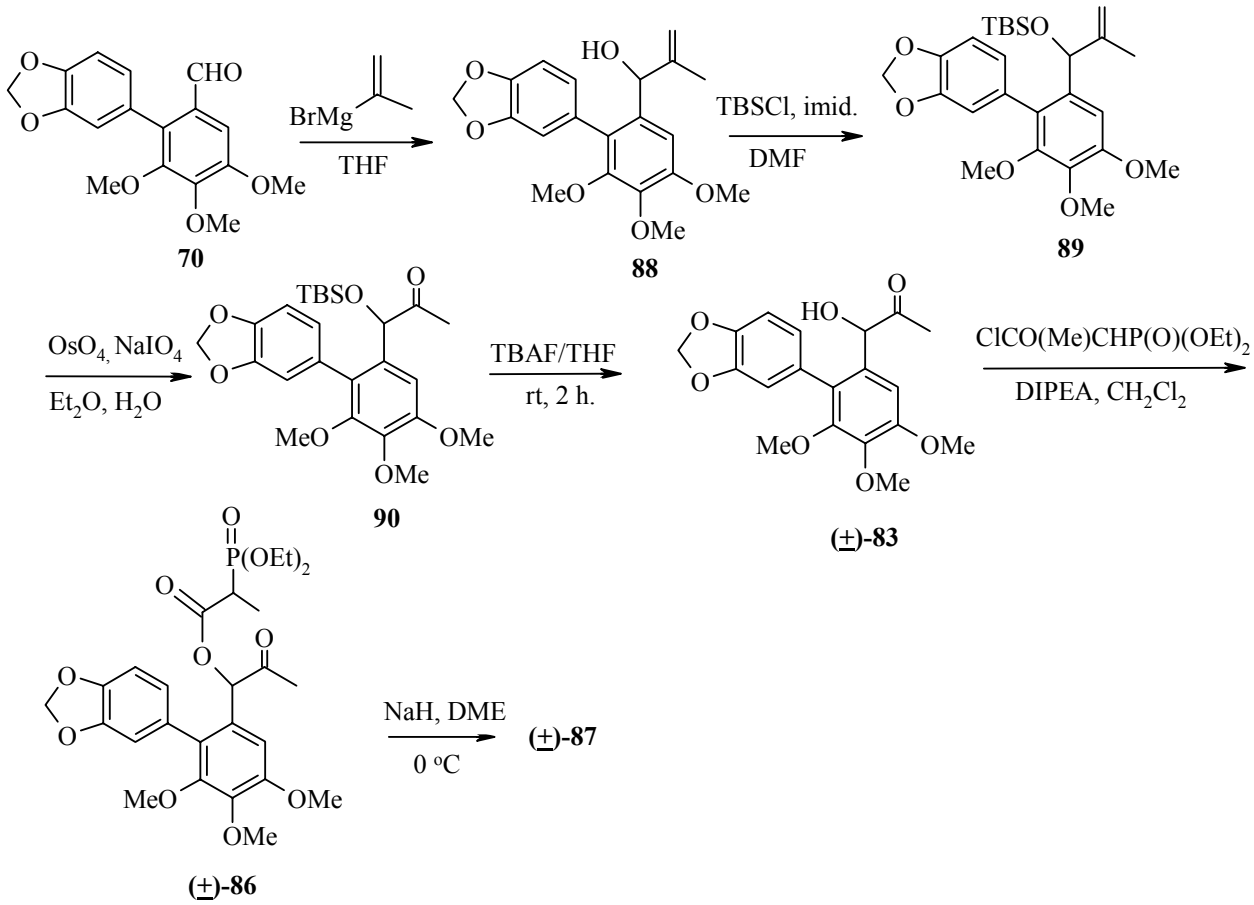
Scheme 28



resulted in the formation of alcohol **88**. In the ^{1}H NMR spectrum of **88**, the methylene protons of the olefin appeared at δ 4.90 as a doublet (J = 8.0 Hz). The benzylic proton appeared as a singlet at δ 5.01. The benzylic hydroxyl group in **88** was protected as its TBS ether using TBSCl and imidazole in DMF. Oxidative cleavage of the olefin using $OsO_4/NaIO_4$ system in Et_2O-water mixture at rt resulted in the formation of methyl ketone **89**. The downfield shift in the chemical shifts of the terminal methyl group and benzylic proton of **89** compared to **88** in the ^{1}H NMR spectrum confirmed the transformation. Finally, (±)-**83** was prepared by deprotection of the silyl ether using TBAF in THF. Absence of resonance

due to the TBS moiety ascertained the transformation. Esterification of (±)-**83** with 2-(diethoxyphosphoryl)propionyl chloride and treatment of the resulting phosphonate with NaH

Scheme 29



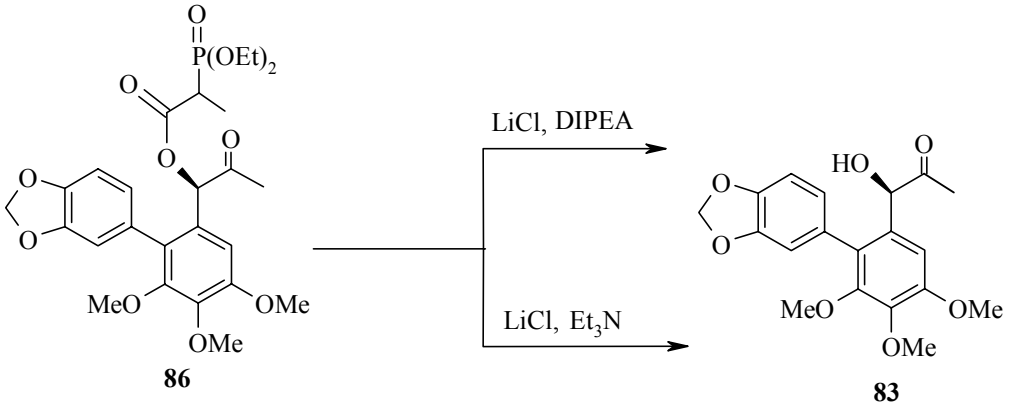
in DME at 0 ^{o}C afforded (±)–**87**. Comparison of Chiral HPLC of **87** and (±)–**87** (chiralcel OD, 5% isopropanol in hexanes) revealed that **87** is 80:20 mixture of enantiomers.

In order to minimize/eliminate racemization, the intramolecular H.W.E reaction was attempted with LiCl/DIPEA (Scheme 30). However, the product was found to be deacylated ketone, **83**. The case was no different when TEA was used instead of DIPEA.

The completion of the synthesis only required hydrogenation of the internal tetrasubstituted double bond in **87**. However, this was found to be a difficult proposition due to the steric hindrance offered by the tetrasubstituted internal double bond. Attempted hydrogenation using Pd/C/H_2 at ntp, 60 psi and 100 psi did not prodce any result.

Gratifyingly, when **87** was exposed to hydrogen at 60 psi pressure and Rh/Al_2O_3 in EtOAc for 18 h, compound **6** was obtained exclusively (Scheme 31).

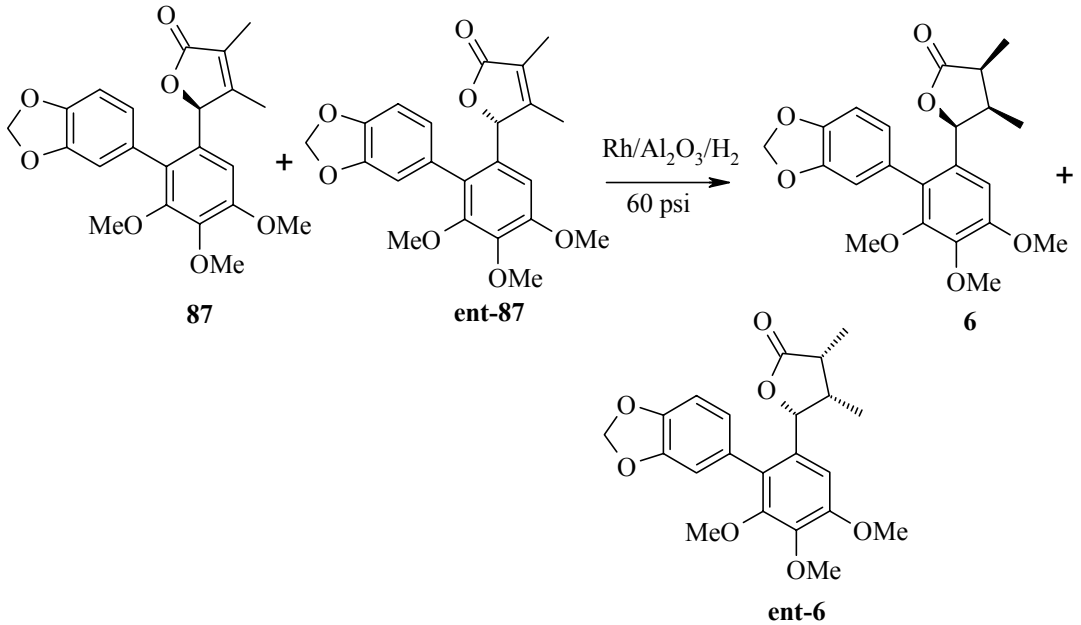
Scheme 30



86 **83**

Chiral HPLC showed that **6** is an 80:20 mixture of enantiomers and were separated (chiralcel OD, 12 % isopropanol in hexanes). ^{1}H NMR spectrum clearly indicated the presence of two atropisomers. However, the ^{1}H NMR values of the synthetic product and that of the natural

Scheme 31

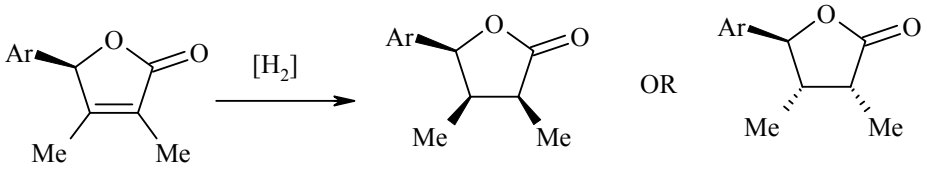


87 **ent-87** **6**

ent-6

product were not in complete agreement with each other. For e. g., the C-3 and C-4 hydrogens resonated at 2.74 and 2.20 ppm while reported at (i) δ 2.36 and 2.02 for natural product and (ii) δ 2.75 and 2.36 for 5-*epi*-eupomatilone-6. Furthermore, an upfield shift in the chemical shifts of C_4–methyl was observed, appearing at 0.55 and 0.57 ppm (of both

atropisomers), compared to the values reported for (i) the natural product at 0.70 and 0.73 ppm and (ii) 5-*epi*-eupometilone-6 at 0.65 and 0.67 ppm. Similarly, C-5 hydrogen in the synthetic product appeared at δ 5.23 and 5.34 as doublets (J = 5.0 Hz) while the same appeared at (i) δ 5.54 and 5.65 (J = 7.0 Hz) for the natural product and (ii) δ 5.00 and 5.10 (J = 4.4 Hz) for 5-epi-eupomatilone-6. These discrepancies in the ^{1}H NMR values of our product at first questioned the selectivity observed in the hydrogenation step, neglecting the steric effects offered by the bulky biaryl group. If the hydrogenation has taken place from the other face, then the product would have been **91**.



(i) 27 **(ii)**

However, the δ values of **91,** which is already reported in the literature, were not matching with our prouduct. To confirm further, NOE studies were undertaken and these studies showed interactions between the lactone ring protons and methyls as shown in figure. 1. H-3, H-4 and H-5 showed NOE with each other, which indicated the *syn* stereochemistry of the substituents on the lactone ring. The interaction between both methyl groups clearly indicated that hydrogenation has gone in a *syn* fashion.

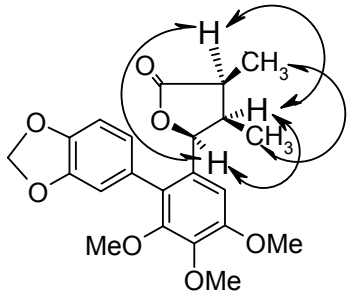
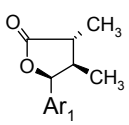
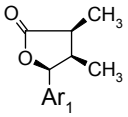
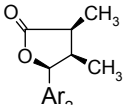
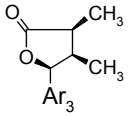
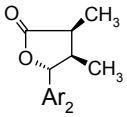
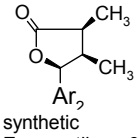


Fig. 1 **nOe studies**

We compared the ^{1}H NMR values of the lactone part of the synthetic product with eupomatilones 3, 4, 6, 7 and 5-*epi*-eupomatilone-6 (other eupomatilones were neglected as the substituents on the lactone ring are not similar with eupomatilone-6) (table 1). This comparison revealed a striking similarity in the δ values of eupomatilone-4, 7 and the synthetic product in which all substituents are *syn* (the J value for C-5 proton is $\simeq$ 5.0 Hz).

Similarly, eupomatilone-3 and the natural product were found to have closely matching δ values.

	 Eupomatilone-3	 Eupomatilone-4	 Natural Eupomatilone-6	 Eupomatilone-7	 synthetic 5-epi- Eupomatilone-6	 synthetic Eupomatilone-6
H-3	2.39 quintet J = 7.4 Hz	2.71 quintet J = 7.4 Hz	i) 2.36, m J = 7.0, 5.2 Hz ii) 2.37, m.	i) 2.64, m $J_{4,Me}$ =$J_{4,3}$ =7.6Hz. ii) 2.67, m.	2.75, m.	2.74, m
H-4	2.04, sextet $J_{4,Me}$=$J_{4,3}$= $J_{4,5}$= 7.4 Hz	2.17,m, $J_{4,Me}$ = $J_{4,3}$ =7.4, $J_{4,5}$=5.2 Hz	i) 2.02, m. $J_{4,Me}$=$J_{4,5}$=7.(, $J_{4,3}$ =5.3 Hz ii) 1.97, m	i) 2.05, m $J_{3,Me}$=$J_{4,3}$=7.6, $J_{5,4}$ = 5.4 Hz ii) 2.16,m.	2.36, m.	2.20, m,
H-5	5.50 d, $J_{4,5}$=7.4 Hz	5.28, dd, $J_{4,5}$= 5.2 Hz;	i) 5.54, d, $J_{4,5}$ = 7.0 Hz ii) 5.65, d.	i) 5.31, dd, $J_{4,5}$ = 5.4 Hz. ii) 5.20, dd.	i) 5.00, d J = 4.4 Hz ii)5.10, d.	i) 5.23, d, J = 5.0 Hz ii) 5.34, d, J = 5.0 Hz
C3-Me	1.18, d J = 7.4 Hz	1.10, d J = 7.4 Hz	i) 1.20, d J = 7.0 Hz ii) 1.19, d.	i) 1.08, d J =7.6 Hz ii) 1.09, d.	i) 1.06, d J = 7.5 Hz. ii) 1.07, d.	1.13, d, J = 7.2 Hz
C4-Me	0.78, d, J = 7.4 Hz	0.59, d, J = 7.4 Hz	i) 0.70, d J = 7.0 Hz. ii) 0.73, d.	i) 0.55, d, J = 7.6 Hz. ii) 0.58, d.	i) 0.65, d, J = 6.7 Hz ii) 0.67, d, J = 6.9 Hz.	i) 0.55, d, J = 7.2 Hz. ii) 0.58, d, J = 7.2 Hz.

These observations lead to a conclusion that the structure of eupomatilone-6 has to be revised.

Experimental

2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxy benzaldehyde (70)

Preparation of Pd (0)

A mixture of $PdCl_2$ (1.8 g, 10.1 mmol) and PPh_3 (1.31 g, 5.0 mmol) in of DMSO (120 mL) was heated to 140 ^oC till a clear solution is obtained. The oil bath was removed and the solution stirred for 15 min. Hydrazine hydrate was then added rapidly (0.2 g, 4.0 mmol) and the mixture immediately cooled with water bath. Crystallization begins at 125 ^oC. At this point, the mixture was allowed to cool without external cooling. The crystals were filtered under nitrogen, washed successively with ethanol (2x50 mL) and ether (2x50 mL), dried, stored under nitrogen and protected from light.

A mixture of $Pd(PPh_3)_4$ (150 mg, 0.13 mmol), benzene (9 mL), aldehyde **5** (1.2 g, 4.3 mmol), 2 M aq. solution of Na_2CO_3 (4.3 mL, 8.6 mmol), EtOH (2 mL) and boronic acid **3** (800 mg, 4.8 mmol) was degassed and refluxed under argon. After 24 h, both the layers were separated and the organic layer washed with water, brine, dried and evaporated. The crude residue on purification on silica gel using light petroleum:EtOAc (19:1) as an eluent gave biaryl aldehyde **70** (1.1 g, 79 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.65 (s, 6 H), 3.95 (s, 6 H), 3.98 (s, 6 H), 6.02 (s, 4 H), 6.62-6.66 (m, 2 H), 6.85 (m, 4 H), 7.26 (s, 2 H), 9.67 (s, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.7, 60.7, 100.9, 105.0, 107.5, 111.0, 124.5, 126.1, 129.7, 133.5, 147.2, 150.9, 152.7, 190.4.

IR ($CHCl_3$) 1679 cm^{-1}.

Analysis calcd. for $C_{17}H_{16}O_6$: C, 64.56; H, 5.06. Found, C, 64.73; H, 5.27 %.

Ethyl (2*E*,*Z*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-acrylate (71)

A mixture of **70** (10 g, 31.6 mmol) and $Ph_3P{=}CHCO_2Et$ (16.5 g, 47.5 mmol) in CH_2Cl_2 (100 mL) were stirred at rt under nitrogen for 5 h. Removal of the solvent followed by chromatographic purification on silica gel by eluting with light petroleum:EtOAc (19:1) afforded **71** (10.5 g, 86 %) as an inseparable mixture of *cis* and *trans* isomers in the ratio 15:85.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, 0.9 H, J = 7.1 Hz), 1.28 (t, 5.1 H, J = 7.1 Hz), 3.56 (s, 0.9 H), 3.61 (s, 5.1 H), 3.84 (s, 0.9 H), 3.88 (s, 0.9 H), 3.93 (s, 5.1 H), 3.94 (s, 5.1 H), 4.11 (q,

0.6 H, *J* = 7.1, 14.2 Hz), 4.20 (q, 3.4 H, *J* = 7.1, 14.2 Hz), 5.73 (d, 0.3 H, *J* = 12.2 Hz), 5.95 (s, 0.6 H), 6.02 (s, 3.4 H), 6.23 (d, 1.7 H, *J* = 16.2 Hz), 6.55 (d, 0.3 H, *J* = 12.2 Hz), 6.62 (dd, 1.7 H, *J* = 1.4, 7.8 Hz), 6.65 (dd, 0.3 H, *J* = 1.4, 7.8 Hz), 6.71 (d, 0.3 H, *J* = 1.4 Hz), 6.72 (d, 1.7 H, *J* = 1.4 Hz), 6.78 (d. 0.3 H, *J* = 7.8 Hz), 6.86 (d, 1.7 H, *J* = 7.8 Hz), 6.96 (s, 1.7 H), 7.11 (d, 0.3 H) 7.48 (d, 1.7 H, *J* = 16.2 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 13.7, 55.5, 59.6, 59.8, 60.4, 60.9, 100.7, 104.6, 107.3, 107.5, 109.3, 110.7, 117.6, 118.9, 123.9, 128.3, 128.6, 130.2, 142.5, 142.7, 143.7, 146.4, 146.6, 146.8, 146.9, 151.2, 152.4, 165.8, 166.3.

IR ($CHCl_3$) 1707 cm^{-1}.

Analysis calcd. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.70. Found: C, 65.57; H, 5.42 %.

Ethyl (2*R*,3*R*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2,3-dihydroxy propionate (72)

To a mixture of $K_3[Fe(CN)_6]$ (21.7 g, 65.9 mmol), K_2CO_3 (9.1 g, 65.9 mmol), $(DHQD)_2PHAL$ (0.18 g, 0.23 mmol), $K_2OsO_4.2H_2O$ (33 mg, 0.09 mmol) and $MeSO_2NH_2$ (2.1 g, 22.0 mmol) in ^{t}BuOH:H_2O (230 mL total volume, 1:1 mixture) at 0 ^{o}C was added olefin **71** (10.5 g, 27.2 mmol) and stirred at 0 ^{o}C. After 10 h, sodium bisulphate (34.5 g) was added to the reaction mixtue at 0 ^{o}C and allowed to warm to rt. ^{t}BuOH was removed under vacuum and the mixture was extracted with EtOAc, washed with 2 N KOH, water, brine, dried (Na_2SO_4) and evaporated. The residue on purification by silica gel chromatography eluting with light petroleum:EtOAc 3:2) afforded the diol **72** (8.3 g, 85 %) as a mixture of atropisomers and the unreacted *cis* olefin **71b** (1.5 g).

$[\alpha]_D$ = +35.18 (*c* 1.3, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (t, 6 H, *J* = 7.1 Hz), 3.51 (s, 6 H), 3.77 (s, 6 H), 3.78 (s, 6 H), 3.95 (m, 6 H), 4.84 (d, 1 H, *J* = 7.3 Hz), 4.86 (d, 1 H, *J* = 7.3 Hz), 5.89 (s, 4 H), 6.54 (m, 4 H), 6.75 (d, 2 H, *J* = 7.8 Hz), 6.94 (s, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 55.6, 60.4, 60.6, 61.1, 70.4, 73.6, 95.9, 100.7, 106.1, 107.8, 110.1, 110.9, 122.8, 123.7, 126.9, 129.1, 134.3, 141.3, 146.4, 147.2, 150.8, 152.4, 172.4.

IR ($CHCl_3$) 1740 cm^{-1}.

Analysis calcd. for $C_{21}H_{24}O_9$: C, 60.0; H, 5.71. Found: C, 60.23; H, 5.57 %.

Cis olefin: **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.21 (t, 6 H, *J* = 7.1 Hz), 3.56 (s, 6 H), 3.84 (s, 6 H), 3.88 (s, 6 H), 4.11 (q, 4 H, *J* = 7.1, 14.2 Hz), 5.73 (d, 2 H, *J* = 12.2 Hz), 5.95 (s, 4 H), 6.55 (d, 2 H, *J* = 12.2 Hz), 6.65 (dd, 2 H, *J* = 1.4, 7.8 Hz), 6.71 (d, 2 H, *J* = 1.4 Hz), 6.78 (d, 2 H, J = 7.8 Hz), 7.11 (s, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 55.5, 59.6, 60.4, 100.7, 107.5, 109.3, 110.7, 118.9, 123.9, 128.3, 128.6, 130.2, 142.7, 146.6, 146.9, 150.7, 151.2, 152.4, 165.8.

IR ($CHCl_3$) 1714 cm^{-1}.

Analysis calcd. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.70. Found: C, 65.35; H, 5.92 %.

Ethyl (2*R*,3*R*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2,3-*O*-isopropylidine-2,3-dihydroxypropionate (73)

A solution of diol **72** (8.3 g, 19.7 mmol), 2,2-dimethoxypropane (3.6 mL, 29.5 mmol) and catalytic *p*-TSA in CH_2Cl_2 (50 mL) were stirred at rt for 1 h and concentrated. The residue was dissolved in EtOAc, washed with water, brine, dried, concentrated and purified by silica gel column chromatography using light petroleum:EtOAc (4:1) to afford **73** (8.5 g, 94 %).

$[\alpha]_D$ = +44.5 (*c* 1.1, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (t, 6 H, *J* = 7.1 Hz), 1.36 (s, 3 H), 1.37 (s, 3 H), 1.55 (s, 6 H), 3.57 (s, 6 H), 3.86 (s, 6 H), 3.89 (s, 6 H), 4.04 (m, 4 H), 4.26 (d, 1 H, *J* = 6.3 Hz), 4.30 (d, 1 H, *J* = 6.3 Hz), 4.97 (d, 1 H, *J* = 6.3 Hz), 5.01 (d, 1 H, *J* = 6.3 Hz), 5.95-5.97 (m, 4 H), 6.47-6.54 (m, 2 H), 6.63-6.78 (m, 4 H), 6.84 (s, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 25.4, 26.9, 55.7, 60.6, 60.7, 61.1, 77.3, 81.3, 100.9, 105.3, 107.4, 107.8, 110.2, 111.2, 122.9, 123.9, 128.6, 129.4, 130.8, 142.2, 146.6, 146.9, 147.2, 151.0, 153.1, 169.8.

IR ($CHCl_3$) 1745 cm^{-1}.

Analysis calcd. for $C_{24}H_{28}O_9$: C, 62.61; H, 6.09 %. Found: C, 62.87; H, 5.77 %.

(2*R*,3*R*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2,3-*O*-isopropylidine-2,3-dihydro-xypropan-1-ol (74)

To a solution of ester **73** (8.5 g, 18.5 mmol) in THF (100 mL) at 0 ^oC was added $LiAlH_4$ (0.7 g, 18.5 mmol) portionwise and the mixture was stirred at 0 ^oC. After 2 h, the reaction mixture was quenched by the addition of EtOAc (10 mL) and water (2 mL) at 0 ^oC and the solid formed filtered off. The filtrate was concentrated and the residue purified on silica gel, eluting with light petroleum:EtOAc 3:2) to afford alcohol **74** (6.0 g, 78 %).

$[\alpha]_D$ = +47.12 (*c* 1.85, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 3 H), 1.39 (s, 3 H), 1.57 (s, 6 H), 3.61 (s, 6 H), 3.70-3.76 (m, 2 H), 3.89 (s, 6 H), 3.92 (s, 6 H), 4.04-4.09 (m, 4 H), 4.77 (d, 1 H, *J* = 8.3 Hz), 4.84 (d, 1 H, *J* = 8.3 Hz), 6.00-6.04 (m, 4 H), 6.57-6.66 (m, 2 H), 6.72-6.74 (m, 4 H), 6.83 (s, 1 H), 6.87 (s, 1 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.6, 26.9, 55.4, 60.2, 60.4, 60.7, 75.1, 75.2, 83.7, 100.6, 105.6, 107.5, 108.5, 110.0, 110.9, 122.7, 123.6, 128.6, 129.1, 130.6, 130.7, 141.8, 146.3, 147.0, 150.9, 152.6.

Analysis calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.22. Found: C, 63.38; H, 6.51 %.

Ethyl (2*S*,3*S*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2,3-dihydroxypropionate (*ent*-72)

To a mixture of $K_3[Fe(CN)_6]$ (3.1 g, 9.4 mmol), K_2CO_3 (1.3 g, 9.4 mmol), $(DHQ)_2PHAL$ (25.0 mg, 0.03 mmol), $K_2OsO_4.2H_2O$ (4.0 mg, 0.01 mmol) and $MeSO_2NH_2$ (0.3 g, 3.1 mmol) in ^{t}BuOH:H_2O (66 mL total volume, 1:1 mixture) at 0 ^{o}C was added olefin **71** (1.5 g, 3.8 mmol) and stirred at 0 ^{o}C. After 10 h, sodium bisulphate (4.9 g) was added to the reaction mixtue at 0 ^{o}C and allowed to warm to rt. ^{t}BuOH was removed under vacuum and the mixture was extracted with EtOAc, washed with 2 N KOH, water, brine, dried (Na_2SO_4) and evaporated. The residue on purification by column chromatography (silica gel, light petroleum:EtOAc 2:3) afforded the diol ***ent*-72** (1.28 g, 87 %) as a mixture of atropisomers and the unreacted *cis* olefin **71b** (0.2 g).

$[\alpha]_D$ = -35.2 (*c* 0.9, $CHCl_3$).

Ethyl (2*S*,3*S*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2,3-*O*-isopropylidine-2,3-dihydroxypropionate (*ent*-73)

A solution of diol ***ent*-72** (1.2 g, 2.8 mmol), 2,2-dimethoxypropane (0.5 mL, 4.2 mmol) and cat. *p*-TSA in CH_2Cl_2 (10 mL) were stirred at rt for 1 h and concentrated. The residue was dissolved in EtOAc, washed with water, brine, dried, concentrated and purified as described earlier for **8** to afford ***ent*-73** (1.1 g, 91 %).

$[\alpha]_D$ = -44.7 (*c* 1.3 $CHCl_3$).

(2*S*,3*S*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2,3-*O*-isopropylidine-2,3-dihydroxy propan-1-ol (*ent*-74)

To a solution of ester ***ent*-73** (1.0 g, 2.2 mmol) in THF (10 mL) at 0 ^{o}C was added $LiAlH_4$ (82.0 mg, 2.2 mmol) portionwise and the mixture was stirred at 0 ^{o}C. After 2 h, the reaction mixture was quenched by the addition of EtOAc (2 mL) and water (1 mL) at 0 ^{o}C and the solid formed was filtered off. The filtrate was concentrated and the residue subjected to column chromatography on silica gel using light petroleum:EtOAc (3:2) as an eluent to afford alcohol ***ent*-74** (0.7 g, 78 %).

$[\alpha]_D$ = -47.7 (*c* 1.8, $CHCl_3$).

(2*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-{(2*R*,3*R*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxy-phenyl)-2,3-*O*-isopropylidine-2,3-dihydroxypropyl}-propionate (75)

To a solution of compound **74** (0.1 g, 0.24 mmol) and (*S*)-Mosher's acid (60.0 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) was added DMAP (2.0 mg) and DCC (54 mg, 0.26 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 2 h and overnight at rt. Filtration and evaporation of filtrate afforded a residue, which on purification by passing through a short bed of silica gel eluting with light petroleum:EtOAc (4:1) afforded **75** (0.1 g, 66%). HPLC conditions: chiralcel OD, 10 % isopropanol in hexanes, retention time 11.18 min, flow rate 0.5 ml/min, λ = 215 nm.

$[\alpha]_D$ = +13.5 (*c* 0.75, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (s, 6 H), 1.52 (s, 6 H), 3.41 (s, 6 H), 3.58 (s, 3 H), 3.59 (s, 3 H), 3.88 (s, 6 H), 3.90 (s, 6 H), 4.07-4.13 (m, 6 H), 4.75 (d, 1 H, J = 7.8 Hz), 4.77 (d, 1 H, J = 7.8 Hz), 5.99-6.01 (m, 4 H), 6.56-6.89 (m, 8 H), 7.38 (m, 10 H);

Analysis calcd. for $C_{32}H_{33}F_3O_{10}$: C, 60.57; H, 5.24. Found: C, 60.81; H, 5.47 %.

(2*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-{(2*S*,3*S*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxy-phenyl)-2,3-*O*-isopropylidine-2,3-dihydroxypropyl}-propionate (76)

To a solution of the compound ***ent*-74** (0.1 g, 0.24 mmol), (*S*)-Mosher acid (60 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) was added DMAP (2 mg) and DCC (54 mg, 0.26 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 2 h and overnight at rt. Filtration and evaporation of filtrate afforded a residue, which on purification by passing through a short bed of silica gel eluting with light petroleum:EtOAc (4:1)afforded **76** (94 mg, 62 %). HPLC conditions: chiralcel OD, 10 % isopropanol in hexanes, retention time 12.97 min, flow rate 0.5 ml/min, λ = 215 nm.

$[\alpha]_D$ = -47.33 (*c* 2.65, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 6 H), 1.51 (s, 3 H), 1.52 (s, 3 H), 3.44 (s, 6 H), 3.59 (s, 3 H), 3.60 (s, 3 H), 3.89 (s, 6 H), 3.90 (s, 6 H), 4.00-4.12 (m, 4 H), 4.17-4.28 (m, 2 H), 4.76 (d, 1 H, *J* = 7.8 Hz), 4.78 (d, 1 H, *J* = 7.8 Hz), 5.95-6.00 (m, 4 H), 6.59-6.75 (m, 4 H), 6.79-6.88 (m, 4 H), 7.36-7.46 (m, 10 H);

Analysis calcd. for $C_{32}H_{33}F_3O_{10}$: C, 60.57; H, 5.24. Found: C, 60.73; H, 5.39 %.

(2*R*,3*R*)-3-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2,3-*O*-isopropylidine-2,3-dihydr-oxypropyl tosylate (77)

To a solution of alcohol **76** (6.0 g, 14.3 mmol) in pyridine (20 mL) was added TsCl (4.1 g, 21.5 mmol) and the mixture was stirred at rt for 6 h. Pyridine was removed under vacuum and the residue was extracted with EtOAc, washed with 1 N HCl, water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography eluting with lght petroleum:EtOAc (4:1) to afford **77** (7.5 g, 91 %).

$[\alpha]_D$ = +44.36 (*c* 1.6, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (s, 3 H), 1.30 (s, 3 H), 1.50 (s, 6 H), 2.45 (s, 3 H), 2.46 (s, 3 H), 3.61 (s, 6 H), 3.65-3.73 (m, 2 H), 3.90 (s, 12 H), 3.81-3.99 (m, 4 H), 4.72 (d, 1 H, *J* = 8.3 Hz), 4.78 (d, 1 H, *J* = 8.3 Hz), 6.02-6.07 (m, 4 H), 6.55-6.60 (m, 1 H), 6.64 (s, 2 H), 6.68-6.70 (m, 1 H), 6.82-6.87 (m, 2 H), 6.85 (s, 2 H), 7.31 (d, 4 H, *J* = 8.3 Hz), 7.68 (d, 4 H, *J* = 8.3 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.1, 26.3, 26.7, 55.4, 60.2, 60.4, 67.6, 75.2, 80.1, 80.2, 100.7, 105.2, 107.6, 107.8, 109.3, 109.7, 110.8, 122.4, 123.7, 127.4, 128.2, 128.8, 129.3, 130.0, 130.2, 132.5, 141.9, 144.3, 146.5, 147.2, 147.3, 150.9, 152.7.

Analysis calcd. for $C_{29}H_{32}O_{10}S$: C, 60.84; H, 5.59; S, 5.59. Found: C, 60.57; H, 5.33; S, 5.48 %.

(1*R*,2*R*)-1-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2-hydroxy-3-*O*-tosyl-propan-1-ol (78)

To a solution of **77** (7.5 g) in MeOH (20 mL) was added HCl (cat.) and the mixture was stirred at rt for 1 h. Solvent was removed in vacuuo and the residue extracted with EtOAc, washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography eluting with light petroleum:EtOAc (3:2) to afford diol **78** (6.1 g, 88 %).

$[\alpha]_D$ = +22.43 (*c* 4.1, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 6 H), 3.60 (s, 3 H), 3.61 (s, 3 H), 3.64-3.80 (m, 2 H), 3.90 (s, 12 H), 4.51 (d, 1 H, *J* = 7.8 Hz), 4.58 (d, 1 H, *J* = 7.8 Hz), 6.02-6.05 (m, 4 H), 6.49-6.69 (m, 4 H), 6.79-6.85 (m, 2 H), 6.87 (s, 2 H), 7.33 (d, 4 H, *J* = 8.3 Hz), 7.69 (d, 4 H, *J* = 8.3 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.7, 56.1, 60.8, 61.0, 69.6, 70.8, 73.1, 101.2, 106.3, 108.3, 110.5, 111.3, 123.2, 124.2, 128.0, 129.2, 130.0, 132.9, 134.3, 142.1, 145.0, 146.9, 147.7, 151.4, 153.1.

Analysis calcd. for $C_{26}H_{28}O_{10}S$: C, 58.64; H, 5.26; S, 6.02. Found: C, 58.57; H, 5.33; S, 5.88 %.

(1*R*,2*R*)-1-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2,3-epoxy-propan-1-ol (79)

Compound **78** (6.1 g, 11.5 mmol) was dissolved in MeOH (30 mL) and K_2CO_3 (2.4 g, 17.4 mmol) was added. The mixture was stirred at rt for 30 min. and concentrated. The residue was dissolved in water and extracted with EtOAc, washed with water, dried (Na_2SO_4) and evaporated. Purification of the residue on silica gel using light petroleum:EtOAc (4:1) as an eluent afforded pure epoxide **79** (3.1 g, 75%).

$[\alpha]_D$ = +41.21 (*c* 1.05, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35-2.40 (m, 2 H), 2.67-2.73 (m, 2 H), 3.05-3.12 (m, 2 H), 3.64 (s, 6 H), 3.91 (s, 6 H), 3.94 (s, 6 H), 4.36 (d, 1 H, *J* = 7.9 Hz), 4.43 (d, 1 H, *J* = 7.9 Hz), 6.02-6.05 (m, 4 H), 6.60-6.76 (m, 4 H), 6.84 (s, 1 H), 6.88 (s, 1 H), 7.04 (s, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 45.4, 55.4, 55.7, 60.4, 60.7, 70.1, 100.8, 105.3, 107.6, 107.8, 110.1, 110.8, 122.7, 123.6, 127.4, 129.2, 134.2, 141.5, 146.5, 147.1, 151.0, 152.9.

Analysis calcd. for $C_{19}H_{20}O_7$: C, 63.33; H, 5.55. Found: C, 63.03; H, 5.79 %.

(1*R*,2*R*)-1-*O*-(Methoxyethoxymethyl)-1-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxy-phenyl)-2,3-epoxypropane (80)

A mixture of compound **79** (3.1 g, 8.6 mmol), MEMCl (1.1 mL, 9.7 mmol), and diisopropylethylamine (1.6 mL, 9.5 mmol) in CH_2Cl_2 (20 mL) were stirred at rt for 8 h and concentrated. The residue was extracted with EtOAc, washed with water, dried (Na_2SO_4), evaporated and the residue purified by silica gel column chromatography eluting with light petroleum:EtOAc (4:1) to afford **80** (3.2 g, 83 %).

$[\alpha]_D$ = +11.0 (*c* 1.4, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.24-2.28 (m, 2 H), 2.59-2.65 (m, 2 H), 3.02-3.11 (m, 2 H), 3.34 (s, 6 H), 3.39-3.48 (m, 4 H), 3.62 (s, 6 H), 3.66-3.72 (m, 4 H), 3.91 (s, 6 H), 3.92 (s, 6 H), 4.29 (d, 1 H, *J* = 7.8 Hz), 4.33 (d, 1 H, *J* = 7.8 Hz), 4.66-4.83 (m, 4 H), 6.01-6.03 (m, 4 H), 6.56-6.65 (m, 2 H), 6.72-6.81 (m, 2 H), 6.83 (s, 1 H), 6.87 (s, 1 H), 6.92 (s, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 43.9, 54.1, 55.4, 58.1, 60.1, 60.3, 66.2, 70.9, 74.5, 74.6, 92.5, 100.5, 105.4, 107.2, 109.8, 110.6, 122.5, 123.4, 127.9, 128.7, 131.7, 141.3, 146.2, 146.8, 146.9, 150.7, 152.5.

Analysis calcd. for $C_{23}H_{28}O_9$: C, 61.60; H, 6.29. Found: C, 61.80; H, 6.49 %.

(1*R*,2*R*)-1-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-1-*O*-(methoxyethoxy-methyl)-propan-2-ol (81)

To a solution of compound **80** (3.2 g, 7.1 mmol) in THF (15 mL) at 0 ^oC was added $LiAlH_4$ (0.27 g, 7.1 mmol) and stirred at 0 ^oC for 3 h. The excess $LiAlH_4$ was quenched by the addition of EtOAc (5 mL) and water (2 mL) at 0 ^oC. The solid formed was filtered, filtrate concentrated to afford a residue which was purified on silica gel, euting with light petroleum:EtOAc (4:1) to give **81** (3.0 g, 94 %).

$[\alpha]_D$ = -21.3 (*c* 0.8, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84 (d, 6 H, *J* = 6.4 Hz), 3.34 (s, 6 H), 3.38-3.44 (m, 4 H), 3.60 (s, 6 H), 3.69-3.81 (m, 6 H), 3.89 (s, 12 H), 4.32 (d, 2 H, *J* = 7.8 Hz), 4.65-4.67 (m, 4 H), 6.01 (s, 4 H), 6.56-6.63 (m, 2 H), 6.70 (s, 2 H), 6.82 (s, 2 H), 6.76-6.86 (m, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.1, 55.7, 58.5, 60.4, 60.6, 67.0, 71.2, 71.3, 79.8, 80.1, 93.2, 93.3, 100.7, 105.3, 107.5, 107.6, 110.4, 111.3, 123.0, 124.3, 129.0, 129.3, 132.7, 132.8, 141.5, 146.3, 147.0, 150.9, 152.6.

Analysis calcd. for $C_{23}H_{30}O_9$: C, 61.33; H, 6.66. Found: C, 61.25; H, 6.40 %.

(1*R*,2*R*)-1-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-1-*O*-(methoxyethoxy-methyl)-propan-2-one (82)

A mixture of compound **81** (3.0 g, 6.66 mmol), PDC (3.75 g, 9.99 mmol) and 4 A^o mol. sieves powder (3.75 g) in CH_2Cl_2 (50 mL) were stirred at rt for 4 h and filtered. The filtrate was concentrated and subjected to purification on silica gel using light petroleum:EtOAc (5:1) as an eluent to afford **82** (2.0 g, 67 %).

$[\alpha]_{Na}$ = -130.7 (*c* 2.16, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.96 (s, 3 H), 1.97 (s, 3 H), 3.32 (s, 6 H), 3.38-3.44 (m, 4 H), 3.62 (s, 6 H), 3.53-3.74 (m, 4 H), 3.85 (s, 6 H), 3.89 (s, 6 H), 4.60-4.82 (m, 4 H), 5.10 (s, 2 H), 6.02 (s, 4 H), 6.55 (s, 2 H), 6.71-6.79 (m, 4 H), 6.85-6.91 (m, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.8, 55.7, 58.6, 60.5, 60.8, 67.2, 71.3, 79.3, 79.5, 93.6, 100.9, 105.8, 107.8, 110.4, 110.1, 124.0, 129.0, 129.6, 142.2, 146.8, 147.3, 151.5, 153.1, 204.7.

IR ($CHCl_3$) 1724 cm^{-1}.

Analysis calcd. for $C_{23}H_{28}O_9$: C, 61.60; H, 6.29. Found: C, 61.83; H, 5.98 %.

(1*R*,2*R*)-1-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-1-hydroxy-propan-2-one (83)

A solution of compound **82** (2.0 g, 4.5 mmol) and PPTS (5.0 g, 20.2 mmol) in ^{t}BuOH (20 mL) was heated at 80 ^{o}C for 12 h. Solvent was removed in vacuuo and the residue purified by silica gel chromatography eluting with light petroleum:EtOAc (3:2) to afford **83** (1.2 g, 75 %).

$[\alpha]_{Na}$ = -67.4 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95 (s, 3 H), 1.96 (s, 3 H), 3.64 (s, 6 H), 3.85 (s, 6 H), 3.91 (s, 6 H), 4.14 (br s, 1 H), 5.01 (s, 2 H), 6.03-6.05 (m, 4 H), 6.40 (s, 2 H), 6.76-6.92 (m, 6 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.5, 55.8, 60.7, 60.8, 76.2, 101.0, 105.3, 107.9, 108.2, 110.6, 111.0, 123.9, 129.0, 129.5, 131.7, 142.5, 146.9, 147.4, 147.5, 151.7, 153.3, 207.2.

Analysis calcd. for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found: C, 63.58; H, 5.48 %.

(1*R*,2*R*)-1-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-1-(2-bromopropionyloxy)-propan-2-one (84)

To a solution of the compound **83** (1.2 g, 3.3 mmol), 2-bromopropionic acid (0.56 g, 3.6 mmol) and DMAP (17.0 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) was added DCC (0.75 g, 3.6 mmol) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 2 h and overnight at rt. The reaction mixture was filtered and evaporated to afford a residue, which on purification by silica gel column chromatography eluting with light petroleum:EtOAc (4:1) afforded **84** (1.3 g, 78 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.58 (m, 6 H), 1.97-1.99 (s, 6 H), 3.63 (s, 6 H), 3.84 (s, 6 H), 3.91 (s, 6 H), 4.37-4.52 (m, 2 H), 5.84-5.86 (m, 2 H), 6.01-6.03 (m, 4 H), 6.53-6.91 (m, 8 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5, 26.5, 39.0, 39.1, 56.1, 60.7, 60.9, 78.5, 101.1, 106.9, 108.0, 108.4, 110.5, 110.8, 123.4, 123.8, 126.0, 126.2, 128.5, 130.7, 143.5, 147.3, 147.8, 151.9, 153.3, 169.1, 200.9.

Anal.calcd. for $C_{22}H_{23}BrO_8$: C, 53.35; H, 4.68. Found: C, 53.17; H, 4.39 %.

(1*R*,2*R*)-1-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-1-{(2-diethoxy-phosphoryl)-propionyloxy}-propan-2-one (86)

To a solution of the compound **83** (1.2 g, 3.3 mmol) and diisopropylethylamine (1.1 mL, 6.6 mmol) in CH_2Cl_2 (5 mL) was added a solution of 2-(diethoxyphosphoryl)-propionyl chloride (1.5 g, 6.6 mmol) in CH_2Cl_2 (2 mL) at 0 ^oC dropwise. After 3 h at 0 ^oC, the reaction mixture was diluted with CH_2Cl_2, washed with dil. HCl, water, brine, dried and evaporated to afford a residue which, on purification by silica gel column chromatography eluting with light petroleum:EtOAc (2:3) afforded phosphonate **86** (1.3 g, 70 %) as a mixture of diastereomers.

$[\alpha]_{Na}$ = -24.9 (*c* 0.8, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14-1.28 (m, 18 H), 1.91-1.99 (m, 6 H), 2.87-3.26 (m, 2 H), 3.56 (s, 3 H), 3.58 (s, 3 H), 3.83 (s, 6 H), 3.86 (s, 6 H), 4.01-4.19 (m, 8 H), 5.81-5.84 (m, 2 H), 5.96-5.99 (m, 4 H), 6.56-6.86 (m, 8 H);

Analysis calcd. for $C_{26}H_{33}O_{11}P$: C, 56.52; H, 5.98. Found: C, 56.61; H, 6.27 %.

(5*R*)-5-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-3,4-dimethyl-5H-furan-2-one (87)

To a solution of the phosphonate **86** (1.3 g, 2.35 mmol) in dry DME (10 mL) under argon at 0 ^oC was added NaH (60 % dispersion in mineral oil, 0.1 g, 2.6 mmol). After stirring for 30 min. at 0 ^oC, the reaction mixture was quenched by the addition of ice. Solvent was removed *in vacuo* and the residue extracted with EtOAc. The organic layer was washed with water, brine, dried (Na_2SO_4) and evaporated. Purification of the residue on silica gel eluting with light petroleum:ethyl acetate (5:1) afforded the lactone **87** (0.82 g, 87 %).

$[\alpha]_{Na}$ = +43.81 (*c* 0.9, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.74 (s, 6 H), 1.85 (s, 6 H), 3.64 (s, 6 H), 3.82 (s, 6 H), 3.91 (s, 6 H), 5.57 (s, 2 H), 6.02 (m, 4 H), 6.23 (s, 2 H), 6.69-6.87 (m, 6 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 8.4, 12.2, 56.0, 60.6, 60.7, 81.6, 100.9, 105.1, 107.8, 108.0, 110.8, 110.9, 123.5, 123.7, 128.2, 128.5, 130.3, 143.0, 146.9, 147.5, 151.6, 153.3, 158.6, 174.2.

IR ($CHCl_3$) cm^{-1} 1752.

Analysis calcd. for $C_{22}H_{22}O_7$: C, 66.33; H, 5.53. Found: C, 66.59; H, 5.71 %.

1-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2-methyl-prop-2-ene-1-ol (88)

To a suspension of activated magnesium (0.22 g, 9.1 mmol) in dry THF (10 mL) under argon was added 2-bromopropene (0.6 mL, 6.7 mmol) at rt over a period of 15 min. After stirring at rt for 30 min, a solution of aldehyde **70** (1 g, 3.1 mmol) in dry THF (5 mL) was added dropwise and the resulting mixture was stirred at rt. After 1 h, the reaction mixture was quenched by the addition of aq. NH_4Cl at 0 ^oC, organic layer was separated, washed with water, brine, dried and evaporated. The residue was purified on silica gel by eluting with light petroleum:EtOAc (4:1) to afford **88** (0.96 g, 86 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 3 H), 1.54 (s, 3 H), 1.82 (br s, 2 H), 3.62 (s, 6 H), 3.88 (s, 6 H), 3.89 (s, 6 H), 4.90 (d, 4 H, J = 8.0 Hz), 5.01 (s, 2 H), 6.00 (s, 4 H), 6.60-6.85 (m, 8 H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.6, 55.9, 60.8, 61.0, 73.3, 100.9, 105.3, 107.8, 110.6, 110.7, 111.2, 123.2, 123.9, 128.7, 129.6, 129.7, 135.6, 141.7, 146.8, 147.3, 151.3, 153.0.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.21; H, 6.37 %.

1-(^{t}Butyldimethylsilyloxy)-1-(2-benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-2-methyl-prop-2-ene (89)

To a solution of the compound **88** (0.1 g, 0.38 mmol) in CH_2Cl_2 (4 mL) was added TBSCl (86 mg, 0.58 mmol) and imidazole (40 mg, 0.58 mmol) and stirred at rt. After 5 h, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was separated, dried, concentrated and the residue purified on silica gel eluting with light petroleum:ethyl acetate (9:1) to afford **89** (0.11 g, 80 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05, 0.07 (2s, 12 H), 0.88, 0.89 (2s, 18 H), 1.56, 1.59 (2s, 6 H), 3.67, 3.94, 3.95 (3s, 18 H), 4.46-4.52 (m, 2 H), 4.71 (s, 2 H), 4.97-5.03 (m, 2 H), 6.05-6.08 (m, 4 H), 6.60-7.01 (m, 8 H);

Anal. Calcd. for $C_{26}H_{36}O_6Si$: C, 66.07; H, 7.68. Found: C, 66.28; H, 7.39 %.

1-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-1-(^{t}butyldimethylsilyloxy)-propan-2-one (90)

To a mixture of diethylether (15 mL), water (15 mL), compound **89** (0.5 g, 1.0 mmol) and OsO_4 (10.0 mg, 5 mol %) was added finely powdered $NaIO_4$ (0.42 g, 2.0 mmol) over a period of 30 min., maintaining the temperature at 25 ^oC. After stirring at 25 ^oC for an additional 80

min., the reaction mixture was extracted with EtOAc, dried (Na_2SO_4) and evaporated to afford compound **90** (0.35 g, 70 %), which was used as such for the next reaction.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04, 0.06 (2s, 12 H), 0.88, 0.89 (2s, 18 H), 1.94 (s, 3 H), 1.95 (s, 3 H), 3.64 (s, 6 H), 3.87 (s, 6 H), 3.89 (s, 6 H), 5.24 (s, 2 H), 6.03 (s, 4 H), 6.52 (s, 2 H), 6.70-6.76 (m, 4 H), 6.85-6.91 (m, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.2, -5.0, 17.9, 25.5, 55.6, 60.5, 60.7, 100.8, 107.5, 107.6, 110.1, 111.8, 122.8, 124.5, 128.1, 129.1, 133.4, 141.8, 146.6, 147.0, 152.6, 207.5.

Anal. Calcd. for $C_{25}H_{34}O_7Si$: C, 63.27; H, 7.22. Found: C, 63.43; H, 7.50 %.

1-(2-Benzo[1,3]dioxol-5-yl-3,4,5-trimethoxyphenyl)-1-hydroxy-propan-2-one (±)-83

To a solution of the compound **90** (0.3 g, 0.6 mmol) in THF was added n-Bu_4NF (1 M solution in THF, 1.2 mL, 1.2 mmol). After stirring at rt for 2 h, the reaction mixture was evaporated and the residue purified on silica gel, eluting with light petroleum:EtOAc (3:2) to afford **(±)-83** (0.20 g, 90 %).

Eupomatilone-6 (88)

Hydrogenation of compound **87** (0.82 g, 2.0 mmol) was carried out using Rh/Al_2O_3 (5 mg) in EtOAc (20 mL) under Hydrogen atmosphere at 60 psi pressure for 20 h in a parr shaker apparatus. The catalyst was filtered, and the filtrate concentrated to afford a residue, which on purification by silica gel column chromatography gave eupomatilone-6 **87** (0.49 g, 60 %) as 80:20 enantiomeric mixture. The enantiomers were separated by Chiral HPLC using chiralcel OD column and 12 % isopropanol in hexanes as an eluent [retention time: 14.75 min (first peak, major isomer); 18.0 min (second peak, minor isomer); flow rate 0.5 ml/min; λ = 254 nm]. The spectral datas of the major isomer (first peak, 1:1 mixture of atropisomers).

$[\alpha]_{Na} = -30^o$ (*c* 0.5, $CHCl_3$);

Atropisomer 1: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.54 (d, 3 H, *J* = 7.1 Hz), 1.13 (d, 3 H, *J* = 7.1 Hz), 2.20 (m, 1 H), 2.74 (m, 1 H), 3.65 (s, 3 H), 3.91 (s, 6 H), 5.32 (d, 1 H, *J* = 5.1 Hz), 6.02 (m, 2 H), 6.58 (dd, 1 H, *J* = 1.2, 8.0 Hz), 6.82 (s, 1H), 6.73 (d, 1 H, *J*=1.2 Hz), 6.87 (d, 1 H, *J* = 8.0 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ 9.7, 9.9, 38.6, 40.7, 56.2, 60.8, 80.5, 101.1, 105.1-130.2, 141.7-152.9, 178.6;

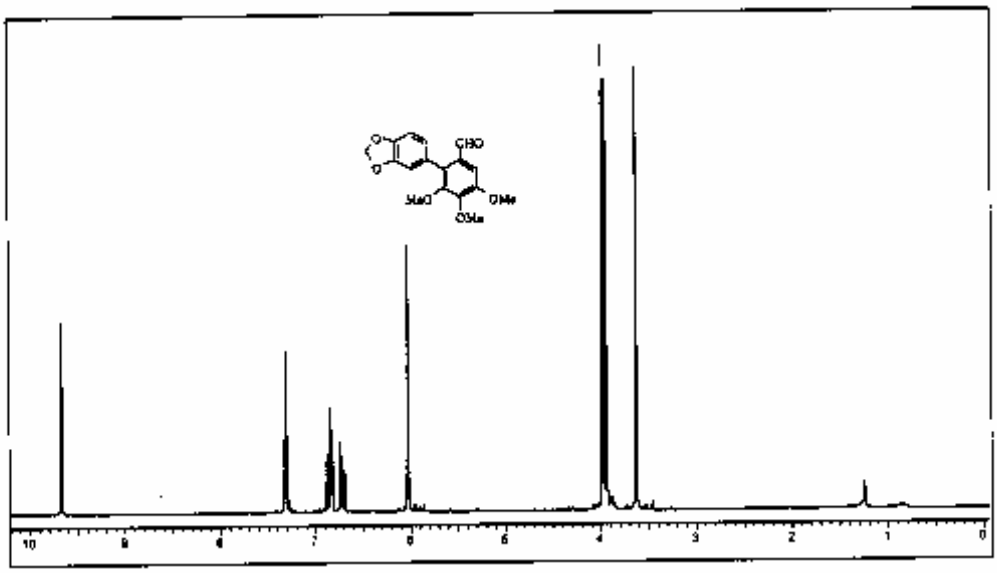
Atropisomer 2: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.56 (d, 3 H, *J* = 7.1 Hz), 1.13, (d, 3 H, *J* = 7.1 Hz), 2.20 (m, 1 H), 2.74 (m, 1 H), 3.66 (s, 3 H), 3.91 (s, 6 H), 5.41 (d, 1 H, *J* = 5.1 Hz),

6.03 (m, 2 H), 6.71 (dd, 1 H, J = 1.2, 8.0 Hz), 6.83 (s, 1 H), 6.62 (d, 1 H, J = 1.2 Hz), 6.88 (d, 1 H, J = 8.0 Hz);

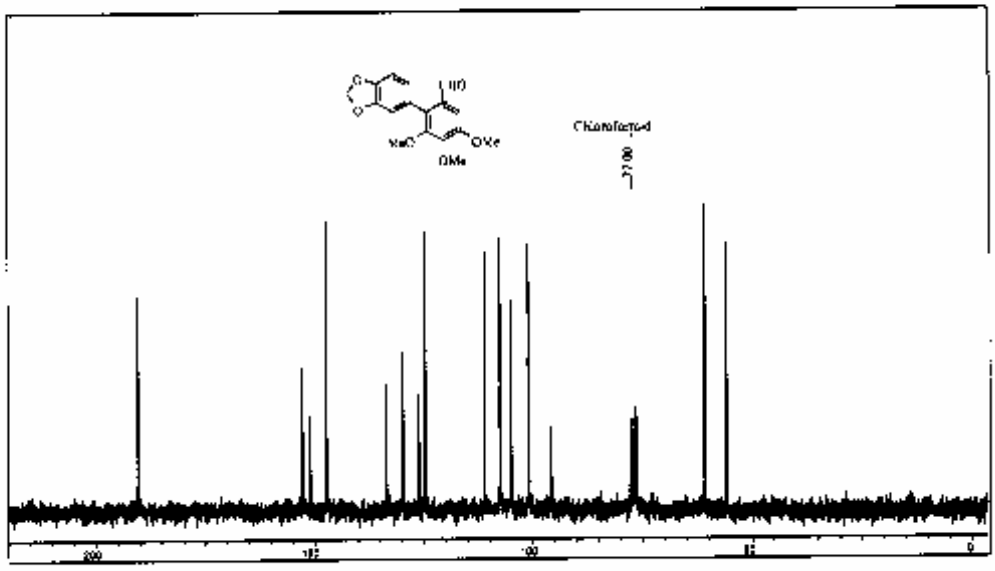
^{13}C NMR (125 MHz, $CDCl_3$): δ 9.8, 9.9, 38.9, 40.7, 56.2, 61.2, 80.6, 101.2, 105.1-130.2, 141.7-152.9, 178.6.

IR ($CHCl_3$) cm^{-1} 1769.

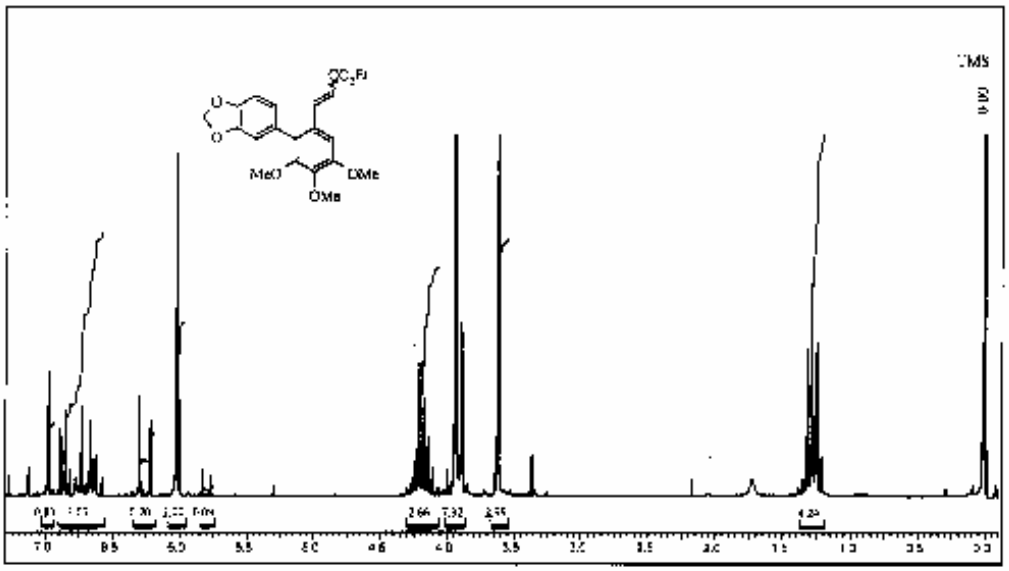
Anal. calcd for $C_{22}H_{24}O_7$: C, 66.0; H, 6.0. Found: C, 65.80; H, 5.74 %.



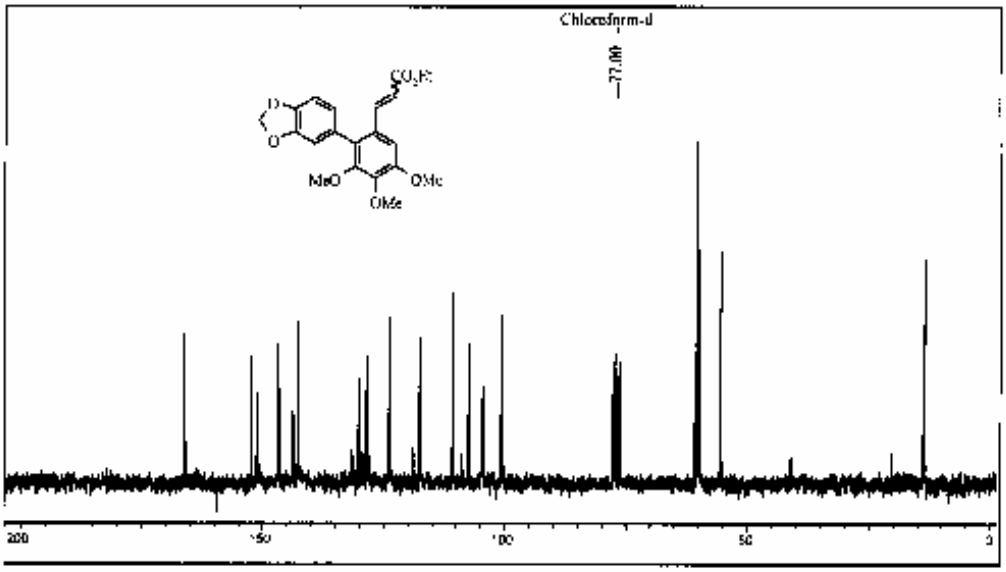
^{1}H NMR spectrum of compound 70 in $CDCl_3$



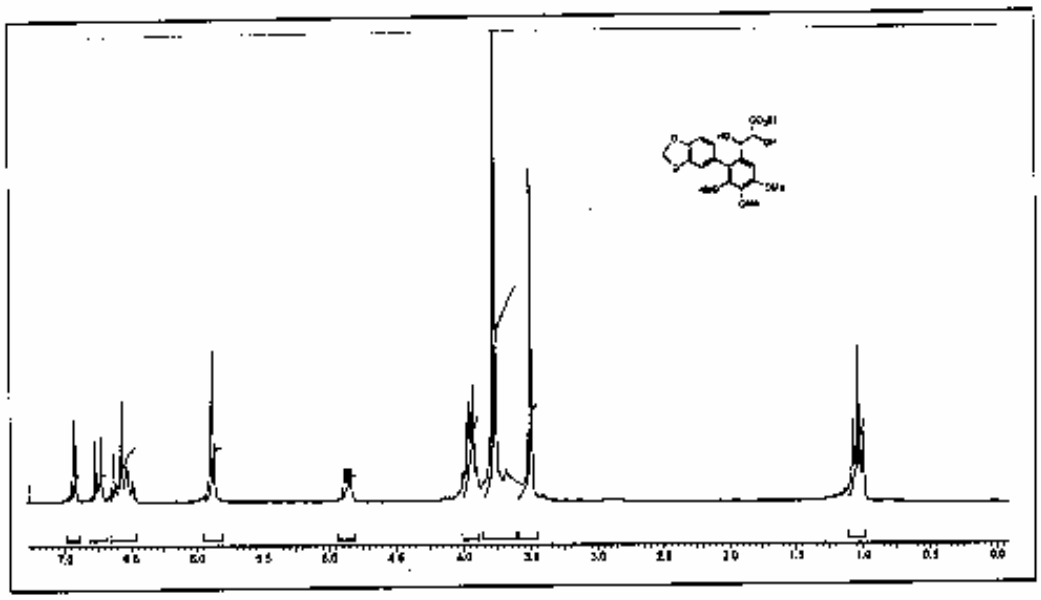
^{13}C NMR spectrum of compound 70 in $CDCl_3$



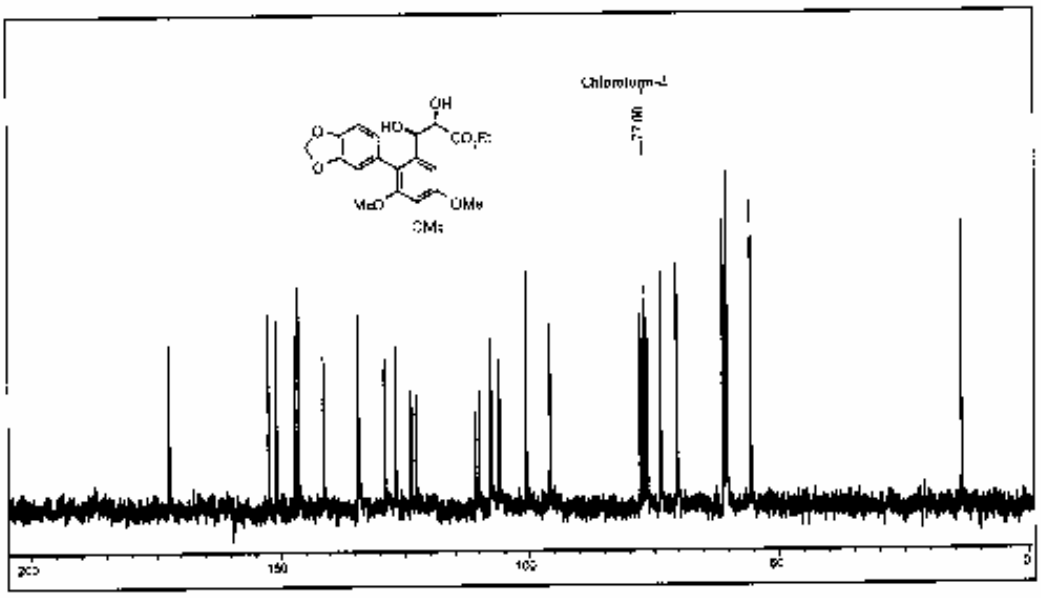
^{1}H NMR spectrum of compound 71 in $CDCl_3$



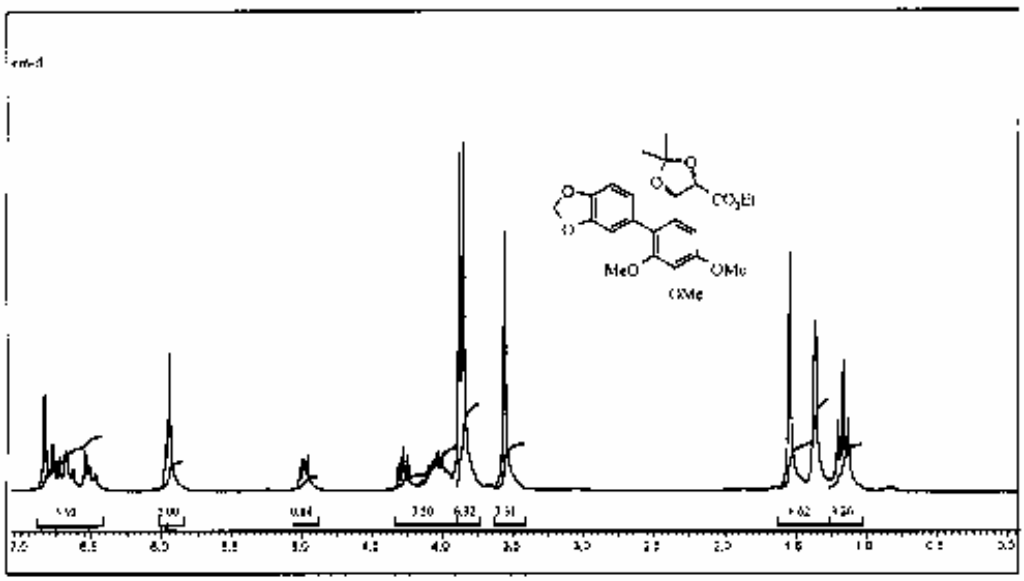
^{13}C NMR spectrum of compound 71 in $CDCl_3$



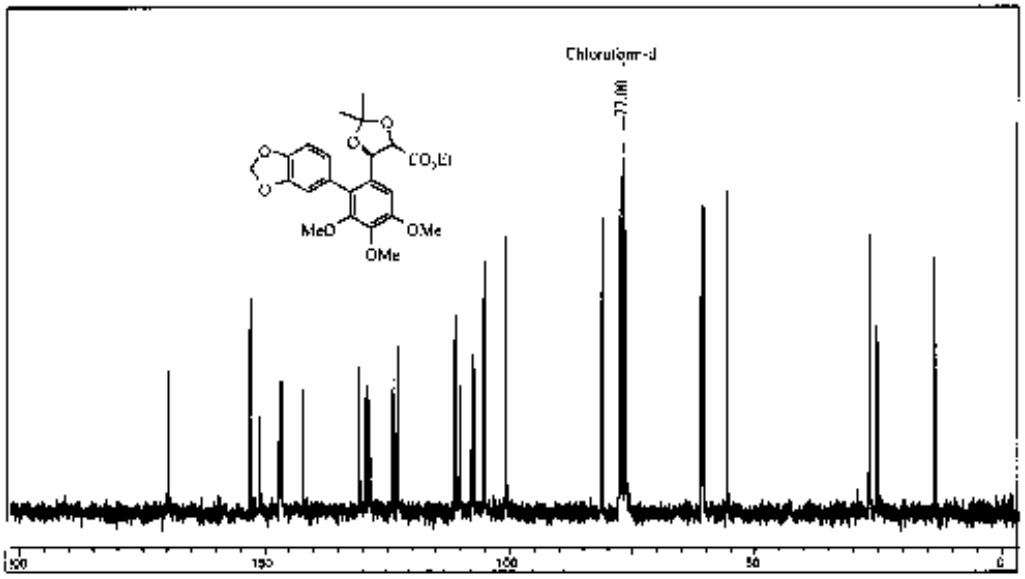
^{1}H NMR spectrum of compound 72 in $CDCl_3$



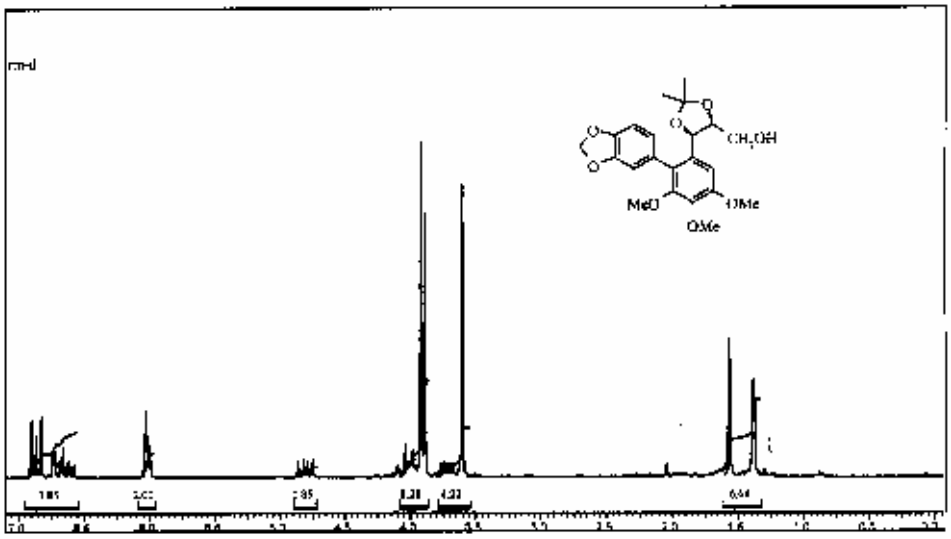
^{13}C NMR spectrum of compound 72 in $CDCl_3$



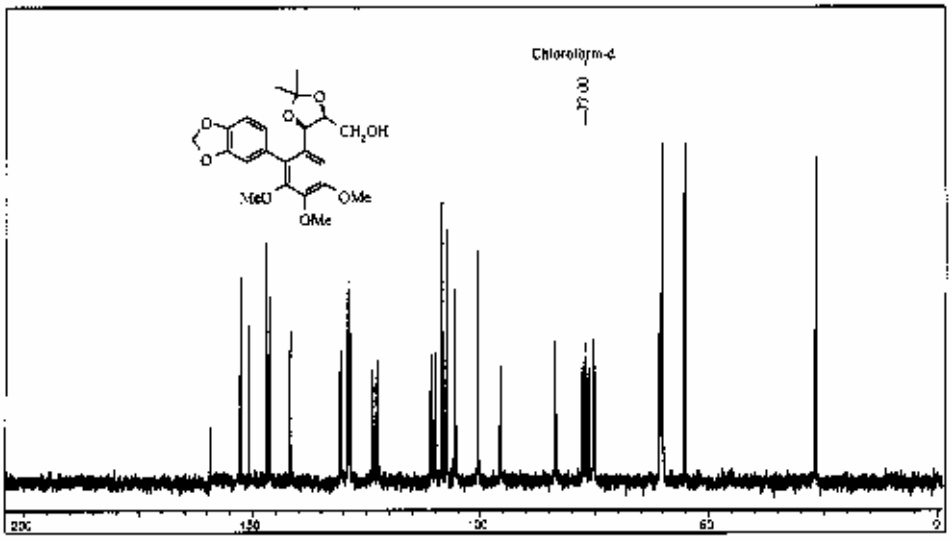
^{1}H NMR spectrum of compound 73 in $CDCl_3$



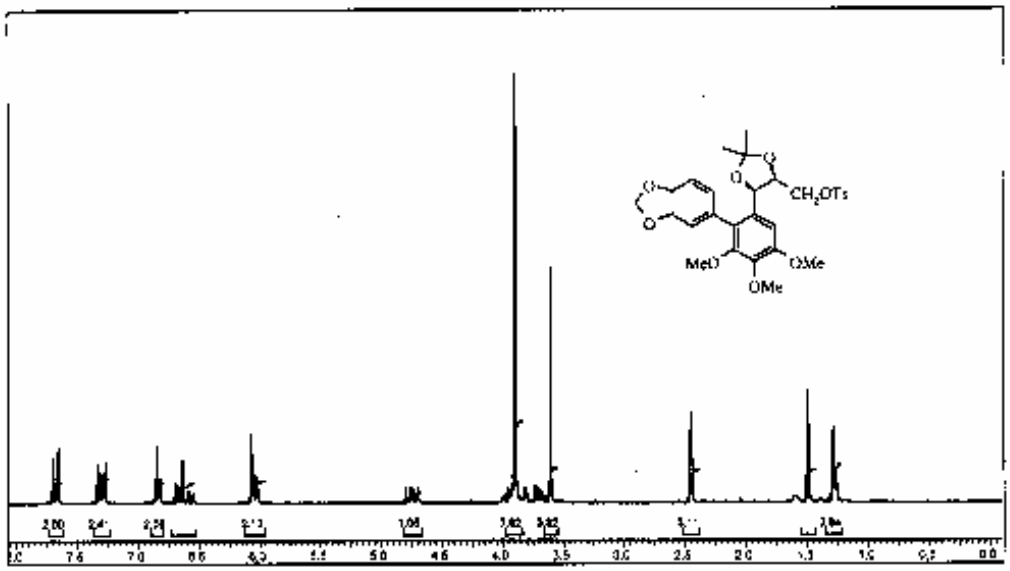
^{13}C NMR spectrum of compound 73 in $CDCl_3$



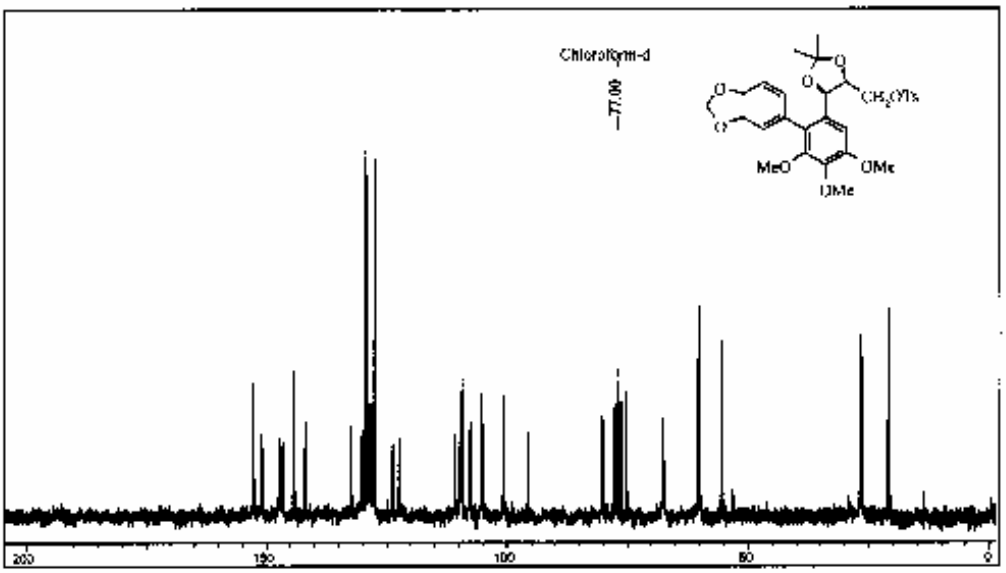
^{1}H NMR spectrum of compound 74 in $CDCl_3$



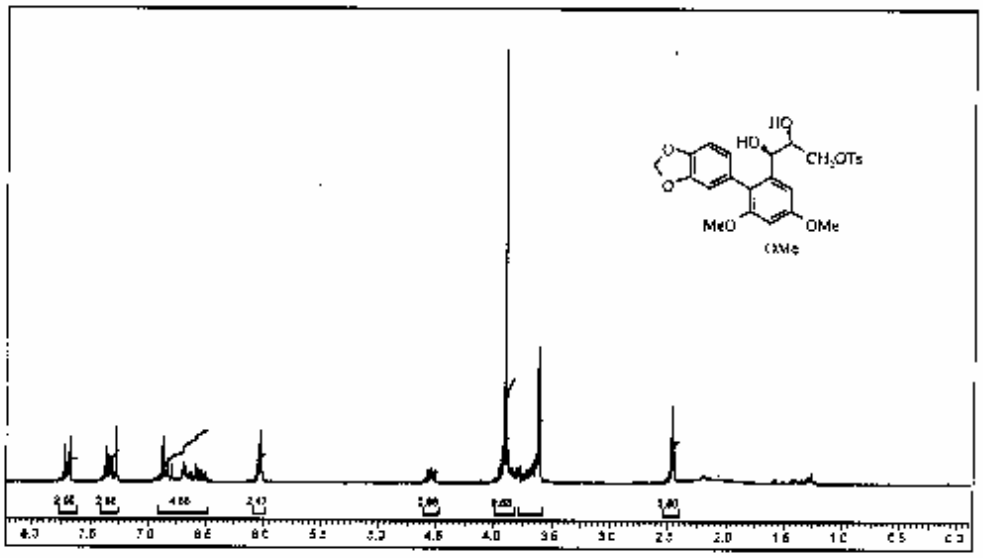
^{13}C NMR spectrum of compound 74 in $CDCl_3$



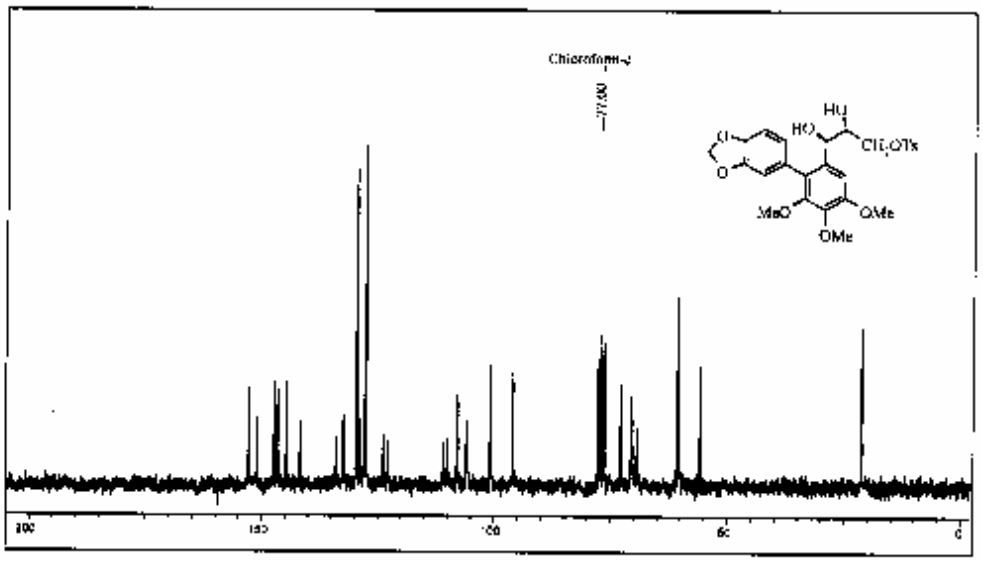
^{1}H NMR spectrum of compound 77 in $CDCl_3$



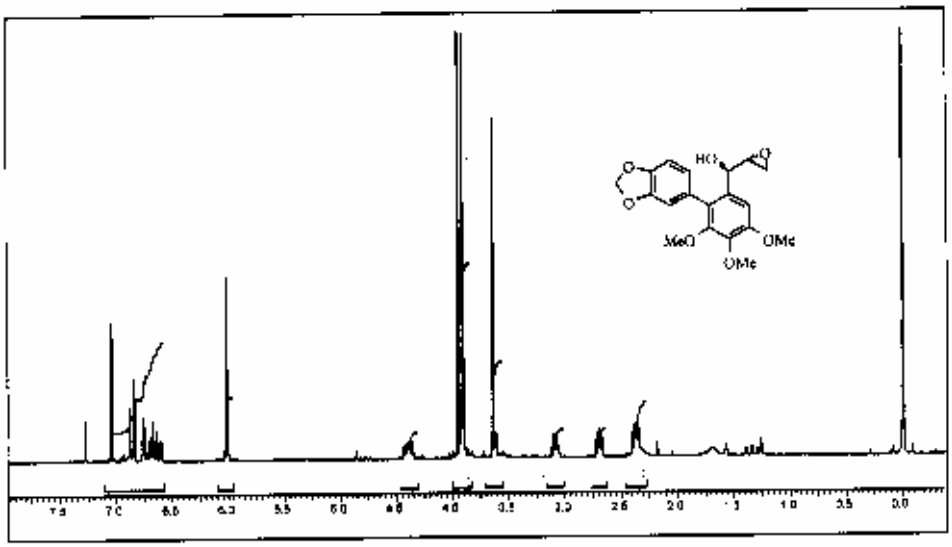
^{13}C NMR spectrum of compound 77 in $CDCl_3$



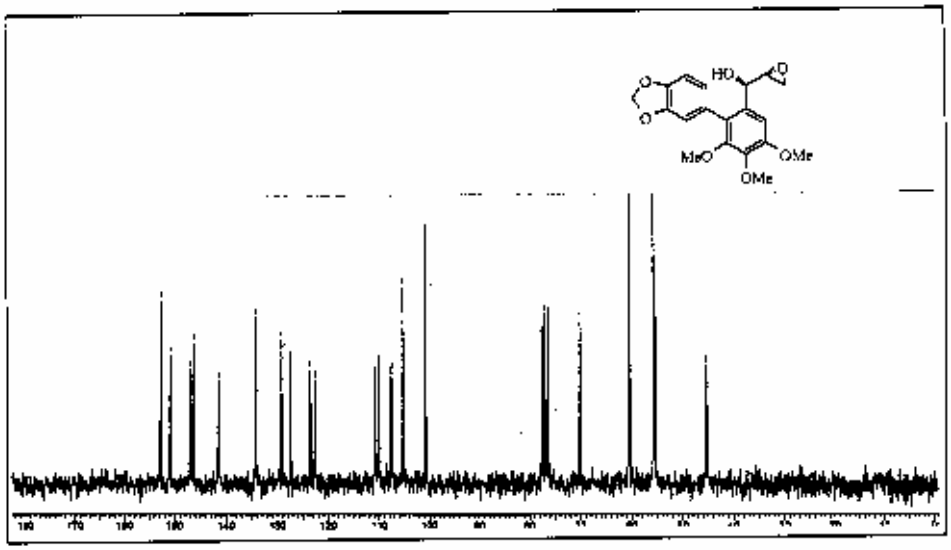
^{1}H NMR spectrum of compound 78 in $CDCl_3$



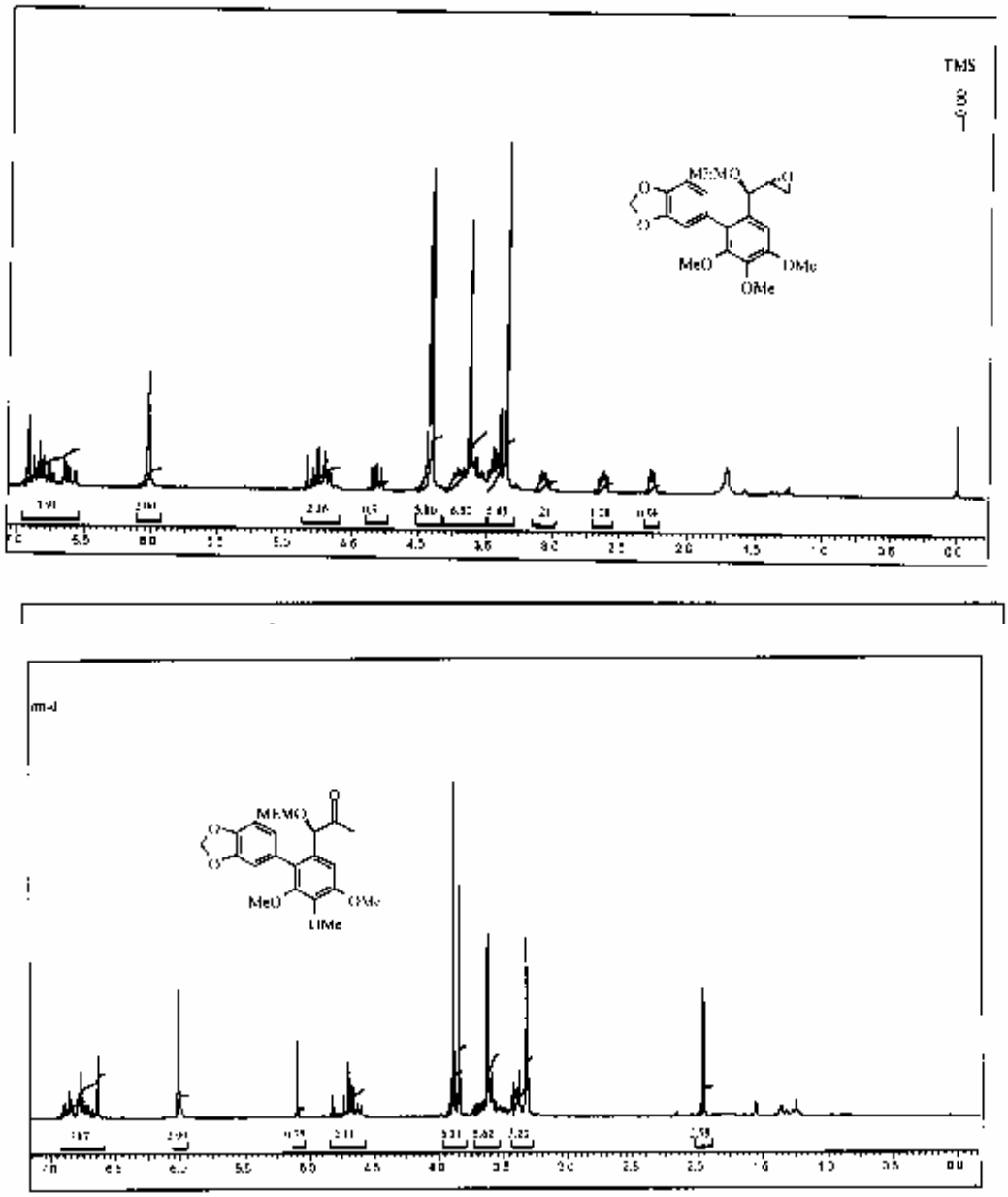
^{13}C NMR spectrum of compound 78 in $CDCl_3$



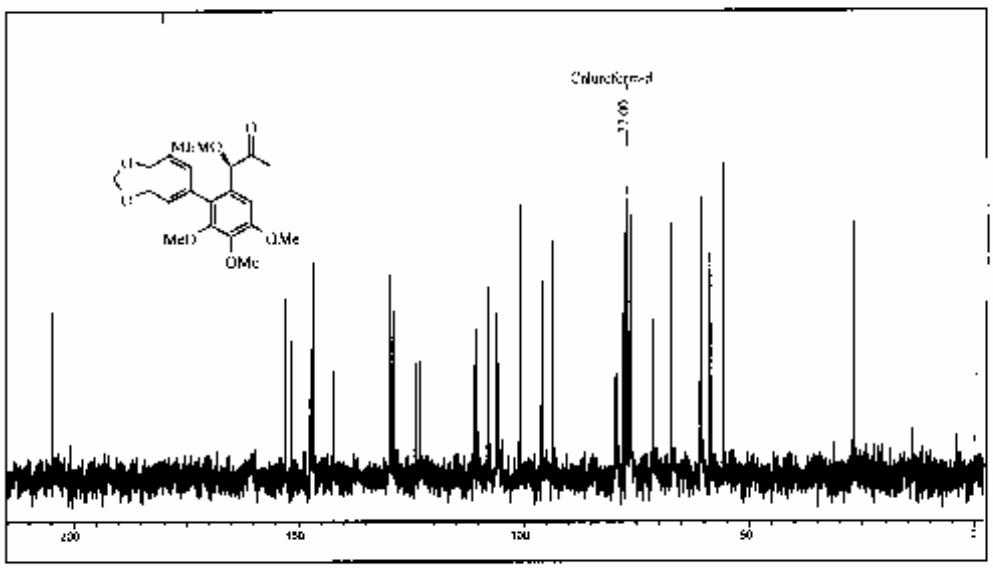
^{1}H NMR spectrum of compound 79 in $CDCl_3$



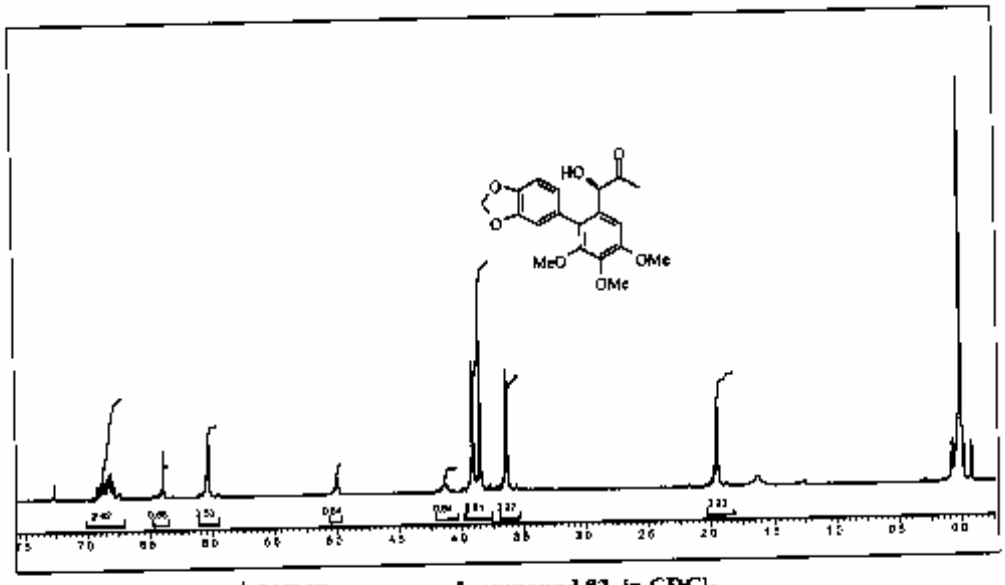
^{13}C NMR spectrum of compound 79 in $CDCl_3$



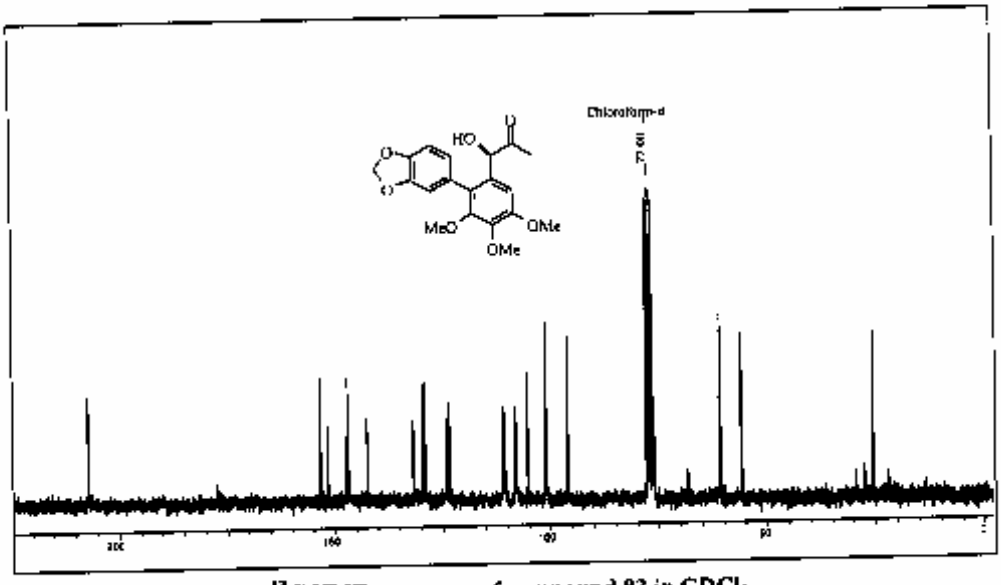
^{1}H NMR spectrum of compound 82 in $CDCl_3$



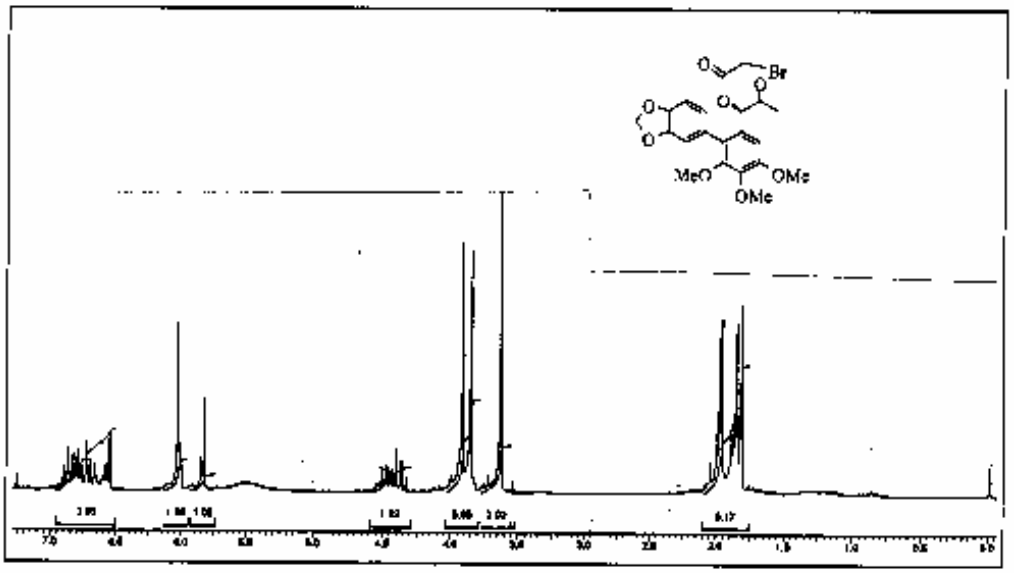
^{13}C NMR spectrum of compound 82 in $CDCl_3$



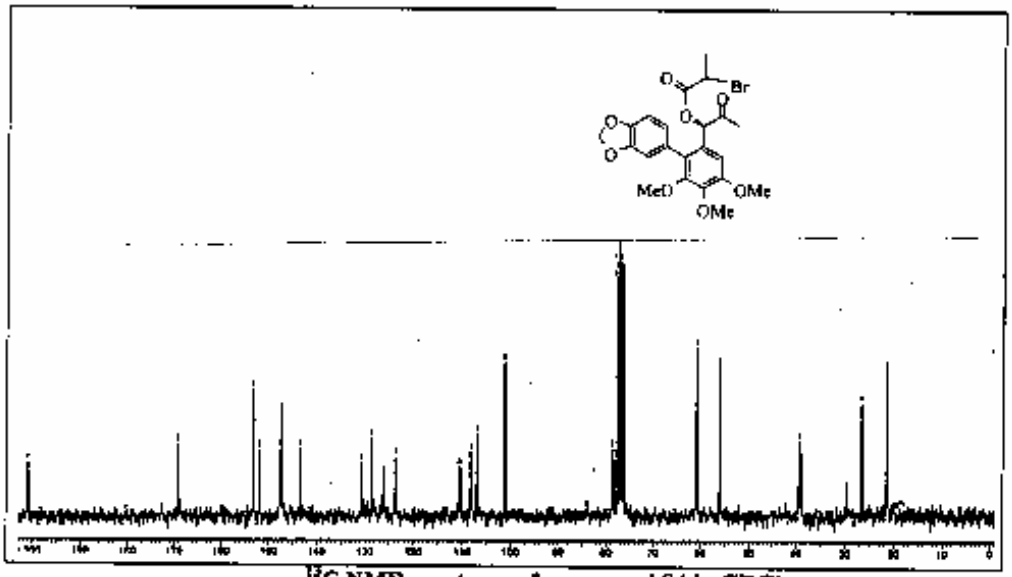
^{1}H NMR spectrum of compound 83 in $CDCl_3$



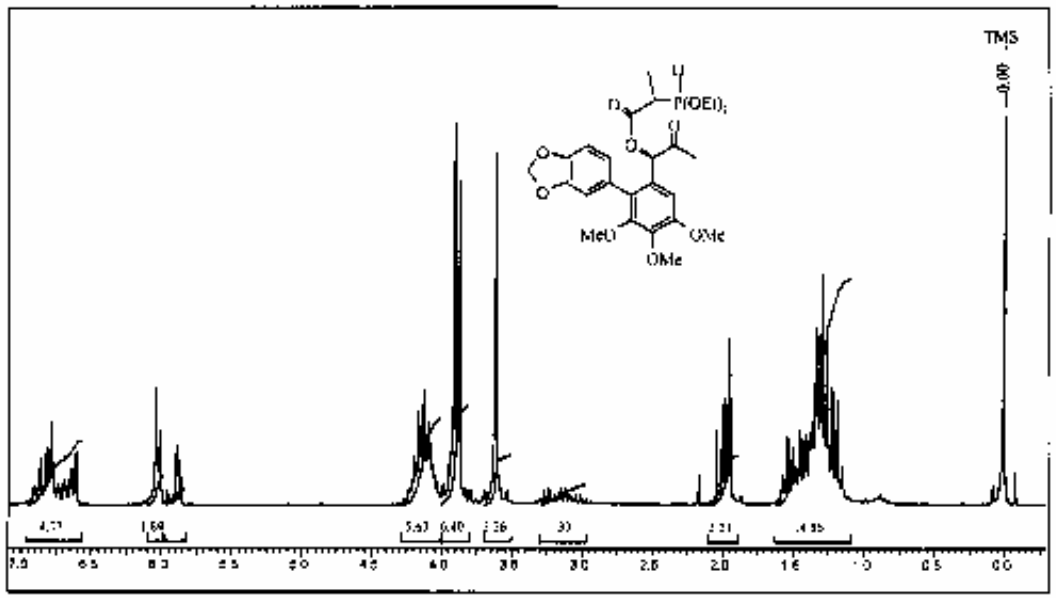
^{13}C NMR spectrum of compound 83 in $CDCl_3$



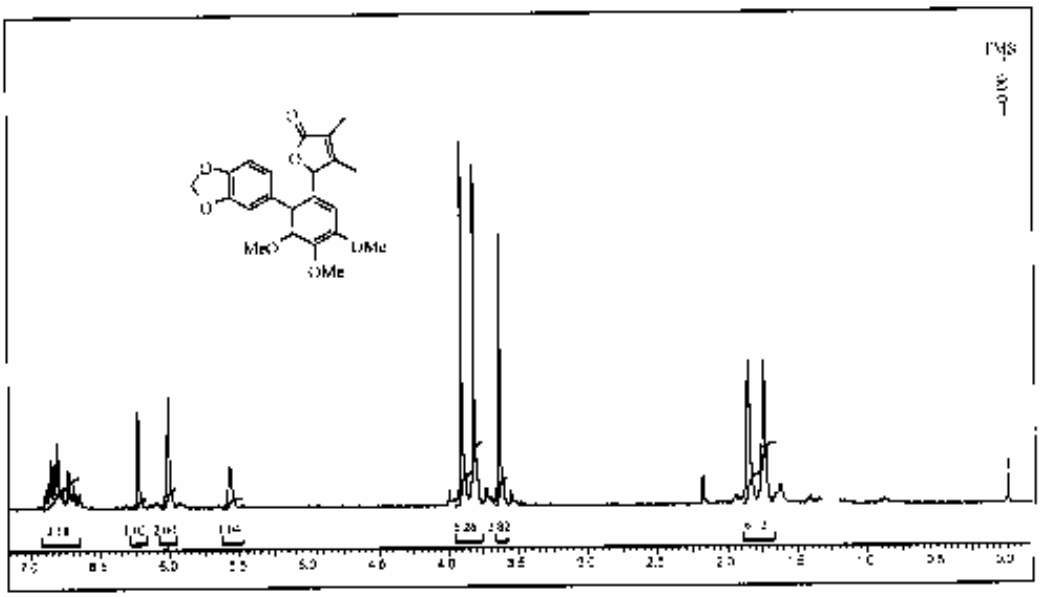
^{1}H NMR spectrum of compound 84 in $CDCl_3$



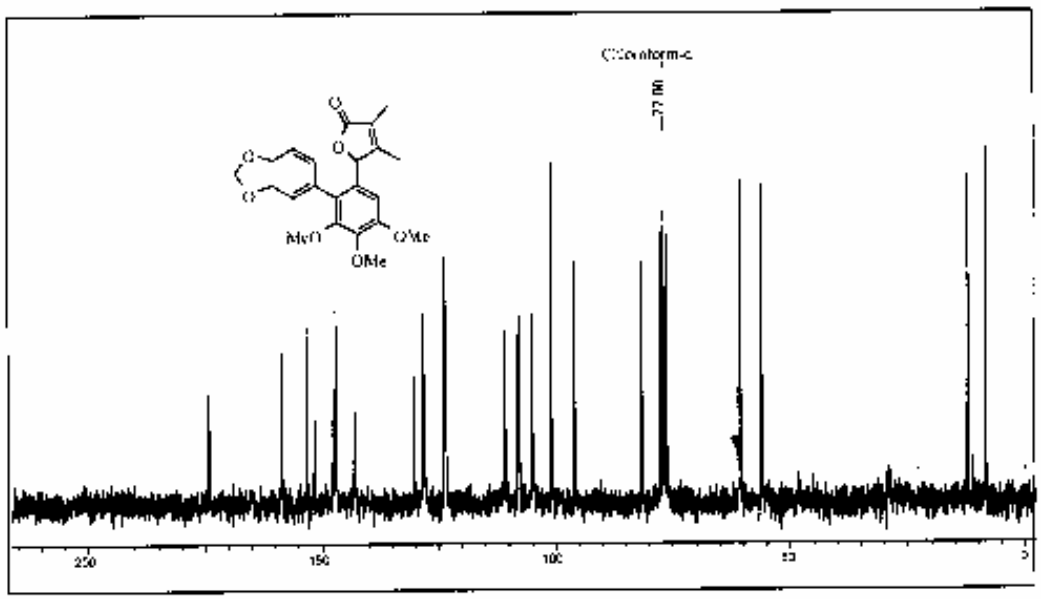
^{13}C NMR spectrum of compound 84 in $CDCl_3$



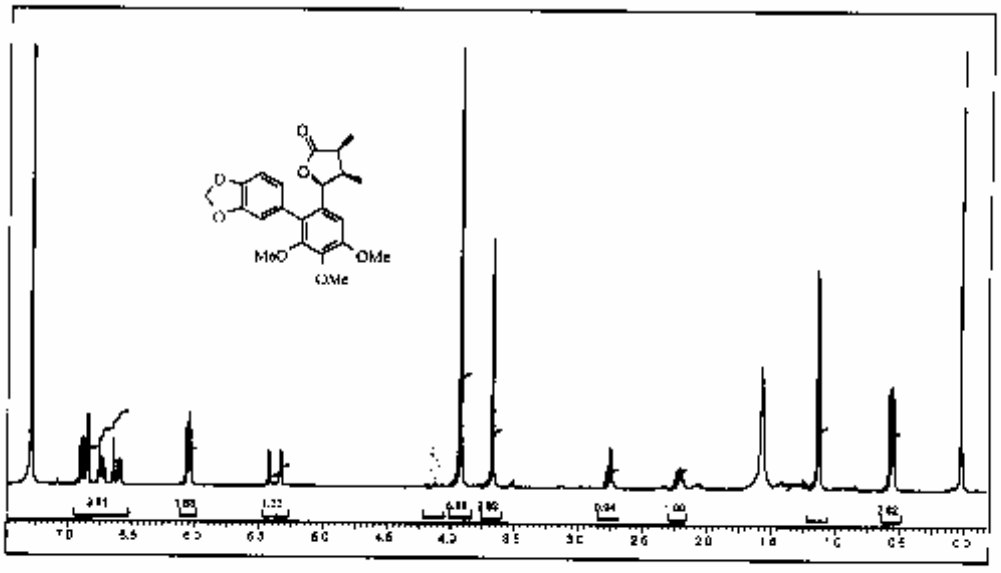
^{1}H NMR spectrum of compound 86 in $CDCl_3$



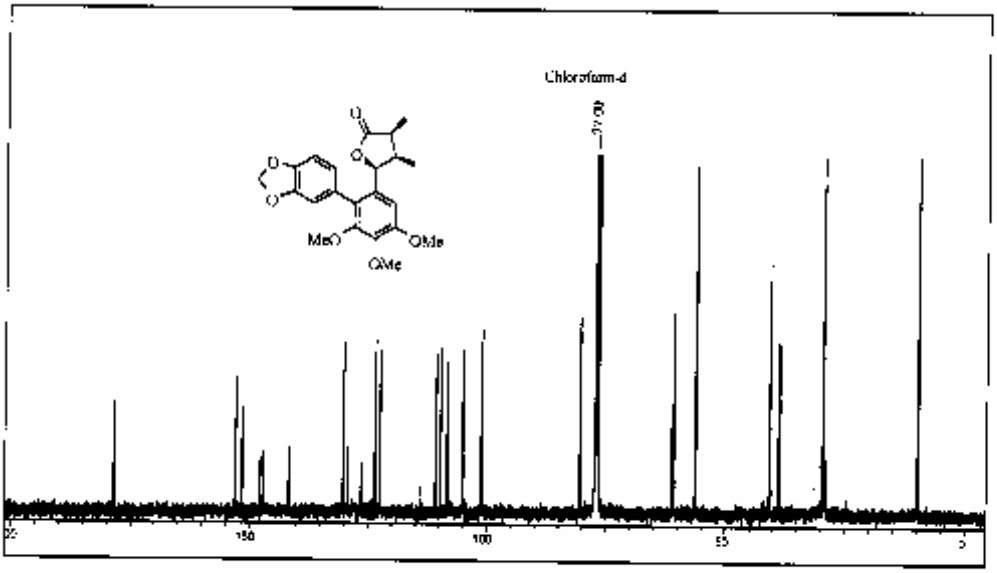
^{1}H NMR spectrum of compound 87 in $CDCl_3$



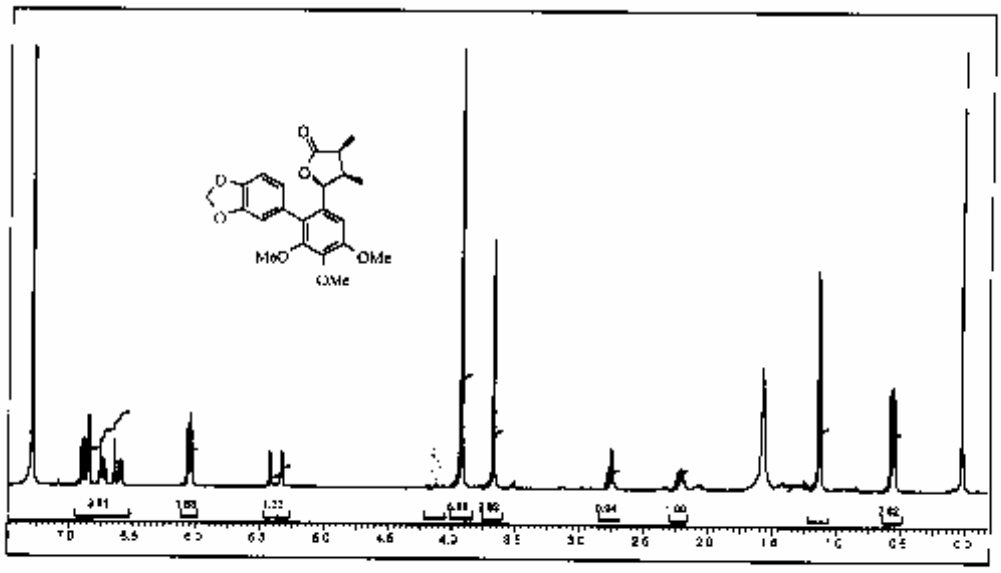
^{13}C NMR spectrum of compound 87 in $CDCl_3$



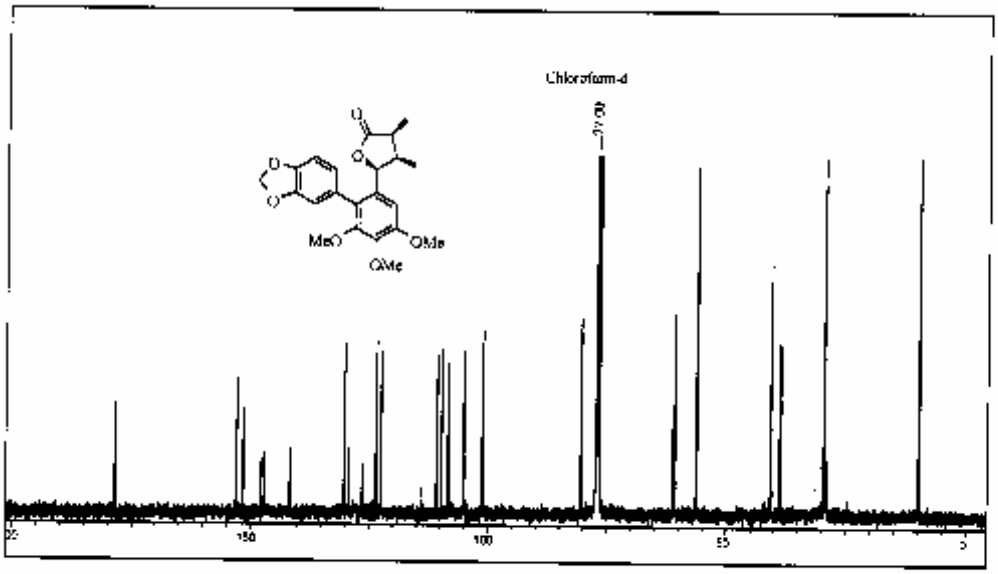
^{1}H NMR spectrum of compound 6 in $CDCl_3$



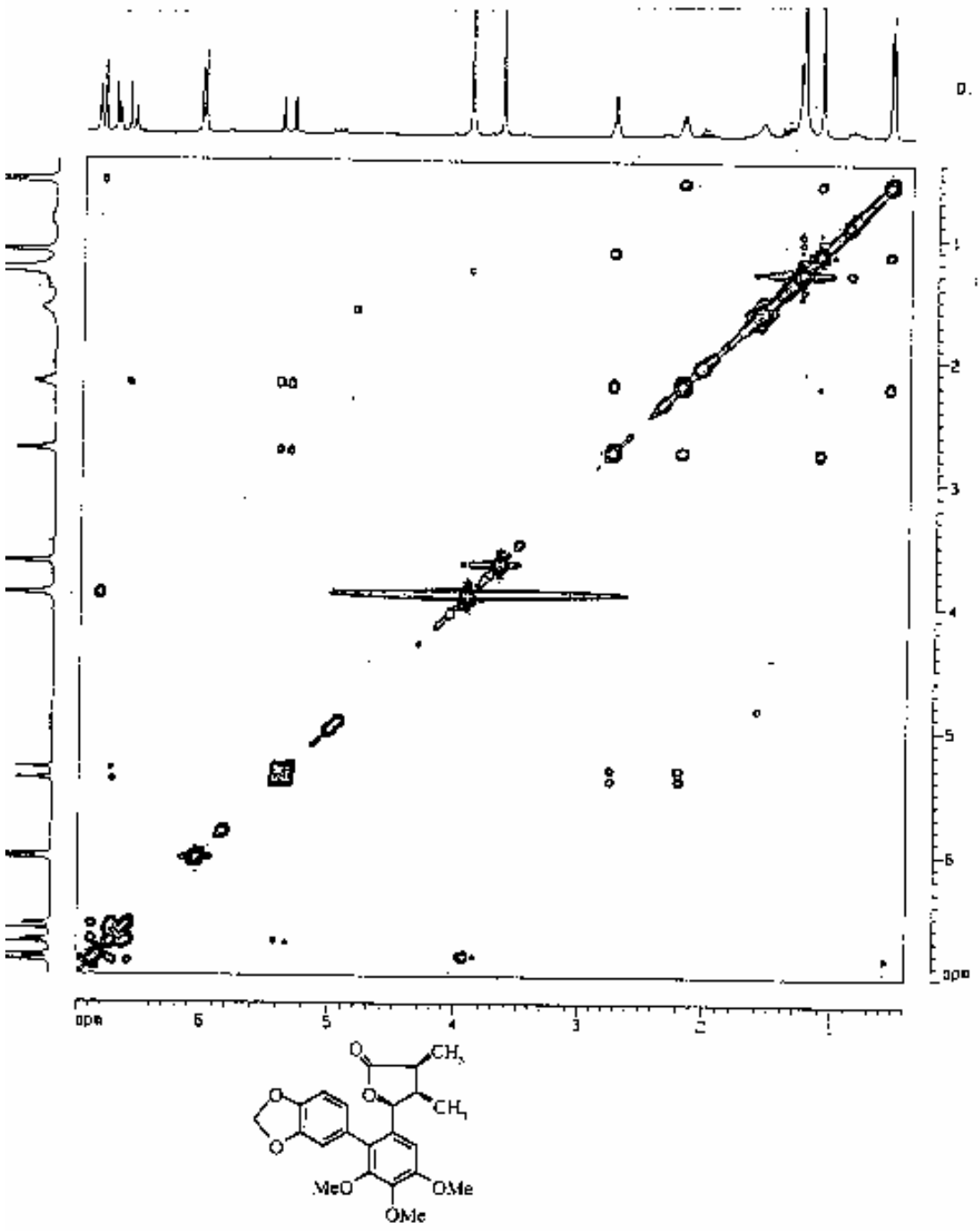
^{13}C NMR spectrum of compound 6 in $CDCl_3$



^{1}H NMR spectrum of compound 6 in $CDCl_3$



^{13}C NMR spectrum of compound 6 in $CDCl_3$



NOE studies of compound 6 in $CDCl_3$

References

1. Haworth, R. D., *Ann. Rep. Prog. Chem.* **1936**, *33*, 266.
2. Gottlieb, O. R. *Phytochemistry*, **1972**, *11*, 1544.
3. *Comprehensive Natural Product Chemistry*, Vol. 1,
4. *Studies in Natural Product Chemistry*, Vol 26, Elsvier Science
5. Cole, J. R.; Weidhopf, R. M. *Chemistry of Lignans,* (Rao C. B. S., ed), p. 307, Andhra University Press, India.
6. MacRae , W. D.; Towers, G. H. N. *Phytochemistry*, **1984**, *23*, 1207.
7. Ward, R. S. *Nat. Prod. Rep*., **1997**, *14*, 43.
8. Carroll, A. R.; Taylor, W. C. *Aust. J. Chem*., **1991**, *44*, 1705.
9. Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc*., **2001**, *123*, 4475.
10. Gao, X.; Nakadai, M.; Snider, B. M. *Org. Lett.*, **2003**, *5*, 451.
11. Torssell, K. G. B. *Natural Product Chemistry*, Wiley, Chichester, 1983; For a review on the synthesis of biaryls, see: Stanforth, S. P. *Tetrahedron*, **1998**, *54*, 263.
12. Thomson, R. H., *The Chemistry of Natural Products*, Blackie and Son., Glasgow, 1985.
13. Noyori, R. *Chem. Soc. Rev.*, **1989**, *18*, 187.
14. Cram, D. J. *Angew. Chem. Int. Ed. Engl.,* **1988**, *27*, 1009.
15. Weber, E. *J. Mol. Graphics*, **1989**, *7*, 12.
16. Mikes, F.; Boshart, G. *J. Chromatogr*. **1978**, *149*, 455.
17. Brandmeier, V.; Feigel, M.; Bremer, M. *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 486.
18. Tabushi, I.; Yamamura, K.; Nabeshima, T. *J. Am. Chem. Soc*., **1984**, *106*, 5267.
19. Yamamura, K.; Ono, S.; Tabushi, I. *Tetrahedron Lett.*, **1988**, *29*, 1797.
20. Gant, T. G.; Meyers, A. I. *Tetrahedron*, **1994**, *50*, 2297; (b) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879.
21. Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090.
22. Bringmann, G.; Menche, D. *Acc. Chem. Res*., **2001**, *34*, 615.
23. Bringmann, G.; Menche, D. *Angew. Chem. Int. Ed. Engl.,* **2001**, *40*, 1687.
24. Nicolaou, K. C.; Li, H., Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T. Y.; Matarajan, S.; Chu, X. J.; Brase, S.; Rubsam, F. *Chem. Eur. J*., **1999**, *5*, 2584.

25. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.,* **2000***, 122*, 12051.

26. Cammidge, A. N.; Crepy, K. V. I. *Chem. Commun.***, 2000***, 18*, 1723.

27. Kamikawa, T.; Hayashi**,** T. *Tetrahedron,* **1999,** *55,* 3455.

28. Lipshutz, B. H.; Liu, Z.-P. *Tetrahedron Lett.,* **1994***, 35*, 5567.

29. Kamikawa, K.; Watanabe, T.; Daimon, A.; Uemura, M. *Tetrahedron*, **2000**, *56*, 2325.

30. Tuyet, T.M.; Harada, T.; Hashimoto, K.; Hatsuda, M.; Oku, A. *J. Org. Chem*., **2000**, *65*, 1335.

31. Rao, A. V. R.; Gurjar, M. K.; Ramana, D. V.; Chheda, A. K. *Heterocycles*, **1996**, *43*, 1.

32. Hong, S.; McIntosh, M. C. *Org. Lett.*, **2002**, *4*, 19; Hong, S.; Lindsay, H. A.; Yaramasu, T.; Zhang, X.; McIntosh, M. C. *J. Org. Chem.*, **2002**, *67*, 2042.

33. Keck, G. E.; Webb, R. R. *J. Am. Chem. Soc.*, **1981**, *103*, 3173.

34. Li, J. J.; Anderson, G. D. *J. Med. Chem.*, **1995**, *38*, 4570; Li, J. J.; Anderson, G. D. *ibid*, **1996**, *39*, 1846.

35. Beugelmans, R.; Boic-Choussay, M.; Tang, Q. *J. Org. Chem.*, **1987**, *52*, 3880.

36. Suzuki coupling: Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.*, **1981**, *11*, 513.

37. Pd (0): Coulson, D. R. *Inorg. Synth.*, **1972**, *13*, 121.

38. Suzuki coupling reviews: Miyaura, N.; Suzuki, A. *Chem. Rev.*, **1995**, *95*, 2457; Matteson, D. M. *Tetrahedron*, **1989**, *45*, 1859.

39. biaryl aldehyde: Larson, E. R.; Raphael, R. A. *J. Chem. Soc. Perk. 1*, **1982**, 521.

40. Sharpless AD: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B.; *Chem. Rev.*, **1994**, *94*, 2483.

41. Dale, T. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.*, **1969**, *34*, 2543; For a review on the nmr determination of enantiomeric purity, see: Parker, D. *Chem. Rev.*, **1991**, *91*, 1441.

42. MEM protection: Corey, E. J.; Gras, J. –L.; Ulrich, P. *Tetrahedron Lett.*, **1976**, *17*, 809.

43. PDC oxidation: Corey, E. J.; Schmidt, G. *Tetrahedron Lett.*, **1979**, *20*, 399.

44. MEM deprotection.. Monti, H.; Leandri, G.; Klos-Ringuet, M.; Ocrriol, C. *Synth. Commun.*, **1983**, *13*, 1021.

45. Esterification with DCC: Neises, B.; Steglich, W. *Angew. Chem.Int. Ed. Engl.*, **1978**, *17*, 552; Hassner, A.; Alexanier, V. *Tetrahedron Lett.*, **1978**, *19*, 4475.
46. Reformatsky: Rathke, M. W. *Org. React.*, **1975**, *22*, 423; Furstner, A. *Organozinc Reagents*, p. 287, Oxford University Press, **1999**; Furstner, A. *Synthesis*, **1989**, 571.
47. Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.*, **1972**, *94*, 7178; Rieke, R. D. *Science*, **1989**, *246*, 1260; Furstner, A. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 164; For a recent paper on the production of reactive metallic powders by sonoreduction, see: Durant, A.; Delplancke, J. L.; Libert, V.; Reisse, J. *Eur. J. Org. Chem.*, **1999**, 2845.
48. Molander, G. A.; Harris, C. H. *Chem. Rev.*, **1996**, *96*, 307; Molander, G. A. *Org. React.*, **1994**, *46*, 211.
49. For a review of butenolide synthesis, see: Rao, Y. S. *Chem. Rev.*, **1976**, *76*, 625.
50. LiCl/DIPEA HWE: Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.*, **1984**, *25*, 2183: Rathke, M. W.; Nowak, M. *J. Org. Chem.*, **1985**, *50*, 2624.
51. $OsO_4/NaIO_4$ chopping of olefin: Pappo, R.; Allen, D. S.; Lemieux, R. U.; Joshnson, W. S. *J. Org. Chem.*, **1956**, *21*, 478.
52. Hydrogenation: Matsubara, J.; Nakao, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.*, **1992**, *33*, 4187.

Introduction

Olefin Metathesis

During the metathesis reaction of olefins, an interchange of the alkylidene groups between pairs of double bond takes place as shown in fig. 1. Soon after its discovery,[1] the reaction found industrial applications in the disproportionation and polymerization of olefins.[2] Classical catalyst systems are derived form early-transition metal halides (eg. SnR_4, $RAlCl_2$) in combination with oxygen containing promoters. The ill-defined character of these catalysts has prohibited extensive application in the organic synthesis. This situation changed when

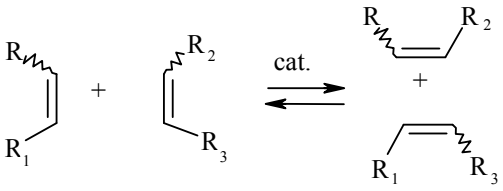
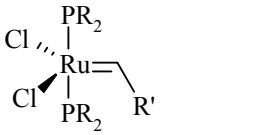


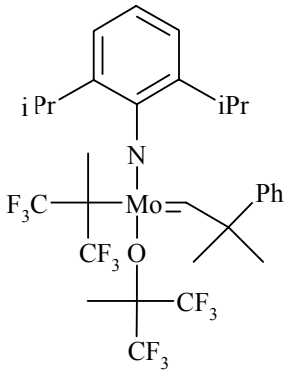
Fig. 1

Osborn,[3] Schrock[4] and Herrmann[5] introduced the first well-defined single component catalysts. These molecules represent either stabilised alkylidene metal complexes or direct



1a : R = Cy, R' = CH=CPh$_2$
1b: R = Cy, R' = Ph

Fig. 2



2

precursors thereof. Whereas the first single component catalyst were based on tungsten and rhenium, most present day applications rely on the ruthenium and molybdenum based catalysts **1** and **2** introduced by Grubbs[6] and Schrock[7] respectively. Catalyst **1** and **2** complement one another in a fortunate way. Owing to its unprecedented tolerance towards polar functional groups, **1** has boosted application in the synthesis of fuctionalized natural products. On the other hand, the less tolerant but more active **2** enables the conversion of highly substituted and otherwise sterically hindered double bonds.[8]

Since the early work of Herisson and Chauvin,[9] it has been generally agreed on that the metathesis reaction proceeds *via* a metallacyclobutane intermediate. Recently, Grubbs and co-workers[10] have obtained insight into the detailed reaction mechanism of **1**. After the displacement of one phosphine ligand by a double bond, [2+2] cycloaddition to the metallacyclobutane carbene takes place. Subsequent cycloreversion yields an alkylidene metallacyclobutane complex, in which the alkylidene moiety of the catalyst has been exchanged for one of the substrates. [2+2] cycloaddition to the second double bond of the substrate and cycloreversion result in the formation of the cyclic product still co-ordinatied to

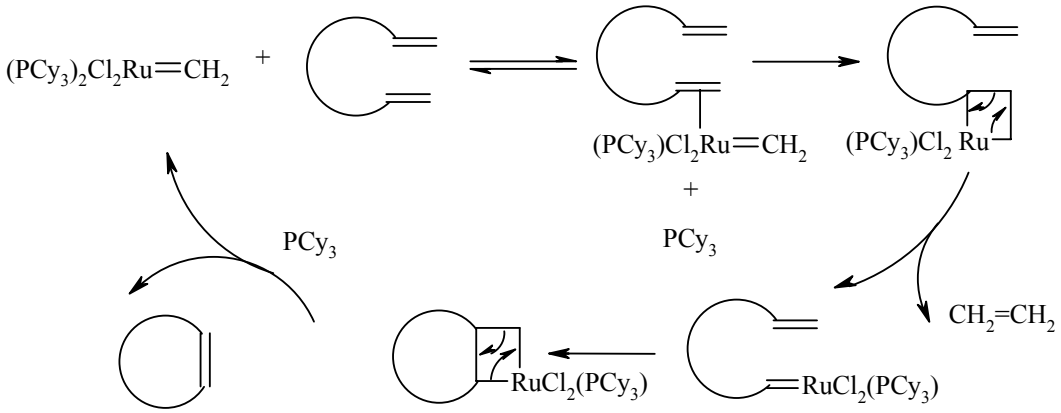


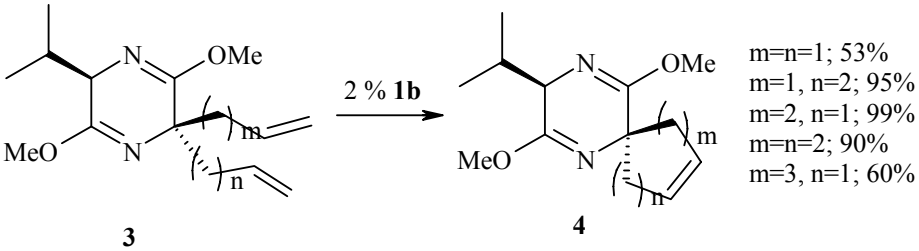
Fig. 3

the metal center. The catalyst is recycled by displacement of the product by the free phosphine. A stable metal-alkylidene intermediate in which one phosphine ligand is displaced in the proposed way was most recently isolated and characterized by Snapper and co-workers.[11]

Synthetic applications of RCM

The ring closure of diolefins competes with acyclic diene metathesis polymerization (ADMET). Thus, cyclization yields depend on various parameters such as ring size, dilution, substrate structure, catalyst and the nature of the stoichiometric byproduct (usually ethylene). Upto now, RCM has been employed for closure of five to 38 membered rings. Four membered rings are not accessible. The influence of ring size is illustrated by a recent work

Scheme 1

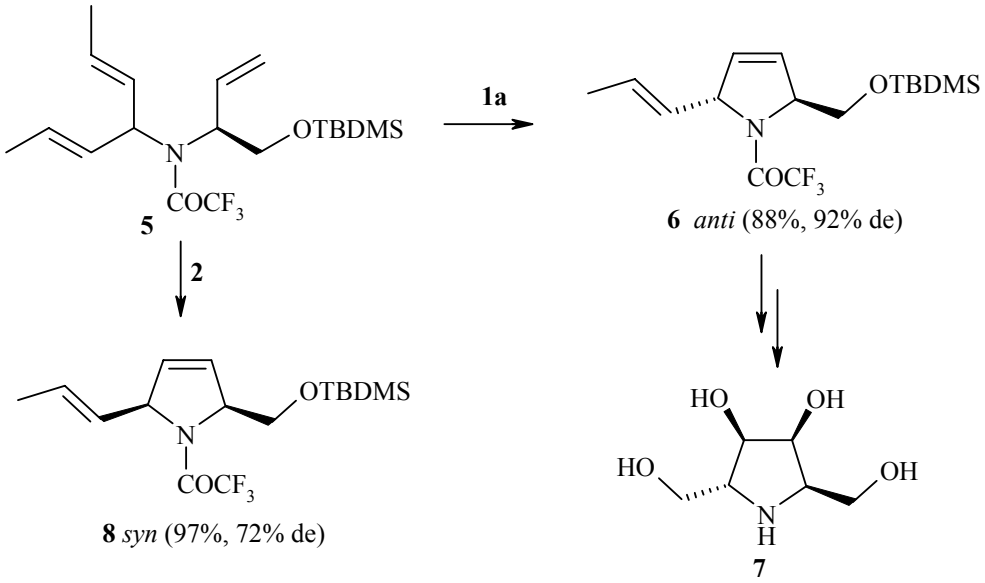


3 **4**

of Hammer and Undheim (Scheme 1).[12]

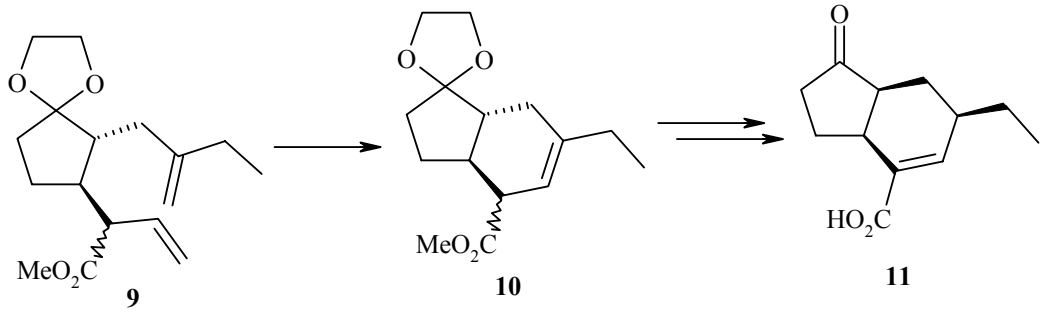
The RCM reaction serves as the key step in a steadily increasing number of natural product syntheses. Thus RCM was used for the preparation of 5 and 6 membered rings of polyhydroxylated pyrrolidine **7**[13] (Scheme 2) and of the carbocyclic coronafacic acid **11**[14] (Scheme 3). The synthesis of pyrrolidine is based on a diastereoselective metathesis reaction. The chiral center already present in

Scheme 2



the acyclic precursor **5** was shown to control the cyclisation with the prochiral diene. To ensure the primary attack on the chiral moiety, differently substituted double bonds were

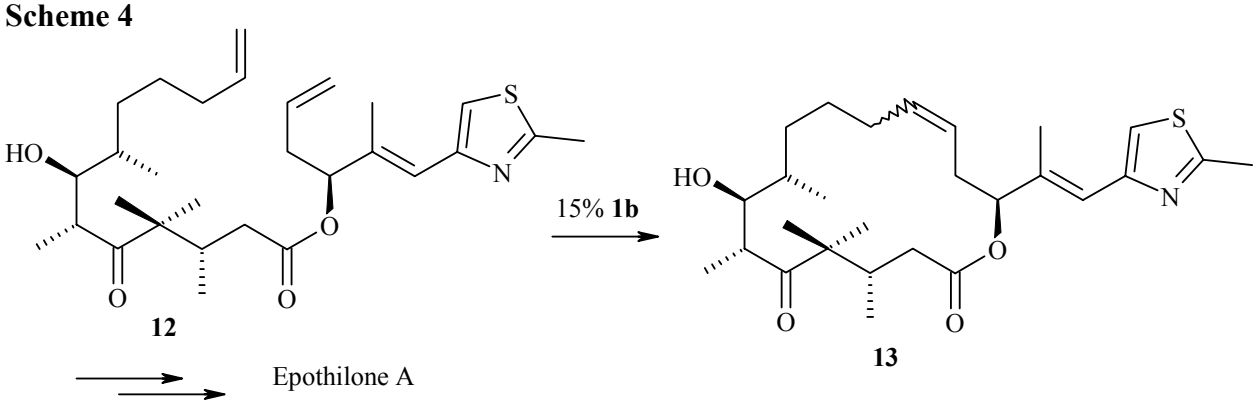
Scheme 3



used. Interestingly, the use of **1a** and **2** respectively, give rise to different diasteromer with acceptable diastereoselectivity in both cases.

A prominent metathesis application is the approach to epothilone A devised by Nicolaou *et al* (Scheme 4).[15]

Scheme 4



Ring closure of diene **12** proceeds smoothly in presence of **1b**. To avoid ADMET, the reaction was performed in highly dilution conditions. The 16-membered cyclic epothilone precursor **13** results as a mixture of *E* and *Z* isomers. This lack of stereocontrol comprises a general problem of the ring closing metathesis reaction that still remains to be solved. The alkyne variant of RCM (ACM), in which two alkynes take part provides an access for the selective synthesis of macrolides with internal *cis*-double bond (fig. 4). Partial hydrogenation

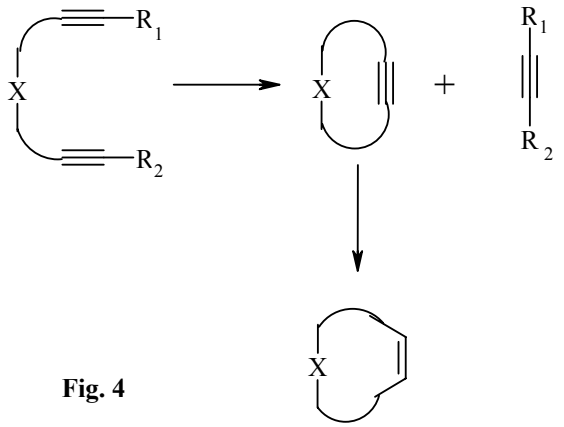


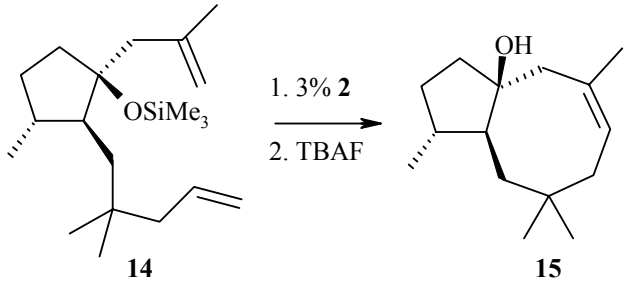
Fig. 4

(Lindlar type reduction) of the resulting alkyne leads to the formation of *cis*-olefins. [16]

The synthetic potential of RCM is best demonstrated by its application to the synthesis of medium sized rings. The synthesis of dactyol **15** by Furstner *et al*[17] relies of the highly active Molybdenum catalyst (Scheme 5).

Grubbs *et al* have studied the effect of olefin substitution on RCM of dienes.[18] They observed that the more active and less selective molybdenum alkylidene **2** does catalyze the RCM of many of the substrates for which **1** was not active. They found that: i) dienes with sterically demanding and/or electron-withdrawing substituents such as Ph, CO_2Me, and ^tBu were cyclized successfully

Scheme 5



14 **15**

with Schrock's molybdenum catalyst but did not cyclize with ruthenium catalyst **1**; ii) ruthenium alkylidene **1** will cyclize dienes with olefinic substituents as sterically demanding as isopropyl in good yield, but will not cyclize a *tert*-butyl substituted diene; iii) tetrasubstituted cyclic olefins could be formed with **2**, but not using alkylidene **1**; iv) dienes with allylic functional groups yielded functionalized cyclic olefins in excellent yields when treated with **1**; v) formation of five-membered ring is the most kinetically favorable and eight-memebered ring formation is the least favorable regardless of the alkylidene used.

Olefin metathesis has proven to be a powerful synthetic tool especially useful in the preparation of cyclic systems. The development of even more active and tolerant catalyst will provide the basis for growing application opportunities.

Section 1: Introdouction

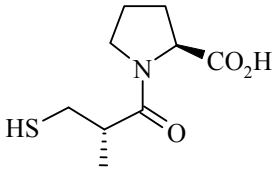
The field of amino acids has gained enormous popularity and relevance in recent years, particularly with the emergence of unnatural analogs as components of molecules with therapeutic potential.[19] The need to replace natural amino acids in peptides with non-proteinogenic counterparts in order to obtain drug-like target molecules has stimulated a great deal of innovation on several fronts.[20] Different areas of expertise have come together to allow a better understanding of interactions of small molecules with biological targets such as enzymes or receptors.[21] These efforts have led to the design of molecules as potentially useful medicinal agents often based on intriguing biological rationales and hypotheses. A scenario, in which a clinically important enzyme is co-crystallized with its natural substrate thus providing crucial and visual information for realistic drug design through synthesis of unnatural analogs, is in fact a practice of common occurrence today.[22]

One of the more exciting areas of research in drug design has been the synthesis of so called peptidomimetic molecules[20, 21] that are expected to have the same therapeutic effects as natural peptide counterparts, with the added advantage of metabolic stability. The field of peptidomimics[23] is progressing at a rapid pace and is now offering solutions to the age-old issues of bioavailability and oral activity.[24]

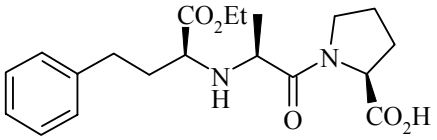
Proline is an important amino acid in many naturally occurring bioactive peptides such as gramicidin and α-melanotropin.[25] Among the 20 naturally occurring amino acids, proline is the only residue found in proteins which play an important role in the investigation of structure, receptor affinity and biological activity of amino acid chimers and peptides due to their unique structural constraints (cyclic and a secondary amine).[26]

Prolines substituted at the 4-position have been shown to enhance the thermal stability of collagen mimetic triple helices. The nature of functional group and the steric constraints imposed by the C-4 substituent can greatly influence the conformation of the pyrrolidine ring as well as the rate of *cis-trans* isomerisation about the amide bond.[27] For these reasons, preparation of 4-substituted prolines is an attractive goal in peptidomimetic chemistry. 4-substituted prolines are useful tools for the investigation of protein-peptide or protein-protein interaction as well as conformation.[28] More over, proline and its 4-substituted derivatives have been

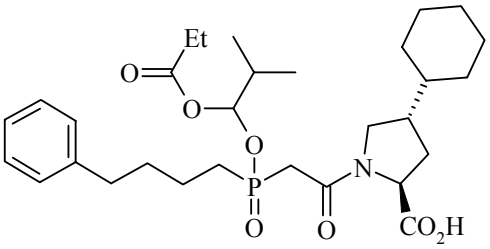
extensively used in the pharmaceutical industry as angiotensin converting enzyme (ACE) inhibitors including captopril (**16**), enalapril (**17**), fosinopril (**18**) and lisinopril (**19**), which are widely introduced to treat hypertension and congestive heart failure.[25] Intensive research in this field has led to the discovery that proline analogues with hydrophobic substituent at the 4-position showed greater activity and duration of action.[29] Prolines with a spiro-carbocycle at C-4 position are an attractive target mainly due to two reasons: i) rigid structural framework; ii) increased hydrophobic nature. Spiro-cyclopentyl proline has been found to posses greater ACE inhibitor activity.[30]



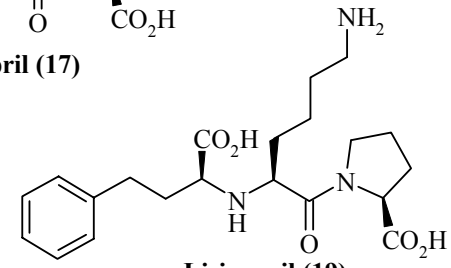
Captopril (16)



Enalapril (17)



Fosinopril (18)

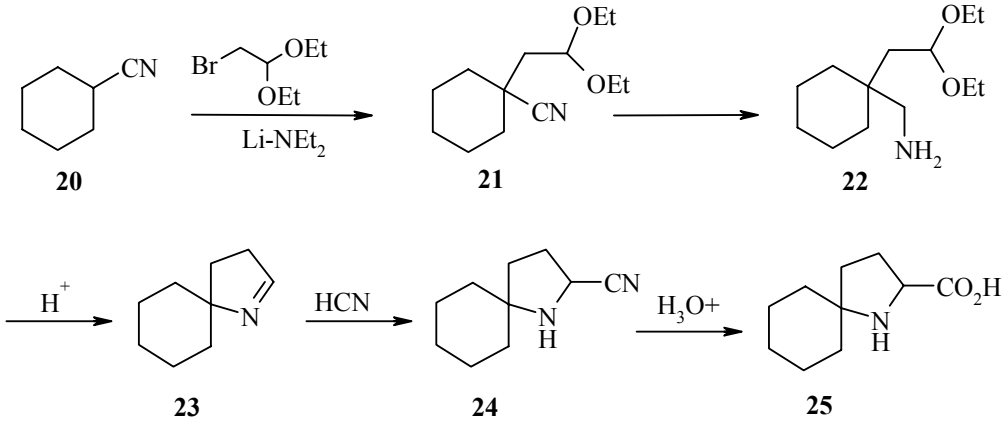


Lisinopril (19)

Angiotensin-converting enzyme (EC 3.4.15.1, ACE) is an important enzyme of the renin–angiotensin–aldosterone system.[31] It converts inactive decapeptide angiotensin-I (AI) to biologically active octapeptide angiotensin-II (AII), which raises blood pressure by vasoconstriction as well as by triggering the formation of sodium and water retaining steroidal hormone, aldosterone, in the human body. Increased serum ACE levels have been associated with hypertension and hypertension-related target organ disorders such as congestive heart failure, left ventricular hypertrophy, acute myocardial infarction and as well as in some nephrological and pulmonary disorders. Because of its clinical relevance, various research groups have been actively engaged and have highlighted different approaches in the synthesis and development of new compounds as potential ACE inhibitors such as captopril, enalapril etc. for the abovementioned disorders.

Teetz *et al*[30] reported a synthesis of racemic spiro[4.5]-2-aza-decan-3-carboxylic acid (**25**) as shown in Scheme 6 from cyanocyclohexane **20**. α-Alkylation followed by reduction of cyano to NH_2 group (**22**) and acid catalyzed cyclization afforded the spirocyclic imine (**23**). Subsequent Strecker synthesis afforded racemic [4.5]spiroproline derivative **25**.

Scheme 6

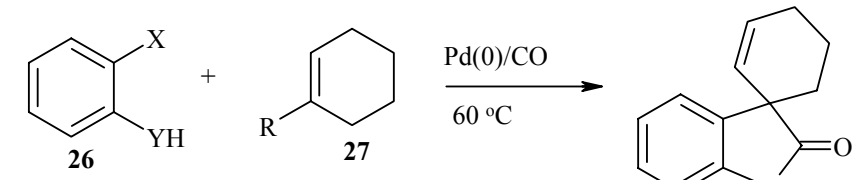


20 **21** **22** **23** **24** **25**

Several methods for the preparation of spiranes[32] have been reported. They include:

i) The palladium catalysed reaction of 2-halophenols and anilines (**26**) with vinyl halides or triflates (**27**) and CO (1 atm) generates 3-spiro-2-oxindoles and 3-spiro-2-(3H)-benzofuranones (Scheme 7).[33]

Scheme 7



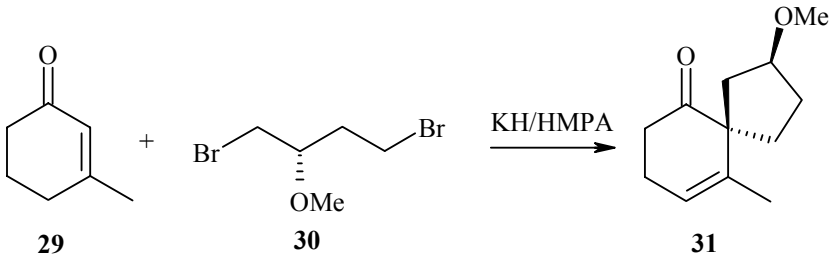
26 **27** **28**

X = I, Y = O
X = Br, Y = NH

R = I
R = OTf

ii) A stereoselective synthesis of spiro[4.5]decanone (**31**) has been achieved by the reaction of 3-methyl-2-cyclohexen-1-one **29** with 2-(*S*)-methoxy-1,4-dibromobutane **30** (Scheme 8).[34]

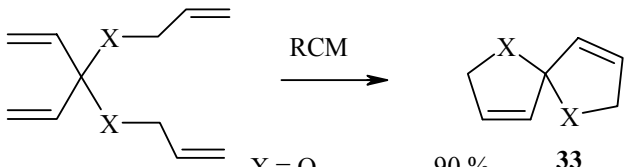
Scheme 8



29 **30** **31**

iii) Bassindale *et al*[35] have utilized tandom ring closing metathesis in the synthesis of a range of functionalised spirocyclic systems (Scheme 9). A preference for 5-membered ring closure over 7-membered ring closure was observed which appears to be a result of kinetically favoured cyclisaton process.

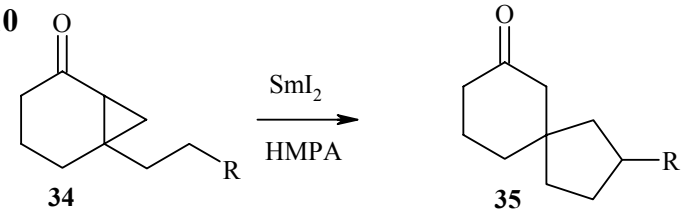
Scheme 9



32 X = O 90 % **33**
X = C 98 %

iv) The one-electron reducing agent SmI_2 mediated opening of cyclopropyl ketones followed by trapping intramolecularly the elecrophile lead to the formation of spiro systems (Scheme 10).[36]

Scheme 10

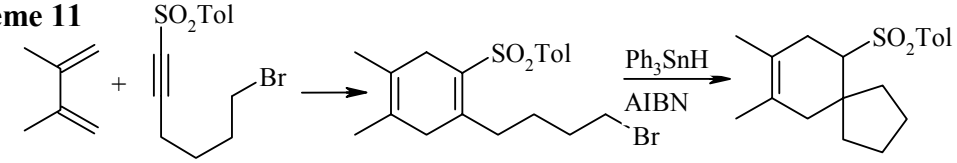


34
R = CHO
R = CO_2Et
R = 

35
R = OH
R = O, O
R = CH_2OH

v) The intramolecular Diels-Alder reaction in which either of the diene or dienophile carries a suitably located homolyzable substituents such as a phenylseleno group can undergo radical cyclization to afford spirocyclic compounds

Scheme 11

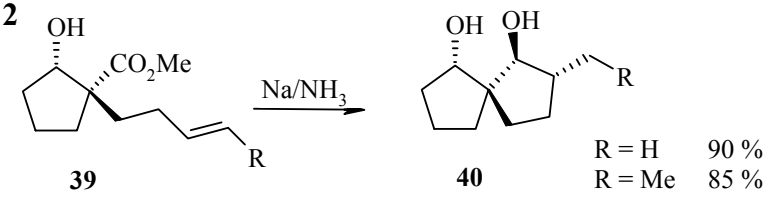


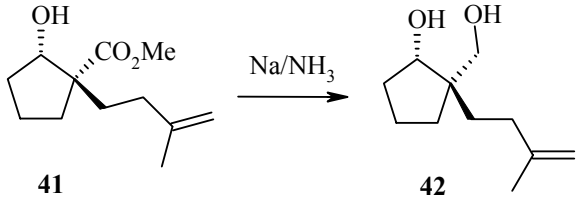
36 **37** **38**

(Scheme 11).[37]

vi) β-hydroxy-δ-ε-unsaturated carboxylate esters such as **39** when reduced with Na/NH_3 afforded spirocyclic compounds **40** in an exo-trig mode (Scheme 12). The reaction is sensitive to steric effects as evident from the reaction of **41** to yield the diol **42**.[38]

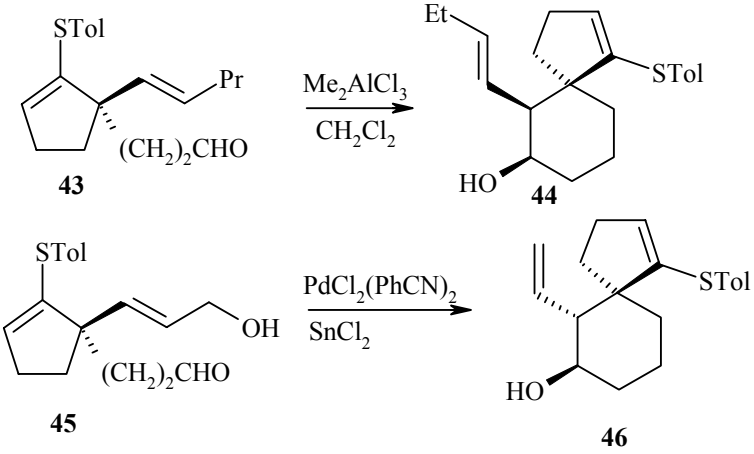
Scheme 12





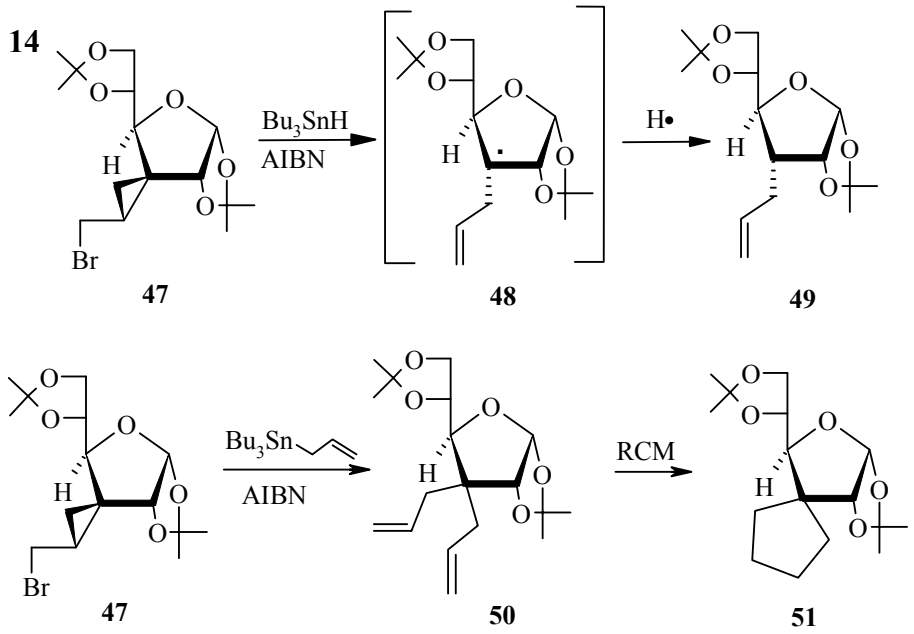
vii) Iwaka *et al*[39] reported the utilization of lewis acid mediated carbonyl ene reaction and a palladium catalysed carbonyl allylation for the synthesis of spiro skeletons **44** and **46** enroute to their formal synthesis of (+)-perhydrohistironicotoxin (Scheme 13).

Scheme 13



viii) Gurjar *et al*[40] utilized the tertiary radical formed during the radical mediated scission of cyclopropyl methyl halides/xanthates with tributyltinhydride (Scheme 14).

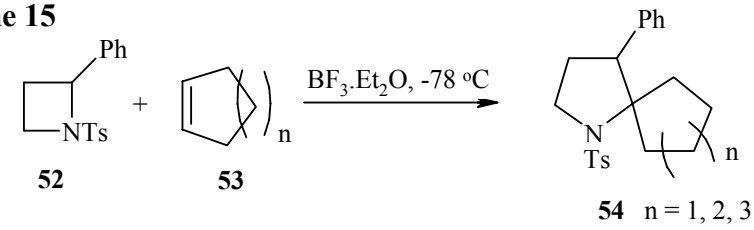
Scheme 14



Quenching of this radical with another allyl moiety lead to *gem*-diallyl systems, which underwent RCM to afford spiro skeletons. This method has found to be effective particularly in carbohydrates.

ix) Mann *et al*[41] reported that *N*-tosyl-2-phenylazetidine can be used as a 1,4-dipole and its reaction with alkenes afforded spiro-pyrrolidines by [4+2] cycloaddition (Scheme 15).

Scheme 15



Present Work

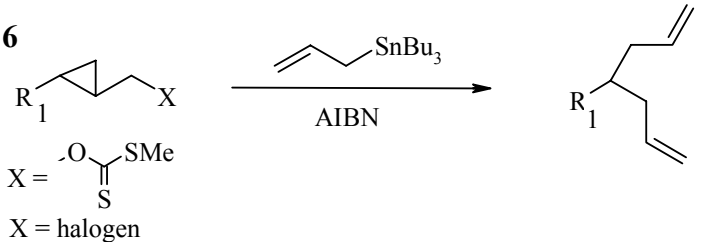
Unnatural and non-proteinogenic amino acids have become very important and attractive targets due to their intrinsic biological activities and applications as conformational modifiers for physiologically active peptides. Among amino acids, proline analogues, with their unique structural constraints play an important role in the investigation of structure, receptor affinity and biological activity of amino acids chimeras and peptides. Among the 20 naturally occurring amino acids, proline is the only residue found in proteins that is cyclic and a secondary amine providing novel constraints. Furthermore, heterocyclic pyrrolidine rings are valuable scaffolds and precursors in natural products and in drug discovery, i. e., kainoid, carbapenems, captopril and gramicidin.

The effect of the proline residue on peptide conformation has been the impetus of the design of various unnatural substituted prolines.[42] These amino acid surrogates have featured in a number of biologically active and highly ordered peptides. Prolines substituted at the 4-position have been shown to enhance the thermal stability of collagen mimetic triple helices. The nature of the functional group and steric constraints imposed by the C-4 substituent can greatly influence the conformation of pyrrolidine ring, as well as the rate of *cis* and *trans* isomerization about the amide bond.

Prolines and its 4-substituted derivatives have been extensively used in the pharmaceutical industry, such as in angiotensin-converting enzyme inhibitors (ACE). Prolines, with hydrophobic substituent at C-4 position showed enhanced activity against angiotensin converting enzyme. Prolines with a spirocarbocycle (spirocyclopentane or spirocyclohexane) at C-4 position have shown greater inhibitor activity. They are prepared in optically pure form by the resolution of racemic mixture.

Very recently, a new protocol to install *gem*-diallyl functionality on an unactivated carbon was reported from this laboratory.[40] The basic premise of this protocol has been the radical mediated ring opening reaction of cyclopropylmethylxanthate/halide with allyl-tri-n-butyltin[43] providing *gem*-diallyl derivative in high yield (Scheme 16).

Scheme 16



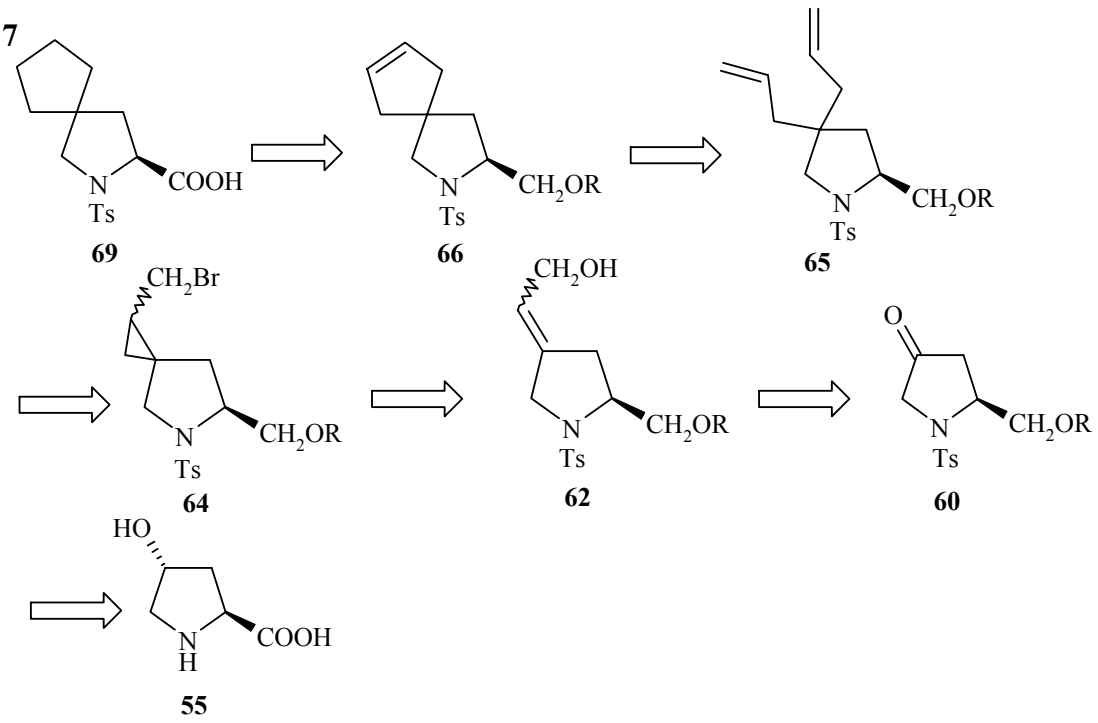
Usually installation of *gem*-diallyl group is carried out on an activated methylene in the presence of base and allyl halide.[44] This classical approach does not work on an unactivated methylene and therefore our approach as described above is significantly important.

As a part of our effort to make *gem*-diallylation a versatile approach, we identified synthesis of spiro-proline derivative (**69**) as a target molecule.

Retrosynthetic analysis

We envisaged that **69** could be obtained by hydrogenation of **66**, which in turn could be obtained by ring closing metathesis reaction of the *gem*-diallyl derivative **65**. We anticipated that the

Scheme 17



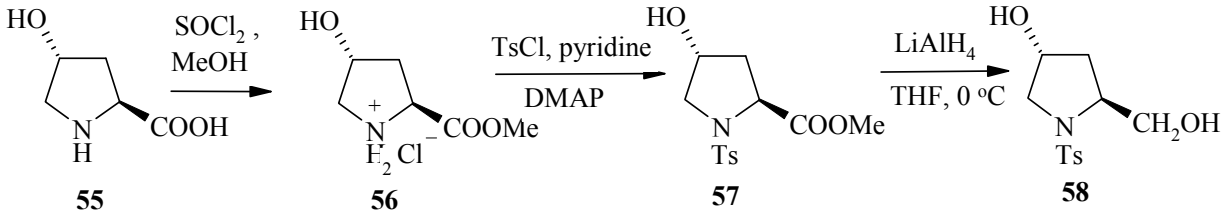
radical ring opening reaction of cyclopropylmethyl bromides with allyl-n-tributyltin leading to the formation of *gem*-diallyl substrates would work in the case of pyrrolidines as well.

Hence, the *gem*-diallyl derivative **65** could be realized by the radical opening of cyclopropyl methyl bromide **64** in presence of allyltri-n-butyltin. In turn, compound **64** would be accessible by cyclopropanation of the allylic alcohol **62** which could be prepared from the ketone **60** by two carbon Wittig homologation and reduction. A careful examination showed that the ketone **60** would be obtained from *trans*-4-hydroxy-L-proline (**55**).

The execution of this strategy is described below.

Commercially available *trans*-4-hydroxy-L-proline **55** was converted into its methyl ester derivative (**56**) by following the reported procedure[45] using $SOCl_2$ and MeOH (Scheme 18). The secondary amine in **56** was protected as its *p*-toluene sulphonate derivate **57** by

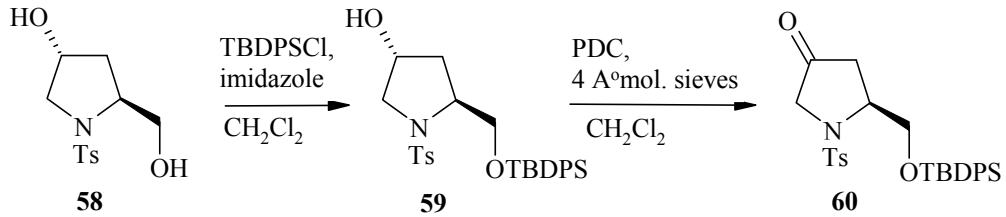
Scheme 18



treating with TsCl in pyridine in presence of DMAP.[46] In the ^{1}H NMR spectrum of **57**, aromatic protons appeared at δ 7.30 and 7.74 as doublets (J = 8.5 Hz). Reduction of the carboxylate ester group of **57** with $LiAlH_4$ afforded the diol **58**. The absence of peak due to the methyl ester and appearance of the methylene protons of CH_2OH group at δ 3.72 (multiplet) substantiated the transformation.

The primary hydroxyl group of the diol **58** was selectively protected as its TBDPS ether (**59**) using TBDPSCl in presence of imidazole in CH_2Cl_2 (Scheme 19). Oxidation of the C_4-OH to the corresponding keto derivatve **60** was accomplished using PDC[47] in CH_2Cl_2 in presence of activated

Scheme 19

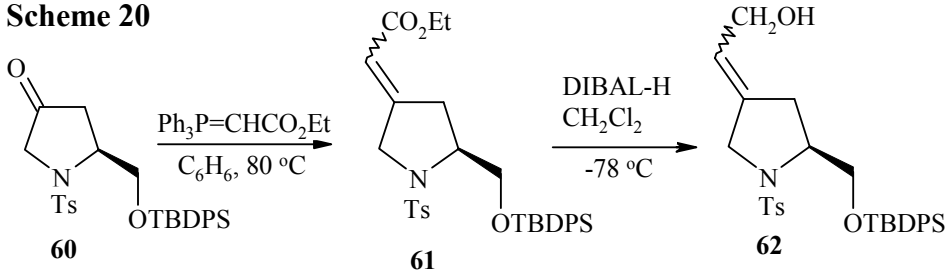


powder 4A^o molecular sieves. In the ^{1}H NMR spectrum of **60**, a downfield shift was observed in the chemical shifts of C-2 and C-4 methylenes when compared with those of **59**.

In the ^{13}C NMR spectrum of **60**, the carbonyl carbon resonated at δ 208.6. The IR spectrum ($\nu_{C=O}$ 1764 cm^{-1}) and elemental analysis further confirmed the structure of **60**.

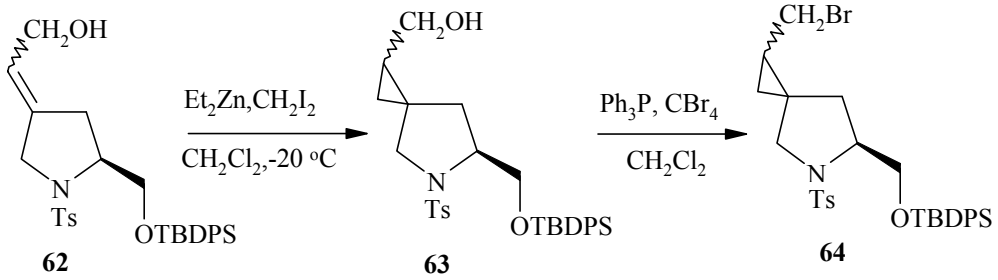
Having the 4-keto derivative **60** in hand, the next task was the synthesis of the allylic alcohol (**62**) for which two carbon Wittig homologation with $Ph_3P{=}CHCO_2Et$ was performed (Scheme 20). The product **61** was found to be a mixture of *E/Z*-isomers, not separable by silica gel column chromatography. In the ^1H NMR spectrum of **61**, two multiplets at δ 5.82 and 5.85 were attributed to the olefinic proton of the *E* and *Z* isomers respectively. All the other resonances

Scheme 20



were in agreement with the assigned structure. As it was expected not to interfere with the sequence of reactions, we decided to continue. Reduction of the α,β-unsaturated ester functionality in **61** to the corresponding allylic alcohol **62** was achieved using DIBAL-H at –78 ^oC in CH_2Cl_2.

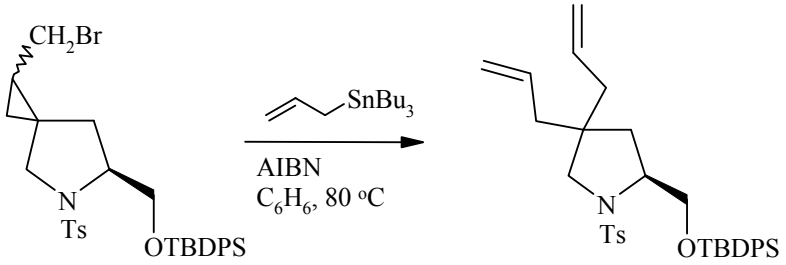
Scheme 21



Cyclopropanation with modified Simmons-Smith protocol[48] using Et_2Zn-CH_2I_2 in CH_2Cl_2 at –20 ^oC provided the cyclopropylmethanol derivative **63** as a mixture of diastereomers (Scheme 21). The ^1H and ^{13}C NMR spectra substantiated the structure of **63** by indicating multiplets at δ 0.10 and 0.45 and at 1.25 due to the cyclopropane ring protons. The next step in our synthetic plan was the conversion of compound **63** to its corresponding bromo derivative **64**, which was achieved in 80 % yield by using PPh_3 and CBr_4 in CH_2Cl_2. The ^1H and ^{13}C NMR spectra were in agreement with the structure (**64**).

The radical opening of cyclopropylmethylbromide **64**, the key reaction of the synthesis was our next concern. Thus, reaction of **64** with allyl-n-tributyltin in presence of AIBN as radical initiator in refluxing benzene resulted in the formation of *gem*-diallyl derivative **65** in 79 % yield (Scheme 22). In the ^{1}H NMR spectrum of **65**, the terminal olefinic methylene protons (=CH_2) appeared at δ 4.80 while the internal olefinic (CH=) protons resonated at δ 5.70. All the other

Scheme 22

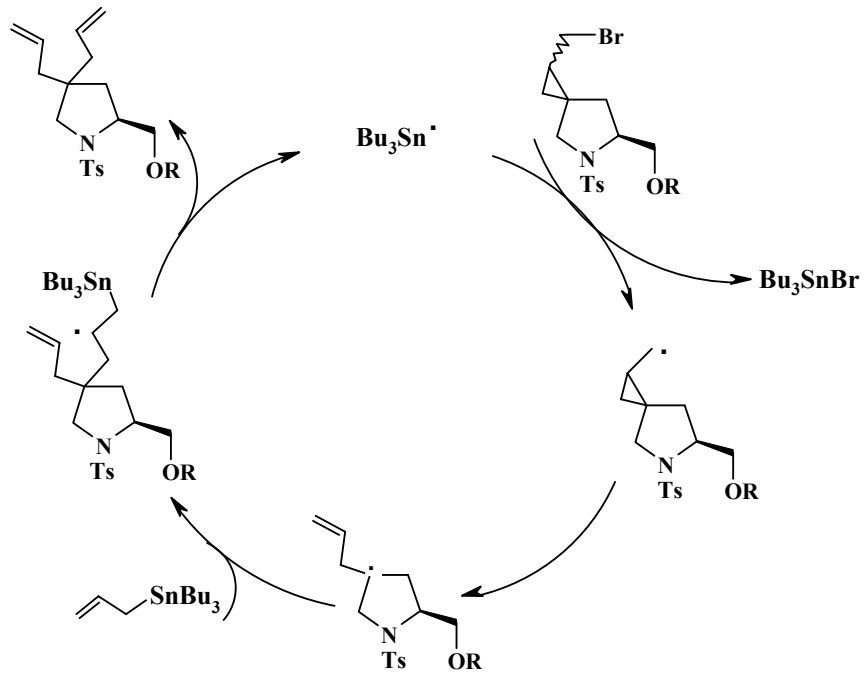


64 **65**

resonances were in agreement with the assigned structure. The structure of **65** was further substantiated by its ^{13}C NMR and mass spectral data.

The mechanism for the installaton of the *gem*-dially group starting from cyclopropyl-

Fig. 5

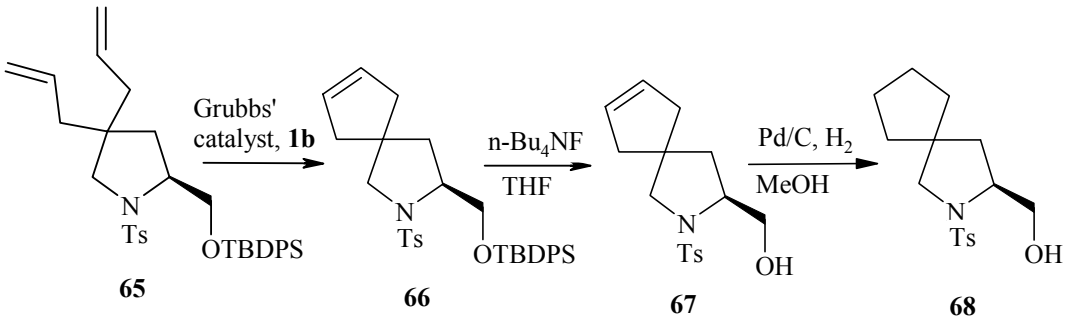


methylbromide is summarized in fig. 5. In the first step, cyclopropylmethylradical generated in the reaction from the corresponding bromo derivative rapidly isomerizes into the

corresponding tertiary homoallyl radical. In the propagation step, the tertiary radical generated adds to allyltri-n-butyltin leading to the adduct radical. Under reflux in benzene, this undergoes fragmentation reaction giving the diallyl derivative and a tributyltin radical, which propagates the cycle.

Ring closing metathesis reaction of the diene **65** with Grubbs' catalyst gave the spiro-cyclopentene pyrrolidine derivative **66** in 96% yield (Scheme 23). The ^{1}H NMR spectrum revealed the presence of multiplets at δ 5.50 and 5.60 corresponding to the internal olefinic

Scheme 23

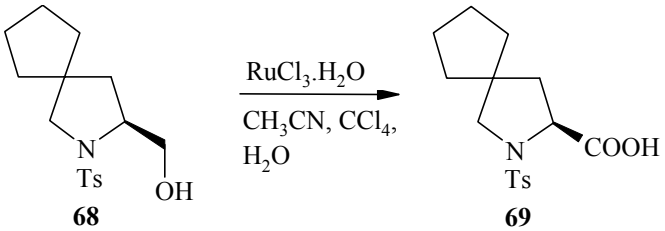


65 **66** **67** **68**

protons. All the other resonances were in agreement with the assigned structure. Deprotection of the silyl ether **66** was carried out with TBAF in THF to afford the primary alcohol **67**. Hydrogenation of compound **67** with Pd/C/H_2 in MeOH gave the saturated spirocyclopentyl prolinol **68**.

Finally the amino acid derivative **69** was obtained by the oxidation of the primary alcohol group in **68** with $RuCl_3.H_2O$ according to Sharpless's protocol.[49] Thus, compound **68** was treated with $RuCl_3.H_2O/NaIO_4$ system in CH_3CN, CCl_4 and H_2O (Scheme 24) to afford **69** in 77 % yield. ^{1}H, ^{13}C NMR, mass and IR spectral data coupled with elemental analysis confirmed the structure of the product **69**. For example, in the ^{1}H NMR spectrum, the proton on C-3 carbon appeared downfield at δ 4.20 as a triplet (J = 8.2 Hz). The C-1 protons

Scheme 24



68 **69**

appeared at δ 3.18 as an ABq (J = 9.1 Hz). In the ^{13}C spectrum of compound **69**, carbonyl

carbon appeared at δ 177.0 while the carbons of the cyclopentane ring appeared at δ 24.3, 24.5, 35.8, 36.3, 42.5 and 49.7. The IR spectra showed absorbance at 1726 (C=O) cm^{-1} characteristic of acid carbonyl group. Elemental analysis was also in support of the structure **69**.

In conclusion, an efficient synthesis of 2-aza spiro-[4.4]-nonane carboxylic acid derivative was achieved by using ring closing metathesis reaction and the radical pathway for the installation of *gem*-diallyl functionality as key steps.

Experimental

Methyl (2*S*)-4-hydroxy-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylate (57)

To a solution of **56** (5.0 g, 34.5 mmol) in pyridine (20 mL) was added TsCl (8.5 g, 44.6 mmol) at 0 ^{o}C and the mixture was stirred at rt for 4h. Pyridine was removed *in vacuo* and the residue extracted with EtOAc, washed with water, brine, dried, concentrated and crystallized from EtOAc to afford pure **57** (9.5 g, 92 %);

m. p. 118 ^{o}C

$[\alpha]_D$ –89.9 (*c* 1.2, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.99-2.44 (m, 2 H), 2.42 (s, 3 H), 3.35 (td, 1 H, *J* =1.7, 11.2 Hz), 3.58 (dd, 1 H, J = 4.4, 11.2 Hz), 3.73 (s, 3 H), 4.34 (t, 1 H, *J* = 8.3 Hz), 4.42 (m, 1 H), 7.30 (d, 2 H, *J* = 8.5 Hz), 7.74 (d, 2 H, *J* = 8.5 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5, 39.3, 53.4, 56.4, 59.4, 69.8, 127.0, 129.5, 134.7, 143.6, 172.6.

Analysis calcd. for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found: C, 51.80; H, 5.86; N, 4.34; S, 10.97 %.

(5*S*)-5-Hydroxymethyl-1-(toluene-4-sulfonyl)-pyrrolidin-3-ol (58)

To a solution of the compound **57** (9.0 g, 30.1 mmol) in THF (100 mL) at 0 ^{o}C was added $LiAlH_4$ (1.1 g, 30.1 mmol) in portions. After 3 h, excess $LiAlH_4$ was quenched by adding water (3 mL) at 0 ^{o}C. The precipitate was filtered and filtrate concentrated to afford a residue, which on purification by silica gel column chromatography with light petroleum:EtOAc (3:2) afforded **58** (7.2 g, 88 %);

$[\alpha]_D$ –51.8 (*c* 1.3, $CHCl_3$);

^{1}H NMR (200 MHz, CD_3COCD_3): δ 1.65-1.77 (m, 1 H), 2.01-2.13 (m, 1 H), 2.44 (s, 3 H), 3.19 (ddd, 1 H, *J* = 1.4, 4.6, 10.7 Hz), 3.55 (dd, 1 H, *J* = 4.6, 10.7 Hz), 3.72 (m, 3 H), 3.88 (d, 1 H, *J* = 3.9 Hz), 3.97 (t, 1 H, *J* = 5.8 Hz), 4.33-4.45 (m, 1 H), 7.42 (d, 2 H, *J* = 8.3 Hz), 7.78 (d, 2 H, *J* = 8.3 Hz);

^{13}C NMR (50 MHz, DMSO-d_6): δ 21.2, 37.4, 56.7, 60.4, 64.4, 68.1, 127.9, 129.8, 134.4, 143.3.

Analysis calcd. for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16; S, 11.82. Found: C, 53.30; H, 6.66; N, 5.37; S, 11.69 %.

(5*S*)-(5-^{t}Butyldiphenylsilyloxymethyl)-1-(toluene-4-sulfonyl)-pyrrolidin-3-ol (59)

A mixture of compound **58** (2.3 g, 8.5 mmol), TBDPSCl (2.4 mL, 9.3 mmol) and imidazole (0.64 g, 9.3 mmol) in DMF (15 mL) were stirred overnight. The reaction mixture was diluted with water, extracted with EtOEt, dried (Na_2SO_4) and concentrated. The residue was purified on a short column of silica gel by eluting with light petroleum:ethyl acetate (4:1) to afford **59** (3.0 g, 70 %);

$[\alpha]_D$ –57.4 (*c* 1.05, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 9 H), 1.73-1.85 (m, 1 H), 2.11-2.23 (m, 1 H), 2.37 (s, 3 H), 3.23-2.26 (m, 1 H), 3.44-3.56 (m, 1 H), 3.75-3.89 (m, 3 H), 4.31 (br s, 1 H), 7.20-7.73 (m, 14 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.6, 20.8, 26.1, 26.3, 37.1, 56.2, 59.0, 65.8, 69.3, 127.0, 126.8, 129.1, 132.6, 132.8, 135.0, 142.5.

MS (EI) m/z: 509 (M^+), 452 (M^+ - ^{t}Bu).

Analysis calcd. for $C_{28}H_{35}NO_4SSi$: C, 65.98;, H, 6.92; N, 2.75; S, 6.29. Found: C, 65.75; H, 7.13; N, 2.48; S, 6.53 %.

(5*S*)-(5-^{t}Butyldiphenylsilyloxymethyl)-1-(*p*-toluenesulfonyl)-pyrrolidin-3-one (60)

A mixture of compound **59** (3.0 g, 5.9 mmol), PDC (3.0 g, 8.0 mmol) and powdered molecular sieves 4A^{o} (3.0 g) in CH_2Cl_2 (100 mL) were stirred at rt for 4 h. The mixture was filtered through a bed of silica gel with EtOEt as an eluent, concentrated and crystallized from $CHCl_3$ to give **60** (2.6 g, 87 %);

m. p. 144 ^{o}C;

$[\alpha]_D$ +34.0 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.00 (s, 9 H), 2.27-2.31 (m, 2 H), 2.42 (s, 3 H), 3.58 (dd, 1 H, *J* = 2.5, 10.3 Hz), 3.82 (d, 2 H, *J* = 3.9 Hz), 4.00 (dd, 1 H, *J* = 2.5, 10.3 Hz), 4.27-4.35 (m, 1 H), 7.27-7.70 (m, 14 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.0, 21.5, 26.6, 40.0, 54.0, 58.0, 67.9, 127.0-143.8, 208.6;

MS (EI) m/z 450 (M^+ - ^{t}Bu).

IR ($CHCl_3$) 1764 cm^{-1} (C=O).

Analysis calcd. for $C_{28}H_{33}NO_4SSi$: C, 66.24; H, 6.55; N, 2.76; S, 6.32. Found: C, 66.03; H, 6.68; N, 2.66; S, 6.46 %.

(5*S*,2*EZ*)-[(5-^{t}Butyldiphenylsilyloxymethyl)-1-(toluene-4-sulfonyl)-pyrrolidin-3-ylidene]-ethanol (62)

A solution of compound **60** (4.0 g, 7.9 mmol) and $Ph_3P{=}CHCO_2Et$ (5.48 g, 15.8 mmol) in benzene (25 mL) was heated under reflux for 24 h. Solvent was removed and the residue passed through a short column of silica gel eluting with light petroleum-ethyl acetate (19:1) to give the α,β-unsaturated ester **61** (4.2 g, 7.3 mmol) as an *E, Z* mixture which was taken in CH_2Cl_2 (100 mL) at –78 ^{o}C and DIBAL-H (2 M solution in toluene, 9.0 mL, 18.0 mmol) was introduced. After stirring at –78 ^{o}C for 45 min., excess DIBAL was quenched by addition of saturated solution of sodium potassium tartrate. The mixture was stirred at rt for 3 h, filtered, concentrated and the product purified on silica gel by eluting with light petroleum:ethyl acetate (4:1) to give **62** (3.6 g, 86 %);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (s, 9 H), 2.14-2.69 (m, 2 H), 2.43 (s, 3 H), 3.48-4.02 (m, 7 H), 5.43 (m, 1 H), 7.20-7.74 (m, 14 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.0, 21.2, 26.6, 30.2, 34.6. 49.1, 52.7, 59.6, 60.6, 65.7, 66.1, 121.5-137.4, 143.1;

MS (EI) m/z 478 (M^+ - ^{t}Bu).

Analysis calcd. for $C_{30}H_{37}NO_4SSi$: C, 67.25; H, 6.96; N, 2.61; S, 5.98. Found: C, 67.59; H, 7.12; N, 2.44; S, 5.78 %;

(6*S*)-{6-((^{t}Butyldiphenylsilyloxymethyl)-5-(toluene-4-sulfonyl)-5-aza-spiro[2.4]hept-1-yl}methanol (63)

To a solution of the compound **62** (3.0 g, 5.8 mmol) in CH_2Cl_2 (30 mL) at –20 ^{o}C was added Et_2Zn (1 M solution in toluene, 16.8 mL, 16.8 mmol) carefully followed by dropwise addition of CH_2I_2 (2.7 mL, 33.5 mmol) and the temperature was maintained overnight. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl and diluted with CH_2Cl_2. Organic layer was separated, dried (Na_2SO_4), evaporated and the residue purified on silica gel by eluting with light petroleum:EtOAc (4:1) to afford **63** (2.4 g, 78 %);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09-0.11 (m, 1 H), 0.43-0.45 (m, 1 H), 0.75-2.0 (m, 3 H), 1.11 (s, 9 H), 2.44 (s, 3 H), 3.07-4.25 (m, 7 H), 7.30 (m, 14 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.0, 21.2, 24.1, 24.6, 26.8, 30.6, 37.0, 51.0, 56.6, 60.5, 60.7, 62.5, 63.1, 65.5, 127.5-135.4, 143.0;

MS (EI) m/z: 548 (M^+ - 1).

Anal. Calcd. for $C_{31}H_{39}NO_4SSi$: C, 67.72; H, 7.15; N, 2.55; S, 5.83. Found: C, 67.56; H, 7.02; N, 2.37; S, 5.91 %;

(6*S*)-1-Bromomethyl-6-(^{t}butyldiphenylsilyloxymethyl)-5-(toluene-4-sulfonyl)-5-aza-spiro[2.4]heptane (64)

To a solution of the compound **63** (2.5 g, 4.5 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC was added Ph_3P (2.4 g, 9.1 mmol) and CBr_4 (3.0 g, 9.1 mmol). The mixture was stirred at the same temperature for 30 min, evaporated and the residue purified by silica gel chromatography eluting with light petroleum:EtOAc (9:1) to afford **64** (2.2 g, 80 %);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.17-0.20 (m, 1 H), 0.42-0.45 (m, 1 H), 0.58-0.60 (m, 1 H), 1.10 (s, 9 H), 1.63-1.72 (m, 2 H), 2.40 (s, 3 H), 3.05-3.78 (m, 4 H), 3.74-3.89 (m, 2 H), 4.03 (m, 1 H), 7.23-7.77 (m, 14 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.9, 19.2, 23.4, 25.3, 28.0, 29.1, 31.3, 34.0, 34.3, 37.1, 56.6, 60.6, 61.1, 65.5, 66.2, 127.6, 127.7, 129.5, 129.7, 133.5, 135.1, 135.6, 143.2.

MS (EI) m/z: 556 (M^+ - 1).

(2*S*)-(2-^{t}Butyldiphenylsilyloxymethyl)-4,4′-diallyl-1-(toluene-4-sulfonyl)-pyrrolidine (65)

A solution of the compound **64** (1.0 g, 1.7 mmol), allyltributyl tin (1.1 mL, 3.4 mmol) and AIBN (20 mg) in toluene (10 mL) were thoroughly degassed with argon and heated at reflux. After 8 h, the reaction mixture was evaporated and the residue purified on silica gel using light petroleum:EtOAc (19:1) to afford **65** (0.74 g, 79 %);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 9 H), 1.56-1.79 (m, 2 H), 1.81 (dd, 2 H, *J* = 3.1, 6.3 Hz), 2.06 (d, 2 H, *J* = 6.3 Hz), 2.38 (s, 3 H), 3.16 (ABq, 2 H, *J* = 10.9 Hz), 3.56-3.66 (m, 1 H), 3.79 (dd, 1 H, *J* = 6.7, 10.1 Hz), 4.01 (dd, 1 H, *J* = 3.3, 10.1 Hz), 4.69-5.03 (m, 4 H), 5.47-5.79 (m, 2 H), 7.13-7.62 (m, 14 H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.25, 21.4, 26.9, 38.85, 39.4, 40.7, 43.7, 58.2, 60.0, 66.3, 118.2, 127.3-136.0, 142.9;

MS (EI) m/z 516 (M^+ - ^{t}Bu).

(3*S*)-(3-^{t}Butyldiphenlsilyloxymethyl)-2-(toluene-4-sulfonyl)-2-azaspiro[4.4]non-7-ene (66)

To a solution of the compound **65** (0.7 g, 1.2 mmol) in CH_2Cl_2 (10 mL) was added Grubbs' catalyst (50 mg, 0.06 mmol) and the mixture stirred at rt for 1h. Solvent was evaporated and

the residue purified on silica gel eluting with light petroleum:ethyl acetate (9:1) to afford **66** (0.64 g, 96 %);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9 H), 1.76-2.28 (m, 6 H), 2.43 (s, 3 H), 3.19 (ABq, 2 H, *J* = 9.5 Hz), 3.60 (m, 1 H), 3.69 (t, 1 H, *J* = 8.3 Hz), 4.11 (dd, 1 H, *J* = 3.2, 9.5 Hz), 5.48-5.52 (m, 1 H), 5.58-5.61 (m, 1 H), 7.2-7.7 (m, 14 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.8, 22.1, 27.5, 42.6, 43.8, 44.8, 48.0, 61.2, 61.7, 67.0, 128.1-136.1, 141.7.

Anal. Calcd. for $C_{32}H_{39}NO_4SSi$: C, 70.42; H, 7.20; N, 2.57; S, 5.87. Found: C, 70.63; H, 7.46; N, 2.68; S, 5.93 %.

(3*S*)-[2-(Toluene-4-sulfonly)-2-aza-spiro[4.4]non-7-ene-3-yl]-methanol (67)

A solution of the compound **66** (0.6 g, 1.1 mmol) was treated with n-Bu_4NF (1 M solution in THF, 1.4 mL, 1.4 mmol) in THF (5 mL) at rt for 1 h. Solvent was removed and the residue purified on a short silica gel column using light petroleum – ethyl acetate (4:1) to give **67** (0.31 g, 93 %);

$[\alpha]_D$ –38.0 (*c* 0.7, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50-1.87 (m, 4 H), 2.29-2.35 (m, 2 H), 2.48 (s, 3 H), 3.32 (ABq, 2 H, *J* = 9.7 Hz), 2.57-3.69 (m, 1 H), 3.76 (brd, 2 H), 5.41-5.46 (m, 1 H), 5.57-5.62 (m, 1 H), 7.35 (d, 2 H, *J* = 7.7 Hz), 7.74 (d, 2 H, *J* = 7.7 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.3, 42.1, 42.5, 43.4, 46.8, 61.4, 62.1, 65.5, 127.4-129.4, 143.4;

Analysis calcd. for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56; S, 10.43 %. Found: C, 62.70; H, 7.02; N, 4.19; S, 10.26 %;

MS (EI) m/z 292 (M^+ - 1).

(3*S*)-[2-(Toluene-4-sulfonyl)-2-aza-spiro[4.4]non-3-yl]-methanol (68)

Compound **67** (0.155 g, 0.5 mmol) and 10 % Pd/C (0.02 g) in methanol (5 mL) were stirred under hydrogen atmosphere at ntp for 3 h. The catalyst was filtered and the filtrate concentrated to give **68** (0.15 g, 96 %);

$[\alpha]_D$ –15.0 (*c* 0.7, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.64-0.98 (m, 2 H), 1.42-1.62 (m, 6 H), 1.69-1.80 (m, 2 H), 2.46 (s, 3 H), 3.23 (ABq, 2 H, *J* = 9.5 Hz), 3.58-3.73 (m, 1 H), 3.78 (brs, 2 H), 7.35 (d, 2 H, *J* = 7.6 Hz), 7.73 (d, 2 H, *J* = 7.6 Hz);

^{13}C NMR (50 MHz, $CDCl_3$):δ 21.3, 24.1, 35.9, 36.4, 41.2, 48.0, 60.5, 62.2, 65.7, 127.3, 129.4, 133.9, 143.5

Analysis calcd.for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53; S, 10.36. Found: C, 61.93; H, 7.76; N, 4.39; S, 10.39 %.

(3*S*)-2-(Toluene-4-sulfonyl)-2-aza-spiro[4.4]nonane-3-carboxylic acid (**69**).

A mixture of **68** (0.31 g, 1.0 mmol), CH_3CN (2 mL), CCl_4 (2 mL), H_2O (2 mL), $NaIO_4$ (0.64g, 3.0 mmol) and $RuCl_3(H_2O)_n$ (4.0 mg, 2.2 mol%) were vigorously stirred at rt for 2 h. The reaction mixture was filtered through a pad of celite, filtrate concentrated and the residue purified on silica gel eluting with light petroleum:EtOAc (1:4) afforded **69** (0.1 g, 77 %);

$[\alpha]_D$ –67.0 (*c* 0.7, $CHCl_3$);

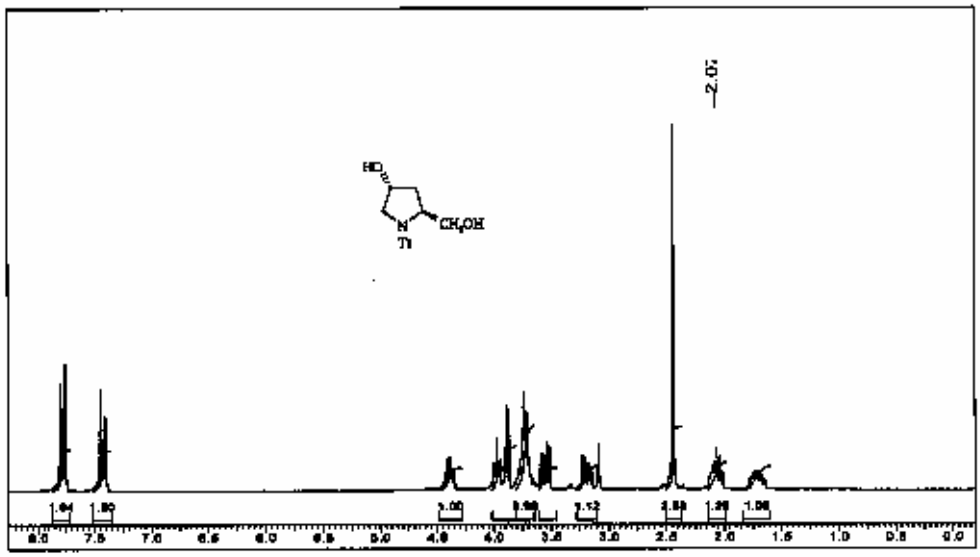
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17-1.24 (m, 2 H), 1.43-1.62 (m, 6 H), 2.02-2.05 (m, 2 H), 2.41 (s, 3 H), 3.18 (ABq, 2 H. *J* = 9.1 Hz), 4.20 (t, 1 H, *J* = 8.2 Hz), 7.29 (d, 2 H, *J* = 9.1 Hz), 7.73 (d, 2 H, *J* = 9.1 Hz), 10.7 (br. s, 1 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 24.3, 24.5, 35.8, 36.3, 42.5, 49.7, 59.1, 60.4, 127.6, 129.6, 134.7, 143.6, 177.0;

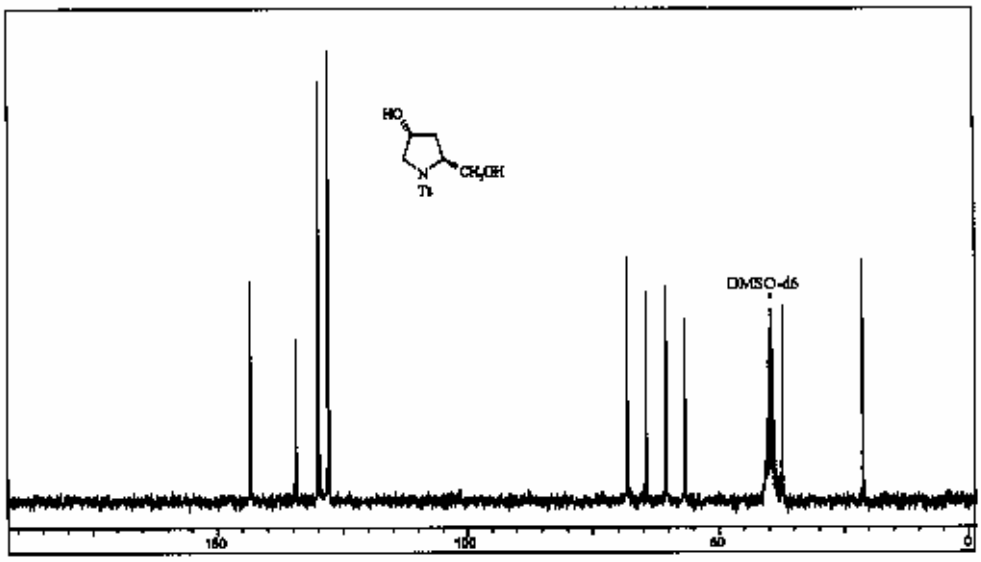
MS (EI) m/z 278 (M^+ - CO_2).

IR ($CHCl_3$) 1726 (C=O), 3012 cm^{-1} (OH).

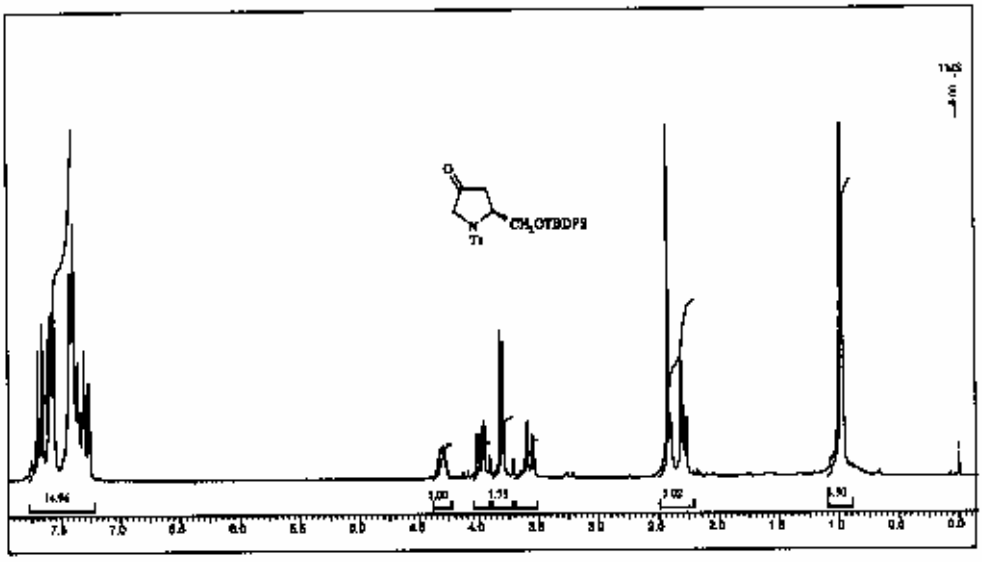
Analysis calcd. for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33; S, 9.91. Found: C, 59.06; H, 6.80; N, 4.15; S, 9.63 %;



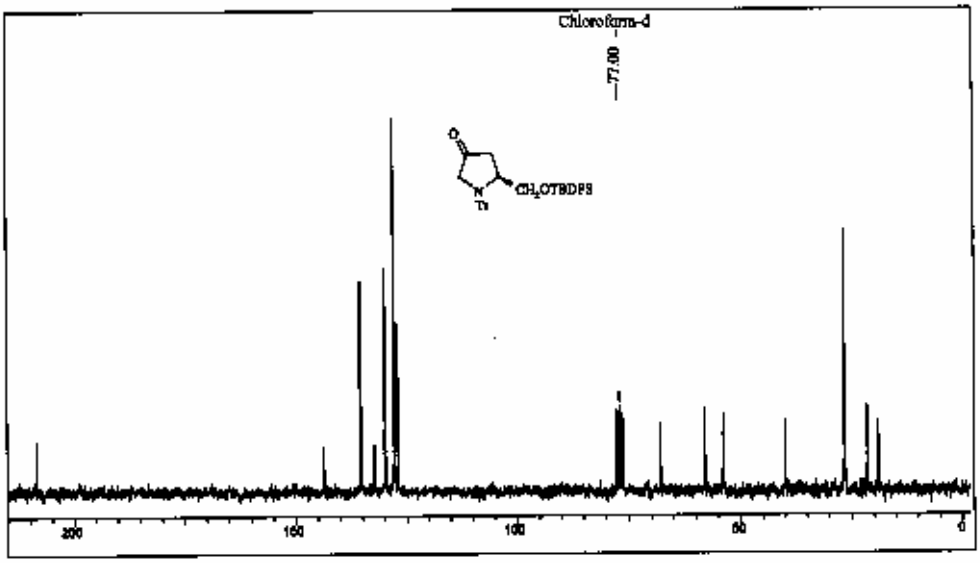
^{1}H NMR spectrum of compound 58 in CD_3COCD_3



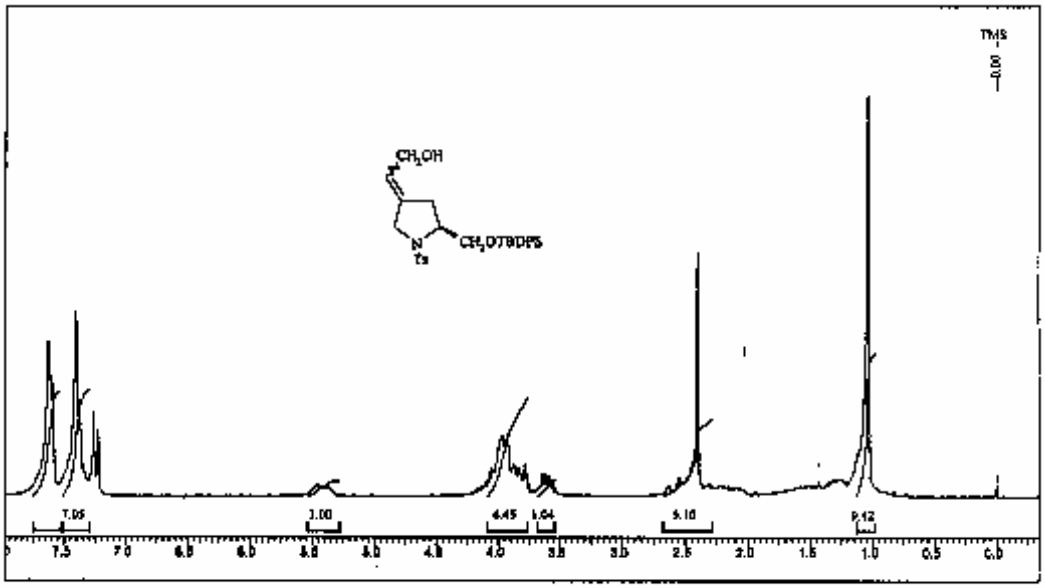
^{13}C NMR spectrum of compound 58 in DMSO-d_6



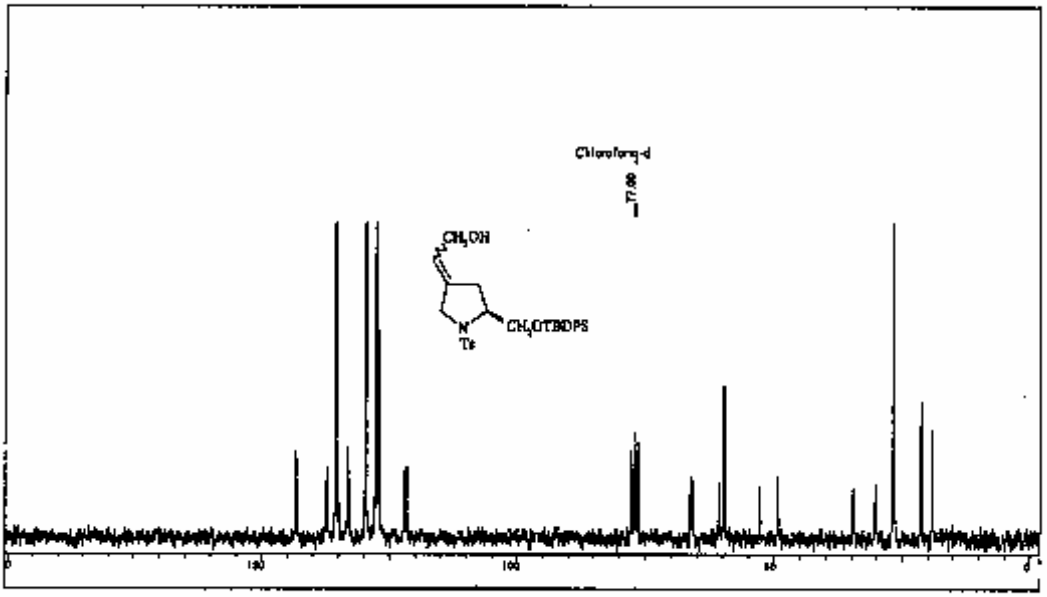
^{1}H NMR spectrum of compound 60 in $CDCl_3$



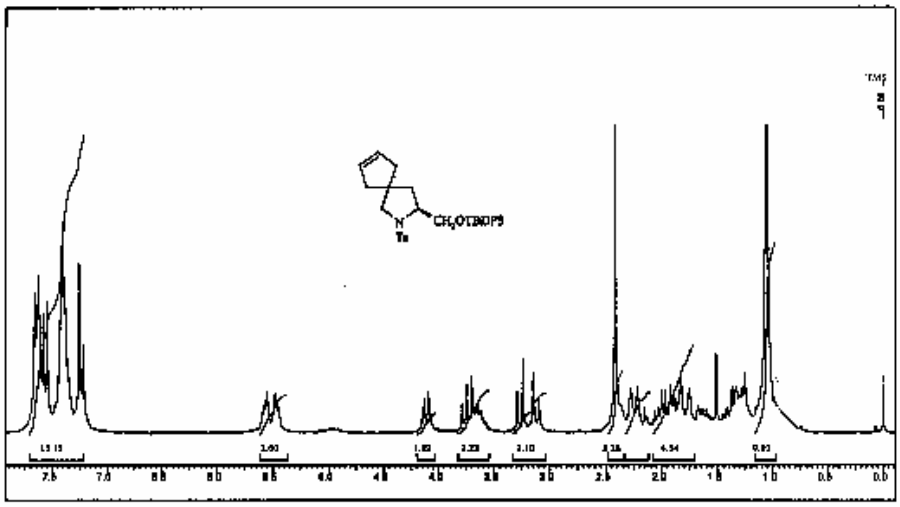
^{13}C NMR spectrum of compound 60 in $CDCl_3$



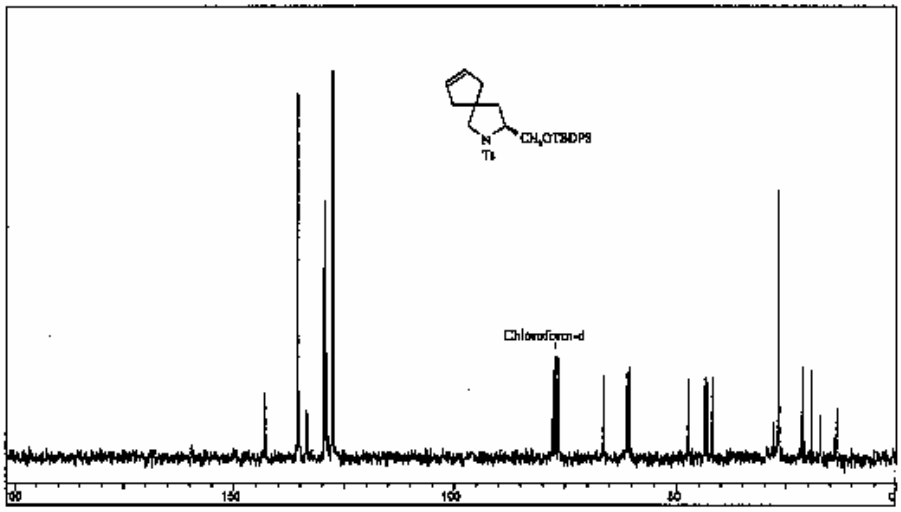
^{1}H NMR spectrum of compound 62 in $CDCl_3$



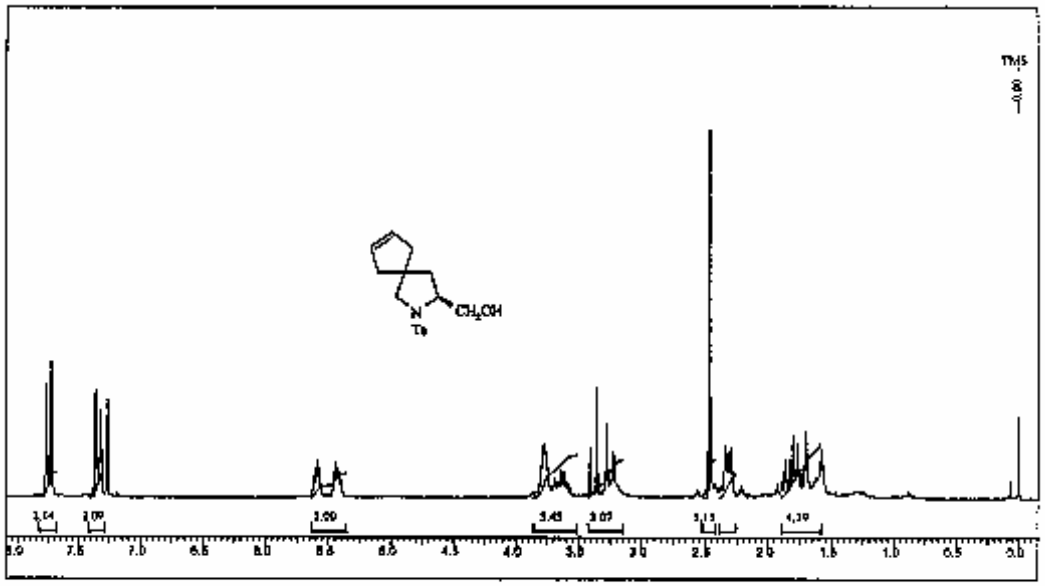
^{13}C NMR spectrum of compound 62 in $CDCl_3$



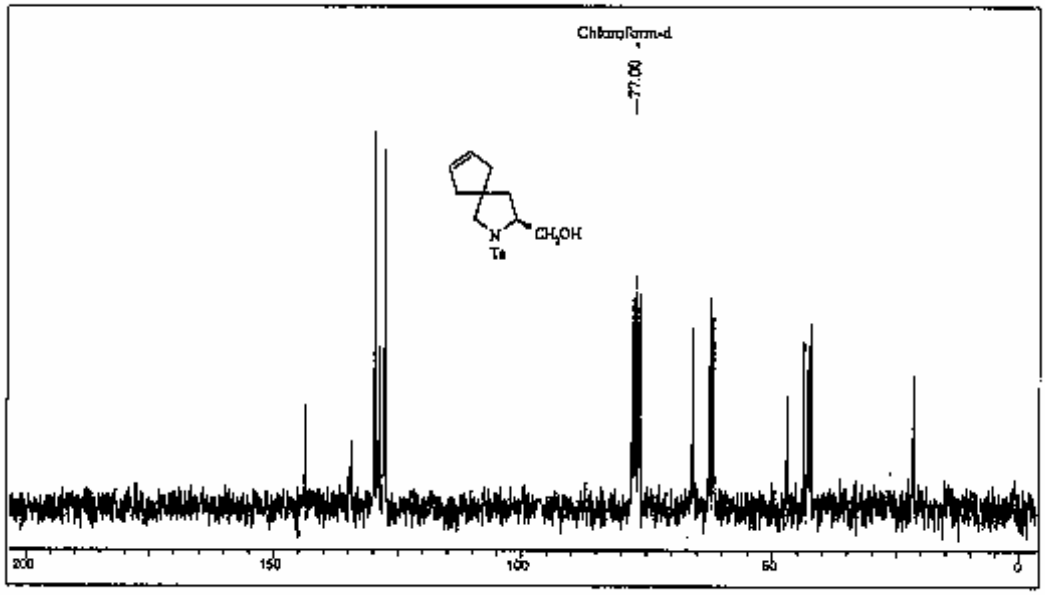
^{1}H NMR spectrum of compound 66 in $CDCl_3$



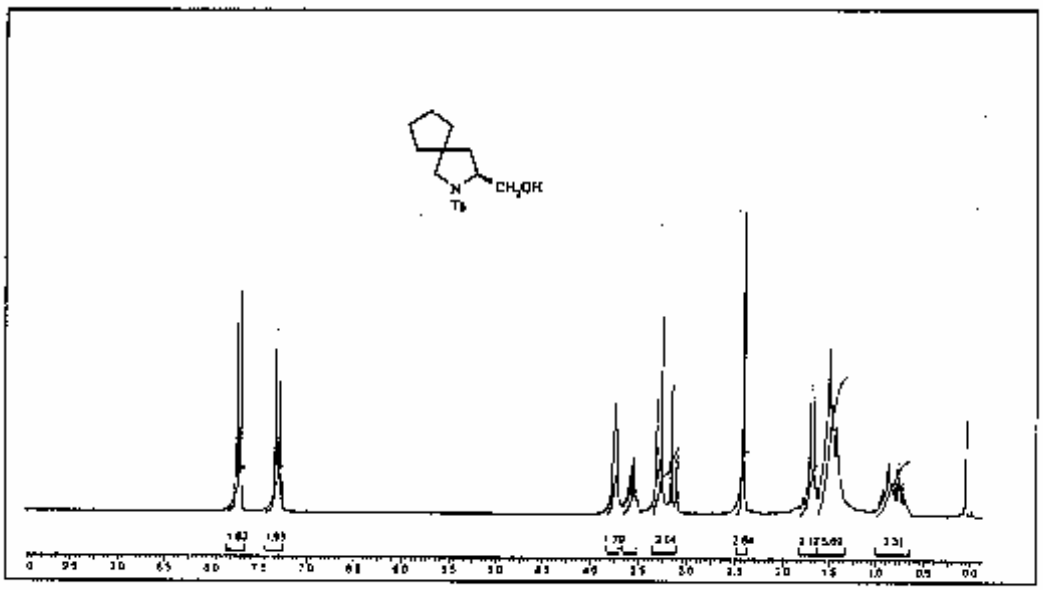
^{13}C NMR spectrum of compound 66 in $CDCl_3$



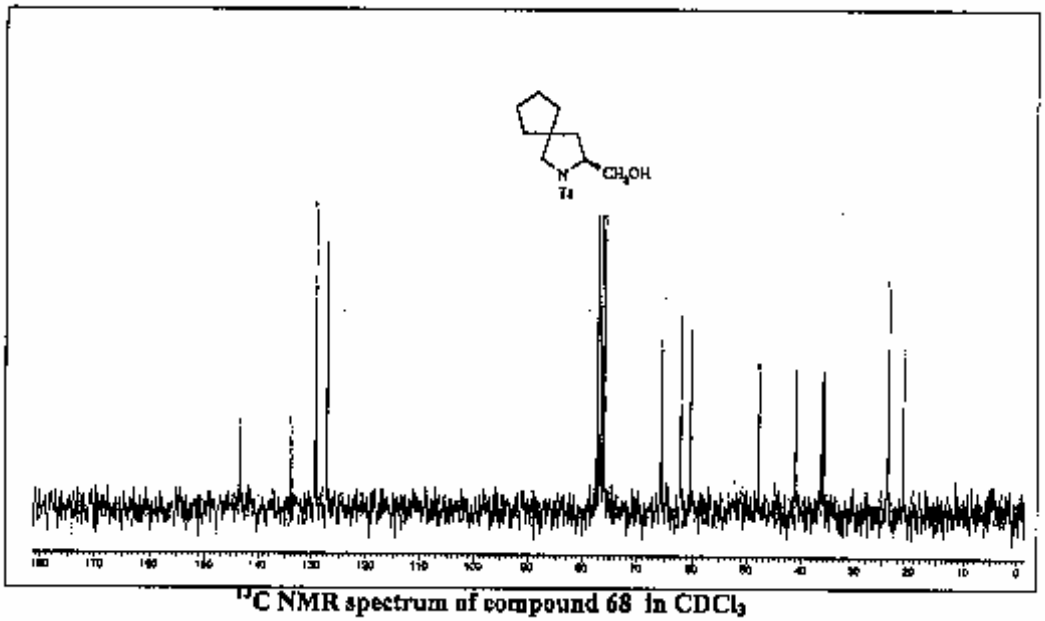
^{1}H NMR spectrum of compound 67 in $CDCl_3$



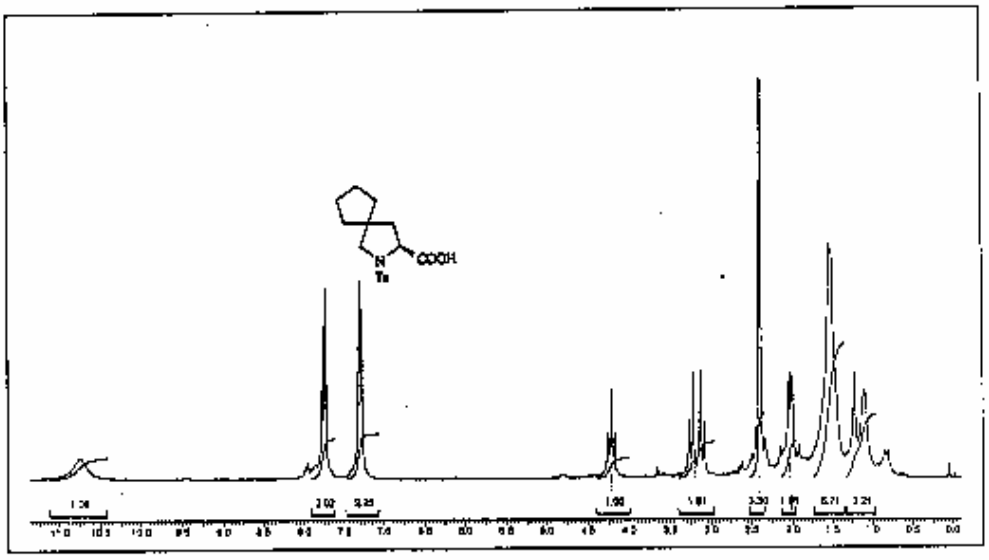
^{13}C NMR spectrum of compound 67 in $CDCl_3$



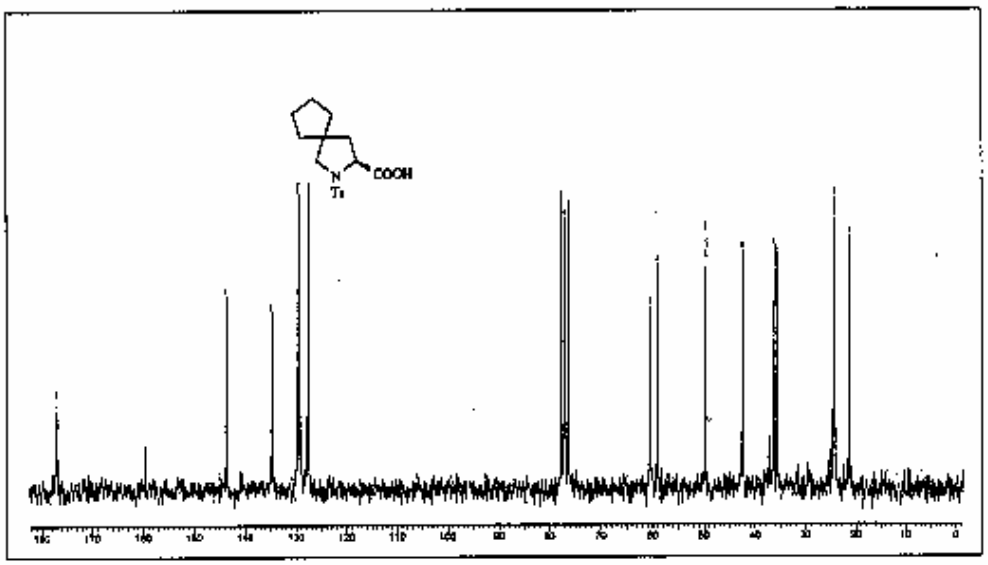
^{1}H NMR spectrum of compound 68 in $CDCl_3$



^{13}C NMR spectrum of compound 68 in $CDCl_3$



^{1}H NMR spectrum of compound 69 in $CDCl_3$



^{13}C NMR spectrum of compound 69 in $CDCl_3$

References

1. Anderson, A. W.; Merckling, M. G. US-2721189, **1955** (*Chem. Abstr*. **1955**, *50*, 3008i).
2. Herrmann, W. A. *Kontakte (Darmstadt)*, **1991**, *3*, 29.
3. Kress, J.; Osborn, J. A.; Amir-Ebrahimi, V.; Ivin, . J.; Rooney, J. J. *J. Chem. Soc. Chem. Commun*. **1988**, 1164; Kress, J.; Osborn, J. A.; Ivin, . J.; Rooney, J. J. *J. Chem. Soc. Chem. Commun*. **1989,** 1234.
4. Schaverien, C. J.; Dewan, J. C.; Schrock, R. R. *J. Am. Chem. Soc*., **1986**, *108*, 2771; Schrock, R. R.; DePue, R. T.; Feldman, J.; Murdzek, J. S.; Yang, D. C. *ibid*, **1988**, *110*, 1423; Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158.
5. Herrmann, W. A.; Kuchler, J. G.; Felixberger, J. K.; Herdtweck, E.; Wagner, W. *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 394; Herrmann, W. A.; Kuhn, F. E.; Fischer, R. W.; Thiel, W. R.; Romao, C. C. *Inor. Chem*., **1992**, *31*, 4431.
6. Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc*., **1992**, *114*, 3974; Nguen, S. T.; Grubbs, R. H.; Ziller, J. W. *ibid*, **1993**, *115*, 9858; Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl*., **1995**, *34*, 2039; Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am.. Chem. Soc*., **1996**, *118*, 100.
7. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc*., **1990**, *112*, 3875.
8. For a review on the application of both catalysts, see: Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl*., **1997**, *36*, 2036.
9. Herisson, J. L.; Chauvin, Y. *Makromol. Chem..,* **1970**, *141*, 161.
10. Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.,* **1997**, *118*, 3887.
11. Tallarico, J. A.; Bonitatebus, P. J.; Snapper, M. L. *J. Am. Chem. Soc.,* **1997**, *119*, 7157.
12. Hammer, K.; Undheim, K. *Tetrahedron*, **1997**, *53*, 2309.
13. Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem. Int. Ed. Engl.,* **1996**, *35*, 2376.
14. Holder, S.; Blechert, S. *Synlett*, **1996**, 505.
15. Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 166.

16. Furstner, A.; Radkowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem*., **2000**, *65*, 8758; Furstner, A.; Seidel, G. *Angew. Chem. Int. Ed. Engl*., **1998**, *37*, 1734.
17. Furstner, A.; Langemann, K. *J. Org. Chem*., **1996**, *61*, 8746.
18. Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.*, **1997**, *62*, 7310.
19. Sardina, F. J.; Rapoport, H. *Chem. Rev.*, **1996**, *96*, 1825.
20. Hanessian, S.; Smith, G. N.; Lombart, H. G.; Lubell, W. D. Tetrahedron, 1997, 53, 12789; Gante, J. *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 1699.
21. Giannis, A.; Kolter, T. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 1244.
22. Appelt, K. et al., *J. Med. Chem.*, **1991**, *34*, 1925.
23. Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.,* **1998**, *2*, 441.
24. Beelay, N. *TIBTECH*, **1994**, *12*, 213.
25. Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.*, **2001**, *66*, 3593.
26. Cheng, W. C.; Liu, Y.; Wong, M.; Kurth, M. J. *J. Org. Chem.*, **2002**, *67*, 5673 and references cited therein.
27. Valle, J. R. D.; Goodman, M. *Angew. Chem. Int. Ed. Engl.*, **2002**, *41*, 1600.
28. Fisk, J. D.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.*, **2000**, *122*, 5443; Vivet, B.; Cavelier, F.; Martinez, J. *Eur. J. Org. Chem.*, **2000**, 807 and references cited therein.
29. Krapcho, J.; Petrillo, E. W. *et al.*, *J. Med. Chem.*, **1988**, *31*, 1148.
30. Teetz, V.; Gaul, H. *Tetrahedron Lett.*, **1984**, *25*, 4483.
31. Bala, M.; Pasha, Q.; Bhardwaj, D. K.; Pasha, S. *Bioorg. Med. Chem.*, **2002**, *10*, 3685.
32. Sannigrahi, M. *Tetrahedron*, **1999**, *55*, 9007.
33. Grigg, R.; Putnikovic, B.; Urch, C. J. *Tetrahedron Lett.*, **1996**, *37*, 695.
34. Galvez, J. M. G.; Angers, P.; Canonne, P. *Tetrahedron Lett.*, **1994**, *40*, 3247.
35. Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.*, **1999**, *40*, 3247.
36. Molander, G. A.; Alonso-Alija, C. *Tetrahedron*, **1997**, *53*, 8067.
37. Clive, D. L. J.; Bergestra, R. J. *J. Org. Chem.*, **1990**, *55*, 1786.
38. Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.*, **1998**, *63*, 3141.

39. Maezaki, N.; Fukuyama, H.; Yagi, S.; Iwaka, C. *J. Chem. Soc. Chem. Commun.*, **1994**, 1835.
40. Gurjar, M. K.; Ravindranadh, S. V.; Karmakar, S. Chem. Commun., 2001, 241.
41. Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun.*, **2001**, 958.
42. Manzoni, L.; Colombo, M.; May, E.; Scolastico, C. *Tetrahedron,* **2001**, *57*, 249. For a review on proline derivatives, see Mauger, A. B.; Witkop, B. *Chem. Rev.,* **1966**, *66*, 47;
43. Yamamoto, Y.; Asao, N. *Chem. Rev.,* **1993**, *93*, 2207.
44. Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron*, **1984**, *41*, 4079; Hanessian, S.; Alpegiani, M. *Tetrahedron*, **1989**, *45*, 941; Praly, J-P. *et al.*, *Eur. J. Org. Chem.*, **2001**, 2939; Bubnov, Y. N.; Pastukhov, F. V.; Ignateuko, I. V. *ibid*, **2000**, 1503.
45. Schumacher, K. K.; Jiang, J.; Joullie, M. M. *Tetrahedron Asymm.*, **1998**, *9*, 47.
46. Andreatta, R. H.; Nair, V.; Robertson, A. V.; Simpson, W. R. J. *Aust. J. Chem..*, **1967**, *20*, 1493.
47. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.*, **1979**, *20*, 399.
48. Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron*, 1968, **24**, 53; Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React*., **1973**, *20*.
49. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B.; *J. Org. Chem.*, **1981**, *46*, 3936.

Section 2: Introduction

Polyether toxins such as brevetoxin, ciguatoxin and halichondrins (**1** – **5**) isolated form marine organisms exhibit a variety of biological properties including cytotoxicity, neurotoxicity, antiviral and antifungal activity.[1] The structural complexity and biological activities of these molecules have resulted in the discovery of new methods for the synthesis of cyclic ethers.[2] Because these natural products have a unique ladder like polycyclic molecular framework consisting of contiguous trans or *cis* fused polyether rings, several new synthetic methods have been aimed at the rapid construction of bi-, tri- and tetra- cyclic systems.[3]

Cis fused pyranofuran (2,6-dioxa[4.3.0]nonane) skelton is ubiquitous among natural products like halichondrins (L &K, J & I, H & G, and B & C rings) and annulated nucleotide

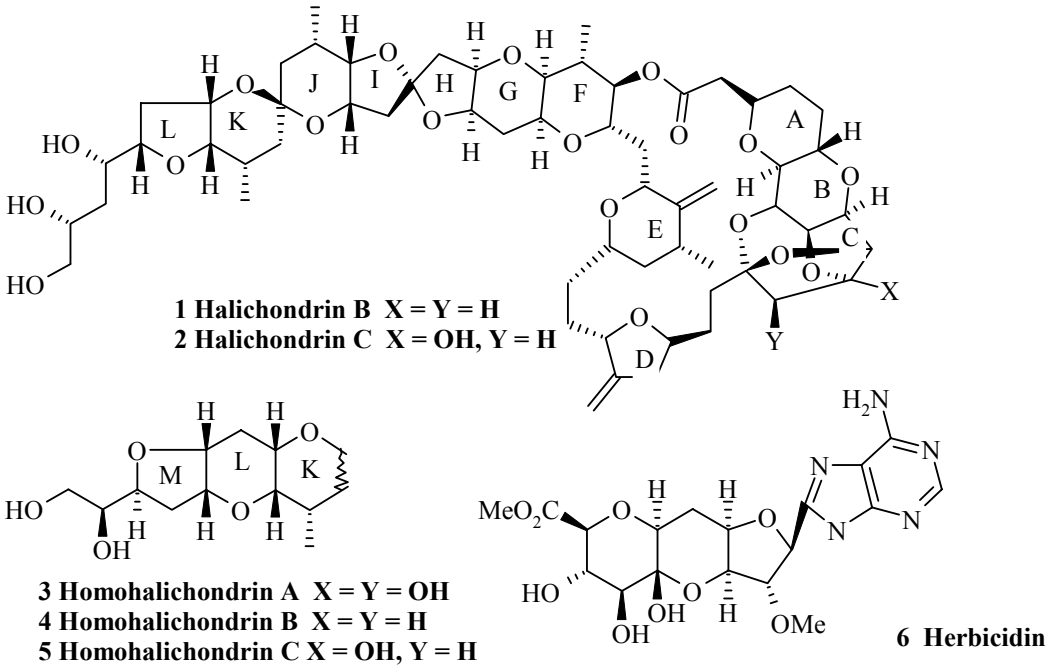


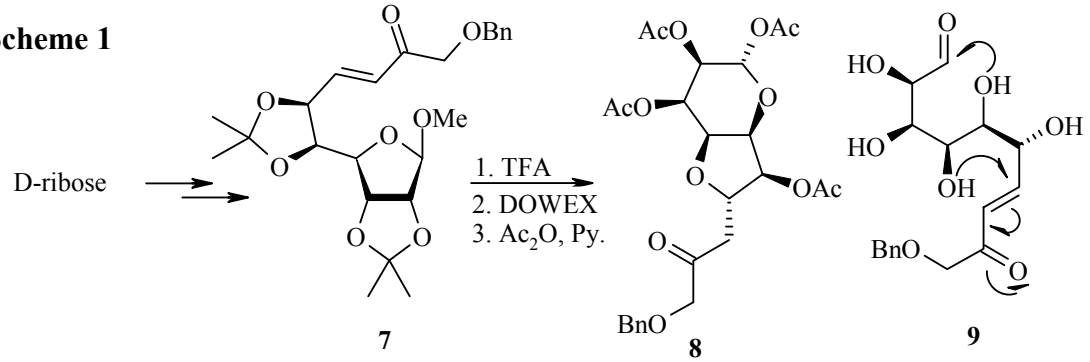
Fig. 1

antibiotics like herbicidin **6**.[4] Carbohydrate based strategies has been widely used for the synthesis of *cis* fused pyranofurans. Generally, epoxide opening-cyclisation reaction, hetero

Michael addition and iodo-lactonization reaction has been used to construct the *cis*-fused bicyclic ether framework.

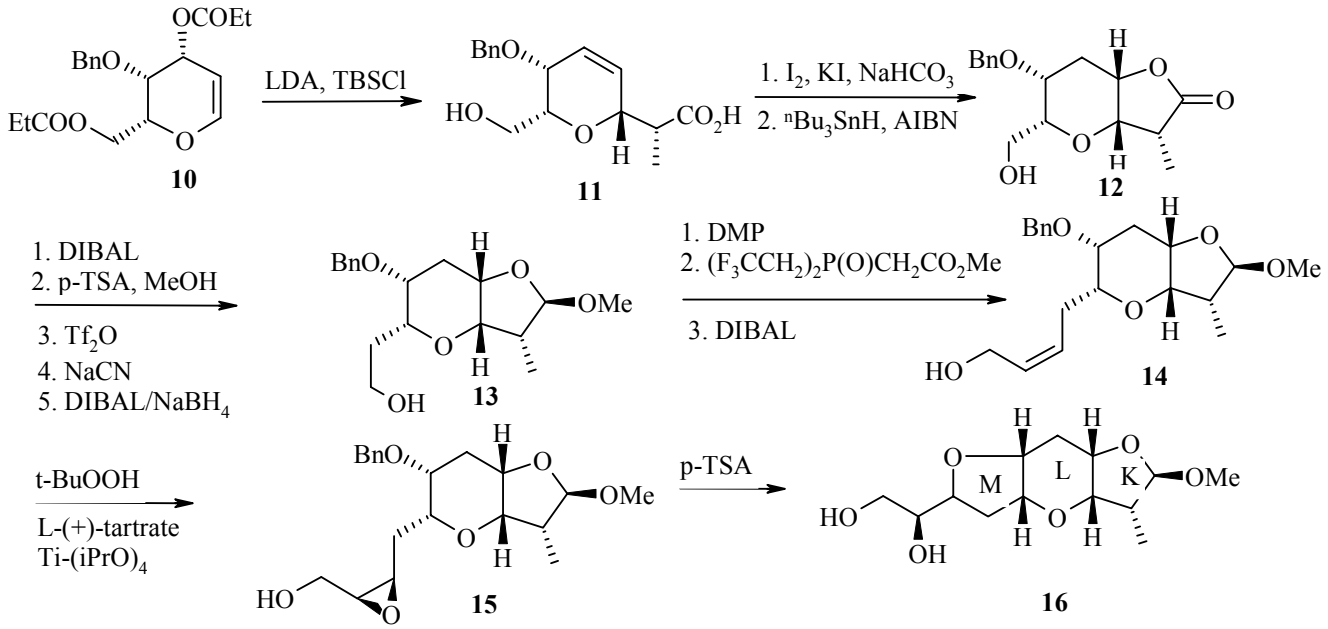
Salomon *et al* reported[5] the synthesis of **8** in their synthesis of B and C rings of halichondrin B from D-ribose by hetero-Michael addition as shown in the Scheme 1. Deketalization of **7** with TFA and treatment with DOWEX 50W produced the acyclic intermediate **9**. Subsequent hemiketalization generated a pyranose and hetero-Michael addition then produced the cis fused pyranofuran **8**.

Scheme 1



Kishi *et al*[6] synthesized M and L rings of homohalichondrin from D-galactose glycal derivative **10** *via* Ireland-Claisen rearrangement, iodolactonisation and intramolecular epoxide

Scheme 2

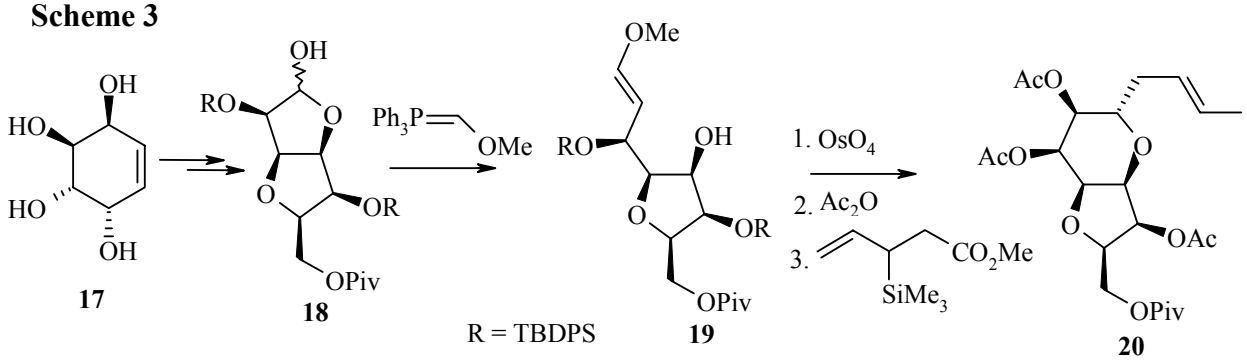


opening–cyclisation reaction as given in Scheme 2. Thus, Ireland-Claisen rearrangement and subsequent iodolactonisation of **10** gave the *cis*-fused bicyclic lactone **12**. **12** was converted

to the allylic alcohol **14** which when subjected to Sharpless asymmetric epoxidation followed by acid catalysed opening furnished **16**.

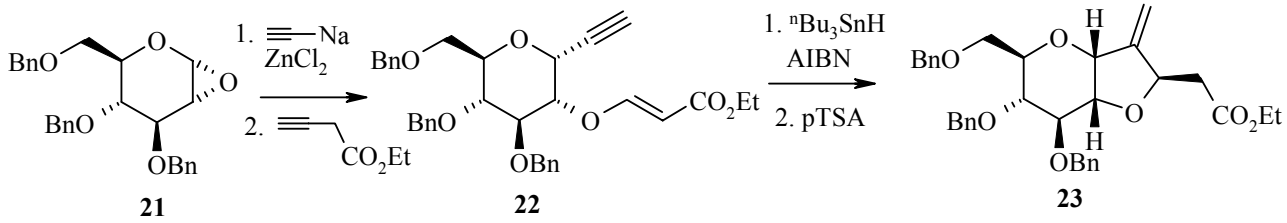
Combining the desymmetrisation protocol of Creigee's trapping carbonyl oxides with internal nucloeophiles with Schrieber's ozonolytic desymmetrisation of simple cycloalkenes to prepare **18**, Burke *et al*[7] synthesized **20** on their way to the B and C rings of halichondrin B from **17** as shown in Scheme 3.

Scheme 3



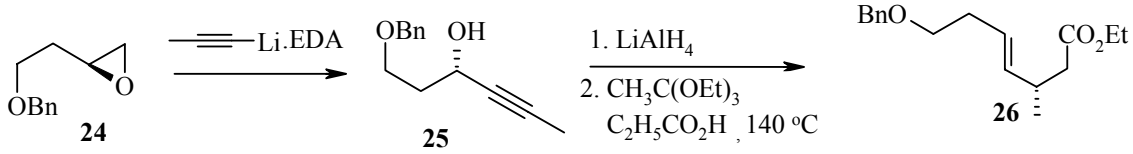
Tributyltin mediated radical cyclization of carbohydrate derived β-(alkynyloxy)acrylates leading to *cis* fused bicyclic ethers has been reported by van Boom et al.[8] Radical cyclisation of **22** by addition of $^{n}Bu_3SnH$ and AIBN in toluene at 80 °C led to the formation of *cis* fused 5,6-bicyclic vinylstannane which on acidic destannylation gave **23**.

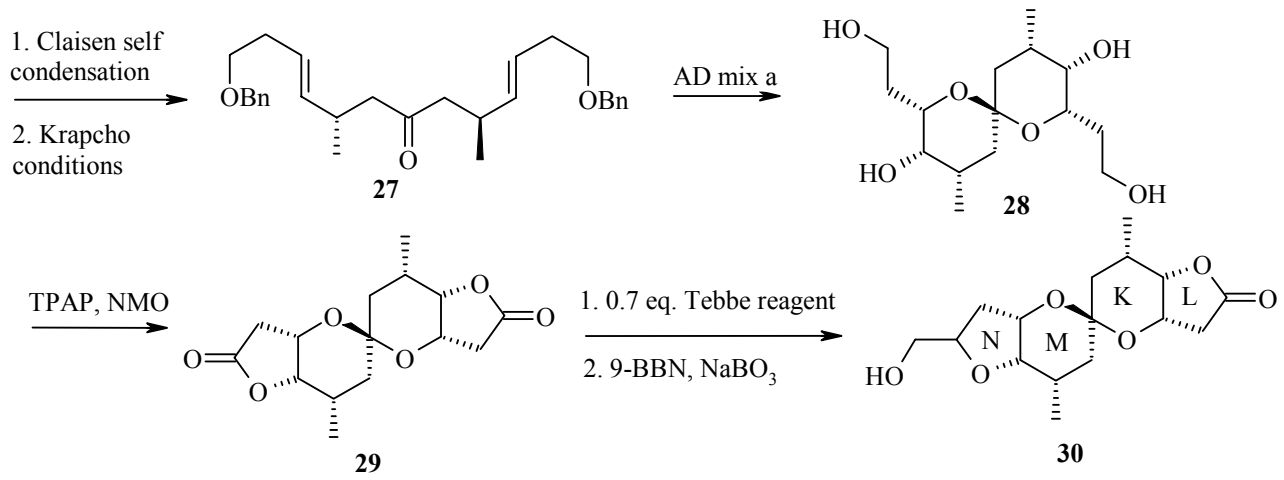
Scheme 4



Burke *et al*[9] has synthesized the N, M, L and K rings of halichondrin B subunit from the known epoxide **24** using Johnson's orthoester Claisen rearrangement and Sharpless asymmetric dihydroxylation as key reactions as shown in Scheme 5.

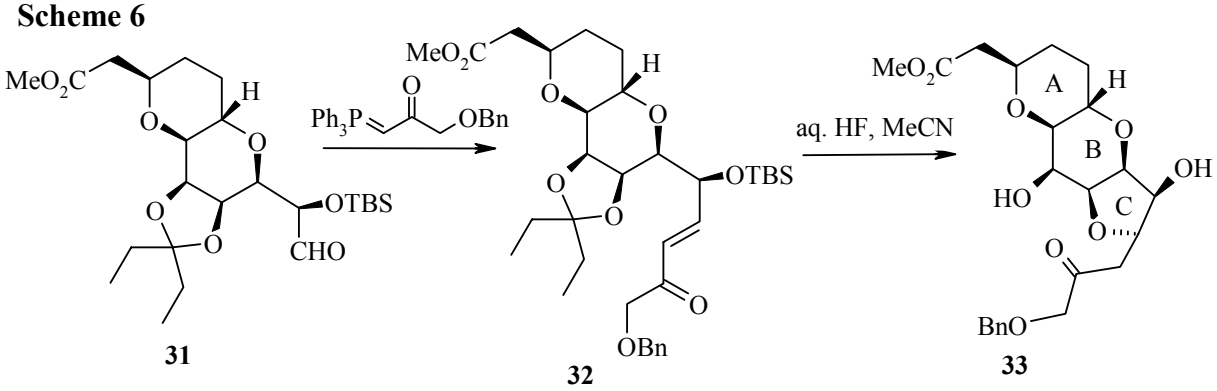
Scheme 5





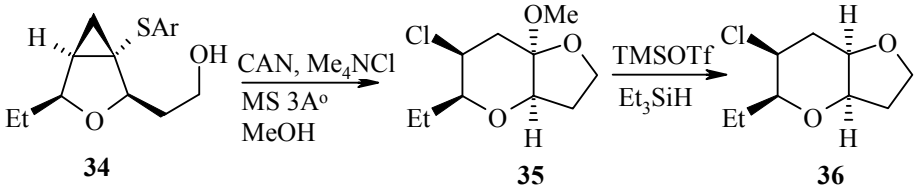
The same authors has succeeded[10] in synthesizing the *cis*-fused B and C rings of halichondrin B from **31** derived from α-D-glucoheptonic –γ-lactone *via* hetero-Michael addition as shown in Scheme 6.

Scheme 6



Ibuka *et al*[11] reported the synthesis of *cis* fused bicyclic ethers *via* CAN mediated ring opening of cyclopropyl sulfides, in presence of Me_4NCl. Oxidation of **34** bearing a hydroxy

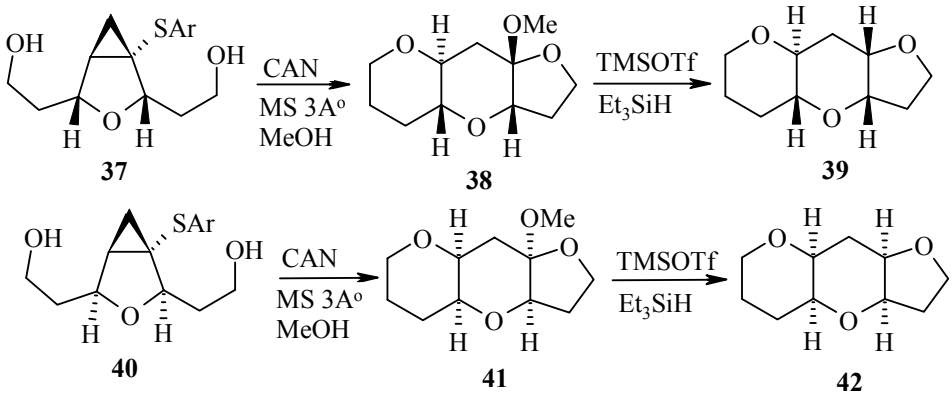
Scheme 7



group in a side chain promotes a S_N^2 type nucleophilic substitution by the hydroxy group along with the cleave of more substituted cyclopropyl carbon-carbon bond, *via* chloride ion attack giving rise to chlorinated fused bicyclic ethers.

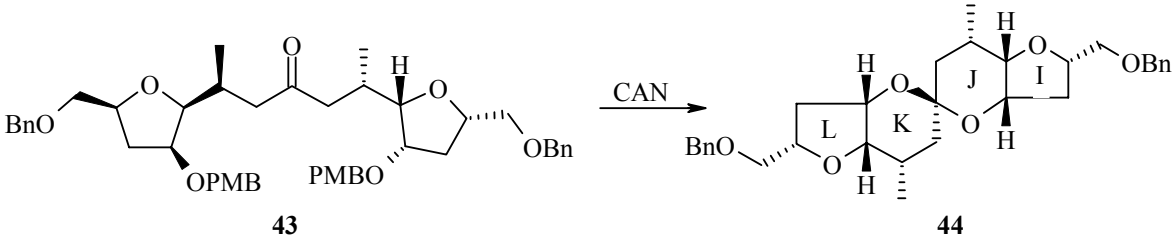
Under the same conditions, in the absence of Me_4NCl, substrates like **37** and **40** underwent double ether ring formation in the same manner.[12]

Scheme 8



Salomons synthesis[13] of the L, K, J and I rings of halichondrin B utilizes the double anomeric effect and the preference for di-equatorial disposition of the methyl substituents on the J and K rings, and thus the CAN mediated deprotection of PMB ether **43** led to spiroketalization in a diastereoselective way under thermodynamic control to afford **44**.

Scheme 9



Present Work

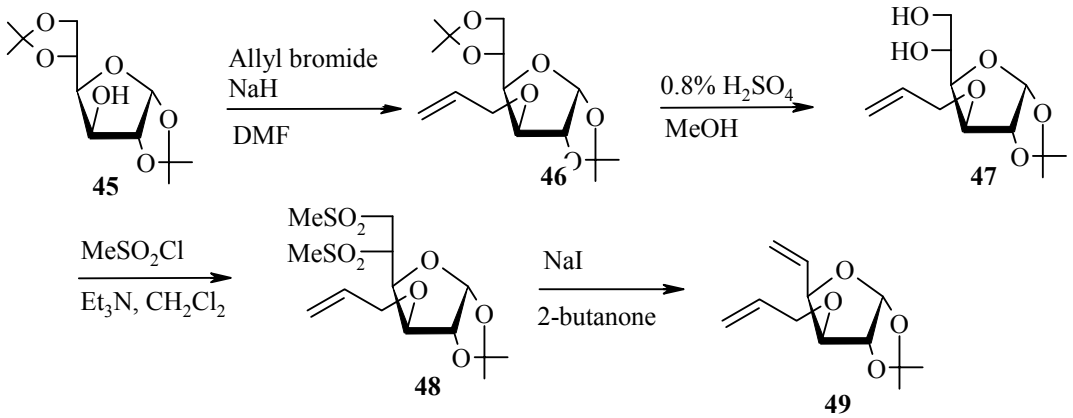
The structural complexity of polyether toxins such as halichondrins makes them most attractive from the synthetic point of view. A considerable amount of effort is presently being devoted to the preparation of simplified models and the total synthesis of these substances. Moreover, as problems in isolating significant quantities of these polyether toxins have limited pharmacological investigation of this class of compounds, the development of efficient strategies for their synthesis are required. The general methods used in polyether synthesis can be divided in to two: i) cyclization by C-O bond formation; ii) cyclization by C-C bond formation. Among these methods, the former has found several applications. However, the recent developments in transition metal alkylidene catalyzed olefin metathesis by Grubbs and Schrock has brought the latter method, i. e. cyclization with C-C bond formation into focus.

Carbohydrates are widely recognized as versatile building blocks in synthetic organic chemistry due to the wealth of functional, conformational and stereochemical information. The diversity and easy availability of these relatively cheap chiral compounds have led to a plethora of applications in the design and synthesis of naturally occurring compounds. The accessibility of carbohydrates in the acyclic (open chains) or cyclic form (furanose or pyranose) not only allows specific manipulations of the individual asymmetric centers, but also at either of the extremities (i. e. reducing or non-reducing end). In addition, the functional groups in monosaccharides offer the opportunity to install a number of neighboring vinyl-*O*-allyl functions, which may present a suitable platform for ring closing metathesis (RCM). This chapter describes the generality, scope and functional group tolerance of ring closing metathesis reaction to give fused bicyclic ethers derived from carbohydrates. Apart from the RCM of dienes, RCM of enynes will also be discussed.

We started our endeavor with 1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose (**45**). The free hydroxyl group at C-3 was allylated using NaH and allyl bromide in DMF to afford **46** (Scheme 10). In the ^{1}H NMR spectrum of **46**, the terminal olefinic protons (=CH_2) appeared as a multiplet at δ 5.19. All the other resonances were in agreement with the assigned structure. Acid catalysed hydrolysis of the 5,6-*O*-isopropylidene group was achieved selectively by using 0.8 % H_2SO_4 in MeOH to afford **47**. The diol **47** was converted to the corresponding di-*O*-mesyl derivative (**48**) using $MeSO_2Cl$ and Et_3N in CH_2Cl_2. In the

^{1}H NMR spectrum, the methyl protons of the mesyl groups appeared as two singlets at δ 3.08 and 3.17. Our next aim was the conversion of **48** to the 5,6-ene derivative, for which

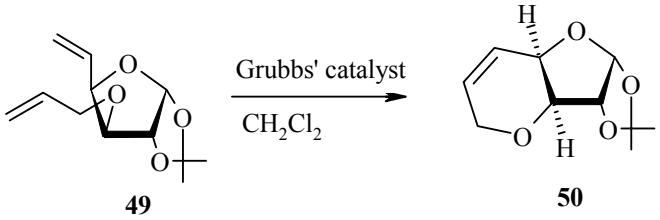
Scheme 10



compound **48** was treated with NaI in 2-butanone under reflux for 18 h to afford **49** in 77 % yield. The ^{1}H NMR and ^{13}C NMR spectra were consistent with the structure.

The RCM reaction of **49** proceeded smoothly with 2 mol % of Grubbs' catalyst in CH_2Cl_2 at rt to afford **50** in quantitative yield (Scheme 11). The ^{1}H, ^{13}C NMR spectral data coupled with elemental analysis confirmed the structure of **50**. For example, in the ^{1}H NMR spectrum, the olefinic protons appeared as a multiplet at δ 6.04 while in the ^{13}C NMR

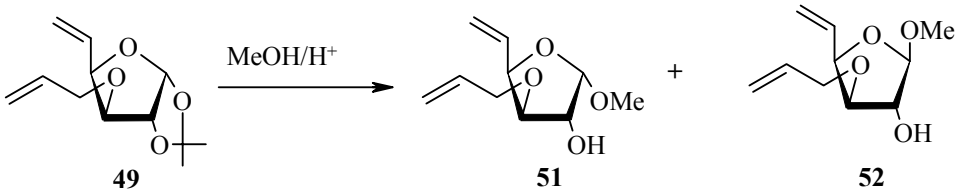
Scheme 11



spectrum, the olefinic carbons appeared at δ 121.3 and 131.8.

In order to expand the scope and versatility of this strategy, we embarked on the preparation of a number of dienes followed by RCM reaction. The methanolysis of isopropylidene protection in **49** was carried out using *p*-TSA in MeOH under reflux conditions to afford a mixture of α and β anomers **51** and **52**, which were separated by silica gel column chromatography (Scheme 12).

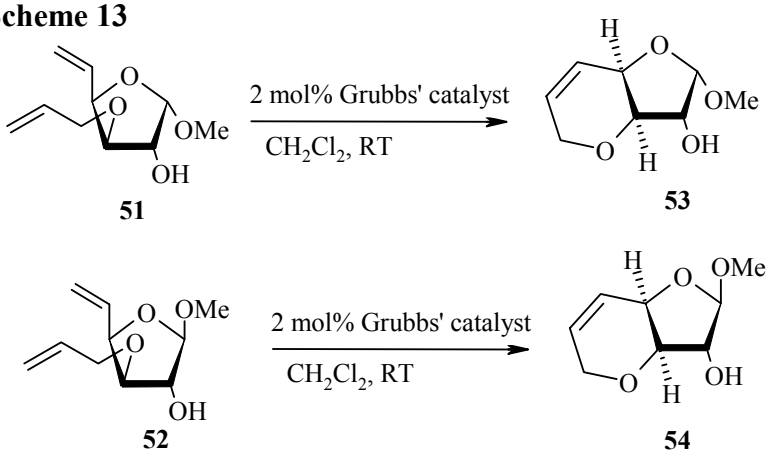
Scheme 12



49 **51** **52**

The RCM reaction of these two substrates proceeded with 2 mol % of Grubbs catalyst to afford **53** and **54** in 90 % yield (Scheme 13). It could be pointed out that the presence of free hydroxyl group did not have any influence on the RCM reaction. In the ^{1}H NMR spectrum of the α-isomer, the olefinic protons were observed as a multiplet at δ 6.04 and the signal due to methoxyl group was observed as a singlet at δ 3.53 while in **54,** the corresponding peaks were observed at δ 6.02 and 3.37.

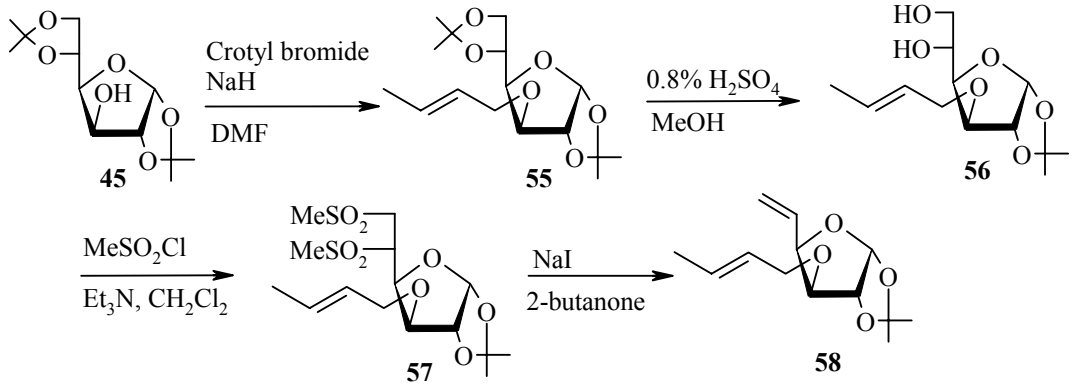
Scheme 13



51 **53** **52** **54**

After the successful results obtained in these examples, next we turned our attention to the RCM of 3-*O*-crotyl-5,6-dideoxy-1,2-*O*-diisopropylidene-α-D-*xylo*-hex-5-enofuranose

Scheme 14

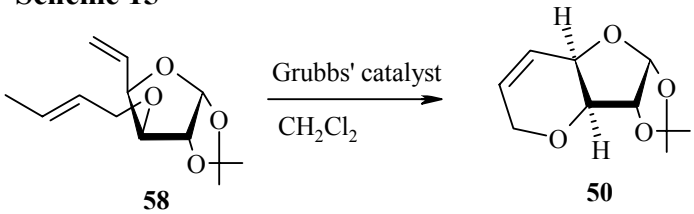


45 **55** **56** **57** **58**

(**58**). Compound **45** was crotylated using NaH and crotyl bromide in DMF (Scheme 14) to afford **55**. In the ^{1}H NMR spectrum of **55**, the vinylic methyl group appeared at δ 1.73 (d, J = 6.4 Hz) while the olefinic protons appeared as a multiplet at δ 5.60. Selective hydrolysis of the primary 5,6-*O*-isopropylidene protection using 0.8 % H_2SO_4 afforded the diol **56** which on treatment with $MeSO_2Cl$ and Et_3N in CH_2Cl_2 afforded the di-*O*-mesyl derivative (**57**) in 95 % yield. The ^{1}H and ^{13}C NMR spectra were in agreement with the assigned structure **57**. Treatment of **57** with NaI in refluxing 2-butanone afforded the required diene **58**. In the ^{1}H NMR spectrum of **58**, the terminal methylene protons of vinyl group (=CH_2) appeared at δ 5.28-5.73 along with the olefinic protons of the crotyl group (CH=CH) while in the ^{13}C NMR sepctrum, the olefinic carbons resonated at δ 118.2, 126.9, 129.2 and 132.5.

The RCM reaction of **58** with 2 mol% Grubbs catalyst in CH_2Cl_2 at rt gave the product in 60 % yield (Scheme 15). The ^{1}H and ^{13}C NMR spectra of the product were

Scheme 15

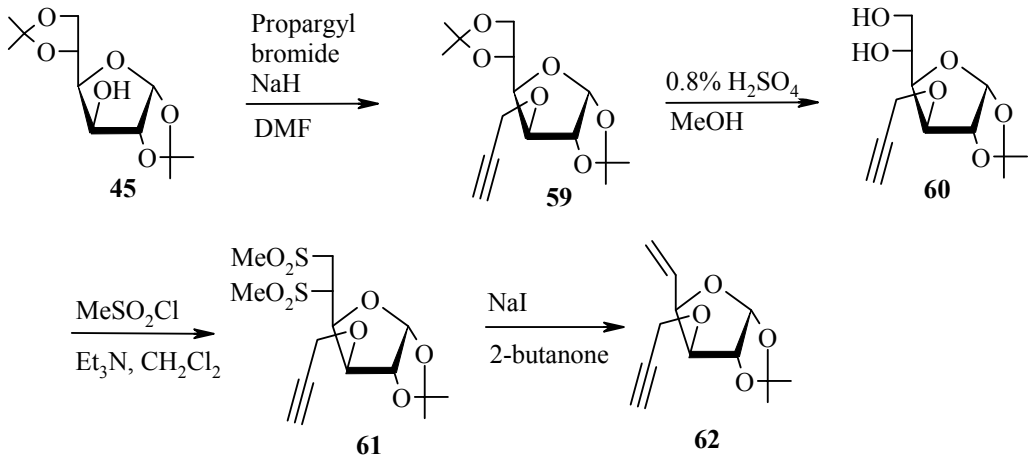


58 **50**

superimposible with those of the product **50** obtained by the RCM of **49**. The specific rotation values of both products were identical {$[\alpha]_D$ = -16.0 (*c* 1.0, $CHCl_3$)}.

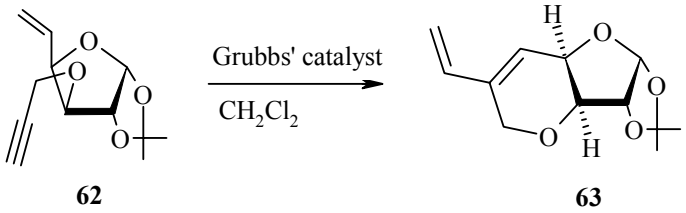
Having established the RCM of dienes, we next planned to investigate the reaction of a novel compound **62**, in which olefin and acetylene groups are placed in juxtaposition capable of undergoing RCM reaction (Scheme 16). For this purpose, **45** was treated with NaH and propargyl bromide in DMF to afford the 3-*O*-propargyl derivative **59** whose ^{1}H and

Scheme 16



^{13}C NMR spectra were in confirmation with the assigned structure. For example, the terminal acetylinic proton appeared as a triplet at δ 2.48 (J = 2.5 Hz). Successive removal of the 5,6-isopropylidene protection was achieved selectively using 0.8 % H_2SO_4 (**60**), mesylation (**61**) and reaction with excess NaI in 2-butanone gave **62**. In the ^{1}H NMR spectrum of **62**, the acetylenic proton was observed at δ 2.46 (t, J = 2.4 Hz) while the olefinic protons appeared as multiplets at δ 5.39 (=CH_2) and 5.87 (=CH). The structure of **62** was further confirmed by ^{13}C NMR spectrum, which showed the olefinic carbons at δ 178.2 and 131.9.

Scheme 17

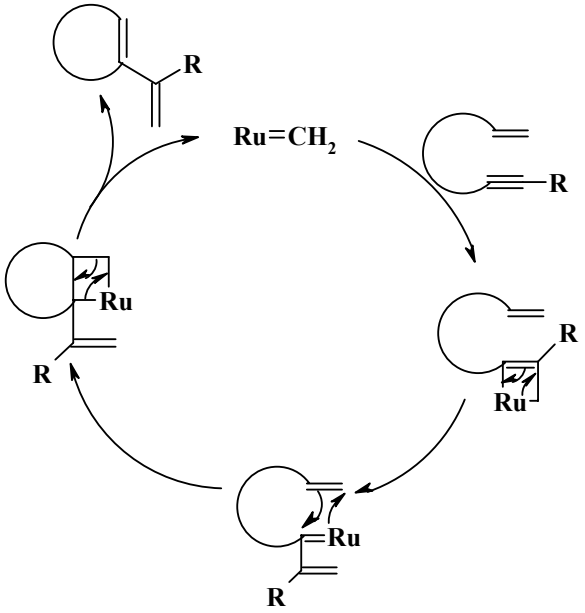


RCM of **62** with 5 mol% of Grubbs' catalyst in refluxing CH_2Cl_2 for 1.5 h afforded the conjugated diene **63** in 75 % yield (Scheme 17).[15] The ^{1}H and ^{13}C NMR spectra substantiated the structure. For example, olefinic protons of the *exo* double bond appeared at δ 5.10 (d, J = 17.8 Hz, =CH_2), 5.14 (d, J = 10.7 Hz, =CH_2) and δ 6.28 (dd, J = 10.7, 17.8 Hz, =CH) while the proton of internal olefin resonated at δ 5.92 (m, =CH). In the ^{13}C NMR, the olefinic carbons were observed at δ 111.4, 116.0, 138.7, 142.3.

Mechanism of enyne metathesis

Intramolecular enyne metathesis is useful for organic synthesis because the terminal alkylidene moiety of alkene migrates on the alkyne carbon to give cyclized product containing diene.[15] The metal carbene reacts with alkyne of enyne to produce metalacyclobutene. A bond cleavage occurs to produce carbene complex and then an intramolecular metathesis reaction with alkene occurs to provide metalacyclobutane which gives metathesis product.

Fig. 2



In conclusion, the RCM approach clearly shows that glycofuranoids having neighbouring vinyl-*O*-allyl, vinyl-*O*-crotyl or vinyl-*O*-propargyl functionalities can be used as starting compounds for the synthesis of highly substituted *cis*-fused oxacycles with a functionalizable internal olefin.

Experimental

3-*O*-Allyl-1,2:5,6-*O*-diisopropylidene-α-D-glucofuranose (46)

To a solution of compound **45** (3.0 g, 11.5 mmol) in DMF (8 mL) at 0 ^{o}C under Argon atmosphere was added sodium hydride (60 % dispersion in mineral oil, 0.55 g, 13.8 mmol). After stirring for 30 min. at rt, allylbromide (1.2 mL, 14.2 mmol) was introduced at 0 ^{o}C. After 2 h, reaction mixture was quenched by adding ice pieces and partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried (Na_2SO_4), concentrated and the crude product purified on silica gel using ethyl acetate-petroleum ether as an eluent (2:8) to give compound **46** (2.9 g, 85 %);

$[\alpha]_D$ = -23.4 (*c* 1.3, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 3 H), 1.36 (s, 3 H), 1.42 (s, 3 H), 1.47 (s, 3 H), 3.93-4.18 (m, 6 H), 4.31-4.35 (m, 1 H), 4.56 (d, 1 H, *J* = 3.5 Hz), 5.16-5.33 (m, 2 H), 5.87 (d, 1 H, *J* = 3.5 Hz), 5.83-6.01 (m, 1 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1, 25.9, 26.5, 26.6, 66.9, 70.9, 72.1, 80.9, 81.0, 82.5, 104.9, 108.5, 111.2, 116.7, 133.9.

Anal. Calcd. for $C_{15}H_{24}O_6$: C, 60.00; H, 8.00. Found: C, 59.83; H, 7.96 %.

3-*O*-Allyl -1,2-*O*-isopropylidene-α-D-glucofuranose (47)

A mixture of **46** (2.0 g, 6.6 mmol), MeOH (2 mL) and 0.8% H_2SO_4 (10 mL) was stirred at room temperature. After 30 h the reaction mixture was neutralized with solid $NaHCO_3$. Solvent was removed on the rotavapour and the residue extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and the crude product purified on silica gel using ethyl acetate-light petroleum as an eluent (7:3) to afford compound **47** (1.4 g, 80 %);

$[\alpha]_D$ = -18.0 (*c* 1.6, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3 H), 1.47 (s, 3 H), 3.68-3.92 (m, 2 H), 4.00-4.28 (m, 5 H), 4.58 (d, 1 H, *J* = 3.5 Hz), 5.24-5.43 (m, 2 H), 5.88-6.03 (m, 1 H), 5.89 (d, 1 H, *J* = 3.5 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.7, 26.2, 63.8, 68.2, 70.7, 79.5, 81.1, 81.9, 104.6, 111.0, 116.9, 133.9.

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.63; H, 7.51 %.

3-*O*-Allyl -5,6-di-*O*-mesyl-1,2-*O*-isopropylidene-α-D-glucofuranose (48)

To a solution of **47** (1.0 g, 3.8 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC was added Et_3N (1.4 mL, 10.4 mmol) followed by methanesulfonyl chloride (0.7 mL, 9.0 mmol). After 1 h at rt, the reaction mixture was partitioned between water and CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated and purified on silica gel by eluting with ethyl acetate-petroleum ether (2:3) to afford compound **48** (1.3 g, 89 %);

$[\alpha]_D$ = -23.0 (*c* 2.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3 H), 1.46 (s, 3 H), 3.08 (s, 3 H), 3.17 (s, 3 H), 4.04 (d, 1 H, *J* = 3.5 Hz), 4.06-4.12 (m, 2 H), 4.35-4.51 (m, 3 H), 4.61 (d, 1 H, *J* = 3.5 Hz), 4.73-4.80 (m, 1 H), 5.25-5.43 (m, 2 H), 5.87 (d, 1 H, *J* = 3.5 Hz), 5.86-6.09 (m, 1 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0, 26.6, 37.4, 38.9, 68.7, 71.2, 74.5, 77.6, 80.7, 81.4, 105.1, 112.2, 117.8, 133.6.

Anal. Calcd. for $C_{14}H_{24}O_8S_2$: C, 43.74; H, 6.29; S, 16.68. Found: C, 43.61; H, 6.57; S, 16.89 %.

3-*O*-Allyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (49)

A mixture of compound **48** (1.0 g, 2.6 mmol) and NaI (3.9 g, 26.0 mmol) were refluxed in 2-butanone (20 mL). After 24 h, the solvent was removed on rotavapour and the residue dissolved in ethyl acetate. The organic layer was washed with $Na_2S_2O_3$, water, dried (Na_2SO_4), evaporated and the residue purified on silica gel eluting with ethyl acetate-light petroleum (1:4) afforded compound **49** (0.45 g, 77 %);

$[\alpha]_D$ = -59.6 (*c* 1.5, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 (s, 3 H), 1.49 (s, 3 H), 3.83 (d, 1 H, *J* = 4.0 Hz), 3.92-4.18 (m, 2 H), 4.59 (d, 1 H, *J* = 4.0 Hz), 4.60-4.63 (m, 1 H), 5.17-5.48 (m, 4 H), 5.73-6.08 (m, 3 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 26.7, 71.0, 81.4, 82.9, 83.4, 104.7, 111.3, 117.1, 118.6, 132.4, 134.0.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.83; H, 7.93 %.

(1*R*,6*R*,8*R*,9*R*)-8,9-Dihydroxy-8,9-*O*-isopropylidene-2,7-dioxabicyclo[3.4.0]non-4-ene (50)

To a solution of the compound **49** (0.4 g, 1.8 mmol) in CH_2Cl_2 (10 mL) under Argon atmosphere was added Grubbs' catalyst (29 mg, 2 mol %) and stirred at room temperature.

After 4 h, the solvent was evaporated and the residue purified on silica gel using ethyl acetate-light petroleum (1:9) as an eluent to afford compound **50** (0.33 g, 95 %);

$[\alpha]_D$ = -16.0 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 3 H), 1.45 (s, 3 H), 3.92 (d, 1 H, *J* = 3.5 Hz), 4.10 (ABq, 2 H, *J* = 15.1 Hz), 4.34 (s, 1 H), 4.56 (d, 1 H, *J* = 3.5 Hz), 5.95 (d, 1 H, *J* = 3.5 Hz), 6.04 (m, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.1, 26.7, 64.4, 70.8, 78.6, 84.2, 105.0, 111.2, 121.3, 131.8.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.60; H, 7.07. Found: C, 60.73; H, 7.36 %.

Methyl 3-*O*-Allyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranoside (51) and Methyl 3-*O*-Allyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-D-*xylo*-hex-5-enofuranoside (52)

A solution of the compound **49** (1.0 g, 4.4 mmol) and *p*-TSA (cat.) in MeOH (20 mL) were refluxed for 5 h and neutralized with Et_3N. Solvent was removed under reduced pressure and the residue extracted with EtOAc, washed with water, dried, evaporated and the residue purified on silica gel by column chromatography eluting with light petroleum:EtOAc (3:2) to afford **51** (0.42 g, 66 %) and **52** (0.21 g, 33%).

Compound **51**:

$[\alpha]_D$ = +125.3 (*c* 0.68, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.51 (s, 3 H), 3.62-3.91 (dd, 1 H, *J* = 3.6, 4.8 Hz), 3.95-4.43 (m, 3 H), 4.51-4.20 (t, 1 H, *J* = 4.8 Hz), 4.98 (d, 1 H, *J* = 3.6 Hz), 5.17-5.48 (m, 4 H), 5.76-6.07 (m, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.7, 71.0, 76.8 79.9, 84.8, 101.8, 116.9, 118.0, 134.1, 134.5.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.24; H, 7.86 %.

Compound **52**:

$[\alpha]_D$ = -31.0 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.34 (s, 3 H), 3.83 (dd, 1 H, *J* = 3.3, 4.7 Hz), 3.93-4.19 (m, 4 H), 4.58 (t, 1 H, *J* = 4.7 Hz), 4.75 (s, 1 H), 5.09-5.33 (m, 4 H), 5.75-6.13 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.5, 71.3, 79.7, 82.0, 84.2, 109.0, 117.2, 117.9, 134.4, 135.0.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.27; H, 8.26 %.

(1*R*,6*R*,8*R*,9*R*)-8-Methoxy-9-hydroxy-2,7-dioxabicyclo[3.4.0]non-4-ene (53)

To a solution of the compound **51** (0.42 g, 2.1 mmol) in CH_2Cl_2 (25 mL) was added Grubbs' catalyst (34 mg, 2 mol %) under argon atmosphere and stirred at rt. After 8 h, solvent was removed and the residue purified on silica gel eluting with EtOAc:light petroleum (2:3) to afford **53** (0.3 g, 90 %).

$[\alpha]_D$ = +52.0 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.89 (br s, 1 H), 3.53 (s, 3 H), 3.84-4.57 (m, 5 H), 5.11 (d, 1 H, *J* = 4.2 Hz), 5.95-6.13 (m, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.9, 64.0, 69.3, 77.4, 80.9, 102.5, 122.3, 131.6.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.64; H, 6.97 %.

(1*R*,6*R*,8*S*,9*R*)-8-Methoxy-9-hydroxy-2,7-dioxabicyclo[3.4.0]non-4-ene (54)

To a solution of the compound **52** (0.21 g, 1.05 mmol) in CH_2Cl_2 (15 mL) was added Grubbs' catalyst (17 mg, 2 mol %) under argon atmosphere and stirred at rt. After 8 h, solvent was removed and the residue purified on silica gel eluting with EtOAc:light petroleum (2:3) to afford **54** (0.16 g, 90 %).

$[\alpha]_D$ = -206 (*c* 0.5, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.37 (s, 3 H), 3.92-4.01 (m, 2 H), 4.15-4.36 (m, 3 H), 4.83 (s, 1 H), 5.93-6.08 (m, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.6, 63.2, 71.8. 80.1, 80.2, 110.2, 123.4, 129.9.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.93; H, 6.81 %.

3-*O*-Crotyl-1,2:5,6-*O*-diisopropylidene-α-D-glucofuranose (55)

Compound **55** was prepared from **45** (3.0 g, 11.5 mmol) as described earlier using sodium hydride (60 % dispersion in mineral oil, 0.64 g, 16.1 mmol) and crotonyl bromide (1.5 mL, 15.0 mmol) in DMF (8 mL) to afford **55** (3.5 g, 96%) after purification on silica gel eluting with ethyl acetate-light petroleum 1:4);

$[\alpha]_D$ = -19.0 (*c* 1.6, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 3 H), 1.36 (s, 3 H), 1.43 (s, 3 H), 1.47 (s, 3 H), 1.73 (d, 3 H, *J* = 6.4 Hz), 3.83-4.09 (m, 6 H), 4.22 (m, 1 H), 4.52 (d, 1 H, *J* = 3.5 Hz), 5.48-5.73 (m, 2 H), 5.83 (d, 1 H, *J* = 3.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2, 25.0, 25.8, 26.4, 26.5, 66.8, 70.6, 72.1, 80.5, 80.8, 82.5, 104.8, 108.3, 111.1, 126.9, 128.9.

Anal. Calcd. for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 60.87; H, 8.14 %.

3-*O*-Crotyl -1,2-*O*-isopropylidene-α-D-glucofuranose (56)

Deprotection of **55** (3.50 g, 11.1 mmol) was done as described earlier using 0.8% H_2SO_4 (10 mL) in MeOH (25 mL) to afford compound **56** (2.23 g, 73%) after purification by silica gel column chromatography eluting with ethyl acetate-petroleum ether 3:7);

$[\alpha]_D$ = -17.5 (*c* 1.0, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ δ 1.30 (s, 3 H), 1.47 (s, 3 H), 1.72 (d, 3 H, *J* = 6.4 Hz), 3.66-3.71 (m, 2 H), 3.94-4.12 (m, 5 H), 4.52 (d, 1 H, *J* = 3.5 Hz), 5.43-5.63 (m, 2 H), 5.87 (d, 1 H, *J* = 3.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 17.2, 25.7, 26.2, 63.7, 68.4, 70.5, 79.4, 80.7, 81.9, 104.5, 111.0, 126.6, 129.4.

Anal. Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.72; H, 7.85 %.

3-*O*-Crotyl-5,6-di-*O*-mesyl-1,2-*O*-isopropylidene-α-D-glucofuranose (57)

Mesylation of **56** (2.2 g, 8.029 mmol) was done as described earlier using Et_3N (3.0 mL, 22.2 mmol) and methanesulfonylchloride (1.9 mL, 24.5 mmol) in CH_2Cl_2 (20 mL) to afford compound **57** (3.3 g, 95%) after purification on silica gel (chromatography using ethyl acetate-petroleum ether 4:6);

$[\alpha]_D$ = -16.1 (*c* 1.0, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (s, 3 H), 1.48 9s, 3 H), 1.74 (d, 3 H, *J* = 6.4 Hz), 3.06 (s, 3 H), 3.12 (s, 3 H), 4.01 (m, 3 H), 4.27-4.48 (m, 2 H), 4.56 (d, 1 H, *J* = 3.6 Hz), 4.59-4.73 (m, 1 H), 5.23 (m, 1 H), 5.50-5.78 (m, 2 H), 5.91 (d, 1 H, *J* = 3.6 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.5, 26.1, 26.7, 37.3, 38.9, 68.7, 70.9, 74.4, 77.7, 80.2, 81.4, 105.1, 112.1, 126.5, 130.4.

Anal. Calcd. for $C_{15}H_{26}O_8S_2$: C, 45.21; H, 6.58. Found: C, 45.38; H, 6.73 %.

3-*O*-Crotyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (58)

Compound **57** (2.0 g, 4.6 mmol) was converted to **58** as described earlier using NaI (5.6 g, 37.3 mmol) in refluxing 2-butanone (40 mL). Compound **58** was obtained in 71 % yield (0.8 g) after purification on silica gel by eluting with ethyl acetate-petroleum ether (1:4);

$[\alpha]_D$ = -54.6 (*c* 1.55, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (s, 3 H), 1.48 (s, 3 H), 1.76 (d, 3 H, *J* = 6.5 Hz), 3.78 (d, 1 H, *J* = 3.7 Hz), 3.96-4.01 (m, 2 H), 4.53 (m, 2 H), 5.28-5.73 (m, 4 H), 5.93 (m, 2 H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 17.4, 26.0, 26.6, 70.7, 81.3, 82.8, 82.9, 104.6, 111.1, 118.2, 126.9, 129.2, 132.5.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.26; H, 8.53 %.

(1*R*,6*R*,8*R*,9*R*)-8,9-Dihydroxy-8,9-*O*-isopropylidene-2,7-dioxabicyclo[3.4.0]non-4-ene (50)

To a solution of the compound **58** (0.1 g, 0.4 mmol) in CH_2Cl_2 (5 mL) was added Grubbs' catalyst (7.0 mg, 2 mol %) under argon atmosphere and stirred at rt. After 12 h, solvent was removed and the residue purified on silica gel eluting with EtOAc:light petroleum (2:3) to afford **50** (0.05 g, 60 %);

$[\alpha]_D$ = -16.0 (*c* 1.0, $CHCl_3$).

3-*O*-Propargyl-1,2:5,6-*O*-diisopropylidene-α-D-glucofuranose (59)

Compound **59** was prepared from **45** (3.0 g, 11.5 mmol) as described earlier using sodium hydride (60 % dispersion in mineral oil, 0.55 g, 13.8 mmol) and propargylbromide (1.2 mL, 13.8 mmol) in DMF (8 mL) in 81 % yield (2.7 g);

$[\alpha]_D$ = -10.6 (*c* 1.2, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3 H), 1.36 (s, 3 H), 1.42 (s, 3 H), 1.48 (s, 3 H), 2.48 (t, 1 H, *J* = 2.5 Hz), 3.89-4.32 (m, 6 H), 4.64 (d, 1 H, *J* = 3.5 Hz), 5.87 (d, 1 H, *J* = 3.5 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2, 26.1, 26.6, 26.7, 57.8, 67.0, 72.3, 74.9, 80.9, 81.4, 82.7, 105.0, 108.6, 111.5.

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.40; H, 7.38. Found: C, 60.62; H, 7.08 %.

3-*O*- Propargyl -1,2-*O*-isopropylidene-α-D-glucofuranose (60)

Compound **60** was prepared from **59** (2.0 g, 6.7 mmol) as described earlier using 0.8% H_2SO_4 (10 mL) in 79 % yield (1.3 g);

$[\alpha]_D$ = -40.7 (*c* 1.0, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ δ 1.35 (s, 3 H), 1.47 (s, 3 H), 2.51 (t, 1 H, *J* = 2.6 Hz), 2.75 (brs, 1 H), 3.66-4.33 (m, 8 H), 4.61 (d, 1 H, *J* = 3.5 Hz), 5.87 (d, 1 H, *J* = 3.5 Hz);

^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 26.4, 57.6, 63.9, 68.5, 74.8, 79.3, 79.6. 81.4, 82.1, 104.8, 111.5.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.63; H, 7.28 %.

3-*O*-Propargyl-5,6-di-*O*-mesyl-1,2-*O*-isopropylidene-α-D-glucofuranose (61)

Compound **61** was prepared from **60** (1.0 g, 3.9 mmol) as described earlier in CH_2Cl_2 (10 mL) using Et_3N (1.4 mL, 10.4 mmol) and methanesulfonyl chloride (0.8 mL, 10.3 mmol) in 87 % yield (1.2 g);

$[\alpha]_D$ = -18.5 (*c* 1.1, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3 H), 1.48 (s, 3 H), 2.52 (t, 1 H, *J* = 2.5 Hz), 3.03 (s, 3 H), 3.11 (s, 3 H), 4.16 (d, 1 H, *J* = 3.6 Hz), 4.26 (d, 1 H, *J* = 2.5 Hz), 4.31-4.48 (m, 2 H), 4.64 (m 1 H), 4.76 (d, 1 H, *J* = 3.6 Hz), 5.08-5.19 (m, 1 H), 5.89 (d, 1 H, *J* = 3.6 Hz);

Anal. Calcd. for $C_{14}H_{22}O_8S_2$: C, 43.97; H, 5.80; S, 16.77. Found: C, 43.75; H, 6.03; S, 16.53 %.

3-*O*-Propargyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (62)

Enyne **62** was prepared from **61** (1.0 g, 2.6 mmol) and NaI (3.9 g, 26.0 mmol) as described earlier (0.43 g, 73 % after purification on silica gel by using ethyl acetate-petroleum ether 2:8);

$[\alpha]_D$ = -52.9 (*c* 1.1, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3 H), 1.46 (s, 3 H), 2.46 (d, 1 H, *J* = 2.4 Hz), 4.07 (d, 1 H, *J* = 3.5 Hz), 4.23 (d, 1 H, *J* = 3.5 Hz), 4.63-4.71 (m 2 H), 5.30-5.48 (m, 2 H), 5.81-6.03 (m, 1 H), 5.94 (d, 1 H, *J* = 3.5 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.4, 24.2, 57.2, 74.9, 78.8, 80.9, 82.2, 82.7, 104.1, 112.5, 118.2, 131.9.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.04; H, 7.35 %.

(1*R*,6*R*,8*R*,9*R*)-8,9-Dihydroxy-8,9-*O*-isopropylidene-4-vinyl-2,7-dioxabicyclo[3.4.0]non-4-ene (63)

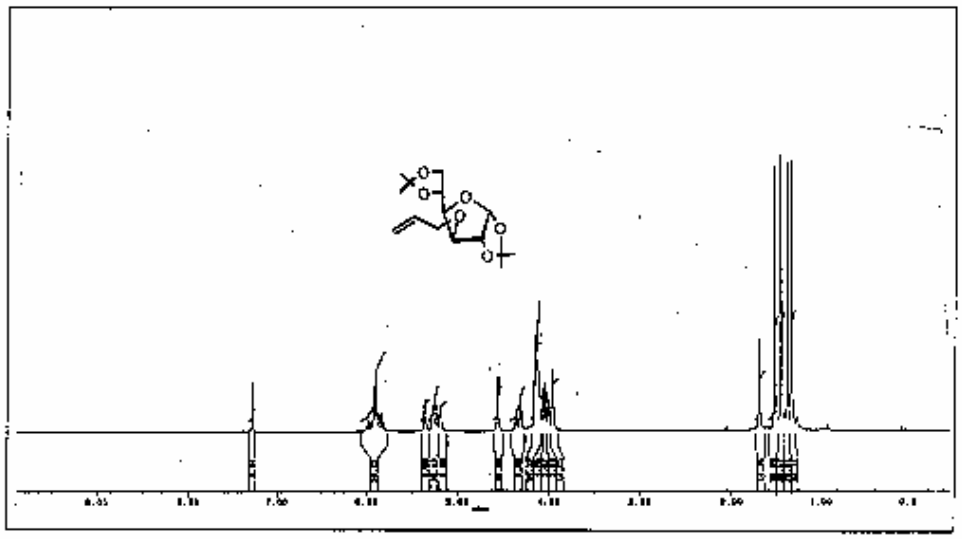
To a solution of the compound **62** (0.4 g, 1.8 mmol) in CH_2Cl_2 (10 mL) under Argon atmosphere was added Grubbs' catalyst (29 mg, 2 mol %) and heated at reflux for 4 h. The solvent was evaporated and the residue purified on silica gel using ethyl acetate-petroleum ether (1:9) as an eluent to afford compound **63** (0.33 g, 90 %);

$[\alpha]_D$ = -26.0 (*c* 0.8, $CHCl_3$);

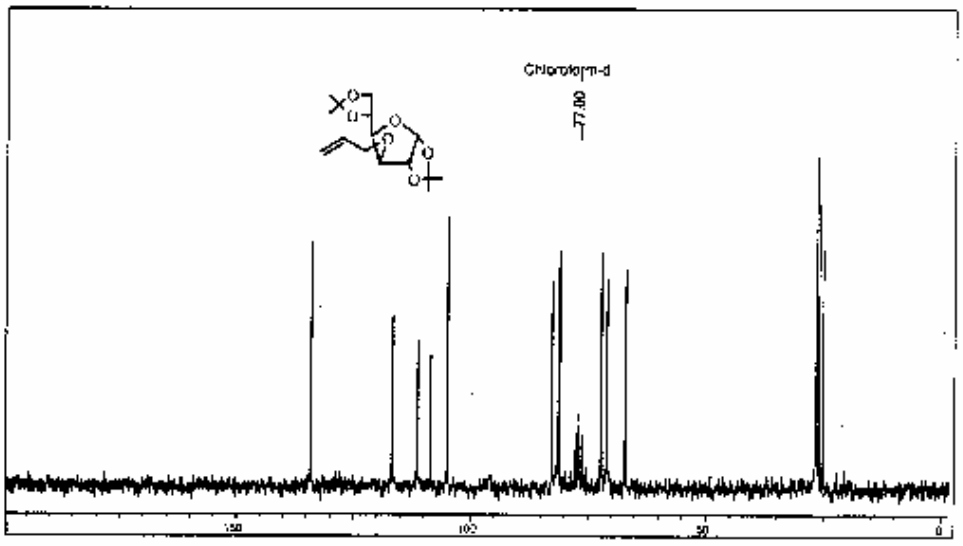
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 3 H), 1.50 (s, 3 H), 3.89 (d, 1 H, *J* = 3.0 Hz), 4.14 (d, 2 H, *J* = 14.2 Hz), 4.46 (m, 2 H), 4.57 (d, 1 H, *J* = 3.0 Hz), 5.10 (d, 1 H, *J* = 17.8 Hz), 5.14 (d, 1 H, *J* = 10.7 Hz), 5.92 (d, 2 H, *J* = 3.0 Hz), 6.28 (dd, 1 H, *J* = 10.7, 17.8 Hz);

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2, 26.5, 64.5, 70.8, 78.7, 84.5, 104.9, 111.2, 111.4, 116.0, 138.7, 142.3.

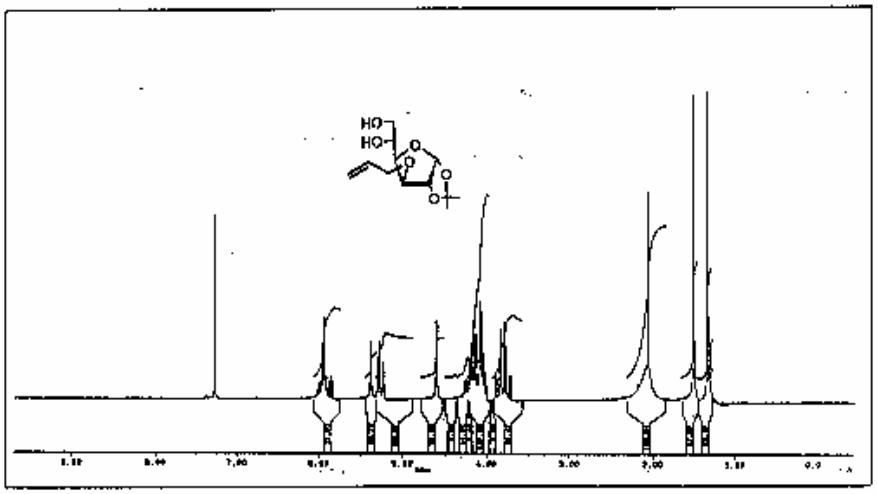
Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.36; H, 7.28 %.



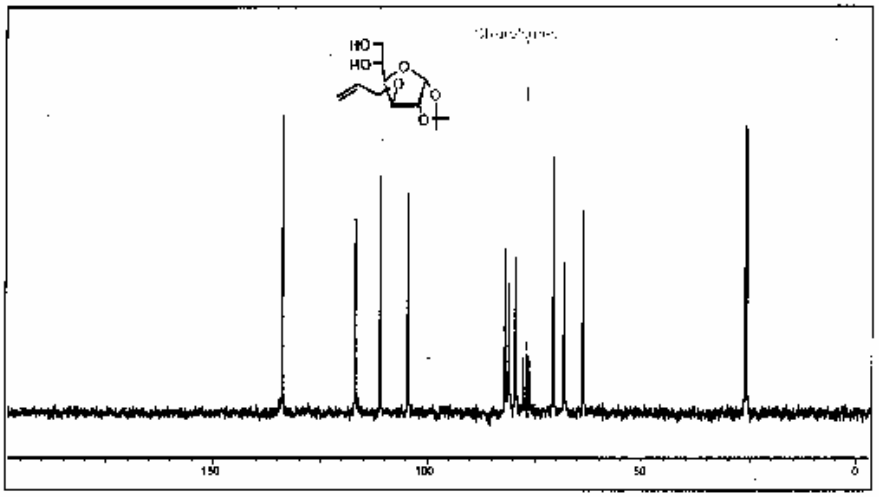
^{1}H NMR spectrum of compound 46 in $CDCl_3$



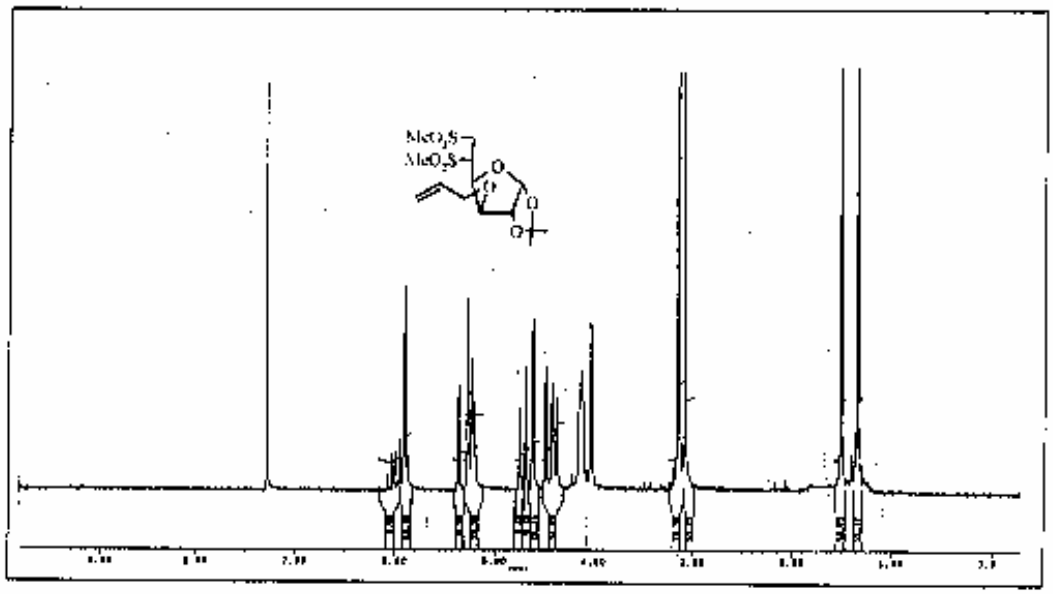
^{13}C NMR spectrum of compound 46 in $CDCl_3$



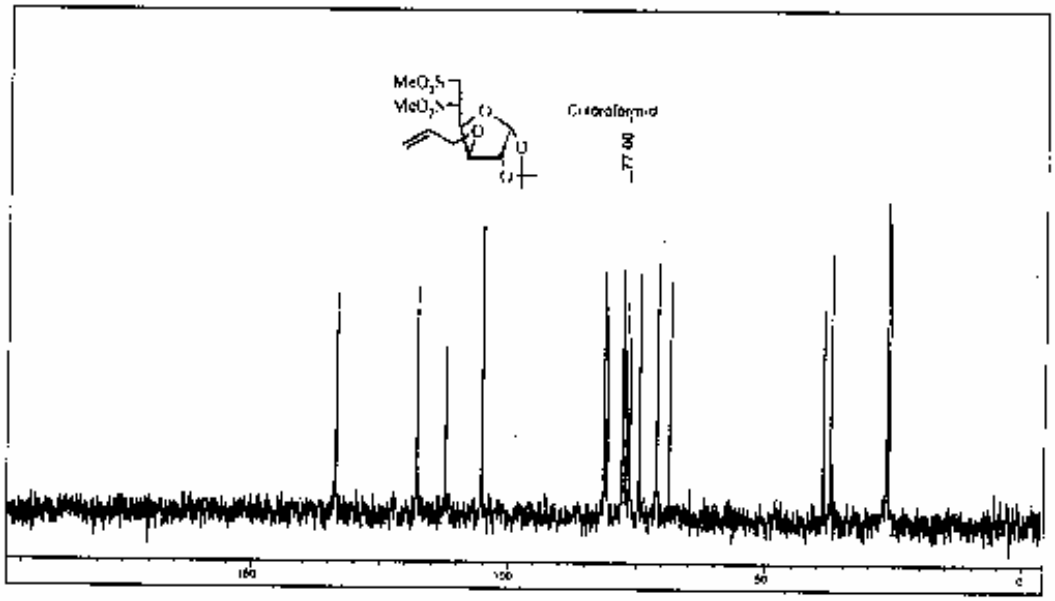
^{1}H NMR spectrum of compound 47 in $CDCl_3$



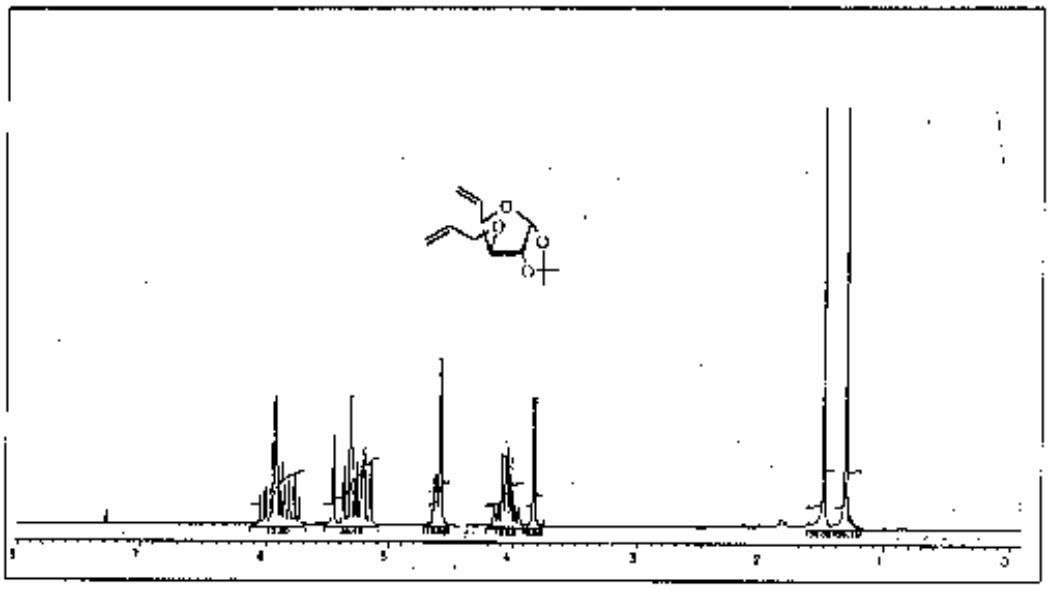
^{13}C NMR of compound 47 in $CDCl_3$



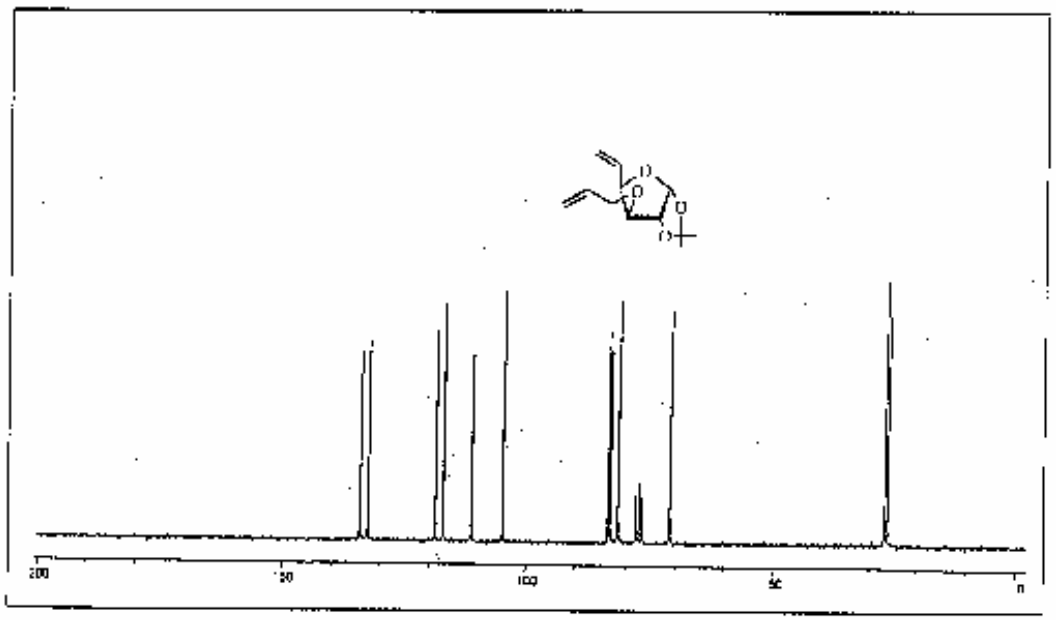
^{1}H NMR spectrum of compound 48 in $CDCl_3$



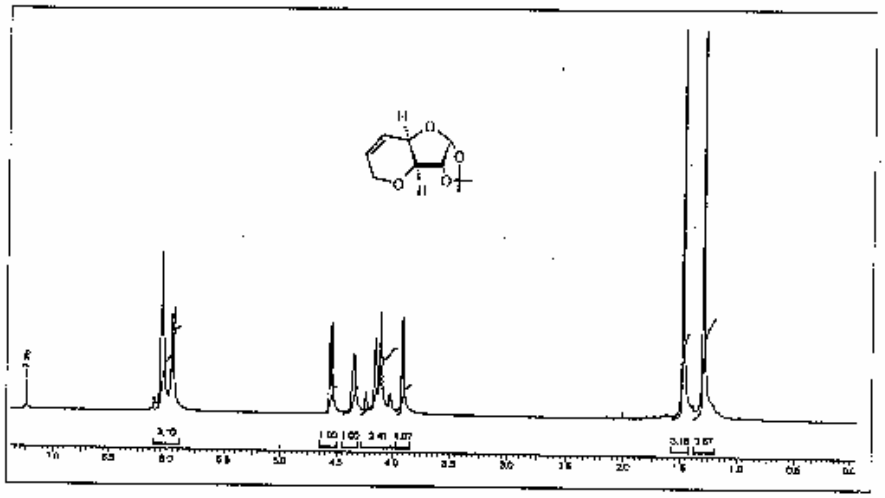
^{13}C NMR spectrum of compound 48 in $CDCl_3$



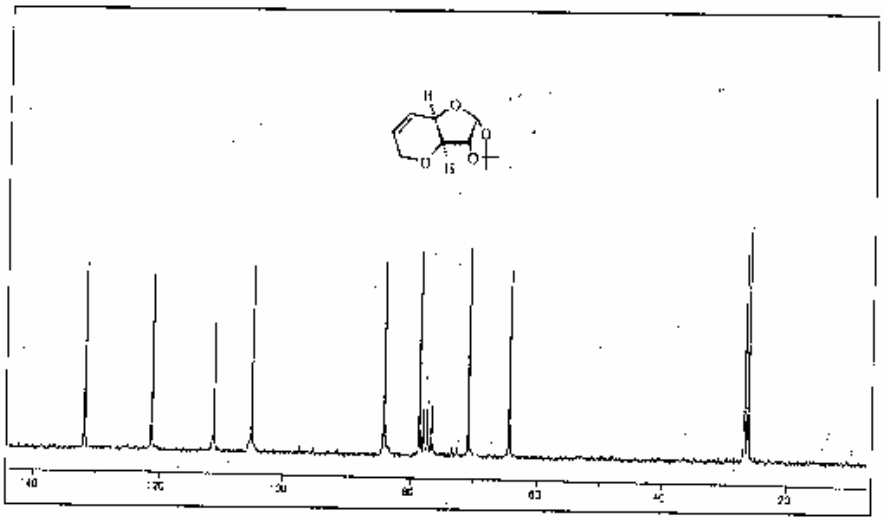
^{1}H NMR spectrum of compound 49 in $CDCl_3$



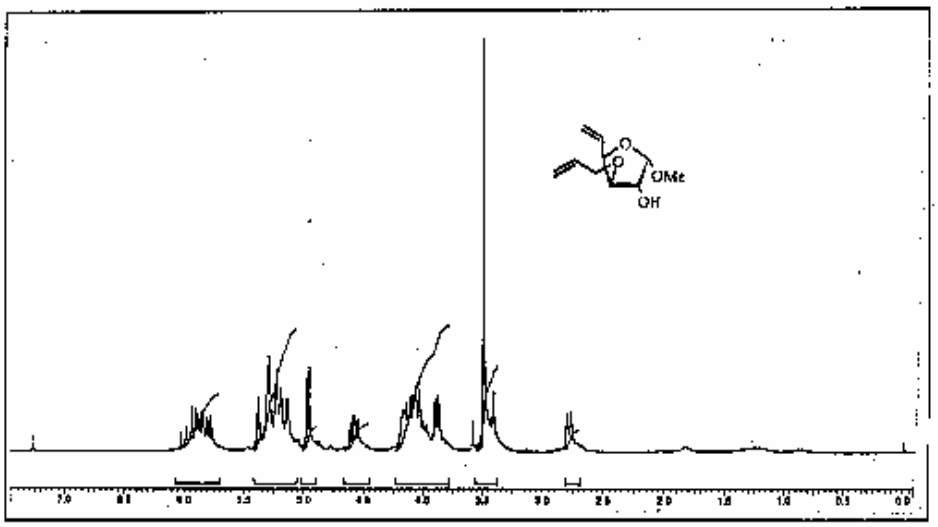
^{13}C NMR spectrum of compound 49 in $CDCl_3$



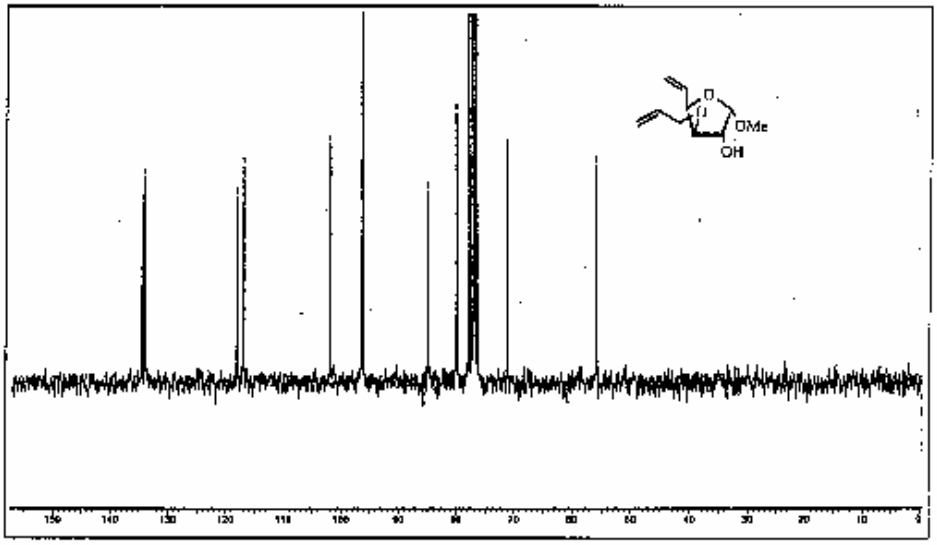
^{1}H NMR spectrum of compound 50 in $CDCl_3$



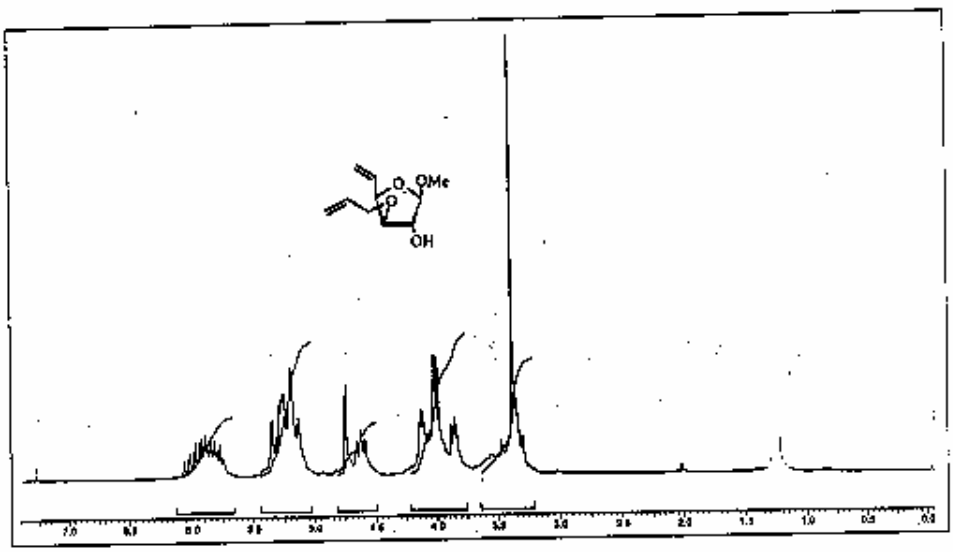
^{13}C NMR spectrum of compound 50 in $CDCl_3$



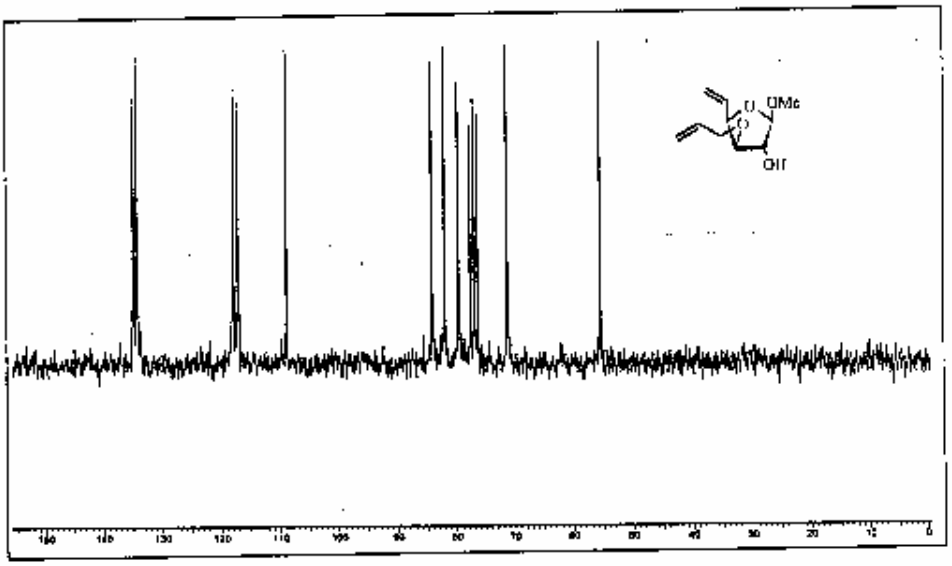
^{1}H NMR spectrum of compound 51 in $CDCl_3$



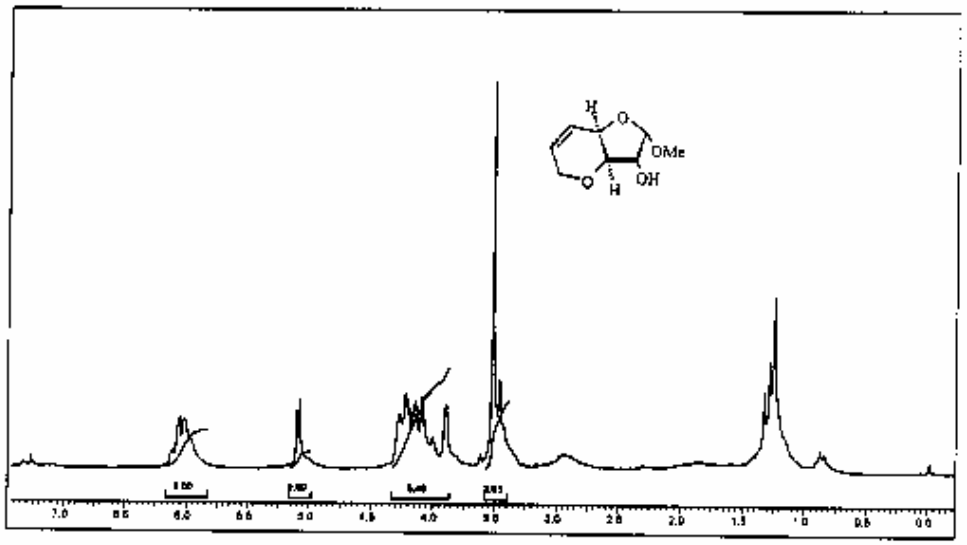
^{13}C NMR spectrum of compound 51 in $CDCl_3$



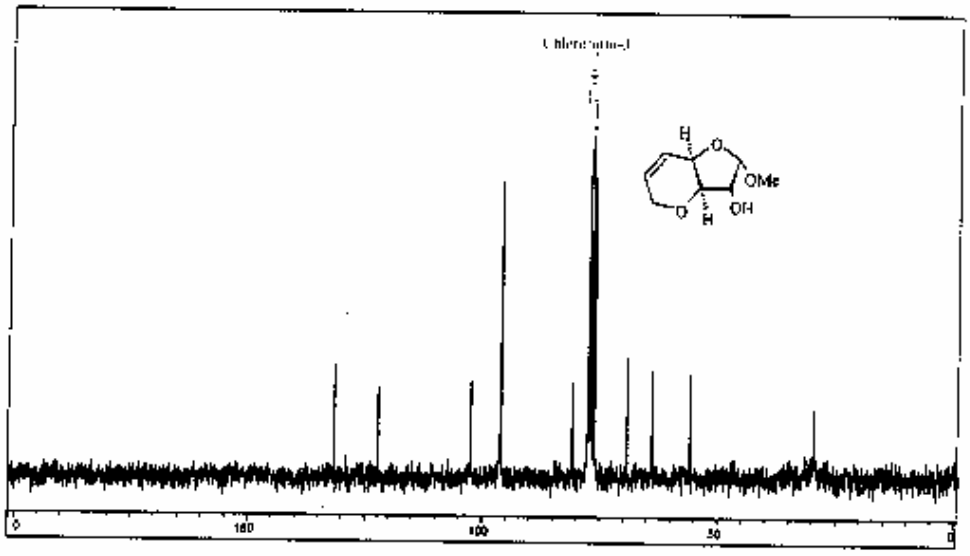
^{1}H NMR spectrum of compound 52 in $CDCl_3$



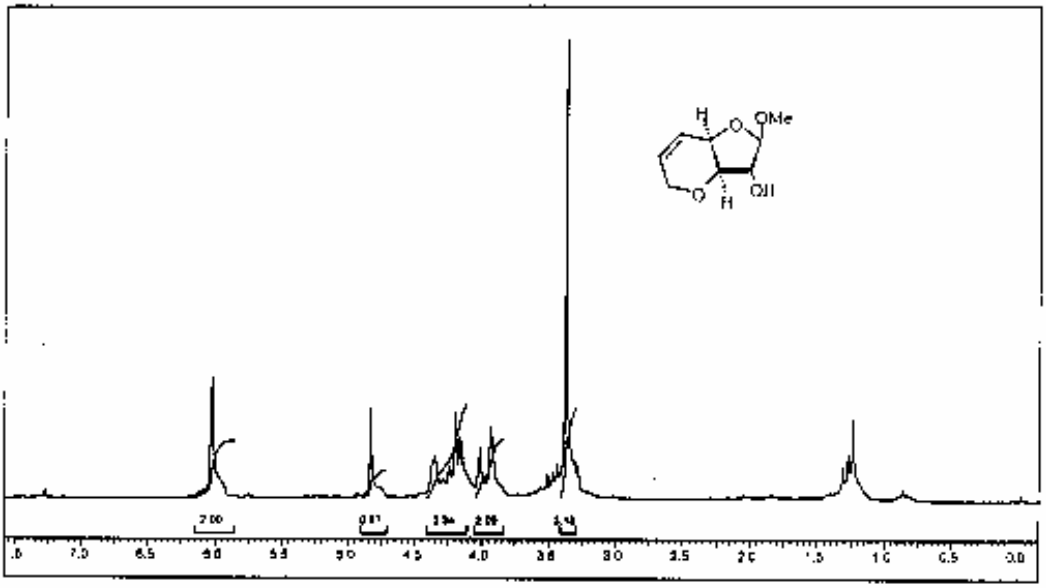
^{13}C NMR spectrum of compound 52 in $CDCl_3$



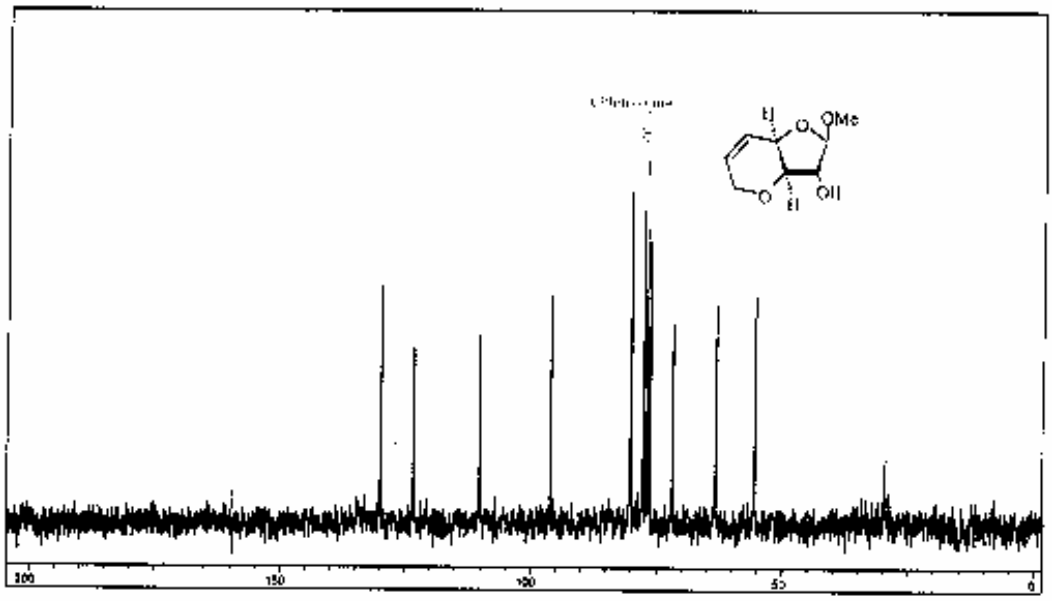
^{1}H NMR spectrum of compound 53 in $CDCl_3$



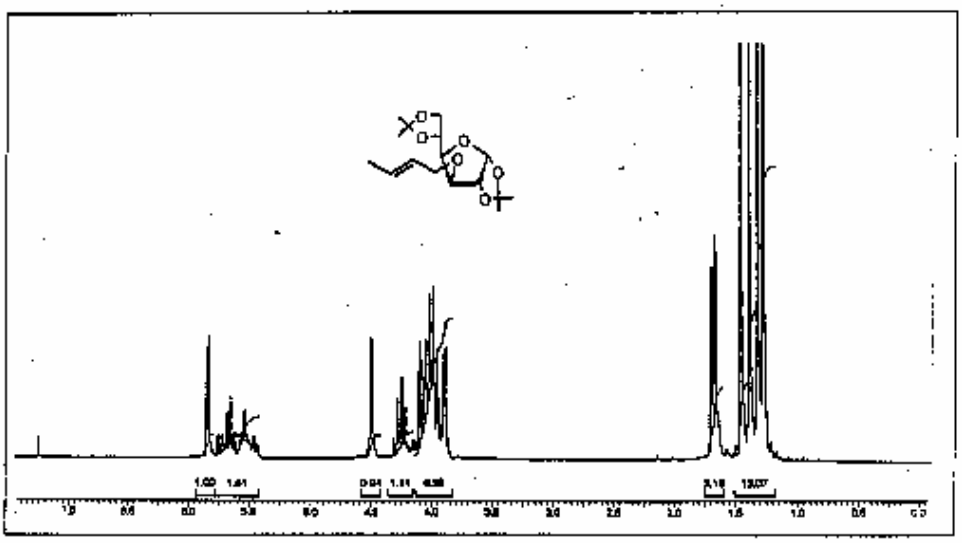
^{13}C NMR spectrum of compound 53 in $CDCl_3$



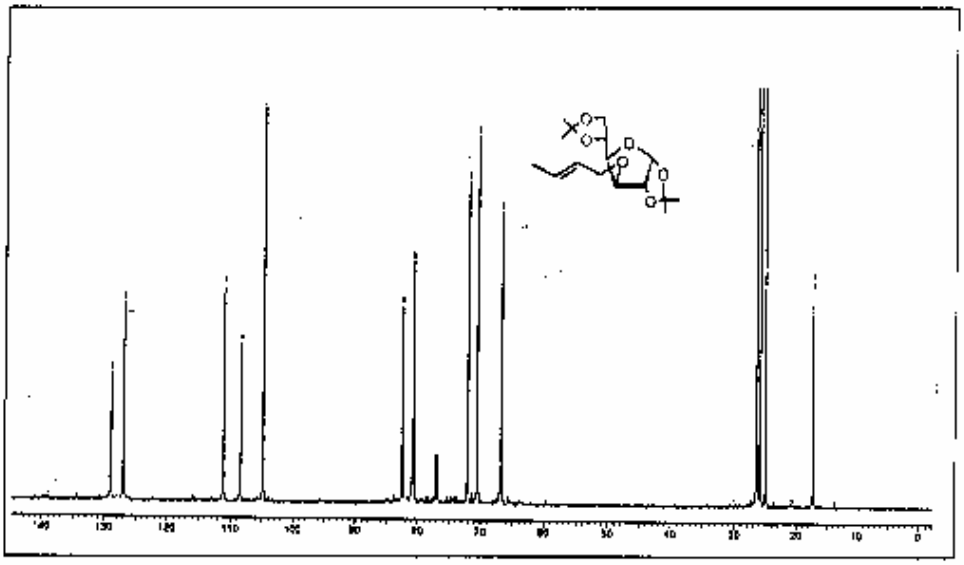
^{1}H NMR spectrum of compound 54 in $CDCl_3$



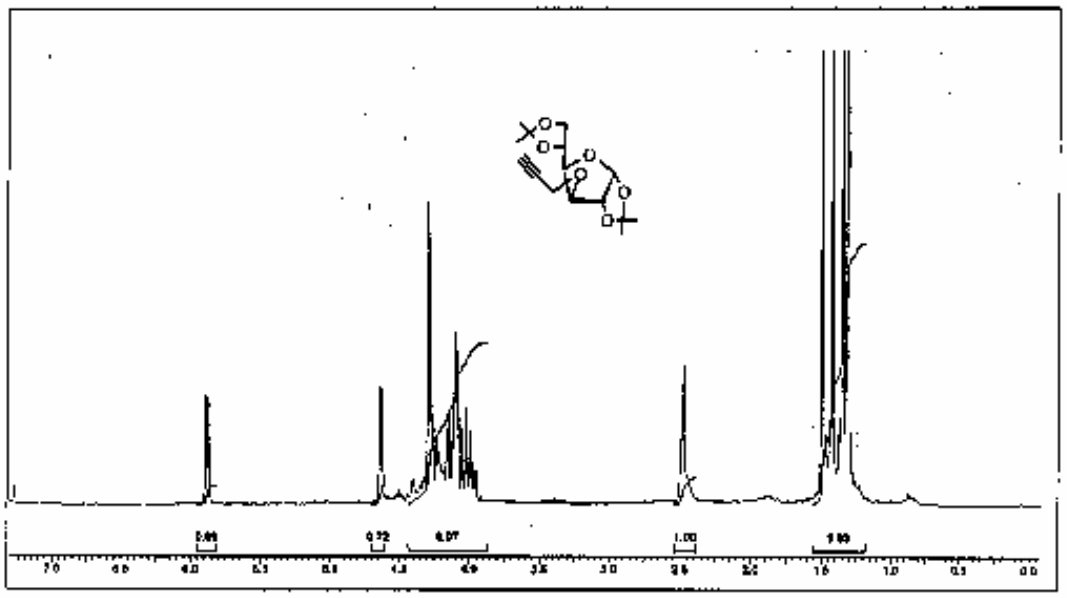
^{13}C NMR spectrum of compound 54 in $CDCl_3$



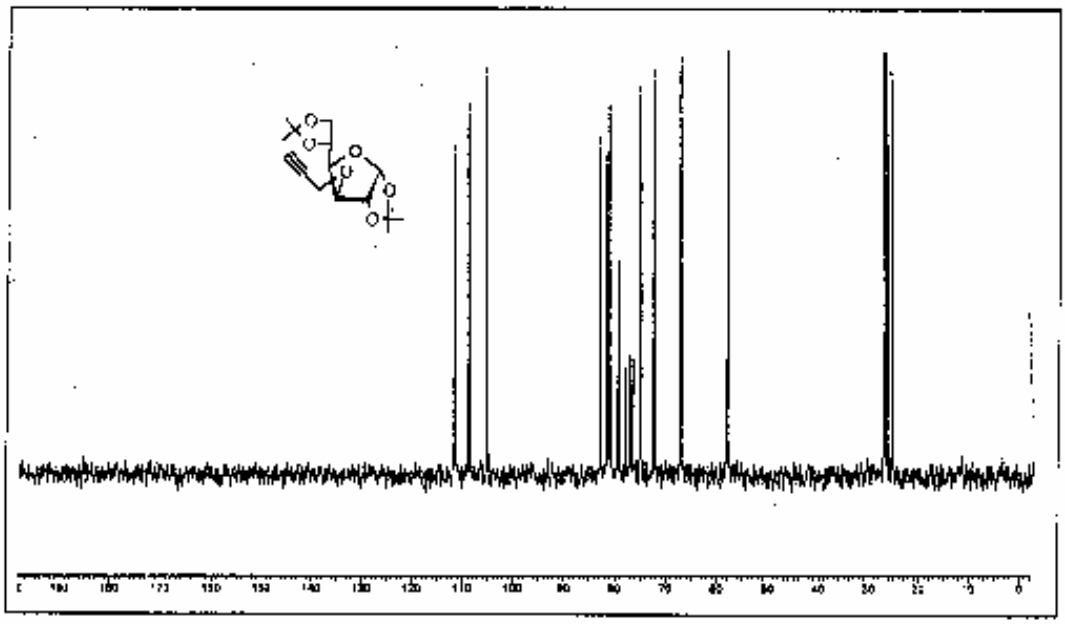
^{1}H NMR spectrum of compound 55 in $CDCl_3$



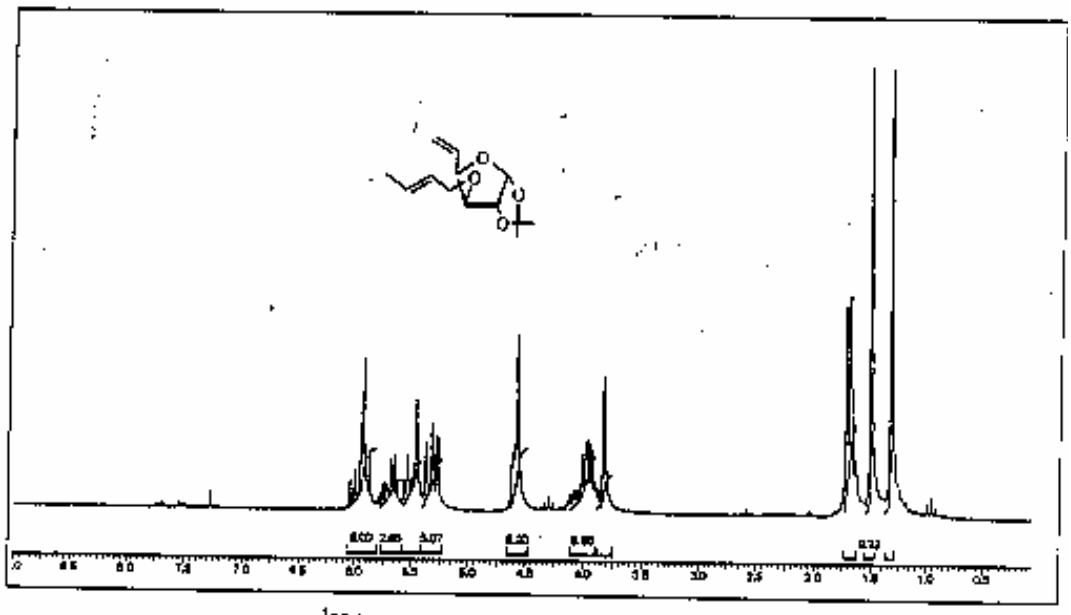
^{13}C NMR spectrum of compound 55 in $CDCl_3$



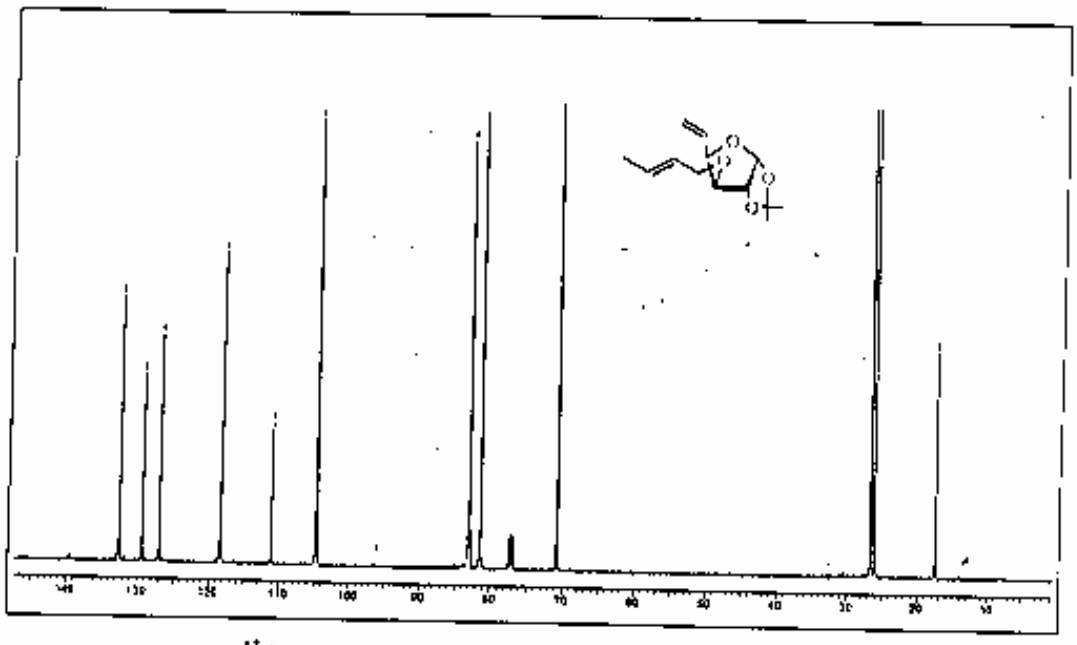
^{1}H NMR spectrum of compound 59 in $CDCl_3$



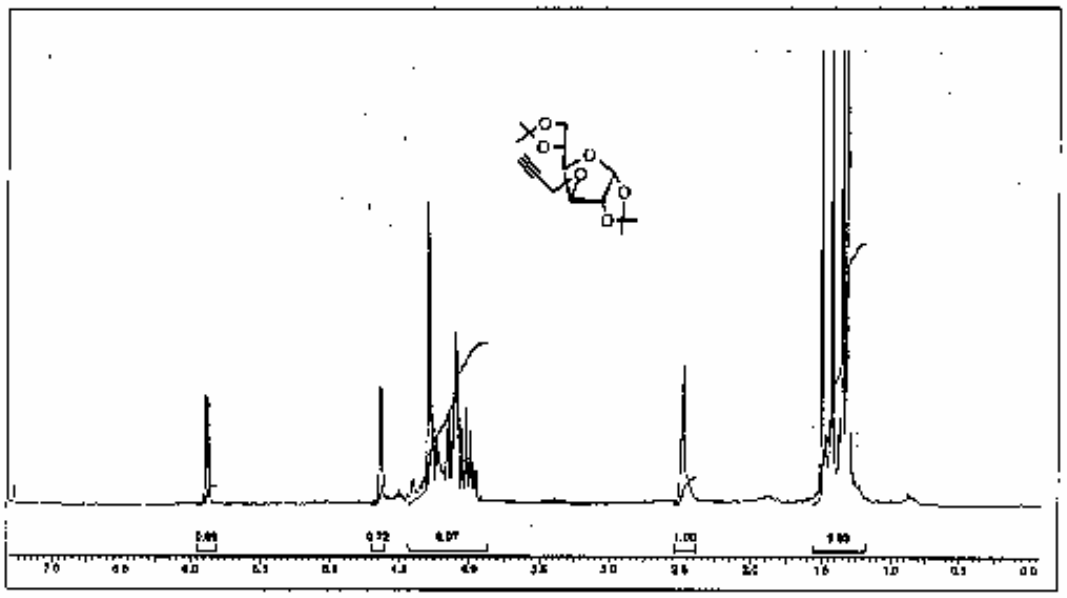
^{13}C NMR spectrum of compound 59 in $CDCl_3$



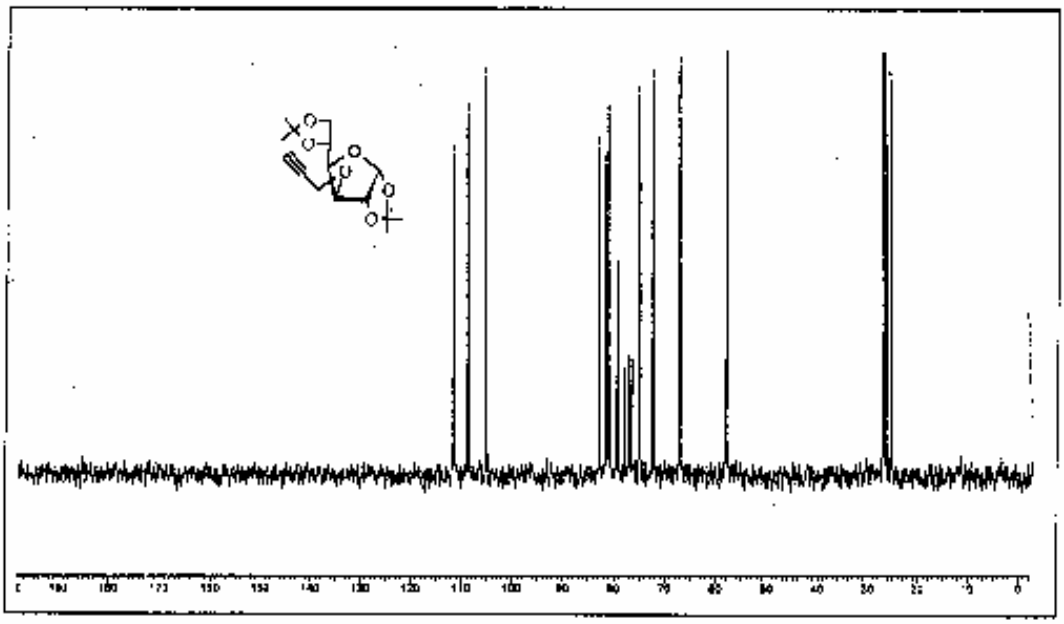
^{1}H NMR spectrum of compound 58 in $CDCl_3$



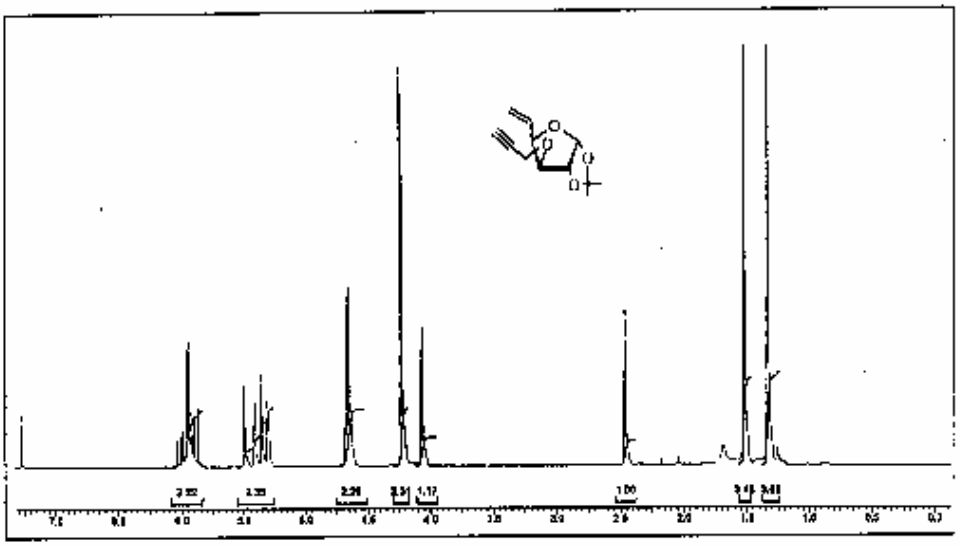
^{13}C NMR spectrum of compound 58 in $CDCl_3$



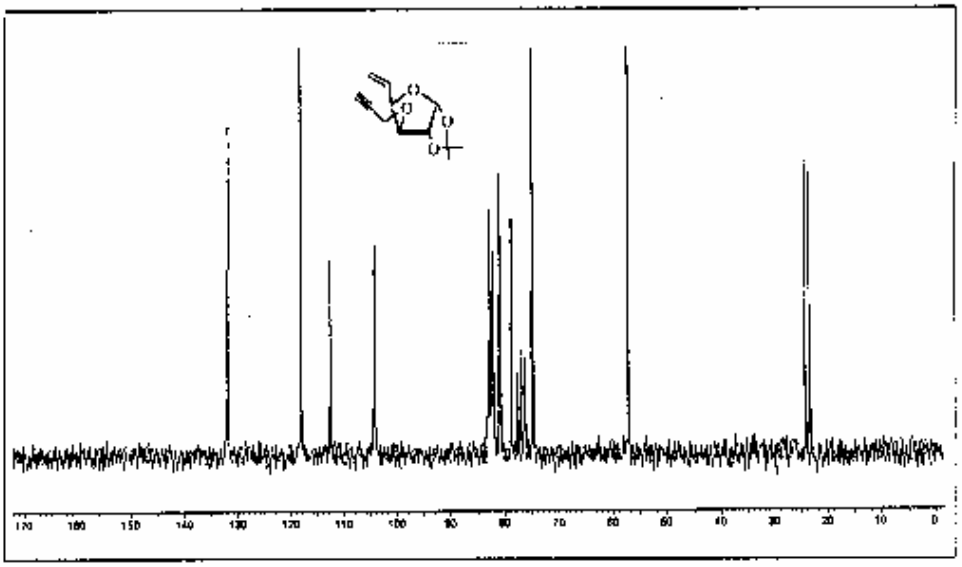
^{1}H NMR spectrum of compound 59 in $CDCl_3$



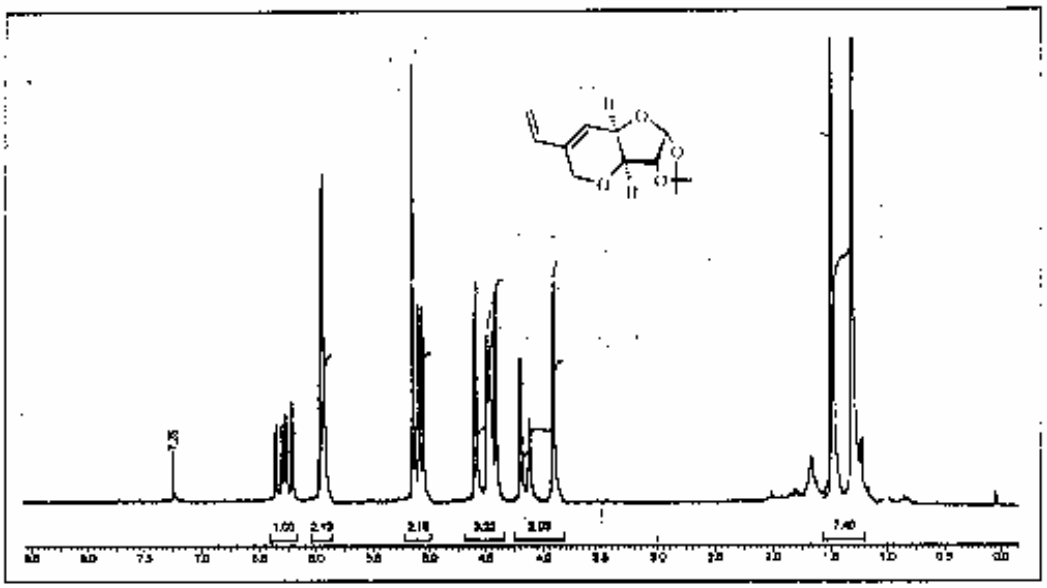
^{13}C NMR spectrum of compound 59 in $CDCl_3$



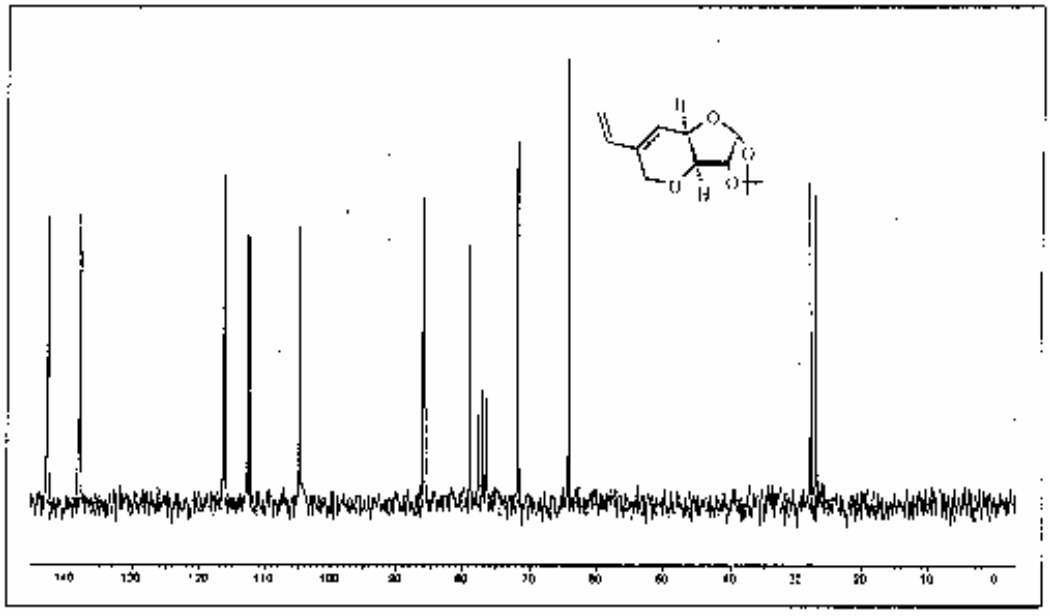
^{1}H NMR spectrum of compound 62 in $CDCl_3$



^{13}C NMR spectrum of compound 62 in $CDCl_3$



^{1}H NMR spectrum of compound 63 in $CDCl_3$



^{13}C NMR spectrum of compound 63 in $CDCl_3$

References

1. For a recent collection of reviews surveying the immense variety of marine natural products, see: *Chem. Rev*. **1993**, *93*, 1671; Faulkner, D. J. *Nat. Prod. Rep.*, **1995**, *12*, 223.
2. Alvarez, E.; Candenas, M.; Perez, R.; Ravelo, J. L.; Martin, J. D. *Chem. Rev.,* **1995**, *95*, 1953; Hiro, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett*., **1999**, *40*, 2811; Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett*., **1999**, *40*, 1337; Fujiwara, K.; Saka, K.; Takaoka, D.; Murai, A. *Synlett*, **1999**, 1037; Bowman, J. L.; McDonald, F. E. *J. Org. Chem.*, **1998**, *63*, 3680; Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.*, **1998**, 1041; Clark, J. S.; Kettle, K. G. *Tetrahedron Lett.*, **1997**, *38*, 123; Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118,* 1565; Rychnovsky, S. D .; Dahanukar, V. H.. *J. Org. Chem*., **1996**, *61*, 7648; Isobe, M.; Hosokawa, S.; Kira, K. *Chem. Lett,* **1996**, 473; Kadota, I.; Jung-Youl, P.; Koumura, N.; Polllaud, G. *Tetrahderon Lett.*, **1995**, *36*, 5777.
3. Mori, Y.; Yagashi, K.; Furukawa, H. *Tetrahedron Lett.*, **1999,** *40*, 7239; Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.*, **1996**, *61*, 4880;Hayashi, N.; Fujisawa, K.; Murai, A. *Tetrahedron Lett.*, **1996**, *37*, 6173; Ravelo, J. L.;regueiro, A.; Rodriguez, J.; de Vera.; Martin, J. D. *Tetrahedron Lett.*, **1996**, *37*, 2869.
4. Knapp, S. *Chem. Rev.*, **1995**, *95*, 1859.
5. Cooper, A. J.; Salomon, R.G. *Tetrahedron Lett.*, **1990**, *31*, 3813.
6. Fang, F. G.; Kishi, Y.; Matelich, M. C.; Scola, P. M. *Tetrahedron Lett.*, **1992**, *33*, 1557.
7. Lambert, W. T.; Burke, S. D. *Org. Lett.*, **2003**, *5*, 515.
8. Leeuwenburgh, M. A.; E. J. N. Litjens, R. E. J. N.; Codée, J. D. C.; Overkleeft, S. H.; van der Marel, G. A.; van Boom, J. H. *Org. Lett.*, **2000**, *2*, 1275.
9. Burke, S. D.; Austad, B. C.; Hart, A. C. *J. Org. Chem.*, **1998**, *63*, 6770.
10. Burke, S. D.; Jung, W. K.; Lambert, W. T.; Phillips, J. R.; Klovning, J. J. *J. Org. Chem.*, **2000**, *65*, 4070.
11. Ibuka, T.; Takemoto, Y.; Hayase, H.; Iwanaga, S.; Yamagata, S.; Iwata, C.; Tanaka, T. *Tetrahedron Lett.,* **1998**, *39*, 7545

12. Takemoto, Y.; Furuse, S.; Hayase, H.; Echigo, T.; Iwata, C.; Tanaka,T.; Ibuka, T. *Chem. Commun.*, **1999**, 2515.
13. DiFranko,E.; Ravikumar, V. T.; Salomon, R. G. *Tetrahedron Lett.*, **1993**, *34*, 3247.
14. Block, E. *Org. React.*, **1984**, *30*.
15. Kinoshita, A.; Mori, M. *Synlett*, **1994**, 1020.