Synthetic studies towards the CMI-977, Calditol and Calanolide

Submitted by

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DECLARATION

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

Date: **(Bethi Sridhar Reddy)**

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CERTIFICATE

The research work presented in this thesis entitled ***"Synthetic studies towards the CMI-977, Calditol and Calanolide"*** has been carried out under my supervision and is bonafide work of **Mr. Bethi Sridhar Reddy**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

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

Date: (Research Guide)

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It gives me immense pleasure to express my deep sense of gratitude to my mentor 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. Working with him was great pleasure and learning experience.

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Whatever I am and whatever I will be in future is because of the goodwill and unstinted support that I have received from my family. 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.

Bethi Sridhar Reddy

- 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 Varian FT-200 MHZ (Gemini), 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 CEC-21-110B, Finnigan Mat 1210 or MICRO MASS 7070 spectrometer at 70 eV using a direct inlet system. FABMS were recorded on a VG auto spec mass 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 reagent in ethanol as development reagents.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C.
- All solvents and reagents were purified and dried 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.

Ac	- Acetyl
AcOH	- Acetic acid
Ac_2O	- Acetic anhydride
BF_3:OEt_2	- Borontrifluoride diethyletherate
Bn	- Benzyl
BnBr	- Benzyl bromide
Bu_3SnH	-Tributyltinhydride
DIBAL-H	- Diisobutylaluminium hydride
DIPEA	- Diisopropylethylamine
DMAP	- *N, N'*-Dimethylaminopyridine
DMDO	-Dimethyldioxirane
DMF	- *N, N'*-Dimethylformamide
DMSO	- Dimethyl sulfoxide
Et	- Ethyl
EtOAc	- Ethyl acetate
EtOEt, Et_2O	-Diethylether
EtOH	- Ethanol
Im	- Imidazole
LDA	- Lithiumdiisopropylamide
MeOH	- Methanol
MEMCl	-Methoxyethoxymethylchloride
NaOMe	- Sodium methoxide
Pd/C	- Palladium on carbon
PMB	- *para*-Methoxy benzyl
PPTS	-pyridinium-*para*-toluenesulphonate
*p*TSA	- *para*-Toluenesulfonic acid
Py	- Pyridine
TBAF	- Tetrabutylammonium fluoride
TBDMS-Cl	- *tert*-Butyldimethylchlorosilane
TEA	- Triethyl amine
THF	- Tetrahydrofuran
TsCl	-*p*-Toluenesulphonylchloride

Contents

Abstract

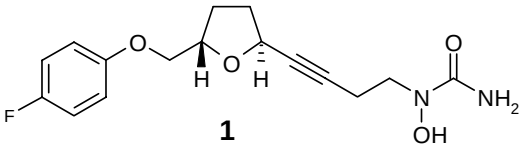
Abstract

The thesis entitled **"Synthetic studies towards the CMI-977, Calditol and Calanolide**" is devided into three chapters. First chapter explains the total synthesis of CMI-977 and it's six membered analogue. The second chapter discusses the total synthesis of 5-*epi* calditol and in the third chapter synthetic studies towards the calanolide carba analogue was discussed.

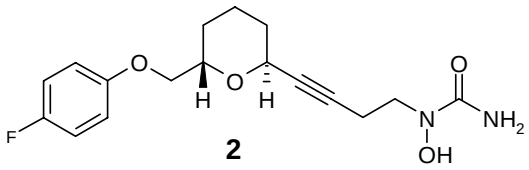
Chapter I.

Total Synthesis of CMI-977 and it's higher analogue.

The role of leukotrienes in inflammatory and allergic responses including arthritis, asthma, psoriasis, and thrombotic deseace has been well recognized. The urge to develop antagonists or inhibitors of leukotrienes biosynthesis to prevent inflammatory responses is an ongoing process. Various 2,5-disubstituted tetrahydrofuran derivatives have been reported with lipoxygenase inhibitory activity. However, (2*S*,5*S*)-5-(4-fluorophenoxymethyl)-2-(1-N-hydroxyureidylbut-3-yn-4-yl)tetrahydrouran (CMI-977) (**1**) is by far the most potent compound reported in this series. In this chapter we explained the total synthesis of this CMI-977 and it's six membered analogue (**2**).



1



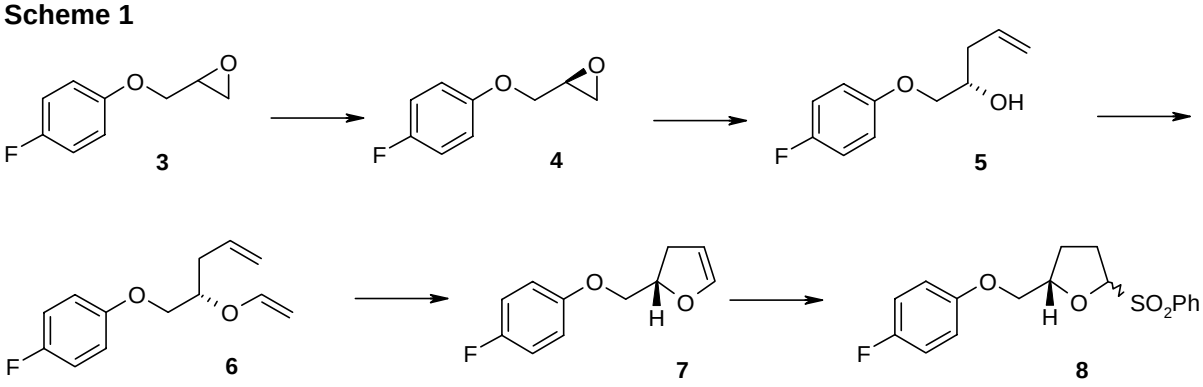
2

Section 1: Synthesis of CMI-977.

The synthesis begins with the hydrolytic kinetic resolution of glycidyl-4-fluorophenylether to get *S*-isomer (**4**) in 92% ee. Subsequent reaction of **4** with vinylmagnesium bromide in the presence of CuCN provided compound **5**. The conversion of free OH group into the vinyl ether **6** was accomplished by treatment of **5** with ethyl vinyl ether and $Hg(OCOCF_3)_2$.

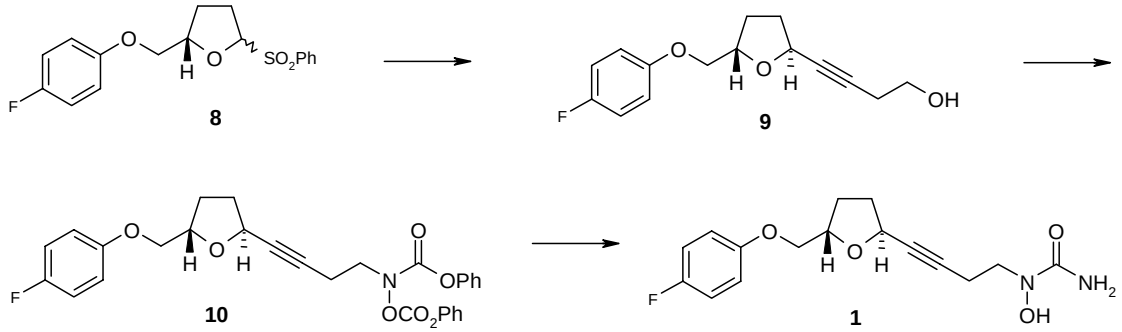
The ring-closing metathesis of **6** in the presence of Grubb's catalyst (5 mol%) in refluxing benzene gave the dihydrofuran derivative **7**, which was treated with benzenesulfinic acid in CH_2Cl_2 to give benzenesulfonyltetrahydrofuran derivative (**8**).

Scheme 1



Subsequent C-C bond formation at C-2 was carried out by treating compound **8** with dialkyl zinc reagent derived from BrMg-C≡C-CH_2-CH_2-OTHP and $ZnBr_2$ followed by deprotection with *p*TSA in methanol to give 7:3 mixture of *trans-cis* isomers. The pure trans isomer was isolated after crystallization. Introduction of *N*-hydroxy urea group was achieved in two steps involving Mitsunobu reaction of **9** with *N*, *O*-bis (phenoxycarbonyl)hydroxylamine followed by treatment of **10** with ammonia in methanol to give CMI-977.

Scheme 2

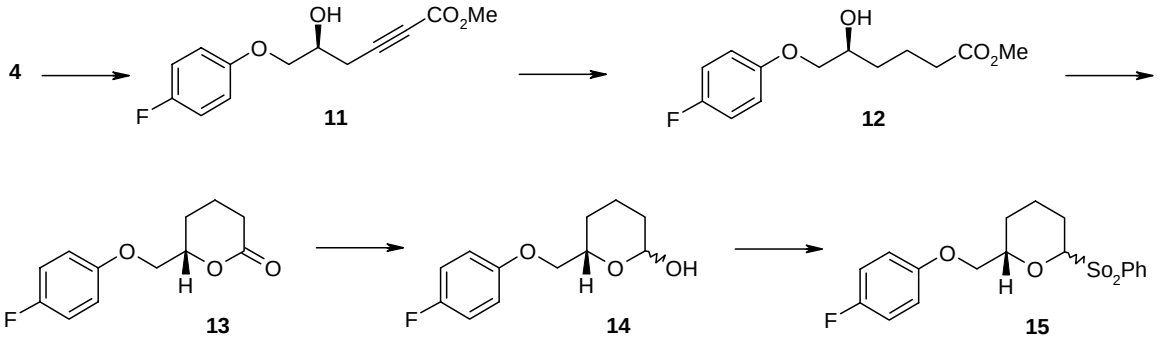


Section 2: Synthesis of CMI-977 six membered analogue.

After the successful synthesis of CMI-977, we decided to evaluate the biological activity by increasing the ring size, hence we started the total synthesis of six membered analogue of CMI-977.

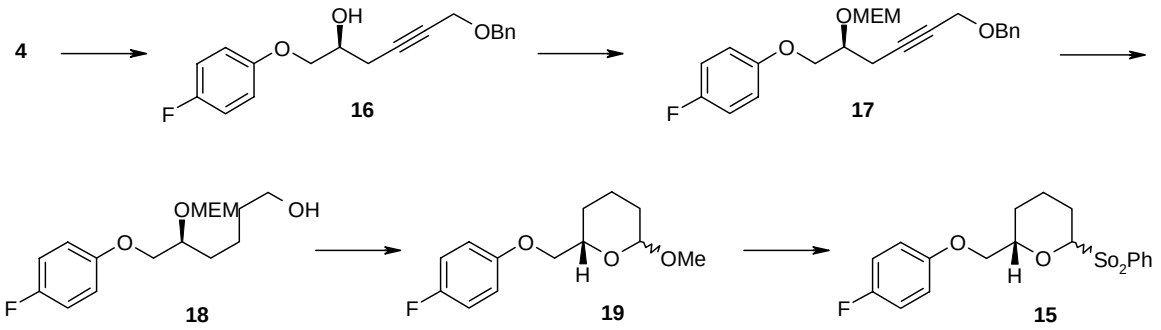
The synthesis starts with the epoxide opening of (*S*)-glycidyl-4-fluorophenyl ether (**4**) with the lithiated methyl propiolate in presence of BF_3OEt_2 to yield alkyne ester (**11**). The alkyne was then reduced to alkane using the catalyst Pd/C in methanol and the resulting methyl ester (**12**) was then cyclised using *p*TSA in refluxing toluene to give tetrahydropyrrolinone (**13**). The lactone was reduced to lactol (**14**) using DIBAL-H in CH_2Cl_2, which was then reacted with benzenesulfinic acid in presence of $CaCl_2$ to yield benzenesulfinyl tetrahydropyran derivative (**15**).

Scheme 3



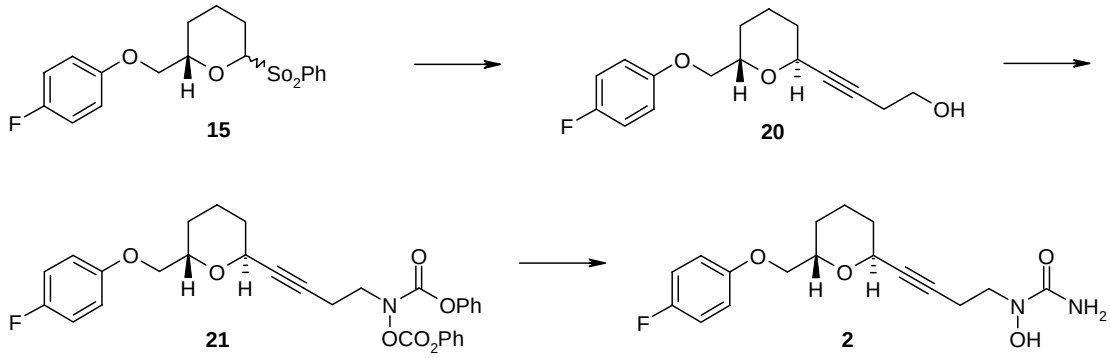
We next tried an alternative route to synthesize the intermediate **15**, in which the starting glycidyl ether was reacted with the anion generated from benzyl ether of propargyl alcohol in presence of BF_3OEt_2 to give alkyne (**16**). The free OH group was protected as MEM ether (**17**) and the alkyne was reduced using Pd/C in methanol to yield saturated alcohol (**18**). The alcohol was subjected to Swern oxidation conditions to give aldehyde, and the MEM group was deprotected using methanolic HCl to yield 2-methoxy tetrahydropyran derivative (**19**). The methoxy group of **19** was then converted to benzenesulfinyl using benzeneslfinic acid and $CaCl_2$ in CH_2Cl_2 to give the intermediate **15** in good yield.

Scheme 4



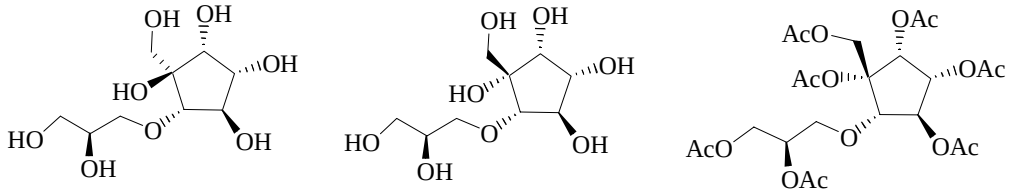
The C-C bond formation at C-2 was carried out by treating compound 15 with dialkyl zinc reagent derived from BrMg-C≡C-CH_2-CH_2-OTHP and $ZnBr_2$ followed by deprotection with *p*TSA in methanol yielded exclusively trans isomer (**20**). Introduction of *N*-hydroxy urea was essentially carried out by the approach used above for CMI-977 to give the six membered analogue of CMI-977 (**2**).

Scheme 5



Chapter II: Synthetic studies towards the Calditol and 5-*epi*-Calditol.

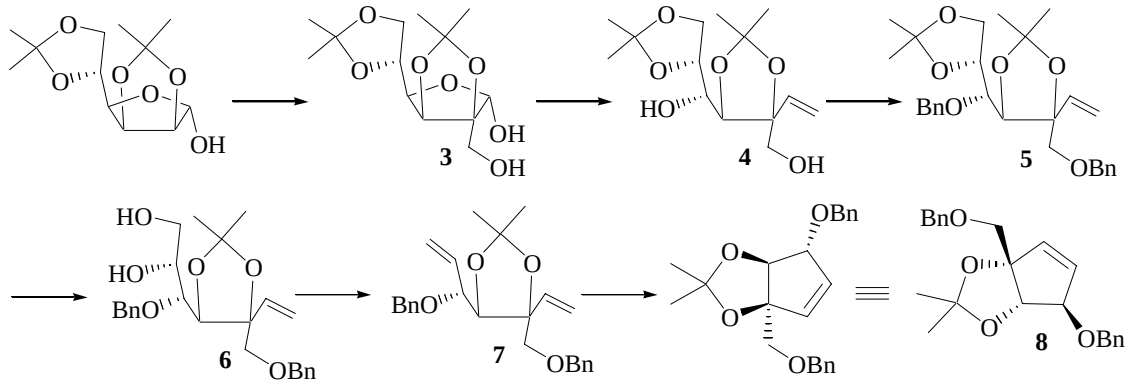
Calditol is a polyol isolated in 1972 from *sulfolobus solfataricus archae*, which is one of the important geochemical agents in the production of sulfuricacid from elemental sulfur in high temperature hydrothermal systems. Although the isolation was made long back, the structure was confirmed recently as substituted cyclopentane.



Calditol **5-*epi*-Calditol (1)** **2**

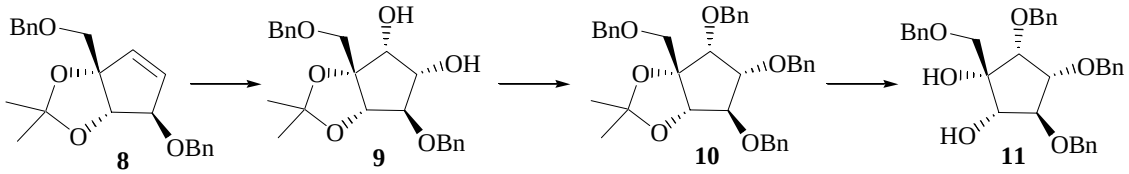
The synthetic strategy for calditol begins with the condensation between diisopropylidene mannofuranose and formaldehyde to give the diol (**3**), which for one carbon elongation was subjected to lactol wittig protocol to yield olefin alcohol (**4**). The two hydroxy groups were protected as benzyl ethers (**5**) using BnBr and NaH, and the terminal isopropylidene group was deprotected in acidic conditions to give diol (**6**). The diol was then dimesylated using mesyl chloride and Et_3N, and elimination was achieved using NaI in refluxing 2-butanone to yield the diene (**7**).

Scheme 1



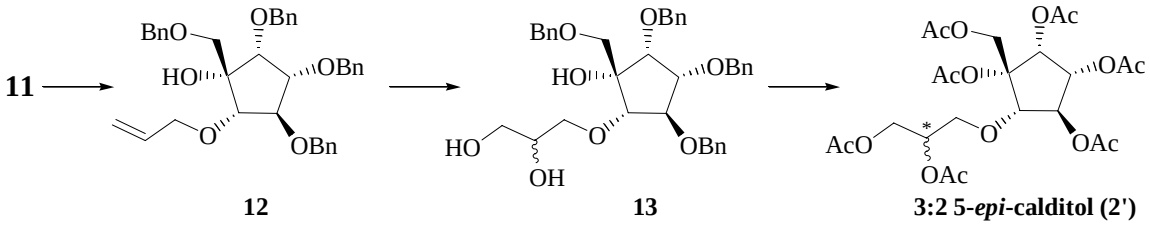
The ring closing metathesis was affected using Grubbs second-generation catalyst in benzene to yield cyclopentene derivative (**8**). The olefin when subjected to dihydroxylation using osmium tetroxide, furnished the diol (**9**) in high stereoselectivity. This may be attributed to the steric hinderance from β-face due to presence of bulky benzyl groups. The diol on bezylation afforded the tetrabenzyl derivative (**10**), which on acetonode deprotection gave another diol (**11**).

Scheme 2



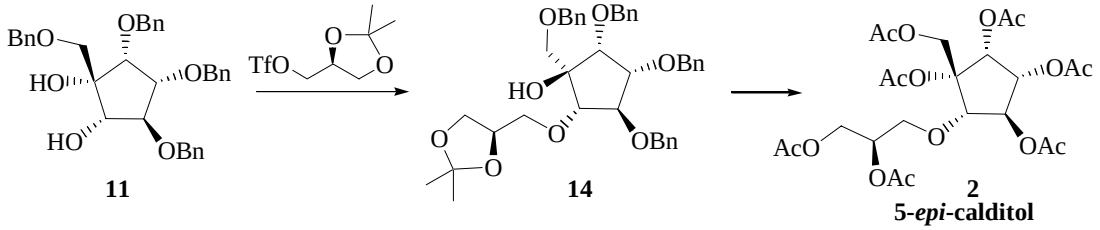
The selective *O*-allylation at secondary hydroxy of diol **11** was carried out to get the corresponding mono allyl derivative (**12**), which was further subjected to asymmetric dihydoxylation to yield the triol (**13**). The diol after debezylation was converted to heptaacetyl derivative (**2'**). Close inspection of the ^{1}HNMR spectrum of **2'**, revealed that the asymmetric dihydroxylation was not achieved with desired degree of stereoselectivity and the product was a 60:40 mixture. To circumvent this problem another route was adopted as shown in scheme 4.

Scheme 3



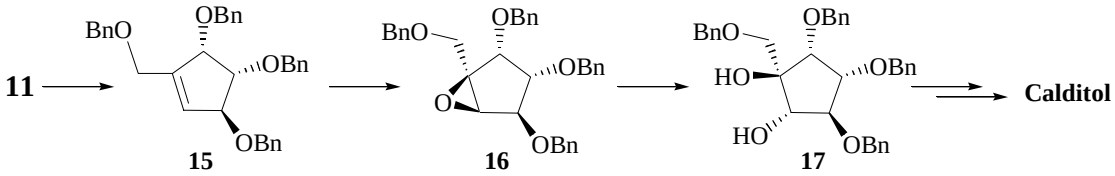
The secondary hydroxy of diol (**11**) was selectively alkylated using triflate derivative of isoprpylidene (*R*)-glycerol to yield compound **14**. Debenzylation followed by actylation afforded hepta-actate of 5-*epi*-calditol (**2**).

Scheme 4



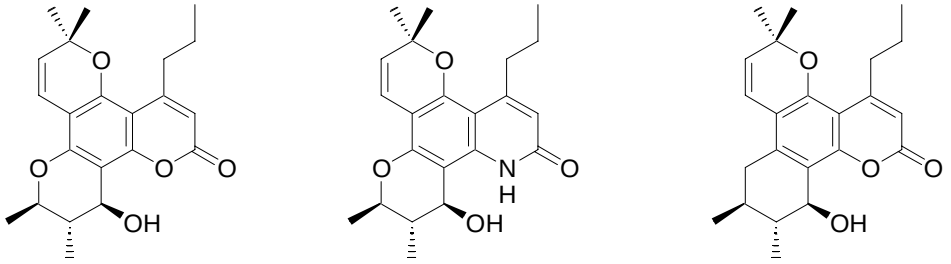
The diol **11** was successfully transformed to the epoxide **16** following a sequence of thiocarbonate formation and its conversion to olefin **15** using Corey-Winter olefination methodology, stereoselective epoxidation resulting exclusively from β-face due to the co-ordination of 3-OBn with *m*-CPBA. Presently, we are pursuing the final oxirane ring opening and attachment of (*R*)-1,2-isopropylideneglycerol unit, and hydrogenation to procure calditol.

Scheme 5



Chapter III.

Synthetic studies towards Carba calanolide

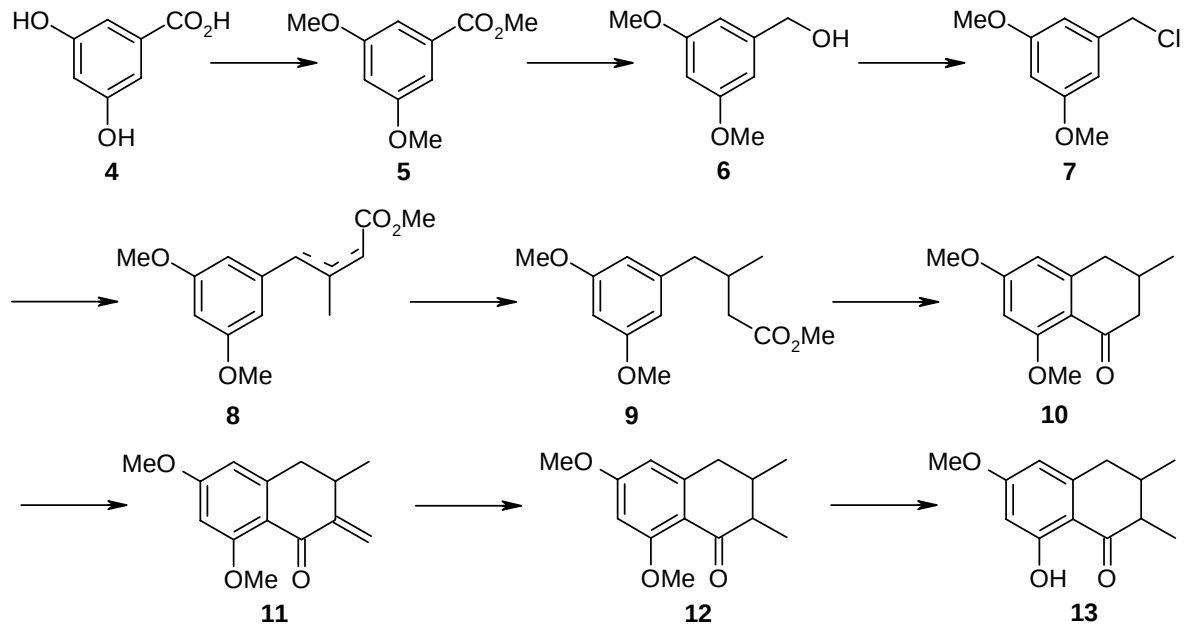


(+/-)-Calanolide (1) **(+/-)-Aza-calanolide (2)** **(+/-)-Carba-calanolide (3)**

Calanolide A (**1**), a di pyranocoumarin isolated from the leaves and twigs of the tropical rain forest tree *calophyllum lanigerum var.austroconaceum*, has been recently identified as a potent representative of a pharmacologically distinct subclass of non-nucleosidal human immunodeficiency virus-1 specific reverse transcriptase inhibitors. In addition calanolide was reported to have shown activity against the azidothymidine-resistant HIV-1 strain and the pyridinone-resistant HIV-1 strain. The aza analogue of the calanolide (**2**) was prepared to study the structure activity relationship and its activity prompted us to undertake the synthesis of carbo calanolide (**3**).

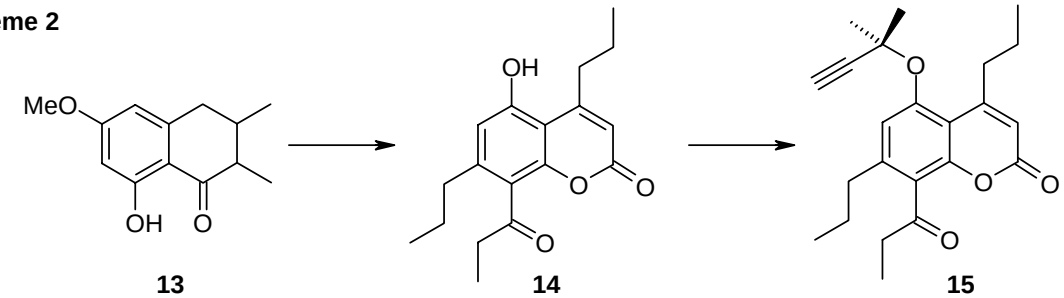
The important part of the calanolide A carba analogue is to synthesise the substituted tetralone, for which we found 3,5-dihydroxy benzoic acid is the suitable starting material. The 3,5-dihydroxy benzoic acid (**4**) was converted to 3,5-dimethoxy benzyl chloride (**7**) by following the sequence of reactions i.e. excessive methylation, $LAlH_4$ reduction and chlorination.

Scheme 1



The chloro compound (**7**) was subjected to Heck type reaction with methyl crotonate and using $Pd(OAc)_2$ as catalyst to get the addition product (**8**). The resulting olefin was hydrogenated with Pd/C under H_2 atmosphere to get the saturated ester (**9**), which was then cyclised to methyl tetralone (**10**) using poly phosphoric acid. The second methyl group was introduced using para formaldehyde and $PhNH(Me)COOCF_3$ salt to afford methylene derivative (**11**), which was subsequently hydrogenated using Pd/C to get dimethyl tetralone (**12**). Selective deprotection of methyl ether was accomplished using BCl_3 to get the keto phenol (**13**).

Scheme 2

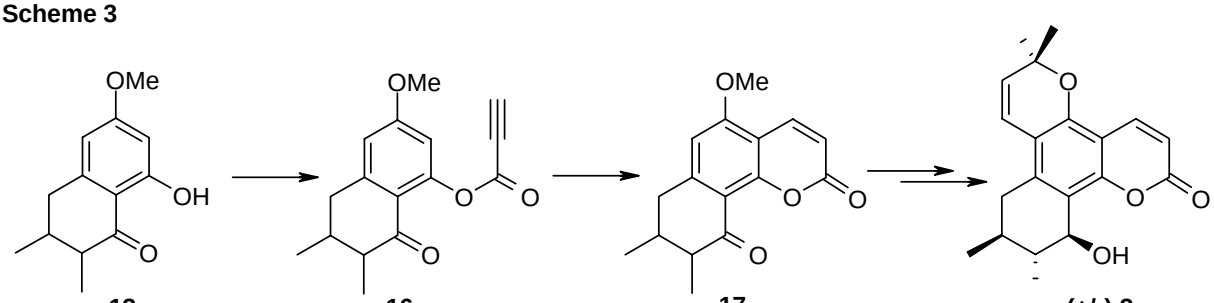


While trying to construct the coumarin ring with compound **13** using ethyl buteryl acetate in triflic acid, although we got the coumarin ring but we ended up with the C-C bond breakage in

tetralone ring, which was conformed after the alkylation of phenol (**14**) using 3-chloro-3-methyl-1-butyne

To overcome this problem compound **13** was alkylated with propargylic acid in presence of DCC to get the alkynoate (**16**) and subjected to $Pd(OAc)_2$/triflic acid conditions to get the coumarin (**17**). The final pyran ring construction and reduction of keto group to get 9-carba calonolide (**3**) were under progress.

Scheme 3



13 **16** **17** **(+/-) 3**

Chapter I

Total Synthesis of CMI-977 and its higher analogue

Introduction

Introduction

According to the estimate of World Health Organization, asthma affects 150 million people worldwide, and the number of patients has doubled over the decade.[1] Asthma occurs when the bronchial tubes swell up and go into a spasm, blocking the passage of air in and out of lungs, which is characterized by wheezing, breathlessness, chest tightness and cough. Asthma can develop at any age, but occurs most-commonly in children. Although no country is immune, it occurs predominantly in industrialized western countries. The severity of asthma often worsens in spring and early summer. Although there is no cure for asthma, it is a disease that can be managed, enabling most people to lead active and productive life. This preliminary discussion will brief the current status of the biological and medicinal aspects of asthma (asthma chemotherapy) that would have eventually formed the basic tenet of our interest to develop the synthesis of anti-asthmatic compounds.

The rapid rise of asthma constitutes the biggest mystery in modern medicine and the exact reasons for the increase still evade the researchers.[2] Although several factors were put forward, like diesel fuel exhaust, allergies, diet, smoking, viral infections, cold air, and physical exercise, it is now concluded that a combination of genetic and environmental factors is responsible for the onset of asthma.[3] While some people are genetically predisposed while others suffer from the early-life allergen exposure, especially air-pollution, damp housing, poor ventilation, dusty carpets, furry pets, cockroaches, and indoor chemicals. A combination of cold air and physical exercise leads to asthma in athletes, esp., cross-country skiers, swimmers, and track-and field runners since they pump, during the race, thousands of cubic meters of cold air. On average, 10% of family budget goes meeting the treatment of asthma. Even passive or second hand smoking by parents especially mothers increases the risk of asthma in children. Infants born of mothers

who smoke have higher risk of developing asthma. The good news is that 95% of asthma is controllable, given proper and continuous medication.

Table (1): Environmental factors responsible for causation and exacerbation of asthma

Allergens Animal dander House dust mites Pollens and molds **Respiratory viral infections** **Weather** Cold air High humidity **Emotional Stress**	**Air pollutants** Tobacco smoke Paint fumes Strong odours Air pollution **Exercise** **Foods (more calories/fat, less fish), additives, preservatives, and certain drugs** **Sulphur dioxide**

The advances in molecular biology indicate that allergy and asthma are not inherited as single-gene disorders and do not show a simple pattern of inheritance. Environmental and genetic factors interact in a complex fashion to produce disease susceptibility and expression. A genetic predisposition to asthma and atopy is influenced by several factors. An increased risk of atopy exists when the mother herself has a history of allergy. Environmental factor **(Table 1)** such as infection in early life (by tuberculosis, hepatitis A, measles, and other unidentified pathogens for which these conditions are markers of) might reduce the risk of developing allergy. Other factors might increase this risk such as exposure to certain allergens, respiratory viral and helminth infection and can cause increased immunoglobulin E (IgE) serum levels. Once asthma is established, attacks can be precipitated or exacerbated by cigarette smoke, aeroallergens, respiratory viral infections, and air pollution. Table **2** provides a list of plausible candidate genes that influence asthma and atopy. These include: genes involved in inflammation (recruitment and activation of inflammatory cells), effector molecules including those that interact with therapeutic agents, genes involved with immune recognition and regulation, and genes that regulate the development and maintenance of the lung.

Table 2: A non-exhaustive list of potential candidate genes that predispose to asthma atopy

Gene Product	**Effector molecules and receptors and their metabolic pathway components**
Cytokines, growth factors and their receptors	β-Adrenoreceptor
GM-CSF	High-affinity receptor for immunoglobulin E
Interleukins 4, 5, 9,10, and 13	Histamine
Interferon γ	Leukotrienes
Tumour necrosis factor α	Platelet-activating factor
Mast cell growth factor	Nitric oxide
Chemokines and their receptors	**Immune regulation and repertoire**
Eotaxin	Human leukocyte antigen complex
Monocyte chemoattractant protein	T-cell receptor
RANTES	Immunoglobulin isotype switching
Interleukin 8	
Miscellaneous	
Integrins and selectins	
Nuclear factor κB	

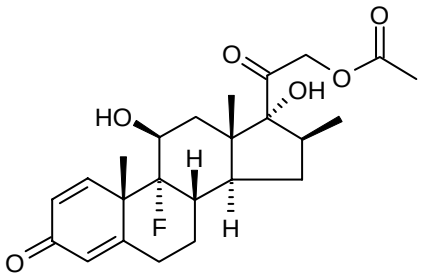
Abbreviations: GM-CSF - granulocyte-macrophage colony-stimulating factor; RANTES - regulated upon activation normal T-expressed secreted ligand.

The present anti-asthmatic therapy is largely based on corticosteroides (inhaled and systemic) and symptomatic treatment and, to the lesser extent, immunotherapy which revolve around the inhibition of various inflammatory mediators that enter the various stages of asthmatic process, *e. g.*, cytokines, chemokines, adhesion molecules, proteinases and growth factors as discussed below:

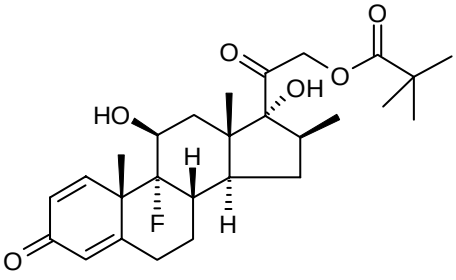
Glucocorticosteroides, β_2-adrenoreceptor agonists and theophylline:

Inhaled β_2-adrenoreceptor agonists are the most effective bronchodilators, currently prescribed for symptomatic relief in asthma.[4] The mechanism of action, i.e., causing smooth muscle relaxation involves camp-dependent and independent pathways. Inhaled glucocorticosteroides, *e.g.*, betamethasone acetate (**1**), dexamethasone pivalate (**2**), fluticasone dipropionate (**3**), and

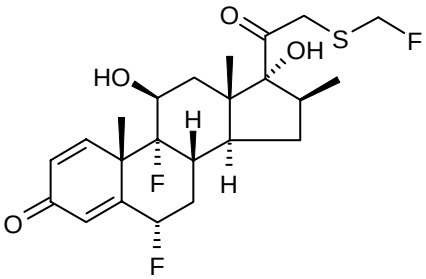
cortisone (**4**) are mainstay therapy for reducing airway inflammation in asthma. The effects of steroids are mediated largely *via* changes in gene transcription: steroid binds to a cytosotic glucocorticoid receptor (GR) and the resulting dimer translocates to the nucleus where it interacts with a glucocorticoid response element (GRE) to increase or decrease gene transcription (*trans*-activation and *trans*-repression respectively). Activated GR can also interact directly with cytoplasmic transcription factors such as activator protein 1 (AP-1), and nuclear factor κB



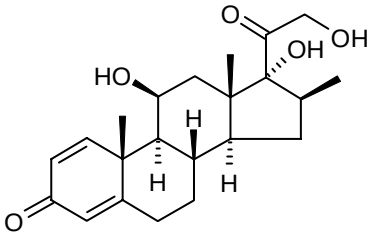
Betamethasone acetate (**1**)



Dexamethasone.pivalate (**2**)



Fluticasone.dipropionate (**3**)

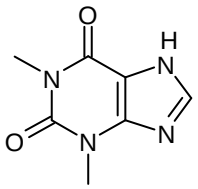


Cortisone (**4**)

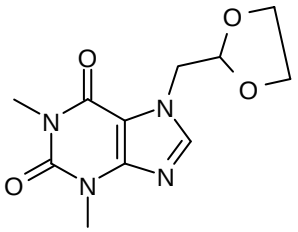
(NF-κB), which alter gene transcription in response to inflammatory stimuli. Salbutamol (**5**) is a potent β_2-adrenergeric receptor antagonist. β_2-adrenergeric receptors are found on the smooth muscle lining airways of the lungs. The binding of salbutamol to β_2-adrenoreceptor causes the conformational change in that G-protein. A GDP (Guanosine 5'-diphosphate) group associated with the G-protein becomes dissociated and is then replaced with a GTP group. This is in turn causes alpha sub unit to dissociate from the G-complex. The dissociated alpha sub unit is then free to move in the membrane and has a binding site for the enzyme adenylyl cyclase. It binds to this enzyme, which catalyses the conversion of ATP (adenosine 5'-triphophate) to cAMP. The

latter activates protein kinase A that transfers the terminal phosphate group of an ATP to several target proteins which leads to muscle relaxation in the airways of lung.

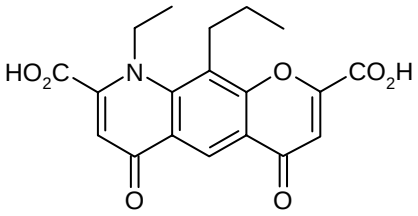
Theophylline (**6**) has a long historic background through its ability to bronchodilate asthmatic subjects. Although limited by side-effects profile, theophylline is effective in reducing the symptoms and improving lung function in patients with mild chronic asthma. Theophylline is believed to inhibit the enzyme PDE4 of specifically cyclic nucleotide phosphodiesterase, an enzyme that catalyses the hydrolysis of intracellular second messengers cAMP and cGMP. Doxophylline (**6a**) and Nedocromyl (**7**) are the drugs work in the inflammatory cells to prevent the release of histamine and other chemicals involved in airway inflammation. They also help in the treatment of exercise-induced asthma.



Theophylline (**6**)

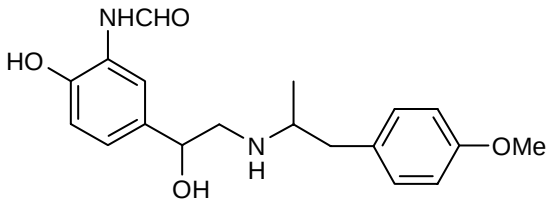


Doxophylline (**6a**)

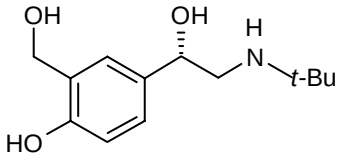


Nedocromil (**7**)

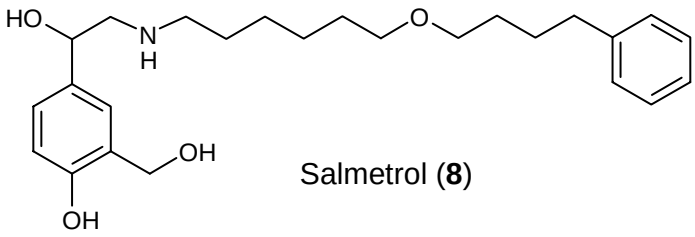
Long action of β_2-adrenoreceptor agonists can be achieved by exosite binding (e.g., salmeterol)[5] (**8**) and by alterations in pharmacokinetics (e.g., formoterol)[6] (**9**). Although highly lipophilic, the extended duration of action of salmeterol appears due to anchoring in the vicinity of the β_2-adrenoreceptor via a second binding interaction (the exosite) near the cytoplasmic face of the fourth trans membrane domain. Also, new steroids are being developed with the aim of maximizing topical anti-inflammatory effects and minimizing adverse systemic effects, as exemplified by RU-24858. Clinical studies have recently demonstrated the benefit of combining long-acting β_2-adrenoreceptor agonists with inhaled steroids, e.g., seretide (salmetrol and fluticasone) combined in a single formulation.



Formoterol (**9**)



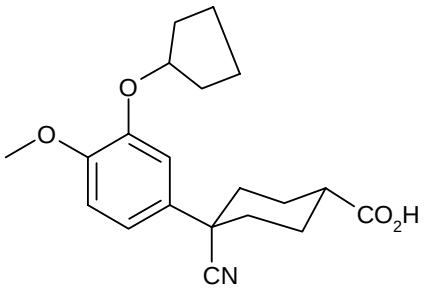
(R)-Salbutamol (**5**)



Salmetrol (**8**)

PDE Inhibitors

Phosphodiesterase-4 that specifically hydrolyses cAMP and is inhibited by the anti-depressant rolipram is selectively expressed in virtually every cell type that has been implicated in the pathophysiology of asthmatic inflammation. For example, V-11294A is a non-toxic and nonemetic orally active PDE-4 inhibitor currently undergoing clinical trial with promising pharmacokinetic activity.



Ariflo (SB-207499) (**10**)

The therapeutic utility of rolipram is limited because of the unwanted side effects, predominantly, nausea, vomiting, and gastric acid secretion. In fact, PDE-4 adopts two slowly interconvertible conformations, PDE-4H and PDE-4L. The inhibition of PDE-4H causes side effects inherent in non-selective, first-generation PDE inhibitors while the inhibition of PDE-4L produces beneficial effects including the suppression of cytokine generation and release. Thus, a PDE inhibitor selective for a specific gene product and the low affinity rolipram-binding site has

therapeutic potential in airways inflammation. Ariflo (SB 207499) (**10**) is an example equipotent with rolipram against PDE-4L but 100-fold less potent against PDE-4H and it has a tenfold selectivity for PDE-4D over the other PDE gene families.[7]

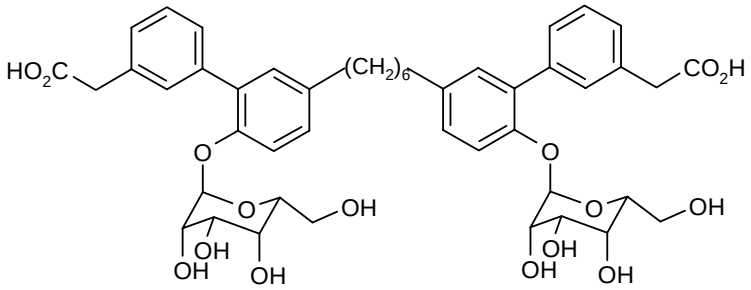
Mediators of T-lymphocyte–eosinophil interactions:

T-lymphocyte-eosinophil interactions are central to the pathophysiology of asthma and the therapeutic possibilities for blocking these interactions can take a variety of directions.[8] Targeting the factors involved in regulation of Th2 ($CD4^+$) differentiation and/or activation is one option. Genomic screening by Millenium Pharmaceuticals has led to the identification of 4000 such factors, which can be broadly classified into three categories: soluble factors including cytokines (*e.g.*, interlukin 4 (IL-4); co-stimulatory molecules (e.g., B7-2/CD86) and transcription factors (including AP-1 and GATA-3). Drugs directed against these factors are being developed to limit Th2 cell involvement in the initiation of asthmatic inflammation. Similarly, a humanized anti-$CD4^+$ antibody (SB 210396) is in clinical trail with encouraging preliminary results. Another approach is to target type-2 cytokines, specifically implicated in the pathophysiology of airway inflammation in asthma. For example, absorption of IL-5 from the circulation using an anti-IL-5 antibody should prevent release of eosinophils from the bone marrow, *e.g.*, SCH 557700.

Adhesion molecules:

Suppression of eosinophil adhesion with consequent inhibition of influx into the lung is a strategy to suppress the asthmatic airway inflammation. Adhesive interactions between cells and cells with extracelluar matrix are essential for a number of pathophysiological conditions including morphogenesis, organization of tissues and organs, regulation of cell immune responses, and inflammatory responses. Cell adhesion molecules play a key role in these phenomena. The selectin family of adhesion molecules, which are expressed on activated endothelial cells (E- and P-selectin), activated platelets (P-selectin), and peripheral blood

leukocytes (L-selectin) are involved in tethering and rolling of leukocytes in the microcirculation, leading to leukocyte tissue infiltration. Interruption of leukocyte-endo-thelium interaction is a current strategy to target asthma. TBC-1269 (**11**) is the lead compound of a series of orally-active, low molecular weight E-, P-, and L-selectin antagonist under development by Texas Biotechnology Corp. for the potential treatment of asthma, and psoriasis.[9] Strategies being investigated include small molecule inhibitors of very late antigen-4 (VLA-4) such as CY9652 (based on the leucine-aspartic acid-valine sequence) and BIO-1211, monoclonal antibodies directed towards VLA-4 and intercellular adhesion molecule 1 (ICAM-1) and inhibition of alpha 1,3-fucosyltranferase VII, as enzyme that regulates selectin function. Other small molecule inhibitors, such as PD144795, act at the transcriptional level to suppress the expression adhesion molecules [E-selectin, vascular cell-adhesion molecule 1(VCAM-1) and (ICAM-1)]. TBC 1269, a simplified analogue of the sialyl Lewis X tetrasaccharide, is a peptidomimetic and non-oligosaccharide, glycomimetic E-selectin antagonist.



TBC-1269 (**11**)

Cytokines

Cytokines play a key role in the chronic inflammation of asthma and appear to orchestrate, amplify, and perpetuate the inflammatory process.[10] Interleukin 4 (IL-4) and IL-5 are considered to be the key mediators in specific allergic asthmatic inflammation. Importantly, IL-4 directs the development of naïve T cells towards the T helper-2 (Th2) subset, which appears to be the dominant phenotype in asthma. IL-4 is critical to the synthesis of IgE by B cells and is involved in eosinophil recruitment in the airways. Soluble truncated recombinant IL-4 receptors

given by nebulisation seem to be the promising candidates with long-lasting and well-tolerated effect.

The chemotactic cytokines (CC chemokines) act by attracting leukocytes (monocytes, basophils, eosinophils, and lymphocytes) to sites of inflammation. They include cell-migration and activation by binding to specific G-protein-coupled cell surface receptors on target cells. These receptors belong to a family of nine related members (CCR1 – CCR9). CC chemokines, especially, eotaxin, monocyte chemoattractant protein 3 (MCP-3) and MCP-4 are highly potent in attracting eosinophils, acting through CCR3 receptor. Small molecule CCR3 receptor antagonists are likely to be the most effective anti-eotaxin agents. Recently, a specific CCR3-mAB has been developed by Leukocytes Inc. that acts as a true CCR3 antagonist – it blocks eosinophil chemotaxins to CC chemokines and prevents Ca^{2+} influx.

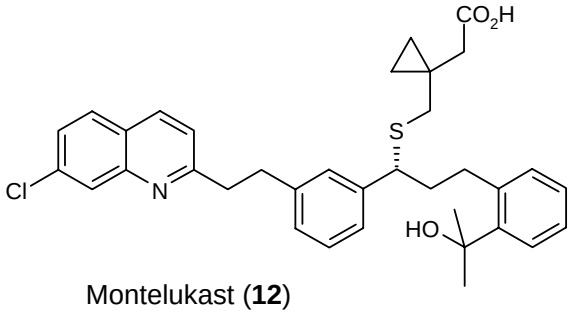
The advancement in understanding the intracellular signaling pathways and inflammatory gene transcription of key pro- and anti-inflammatory cytokines is laying the foundation for a new era in anti-inflammatory drug discovery. Inflammatory gene transcription is regulated by a number of transcription factors, mostly AP-1 and NF-κB. These factors are activated by specific kinases, inhibition of which may suppress an array of cytokine/ chemokine genes. SP650003 and SP100030 are the small molecule inhibitors which attenuate NF- κB/AP-1-dependant gene transcription.[11] In addition, SP100030 also inhibits transcription of IL-2, IL-8, TNF-α and GM-CS factor genes with similar IC_{50} – thus holding great promise in the treatment of asthma.

MAP kinase inhibition:

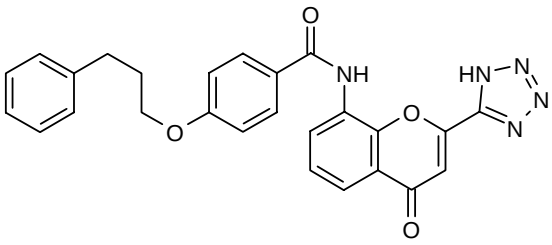
A novel family of mutagen activated protein kinases (P38 MAP kinases) are intimately involved in the generation of pro-inflammatory cytokines.[12] Pyridinyl imidazoles exemplified by SB 203580 and SB 202190 supress the generation of IL-1 and tumour necrosis factor (TNF) from human monocytes and IL-4-induced CD23 expression and enhance the spontaneous apoptosis of human eosinophils.

Inflammatory mediator receptor antagonists:

Small molecule receptor antagonists for a number of inflammatory mediators have been developed. Trailing for so long in the wake of other putative mediators, the cysteinyl leukotrienes have assumed a central role in asthma and in drug development with *Cys*T_1 receptor antagonists such as montelukast (**12**), pranulakast (**13**), and zafirlukast (**16**) being the first new treatment for asthma in 25 years.[13] The cysteinyl LTs C_4, D_4, and E_4 produced by resident mast cells and by infiltrating eosinophils and basophils are implicated in bronchial constriction and submucosal odema of airways in asthmatics. The biosynthesis of LTs is initiated by activation signals of Ca^{2+} influx which then activates and translocates cytosolic phospholipase A_2 to the nuclear membrane, where it catalyses the release of arachidonic acid from phospholipids.[14]



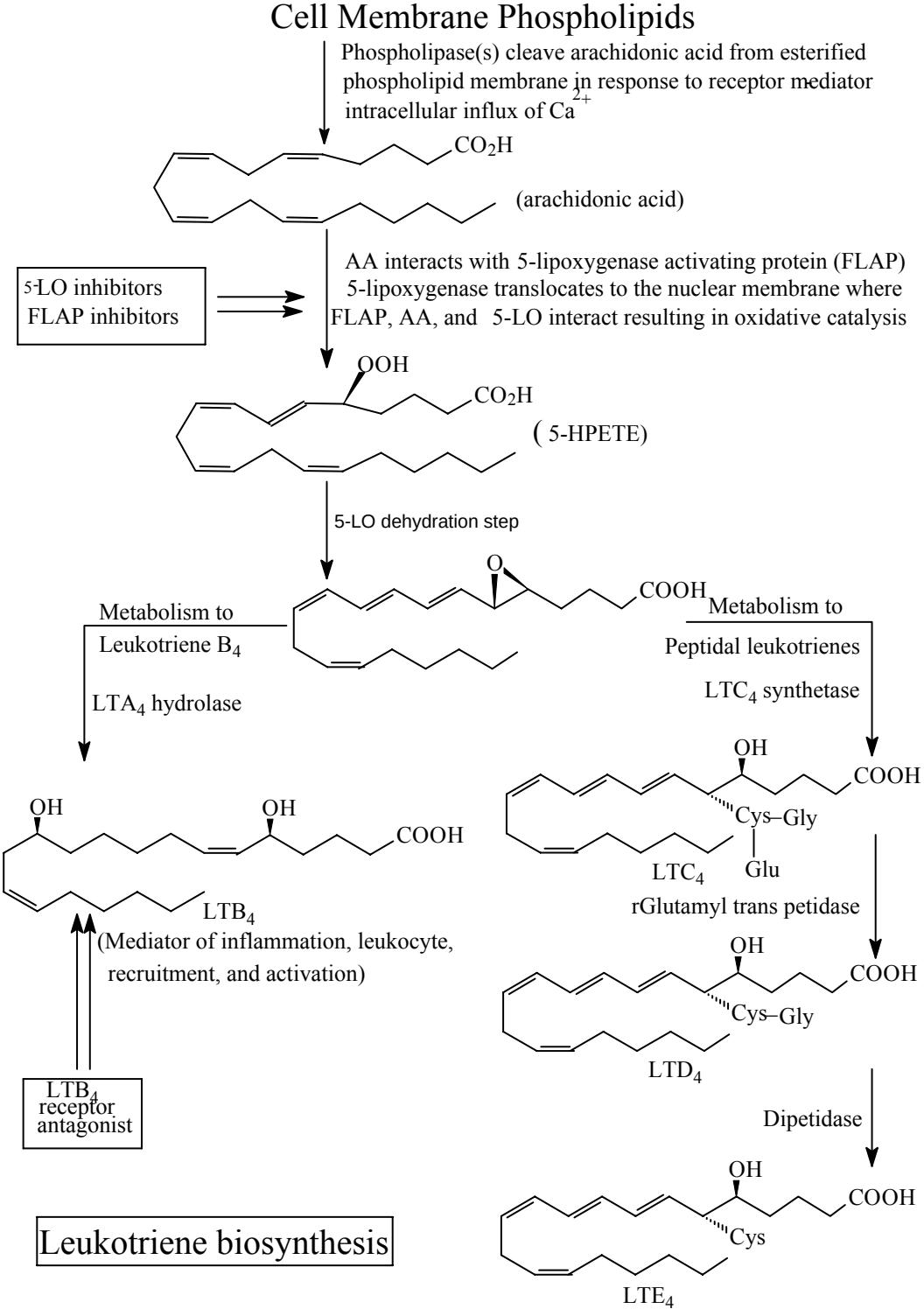
Montelukast (**12**)



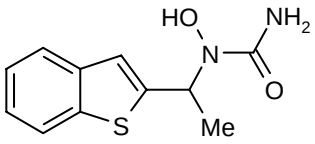
Pranulakast (**13**)

Arachidonic acid is subsequently presented by an 18 kDA intergral perinuclear protein and 5-lipoxygenase (5-LO)-activating protein (FLAP) to 5-LO which is also translocated to the nuclear membrane. 5-LO catalysed the sequential formation of 5-HPETE and LTA_4. LTA_4 is then conjugated with reduced glutathione by LTC_4 synthase, the only enzyme committed to the biosynthesis of LTC_4. Human LTC_4 synthase has been cloned and mapped on human chromosome 5 (5q35) distal to genes relevant to allergic diseases such as IL-4 and IL-5. Cell activation by cytokines modulates the dynamics of arachidonic acid pools causing the redistribution of these fatty acids, which in turn, is largely responsible for the amount and type of eicosanides immunologically produced by inflammatory cells. The removal of glutamate from LTC_4 by the enzyme γ-glutamyltranspeptidase (GTP) gives the corresponding cysteinylglycinyl-

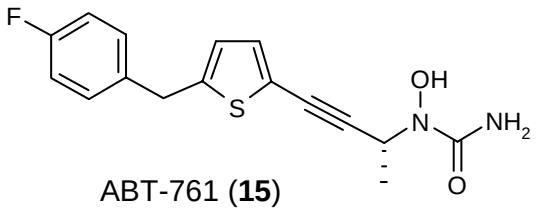
5-hydroxy (7E, 9E, 11Z, 14Z)-eicosatetraenoic acid, leukotriene D_4 (LTD_4) which on further peptido hydrolysis by the enzyme dipeptidase gives leukotriene E_4 (LTE_4).



Hence, 5-LOinhibitor, 5-LO-activating protein antagonist, and *cys*L-T receptor antagonists are the three class of LTs modulators, and subsequently as drug targets now in clinical

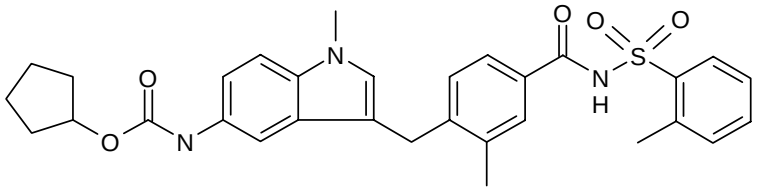


Zileuton (**14**)



ABT-761 (**15**)

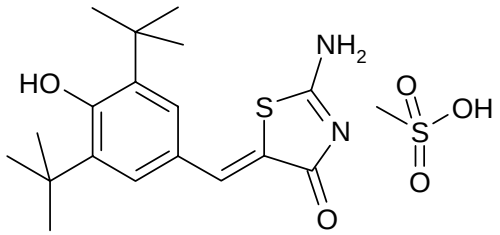
practice. Zileuton (**14**) is a selective orally active inhibitor of 5-lipoxygenase from Abbot, proven to exert anti-inflammatory and anti-allergic effects in animal models and humans.[15] This drug, introduced in market in early 2000, was clearly by FDA for prevention and chronic treatment of asthma in patients of at least 12 years of age. Another lead discovery, (R)-(+)-N-[3-[(4-flurophenyl)methylene]-2-thienyl-1-methylene-2-propynyl]-N-hydroxyurea (ABT-761) (**15**) is under -going final clinical trails with potent 5-LO inhibiting activity and minimal side effects.[16] Zafirlukast is a potent leukotriene receptor antagonist, which improves the symptom, and pulmonary function, reduces the use of rescue bronchodilation medication and reduces the likelihood of asthma exacerbation.



Zafirlukast **(16)**

CI-1004 (PD-136095) (**17**) is a dual inhibitor of lipoxygenase and cyclooxygenase-2 (COX-2) inhibitor that is currently under development by Parke-Davis as a potential treatment for asthma.[17] It is recognized that an inducible form of cyclooxygenase (COX-2) is upregulated in inflammatory processes, significant efforts are ongoing to identify highly selective COX-2 inhibitors with the aim to separate the beneficial actions from the side effects of non-steroidal anti-inflammatory drugs (NSAIDs). On the other hand, leukotrienes, produced through the 5-lipoxygenase (5-LO) enzyme pathway also contribute to NSAID-induced side effects. When

evaluated against the formation of $PGF_{2\alpha}$ (a product of COX formation) and LTB_4 (a product of 5-LO), it was found to inhibit potentially both 5-LO (IC_{50} =0.77 μM) and COX (IC_{50} =0.39 μM).



CI-1004 (**17**)

Immunoglobulin E (IgE) inhibitors:

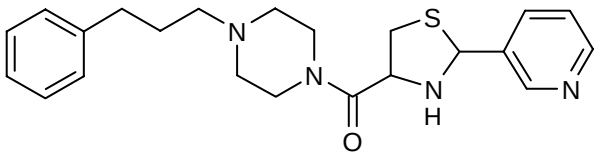
Anti-IgE therapy is one of the newest approaches to asthma therapy. Exposure to an allergen in a susceptible individual causes T-lymphocytes to send signal to B-lymphocytes initiating the production of IgE antibodies. For every allergen, specific IgE antibodies are produced within a few weeks of exposure. Some IgE antibodies bind to Foepsilon RI receptors on mast cells and eosinphils in the skin, while the others remain free floating in the bloodstream. Mast cells in the skin and mucosal layers of the respiratory tract contain the inflammatory mediators that cause the symptoms of allergic rhinitis: histamine, leukotrienes and prosta-glandins. These mediators are released every time that an allergen crosslinks mast cell-bound IgE. Reexposure to an allergen causes mast cells in the nose and sinuses to become activated by IgE antibodies, releasing inflammatory mediators, and causing the symptoms of runny nose, teary eyes and itchiness. Anti-IgEs inhibit of neutralize free IgE as well as downregulating the production of IgE by B cells. Olizumab, a humanized anti-IgE monoclonal antibody, developed by Genetech has been shown effective for moderate to severe asthma in both children and adults in phase III clinical trails in double-blind, randomized, placebo-controlled studies.[18]

Adenosine inhibitor

Adenosine is a natural nucleoside involved in bronchial constriction in asthmatics whose effects are mediated through four receptor subtypes: $A_{1,}$ A_{2a}, A_{2b}, and A_3 receptors. Adenosine

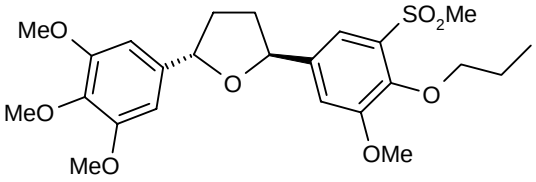
free, antisense oliogonucleotides (RASONS) block specifically, at the mRNA level, the formation of numerous mediators and their respective receptors.[19] These include NF-κB, major basic protein 5-lipoxygenase, leukotriene C_4 (LTC_4) synthase, IL-4, IL-5 and adenosine. **PAF antagonists**

Platelet activating factor is a phospholipid, exhibiting potent pro-inflammatory effects. It is produced by a number of cells, including eosinophils, basophils, neutrophils, macrophages, and endothelial cells. YM-461 (**18**) is a selective, potent and orally active PAF antagonist.[20]

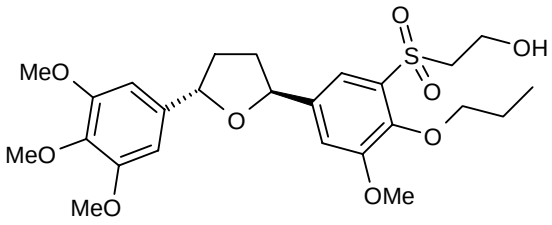


YM-461 (18)

2,5-disubstitutedtetrahydrofurans have been investigated for their role as PAF antagonists. In general, *trans*-isomers have been found to be more potent than cis isomers. Further structure activity studies indicated that more potent PAF antagonists contained an electron-withdrawing group on one but not both aromatic rings. These features are incorporated in L-659, 989 (**19**) in which a metabolically stable methylsulphone serves as the electron withdrawing functional unit and a trimethoxy aryl ring is appended at C_5. In order to achieve increased metabolic activity and pharmacokinetic profile, polar head group modifications were investigated from which the (2*S*, 5*S*)-*trans*-isomer of MK-287 (**20**) emerged as a potent, specific and orally active PAF receptor antagonist and chosen for clinical trail.[21]



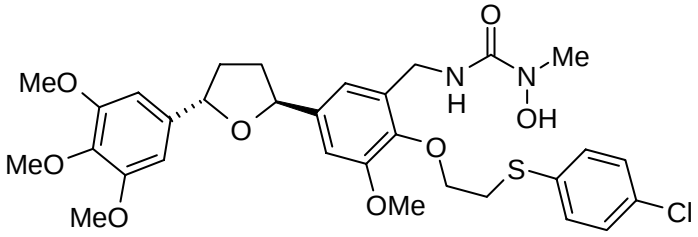
L-659,989 (19)



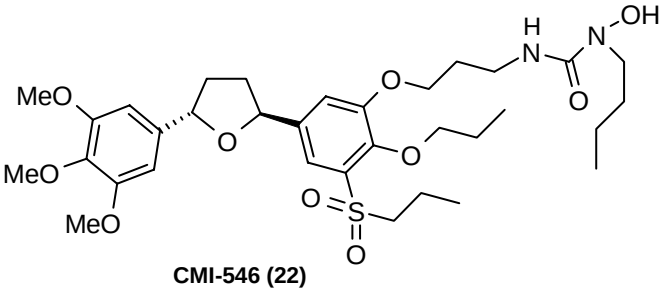
MK-287 (20)

Since both PAF and leukotriene are released simultaneously from leukocytes and upon

cellular activation, act synergistically in many biological models, a single compound which inhibits the actions of both PAF and leukotrienes may offer certain therapeutic advantages in terms of efficacy and pharmcokinetics over reagents which inhibits either mediator alone. The basic knowledge that 2,5-diaryltetrahydrofuran class of compounds are PAF inhibitors while hydroxy ureas are potent 5-LO inhibitors, the introduction of hydroxy urea functionality onto certain scaffolds carrying THF skeleton should provide the candidates with dual inhibition. The inhibiting activity of hydroxy urea derivative is probably due to chelation of Fe^{3+} required for oxidative catalysis in leukotriene biosynthesis. Recently, Cytomed Inc. has reported CMI-392 (**21**) and CMI-546 (**22**) as a potent dual 5-LO and PAF inhibitor, which is currently being evaluated in human clinical trails as a novel-inflammatory agent. CMI-392 showed very potent and balanced activities against both 5-LO and PAF and more potency than zileuton in 5-LO inhibition and equally potent as MK-287 as PAF antagonist.[22]



CMI-392 (21)



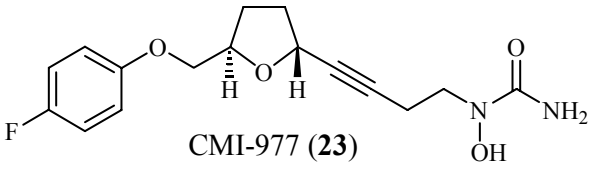
CMI-546 (22)

In conclusion, the old drugs, which are now used as mainstay therapy, mainly, NSAIDs and corticosteroides are flawed with their limited efficacy and inadequate safety profiles. Several gene targets that control cell influx and activation, inflammatory mediator release and activity and tissue proliferation and degradation have been identified. Since multiple gene products have

been identified at the site of inflammation, there has been a surge of interest in identifying intracellular signaling targets, including transcription factors that control inflammatory gene expression, and which are amenable to drug discovery. The recent advances in the pathophysiology of asthma, together with advances in drug development bodes well for the introduction of rational therapy in 21st century where leukotriene antagonists boom as promising drugs in the days ahead.[23]

Brief discussion on synthetic strategies developed in our laboratory:

CMI-977 belongs to lignan family of 2,5-disubstituted tetrahydrofurans, featured with diverse substitution and *trans*-juxtapositioned ring and is chirally homogeneous (all other three stereoisomers have shown poor pharmacological profile). The unique structural ensemble augmented with eutomer-dependent attractive therapeutic index should invite the proposal to undertake a 'single enantiomer synthesis' that would deliver the target molecule with relevant stereochemical information and the functionalities at their respective positions.

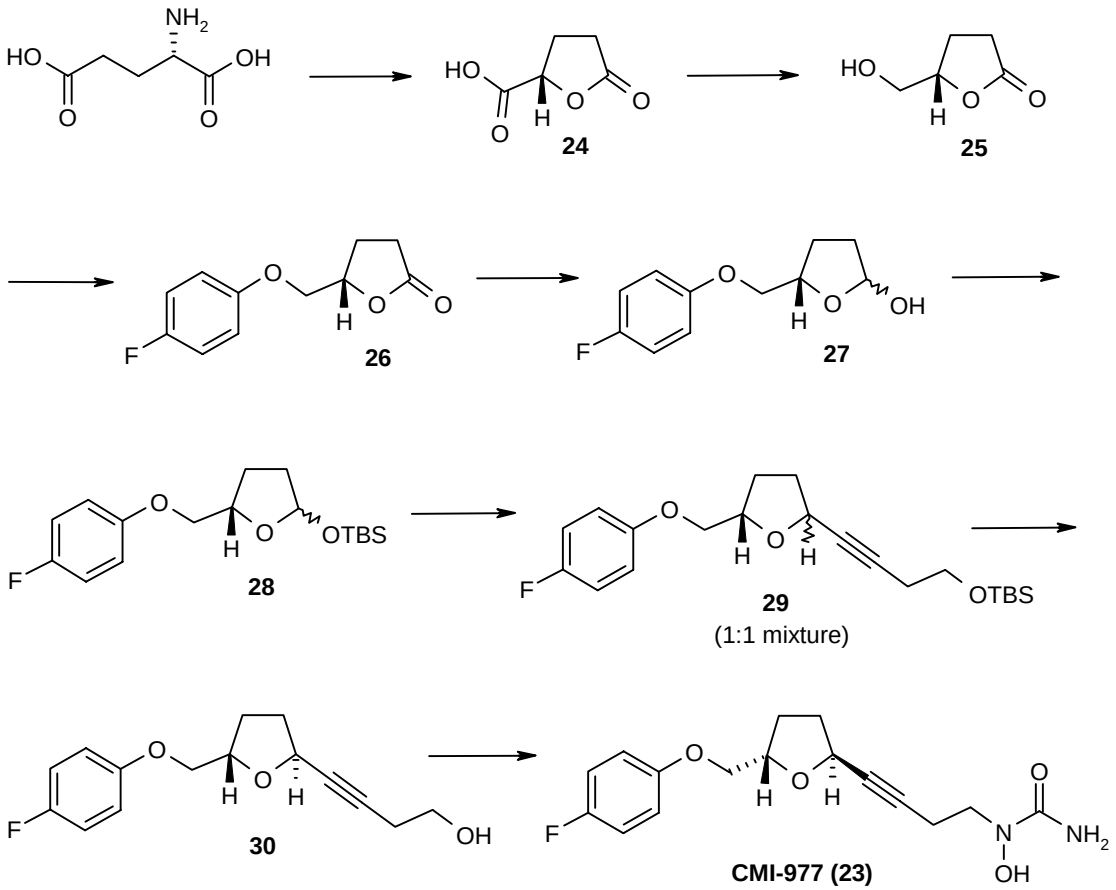


CMI-977 (**23**)

Except the inaugural medicinal chemistry route by Cytomed Inc., much of the synthetic chemistry for CMI-977 has been explored in our laboratory. The original discovery route (scheme **1**) was developed by choosing (*S*)-(+)-hydroxymethyl-γ-butyrolactone (**25**) as core chiral synthon, easily derivable from chiral pool L-glutamic acid.[24] Nucleophilic substitution with lithium 1-*tert*-butyldimethylsilyoxybutynide at the anomeric centre of intermediate (**28**) after anomeric activation with TMSBr yielded a *cis*/*trans* mixture (**29**) without any stereoselectivity (1:1 mixture). The desired *trans*-butynol (**30**) was obtained after fluorolysis of silyl ether, followed by repeated recrystallisation (*cis* isomer- liquid, *trans*- solid). The final

target was reached from here, through the intervention of Abbott technology to introduce *N*-hydroxyureidyl moiety.

Scheme 1

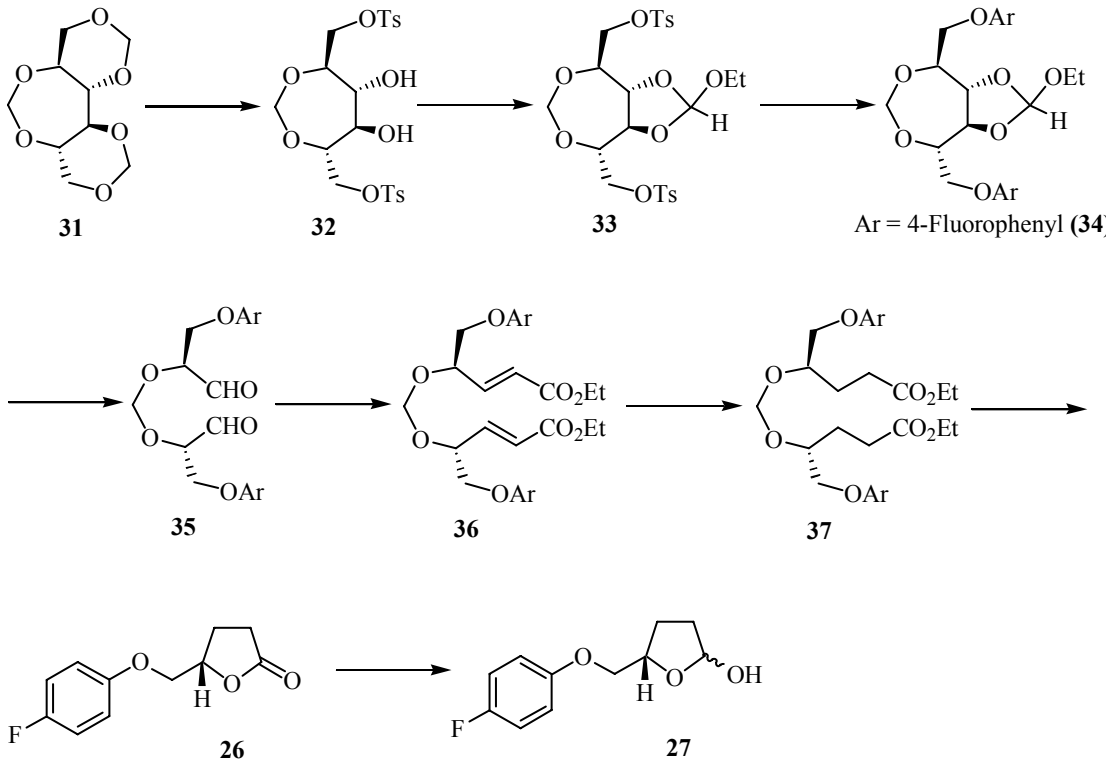


This discovery route was plagued with several problems that mitigated against efficient scale up and cost effective production of the target molecule. Many reactions necessitated cryogenic conditions; silyl protecting groups were used in numerous instances. The atom economy in the protection-deprotection sequence was not in the desired direction. The initial Mitsunobu coupling and follow-up steps generated lot of hazardous waste that was difficult to dispose. Above all, the preponderant issue was that the C-C bond formation at the anomeric centre was in totally non-stereodirective fashion, resulting in 1:1 mixture of *cis*/*trans* isomers whose separation to furnish the *trans* material involved tedious column chromatography or

repeated recrystallisation. Hence, the undesired formation of *cis*-isomer by half after several steps was a major concern.

The problems encountered hitherto prompted us to undertake route-selection efforts to devise novel, cost-effective synthesis of CMI-977 that would be amenable to large-scale production. Four routes were simultaneously developed in our laboratory that would effectively address the aforesaid problems. The two synthetic routes, developed by our colleagues[25] would essentially hang around the lactol (**27** in scheme **1**) with adroit manipulation of pre- and post-steps of this intermediate.

Scheme 2



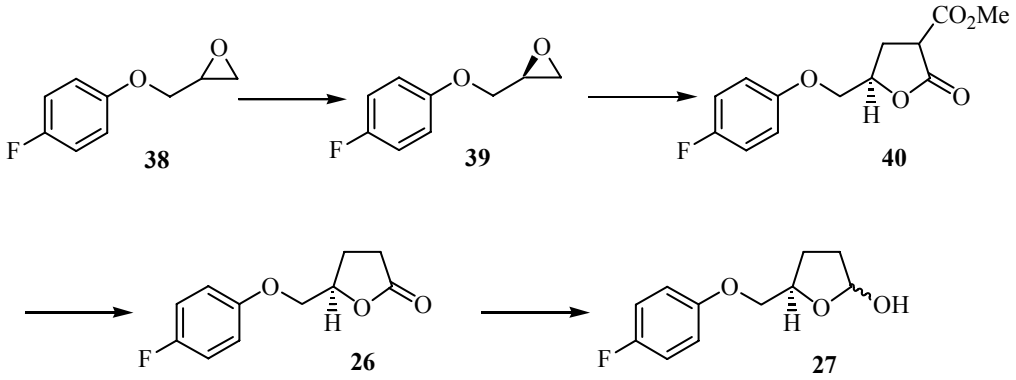
First discovery route for CMI-977 starting from D-Mannitol

The first synthetic route begins with the conversion of tri-*O*-methylene-D-mannitol (**31**) into its tetraacetyl derivative using Ac_2O, AcOH, conc. H_2SO_4, followed by Zamplen deacetylation condition to give the tetrol as a white crystalline solid. Two primary hydroxyl groups were selectively protected as tosylates and the 3,4-diol as ethoxymethylidene ether to

provide **33**. Nucleophilic displacement of tosyl group with 4-fluorophenol in alkali medium (**34**), followed by orthoester deprotection gave the 3,4-diol derivative (**34a**). Oxidative cleavage of 3,4-diol followed by stable two-carbon Wittig reaction gave the α, β-unsaturated ester **36**. The reduction in presence of Pd/C followed by acid catalysed cyclization resulted into two equivalents of desired lactone **26**, which was reduced with DIBAL-H, provided the intermediate lactol **27** in good yield.

The second strategy begins with the hydrolytic kinetic resolution of (±)-glycidyl-4-fluorophenyl ether (**38**) with (R,R)-salen-CO(III)-OAc and 0.55 eq. of H_2O gave (S)-glycidyl-4-fluorophenyl ether (**39**) (92% ee) along with (R)-1-(4-fluorophenyl)-glycerol (97% ee). Two carbon homologation with concomitant lactone formation was achieved by treatment of compound **39** with the sodium salt of diethyl malonate to furnish the corresponding 2-carbethoxy-4-fluorophenoxymethyl-γ-butyrolactone (**40**). Convenient decarboxylation using DMA/ $MgCl_2.6H_2O$ and H_2O provided lactone (**26**). Partial reduction with DIBAL-H at -78^{0}C provided the lactol (**27**) in quantitative yield.

Scheme 3

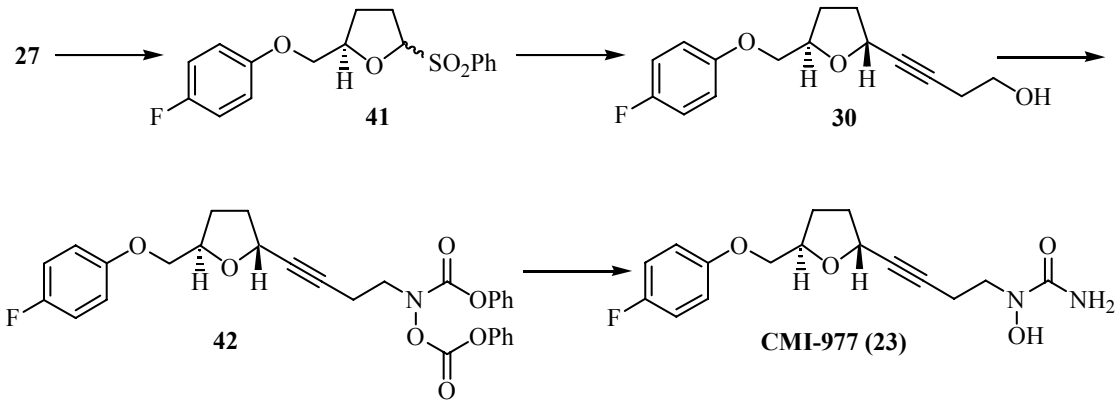


Second strategy for CMI-977 from 4-fluorophenol

The key transformation was diastereoselective C-C bond formation *via* nucleophilic substitution of 2-benzenesulphonyltetrahydrofuran, as authored by S.V. Ley, which gave the 70:30 mixture of *trans:cis* alcohol [separable through crystallisation of the crude product from ether-light petroleum to yield the pure *trans* alcohol (**30**)]. The Mitsunobu reaction of O-

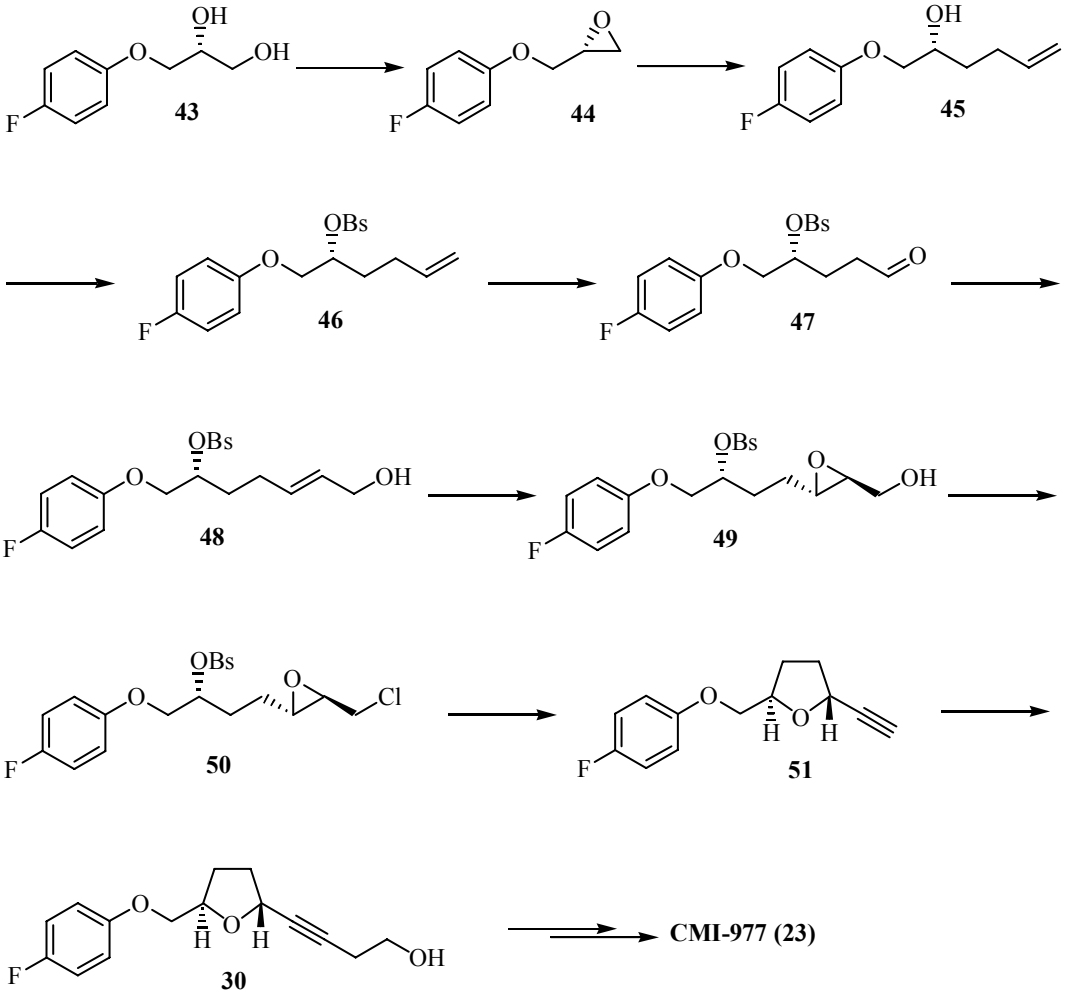
methoxyphenylmethyl-N-phenoxycarbonyl hydroxylamine with trans alcohol (**30**) in the presence of TPP/DEAD in anhydrous THF provided the alkynyl urethane (**42**). Treatment of **42** with methanolic ammonia followed by recrystallisation from ethyl acetate-light petroleum furnished pure CMI-977 (**23**). These approaches adequately addressed all the concerns faced in the discovery route, but still suffer from the diastereoselective excess.

Scheme 4



The third synthetic route, describes the total synthesis of CMI-977 in a complete stereocontrolled fashion.[26] The assembly of tetrahydrofuran ring with suitable appendages of appropriate stereochemistry through the central transformation "double elimination-cum-intramolecular S_N2 ring closure" constitutes a *de novo* strategy. The *R*-diol formed during the hydrolytic kinetic resolution of 4-flurophenyl glycidyl ether was used as starting material for the synthesis. The diol (**43**) was converted through cyclic orthoester methodology of Sharpless et al in one pot to the *R*-glycidyl ether (**44**) and then to **45** in two steps. The olefin (**45**) was converted to epoxymethyl chloride (**50**), through a sequence of steps. Double-elimination was effected by exposure of **50** to LDA to afford THF-acetylene derivative (**51**). Thus, this central transformation uneventfully framed the main skeleton in one pot with appropriate substitution and crucial stereochemistry. Saito's protocol was next deployed to obtain homopropargyl alcohol (**30**), which was converted into CMI-977 (**23**) with the same approach described above (scheme 4).

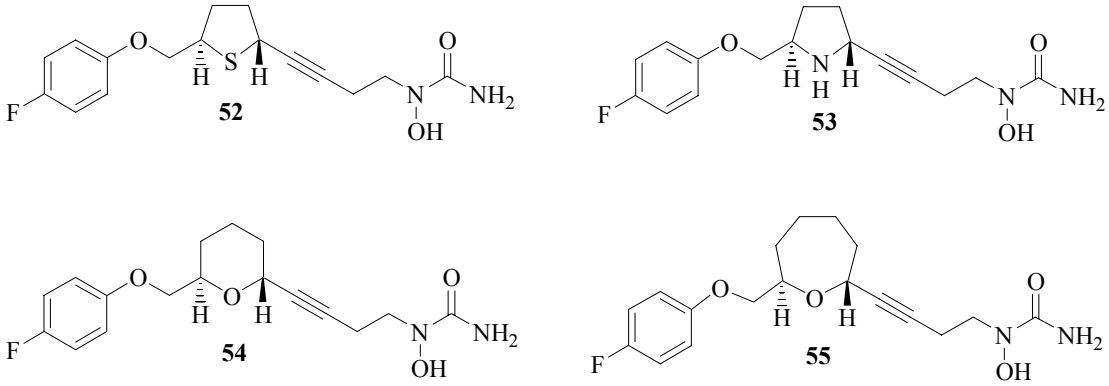
Scheme 5



We anticipate that the enantioselective synthetic strategy, detailed above, could be extented to prepare the corresponding antipode through stereotuning of hydrolytic kinetic resolution in the very beginning step and Sharpless epoxidation and also a pool of analogues of varying diversity by incorporating appropriate changes in the main strategy for diversity-oriented synthesis.

The fourth synthetic strategy for CMI-977 was described in the proceeding section as present work, which involves olefin metathesis as key step. Given below were some of the analogues of CMI-977 (Figure1), which were designed to synthesize in our laboratory to study the structure activity relationship.

Figure 1



Various analogues of CMI-977 designed

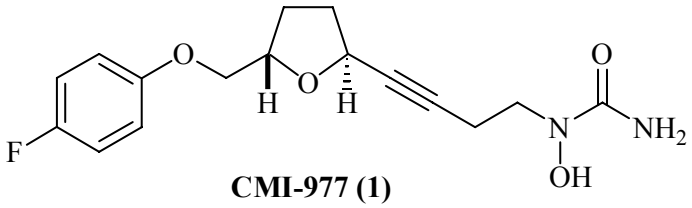
Section I

Synthesis of CMI-977

Presentwork

Present Work

Today, at the start of this 21st century, the search for new anti-asthmatic agents remains unabated. The reason is that there is currently no complete cure for asthma; presently, treatment of condition depends primarily upon inhaled glucocorticoides to reduce inflammation and inhaled bronchodilators to reduce symptoms. Such treatments are far from ideal and significant effort is being directed in both academic and commercial laboratories to the development of more efficacious and safer drugs, especially those that are orally active. The path-breaking advances in understanding the pathology of asthma and subsequent discovery of new drug targets, together with tremendous burst of innovation in drug development, have propelled the pharmaceutical majors for the introduction of safer and efficacious drugs at the brink of this century, *i.e*., novel immunological strategies using genomic tools. In this scenario, Cytomed Inc. USA has recently announced the development of CMI-977, (2*S*,5*S*)-*trans*-5-(4-fluorophenoxy)methyl-2-(4-*N*-hydroxyureidyl-1-butynyl)tetrahy drofuran (**1**) for final clinical trails for chronic asthma.[27]



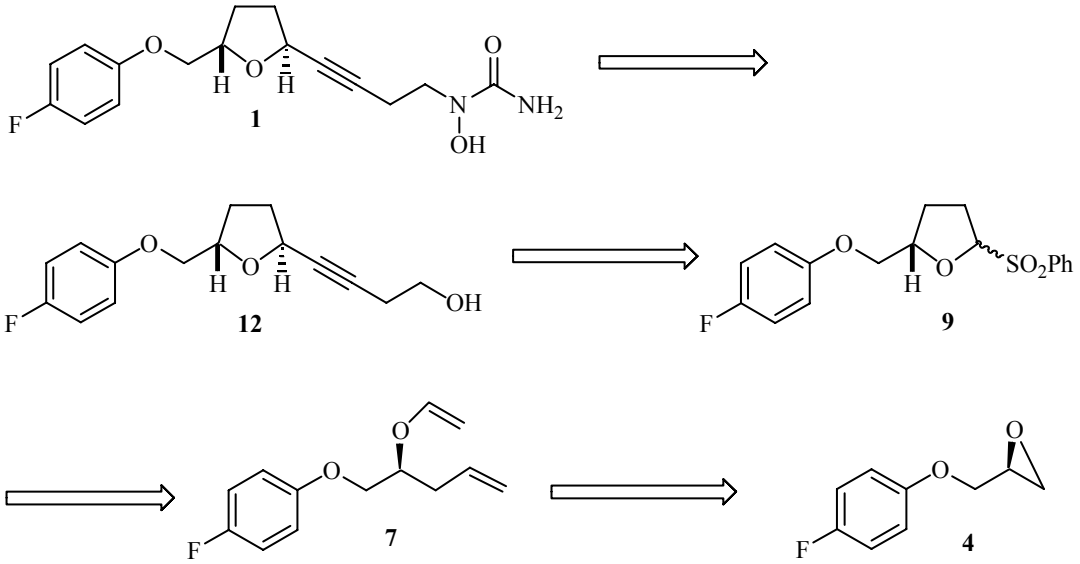
CMI-977 (1)

It acts primarily by inhibiting the 5-lipoxygenase pathway and thus blocking the production of inflammatory mediator, leukotrienes. CMI-977 has successfully been evaluated in animal models. In guinea pigs, oral administration of CMI-977 effectively blocks ovalbumin-induced bronchoconstriction, airway eosinophil accumulation, and plasma extravasation. CMI-977 blocked LTB_4 production with IC_{50} of 117 nm and 10mg/Kg inhibited eosinophil influx by 63%. Data from phase IIa trial out of one randomized, double-blind, placebo-controlled analysis to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of CMI-977 in normal subjects, showed that PK/PD profile is comparable with a single dose of zileuton, i.e.,

it may administered orally once or twice a day. Overall, CMI-977 has shown a high degree of potency, excellent oral bioavailability and exceptionally favourable safety profile.[28]

CMI-977 belongs to lignan family of 2,5-disubstituted tetrahydrofurans, featured with diverse substitution and *trans*-juxtapositioned ring and is chirally homogeneous (all other three stereoisomers have shown poor pharmacological profile). The unique structural ensemble augmented with eutomer-dependent attractive therapeutic index should invite the proposal to undertake a 'single enantiomer synthesis' that would deliver the target molecule with relevant stereochemical information and the functionalities at their respective positions.

Scheme 1



Retrosynthetic Analysis

The retrosynthetic analysis for our synthetic endeavor was planned using a 'tactical combination of transformations', as outlined in scheme 1.

Synthetic Approach:

The synthesis was initiated with the preparation of (*S*)-4-fluorophenylglycidyl ether (**4**); in which 4-fluorophenol was treated with epichlorohydrin (**2**) in the presence of K_2CO_3 and anhydrous acetone to afford the racemic 4-fluorophenylglycidyl ether. Compound **4** could have been synthesized directly by using (*R*)-epichlorohydrin and 4-fluorophenol, but the cost and

lower *ee* are issues which were cinsidered for the present studies. Therefore, we felt to use the hydrolytic kinetic resolution approach by Jacobsen for the preparation of **4.**

A brief overview on Jacobson's hydrolytic kinetic resolution:

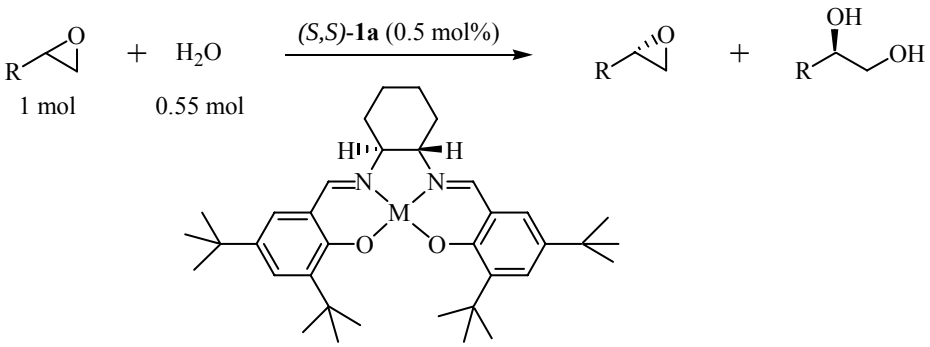


Figure 1

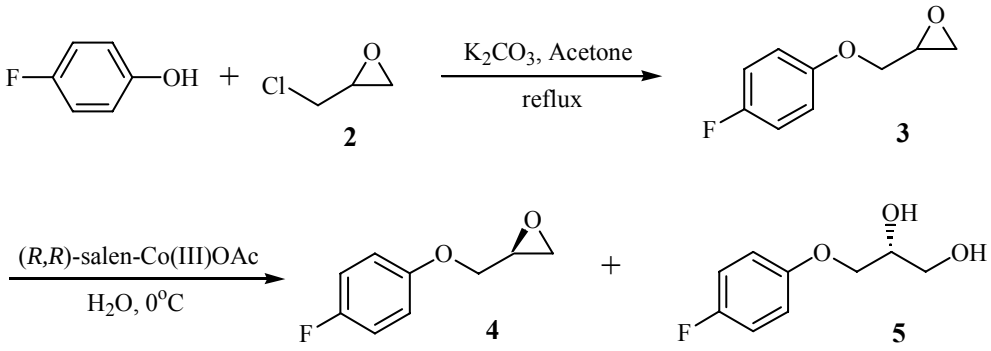
In 1997 Jacobsen group reported a powerful tool to resolve the terminal epoxide by describing the hydrolytic kinetic resolution (HKR) process.[29] *Epoxides are versatile building blocks for organic synthesis. However, terminal epoxides are arguably the most important subclass of these compounds, and no general and practical method exists for their production in enantiomereically pure form. Terminal epoxides are available very inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, given an economical and operationally simple method. Readily accessible synthetic catalyst (chiral cobalt based salen complexes) have been used for the efficient asymmetric hydrolysis of terminal epoxides. This process uses water as the only reagent, no added solvent, and low loading of recyclable catalyst (<0.5 mole percent), and it affords highly valuable terminal epoxides and 1,2-diols in high yield with high enantiomeric enrichment.*

*Accordingly, (R,R)-salen Co(III)OAc (HKR catalyst) complex with 0.55 eq. of H_2O effect the resolution of racemic terminal epoxide providing the optically pure epoxide and corresponding optically pure diol in good chemical and optical purity. The nonvolatile residue obtained after the distillation of epoxide and diol contained reduced complex **1**, from which*

*active catalyst **1a** was regenerated by treatment with acetic acid in air, such that the catalyst could be recycled with no observable loss in activity or selectivity.*

The HKR is an attractive procedure for the preparation of optically enriched terminal epoxides and 1,2-diols. The criteria for evaluating the practicality of chemical processes such as this one have become increasingly stringent. High standards of yield and selectivity in product formation must be met, but additional issues such as reagent cost, volumetric productivity, waste generation, reagent toxicity, and handling risks weigh more heavily than ever before. With these criteria positively met, the HKR appears to hold significant potential for large-scale application.

Scheme 2

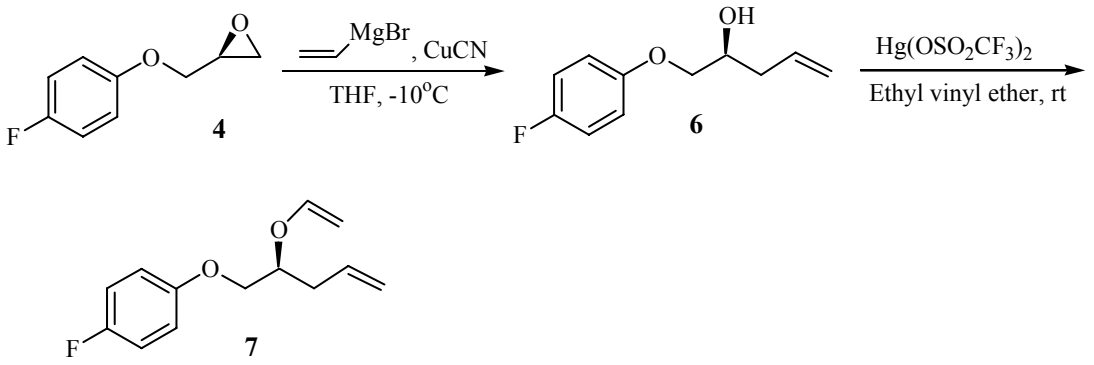


Accordingly the catalyst (*R,R*) salen Co(III)OAc was synthesized as per the literature procedure in good yield.[30] The (±)-4-fuorophenylglycidyl ether (**3**) was then subjected to hydrolytic kinetic resolution conditions using 0.5 mol % of (*R,R*)-salen-Co(III)OAc and 0.55 equivalent of distilled water at 0 °C to afford the (*S*)-4-fuorophenylglycidyl ether (**4**) with 92% ee along with (*R*) -1-*O*-(4-flurophenyl)glycerol (**5**) with 97% ee. The ^{1}H and ^{13}C NMR spectra of **4** and **5** were in agreement with the assigned structures.

The allyl alcohol **6** was derived by the regioselective ring opening of **4** with the vinylmagnesium bromide in the presence of catalytic CuCN in dry THF.[31] The structure of compound **6** was analyzed by its ^{1}H NMR spectrum in which the peaks due to epoxide protons (at 2.73 and 2.88 ppm) were missing and the presence of olefinic protons was conspicuous with signals in the downfield region at 5.14 ppm (CH_2=) and at 5.84 ppm (-CH=), whereas allylic

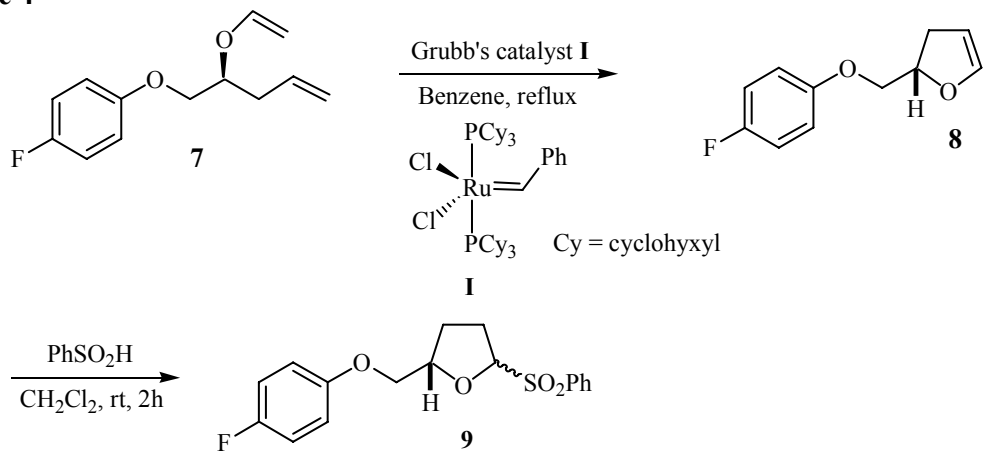
methylene protons resonated at 2.35 ppm. The ^{13}C NMR spectrum of **6** further supported the assigned structure with the prominent existence of olefinic signals at 117.6 and 133.6 ppm.

Scheme 3



The allyl alcohol **6** was then treated with freshly distilled ethyl vinyl ether and 0.1 equivalent of $Hg(OCOCF_3)_2$ at room temperature[32] to afford the corresponding vinyl ether **7**. In its ^1H NMR spectrum, the typical *O*-vinyl group signals were distinctly seen as three sets doublet of doublets at 4.04, 4.34 and 6.38 ppm (two terminal olefinic protons and one vinylic proton) while rest of the spectrum was in complete conformity with the assigned structure.

Scheme 4



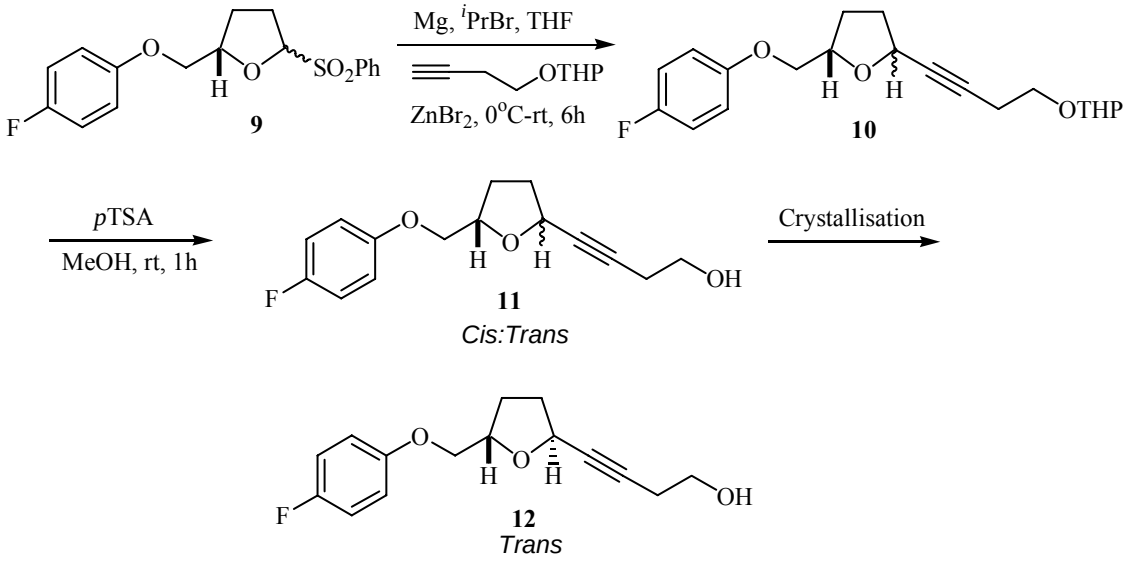
The ring closing metathesis of the diene (**7**) was achieved using Grubbs' 1st generation catalyst.[33] Accordingly treatment of **7** with 5 mol% of catalyst in refluxing benzene for 20 h afforded the dihydrofuran derivative (**8**). The structure of **8** was confirmed by its ^1H NMR spectrum, in which characteristic signals due to double bond were seen at 4.90 ppm as a multiplet and 6.29 ppm as a doublet. The two methylene proton signals were located at 2.48 and 2.82 ppm.

The structure was further confirmed by the ^{13}C NMR spectrum in which olefinic carbons were positioned at 98.8 and 145.2 ppm.

The side chain 4-*N*-hydroxymethyl-1-butynyl moiety of CMI-977 was constructed using Ley's protocol[34] of nucleophilic addition on oxenium ion generated from 2-benzenesulfonyl tetrahydrofuran. Compound **8** was treated with benzenesulfinic acid in dry CH_2Cl_2 at room temperature followed by work up to provide the crystalline sulfone derivative **9** in 81% yield. In the ^1H NMR spectrum of **9**, peaks related to ring proton H-2 of furan ring appeared as two sets of multiplets at 4.89 and 4.94 ppm indicature of the presence of diastereomeric mixture. The aromatic protons of sulfone group appeared as two sets of multiplets at 7.58 and 7.88 ppm while rest of the spectrum was in complete agreement with the assigned structure.

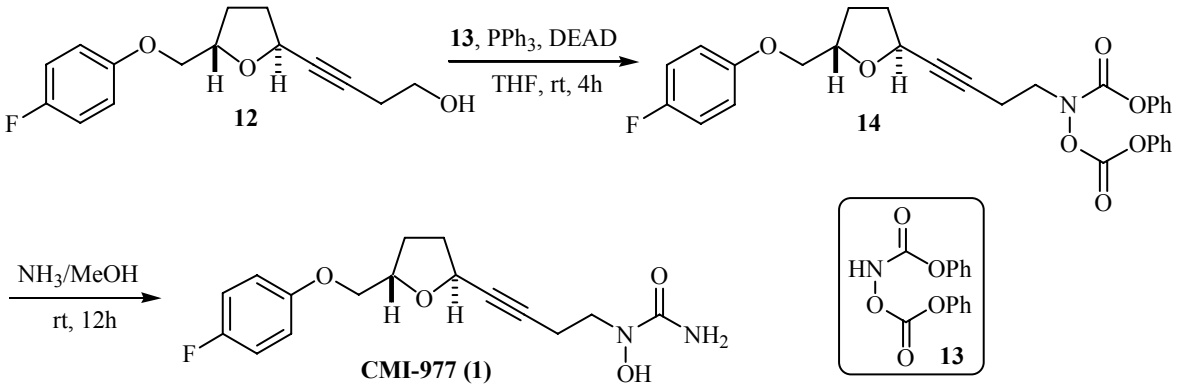
The sulphone intermediate **9** was reacted with the dialkylzinc reagent (generated *in situ* by the addition of 4-tetrahydropyranyloxy-1-butynylmagnesium bromide to zinc bromide in THF at ambient temperature) at room temperature for 6 h to provide (2*RS*,5*S*)-5-(4-fluorophenoxy-methyl)-2-(1-tetrahydropyranyloxy-3-butyn-4-yl)tetrahydrofuran (**10**), which was subsequently stirred with catalytic amount of *p*TSA in methanol for 1 h to cleave the THP group and retrieve the homopropargyl alcohol **11**.

Scheme 5



The HPLC analysis and the ^{1}H NMR spectrum of **11** revealed the formations of *cis*-*trans* diastereomers in 3:7 ratio. Crystallization of crude product twice from ether-hexane yielded the pure *trans* (2*S*,5*S*)-5-(4-flurophenoxymethyl)-2-(1-hydroxy-3-butyn-4-yl)-tetrahydrofuran (**12**) with HPLC purity above 96%. The structure was unambiguously derived by comparison of relevant chemical shifts in the ^{1}H NMR spectrum of the authentic **12**.[24] The signals due to the methylene protons of tetrahydrofuran ring appeared between 1.88-2.24 ppm region, whereas signals for H-2 and H-5 protons of the furan ring resonated at 4.73 and 4.45 ppm respectively. NOE studies and single crystal X-ray crystallography data showed that the relative stereochemistry of the ring protons H-2 and H-5 of compound **12** was *trans*. The ^{13}C NMR spectrum further supported the assigned structure of **12**. The optical rotation $[\alpha]_D$ -34.2 (c 1.3, $CHCl_3$) was comparable to the reported value {lit.[24], $[\alpha]_D$ -34 (c 1, $CHCl_3$)}.

Scheme 6



Introduction of *N*-hydroxyurea group at the terminal carbon of homopropargyl side chain was achieved by using *N*,*O*-bis(carbo-phenoxy)hydroxyl amine (**13**) in order to complete the total synthesis of CMI-977. Synthesis of *N*,*O*-bis(carbophenoxy)hydroxyl amine (**13**) was carriedout by the literature procedure using $NH_4OH.HCl$ and two equivalents of phenyl chloroformate.[35] Compound **12** was subjected to the Mitsunobu reaction[36] with the *N*,*O*-bis(carbophenoxy)hydroxyl amine (**13**), TPP and diethylazodicarboxylate (DEAD) in anhydrous THF to afford **14**. The appearance of the signals relevant to ten protons of phenoxy group (two

phenyls) in the ^{1}H NMR spectrum at 7.05-7.45 ppm as a multiplet was the clear indication of Urethane group. The rest of the protons had expected chemical shifts.

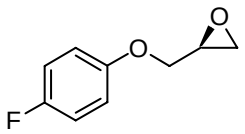
The last endeavor involved the ammonolysis of urethane group to generate hydroxy urea derivative. Thus, exposure of compound **14** to saturated methanolic ammonia solution at room temperature for 12 h followed by workup afforded the final product CMI-977 (**1**) as a white crystalline solid. The structure of **1** was confirmed by comparing its ^{1}H NMR, ^{13}C NMR, optical rotation and melting point with that of authentic sample.[24]

In conclusion, we have demonstrated a short and stereoselective synthesis of CMI-977 using (±)-4-fluorophenyl glycidyl ether as a starting material and hydrolytic kinetic resolution approach to resolve the enantiomers. The tetrahydrofuran ring was effectively constructed using ring-closing metathesis of vinyl ether while stereoselective introduction of 1-*N*-hydroxyureidyl-3-butyn-5yl side chain was achieved by C-alkylation on 2-benzenesulphonyl derivative. The drug – lead CMI-977, recently rechristened as LDP-977, is currently undergoing advanced phase clinical studies and hope, it will hit the high street of drug market soon to ameliorate the sufferings of asthmatic patients worldwide.

Experimental

Experimental

(*S*)-4-Fluorophenyl glycidyl ether and (*R*)-1-O-(4-fluorophenyl)glycerol (4).



To a solution of 4-fluorophenol (40 g, 0.35 mol) in acetone (350 ml) was added dry K_2CO_3 (148 g, 1.05 mol) and epichlorohydrin (95 ml, 1.05 mol). The reaction mixture was heated at 60 °C for 12 h., filtered and filtrate distilled under reduced pressure (b.p.160-170°C/9mm) to afford pure (*R/S*)-glycidyl-4-fluorophenyl ether (52 g, 85%) as a colourless liquid. To an ice-cooled solution of (*R/S*)-glycidyl-4-fluorophenyl ether (52 g, 0.31 mol) and (*R*,*R*)- Salen-Co(III) acetate (1.03 g, 1.54 mmol) was added distilled water (3.06 ml, 0.17 mol) over a period of 1 h and stirred for 18 h. The catalyst was filtered and the filtrate distilled under reduced pressure to give first (*S*)-glycidyl-4-fluorophenyl ether (**4**) (22 g, 85%) as a colourless liquid.

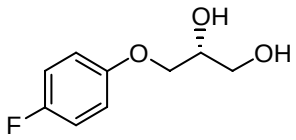
Boiling point : 160 –170 °C /9mm

$[\alpha]_D$: + 5° (c 2.3, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 2.68 (dd, *J* = 4.5, 2.2 Hz, 1H), 2.85 (t, *J* = 4.5 Hz, 1H), 3.27 (m, 1H), 3.89 (dd, *J* = 15.7, 6.7 Hz, 1H), 4.11 (dd, *J* = 15.7, 4.5 Hz, 1H), 6.74-7.02 (m, 4H);

^{13}C NMR ($CDCl_3$, 50MHz) : δ 44.1, 49.8, 69.1, 115.4, 115.6, 115.8, 154.3, 159.6.

The mother liquor then afforded the diol (**5**)



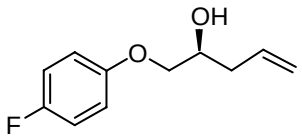
Melting point : 58-59° C

$[\alpha]_D$: - 9.6° (c 1.6, EtOH)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 2.08 (bs, 1H), 2.77 (bs, 1H), 3.64-3.90 (m, 2H), 3.93-4.16 (m, 3H), 6.73-7.03 (m, 4H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 63.6, 69.7, 70.4, 115.4, 115.6, 116.1, 154.4, 159.8.

(2*S*)-1-(4-Fluorophenoxy)pent-4-en-2-ol (6).



To a suspension of magnesium (1.63 g, 67.9 mmol) in dry THF (20 ml) at 0 °C was added a solution of vinyl bromide (3.6 g, 33.9 mmol) in THF (15 ml). After 0.5 h, CuCN (60 mg, 0.68 mmol) and (*S*)-4-fluorophenyl glycidyl ether (**4**) (4.0 g, 23.8 mmol) were added and stirred for 1 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl, concentrated and the residue partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4), concentrated and the residue was purified on silica gel using ethyl acetate light petroleum (1:4) as eluent to afford **6** (3.64 g, 78%) as colorless liquid.

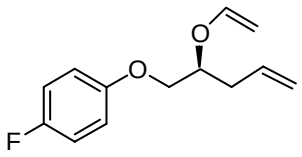
$[\alpha]_D$: + 15.0° (c 2.3, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 2.35 (dt, *J* = 1.4, 7.3 Hz, 2H), 2.51 (bs, 1H), 3.84 (dd, *J* = 5.8, 9.3 Hz, 1H), 3.92 (dd, *J* = 4.4, 9.3 Hz, 1H), 4.0 (m, 1H), 5.14 (m, 2H), 5.84 (m, 1H), 6.82 (m, 2H), 6.95 (m, 2H).

^{13}C NMR ($CDCl_3$, 125MHz) : δ 37.54, 69.06, 71.80, 115.28, 115.34, 115.52, 117.60, 133.61, 154.46, 157.99.

Anal: Calcd for ($C_{11}H_{13}FO_2$): C, 67.35, H, 6.63. Found: C, 67.45, H, 6.73.

(2*S*)-2-Ethenoxy-1-(4-fluorophenoxy)-4-pentene (7).



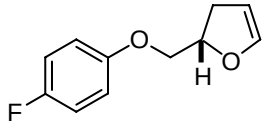
A mixture of compound **6** (3.6 g, 18.4 mmol), ethyl vinyl ether (350 ml) and $Hg(OCOCF_3)_2$ (0.8 g, 1.8 mmol) was stirred for 12 h at room temperature. The reaction mixture was neutralized with saturated $NaHCO_3$ solution, concentrated and partitioned between ether and water. The organic layer was dried (Na_2SO_4), concentrated and the crude product was purified on silica gel using ethyl acetate light petroleum (1:9) as eluent to give **7** (2.85 g, 70%) as a liquid.

$[\alpha]_D$: + 3.7° (c 2.6, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 2.49 (dt, *J* = 1.5, 7.3 Hz, 2H), 3.97 (m, 2H), 4.04 (dd, *J* = 1.9, 6.8 Hz, 1H), 4.14 (m, 1H), 4.34 (dd, *J* = 1.9, 14.2 Hz, 1H), 5.15 (m, 2H), 5.84 (m, 1H), 6.38 (dd, *J* = 6.8, 14.2 Hz, 1H), 6.84 (m, 2H), 6.95 (m, 2H).

Anal: Calcd for ($C_{13}H_{15}FO_2$): C, 70.25, H, 6.80. Found: C, 70.38, H, 6.72.

(2*S*)-2-(4-Fluorophenoxymethyl)-2,3-dihydro-2H-furan (8).



A solution of compound **7** (2.8 g, 12.6 mmol) and Grubbs' catalyst (0.52 g, 0.63 mmol) in benzene (750 ml) was heated under reflux for 20 h. The reaction mixture was concentrated and the residue was purified on silica gel using ethyl acetate light petroleum (1:9) as eluent to give **8** (1.27 g, 52%) as a liquid.

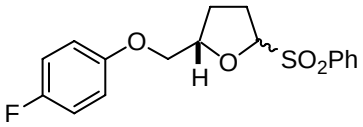
$[\alpha]_D$: + 95° (c 2.3, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 300MHz) : δ 2.48 (m, 1H), 2.82 (m, 1H), 3.89 (dd, *J* = 6.6, 9.9 Hz, 1H), 4.03 (dd, *J* = 4.2, 9.9 Hz, 1H), 4.90 (m, 2H), 6.29 (d, *J* = 2.2 Hz, 1H), 6.81 (m, 2H), 6.95 (m, 2H).

^{13}C NMR ($CDCl_3$, 75MHz) : δ 31.77, 70.68, 78.77, 98.85, 115.58, 115.79, 115.88, 145.24, 155.01, 159.10.

Anal: Calcd for ($C_{11}H_{11}FO_2$): C, 68.03, H, 5.71. Found: C, 68.18, H, 5.65.

(2*RS*, 5*S*)-2-(Benzenesulfonyl)-5-(4-fluorophenoxymethyl)tetrahydrofuran (9).



To an ice-cooled solution of freshly prepared benzenesulfinic acid (1.1 g, 7.4 mmol) in CH_2Cl_2 (10 ml), was added a solution of compound **8** (1.2 g, 6.2 mmol) in CH_2Cl_2 (10 ml) and stirred for 2 h. Then the reaction mixture was filtered through a pad of celite and the organic layer was washed with aqueous $NaHCO_3$ solution. The combined organic layer was dried (Na_2SO_4), concentrated and purified on silica gel using ethyl acetate light petroleum (1:7) as eluent to give **9** (1.68 g, 80%) as white solid.

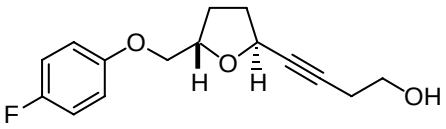
Melting Point : 112-113 °C.

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.90-2.95 (m, 4H), 3.86-4.28 (m, 2H), 4.56 (m, 1/3H), 4.73 (m, 2/3H), 4.89 (m, 1/3H), 4.94 (m, 2/3H), 6.70-7.05 (m, 4H), 7.58 (m, 3H), 7.88 (m, 2H).

^{13}C NMR ($CDCl_3$, 75MHz) : δ 25.72, 26.90, 69.95, 80.50, 94.65, 115.51, 115.66, 115.97, 129.0, 129.18, 129.27, 133.84, 155.01, 159.76.

Anal: Calcd for ($C_{17}H_{17}FO_4S$): C, 60.70, H, 5.09. Found: C, 60.62, H, 5.15.

(2*S*,5*S*)-5-(4-Fluorophenoxymethyl)-2-(1-hydroxy-3-butyn-4-yl)tetrahydrofuran (12).



To a solution of isopropylmagnesium bromide [prepared from 0.35g (14.7 mmol) of magnesium and 1.2 g (9.8 mmol) of isopropyl bromide in THF] was added 4-tetrahydro-pyranyloxy-1-butyne (1.5 g, 9.8 mmol) in anhydrous THF (5 ml). After 30 min, freshly prepared

1 M solution of $ZnBr_2$ (5.9 ml, 5.9 mmol) in THF was introduced followed by the addition (after 45 min) of compound (2*RS*, 5*S*)-2-(benzenesulfonyl)-5-(4-fluorophenoxymethyl)tetrahydrofuran (1.65 g, 4.9 mmol) in THF and stirred for 6 h. The reaction mixture was quenched with saturated NH_4Cl, concentrated and the residue was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and concentrated to give **10**. The crude product was stirred with *p*TSA (0.02 g) in MeOH (10 ml) for 1 h, neutralized with Et_3N and concentrated to provide **11**. The HPLC analysis on ODS column with MeOH and water solvent system (60:40), showed 70:30 ratio of diastereomers. The residue was crystallized twice from ether-light petroleum to yield the pure trans-alcohol (**12**) (0.65 g, 50%) with 96% HPLC purity.

Melting Point : 76 °C; [lit. M.P.:77-79 °C].

$[\alpha]_D$: - 34.2° (c 1.3, $CHCl_3$); [lit. $[\alpha]_D$ -34 (c 1, $CHCl_3$)].

^1H NMR ($CDCl_3$, 200MHz) : δ 1.88 (m, 1H), 2.05 (m, 1H), 2.24 (m, 2H), 2.48 (t, *J* = 6.2 Hz, 2H), 3.69 (t, *J* = 6.2 Hz, 2H), 3.91 (d, *J* = 4.7 Hz, 2H), 4.45 (m, 1H), 4.73 (m, 1H), 6.85 (m, 2H), 6.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 22.97, 27.68, 33.32, 60.74, 68.89, 70.64, 76.76, 81.13, 82.13, 115.35, 115.55, 115.80, 154.80, 159.55.

Anal: Calcd for $C_{15}H_{17}FO_3$: C, 68.18, H, 6.44. Found: C, 68.51, H, 6.35.

***N*,*O*-bis-phenoxycarbonylhydroxylamine (13):**

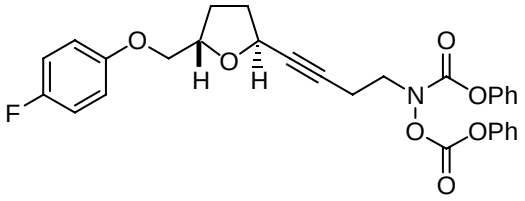
To a solution of sodium bicarbonate (21.5 g, 0.256 mol) in water (150 ml) at 0 °C was added hydroxylamine hydrochloride (8.8 g, 0.127 mol). The reaction mixture was stirred for 30 min and phenylchloroformate (60 g, 0.383 mol) was introduced directly into the vigorously stirred mixture. Sodium bicarbonate (32.3 g, 3.85 mol) in water (300 ml) was added to the mixture. The mixture was stirred for 30 min., the ice-bath removed and stirring continued for an additional 2 h at room temperature. The resultant suspension was filtered and the filter cake washed with water. The wet filter cake was collected, suspended in hexane, filtered and again

washed with hexane. The solid was kept at 0 °C overnight to afford *N*,*O*-bis-phenoxycarbonyl-hydroxylamine (23.5 g, 68%) as a solid.

Melting point : 80-82 °C;

^{1}H NMR ($CDCl_3$, 200MHz) : δ 7.26(m, 5H), 7.42 (m, 5H) and 8.54 (s, 1H).

(2*S*,5*S*)-5-(4-Fluorophenoxymethyl)-2-(1-*N*,*O*-bis-(phenoxycarbonyl)hyroxylamino-3-butyn-4-yl)tetrahydrofuran (14).



To a stirred ice cooled solution of trans alcohol **12** (0.62 g, 2.3 mmol) in THF (10 ml) were added triphenylphosphine (0.74 g, 2.8 mmol) and N,O-bis-(phenoxycarbonyl)-hydroxylamine (**13**) (0.64 g, 2.8 mmol). After 10 min, diethylazodicarboxylate (DEAD) (0.49 g, 2.8 mmol) was added dropwise at 0 °C and stirred for 4 h at room temperature. The reaction mixture was concentrated and the residue was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4), concentrated and the crude product was purified on silica gel using ethyl acetate-light petroleum (1:6) as eluent to give **14** (1.1 g, 90%) as a white solid.

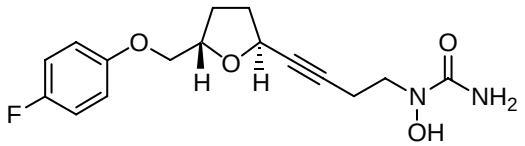
Melting point : 85-86 °C.

$[\alpha]_D$: - 18.4° (c 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.76 (m, 1H), 1.95 (m, 1H), 2.13 (m, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 3.79 (dd, *J* = 2.0, 4.5 Hz, 2H), 3.95 (t, *J* = 6.8 Hz, 2H), 4.33 (m, 1H), 4.63 (m, 1H), 6.70-6.95 (m, 4H), 7.05-7.45 (m, 10H).

Anal: Calcd for $C_{29}H_{26}FNO_7$: C, 67.04, H, 5.04, N, 2.70. Found: C, 67.42, H, 5.35, N, 2.92.

(2*S*,5*S*)-5-(4-Fluorophenoxymethyl)-2-(1-N-hydroxyureidyl-3-butyn-4-yl)tetrahydrofuran (CMI-977) (1).



To a solution of **14** (1.0 g, 1.9 mmol) in methanol (5 ml) was added saturated methanolic ammonia solution (10 ml) and stirred for 12 h at room temperature. The reaction mixture was concentrated and the residue was purified on silica gel using ethyl acetate-light petroleum (1:1) as eluent to afford **1** (0.39 g, 64%) as a white solid.

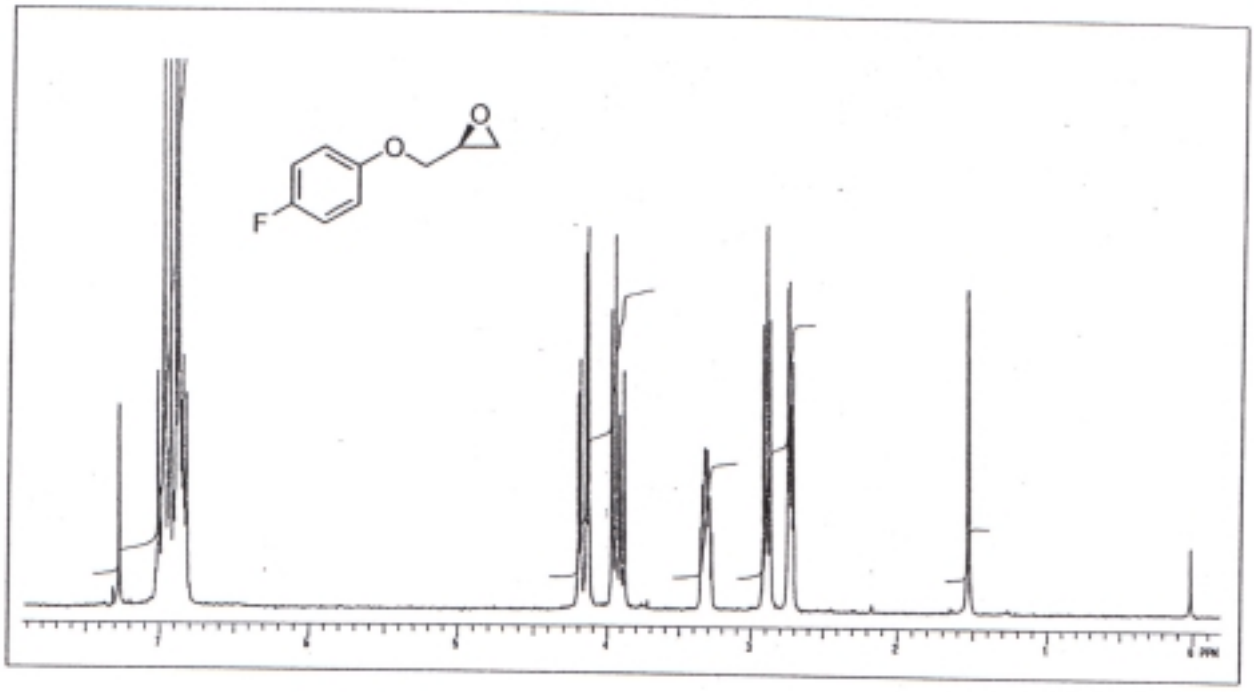
Melting point : 107-108 °C.

$[\alpha]_D$: - 47° (c 1.1, CH_3OH); lit. $[\alpha]_D$ -47.8 (c 0.3, CD_3OD).

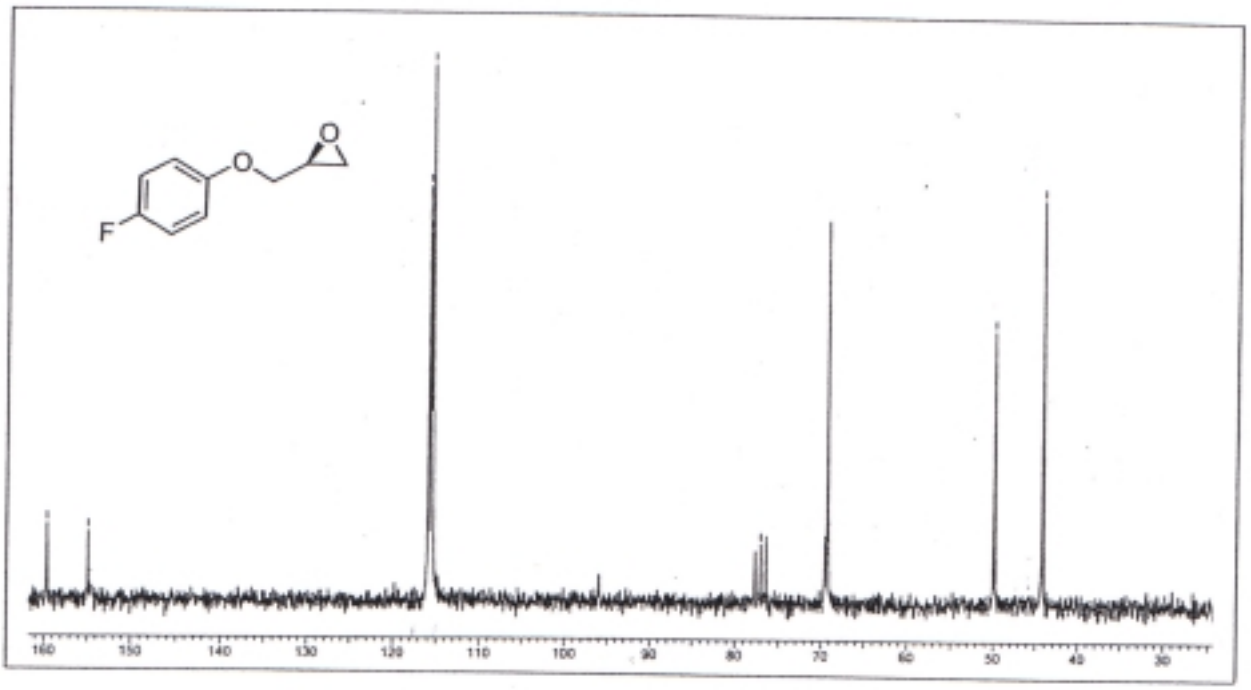
^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.82 (m, 1H), 2.01 (m, 1H), 2.22 (m, 2H), 2.54 (t, *J* = 7.9 Hz, 2H), 3.68 (t, *J* = 7.9 Hz, 2H), 3.91 (m, 2H), 4.46 (m, 1H), 4.73 (m, 1H), 5.68 (bs, 2H), 6.78-7.02 (m, 4H), 8.95 (s, 1H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 17.13, 27.66, 33.28, 48.62, 69.08, 70.36, 76.72, 80.72, 82.80, 115.50, 115.63, 115.97, 154.98, 159.70, 161.84.

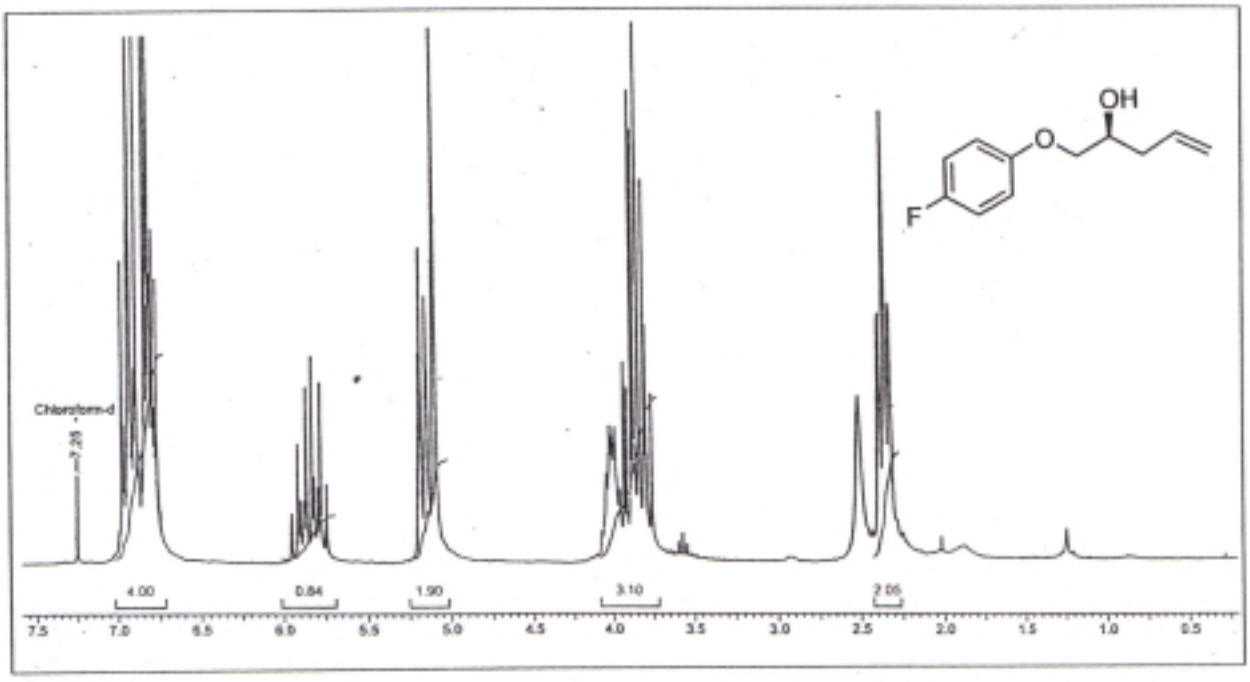
Anal: Calcd for ($C_{16}H_{19}FN_2O_4$): C, 59.62, H, 5.94, N, 8.69. Found: C, 59.74, H, 5.88, N, 8.77.



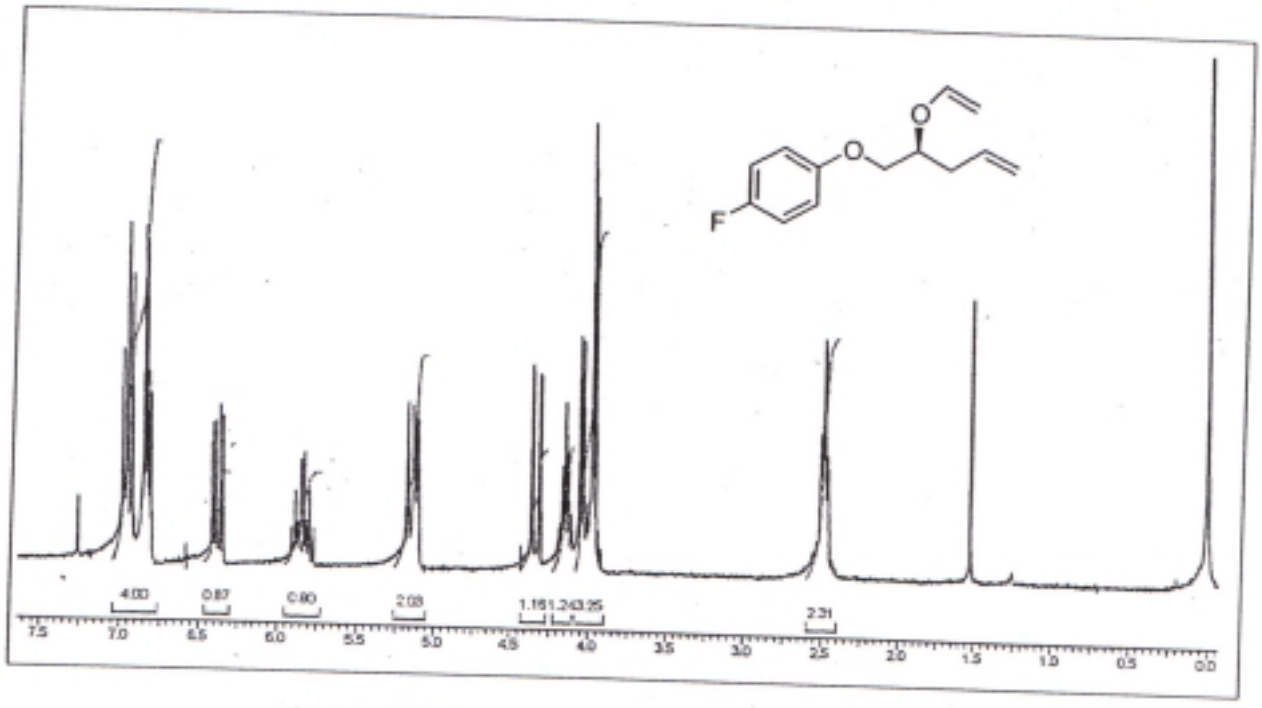
^{1}H NMR Spectrum of compound 4 in $CDCl_3$



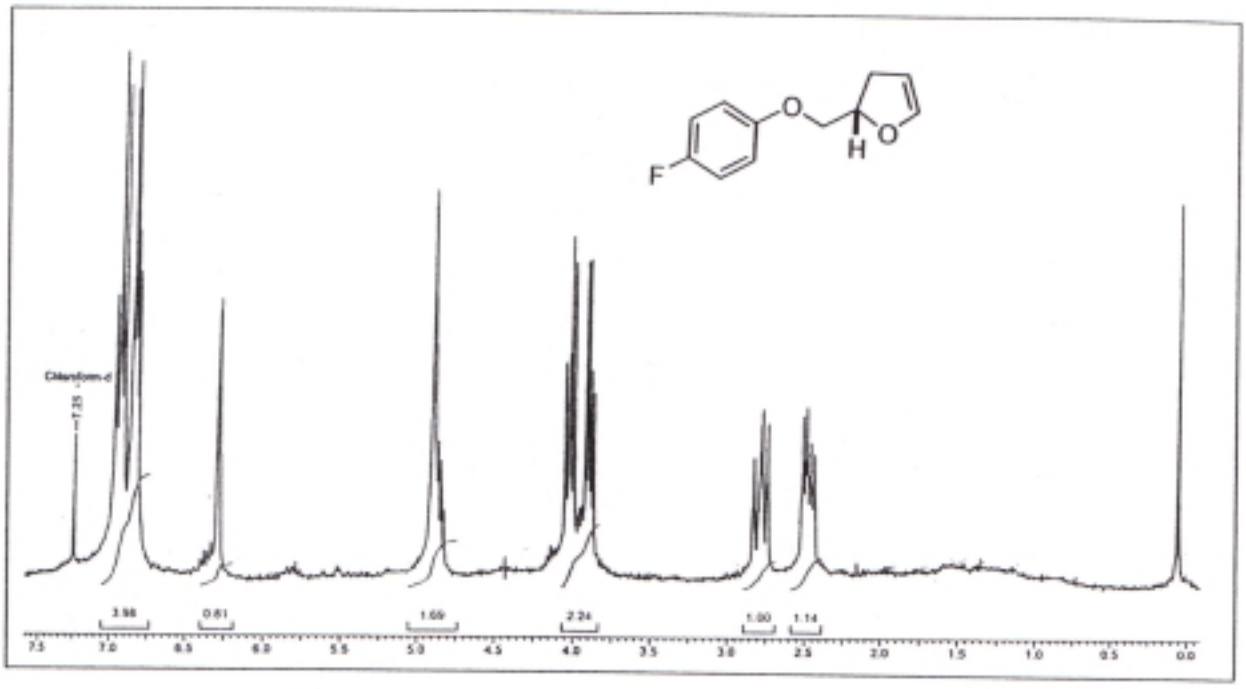
^{13}C NMR Spectrum of compound 4 in $CDCl_3$



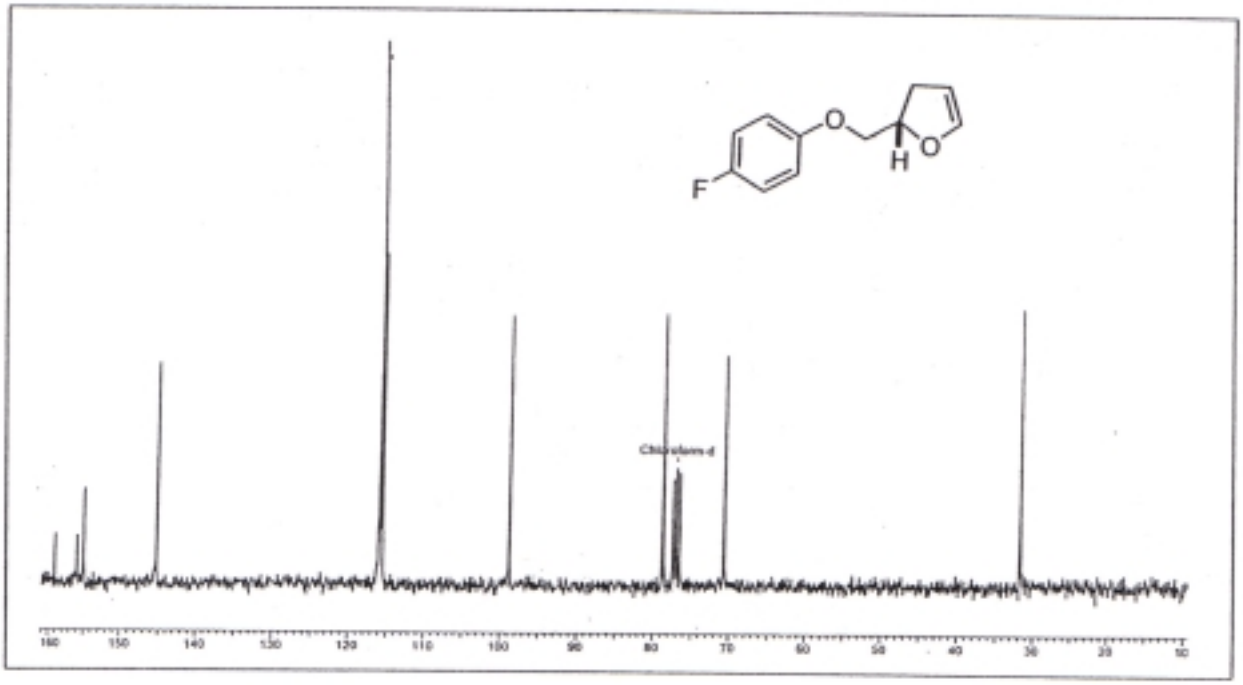
^{1}H NMR Spectrum of compound 6 in $CDCl_3$



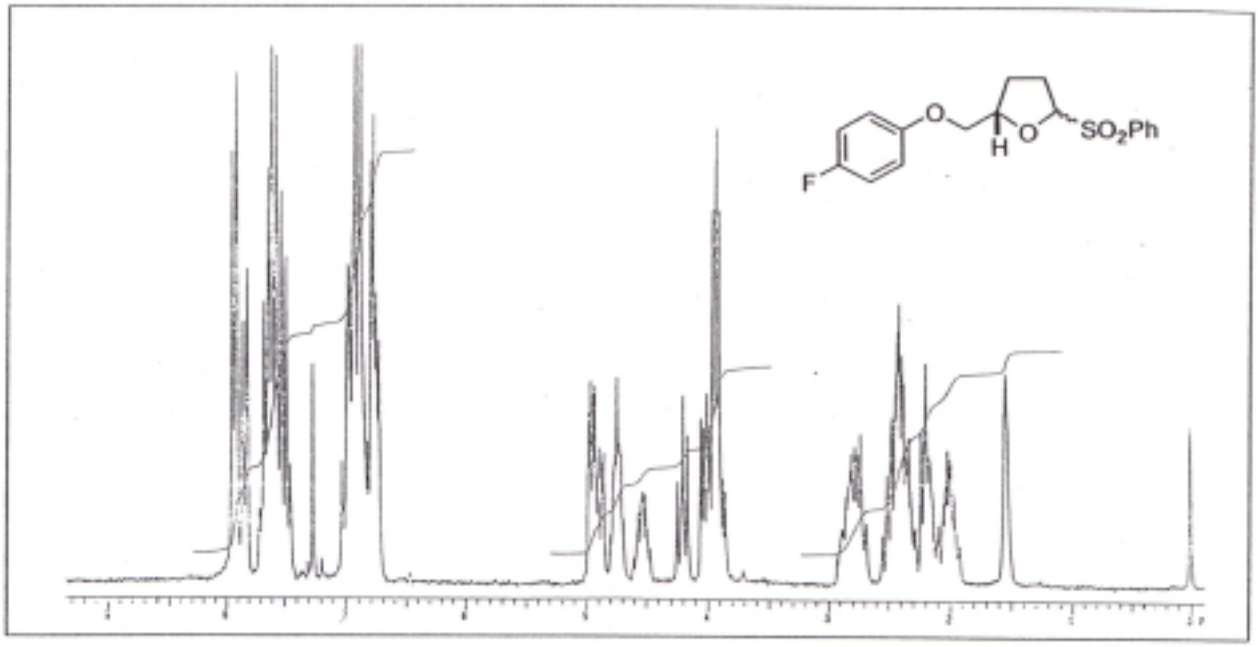
^{1}H NMR Spectrum of compound 7 in $CDCl_3$



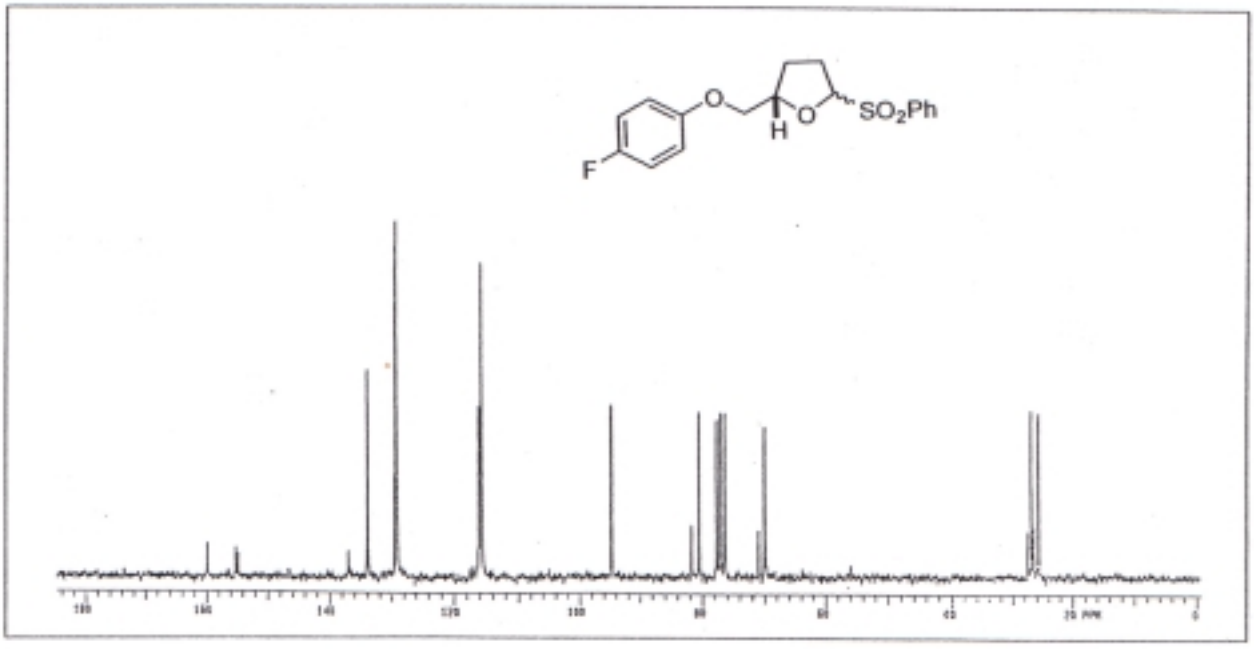
^{1}H NMR Spectrum of compound 8 in $CDCl_3$



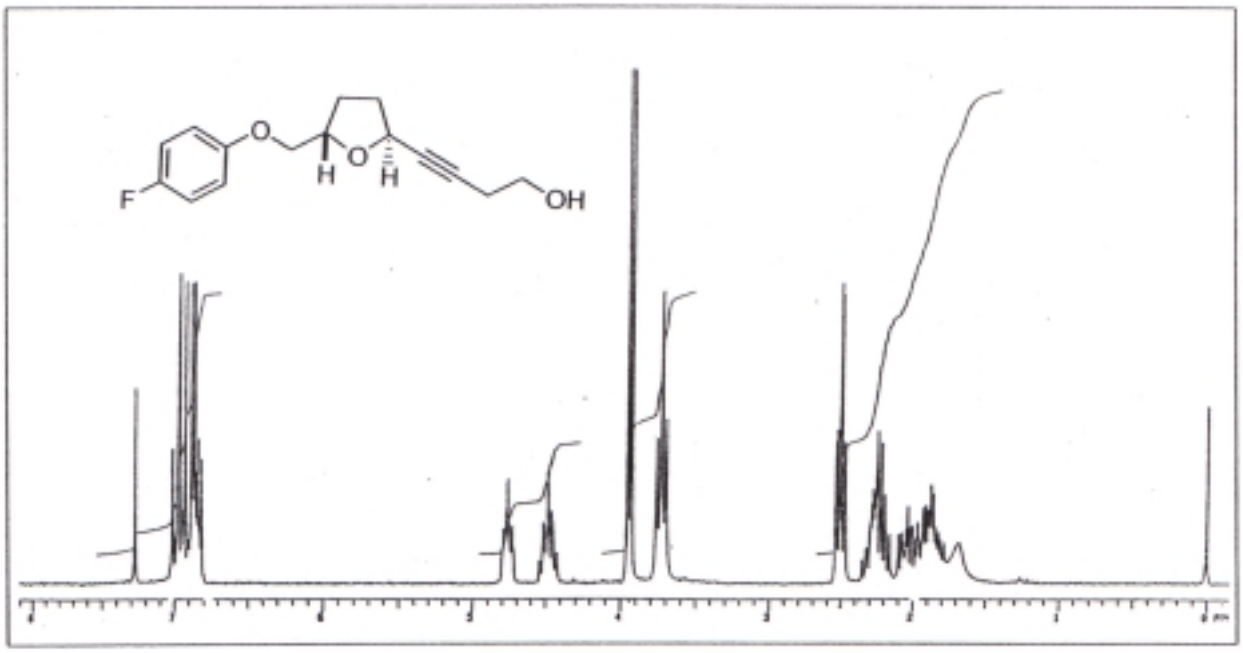
^{13}C NMR Spectrum of compound 8 in $CDCl_3$



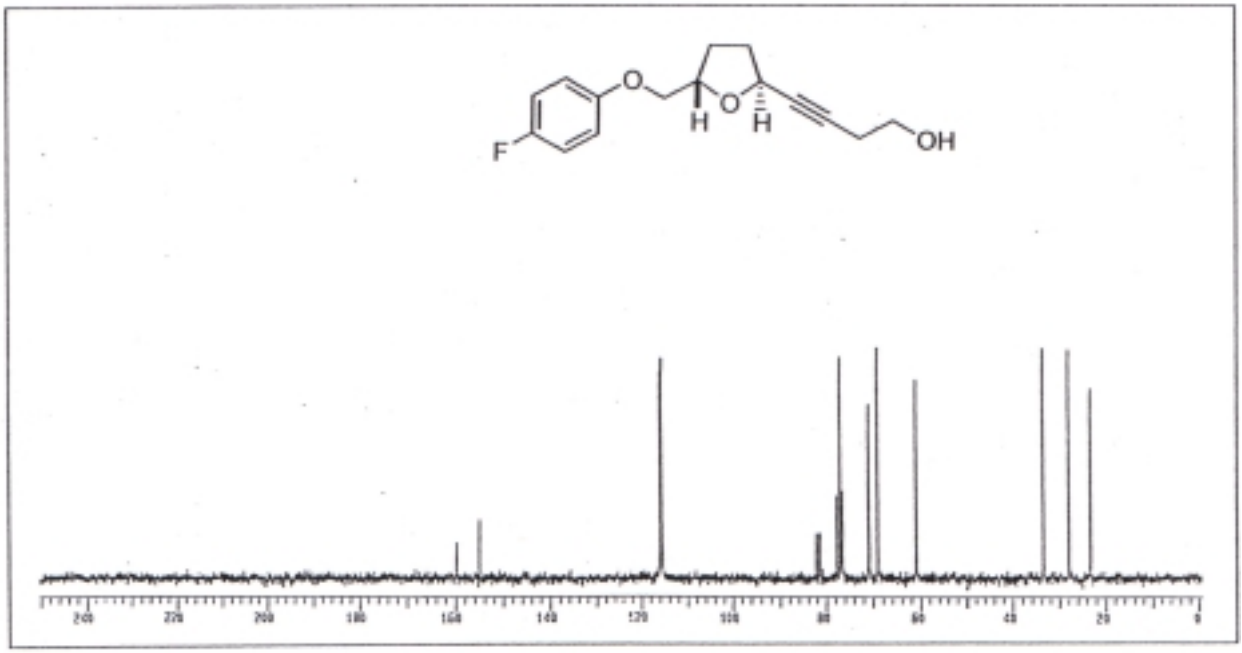
^{1}H NMR Spectrum of compound 9 in $CDCl_3$



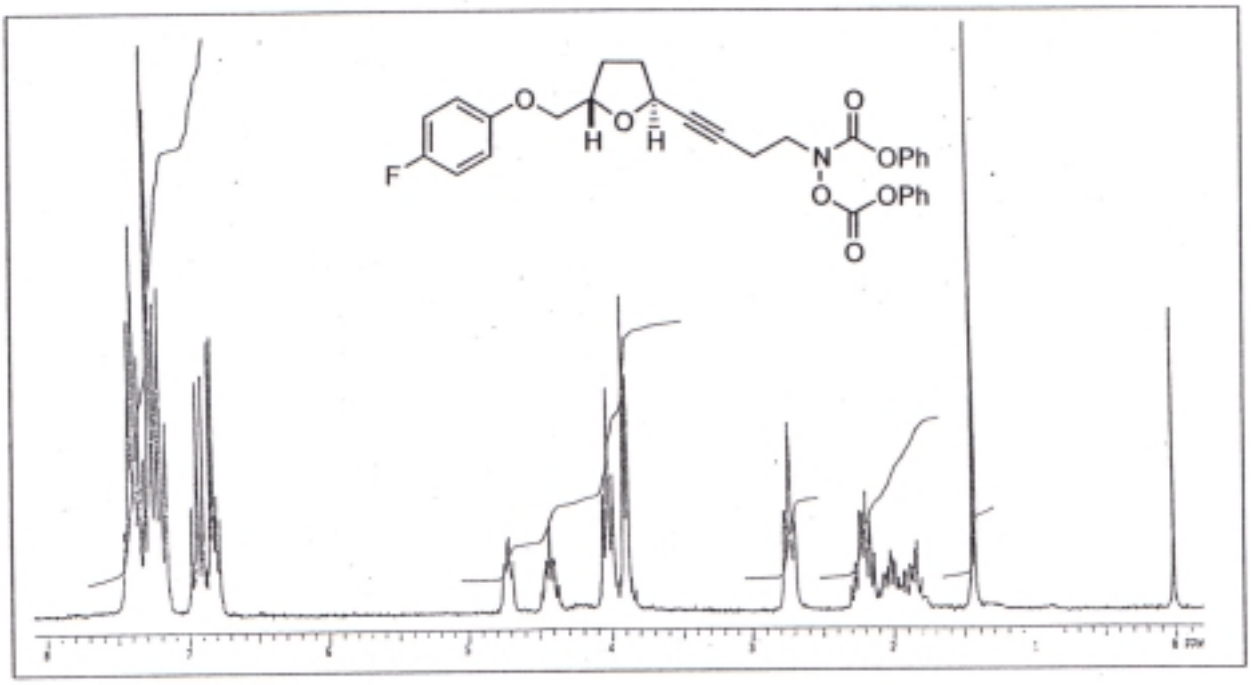
^{13}C NMR Spectrum of compound 9 in $CDCl_3$



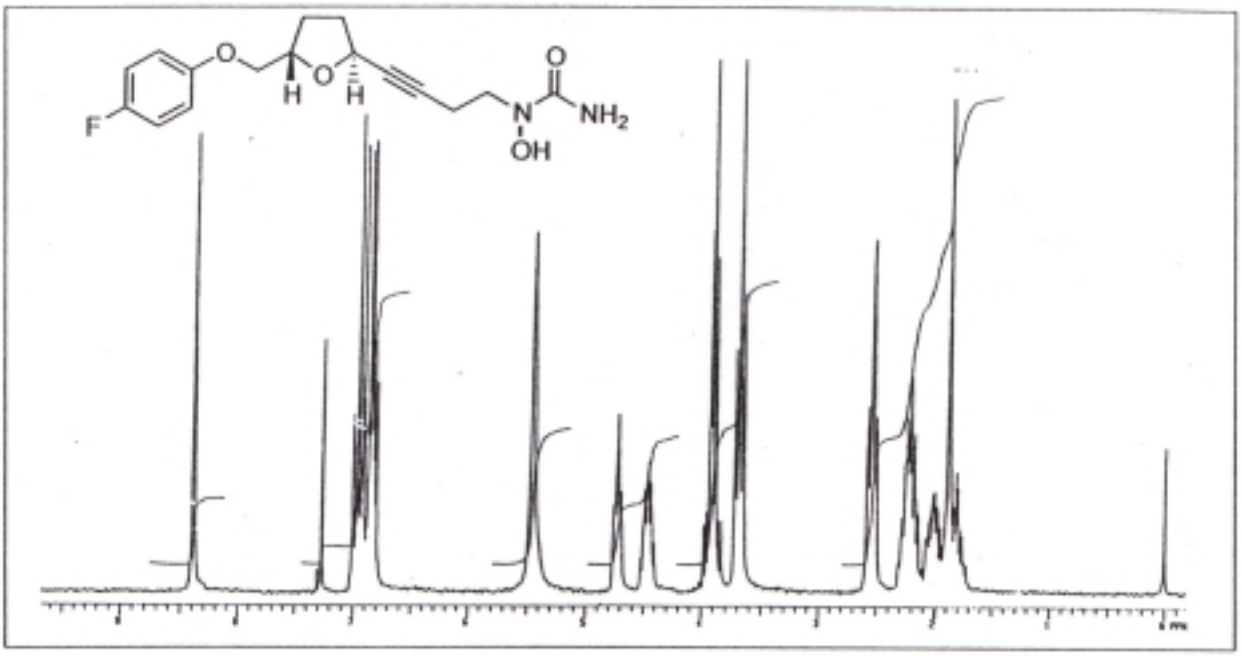
^{1}H NMR Spectrum of compound 12 in $CDCl_3$



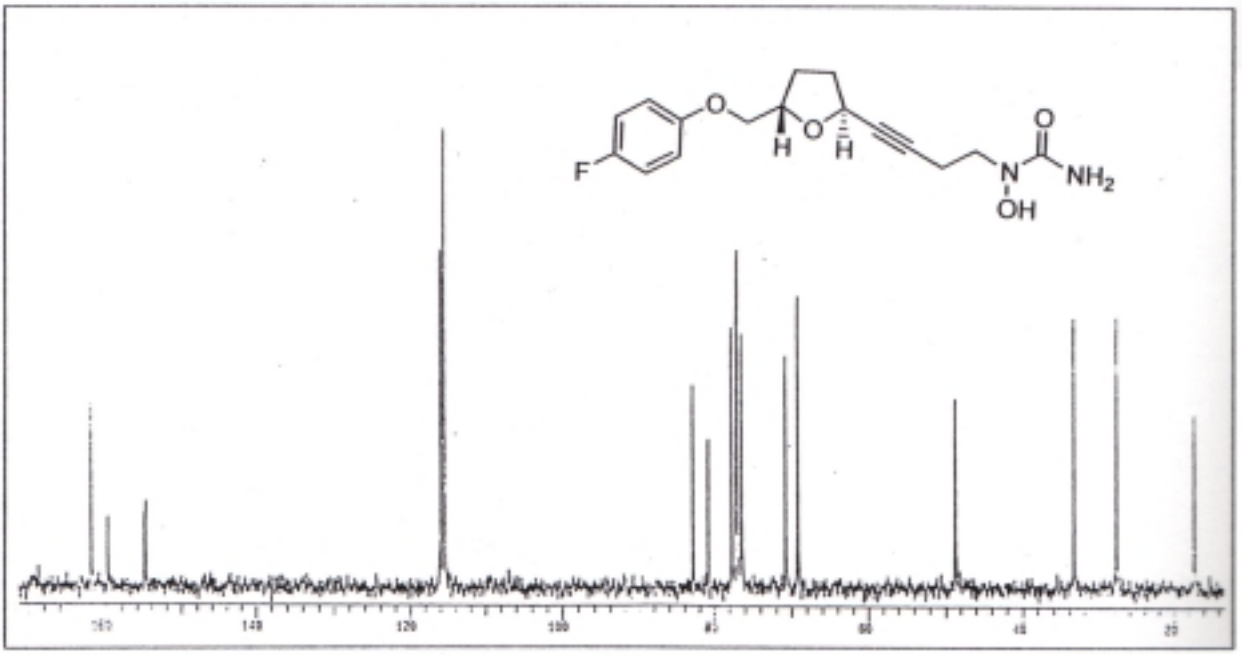
^{13}C NMR Spectrum of compound 12 in $CDCl_3$



^{1}H NMR Spectrum of compound 14 in $CDCl_3$



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



^{13}C NMR Spectrum of compound 1 in $CDCl_3$

Section II

Synthesis of CMI-977 six membered analogue

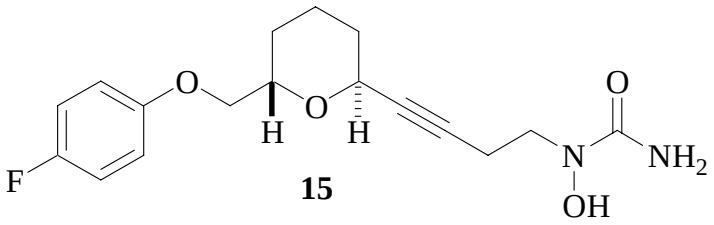
Presentwork

Present Work

The advent of genomic science, rapid DNA sequencing, combinatorial chemistry, cell based assays and automated high-throughput screening have led to the new paradigm in 'drug discovery' at the dawn of 21st century.[37] Recombinant proteins and monoclonal antibodies under the charm "biopharmaceuticals" have greatly enriched our therapeutic armamentarium. Genomic science, combined with bioinformatics tools, allow us to dissect the genetic basis of multifactorial diseases and to determine the most suitable points of attack for future medicines, there by increasing the number of treatment options. Computational revolution through simulation of molecular processes in cells and predictions of drug effects in humans will advance pharmaceutical research. Prognostic genotyping and diagnostic molecular profiling may soon cause fundamental changes in the practice of health care of new world order.[38]

Protein-protein interactions, e.g., the binding of immunoglobulin E, vascular endothelial growth factor or IL-2 or IL-5 to their respective receptors, represent very attractive drug targets in the case of allergies and asthma. Traditional small molecule drug discoveries have largely failed with these targets. However, protein-protein interfaces have "hot spots" small regions that are critical to binding and that have the same size as small molecules. The targeting of these hot spots by small molecules may turn out to be capable of undesirable protein-protein interactions. Combinatorial chemistry comes in handy, in this aspect, to expose a large number of hypothetical targets that are incorporated into in vitro or cell based assays to large number of compounds representing numerous variations on a greater number of themes in high throughput configurations. Many 'hit-compounds' that elicit a positive response to a particular assay would like to give rise to few 'lead compounds' that show positive response in complex models (cells and animals). This will advance to lead optimization and discovery. Hence, target oriented synthesis has effectively been replaced by diversity oriented synthesis, leading to structurally-complex small molecules, in modern drug discovery. In this background, in the aftermath of

completion of enantioselective synthesis of anti-asthmatic lead candidate, CMI-977, it was planned in our laboratory to synthesize a library of similar compounds that will differ in ring size, heteroatom, side chain length/homologation etc., without disturbing the main 'pharmacological core' responsible for activity that will lead to systematic investigation of structure-activity relationship.



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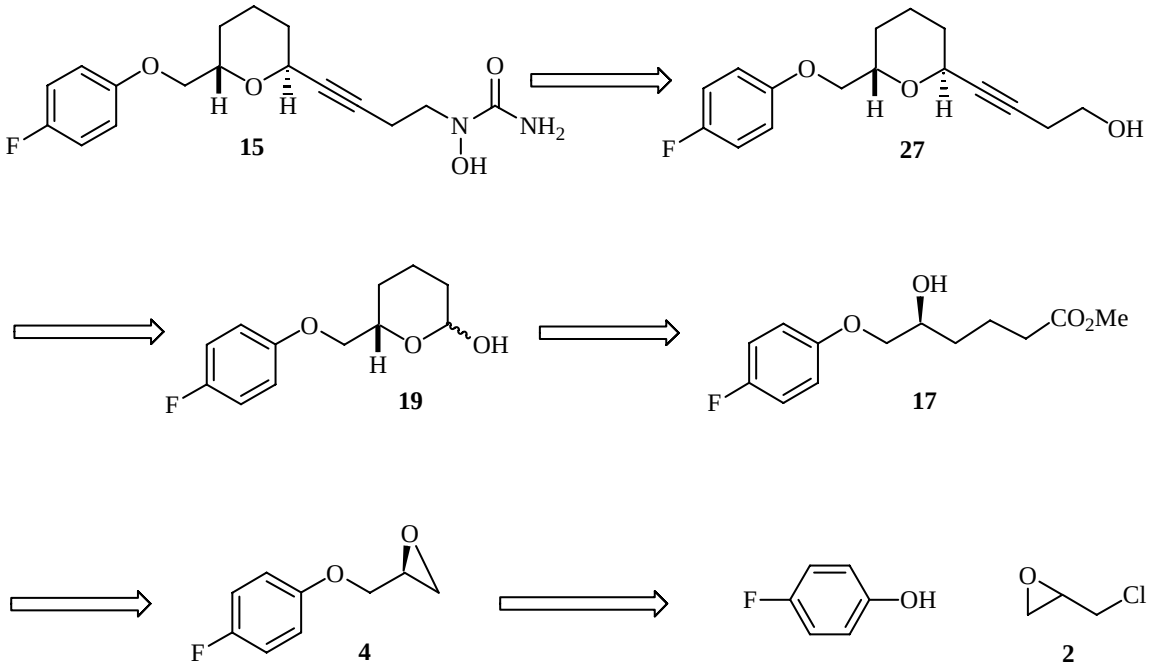
Out of the core group formed for analogues making, we were interested in the six-membered analogue of CMI-977 since the tetrahydropyran ring has the ability to possess different conformers, we were encouraged to take up the synthesis and study the pharmacological profile of the same.

We chose to implement an analogous technology to construct this molecule based on our experience in CMI-977. The synthetic planning was construed to arise from the heuristic operations, as described in the retrosynthetic analysis (Scheme 1). The first strategic disconnection was *N*-hydroxy urea moiety to provide the intermediate **27**. Compound **27** itself made up of by the C-C bond formation protocol in which, the homopropargyl part can be added to the 6-membered oxenium ion, where the diastereo induction is possible through the inherent chirality of the substrate. Accordingly, the potential electrophilic counterpart that undergoes addition at C-2 position is substituted tetrahydropyran (**19**), which intern can be prepared from the epoxide opening and subsequent cyclisation of 4-fluorophenyl glycidyl ether with corresponding propargylic unit.

Scheme 6

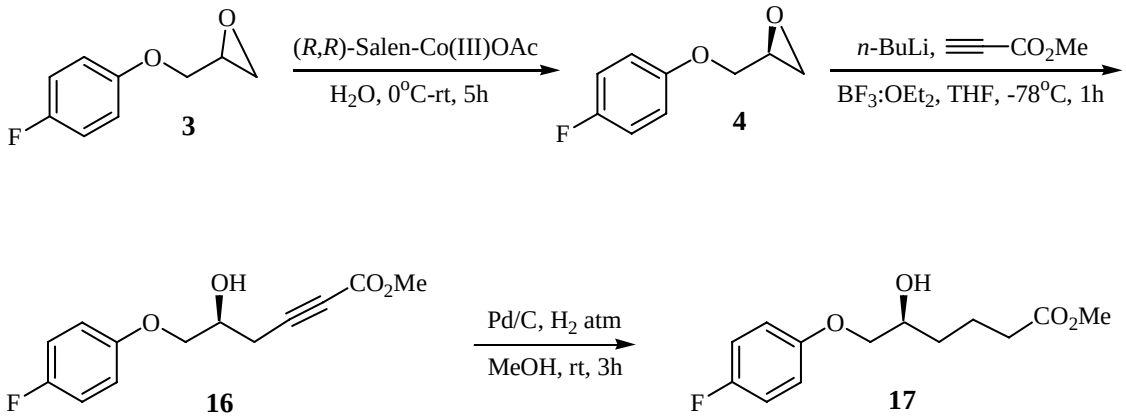


Retrosynthetic Analysis

Synthetic approach:

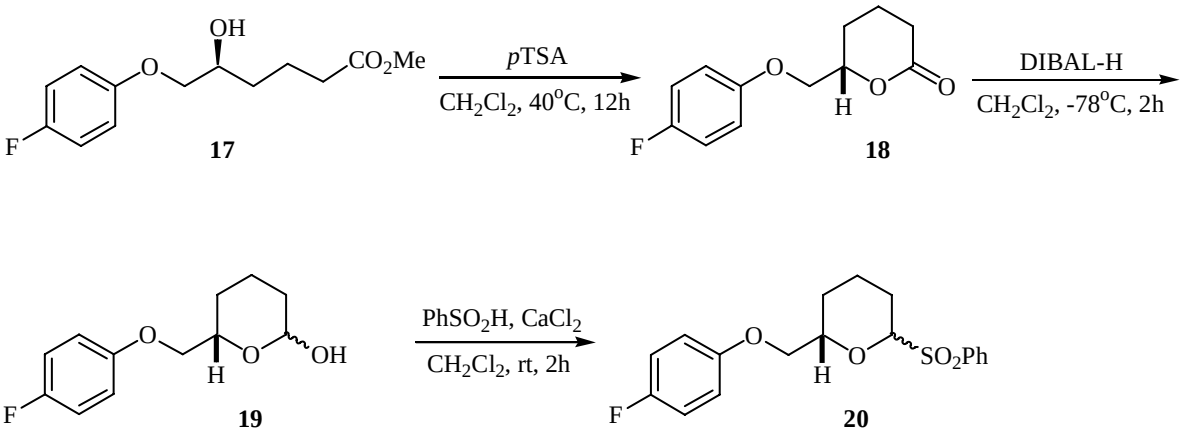
The synthetic endeavor began with the regioselective epoxide opening of (*S*)-4-fluoro phenylglycidyl ether (**4**) (the synthesis of this compound was discussed in the previous section) with methyl propiolate and *n*-BuLi as base in the presence of BF_3:OEt_2 in THF at –78 °C to provide methyl-(*S*)-6-(4-fluorophenoxy)-5-hydroxy-2-hexynoate (**16**)[39] (scheme **7**). The structure of **16** was confirmed by its ^{1}H NMR spectrum, in which signals corresponding to epoxide protons (at 2.68 and 2.85 ppm) were absent. The methylene group protons adjacent to acetylene group appeared at 2.71 ppm as a doublet. The rest of the spectrum was in complete agreement with the assigned structure. Compound **16** was then hydrogenated using 10% Pd/C in methanol under H_2 atmosphere to afford the saturated hydroxy-ester (**17**). The structure of compound **17** was confirmed by its ^{1}H NMR spectrum, in which a signal due to alkyl side chain appeared between 1.5-1.9 ppm. The methoxy group appeared at 3.68 ppm as a singlet.

Scheme 7



The saturated ester (**17**) was subjected to acid catalysed cyclisation using *p*TSA as catalyst in CH_2Cl_2 to provide the δ-valerolactone (**18**). The ^{1}H NMR spectrum of **18** was in agreement with the structure assigned. The IR spectrum showed lactone carbonyl at 1742 cm^{-1}. In order to introduce the side chain, the lactone derivative (**18**) was reduced using DIBAL-H in CH_2Cl_2 at –78 °C to afford the corresponding lactol **19**. The lactol without any further purification was quantitatively converted to its sulphone derivative **20** using freshly prepared phenyl sulfinic acid and calcium chloride in CH_2Cl_2 (Scheme **8**). The structure of the compound **20** was supported by its ^{1}H NMR spectral data.

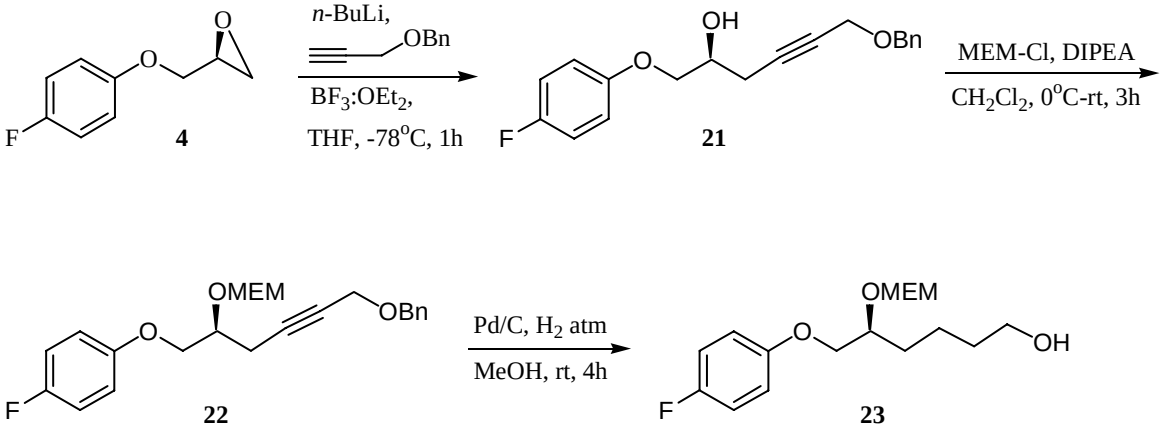
Scheme 8



Compound **20** was alternatively prepared by a route quite similar to the one described above. We observed that instead of propiolic acid, propargyl alcohol as a nucleophile to open epoxide (4) was high yielding and cost effective.

Accordingly the synthesis started with the regioselective epoxide opening of (*S*)-4-fluoro phenylglycidyl ether (**4**) with benzyloxy prop-2-yne and *n*-BuLi in the presence of BF_3:OEt_2 in THF at –78 °C to provide (2*S*)-6-benzyloxy-(4-fluorophenoxy)-hex-4-yn-2-ol (**21**)[40] (Scheme **9**). The structure of **21** was confirmed by its ^{1}H NMR spectrum, in which signals corresponding to methylene protons adjacent to acetylene group appeared at 2.65 ppm as a multiplet. Resonances due to benzyl group were observed. In the ^{13}C NMR spectrum, acetylene carbons appeared at 78.5 and 82.4 ppm. Compound **21** was protected as its MEM (methoxy ethoxy methyl) ether derivative (**22**) using MEM-Cl and diisopropylethylamine in CH_2Cl_2 to afford the compound **22** in 85% yield (Scheme **9**). The structure of compound **22** was analyzed by its ^{1}H NMR spectrum, in which singlets at 3.4 ppm and 4.9 ppm due to MEM group were localized. The ^{13}C NMR spectrum further supported the assigned structure of **22**..

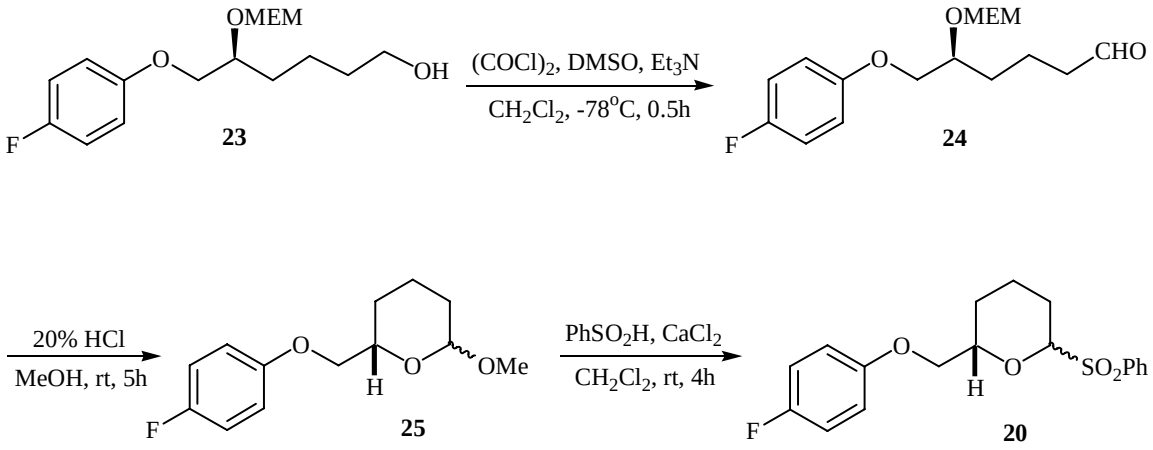
Scheme 9



Compound **22** was hydrogenated using 10% Pd/C in MeOH to afford the alcohol (**23**). The structure of **23** was confirmed by its ^{1}H NMR spectrum, in which signals were located in the upfield region which were attributed to methylene protons. Compound **23** was then oxidized by

using oxalyl chloride, DMSO and triethyl amine in CH_2Cl_2 at –78 °C (under Swern conditions) to provide the aldehyde (**24**) which, without characterization was treated with 20% methanolic HCl solution to afford the 2-methoxy derivative (**25**) as a diastereomeric mixture. The structure of the compound **25** was established by its ^{1}H NMR spectrum, in which peaks corresponding to the H-5 and H-2 ring protons resonated at 4.1 and 4.80 ppm while a singlet of OCH_3 protons was found at 3.45 ppm.

Scheme 10

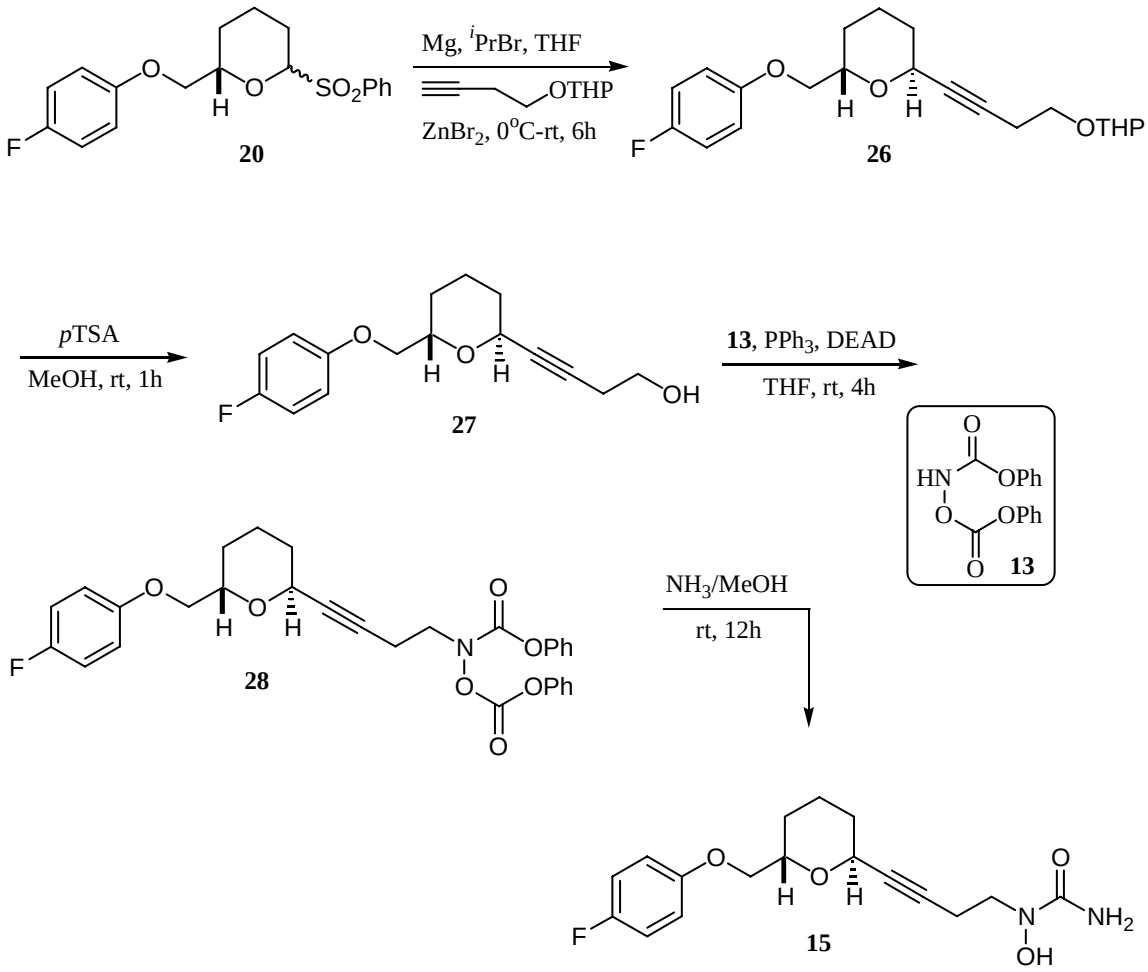


(6*S*)-6-(4-Fluorophenoxymethyl)-2-methoxy-tetrahydro-pyran (**25**) was quantitatively converted into its sulphone derivative (**20**) using freshly prepared phenyl sulfinic acid and calcium chloride in CH_2Cl_2 (Scheme **10**). The spectroscopic data of this sample compared well with the product prepared earlier in scheme 8.

The sulphone intermediate (**20**) was treated with dialkyl zinc reagent, (derived *in situ* from BrMg-C≡C-CH_2CH_2OTHP and $ZnBr_2$ in anhydrous THF at 0°C) to give (2*S*,6*S*)-6-(4-fluorophenoxymethyl)-2-(4-tetrahydropyranoyl-1-butyne)-tetrahydropyran (**26**). Subsequently **26** was treated with a catalytic amount of *p*TSA in methanol at room temperature for 1 h to deprotect the THP group affording the (2*S*,6*S*)-6-(4-flurophenoxymethyl)-2-(1-hydroxy-3-butyn-4-yl)-tetrahydropyran (**27**). The optical purity of 96% was determined by HPLC analysis on ODS

column. The structure of **27** was confirmed by its ^{1}H NMR spectrum in which methylene protons of homopropargyl side chain were located. The NOE studies on **27** showed that H-2 and H-6 had *trans* configuration. The ^{13}C NMR spectrum further established the assigned structure of **27**.

Scheme 11



Our next concern was to introduce the N-hydroxyurea group at the terminal carbon of acetylene side chain. The Mitsunobu reaction of 27 with *N*,*O*-bis(carbophenoxy)hydroxyl amine (**13**) in the presence of triphenylphosphine and DEAD in anhydrous THF at room temperature for 4 h furnished the (2*S*,6*S*)-6-(4-fluorophenoxymethyl)-2-(1-*N*,*O*-bis-(phenoxycarbonyl)-hydroxyl-amino-3-butyn-4yl)-tetrahydropyran (**28**). In the ^{1}H NMR spectrum of the compound **28**, the

signals corresponding to substituted N-hydroxy urea derivative were observed particularly aromatic protons (7.05-7.45 ppm).

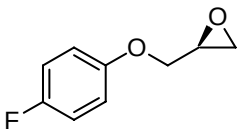
Treatment of **28** with saturated methanolic ammonia at room temperature for 12 h provided the target molecule i.e. six membered analogue of CMI-977 (**15**) as a white solid. The structure of compound **15** was established by its ^{1}H NMR spectrum, in which two triplets corresponding to methylene groups of homopropargylic chain were seen at 3.65 and 3.82 ppm. A broad singlet at 5.77 ppm was attributed to NH_2. The characteristic signal of N-OH resonated at 8.95 ppm. The ^{13}C NMR spectrum revealed C=O signal at 161.8 ppm.

In conclusion, we have demonstrated a stereoselective synthesis of six membered analogue of CMI-977. In the C-C bond formation using Ley's approach, we ended up with single diastereomer, which was attributed to the anomeric effect.

Experimental

Section-II: Experimental

(*S*)-4-Fluorophenyl glycidyl ether and (*R*)-1-O-(4-fluorophenyl)glycerol (4).



To a solution of 4-fluorophenol (40 g, 0.35 mol) in acetone (350 ml) was added dry K_2CO_3 (148 g, 1.05 mol) and epichlorohydrin (95 ml, 1.05 mol). The reaction mixture was heated at 60 °C for 12 h, filtered and filtrate distilled under reduced pressure (b.p.160-170 ^oC/9mm) to afford pure (*R*,*S*)-glycidyl-4-fluorophenyl ether (52 g, 85%) as a colourless liquid. (*R*,*R*)-Salen-Co(III) catalyst (1.03 g, 1.54 mmol) was added to (*R/S*)-glycidyl-4-fluorophenyl ether (52 g, 0.31 mol), followed by dropwise addition of water (3.06 ml, 0.17 mol) over 1 h at 0°C. The reaction mixture was allowed to come to room temperature and stirred for 18 h. The reaction was filtered and the filtrate distilled under reduced pressure to give (*S*)-glycidyl-4-fluorophenyl ether (22 g, 85%) as a colourless liquid.

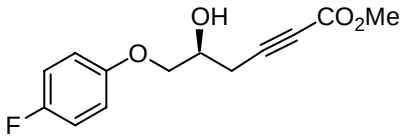
Boiling point : 160 –170 °C /9mm

$[\alpha]_D$: + 5° (c 2.3, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 2.68 (dd, *J* = 4.5, 2.2 Hz, 1H), 2.85 (t, *J* = 4.5 Hz, 1H), 3.27 (m, 1H), 3.89 (dd, *J* = 15.7, 6.7 Hz, 1H), 4.11 (dd, *J* = 15.7, 4.5 Hz, 1H), 6.74-7.02 (m, 4H);

^{13}C NMR ($CDCl_3$, 50MHz) : δ 44.1, 49.8, 69.1, 115.4, 115.6, 115.8, 154.3, 159.6.

Methyl (*S*)-6-(4-fluorophenoxy)-5-hydroxy-hex-2-ynoate (16):



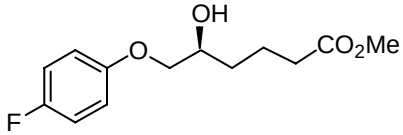
A solution of *n*-BuLi in hexane (11.4 ml, 26.8 mmol) was added to a solution of methyl propiolate (2.25 g, 26.8 mmol) in THF (15 ml) at –78 °C under N_2 atmosphere. The reaction was stirred for 20 min and then BF_3:OEt_2 (3.4 ml, 26.8 mmol) was added. After 20min a solution of (*S*)-glycidyl-4-fluorophenyl ether (**4**) (3 g, 17.8 mmol) in THF (10 ml) was added and stirring continued for 1 h at –78 ^oC. The reaction was quenched with aq.NH_4Cl, extracted with ethyl acetate, dried (Na_2SO_4), and concentrated. The crude product was purified on silica gel using ethyl acetate-light petroleum (1:4) as eluent to afford methyl (*S*)-6-(4-fluorophenoxy)-5-hydroxy-hex-2-ynoate (**16**) (2.5 g, 60%) as a yellow liquid.

$[\alpha]_D$: + 15.5° (c 1.2, $CHCl_3$)

^1H NMR ($CDCl_3$, 200MHz) : δ 2.62 (d, *J* = 5 Hz, 1H), 2.71 (d, *J* = 5.6 Hz, 2H), 3.76 (s, 3H), 3.92-4.02 (m, 2H), 4.2 (m, 1H), 6.8-7.02 (m, 4H).

Anal: Calcd for $C_{13}H_{13}FO_4$: C, 61.9, H, 5.19. Found: C, 62.12, H, 5.07.

Methyl (*S*)-6-(4-fluorophenoxy)-5-hydroxy-hexanoate (17):



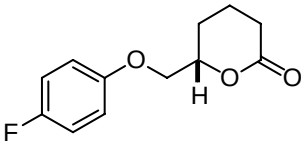
A mixture of **16** (2.5 g, 9.9 mmol), methanol (20 ml) and 10% Pd/C (250 mg) was stirred under H_2 at normal pressure and temperature for 3 h. The reaction mixture was filtered through a pad of celite, washed with methanol and concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum (1:4) as eluent to give **17** (2.15 g, 85%) as a colourless liquid.

$[\alpha]_D$: + 8° (c 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.55-1.9 (m, 4H), 2.3-2.43 (t, *J* = 6.5 Hz, 2H), 2.5 (s, 1H), 3.68 (s, 3H), 3.76-4.02 (m, 3H), 6.76-7.02 (m, 4H).

Anal: Calcd for $C_{13}H_{17}FO_4$: C, 60.93, H, 6.69. Found: C, 60.75, H, 6.52.

(6*S*)-6-(4-Fluorophenoxymethyl)-tetrahydropyran-2-one (18):



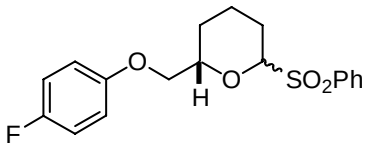
A solution of **17** (0.8 g 3.12 mmol), CH_2Cl_2 (20 ml) and catalytic *p*TSA (10 mg) was stirred at 40 °C for 12 h. It was neutralised with sodium bicarbonate and extracted with dichloromethane. The organic layer was dried (Na_2SO_4), concentrated and the crude product was purified on silica gel using ethyl acetate-light petroleum (1:3) as eluent to give **18** (0.5 g, 70%) as a colourless liquid.

$[\alpha]_D$: + 19° (c 0.8, $CHCl_3$) ;

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.7-2.15 (m, 4H), 2.48-2.7 (m, 2H), 3.95-4.15 (m, 2H), 4.55-4.7 (m, 1H), 6.77-7.0 (m, 4H).

Anal: Calcd for $C_{12}H_{13}FO_3$: C, 64.28, H, 5.84. Found: C, 64.42, H, 5.68.

(2*RS*, 6*S*)-2-Benzenesulfonyl-6-(4-fluorophenoxymethyl)-tetrahydropyran (20):



To solution of **18** (0.5 g, 2.23 mmol) in CH_2Cl_2 (20 ml) at –78 °C was added DIBAL-H (1 ml, 2M, 2.4 mmol) and stirred for 3 h. It was then quenched with potassium sodium tartrate, extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated to afford **19** (0.42 g, 85%).

In an another flask benzenesulfinic acid sodium salt (0.6 g) was dissolved in 25% HCl and then extracted twice with ethyl acetate, dried (Na_2SO_4) and concentrated to give benzene-sulfinic acid (0.4 g). To an ice-cooled mixture of benzenesulfinic acid (0.32 g, 2.23 mmol) and

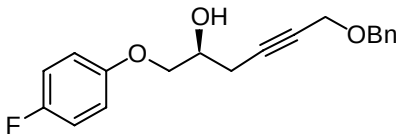
calcium chloride (0.25 g, 2.23 mmol) in dry CH_2Cl_2 a solution of **19** (0.42 g, 1.86 mmol) in dry CH_2Cl_2 (5 ml) was added and stirred for 4 h. The reaction mixture was then filtered through a pad of celite and washed with CH_2Cl_2. The combined organic layer was washed with saturated aq.Na_2CO_3, water, dried (Na_2SO_4), concentrated and the residue was purified on silica gel using light petroleum-ethyl acetate (3:1) as eluent to afford **20** (0.5 g, 70%).

Melting point : 124-126 °C

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.55 (m, 2H), 1.75-2.0 (m, 2H), 2.2-2.4 (m, 1H), 2.6-2.8 (m, 1H), 3.75-3.9 (m, 2H), 4.65 (d, *J* = 5.0 Hz, 1H), 4.85-5.0 (m, 1H), 6.7-7.0 (m, 4H), 7.5-7.7 (m, 3H), 7.95 (d, *J* = 5.4 Hz, 2H).

Anal: Calcd for ($C_{18}H_{19}FO_4S$): C, 61.70, H, 5.47. Found: C, 61.54, H, 5.52.

(2*S*)-6-Benzyloxy-1-(4-fluorophenoxy)-hex-4-yn-2-ol (21):



To a solution of benzyloxy-prop-2-yne (2.3 g, 16 mmol) in dry THF (25 ml) at –78 °C was added *n*-BuLi in hexane (10.7 ml, 16 mmol). After 20 min, BF_3:OEt_2 (2 ml, 16 mmol) was introduced and stirring continued for 20 min at –78 °C. A THF solution of (*S*)-glycidol-4-fluorophenyl-ether (1.8 g, 10.7 mmol) was added. After 1 h at –78 ^{o}C, the reaction was quenched by adding aqueous NH_4Cl, extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using ethyl acetate-light petroleum (1:4) as eluent to give **21** (2 g, 65%) as a yellow liquid.

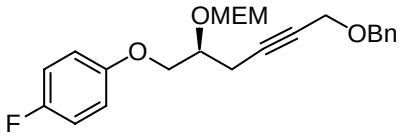
$[\alpha]_D$: + 13° (c 1.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 2.65 (m, 2H), 3.95-4.10 (m, 2H), 4.13-4.21 (m, 3H), 4.6 (s, 2H), 6.8-7.02 (m, 4H), 7.30-7.38 (m, 5H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 23.8, 57.4, 68.4, 71.1, 71.4, 78.5, 82.4, 115.4, 115.5, 116.0, 127.8, 127.9, 128.3, 137.2, 154.5, 159.7.

Anal: Calcd for ($C_{19}H_{19}FO_3$): C, 72.6, H, 6.09. Found: C, 72.78, H, 6.17.

(2*S*)-6-Benzyloxy-1-(4-fluorophenoxy)-2-(methoxyethoxymethyloxy)-4-hex-4-yne (22):



To an ice cooled solution of **21** (2 g, 6.4 mmol) and *N*-ethyldiisopropylamine (1.7 ml, 9.5 mmol) in CH_2Cl_2 (8 ml) MEM-chloride (1.1 ml, 9.5 mmol) was added and stirred for 3 h at room temperature. The solvent was concentrated and the residue purified on silica gel using ethyl acetate-light petroleum (1:4) as eluent to yield **22** (2.2 g, 85%) as a yellow liquid.

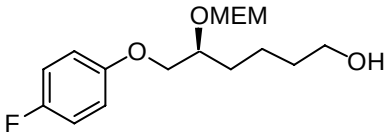
$[\alpha]_D$: + 22.4 (c 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 2.65-2.75 (m, 2H), 3.39 (s, 3H), 3.55 (t, *J* = 4.8 Hz, 2H), 3.78 (t, *J* = 4.8 Hz, 2H), 4.11 (s, 2H), 4.16 (m, 3H), 4.56 (s, 2H), 4.89 (s, 2H), 6.8-7.02 (m, 4H), 7.3-7.35 (m, 5H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 21.9, 57.3, 58.7, 66.9, 69.4, 71.1, 71.4, 73.7, 77.9, 82.5, 94.7, 115.3, 115.4, 115.8, 127.5, 127.7, 128.1, 137.3, 154.6, 159.5.

Anal: Calcd for ($C_{23}H_{27}FO_5$): C, 68.64, H, 6.76. Found: C, 68.78, H, 6.82.

(2*S*)-1-(4-Fluorophenoxy)-2-(methoxyethoxymethyloxy)-hexan-6-ol (23):



To a solution of **22** (2.2 g, 5.4 mmol) and 10% Pd/C (250 mg) in MeOH (20 ml) was stirred under H_2 at normal pressure and temperature for 4 h. The reaction mixture was filtered through celite, washed with excess methanol. The combined extract was concentrated and

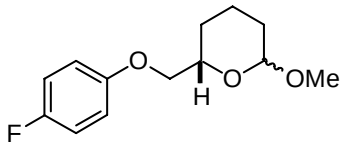
purified on silica gel using ethyl acetate-light petroleum (2:3) as eluent to give **23** (1.3 g, 76%) as a colourless liquid.

$[\alpha]_D$: + 18.3° (c 1.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.5-1.7 (m, 6H), 3.35 (s, 3H), 3.5 (t, *J* = 4.8 Hz, 2H), 3.65 (t, *J* = 4.8 Hz, 2H), 3.7-3.8 (m, 2H), 3.85-3.95 (s, 3H), 4.75-4.95 (dd, *J* = 12.6, 6.0 Hz, 2H), 6.75-7.0 (m, 4H).

Anal: Calcd for ($C_{16}H_{25}FO_5$): C, 60.74, H, 7.97. Found: C, 60.62, H, 8.09.

(2*RS*, 6*S*)-6-(4-Fluorophenoxymethyl)-2-methoxy-tetrahydropyran (25):

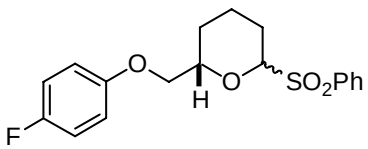


To a solution of **23** (1.25 g, 3.9 mmol) and oxalyl chloride (0.7 ml, 7.9 mmol) in dry CH_2Cl_2 at –78 °C was added dry DMSO (1.12 ml, 15.8 mmol). The stirring was continued at –78 °C for 30 min and Et_3N (3.15 ml, 23.7 mmol) was added. The reaction mixture was extracted with CH_2Cl_2 and dried (Na_2SO_4) and concentrated to afford the product which was stirred with 20% methanolic HCl at room temperature for 5 h neutralised with Na_2CO_3. The reaction mixture was extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum (1:3) as eluent to give a *cis-trans* mixture (2*RS*,6*S*)-6-(4-fluorophenoxymethyl)-2-methoxy-tetrahydropyran (**25**) (0.6 g, 80%) as a yellow syrup.

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.6-2.0 (m, 6H), 3.45 (s, 3H), 3.9-3.96 (m, 2H), 4.0-4.15 (m, 1H), 4.8 (s, 1H), 6.8-7.01 (m, 4H).

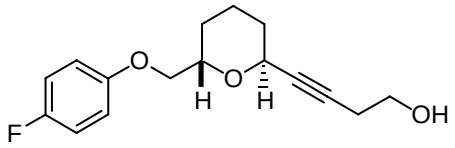
Anal: Calcd for ($C_{13}H_{17}FO_3$): C, 64.98, H, 7.13. Found: C, 64.82, H, 7.22.

(2*S*,6*RS*)-6-Benzenesulfonyl-2-(4-fluorophenoxymethyl)-tetrahydropyran (20) from 25:



Compound **20** was prepared essentially by the same procedure from **25** as described before to give **20**, and found identical with the sample prepared earlier.

(2*S*,6*S*)-6-(4-Fluorophenoxymethyl)-2-(4-hydroxybutyn-1-yl)-tetrahydropyran (27):



To a suspension of magnesium (0.14 g, 5.7 mmol) and 1,2-dibromoethane in dry THF (5 ml) was added a solution of isopropylbromide (0.3 ml, 2.86 mmol) in THF. After 1 h 4-tetra-hydropyranoyl-1-butyne (0.44 g, 2.86 mmol) in THF (2 ml) was added, the mixture was stirred for 30 min, cooled to 0 °C and freshly prepared $ZnBr_2$ solution (2 ml, 1.7 mmol) in THF was introduced dropwise. After 45 min at room temperature compound **20** (0.5 g, 1.43 mmol) in THF (4 ml) was added and the mixture stirred for 3 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C, THF was removed and the residue extracted with ethyl acetate, dried (Na_2SO_4) and concentrated to give **26**. The crude product was dissolved in methanol (5 ml) and 5% HCl in methanol (10 ml) was added. The reaction mixture was stirred at room temperature for 2 h and neutralised with saturated aq Na_2CO_3 solution and concentrated. The residue was extracted with ethyl acetate, dried (Na_2SO_4), concentrated and the crude product was purified on silica gel using ethyl acetate-light petroleum (2:3) as eluent to give **27** (0.24 g, 70%) as a colourless liquid.

$[\alpha]_D$: - 32° (c 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.6-2.0 (m, 6H), 2.55 (m, 2H), 3.73 (t, *J* = 6.35 Hz, 2H), 3.8-4.0 (m, 2H), 4.15-4.3(m, 1H), 4.8 (s, 1H), 6.8-7.0 (m, 4H).

^{13}C NMR ($CDCl_3$, 125MHz) : δ 18.88, 23.18, 27.04, 30.38, 61.11, 65.52, 69.96, 71.92, 80.08, 84.02, 115.12, 115.63, 115.72, 115.79, 154.97, 158.28.

Anal: Calcd for ($C_{16}H_{19}FO_3$): C, 69.06, H, 6.83. Found: C, 68.98, H, 7.05.

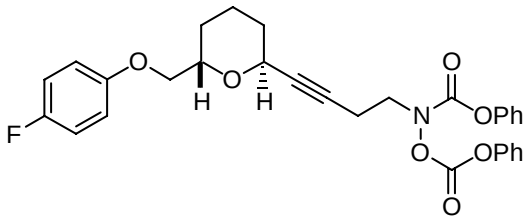
***N,O*-Bis-phenoxycarbonylhydroxylamine (13):**

To a solution of sodium bicarbonate (21.5 g, 0.256 mol) in water (150 ml) at 0°C was added hydroxylamine hydrochloride (8.8 g, 0.127 mol). The reaction mixture was stirred for 30min. and phenylchloroformate (60 g, 0.383 mol) was introduced directly into the vigorously stirred mixture. Sodium bicarbonate (32.3 g, 3.85 mol) in water (300 ml) was added to the mixture. The mixture was stirred for 30 min., the ice-bath removed and stirring continued for an additional 2 h at room temperature. The resultant suspension was filtered and the filter cake washed with water. The wet filter cake was collected, suspended in hexane, filtered and again washed with hexane. The solid was kept at 0°C overnight to afford N,O-bis-phenoxycarbonylhydroxylamine (23.5 g, 68%) as a solid.

Melting point : 80-82 °C ;

^{1}H NMR ($CDCl_3$, 200MHz) : δ 7.26 (m, 5H), 7.42 (m, 5H) and 8.54 (s, 1H).

(2*S*,6*S*)-6-(4-Fluorophenoxymethyl)-2-(4-N,O-bis-phenoxycarbonylhydroxylamino-1-butynyl)-tetrahydropyran (28):



To an ice cooled solution of **27** (0.23 g, 0.83 mmol) in dry THF (10 ml), triphenyl-phosphine (0.26 g, 0.99 mmol) and *N,O*-bis-phenoxycarbonyl hydroxylamine (**13**) (0.26 g, 0.95 mmol) were added. After 15 min., diethylazodicarboxylate (0.173 g, 0.99 mmol) was added dropwise and stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was purified on silica gel using ethyl acetate-light petroleum (1:3) as eluent to yield **28** (0.3 g, 70%).

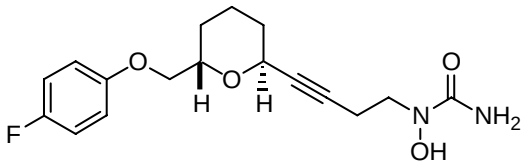
Melting point : 115-116 °C

$[\alpha]_D$: - 18.4° (c 1.32, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.45-1.8 (m, 6H), 2.75 (t, *J* = 6.8 Hz, 2H), 3.75-3.9 (m, 2H), 4.0-4.1 (t, *J* = 7.32 Hz, 2H), 4.15-4.3 (m, 1H), 4.8 (s, 1H), 6.7-6.95 (m, 4H), 7.1-7.45 (m, 10H).

Anal: Calcd for ($C_{30}H_{28}FNO_7$): C, 67.53, H, 5.29, N, 2.63. Found: C, 67.72, H, 5.13, N, 2.54.

(2*S*,6*S*)-6-(4-Fluorophenoxymethyl)-2-(4-N-hydroxyureidyl-1-butynyl)-tetrahydropyran (15):



A solution of **28** (0.3 g, 0.56 mmol) and saturated methanolic ammonia solution (10 ml) were stirred at room temperature for 12 h. Methanol was evaporated and the residue purified on silica gel using light petroleum-ethyl acetate (2:3) as eluent to give **15** (0.12 g, 65%).

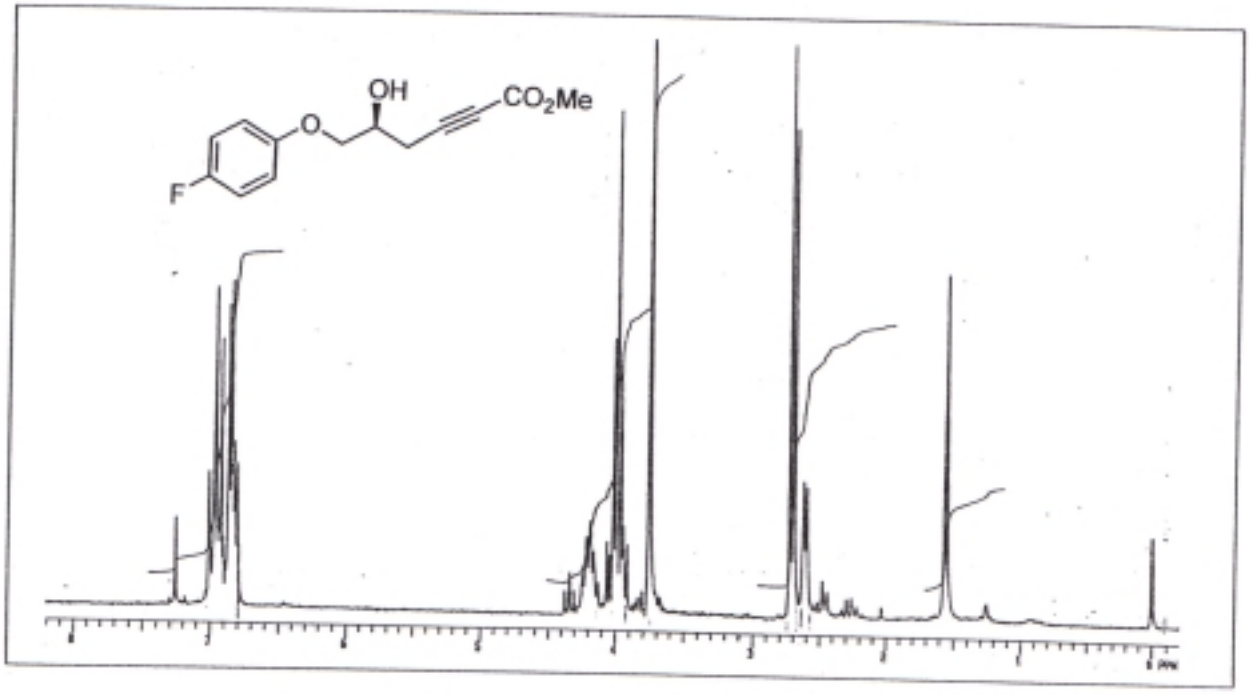
Melting point : 98-99 °C

$[\alpha]_D$: - 28.6° (c 1.2, $CHCl_3$)

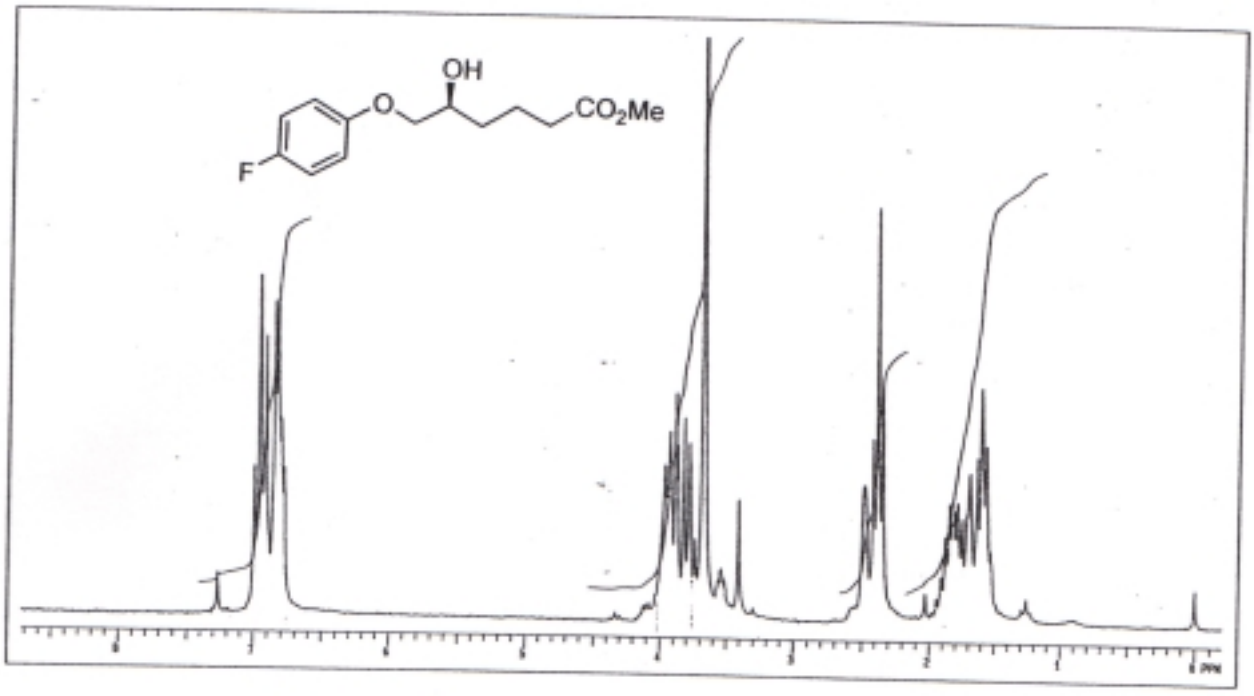
^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.5-2.0 (m, 6H), 2.45-2.6 (t, *J* = 6.35 Hz, 2H), 3.65 (t, *J* = 7.32 Hz, 2H), 3.75-3.9 (m, 2H), 4.1-4.3 (m, 1H), 4.75 (s, 1H), 5.7-5.85 (s, 2H), 6.75-7.0 (m, 4H), 8.8-9.1 (s, 1H).

^{13}C NMR ($CDCl_3$, 125MHz) : δ 17.15, 18.71, 27.80, 30.40, 48.95, 65.43, 69.98, 72.24, 79.53, 84.54, 115.52, 115.82, 115.94, 116.03, 155.01, 159.01, 161.84.

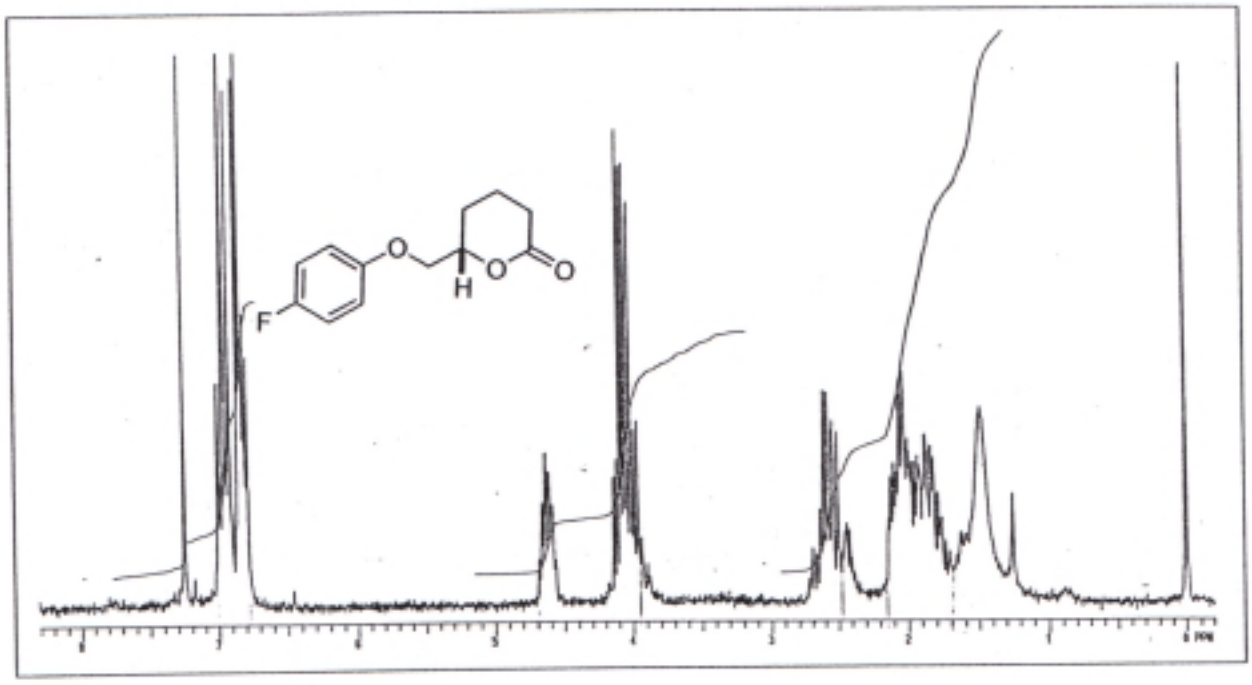
Anal: Calcd for ($C_{17}H_{21}FN_2O_4$): C, 60.71, H, 6.29, N, 8.33. Found: C, 60.60, H, 6.42, N, 8.25.



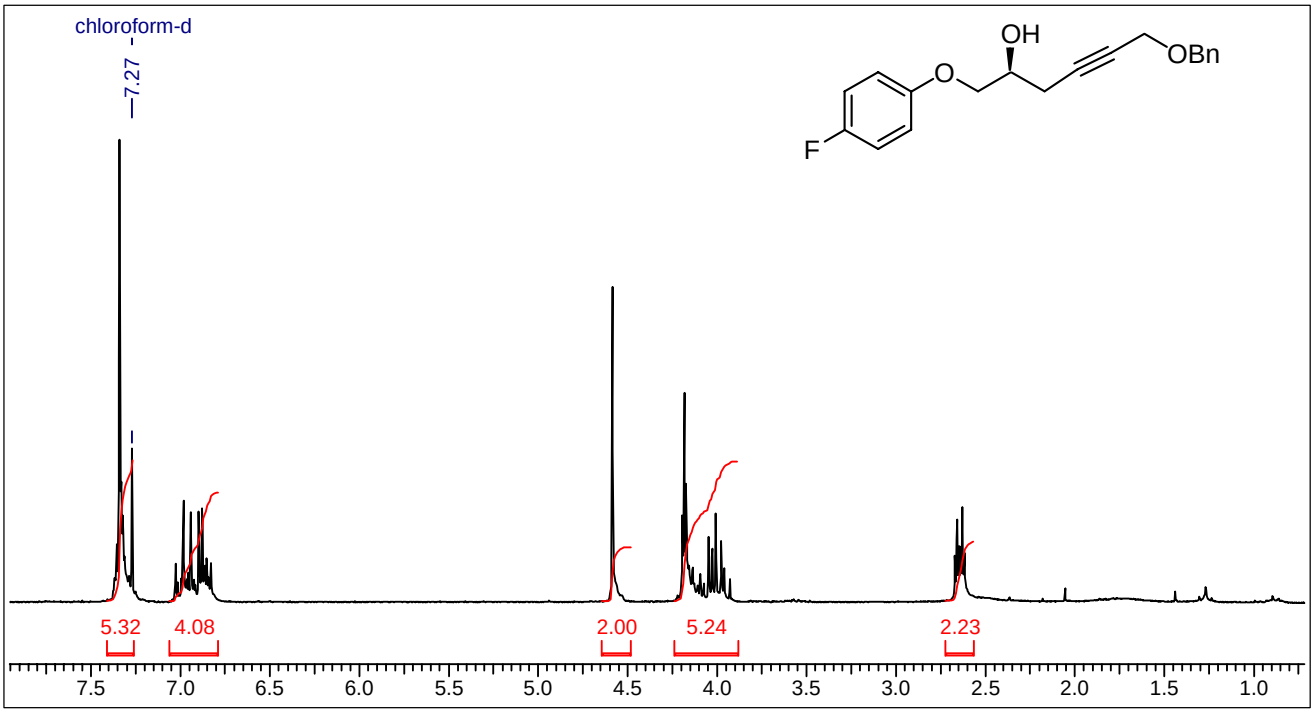
^{1}H NMR Spectrum of compound 16 in $CDCl_3$



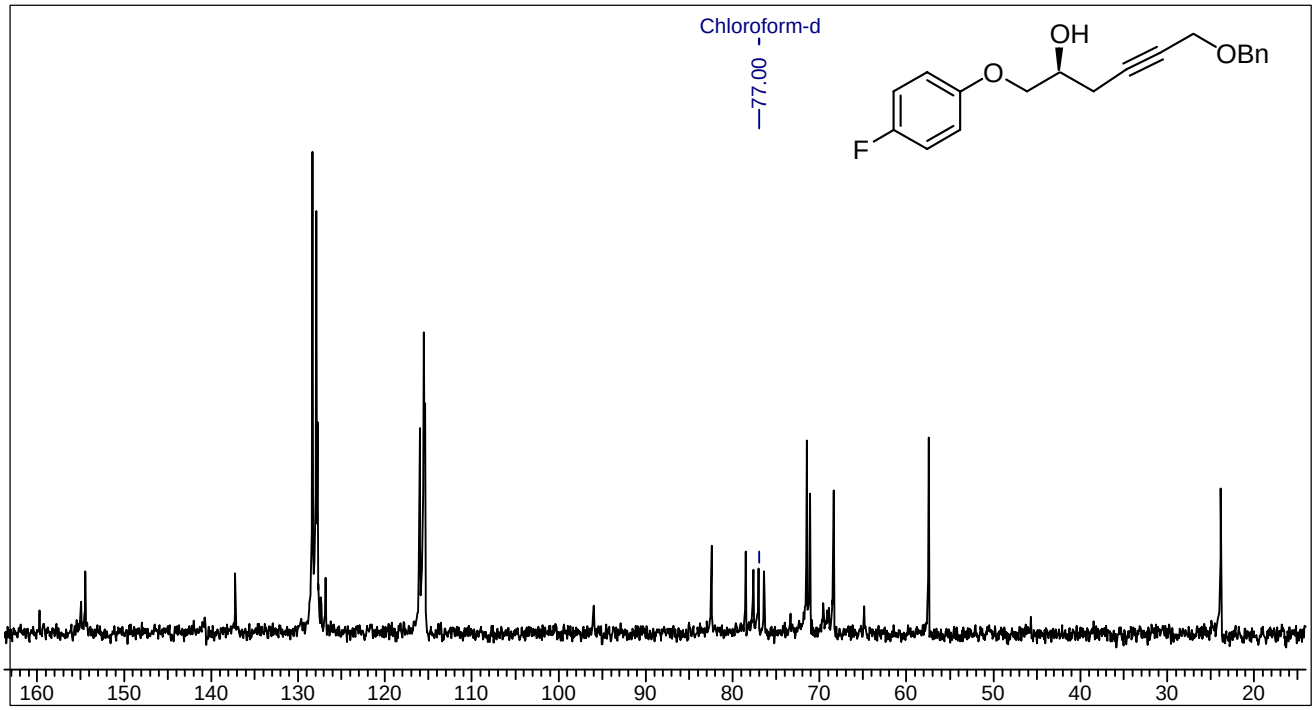
^{1}H NMR Spectrum of compound 17 in $CDCl_3$



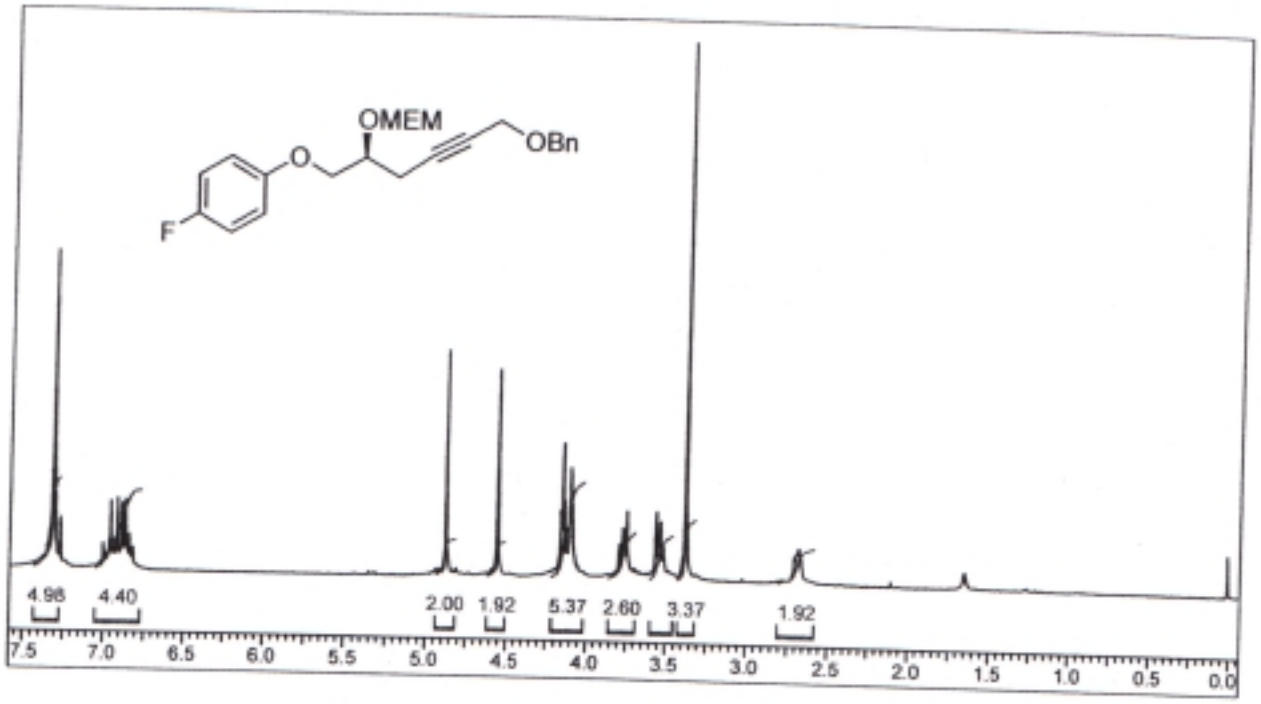
^{1}H NMR Spectrum of compound 18 in $CDCl_3$



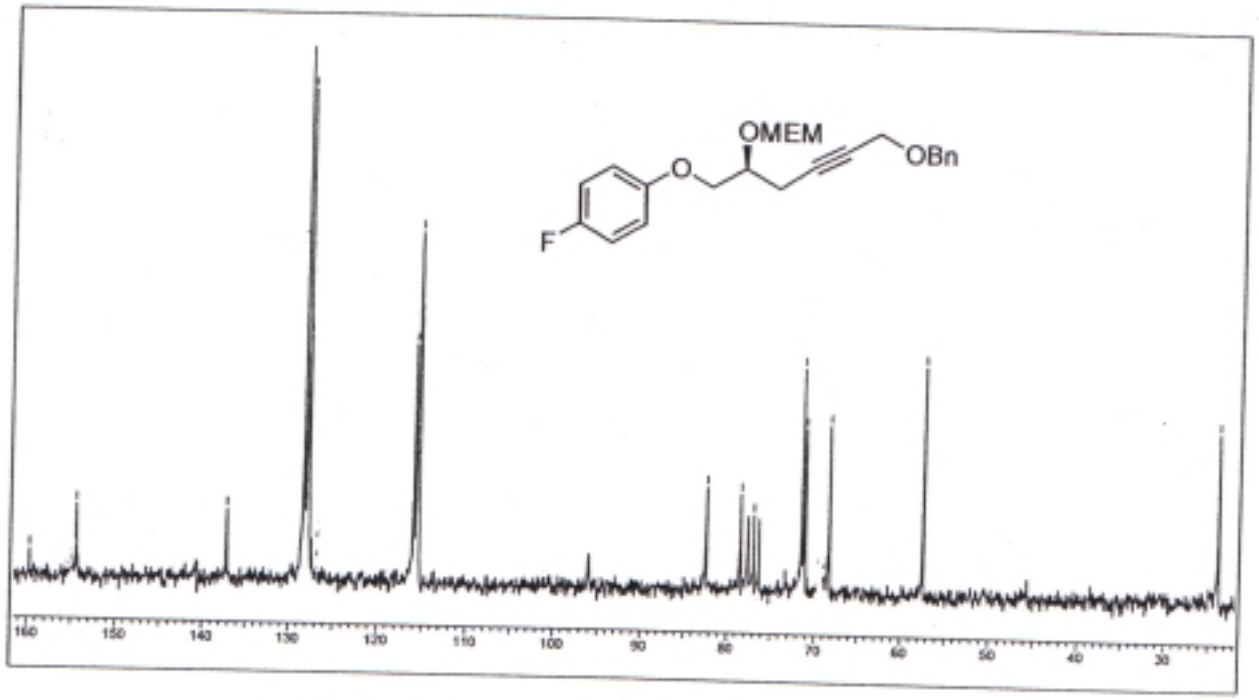
^{1}H NMR Spectrum of compound 21 in $CDCl_3$



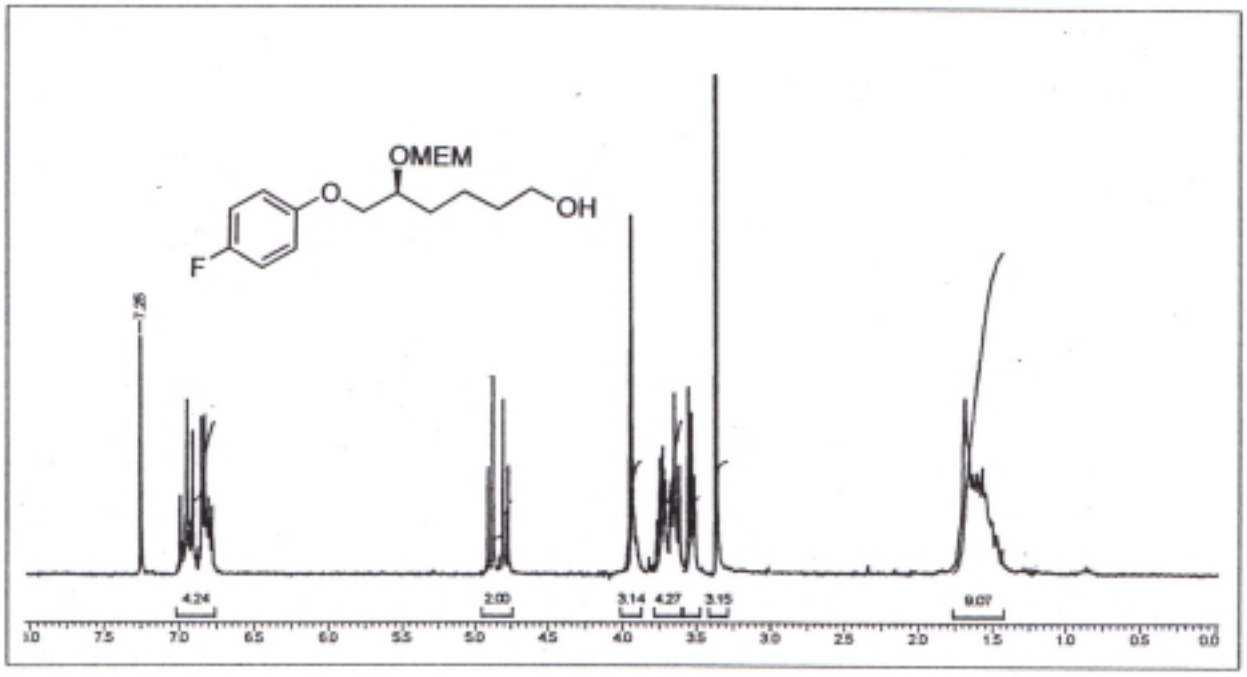
^{13}C NMR Spectrum of compound 21 in $CDCl_3$



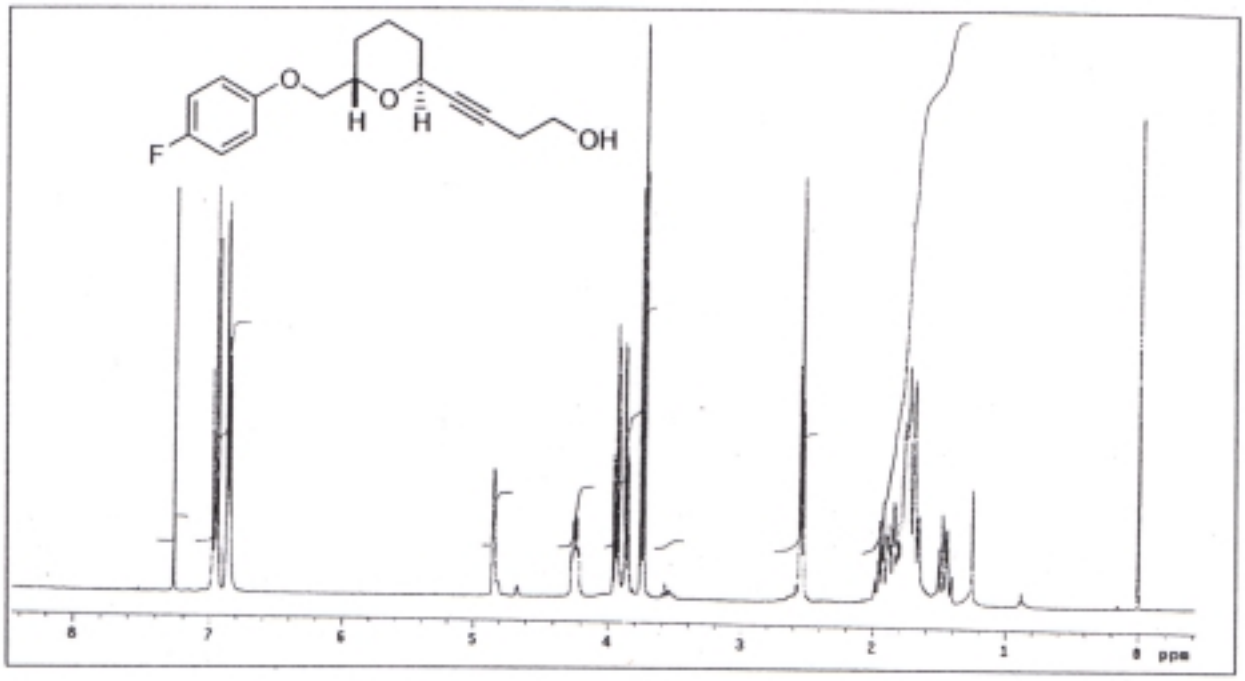
^{1}H NMR Spectrum of compound 22 in $CDCl_3$



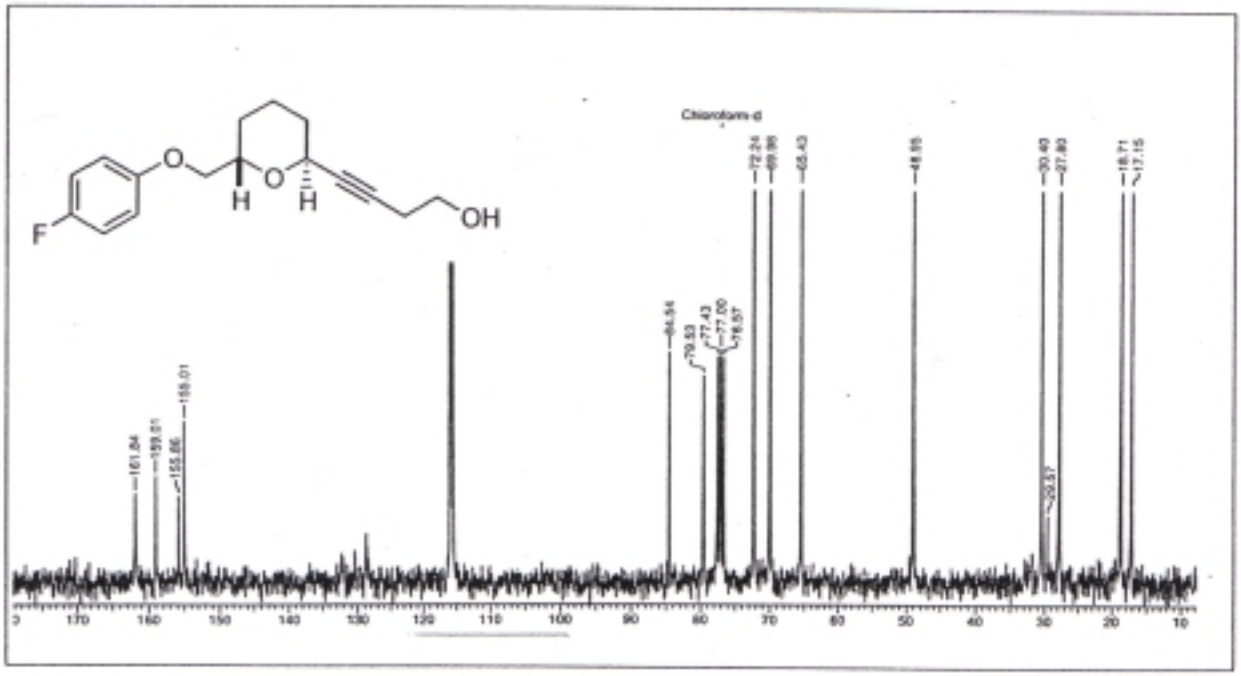
^{13}C NMR Spectrum of compound 22 in $CDCl_3$



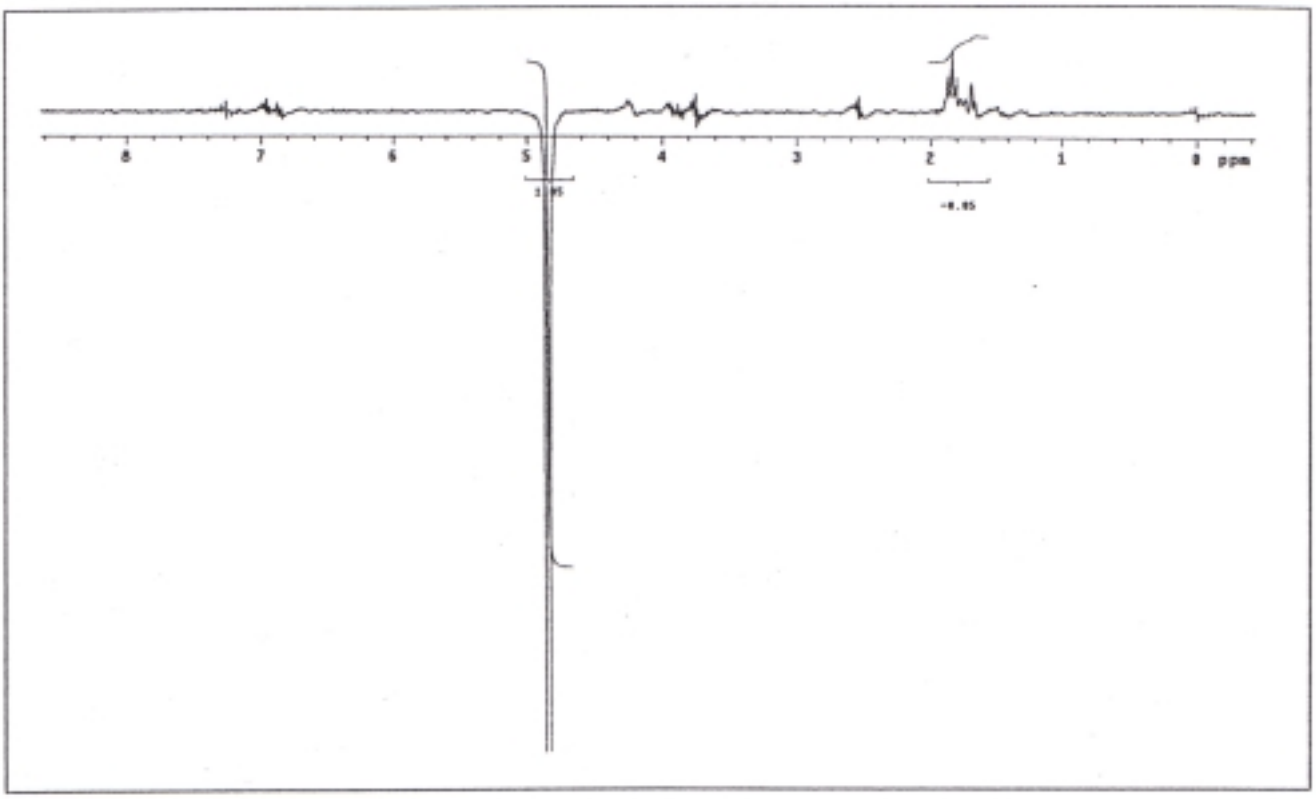
^{1}H NMR Spectrum of compound 23 in $CDCl_3$



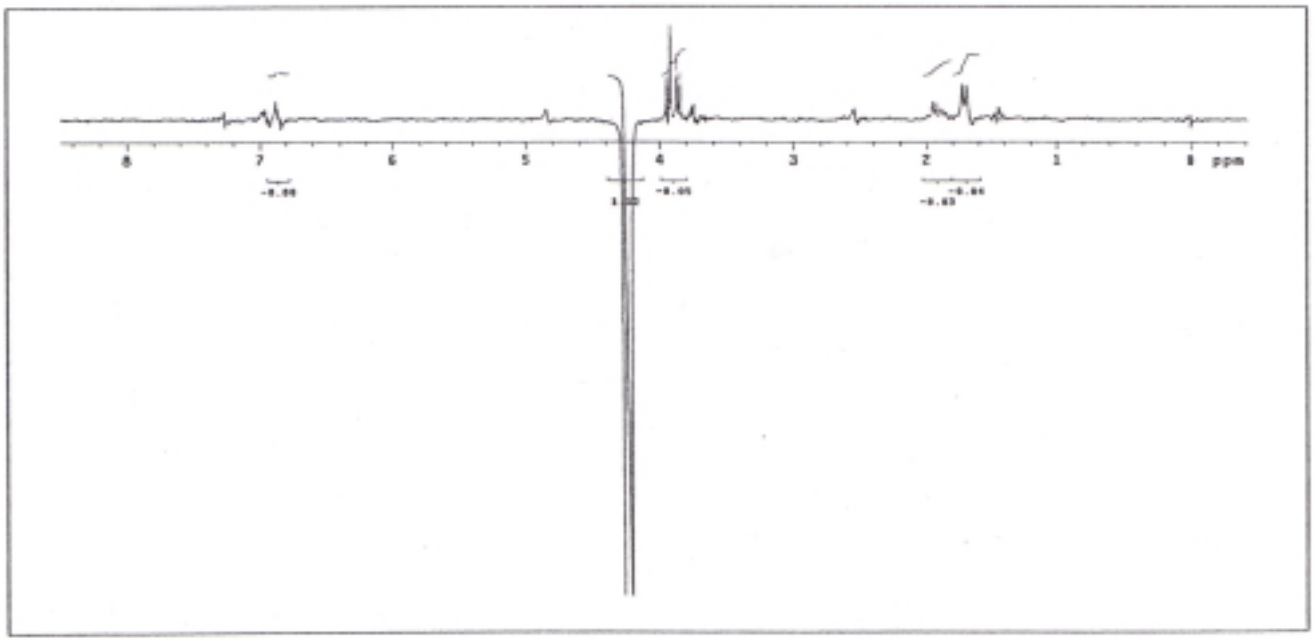
^{1}H NMR Spectrum of compound 27 in $CDCl_3$

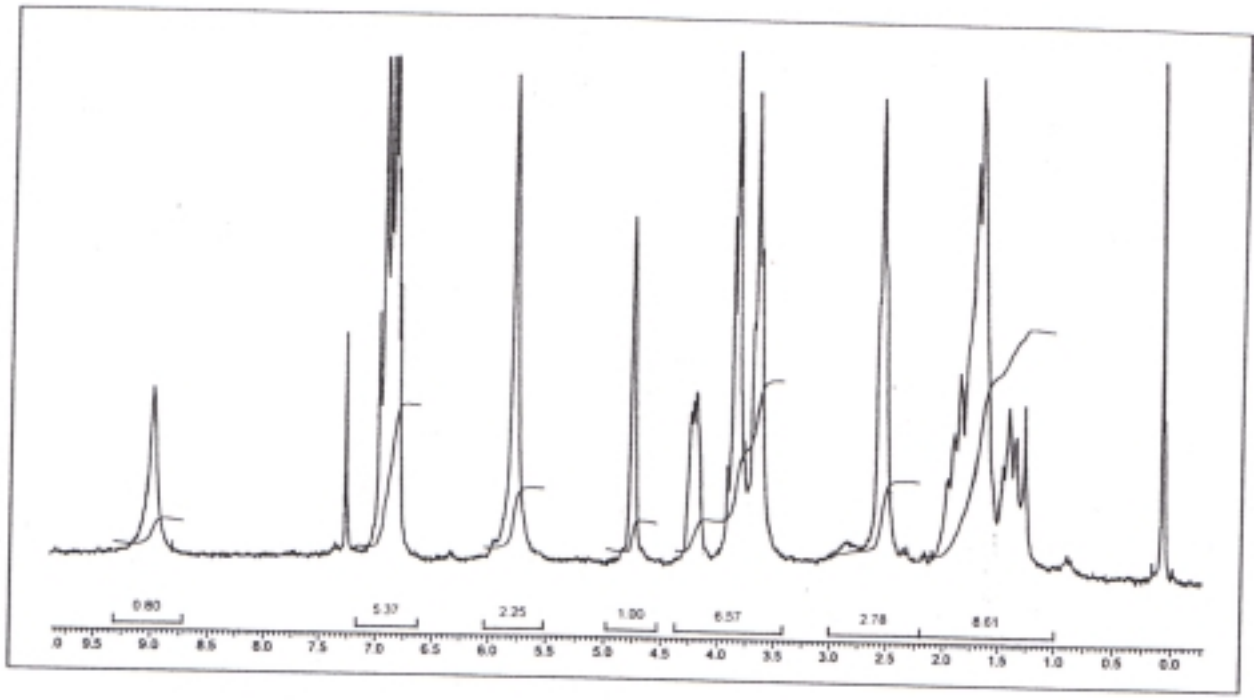


^{13}C NMR Spectrum of compound 27 in $CDCl_3$

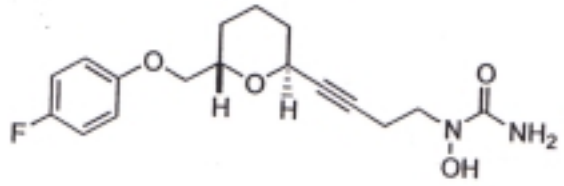


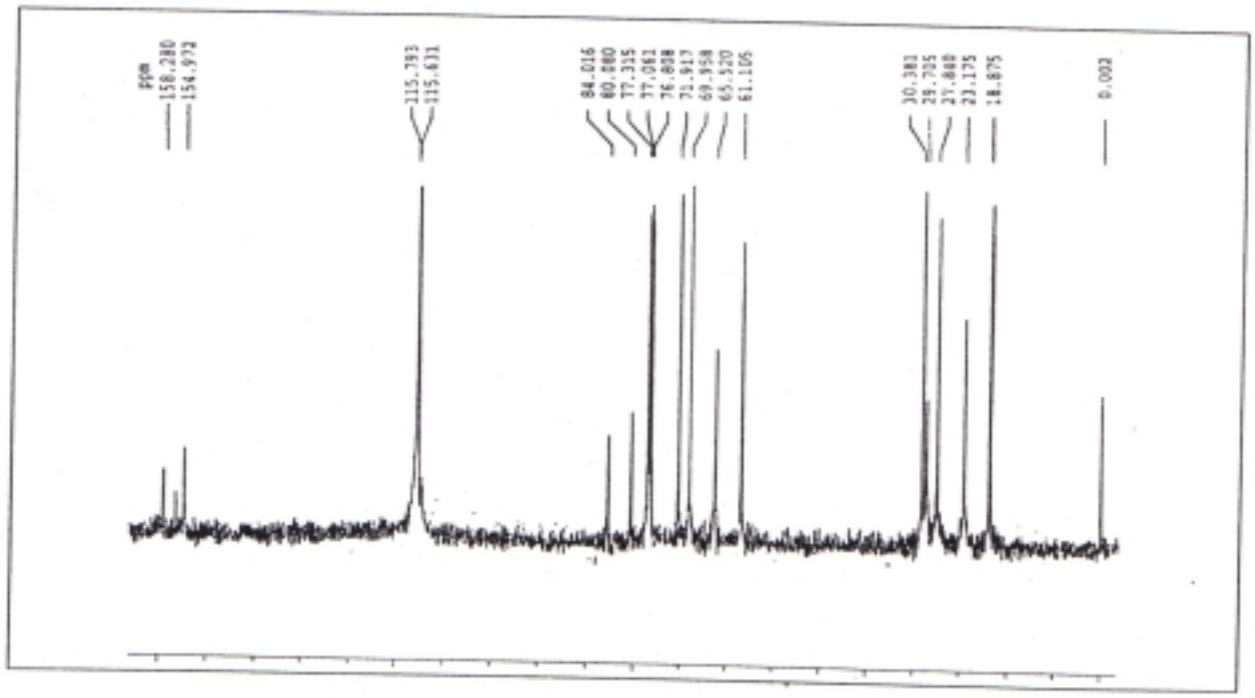
NOE studies of compound 27





^{1}H NMR Spectrum of compound 15 in $CDCl_3$





^{13}C NMR Spectrum of compound 15 in $CDCl_3$

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Chapter II

Synthetic studies towards the Calditol and 5-epi-Calditol

Introduction

Introduction

Glycosidase inhibitors have been subject to extensive reviewing during the past decade. As glycoside cleavage is a biologically widespread process, glycosidase inhibitors have many potential medical applications. Inhibition of intestinal α-glycosidases can be used to treat diabetes through the lowering of blood glucose levels, and several α-glycosidase inhibitors are being marketed against type 2 diabetes.[1] An alternative way of treating diabetes that has been explored recently is through inhibition of glycogen phosphorylase. Glycosidases are also involved in the trimming of cell and viral surface oligsaccharides, which also can be used as a therapeutic target. Inhibition of these glycosidases can disrupt biosynthesis of oligosaccharides and hence cell – cell or cell – virus recognition processes. This principle is used in the anti-influenza neuraminidase inhibitors that have recently been marketed[2] and is also the basis for the potential use of α-glycosidase inhibitors against HIV,[3] Gauchers disease, hepatitis, and cancer.

Two general class of glycosidase inhibitors can be defined: (i) natural products and synthetic analogues whose design has been inspired by the inhibitory activity of the natural inhibitors and (ii) inhibitors whose design has been rationally conceived from the mechanism of the enzymatic reaction. The later class of inhibitors comprises transition-state analogues of the glycoside cleavage process,[4] mechanism based inactivators,[5] and conformationally locked molecules.[6] A major goal of glycosciences has been to design and synthesize new generations of glycosidase inhibitors with which chemists might exert more potent effective control over glycoside hydrolysis. Aside from their potential value in basic biochemical research, several synthetic glycosidase inhibitors have already demonstrated promising therapeutic applications in the area of both diabetes management and antiviral chemotherapy (Figure 1).

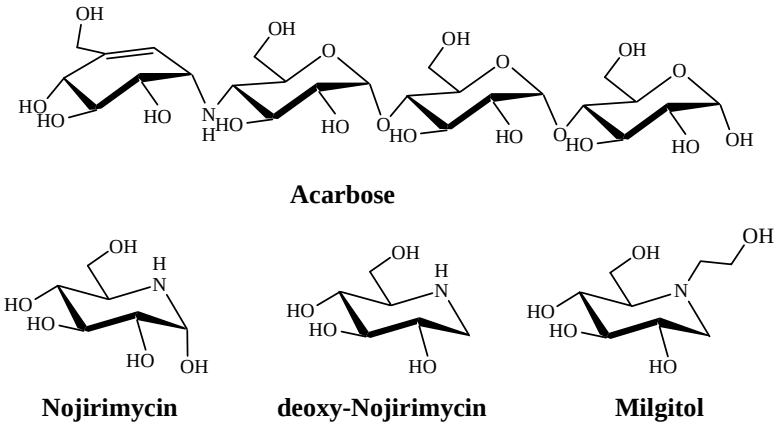


Figure 1. *Some Commercial Glycosidase Inhibitors*

Inhibitors of glycoside-processing enzymes have traditionally been molecules, which share direct structural homology with the natural enzymatic substrate-often polyhydroxylated six-membered heterocyclic rings.[7] The reported isolation of allosamidin in 1986[8] opened the way to recognition that aminohydroxy-substituted five-membered carbocyclic rings (aminocyclopentitols) can have powerful and specific inhibitory activity against glycosidases, which normally accept six-membered pyranoside substrates. Since with this initial report, four other such aminocyclopentitols have been reported – the mannostatins,[9] the trehalase inhibitors trehalostatin and trehazolin,[10] and Merrell Dow's cyclopentylamine[11] (Figure 2).

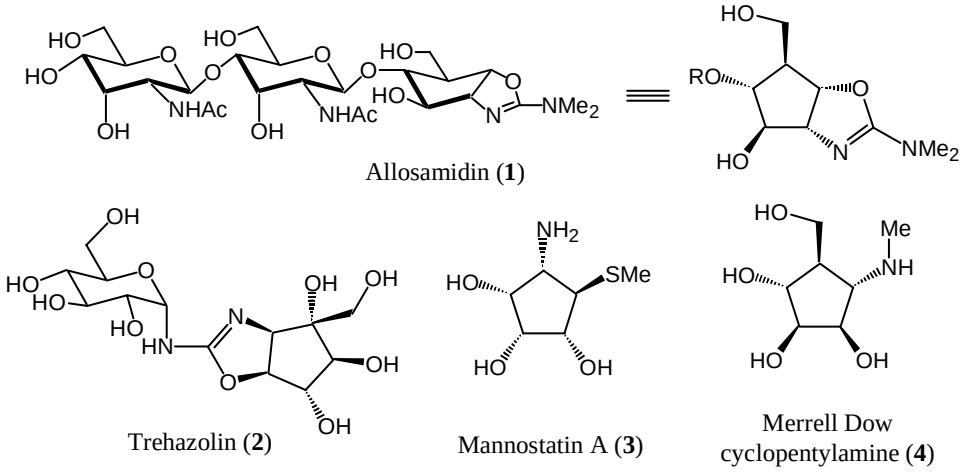


Figure 2. *Cyclopentitol- Containing Glycosidase Inhibitors*

The intensitive synthetic investigations of aminocyclopentitols are a result not just of the challenging density and juxtaposition of functionality but of their biological activity as glycosidase inhibitors. The superiority of five-membered ring inhibitors over six-membered ring analogues (which more closely resemble the enzymatic substrates) may be related to the energetic costs associated with distortion of the natural chair conformations of six-membered rings to match the enzymatic transition state.

The chemical syntheses of densly functionalized aminocyclopentitols, the key structural motif shared by the many of glycosidase inhibitors, form the nucleus of this discussion. Even prior to knowledge of their existence in nature, a number of chemical routes to cyclopentitols had already been studied and developed.[12] In fact, a racemic synthesis of aristeromycin,[13] the first natural cyclopentitol reported, preceded its isolation. However, progress in this field had lagged well behind that of their cyclohexitol counterparts until the discovery of natural aminocyclopentitols such as the carbocyclic nucleosides. The synthesis of such nucleosides attracted considerable additional interest following the outbreak of the AIDS epidemic, and the discovery of the aminocyclopentitol glycosidase inhibitors has seen another flourish of activity in the area of aminocyclopentitol synthesis.

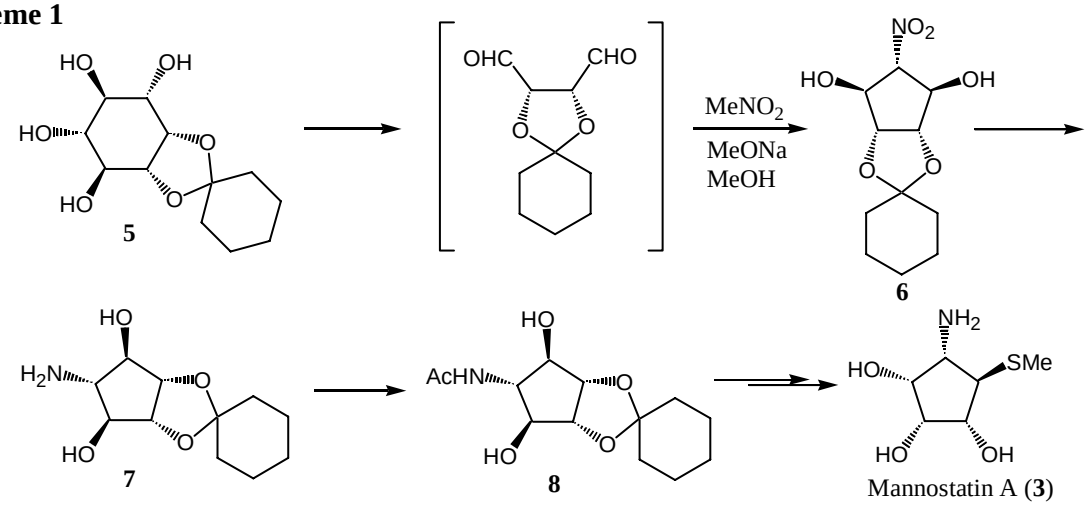
The majority of strategies adopted to obtain aminocyclopentitols can be divided broadly into two groups. The first of these (1), and the most important historically speaking, is that which is comprises carbohydrate-based approaches which can themselves be classified according to the method chosen to form the carbocyclic ring, of which there are three: a) aldol like reactions, b) 1,3-dipolar cycloaddition reactions, and c) radical reactions. The second broad category (2) of approaches to natural aminocyclopentitols is that which comprises methods entailing the functionalization of a preformed but ‘naked’ unsaturated cyclopentane framework. This second category can be divided further into methods, which involve desymmetrization of substituted cyclopentene-4-*meso*-diols and those involving heterocycloadditions of cyclopentadienes.

Brief discussion on different methods employed in the syntheses of cyclopentitols:

1a) Aldol Like Reactions:

Aldol-type routes are by far the oldest known chemical methods by which to synthesize polyhydroxy carbocycles. As the dialdehydes in question are derived from myo-inositol, the reaction is in effect a ring fragmentation – contraction of a cyclohexitol.

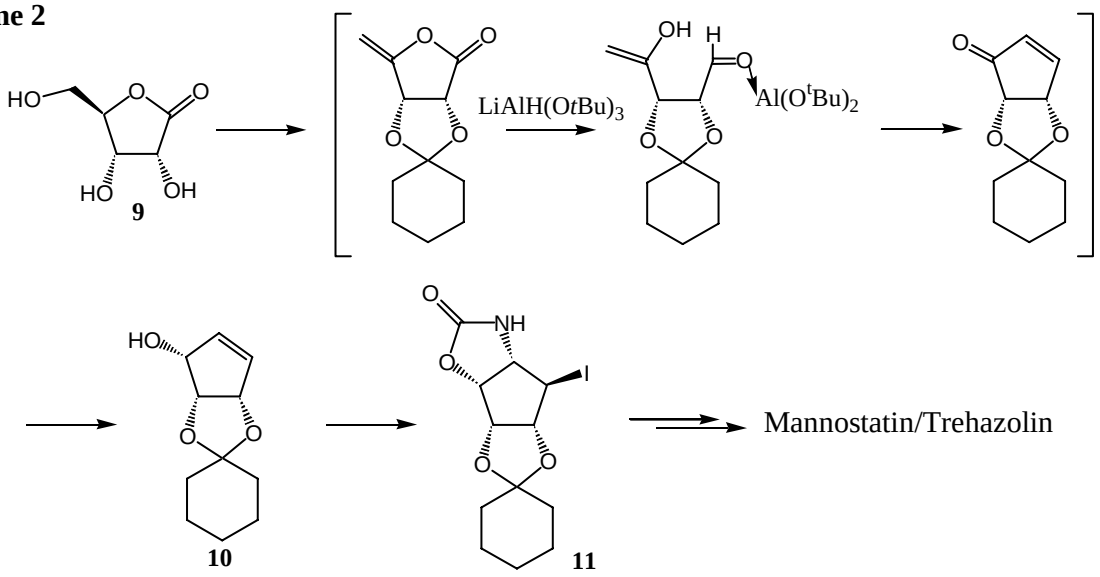
Scheme 1



Inspite of the fact that racemic mixtures are obtained, this strategy has been exploited in the synthesis of mannostatins, trehazolin, and numerous analogues. The key step in the Ogawa and Yuming's[14] approach towards mannostatin A is a formal ring contraction using a base catalyzed nitromethane cyclization of the dialdehyde derived from the starting sugar. Periodate oxidation of (-+)-1,2-O-cyclohexylidene-myo-inositol **5** (also used by these same authors in the synthesis of trehazolin) and reaction of the resulting dialdehyde with nitromethane in the presence of sodium methoxide gave the cyclopentitol derivative **6**. This was transformed into racemic mannostatin A in five steps from resulting aminocyclopentitol (Scheme 1).

Another aldol like reaction involvesan intermediate enolate **10** (or enol complex) generated from a ribonolactone-derived 5-exo-enol ether to give an enone, which has subsequently served in routes to mannostatin and trehazolamine. Knapp *et al*[15] used this approach for constructing the aminocyclopentitol moiety in the synthesis of trehazolin (Scheme 2).

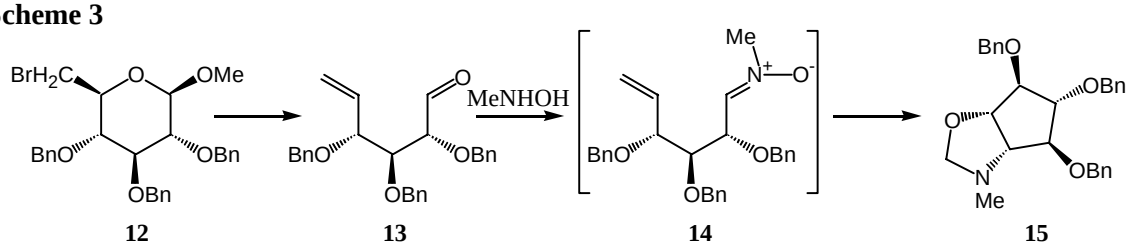
Scheme 2



1b) 1,3-Dipolar cycloaddition reactions:

1,3-Dipolar cycloaddition reactions, which give cyclopentitol – isoxazolidenes via intramolecular trapping 5-enal derived nitrones by alkenes, were originally developed with the synthesis of compounds such as natural carbocyclic nucleosides in mind. Vasella and Bernet[16] demonstrated prior to the discovery of allosamidiine related aminocyclopentitols, for example, cyclopentitol **15** (Scheme 3), could be obtained via intramolecular cycloaddition of sugar-derived nitrones. A reductive elimination (Vasella-Bernet Fragmentation) of the easily available primary bromo sugar **12** provided the required unsaturated aldehyde **13**. Exposure of this key alkenal **13** to *N*-methyl-hydroxylamine led, via a nitrone intermediate, to the isoxazolidine **15** as the major product.

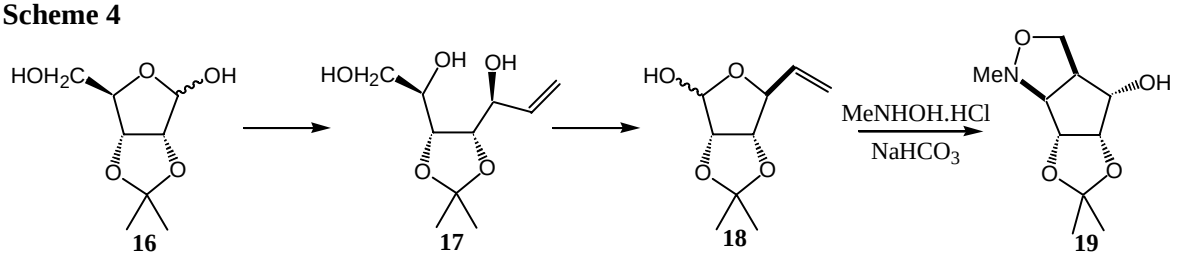
Scheme 3



Shing and co-workers[17] have exploited this nitrone cycloaddition to obtain the allosamizoline-like aminocyclopentitol. The alkene **17** was obtained through a Grignard reaction

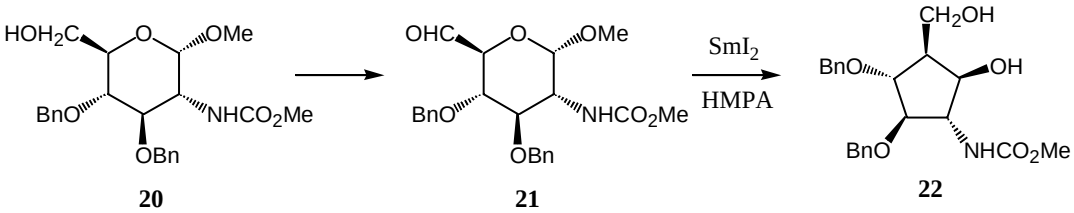
on hemiacetal **16**, stereoselectivity arising presumably through chelation control. The later was exposed to periodate oxidation and the resulting hemiacetal **18** treated with *N*-methyl-hydroxylamine to give the cycloaddition product **19** (Scheme 4).

Scheme 4



Sinaý and co-workers[18] have reported a samarium(II) iodide-induced ring contraction to obtain aminocyclopentitol, related to allosamizoline (Scheme 5). Swern oxidation of the known amino alcohol derivative **20** gave the corresponding aldehyde **21** which when treated with samarium(II) iodide and HMPA to obtain the cyclopentitol **22** in 55% yield as a single diastereomer. The reaction was proposed to follow an aldol type mechanism.

Scheme 5

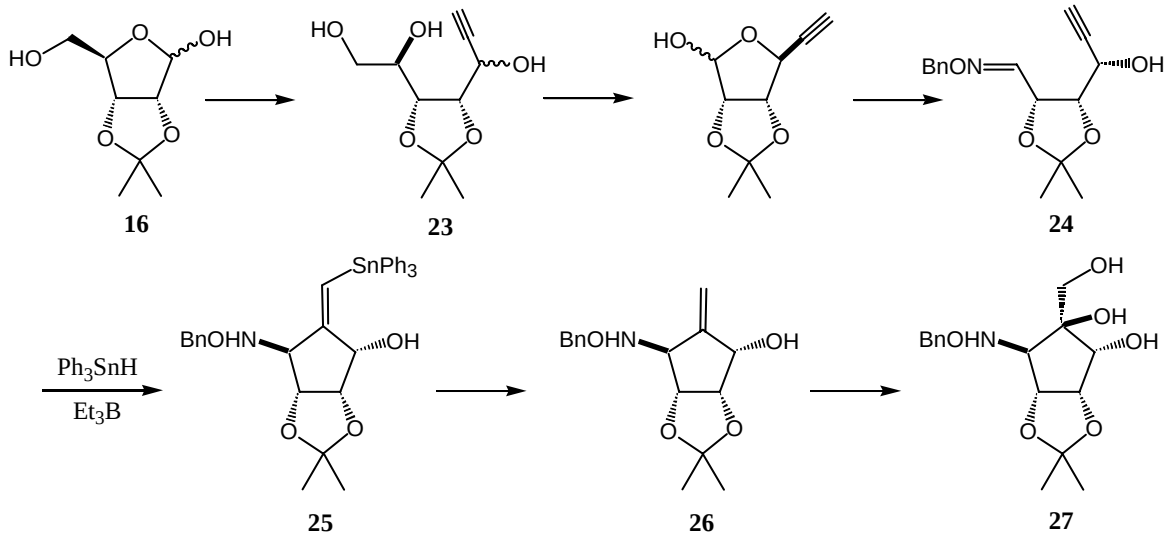


1c) Radical reactions:

Marco – Contelles and co-workers[19] have described the synthesis of aminocyclo-pentitols, via a free radical cyclization of enantiomerically pure, sugar derived, alkyne-tethered oxime ethers. Early studies on these carbohydrate-derived 5-oximinoalkyl radicals were intended *simply* to study their chemistry. These species were found to cyclize to aminocyclopentitols selectively and in high yield. For example, 2,3-O-isopropylidene-D-ribose **16** was converted into the hemiacetal via a grignard reaction followed by oxidative periodate cleavage of the intermediate diol **23**. In situ oximation of the resulting hemiacetal gave the key alkyne-tethered oxime **24**. The latter, on treatment with triphenyltin hydride in the presence of triethylborane,

cyclized smoothly by a 5-exo process and with complete diastereoselectivity to give the carbocycle **25**. Reductive destannylation of **25** and subsequent dihydroxylation the resulting exo-methylene derivative **26** accomplished the synthesis of aminocyclopentitol **27**.

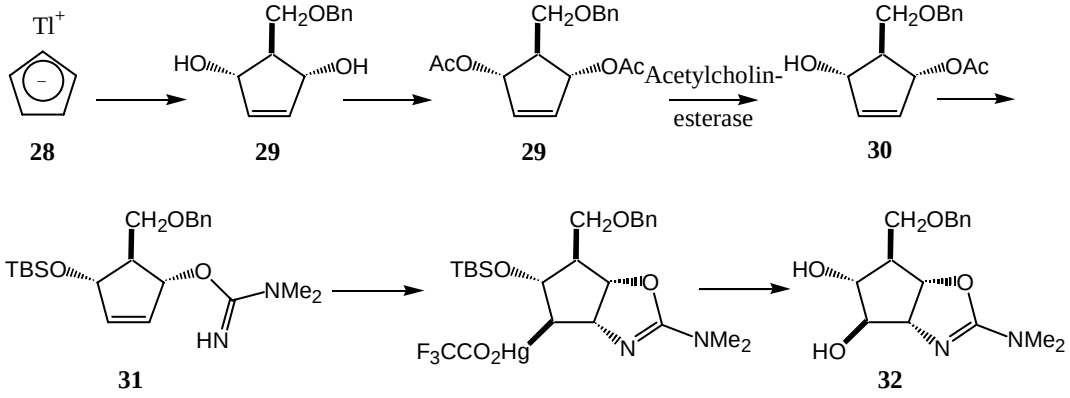
Scheme 6



2a) Desymmetrization of *meso*-diols:

The classical method for desymmetrization of meso-diols is that using enzymes, and it had already found use in approaches to prostaglandins and carbocyclic nucleosides before being exploited in the synthesis of aminocyclopentitols. In the Shrader and Imperiali's[20] approach to the allosamizoline, the alcohol **30** served as the key intermediate and was derived from a *meso*-diol **29** using an enzymatic resolution step (Scheme 7).

Scheme 7

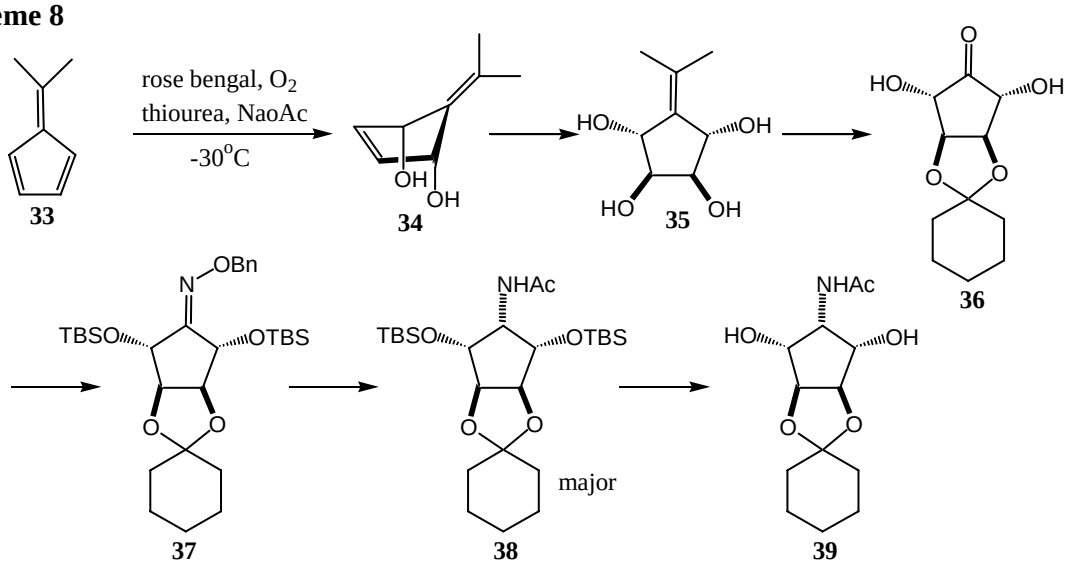


Subsequent protection of the alcohol **30**, deacetylation and treatment with sodium hydride and neat dimethyl cyanamide to give the aminoimidate **31**. Mercury (II)-mediated cyclization of the later gave the alkylmercurium intermediate, which underwent a radical oxygenation on reaction with molecular oxygen, which added exclusively to the convex face of the bicyclic ring system, to give the aminocyclopentiol moiety **32** of allsamizoline.

2b) Diels – Alder reactions:

Diels – Alder reactions have been relatively less used than the corresponding [3 + 2] cycloaddition reactions in the syntheses of polyhydroxycyclopentitols. Ganem and colleagues[21] have obtained a racemic aminocyclopentitol moiety of trehazoline using the [4 + 2] heterocyclo-addition of singlet oxygen on dimethylfulvene. Rose bengal-sensitized photooxidation of fulvene **33** gave the 1,4 diol **34**.

Scheme 8



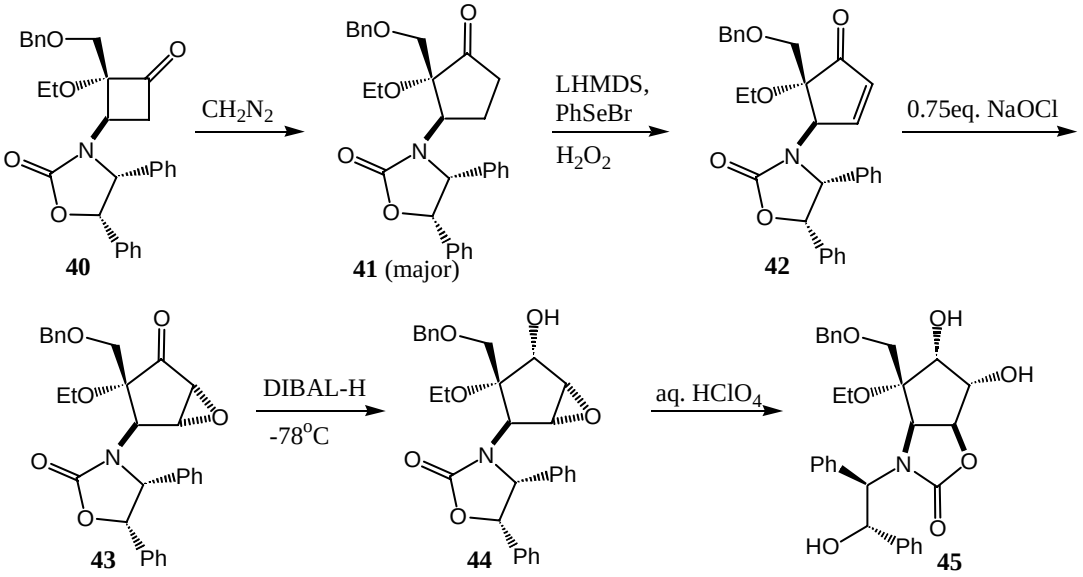
The inclusion of thiourea and an acid trap in the reaction medium suppressed the formation of mixtures of products usually observed in this transformation. Hydroxylation by catalytic osmylation gave tetrol **35**, the observed selectivity being determined by the conformational preference of the diol. Protection of the *cis*-vicinal diol as its cyclohexyl-idene acetal, followed by ozonolysis of the *exo*-methylenic bond, gave the dihydroxy ketone **36**. This

ketone was transformed into the corresponding oxime then silylated to give the protected oxime **37**. This protection strategy secured the stereoselective reduction of the oxime in the sense desired. Thus, oxime **37** on treatment with borane followed by acetylation gave a 6:1 mixture of acetamides. The target *meso*-diol **39** was subsequently obtained from major diastereomer.

3) Few other strategies involved in the synthesis of cyclopentitols:

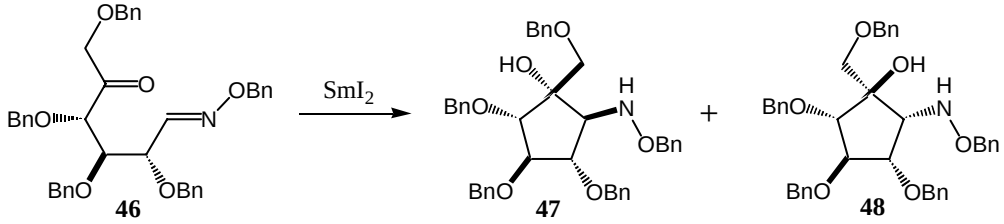
Hegedus and co-workers[22] reported the synthesis of functionalised cyclopentenone **42** by the diazomethane ring expansion of cyclobutanone **40** (Scheme 9).

Scheme 9



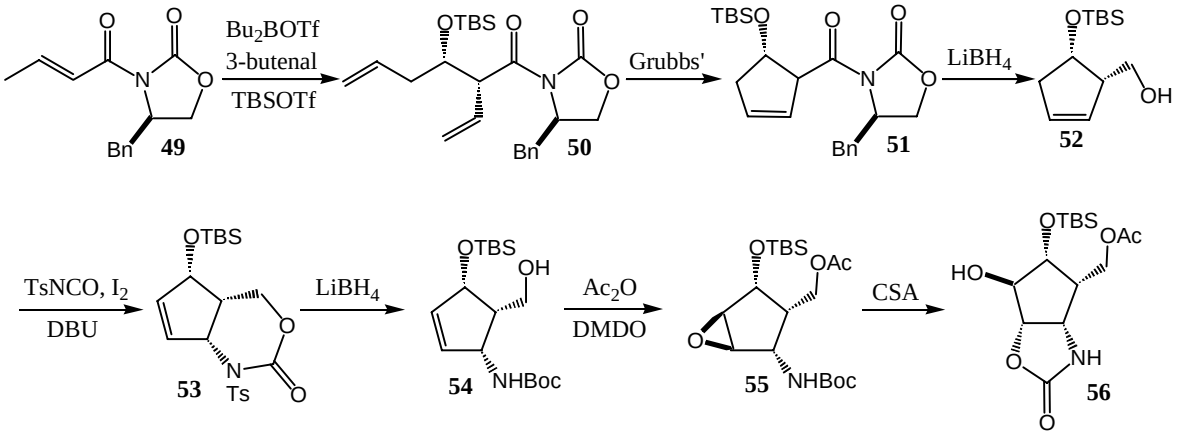
Chiara *et al*[23] were reported an efficient method for the preparation of polyfunctionalized aminocyclopentitols (**47**, **48**) from readily available carbohydrate templates by a highly stereo-selective intramolecular reductive coupling of carbonyl-tethered oxime ethers (**46**), promoted by samarium diiodide (Scheme 10).

Scheme 10



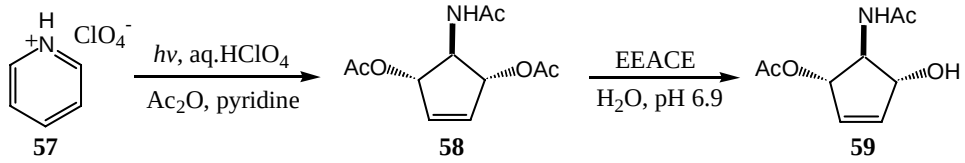
Crimmins *et al*[24] described an asymmetric synthesis of the aminocyclopentitol pseudo-sugar of trehazoline (**56**) using the combination of an asymmetric Evans aldol and ring closing metathesis reactions to construct a cyclopentitol ring with the control of both relative and absolute stereochemistry (Scheme 11).

Scheme 11



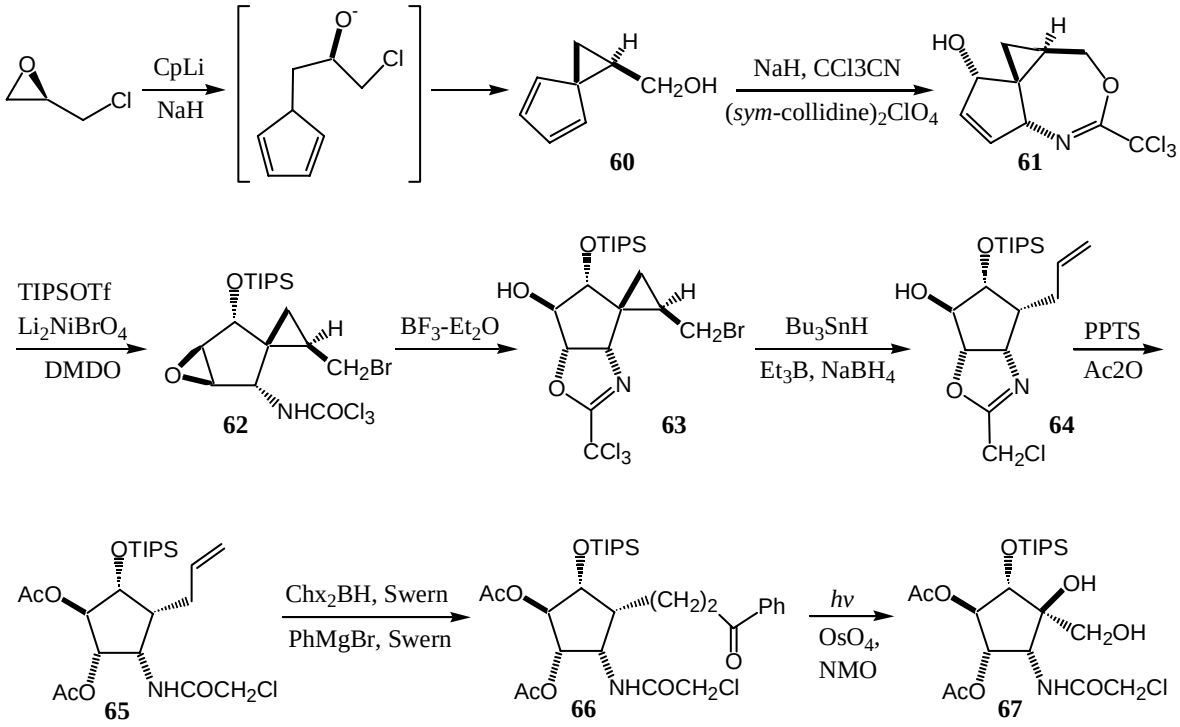
Mariano and co-workers[25] reported the preparation of acetoxyaminocyclopentitol (**59**) in nonracemic form by using combination of pyridinium salt photochemistry and enzymatic desymmetrization (using electric eel acetylcholinesterase).

Scheme 12



Ledford and Carreira[26] have reported an enantioselective synthesis for aminocyclopentitol moiety (**67**) in their total synthesis of trehazolin starting with optically active 1-(hydroxymethyl)-spiro-[2,4]-cyclohepta-4,6-diene (**60**), itself derived in a key step from epichlorohydrine and cyclopentadiene (Scheme 13).

Scheme 13



This introduction, thus provides a brief summary of commonly used strategies for the synthesis of aminocyclopentitols, and cyclopentitol containing natural glycosidase inhibitors. A careful examination of the previous work in this field clearly indicates that samarium iodide mediated intramolecular pinacol coupling of suitably disposed ketoaldehydes is a popular strategy in the synthesis of cyclopentiol/aminocyclopentitol natural products. Additionally, from the strategies described above, it was clear that a "***unified intermediate***" approach for the synthesis of various cyclopentitols and aminocyclopentitols has not been attempted so far. Here in we describe our preliminary attempts towards the synthesis of a differentially protected cyclopentiol and its application for the synthesis of 5-*epi*-calditol.

Presentwork

Present Work

The essential role played by oligosaccharides in the proper functioning of living organisms is now well established.[27] It is not thus surprising that a number of natural and synthetic inhibitors of glycosidases, enzymes implicated in the biosynthesis of these oligosaccharides, have been found to induce far reaching biological effects.[28] The promise that such effects might be exploited to advantage in medicine and agriculture has encouraged a sustained quest for more potent and specific inhibitors, and screening, hand in hand with creative chemical design, has in recent years seen the discovery of an impressive number of mono- and polysaccharide sugar mimics which behave as glycosidase inhibitors. The poly hydroxy azasugar motif is the typical characterization for the known glycosidase inhibitors such as nojirimycin (contains pyranose ring of azasugar), bacteriohopanetetrol[29] and trehazolin,[10] which contains aminocyclopentitol rings. Natural carbocyclic nucleosides such as aristeromycin, neoplanocin A also having the aminocyclopentitol ring, and possess greater metabolic stability to the phosphorylase enzymes which cleave the glycosidic linkage of normal nucleosides.

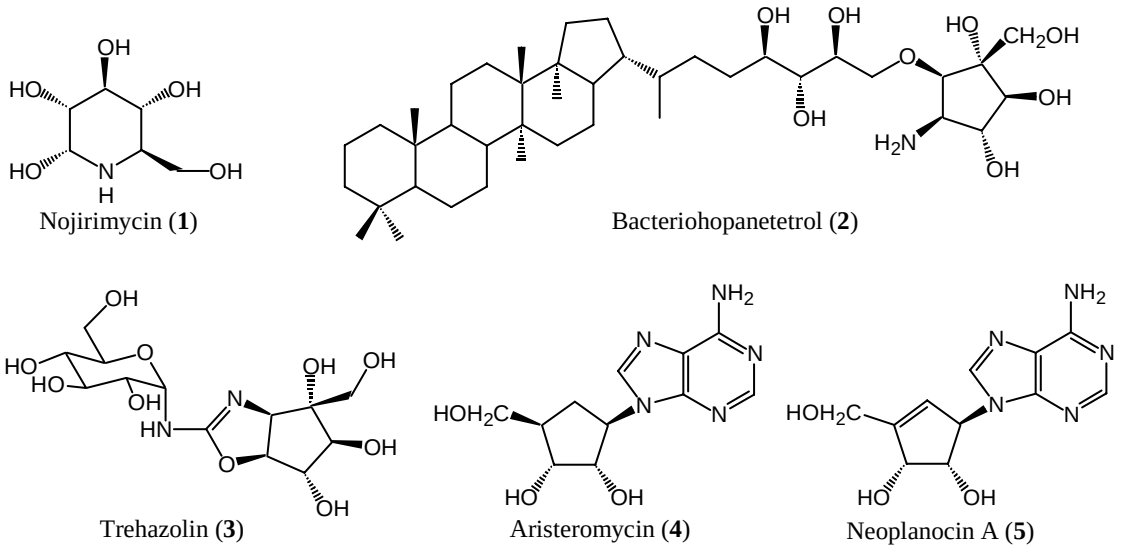
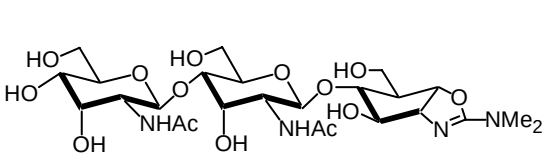
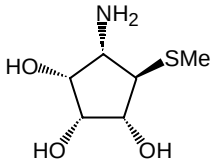


Figure 1. *Cyclopentitol Containing Natural Products*

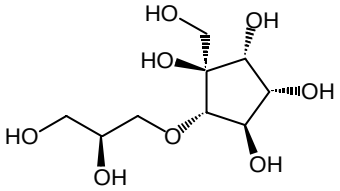
A great deal of efforts has been made for the synthesis of highly substituted cyclopentanes since they were frequently found as the integral part of many important natural products. Recently, cyclopentitols, polyhydroxylated cyclopentanes, have been the focus of much attention from synthetic chemists mainly because aminocyclopentitols such as allosamidin, mannostatin, and trehazolin, have been recognized as strong glycosidase inhibitors. These naturally occurring inhibitors and their synthetic analogues are in great value as the tool for basic biochemical research and as the potential therapeutic agents.



Allosamidin (**6**)



Mannostatin A (**7**)



Calditol (**8**)

Figure 2. *Cyclopentitol Containing Natural Products*

In addition to prokaryotes and eukaryotes, archaea have been introduced, on the basis of 16S ribosomal RNA sequence analysis, as the third group of living organisms. Calditol (**8**) was isolated as a cell wall component of *Sulfolobus solfatiricus*, which is a sulfur-oxidising archaea characterized by aerobic growth at high temperature and low pH in the presence of elemental sulfur.[30] Organisms of this genus are usually found in sulfur-containing habitats such as acidic hot springs and responsible for the production of sulfuric acid from elemental sulfur. Its absolute structure was the subject of speculation for a long time, and Sinaý and co-workers resolved the issue once and for all by the total synthesis of calditol and its possible isomers.[31] Although several methods are available for the synthesis of these cyclopentitols, samarium iodide mediated intramolecular pinacol coupling of suitably disposed ketoaldehydes seems to be a popular strategy in the synthesis of many of these naturally occurring cyclopentitols (*e.g.* calditol, trehazolin, bacteriohopanetriol *etc*).

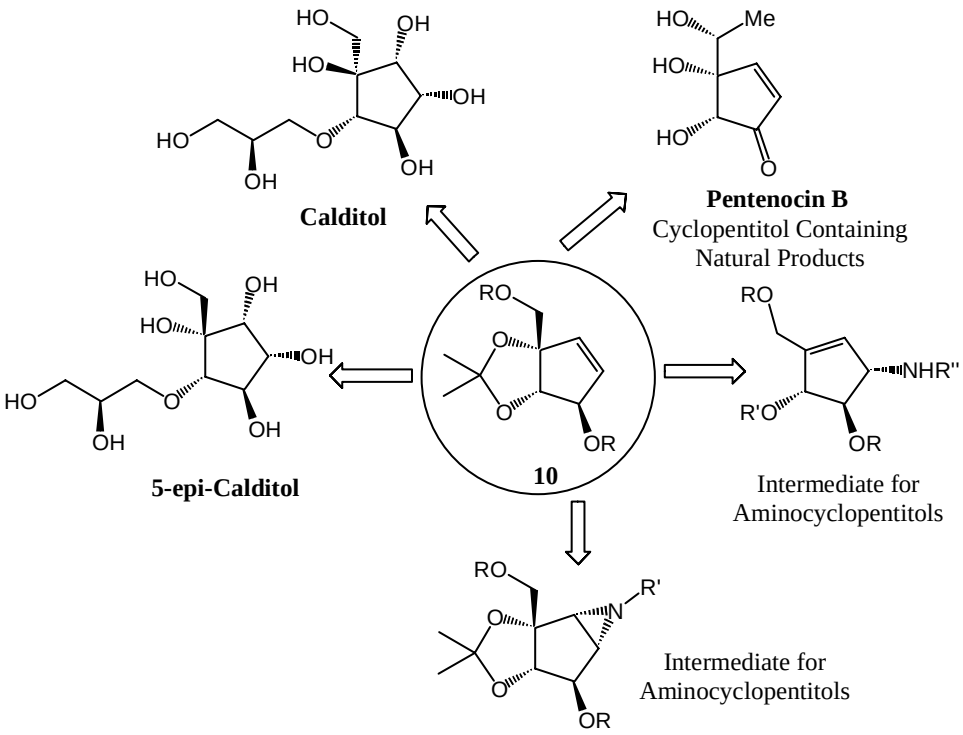


Figure 3. *Strategy Towards Cyclopentitol Containing Natural Products*

Intrigued by the structural similarity between the cyclopentitol moieties of various natural products, we initiated a program directed towards the synthesis of these subunits preferably using a common starting point. Herein we describes the synthesis of a differentially protected cyclopentitol derivative **10**, its stereoselective dihydroxylation and conversion of the resulting diol into 5-*epi*-calditol **9**.

Retrosynthetic Analysis for 10 and its Application to 5-epi-Calditol 12:

As revealed in the above general strategy (Figure 1), the central point for out synthetic schemes is the synthesis of the differentially protect cyclopentitol **10**. Keeping the ring closing metathesis as the key reaction in the preparation of the **10**, we arrived to the following important steps: a) The ring closing olefin metathesis of a highly substituted diene b) Protecting group differenciation of the corresponding tetrol c) The diene can be obtained starting from di-isopropylidene manno furanose.

Coming to the synthesis of 5-epi-Calditol, important features in the synthesis of 5-epi-calditol were a) Selective *O*-alkylation of **20** using an allyl halide, and cat. Asymmetric dihydroxylation. The first strategic disconnection will give the compound **20**, which in turn can be obtained from the stereoselective dihydroxylation of the cyclopentene **10**.

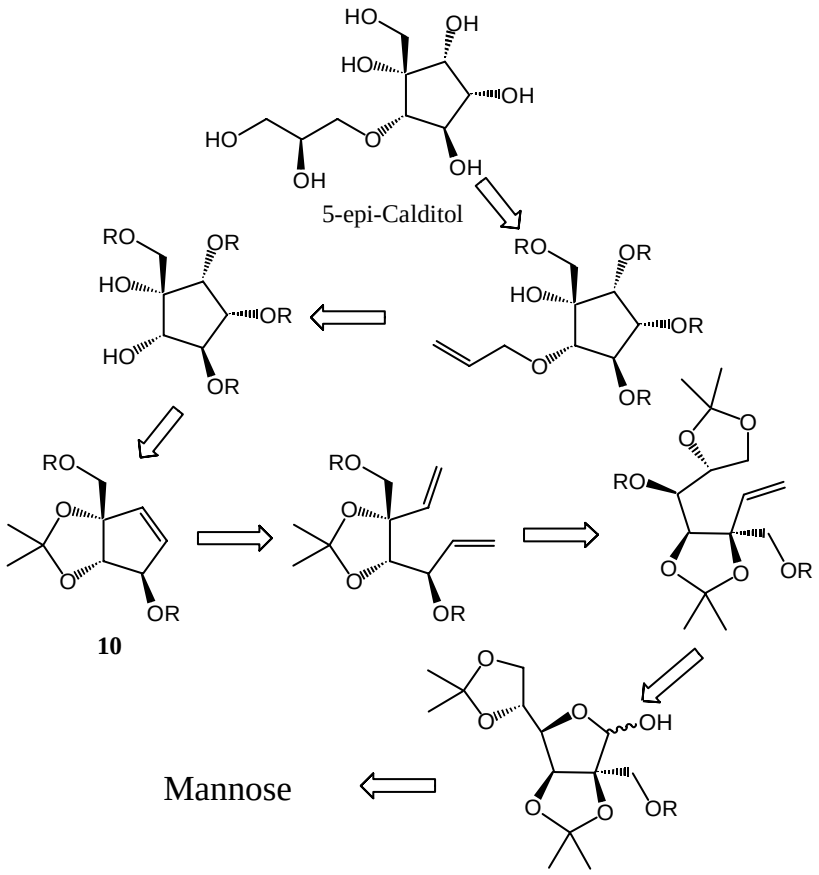


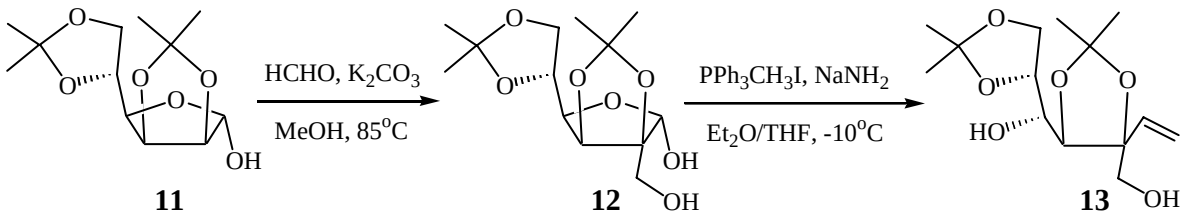
Figure 4. *Strategy Towards the Key Cyclopentitol* **10** *and towards 5-epi-Calditol*

Synthetic Approach

The synthetic endeavor began with the condensation reaction between di-isopropylidene mannofuranose (**11**) and formaldehyde in the presence of K_2CO_3 in methanol to get the alcohol **12**,[32] whose structure was conformed by comparing the ^{1}H, ^{13}C spectra and optical rotation values with that of literature values. The lactol **12** was then subjected to Wittig olefination conditions using PPh_3CH_3I and sodamide at -20°C to give the olefin diol (**13**). The structure of

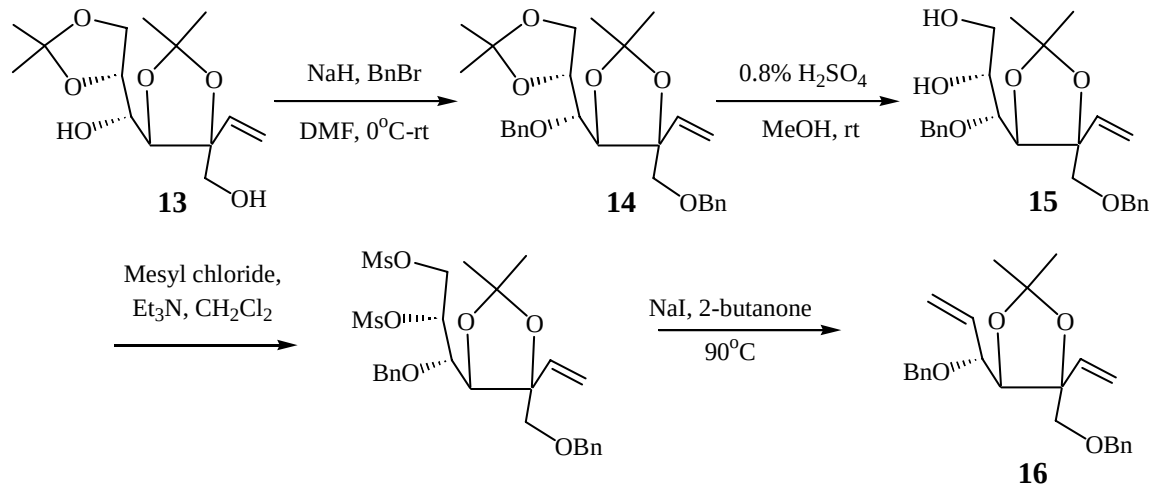
olefin diol was confirmed by the ^{1}H NMR spectrum, in which signals due to the olefinic protons appeared at 5.32 and 5.92 ppm. The ^{13}C NMR spectrum further supported the structure of compound **13**.

Scheme 1



The olefin diol (**13**) was then protected as its dibenzyl ether using benzyl bromide and NaH in DMF to afford the compound **14** in quantitative yield. In the ^{1}H NMR spectrum, a multiplet between 4.2-4.7 ppm due to benzylic protons and a multiplet between 7.2-7.4 ppm due to aromatic protons were observed. ^{13}C NMR spectrum was further confirmed the structure of compound **14**. Cleavage of 5, 6-isopropylidene group of compound **14** was accomplished using 0.8% H_2SO_4 in methanol to get the diol (**15**), whose structure was confirmed by its ^{1}H NMR spectrum as well as ^{13}C NMR spectrum, in which two out of four singlets due to two isopropylidene groups (between 1.27-1.53 ppm in ^{1}H NMR and between 25.0 – 28.0 ppm in ^{13}C NMR) were absent and the rest of the spectrum was in complete agreement with the assigned structure.

Scheme 2



The diol **15** was then treated with methanesulfonyl chloride and triethylamine in CH_2Cl_2 to afford the dimesylated compound in quantitative yield. The dimesyl compound without any further purification was then subjected to the elimination conditions using sodium iodide in refluxing 2-butanone to procure the diene **16**.[33] Structure of the diene was elucidated by its ^1H NMR spectrum, in which six olefinic proton signals were appeared between 5.2-5-7 ppm (internal olefinic proton of the newly formed olefin showed the signal as ddd at 5.64 ppm). The structure was further confirmed by ^{13}C NMR spectroscopy.

A brief overview on olefin metathesis (RCM):

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

Olefin metathesis can be utilized in three closely related type of reactions: (A), ring-opening metathesis polymerization (ROMP); (B), ring closing metathesis (RCM); and

type (C), acyclic cross metathesis which when carried out on diolefins results in polymers (ADMET). It is now generally accepted that the mechanism of both cyclic and acyclic olefin metatheses proceeds through a series of metallacyclobutanes and carbene complexes (Figure 5).

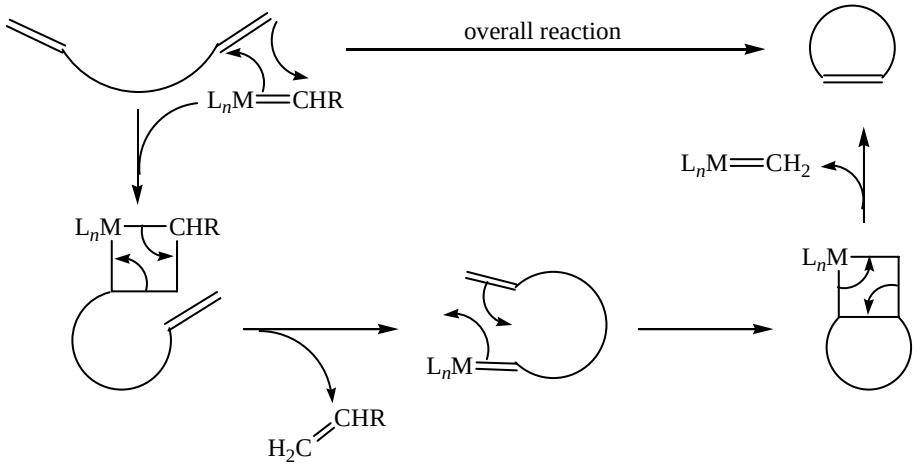


Figure 5

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

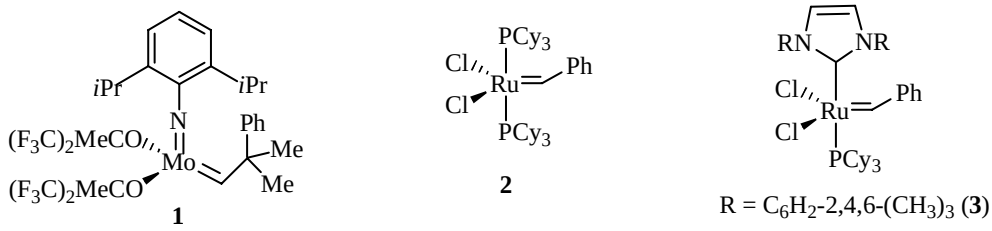


Figure 6

*The alkylidene – metal complexes, which are widely used for the RCM, include the alkoxy-imido molybdenum complex **1** and the benzylidene ruthenium complex **2**. The molebdenum complex **1** exhibits the higher reactivity of the two toward a broad range of substrates with many steric or electronic variations; however, it also suffers from extreme sensitivity to air and moisture as well as decomposition upon storage. To increase the utility of the ruthenium family of the complexes by increasing their activity, Grubbs et al recently prepared ruthenium based complexes coordinated with 1,3-dimesitylimidazol-2-ylidene ligands **3**. These complexes exhibited a high ring-closing metathesis activity similar to that of the molybdenum complex **1**, yet have also retained*

*the remarkable air and water stability characteristic of the parent benzylidene ruthenium complex **2**. The superior activity of **3** includes high rates of ROMP for low-strain substrates and even the ROMP of sterically hindered substrates containing trisubstituted olefins such as 1,5-dimethyl-1,5-cyclooctadiene. The catalyst **3** was able to perform the RCM of sterically demanding dienes to form tri- and tetrasubstituted olefins. In addition catalyst **3** produced the first example of cross-metathesis to yield a trisubstituted olefin, as well as CM and RCM reactions where one partner is directly functionalized with a deactivating group, such as acrylate or siloxane. Although the exact mechanism of this complex **3** activity remains unclear, recent results indicate that this may be due to slower phosphine dissociation. Other studies suggest that the bulky mesityl groups in this catalyst may contribute to high activity, in part because of interactions with the alkylidene moiety.*

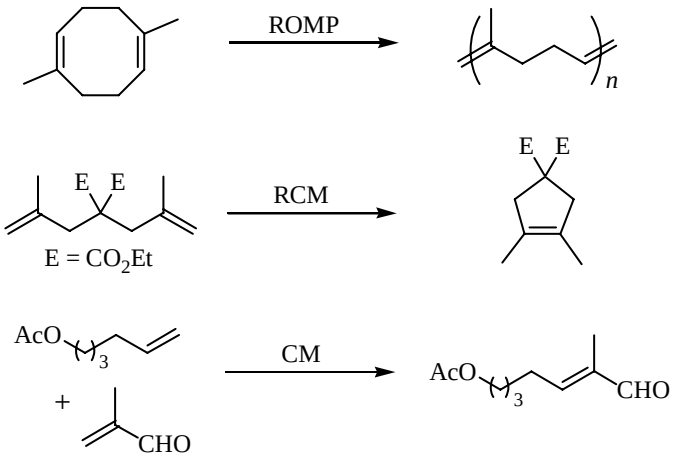
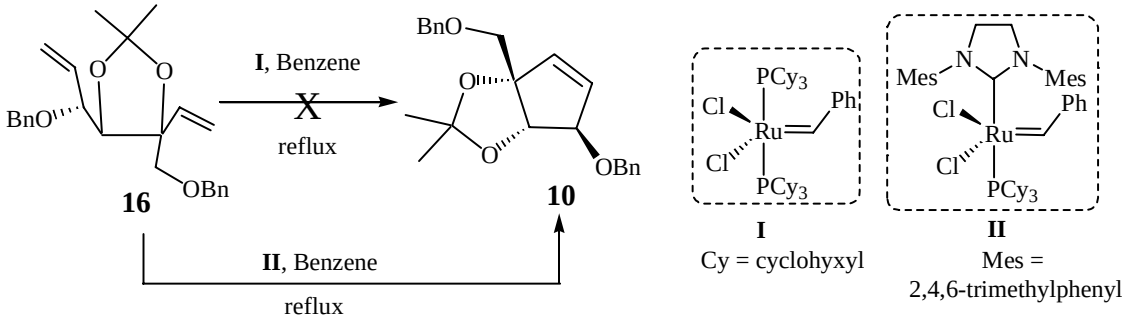


Figure 7

After having an easy access for the preparation of the key diene **16**, we next focused our attention on its ring closing metathesis. As expected, the ring-closing olefin metathesis using Grubbs' 1st generation catalyst (**I**), in refluxing benzene for two days, was found to be unsuccessful. As indicated earlier, it was mainly because of sterichindrance around on of the olefin. Although, Eustache and co-workers[34] reported the successful RCM of a similar diene using Schrock's catalyst, however, because of the superior stability as well as commercial availability of the Grubbs' 2nd generation catalyst we intended to use it in the present context.[35]

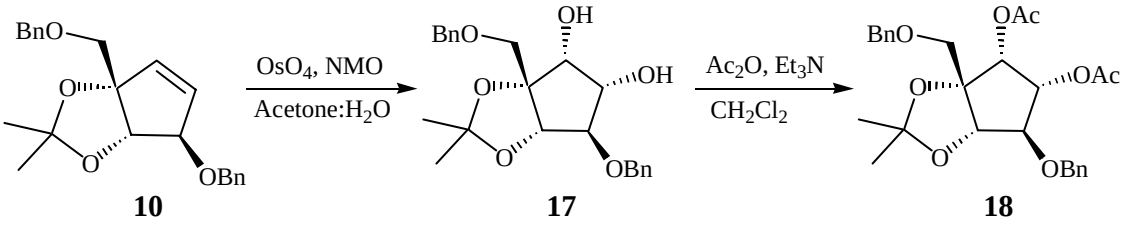
Gratifyingly, the RCM of **10** with 2nd generation Grubbs' catalyst (**B**) was facile and the key cyclopentitol derivative **5** was obtained along with the unreacted **10**. The structure of the compound **10** was elucidated by its ^{1}H NMR spectrum, in which only two out of six olefinic proton signals were resonated at 5.9 and 6.05 ppm when compared with the diene. In the ^{13}C NMR spectrum only two olefinic carbons resonated at 132.0, 137.6 ppm, thus confirming the assigned structure of cyclopentene **10**.

Scheme 3



The cyclopentene derivative (**10**) was then dihydroxylated using catalytic osmium tetroxide and *N*-methyl morpholine oxide in acetone and water solvent system to afford exclusively one diol **17**. The constitution of **17** was confirmed by the absence of olefinic signals in its ^{1}H NMR as well as in ^{13}C NMR spectrum and the rest of the spectrum was in complete agreement with the assigned structure.

Scheme 4



For convenience in establishing the stereochemistry of the two hydroxyl groups, we converted the diol **17** into its diacetate derivative **18** using acetic anhydride and triethylamine and characterized this diacetate using 2D-NMR techniques. In the ^{1}H NMR spectrum of **18**, H(1) and

H(2) appeared downfield at 5.21 (d, *J* = 5.2 Hz) and 5.29 (dd, *J* = 7.3, 5.2 Hz) ppm, respectively. The observed NOE's between H(1) and H(6)/H(6'), H(4) and H(1)/H(2) in the NOESY spectrum of **11-Ac** clearly indicated a *syn*-spacial relation between these protons thus confirming its assigned structure ((Figure 7). Since the stereochemistry of H4 and H6 H6' protons were fixed, so we came to a conclusion that the dihydroxylation was occurred from α-face only, it may also be attributed to the bulky protection groups present in the adjacent of the olefin. After confirming the configuration of the diol **17**, we proceeded to accomplish the synthesis of 5-*epi*-calditol.

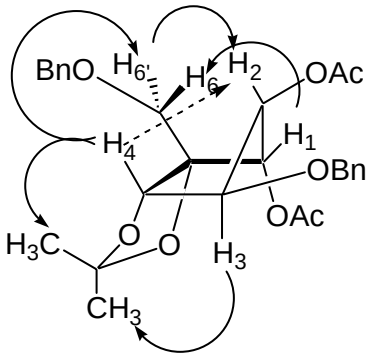
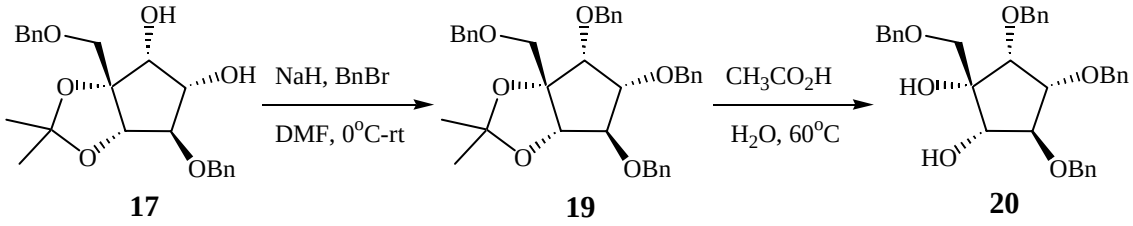


Figure 8. *NOE observed for compound* **18**

The diol **17** was then protected as its benzyl ether using NaH and benzyl bromide in DMF to afford the tetrabenzyl compound **19** quantitatively. The structure of the compound **19** was confirmed by its ^{1}H NMR spectrum, in which the integration for number of protons increased by twofold in the benzylic region as well as in the aromatic region. The structure was further confirmed by its ^{13}C NMR spectrum. The isopropylidene group of compound **19** was deprotected using warm acetic acid to afford the diol **20** in good yield. In the ^{1}H NMR and ^{13}C NMR spectra clearly shown the absence of characteristic isopropylidene signals, thus confirming the assigned structure of the diol **20**.

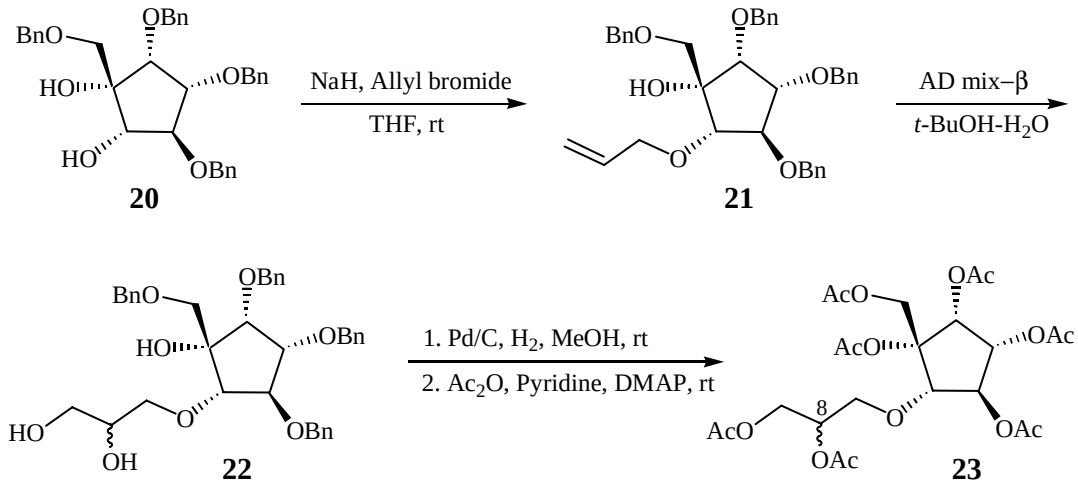
Scheme 5



17 **19** **20**

As it was indicated in the earlier retrosynthetic strategy, our intended strategy for the installation of the glycidyl ether unit was the selective allylation of HO-C(4) of compound **20** and the Sharpless asymmetric dihydroxylation of resulting allyl ether. The diol **20** was selectively alkylated using allyl bromide and NaH in THF to afford the allyl ether **21**. The structure of the compound **21** was confirmed by its ^{1}H NMR spectrum, in which signals due to the olefinic protons were observed at 5.19 and 5.85 ppm and rest of the protons were resonated at their expected values. The olefin was subjected to the Sharpless asymmetric dihydroxylation[36] conditions using ADmix-β in t-BuOH/ H_2O system afforded the triol (**22**). The structure of the triol **22** was confirmed by its ^{1}H NMR and ^{13}C NMR spectra, in which the characteristic olefinic signals were absent.

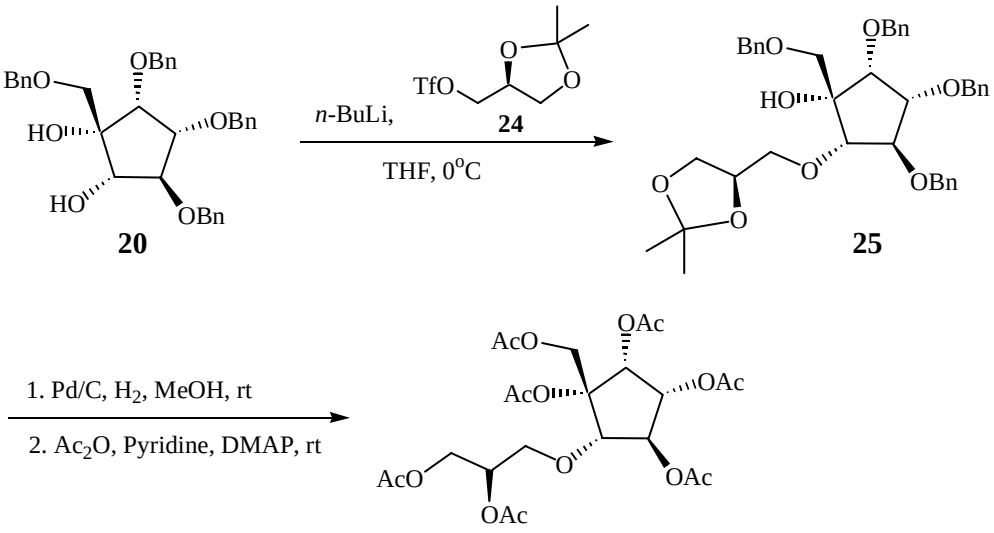
Scheme 6



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

Benzyl ethers of the triol was then deprotected using Pd/C in methanol under H_2 atmosphere to afford the 5-*epi*-calditol, which for further characterization was converted into hepta acetate derivative (**23**) using acetic anhydride in pyridine and catalytic dimethyl aminopyridine and compared its ^1H, ^{13}C NMR (in 500MHz) and optical rotation with that of literature values. In ^1H NMR and ^{13}C NMR spectra of compound **9**, 1:1 mixture of peaks were observed, because of C(8) chiral centre, whose diastereomeric excess was not confirmed after the asymmetric dihydroxylation step. After being met with discouraging results in the asymmetric dihydroxylation, we next focused our attention on alkylation of the diol **20** directly with the corresponding glycerol derivatives.

Scheme 7



5-*epi*-calditol per acetate (**23**)

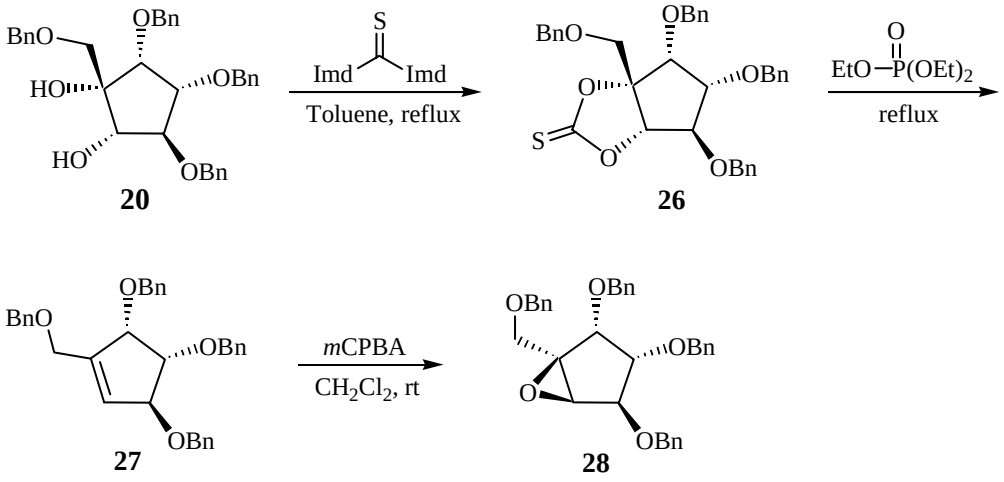
After initial investigations with different 2.3-*O*-isopropylidine (*R*)-glyceryl halides as well as with corresponding 1-*O*-sulphonates, we found that 2,3-*O*-isopropylidine-(*R*)-glycerol-1-*O*-triflate (**24**) was the suitable substrate for alkylation. Accordingly the diol **20** was selectively alkylated using triflate derivative (**24**) and *n*-BuLi in THF to afford the mono alkylated compound (**25**). In the ^1H NMR and ^{13}C NMR spectra, two characteristic singlets due to the isopropylidine group were observed (at 1.32-1.36 ppm in ^1H NMR and 25.5, 26.8 ppm in ^{13}C

NMR), and the rest of the spectra were in complete agreement with the assigned structure, thus confirming the formation of compound **25**.

The benzyl ethers of compound **25** were deprotected using Pd/C in methanol under H_2 atmosphere, in which the isopropylidine group was also cleaved to afford the 5-*epi*-calditol (**9**). The compound **9** without any further characterization was per acetylated using acetic anhydride in pyridine and catalytic dimethylaminopyridine to afford the hepta-acetyl derivative **23**, whose ^{1}H, ^{13}C NMR data and optical rotation were compared with that of literature one to confirm the formation of optically pure 5-*epi*-calditol per acetate.

After the successful synthesis of 5-epi-calditol, we were intended to synthesize the calditol by inverting the chirality at C-5 of **20** and other naturally occurring aminocyclopentitol derivatives from intermediate **10** using the Overman aza-Claisen rearrangement and epoxidation and subsequent inter/intramolecular opening with amino-nucleophiles.

Scheme 8



Accordingly, the compound **20** was converted into corresponding thio carbonyl ester by the treatment of thiocarbonyl diimidazole in refluxing toluene to afford the ester **26** in quantitatively. The compound **26** without any further analysis subjected to Corey Winter olefination conditions using refluxing triethylphosphite to afford the olefin **27**. In the ^{1}H NMR

spectrum of compound **27**, the distinguishing olefinic proton resonated at 5.96 ppm and the rest of the spectrum was in complete conformity with the assigned structure.

The olefin **27** was then treated with metachloro perbenzoic acid in CH_2Cl_2 as solvent to give the epoxide **28** as a single diasteromer. The diastereomeric excess can be attributed to the bulky protecting groups (benzyls) present either side in the olefin. The structure of the epoxide **28** was confirmed by its ^{1}H and ^{13}C NMR analysis, where the presence of typical epoxide signal (at 3.30 ppm in ^{1}H NMR and at 57.8 ppm in ^{13}C NMR) was supported the formation of epoxide. After having epoxide in hand, our efforts in ring opening of the epoxide with various nucleophiles resulted in vain. It may be because of steric hindrance in the molecule caused by the benzyl groups towards the incoming nucleophiles.

Table 1. *Different conditions employed for the ring opening of epoxide* **28**.

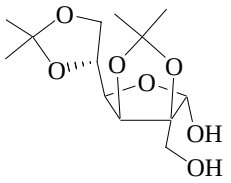
S.No	Reagents and Condition	Result
1	Allyl alcohol, n-BuLi, THF, -20°C	No reaction
2	NaOH, THF/H_2O, heating	No reaction
3	NaOH, nBu_4NOH, THF/H_2O, heating	No reaction
4	Al_2O_3, Et_2O/H_2O, rt	No reaction
5	Bu_3P, Ac_2O, Toluene	No reaction
6	Cat $HClO_4$, DMSO/H_2O, heating	No reaction

In conclusion, we have provided a simple preparative procedure for the synthesis of differentially protected cyclopentitol **10**, and its application towards the diastereoselective synthesis of 5-epi-calditol. Although we were unable to make the suitable cyclopentitol having the inverted C-5, however, during this endeavour we have learned that epoxidation of the corespondic trisubstitued internal olefin occurs exclusively syn to 3-OBn. Presently work towards the synthesis of naturally occurring aminocyclopentitol derivatives using **10** as well as **28** are in progress. On the other hand, we are also pursuing the total synthesis of natural pentenocin-B using **10** as an advanced intermediate.

Experimental

Experimental

2-*C*-(Hydroxymethyl)-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (12):



A suspension of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose **11** (15.4 g, 63 mmol) and K_2CO_3 (11.2 g, 81 mmol) in MeOH (200 ml) was treated with 37% aqueous formaldehyde (120 ml) and stirred for two days at 85°C. The solution was neutralized with 10% aqueous H_2SO_4, concentrated and extracted with chloroform. The combined organic layer was dried (Na_2SO_4), concentrated and purified by column chromatography (ethyl acetate-light petroleum, 1:1) to afford the crossed aldol product **12** as a white solid (13.0 g, 76%).

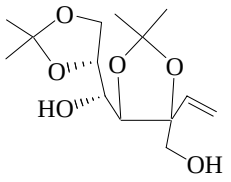
$[\alpha]_D^{25}$: +11° (c 1.0, MeOH).

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.41-1.48 (4s, 12H), 4.0-4.14 (m, 4H), 4.35-4.43 (m, 2H), 4.64 (d, *J* = 2.9 Hz, 1H), 5.34 (d, *J* = 2.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 25.1, 26.7, 27.2 (2C), 62.5, 63.2, 66.6, 66.9, 72.8, 73.0, 80.8, 82.0, 82.8, 89.3, 93.7, 97.5, 103.5, 109.0, 113.5, 113.7.

CHN Anal: Calcd for $C_{13}H_{22}O_7$: C, 53.78, H, 7.64. Found: C, 53.52, H, 7.72.

2-*C*-Ethenyl-2,3:5,6-di-*O*-isopropylidene-D-mannitol (13):



A solution of lactol **12** (5 g, 22.9 mmol) in THF (25 ml) at –10°C was treated with methylene(tripheyny)phosphorane [generated from PPh_3CH_2I (32.4 g, 80.3 mmol) and $NaNH_2$

(2.95 g, 75.7 mmol) in dry Et_2O:THF (80:40 ml)] and the contents were stirred at room temperature for 10 h. The reaction mixture was quenched with saturated NH_4Cl solution, portioned between ether-water, ether layer was separated, dried (Na_2SO_4) and concentrated. Purification of the residue over silica gel column (ethyl acetate/light petroleum, 1:2) gave the olefine diol **13** (5.5 g, 83%) as a color less oil.

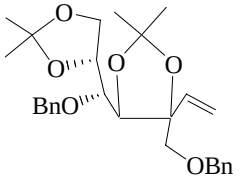
$[\alpha]_D^{25}$: +21.3° (c 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200MHz) : δ1.32, 1.38, 1.44, 1.50 (4s, 12H), 2.45 (d, *J* = 6.3 Hz, 2H), 3.53 (bs, 3H), 3.94-4.06 (m, 3H), 4.32 (d, *J* = 2.4 Hz, 1H), 5.28 (dd, *J* = 2.0, 10.7 Hz, 1H), 5.47 (dd, *J* = 2.0, 17.1 Hz, 1H), 5.92 (dd, *J* = 10.7, 17.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 25.2, 26.6, 26.9, 27.8, 65.4, 67.0, 69.5, 76.4, 78.2, 84.7, 108.5, 109.3, 116.0, 136.8.

CHN Anal: Calcd for $C_{13}H_{21}O_6$: C, 57.13, H, 7.74. Found: C, 57.35, H, 7.52.

2-*C*-Ethenyl-1,4-di-*O*-benzyl-2,3:5,6-di-*O*-isopropylidene-D-mannitol (14):



An ice-cooled solution of the olefin diol **13** (5.5 g, 19.1 mmol) in dry DMF (20 ml) was treated with NaH (1.68 g, 60% dispersion in oil, 40 mmol) and stirred for 30 min. Then the reaction mixture was treated with benzyl bromide (5 ml, 42 mmol) drop wise at 0°C and the stirring was continued for an additional 4 h at room temperature. The reaction mixture was quenched with ice water and partitioned between water and ether. The combined ether layer was dried (Na_2SO_4), concentrated and the residue was purified over silica gel column using ethyl acetate and light petroleum as an eluent (1:9) to furnish **14** (8.0 g, 90%) as a colorless oil.

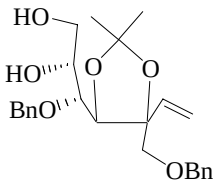
$[\alpha]_D^{25}$: +8.5° (c 1.4, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.27, 1.35, 1.43, 1.53 (4s, 12H), 3.55 (d, *J* = 10.3 Hz, 2H), 3.75 (dd, *J* = 6.8, 4.4 Hz, 1H), 3.92 (d, *J* = 6.8 Hz, 2H), 4.11-4.18 (m, 1H), 4.25 (d, *J* = 7.3 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.78 (d, *J* = 11.2 Hz, 1H), 5.24 (dd, *J* = 2.0, 10.7 Hz, 1H), 5.48 (dd, *J* = 2.0, 17.1 Hz, 1H), 6.0 (dd, *J* = 10.7, 17.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 25.2, 26.1, 26.4, 27.6, 65.7, 73.5, 74.5, 76.4, 77.5, 81.3, 83.8, 108.2, 108.6, 116.1, 127.2, 127.4, 127.6, 127.9, 128.2, 136.5, 137.8, 138.4.

CHN Anal: Calcd for $C_{28}H_{36}O_6$: C, 71.77, H, 7.74. Found: C, 72.02, H, 7.61.

2-*C*-Ethenyl-1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-D-mannitol (14):



A solution of compound **14** (8.0 g, 17.1 mmol) and 0.8% aqueous H_2SO_4 (1 ml) in MeOH (30 ml) was stirred at room temperature for 6 h. Neutralization of the reaction mixture with aqueous $NaHCO_3$, concentration, extraction with ethyl acetate and purification over a silica gel column (ethyl acetate/light prtroleum 1:1) gave the diol **15** (6.66 g, 91%) as a colorless oil.

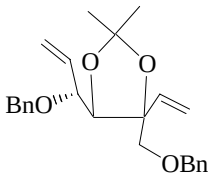
$[\alpha]_D^{25}$: +18.2° (c 1.2, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.44 (s, 3H), 1.65 (s, 3H), 3.10 (bs, 2H), 3.52 (d, *J* = 10.1 Hz, 1H), 3.60 (d, *J* = 10.1 Hz, 1H), 3.92 (br.d, *J* = 4.6 Hz, 1H), 3.99 (dd, *J* = 2.0, 4.9 Hz, 1H), 3.92 (t, *J* = 4.7 Hz, 1H), 4.46-4.71 (m, 4H), 4.78 (d, *J* = 11.2 Hz, 1H), 5.26 (dd, *J* = 1.8, 10.6 Hz, 1H), 5.50 (dd, *J* = 1.8, 17.2 Hz, 1H), 5.98 (dd, *J* = 10.6, 17.2 Hz, 1H), 7.25-7.34 (m, 10H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 26.3, 27.8, 63.1, 71.0, 73.6, 73.8, 74.7, 79.9, 80.0, 84.2, 108.3, 116.7, 127.6, 127.7, 127.9, 128.3, 136.2, 137.6, 138.1.

CHN Anal: Calcd for $C_{25}H_{32}O_6$: C, 70.07, H, 7.53. Found: C, 69.76, H, 7.42.

5,6-Dideoxy-2-*C*-ethenyl-1,4-di-*O*-benzyl-2,3-*O*-isopropylidene-D-*lyxo*-hex-5-enitol (14):



To an ice-cooled solution of diol **15** (6.6 g, 15.4 mmol) and CH_2Cl_2 (30 ml) was added Et_3N (5.4 ml, 38.5 mmol) and methanesulphonyl chloride (2.6 ml, 34 mmol) and stirred for 4 h at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4), concentrated. The resulting crude product (7.7 g, 86%) was dissolved in 2-butanone (50 ml) and NaI (4.94 g, 32.9 mmol) was added to the reaction mixture and the contents were refluxed it for 6 h. The reaction mixture was filtered and the precipitate was washed with ethyl acetate. The combined filtrate was partitioned between water and ethyl acetate and organic layer was separated, dried (Na_2SO_4), concentrated and purified over a silica gel column (ethyl acetate/light petroleum, 1:9) to obtain the diene **16** (4.25 g, 70% for two steps) as a pale yellow oil.

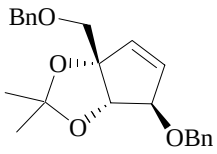
$[\alpha]_D^{25}$: +30.6° (c 1.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500MHz) : δ 1.49, 1.57 (2s, 6H), 3.44 (d, *J* = 10.5 Hz, 1H), 3.47 (d, *J* = 10.5 Hz, 1H), 3.88 (t, *J* = 8.3 Hz, 1H), 4.38 (d, *J* = 8.3 Hz, 1H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.52 (d, *J* = 12.4 Hz, 1H), 4.62 (d, *J* = 12.3 Hz, 1H), 4.64 (d, *J* = 12.3 Hz, 1H), 5.20 (dd, *J* = 1.8, 10.8 Hz, 1H), 5.27-5.32 (m, 2H), 5.47 (dd, *J* = 1.8, 17.1 Hz, 1H), 5.64 (ddd, *J* = 8.3, 10.8, 17.1 Hz, 1H), 5.77 (dd, *J* = 10.8, 17.1 Hz, 1H), 7.28-7.35 (m, 10H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 26.5, 27.8, 70.0, 72.9, 73.5, 79.5, 80.3, 84.0, 108.2, 116.4, 120.2, 127.1, 127.5, 128.0, 128.2, 134.0, 136.2, 138.1, 138.5.

CHN Anal: Calcd for $C_{25}H_{30}O_4$: C, 76.11, H, 7.66. Found: C, 76.32, H, 7.55.

(1*S*,4*R*,5*S*)-1-benzyloxylmethyl-4-*O*-benzyl-1,5-*O*-isopropylidene-cyclopent-2-en-1,4,5-triol (10):



A solution of compound **16** (1.0 g, 2.54 mmol), Grubb's 2nd generation catalyst (30 mg, 0.05 mmol) and benzene (100 ml) was refluxed under argon atmosphere for 6 h. The reaction mixture was cooled, evaporated and the crude product was purified by column chromatography using ethyl acetate- light petroleum (1:9) as an eluent to afford the cyclopentene **10** (0.75 g, 81%) as a colourless oil.

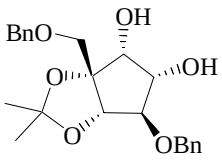
$[\alpha]_D^{25}$: -41.7° (c 0.9, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.36, 1.42 (2s, 6H), 3.61 (d, *J* = 10.3 Hz, 1H), 3.66 (d, *J* = 10.3 Hz, 1H), 4.42 (br s, 1H), 4.47 (d, *J* = 2.4 Hz, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.62 (s, 2H), 4.68 (d, *J* = 12.1 Hz, 1H), 5.90 (d, *J* = 2.3, 5.8 Hz, 1H), 6.05 (br d, *J* = 5.8 Hz, 1H), 7.28-7.35 (m, 10H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 27.7, 28.1, 71.5, 73.5, 84.4, 87.4, 94.7, 112.2, 127.4, 127.5, 128.2, 128.3, 132.0, 137.6, 138.1, 138.2.

CHN Anal: Calcd for $C_{23}H_{26}O_4$: C, 75.38, H, 7.15. Found: C, 75.14, H, 7.02.

(1*S*, 2*R*, 3*R*,4*R*,5*S*)-1-benzyloxylmethyl-4-*O*-benzyl-1,5-*O*-isopropylidene-1,2,3,4,5-cyclopentanpentol (17):



A solution of olefin **10** (0.75 g, 2.05 mmol) in acetone-water (20 ml, 1:1) was treated with osmium tetroxide (10 mg, 0.041 mmol, 2 mol%), NMO solution (0.42 ml, 2.05 mmol) and stirred for 12 h at room temperature. Then Na_2SO_3 was added and the reaction mixture was stirred for 1 h at rt. The reaction mixture was partitioned between ethyl acetate and water and the organic layer separated, dried (Na_2SO_4), concentrated and purified by column chromatography (ethyl acetate/light petroleum, 3:7) to obtain the diol **17** (0.66 g, 80%) as a colourless liquid.

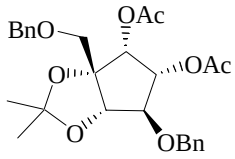
$[\alpha]_D^{25}$: +22.5° (c 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.38, 1.47 (2s, 6H), 3.02 (bs, 2H), 3.52 (d, *J* = 10.1 Hz, 1H), 3.59 (d, *J* = 10.1 Hz, 1H), 3.85 (d, *J* = 4.9 Hz, 1H), 3.92 (dd, *J* = 1.9, 4.9 Hz, 1H), 4.05 (t, *J* = 4.9 Hz, 1H), 4.4 (d, *J* = 1.9 Hz, 1H), 4.50-4.64 (m, 4H), 7.25-7.40 (m, 10H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 26.7, 27.1, 71.8, 72.8, 73.2, 73.6, 77.1, 85.0, 86.1, 87.5, 113.3, 127.6, 127.7, 128.3, 128.4, 137.6, 137.9.

CHN Anal: Calcd for $C_{23}H_{28}O_6$: C, 68.98, H, 7.05. Found: C, 69.15, H, 7.14.

(1*S*, 2*R*, 3*R*,4*R*,5*S*)-2,3-Di-*O*-acetyl-1-benzyloxylmethyl-4-*O*-benzyl-1,5-*O*-isopropylidene--1,2,3,4,5- cyclopentanpentol (18):



At rt, a suspension of compound **17** (20 mg, 0.05 mmol) in pyridine (1 ml) and DMAP (5 mg) was treated with acetic anhydride (0.12 ml, 0.125 mmol) and stirred for 4h. The reaction mixture was concentrated and the residue was purified over a silica gel column using 1:4 ethyl acetate and light petroleum as an eluent to furnish the diacetate **18** (21 mg, 89%) as a colorless oil.

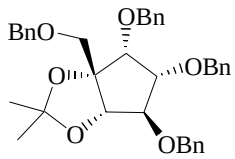
$[\alpha]_D^{25}$: +47.6° (c 1.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500MHz) : δ 1.35, 1.47 (2s, 6H), 2.04, 2.09 (2s, 6H), 3.60 (d, *J* = 10.6 Hz, 1H), 3.61 (d, *J* = 10.6 Hz, 1H), 4.12 (dd, *J* = 2.9, 7.3 Hz, 1H), 4.45 (d, *J* = 2.9 Hz, 1H), 4.58 (d, *J* = 12.1 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 5.21 (d, *J* = 5.2 Hz, 1H), 5.29 (dd, *J* = 5.2, 7.3 Hz, 1H), 7.25-7.34 (m, 10H).

^{13}C NMR ($CDCl_3$, 125MHz) : δ 20.7, 20.8, 27.1, 27.4, 72.0, 72.9, 73.1, 73.9, 75.6, 85.0, 85.1, 86.6, 114.1, 127.6, 127.7, 127.8, 128.4, 128.5, 137.6, 137.8, 169.3, 169.5.

CHN Anal: Calcd for $C_{26}H_{29}O_8$: C, 66.51, H, 6.23. Found: C, 66.36, H, 6.32.

(1*S*, 2*R*, 3*R*,4*R*,5*S*)- 1-benzyloxylmethyl-2,3,4-tri-*O*-benzyl-1,5-*O*-isopropylidene--1,2,3,4,5- cyclopentanpentol (19):



An ice-cooled solution of the diol **17** (0.6 g, 1.5 mmol) in dry DMF (3 ml) was treated with NaH (0.13 g, 60% dispersion in oil, 3.3 mmol) and stirred for 30 min. To this, benzyl bromide (0.39

ml, 3.3 mmol) was added dropwise at 0°C and the stirring continued for additional 6 h at room temperature. The reaction mixture was quenched with ice water, partitioned between water and ether. The combined organic layer was dried (Na_2SO_4), concentrated and the residue was purified over by column chromatography (ethyl acetate/light petroleum, 1:9) to give **19** (0.83 g, 95%) as a colorless oil.

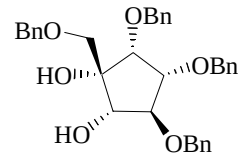
$[\alpha]_D^{25}$: +50.6° (c 0.9, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.41, 1.54 (2s, 6H), 3.44 (d, *J* = 10.3 Hz, 1H), 3.51 (d, *J* = 10.3 Hz, 1H), 3.68-3.78 (m, 2H), 4.22-4.90 (m, 10H), 7.24-7.35 (m, 20H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 27.0, 27.9, 71.8, 72.1, 73.0, 73.5, 73.9, 77.1, 82.6, 85.5, 87.2, 88.0, 114.1, 127.4 (10C), 128.0 (10C), 137.7 (2C), 138.4 (2C).

CHN Anal: Calcd for $C_{37}H_{40}O_6$: C, 76.53, H, 6.94. Found: C, 76.35, H, 7.06.

(1*S*, 2*R*, 3*R*,4*R*,5*S*)- 1-Benzyloxylmethyl-2,3,4-tri-*O*-benzyl-1,2,3,4,5- cyclopentanpentol (20):



A solution of compound **19** (0.8 g, 1.38 mmol) and 80% aqueous acetic acid (10 ml) was heated at 70°C for 4 h. Azeotripical removal of acetic acid from the reaction mixture using benzene as azeotrope and the purification of the crude product over a silica gel column using ethyl 2:3 acetate-light petroleum as an eluent afforded the diol **20** (0.6 g, 80%) as colorless oil.

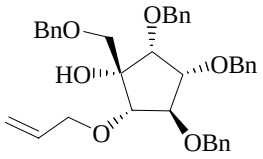
$[\alpha]_D^{25}$: -25.1° (c 1.2, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 2.85 (bd, *J* = 6.7 Hz, 1H), 3.40 (d, *J* = 11.9 Hz, 2H), 3.45 (s, 1H), 3.83 (d, *J* = 3.2 Hz, 1H), 3.89 (bs, 2H), 3.96 (d, *J* = 5.2 Hz, 1H), 4.46-4.74 (m, 8H), 7.24-7.33 (m, 20H).

^{13}C NMR ($CDCl_3$, 50MHz) : δ 70.7, 71.9, 72.4, 73.2, 73.7, 76.3, 77.0, 78.4, 81.2, 88.6, 127.7, 127.9, 128.0, 128.1, 128.5, 138.0, 138.3, 138.4.

CHN Anal: Calcd for $C_{34}H_{36}O_6$: C, 75.53, H, 6.71. Found: C, 75.80, H, 6.58.

(1*S*, 2*R*, 3*R*,4*R*,5*S*)- 1-Benzyloxylmethyl-5-*O*-allyl-2,3,4-tri-*O*-benzyl-1,2,3,4,5-cyclopentanpentol (21):



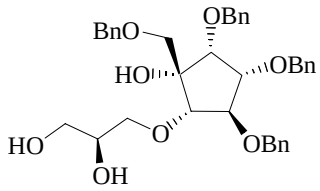
To an ice cooled solution of diol **20** (0.2 g, 0.37 mmol) in THF (2 ml) was added NaH (18 mg, 60% dispersion in oil, 0.44 mmol) and allyl bromide (0.04 ml, 0.44 mmol) and stirred for 2 h at room temperature. The reaction mixture was then quenched with ice water and partitioned between water and ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and the residue was purified by column chromatography (ethyl acetate/light petroleum,1:3) to furnish **21** (0.16 g, 76%) as colorless oil.

$[\alpha]_D^{25}$: + 32.5° (c 1.2, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 3.19 (s, 1H), 3.39 (s, 2H), 3.65 (d, *J* = 5.6 Hz, 1H), 3.76 (t, *J* = 5.3 Hz, 1H), 3.85 (d, *J* = 5.3 Hz, 1H), 3.97-4.15 (m, 3H), 4.41-4.72 (m, 8H), 5.10-5.26 (m, 2H), 5.85 (m, 1H), 7.10-7.35 (m, 20H).

CHN Anal: Calcd for $C_{37}H_{40}O_6$: C, 76.53, H, 6.94. Found: C, 76.82, H, 7.14.

Sharpless Asymmetric Dihydroxlation of Allyl Ether 21:



A mixture of compound **21** (0.15 g, 0.26 mmol) and Admix-β (0.35 g) in *t*-Butanol (1ml)-water (1 ml) were stirred for 18 h at 0°C. Then Na_2SO_3 was added to the reaction mixture, stirred for 1 h, concentrated and extracted with ethyl acetate. Combined organic layer was dried (Na_2SO_4), concentrated and the residue was purified on silica gel using ethyl acetate-light petroleum as eluent (2:3) to furnish the triol **22** (0.12 g, 78%) as colorless oil.

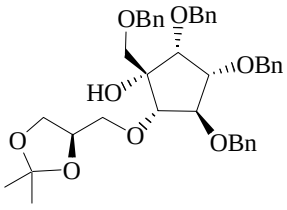
$[\alpha]_D^{25}$: +12.4° (c 1.2, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 3.42 (s, 2H), 3.54-3.86 (m, 8H), 4.11 (t, *J* = 5.8 Hz, 1H), 4.48-4.73 (m, 8H), 7.24-7.40 (m, 20H).

^{13}C NMR ($CDCl_3$, 75MHz) : δ 63.9, 70.8, 70.9, 71.8, 72.6, 73.1, 73.5, 73.7, 77.4, 77.9, 80.7, 83.7, 87.5, 127.9, 128.2, 128.5, 138.0, 138.1, 138.3.

CHN Anal: Calcd for $C_{37}H_{42}O_8$: C, 72.29, H, 6.89. Found: C, 72.13, H, 6.96.

Selectuve 2°-OH Alkylation of Diol 20:



To an ice-cooled solution of diol **20** (0.2 g, 0.37 mmol) in dry THF (2 ml) was added 1.6M solution of n-BuLi (0.37 ml, 0.55 mmol) and stirred for 20 min at same temperature. A solution

of R-1.2-*O*-isopropyledene-*O*-triflate (**24**) (0.13 g, 0.55 mmol) in THF (1 ml) was added dropwise and stirred for 6 h at 0°C, then quenched with aqueous NH_4Cl and partitioned between water and ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and the residue was purified on silica gel using ethyl acetate and light petroleum as eluent (1:4) to furnish **25** (0.14 g, 63%) as colorless oil.

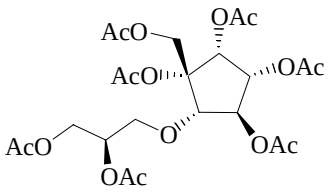
$[\alpha]_D^{25}$: +25.2° (c 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200MHz) : δ 1.32 (s, 3H), 1.36 (s, 3H), 3.24 (bs, 1H), 3.40 (m, 2H), 3.57-3.70 (m, 3H), 3.76-3.85 (m, 2H), 3.90-4.0 (m, 2H), 4.13 (m, 1H), 4.21 (m, 1H), 4.45-4.72 (m, 8H), 7.21-7.35 (m, 20H).

^{13}C NMR ($CDCl_3$, 75MHz) : δ 25.5, 26.8, 66.9, 70.3, 71.7, 72.1, 72.4, 73.4, 73.5, 74.7, 77.2, 77.8, 80.6, 83.8, 87.6, 109.3, 127.6, 127.8, 128.1, 128.3, 137.8, 137.9, 138.1, 138.4.

CHN Anal: Calcd for $C_{40}H_{46}O_6$: C, 73.37, H, 7.08. Found: C, 73.53, H, 6.96.

5-*Epi*-calditol-hepta-acetate:



To a solution of compound **25** (0.1 g, 0.16 mmol) in MeOH-AcOH (1:0.01)(2 ml) was added catalytic Pd/C (5 mg) and stirred for 6 h under H_2 atmosphere. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to afford the crude heptol (**25a**, 31 mg), which was used as such in the next reaction without further purification.

To an ice-cooled solution of compound **25a** (31 mg, 0.12 mmol) in pyridine (0.5 ml) was added acetic anhydride (0.12 ml, 1.2 mmol), catalytic amount of DMAP and stirred for 12 h at room

temperature. The reaction mixture was then concentrated and purified on silica gel using ethyl acetate and light petroleum as eluent (2:3) to furnish **23** (53 mg, 61% for two steps).

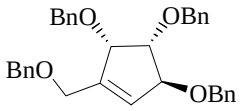
$[\alpha]_D^{25}$: +16.2° (c 0.6, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500MHz) : δ 2.06-2.12 (7s, 21H), 3.52 (dd, *J* = 4.3, 10.1 Hz, 1H), 3.78 (dd, *J* = 0.8, 2.4 Hz, 1H), 3.88 (dd, *J* = 4.8, 10.1 Hz, 1H), 4.13 (dd, *J* = 6.9, 12.0 Hz, 1H), 4.17 (d, *J* = 12.8 Hz, 1H), 4.29 (dd, *J* = 3.9, 12.0 Hz, 1H), 4.87 (d, *J* = 12.8 Hz, 1H), 5.10-5.18 (m, 2H), 5.20 (t, *J* = 5.7 Hz, 1H), 5.32 (dd, *J* = 2.8, 6.3 Hz, 1H), 5.61 (dd, *J* = 0.8, 5.2 Hz, 1H)

^{13}C NMR ($CDCl_3$, 125MHz) : δ 20.4, 20.7, 20.8, 20.9, 21.2, 61.9, 62.5, 69.2, 70.1, 71.7, 73.3, 80.5, 82.8, 83.2, 169.4, 169.6, 170.0, 170.1, 170.5.

CHN Anal: Calcd for $C_{23}H_{32}O_{15}$: C, 50.36, H, 5.88. Found: C, 50.52, H, 5.72.

(2*R*, 3*R*, 4*R*)-1-benzyloxylmethyl-2,3,4-tri-*O*-benzyl-cyclopent-5-en-2,3,4-triol (26):



A mixture of diol **20** (0.2 g, 0.37 mmol) and thiocarbonyl diimidazole (80 mg, 0.44 mmol) in toluene (5 ml) was refluxed for 8h. Then the reaction mixture was concentrated and purified on silica gel using ethyl acetate-light petroleum (1:4) as eluent to afford the thiocarbonyl ester (**26**) in quantitative yield.

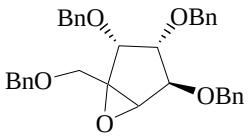
The compound **26** (0.21 g, 0.37 mmol) and triethylphosphite (5 ml) were refluxed at 155°C for 6h. The triehtylphosphite was removed by distillation and the residue was purified on silica gel using ethyl acetate-light petroleum (1:4) as eluent to afford the olefin **27** (0.13 g, 72%) as pale yellow coloured liquid.

$[\alpha]_D^{25}$: + 28.6° (c 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200MHz) : δ 3.98 (dd, *J* = 4.7, 5.8 Hz, 1H), 4.05 (d, *J* = 1.8 Hz, 2H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.49 (br.d, *J* = 1.6 Hz, 1H),4.52 (d, *J* = 12.0 Hz, 1H), 4.58-4.63 (m, 5H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.76 (m, 1H), 5.96 (br.d, *J* = 1.6 Hz, 1H), 7.24-7.35 (m, 20H).

CHN Anal: Calcd for $C_{34}H_{34}O_4$: C, 80.6, H, 6.76. Found: C, 80.24, H, 7.04.

(1*R*, 2*R*, 3*R*,4*R*,5*R*)-1,5-Anhydro-1-benzyloxylmethyl-2,3,4-tri-*O*-benzyl-1,2,3,4,5-cyclopentanpentol (28):



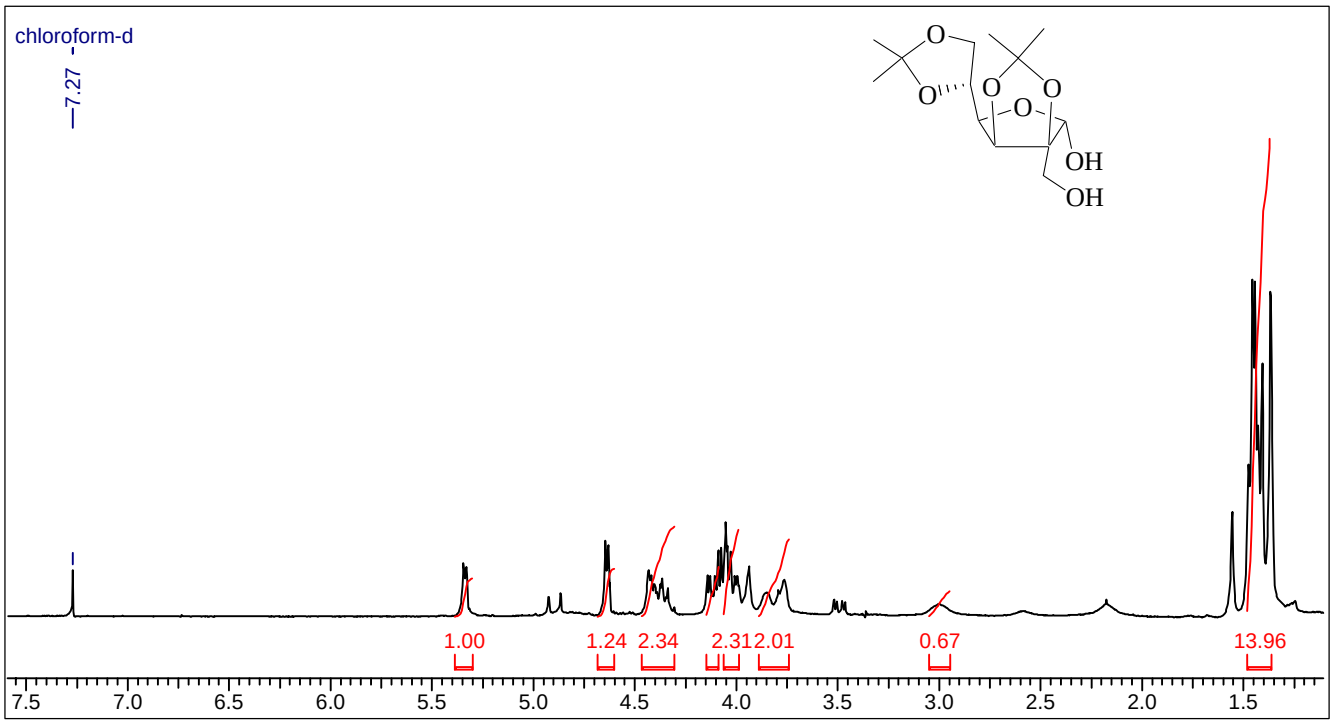
To a solution of olefin **27** (0.1 g, 0.2 mmol) in CH_2Cl_2 (2 ml) was added *meta*-chloroperbenzoic acid (72 mg, 0.41 mmol) and stirred for 6 h at room temperature. The reaction mixture was filtered through a pad of celite, the filtrate was concentrated and purified on silica gel using ethyl acetate-light petroleum as eluent to afford the epoxide **28** (70 mg, 68%).

$[\alpha]_D^{25}$: + 42.7° (c 0.9, $CHCl_3$).

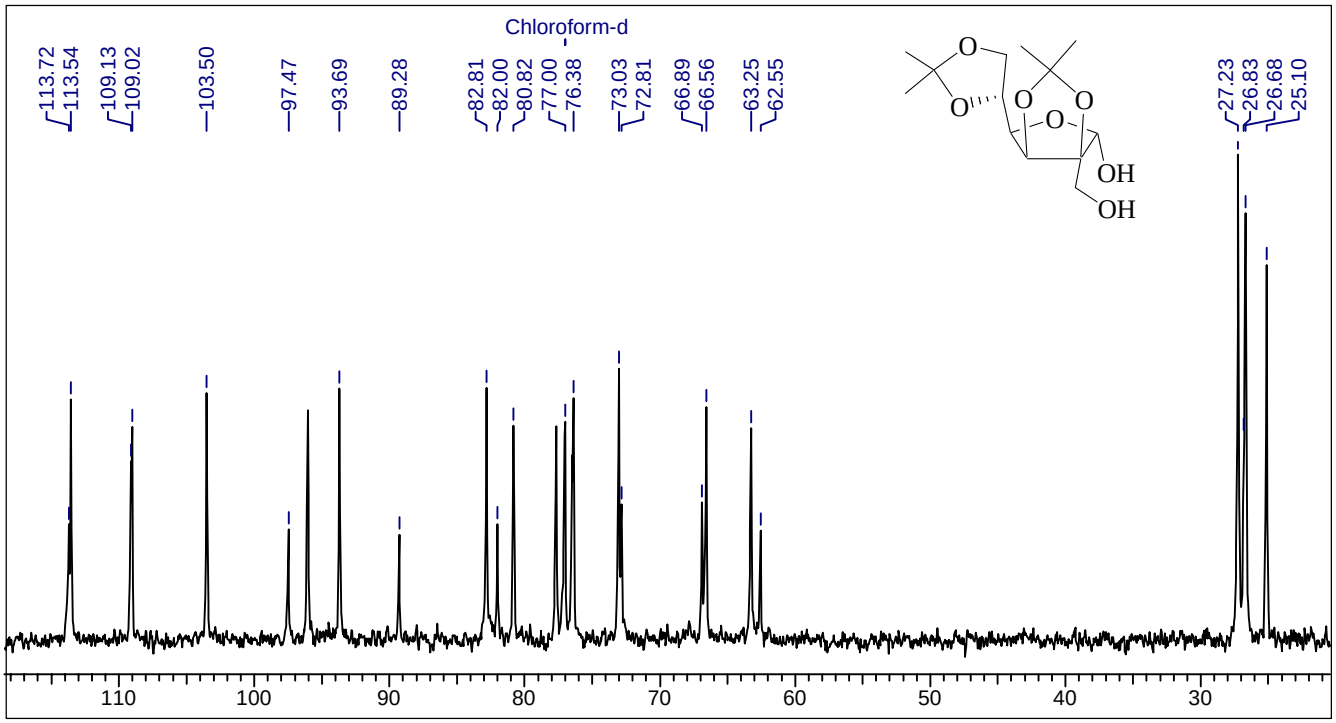
^{1}H NMR ($CDCl_3$, 200MHz) : δ 3.30 (d, *J* = 11.5 Hz, 1H), 3.35 (s, 1H), 3.86 (dd, *J* = 4.9, 6.5 Hz, 1H), 4.18-4.21 (m, 3H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.57-4.62 (m, 4H), 4.69 (s, 2H), 4.77 (d, *J* = 11.2 Hz, 1H), 7.25-7.36 (m, 20H).

^{13}C NMR ($CDCl_3$, 125MHz) : δ 57.8, 63.9, 67.2, 72.2, 72.7, 73.3, 74.5, 74.6, 82.2, 82.8, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 138.0, 138.3, 138.4 (2C).

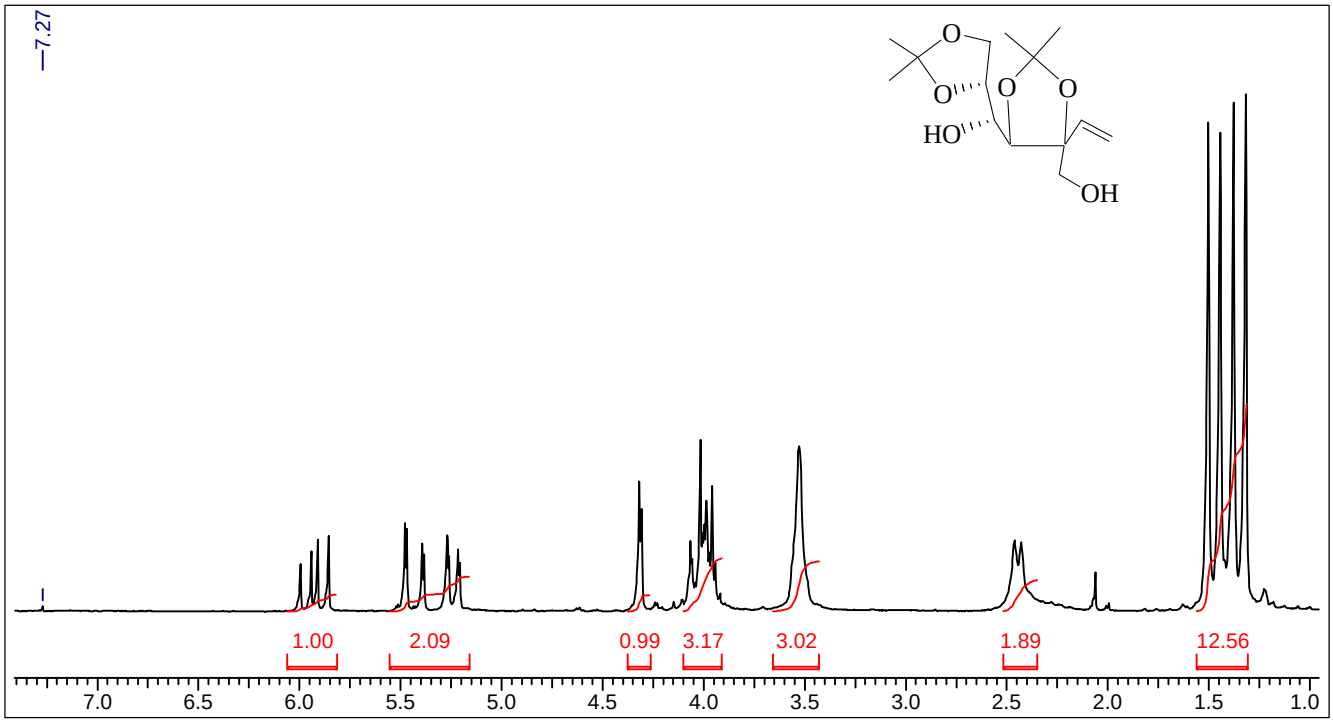
CHN Anal: Calcd for $C_{34}H_{34}O_5$: C, 78.14, H, 6.56. Found: C, 77.86, H, 6.33.



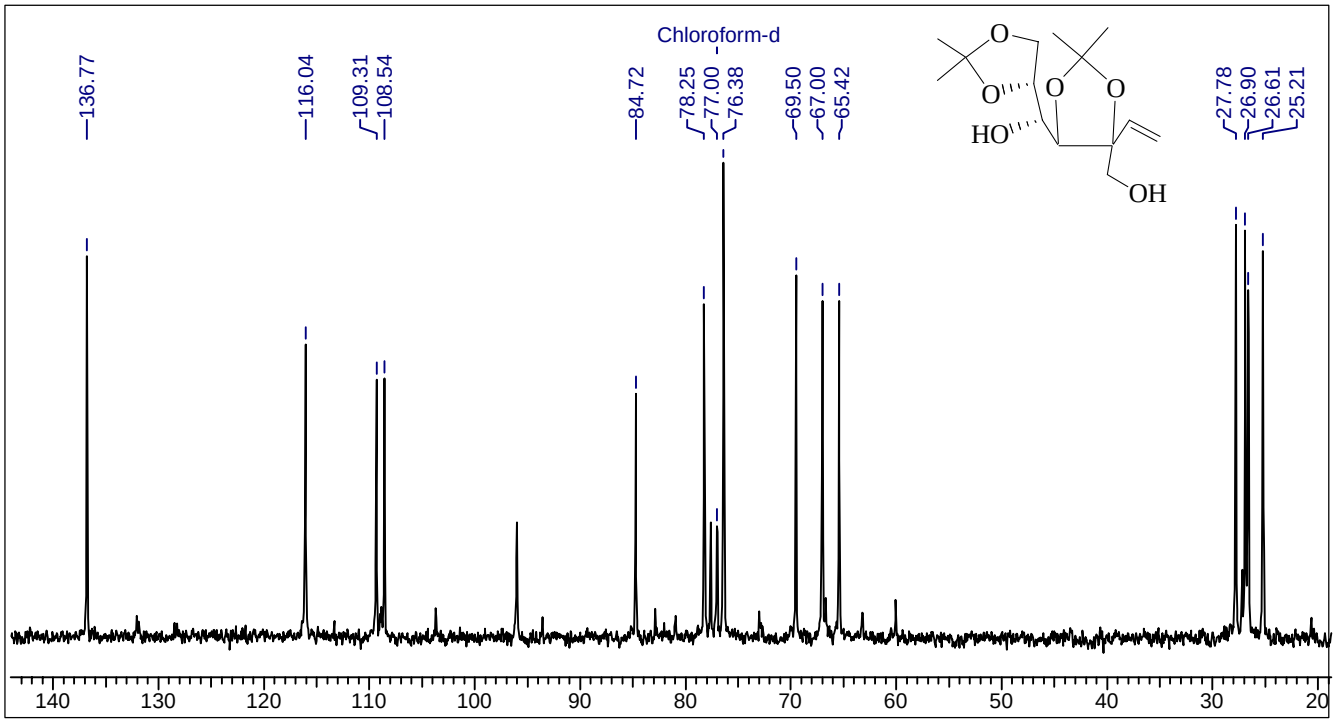
^{1}H NMR Spectrum of compound 12 in $CDCl_3$



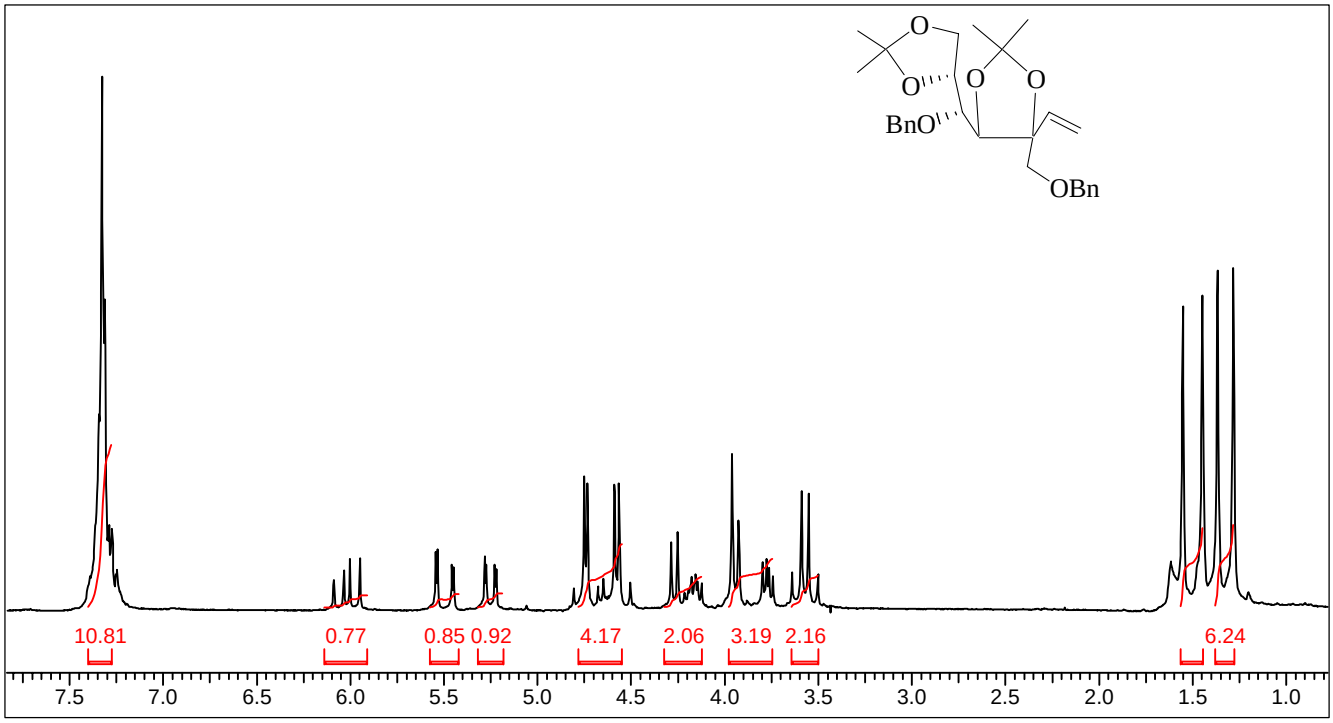
^{13}C NMR Spectrum of compound 12 in $CDCl_3$



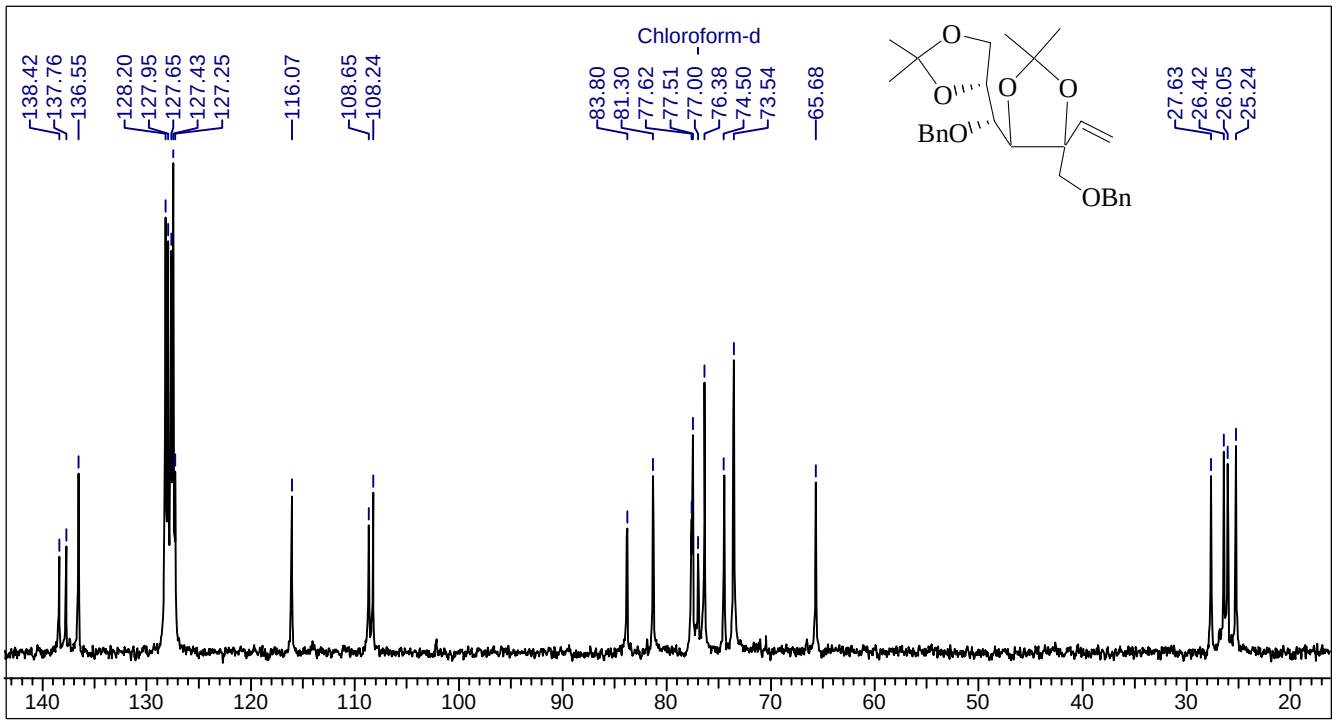
^{1}H NMR Spectrum of compound 13 in $CDCl_3$



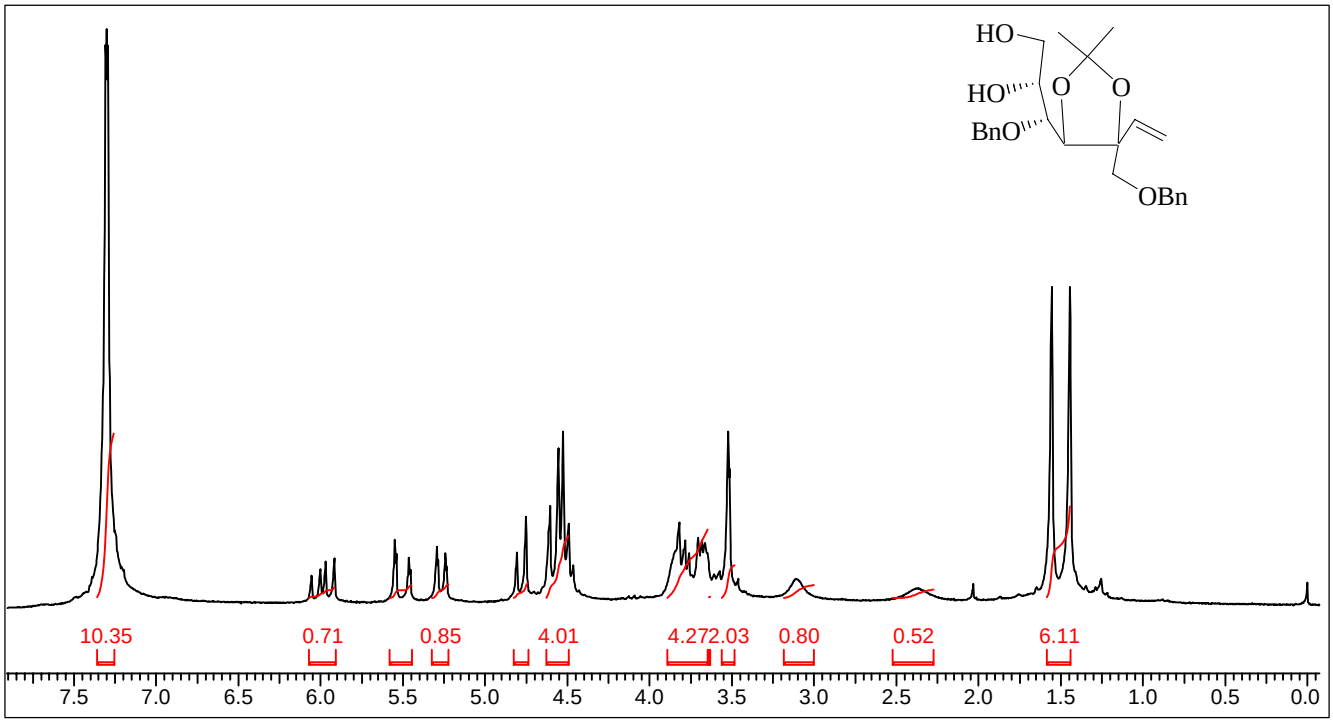
^{13}C NMR Spectrum of compound 13 in $CDCl_3$



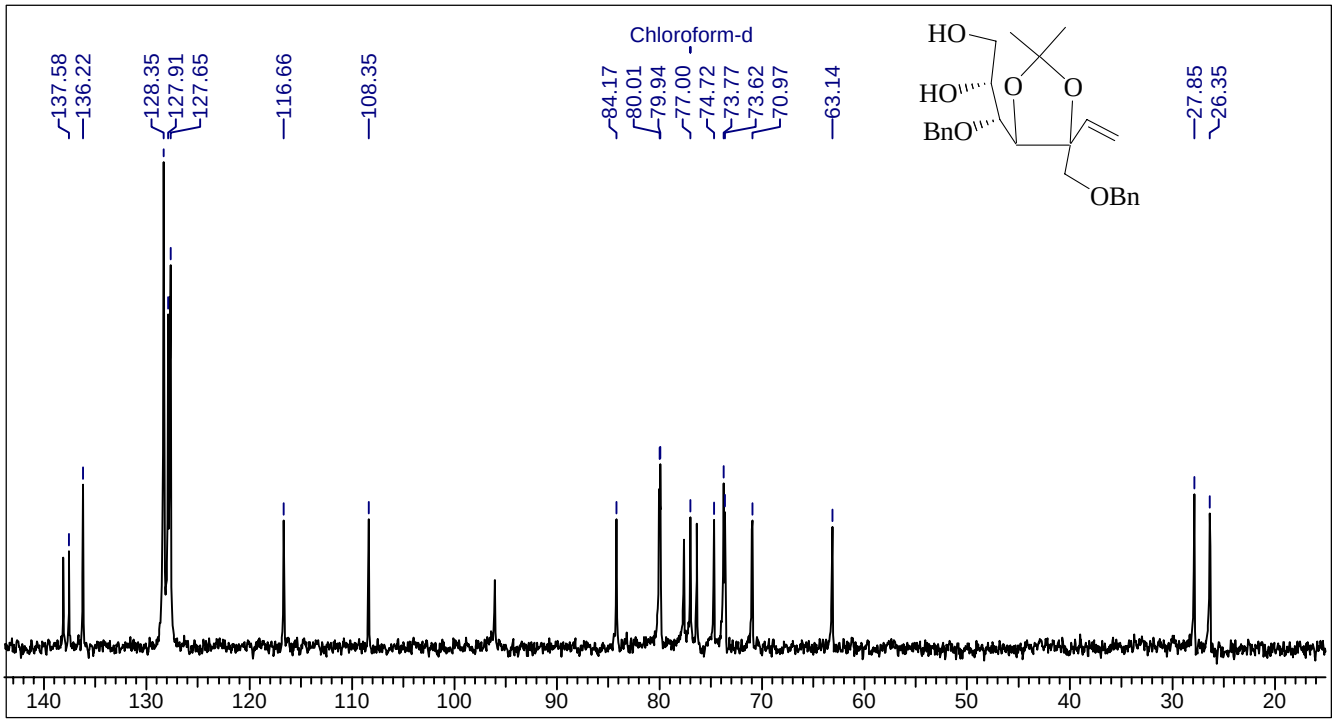
^{1}H NMR Spectrum of compound 14 in $CDCl_3$



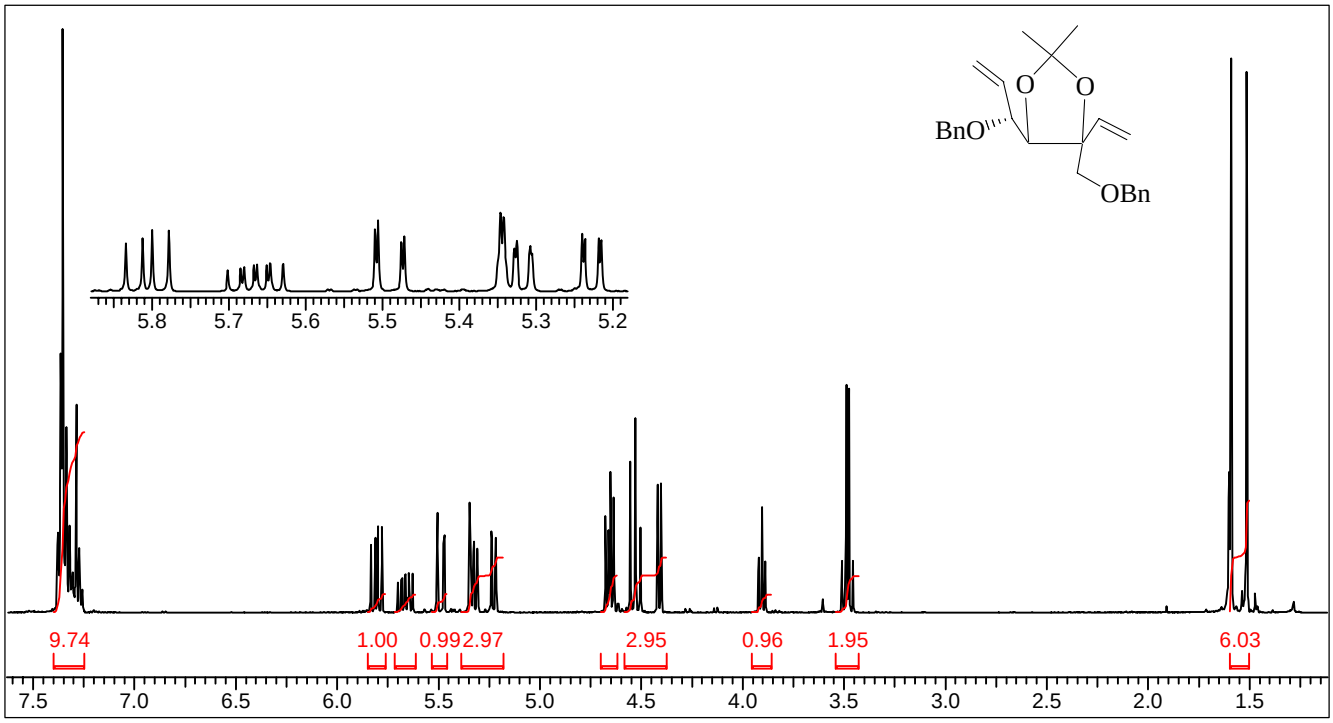
^{13}C NMR Spectrum of compound 14 in $CDCl_3$



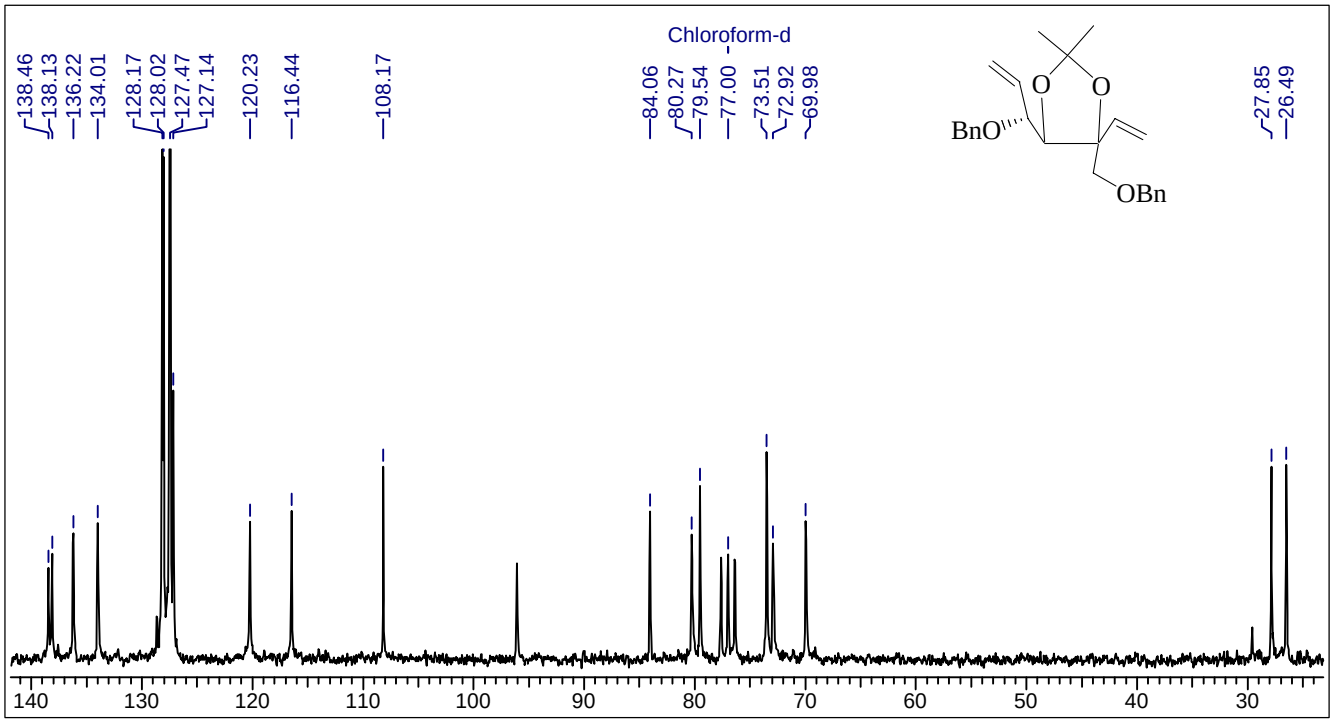
^{1}H NMR Spectrum of compound 15 in $CDCl_3$



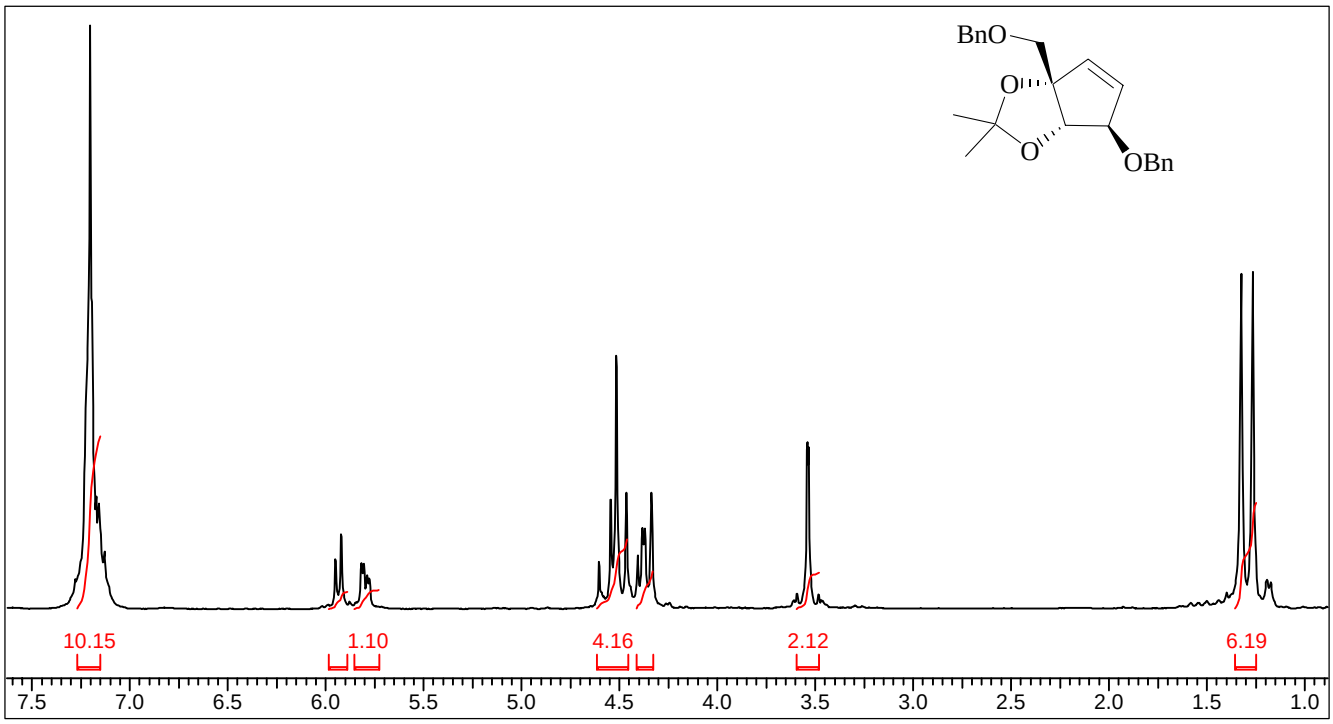
^{13}C NMR Spectrum of compound 15 in $CDCl_3$



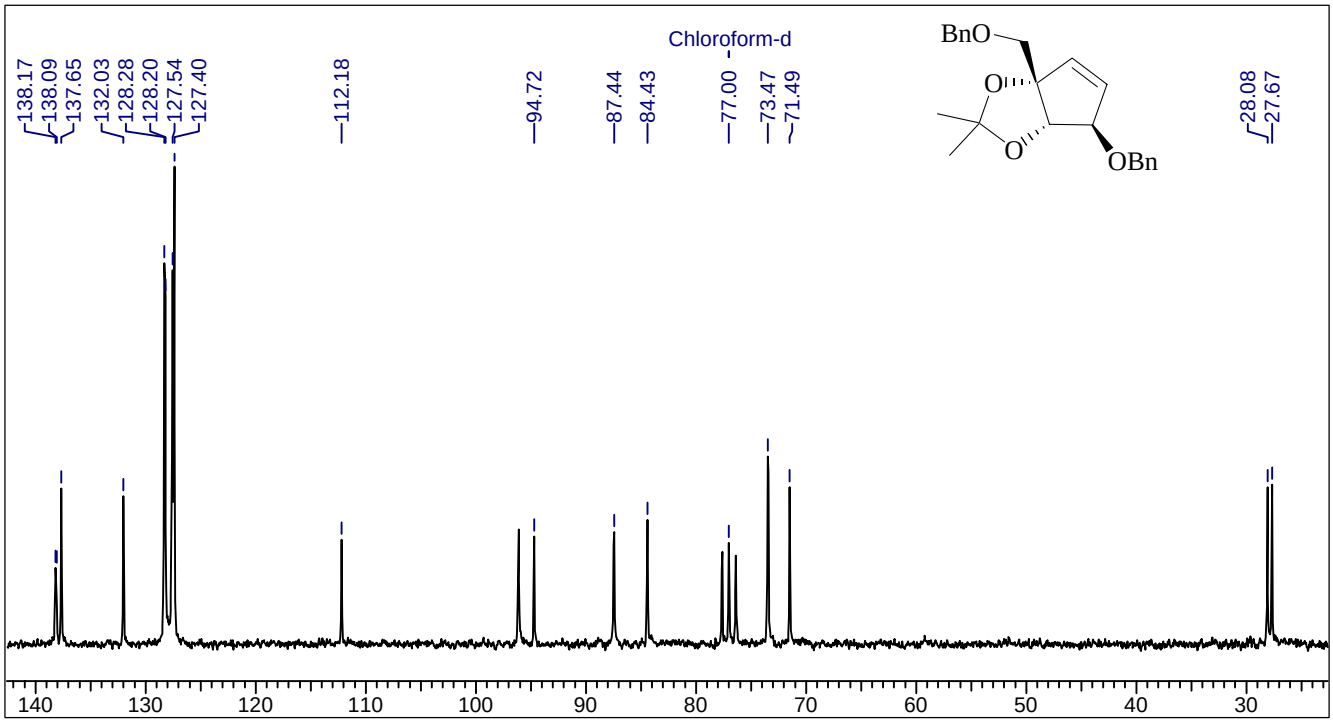
^{1}H NMR Spectrum of compound 16 in $CDCl_3$



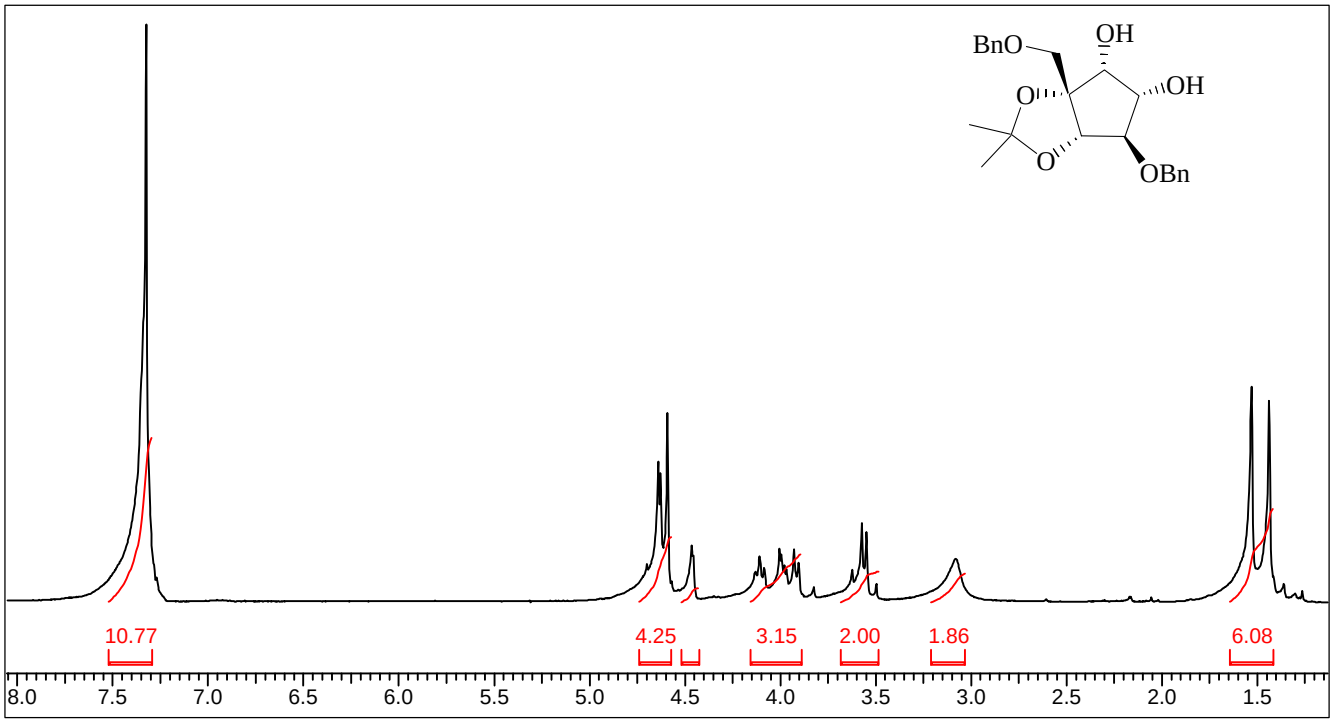
^{13}C NMR Spectrum of compound 16 in $CDCl_3$



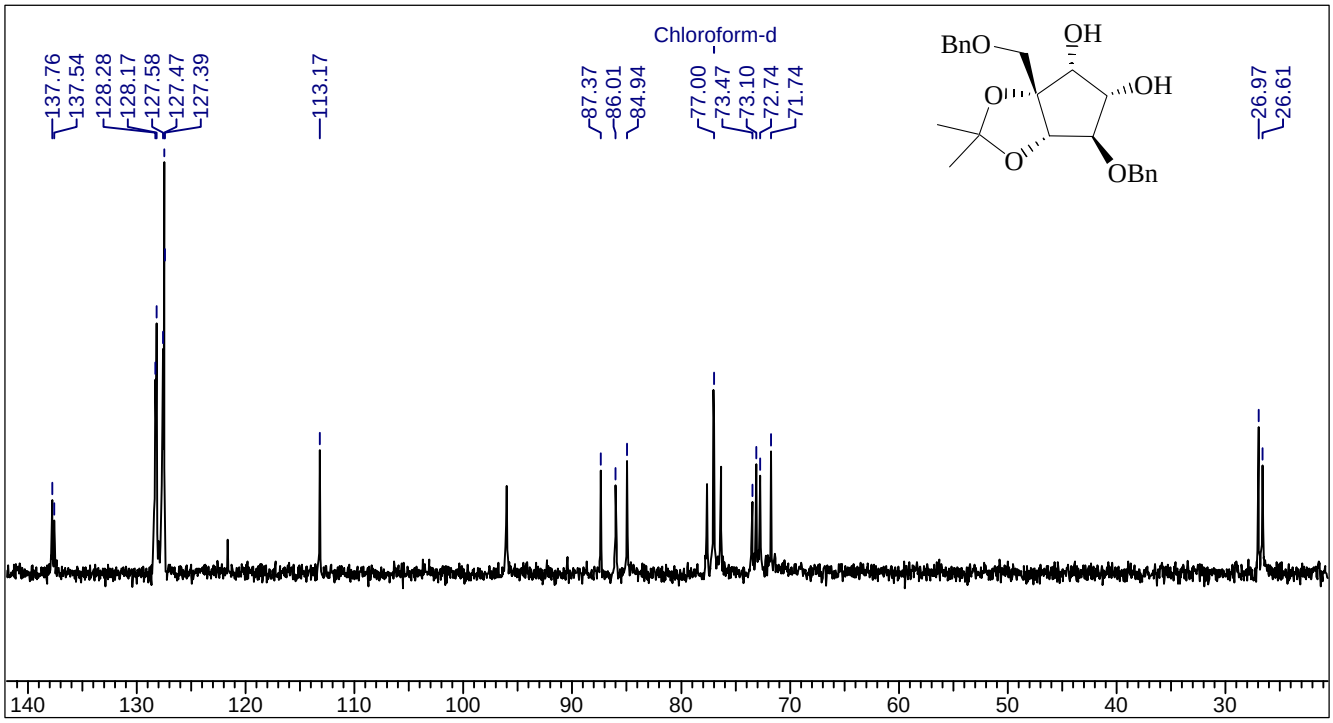
^{1}H NMR Spectrum of compound 10 in $CDCl_3$



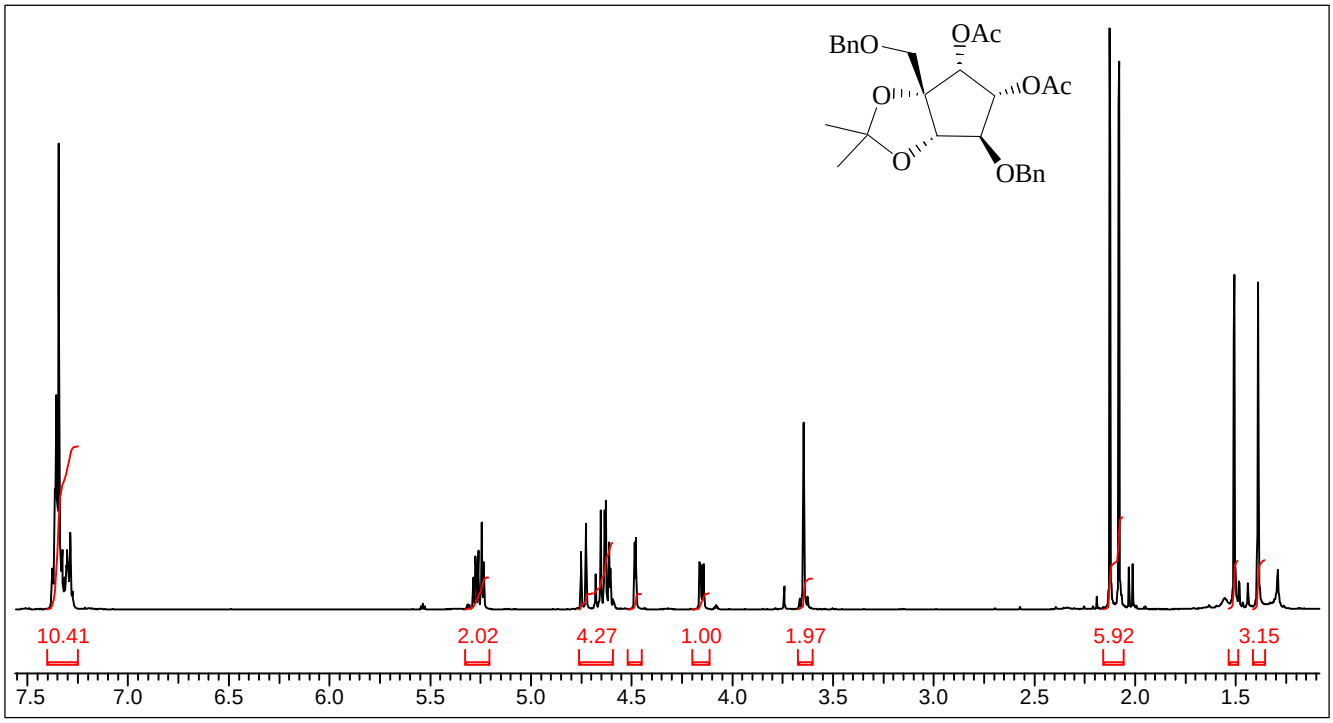
^{13}C NMR Spectrum of compound 10 in $CDCl_3$



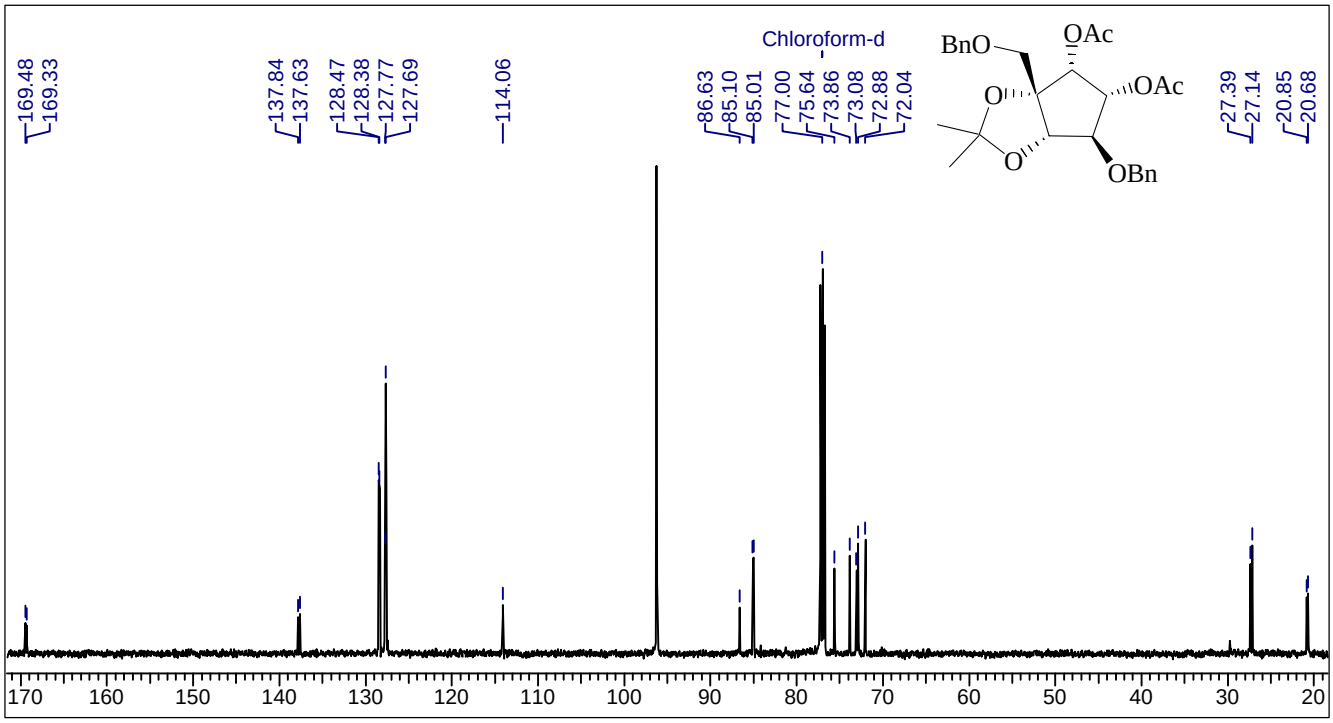
^{1}H NMR Spectrum of compound 17 in $CDCl_3$



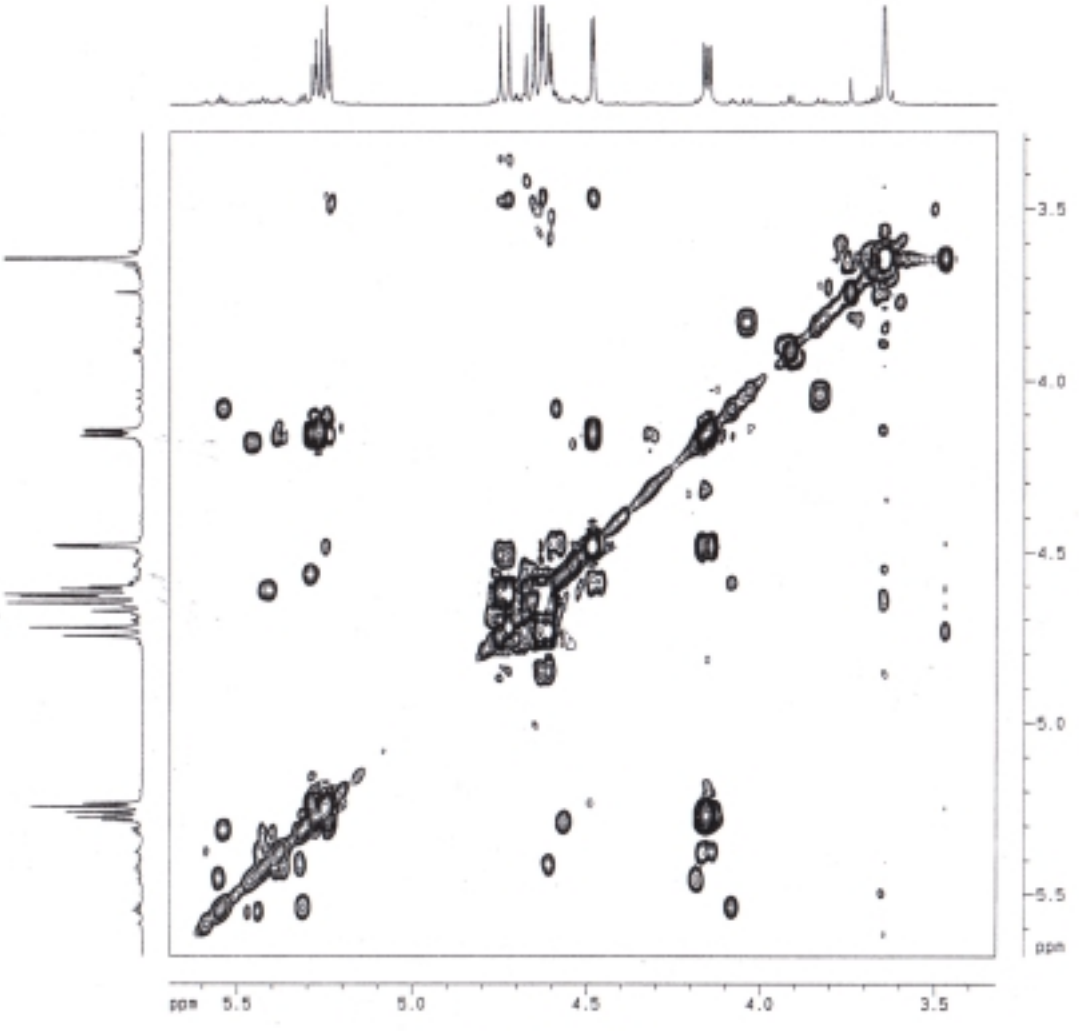
^{13}C NMR Spectrum of compound 17 in $CDCl_3$



^{1}H NMR Spectrum of compound 18 in $CDCl_3$

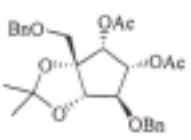


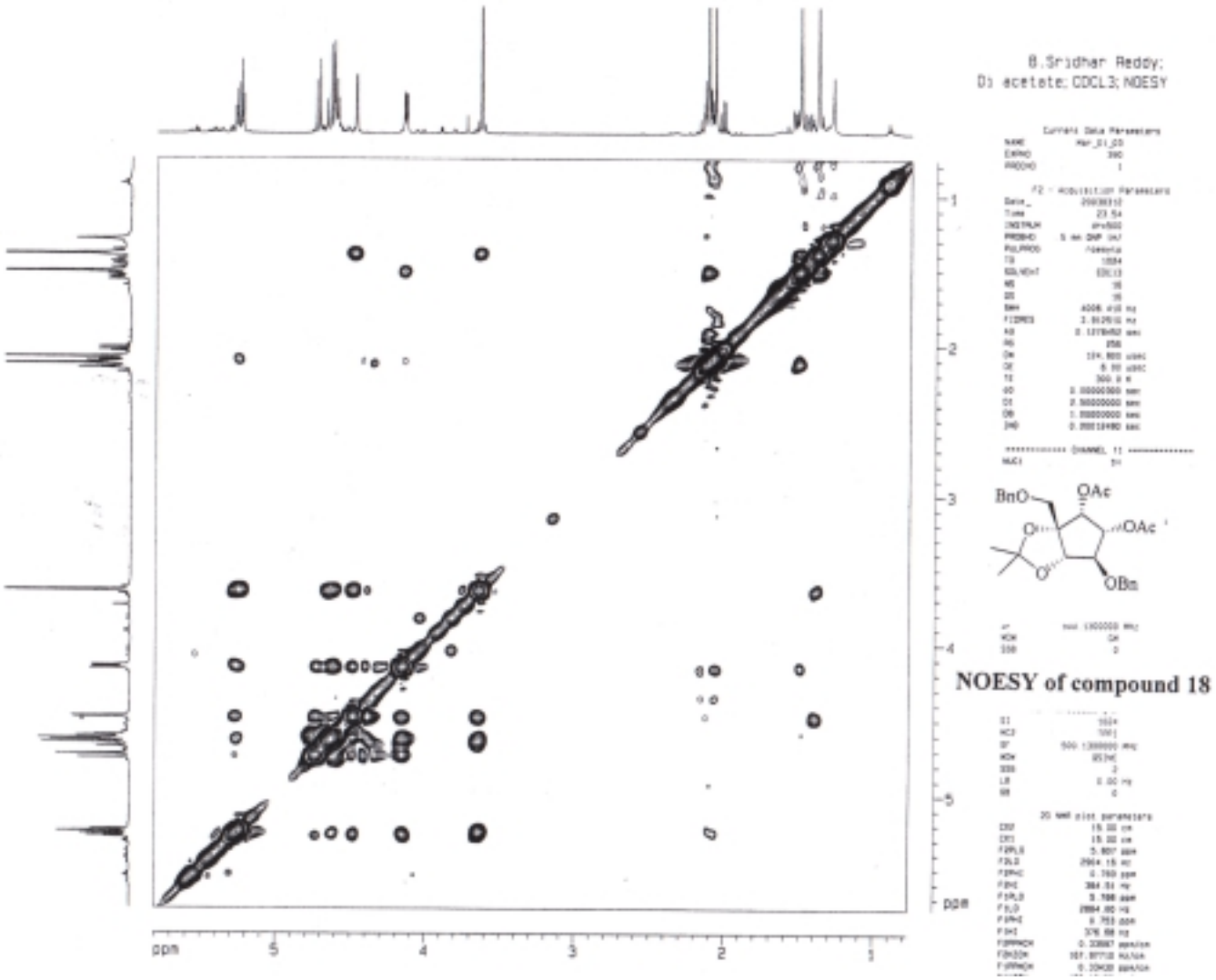
^{13}C NMR Spectrum of compound 18 in $CDCl_3$



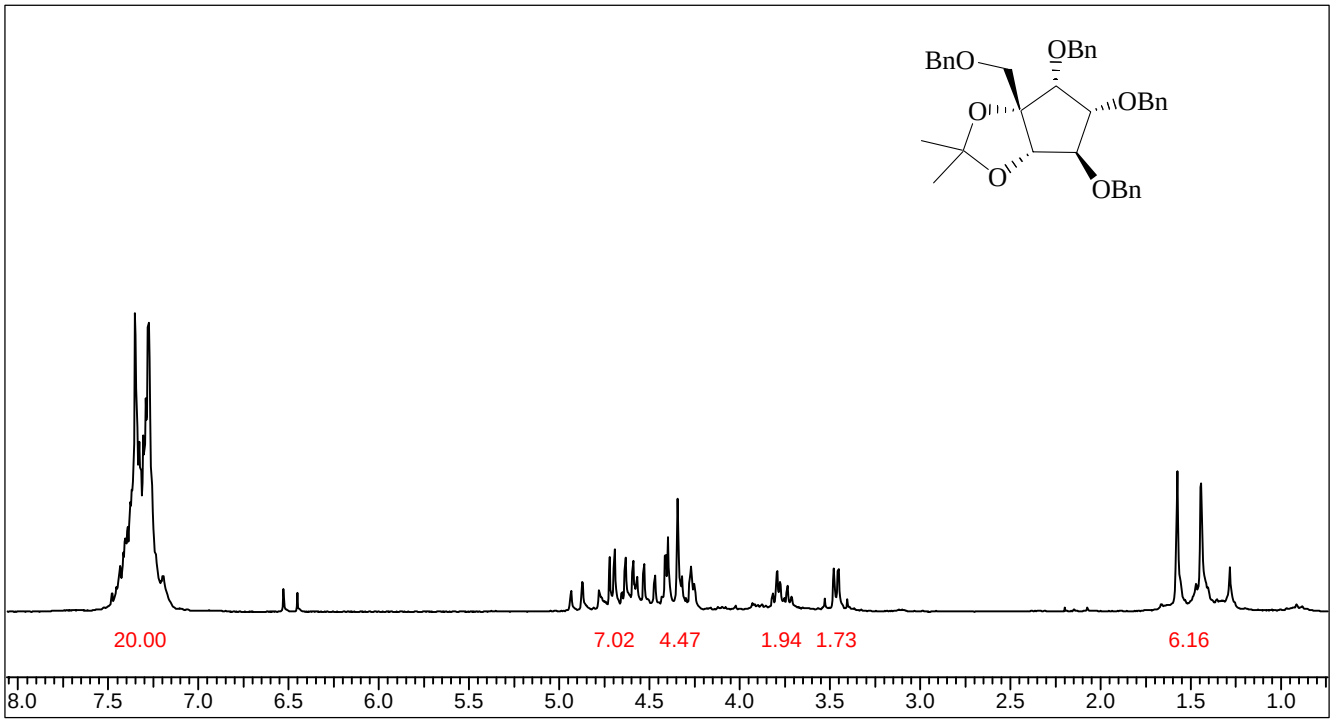
COSY of compound 18

B.Sridhar Reddy;
D1 acetate; CDCL3; Cosy45.

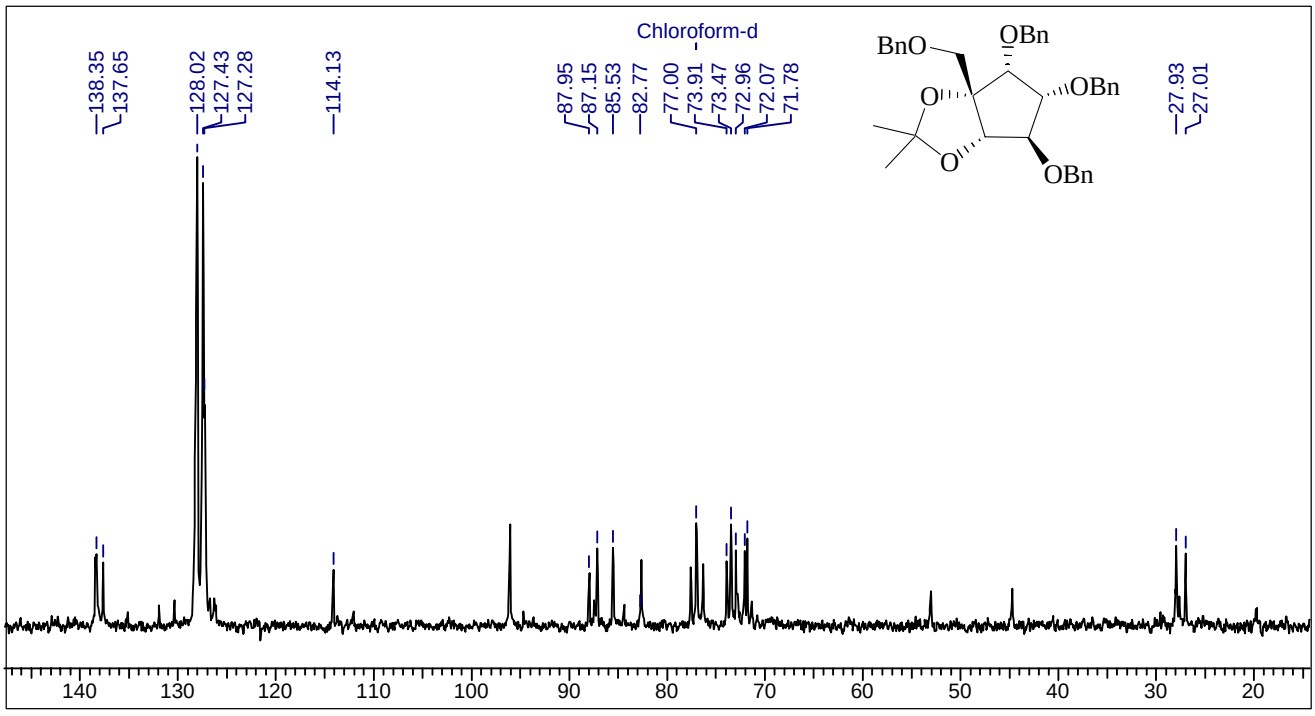




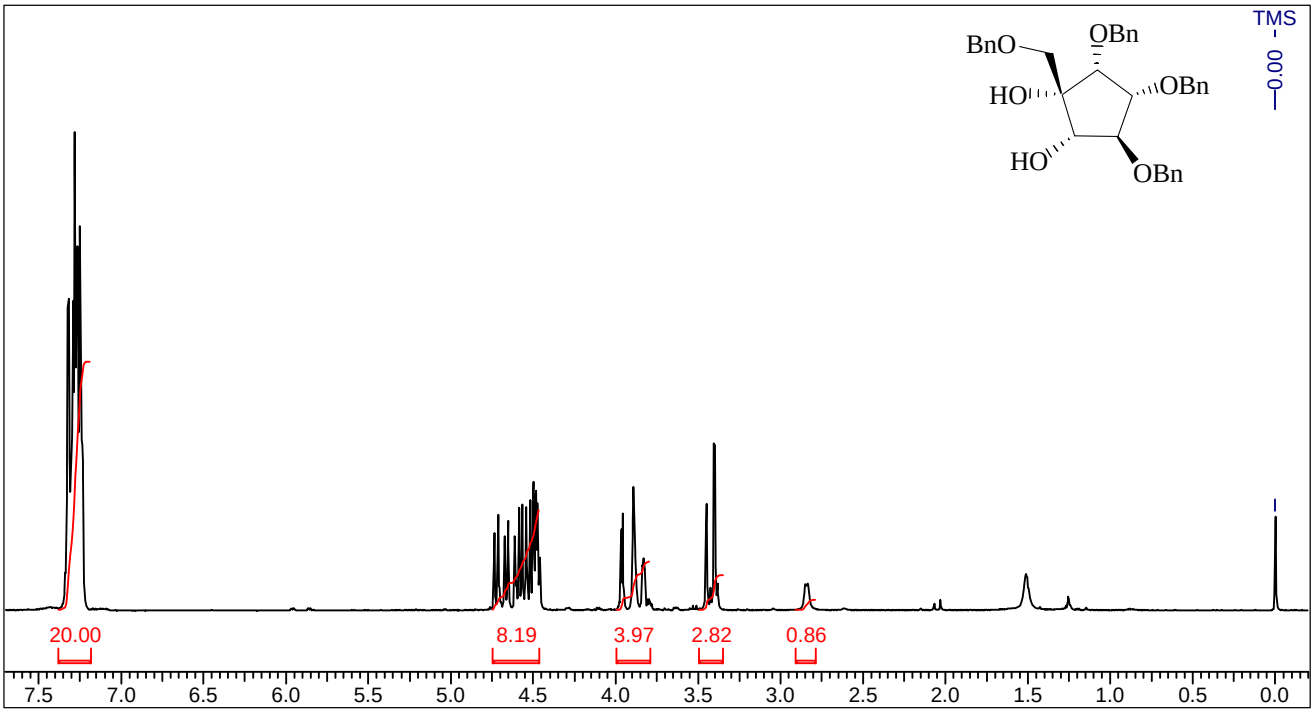
NOESY of compound 18



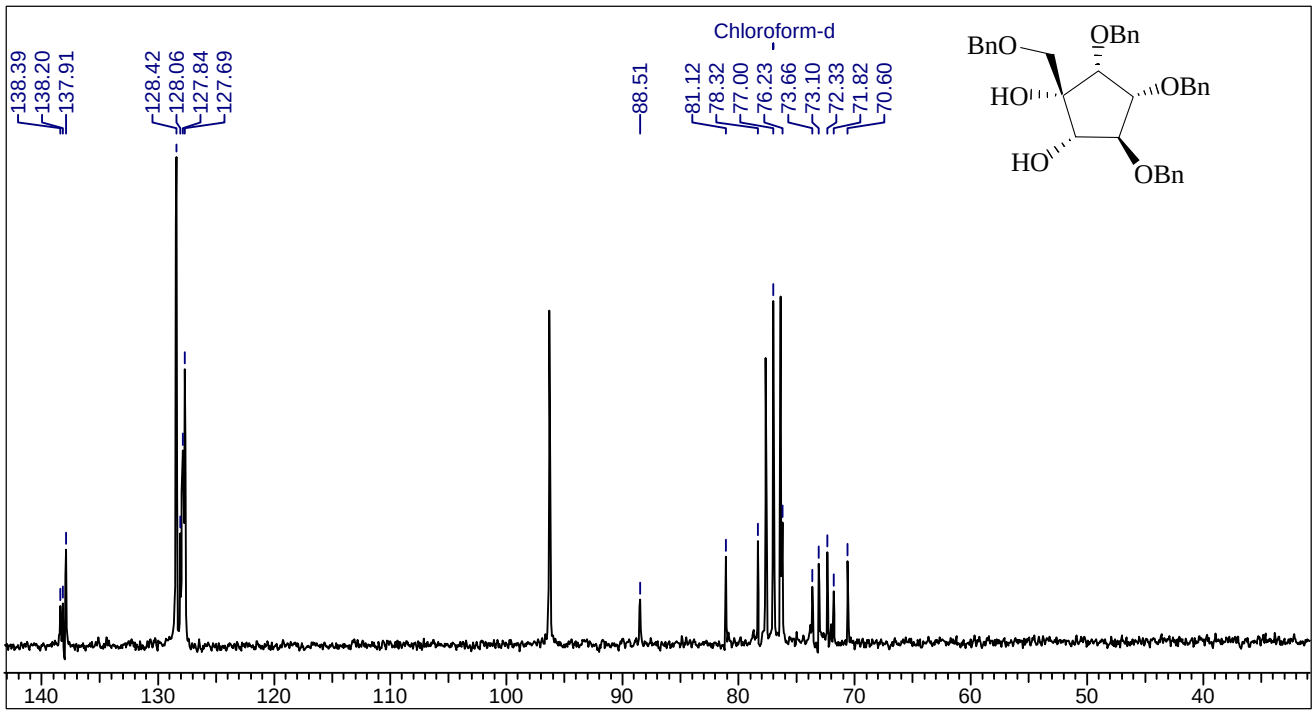
^{1}H NMR Spectrum of compound 19 in $CDCl_3$



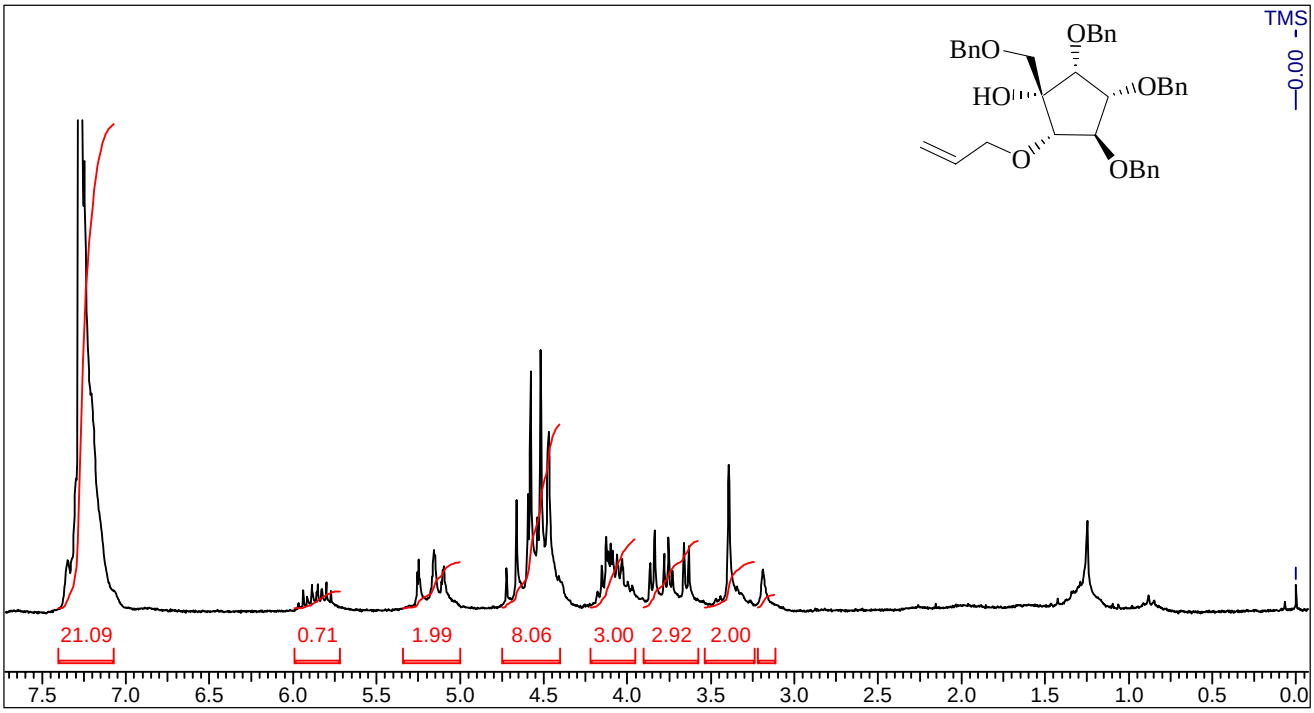
^{13}C NMR Spectrum of compound 19 in $CDCl_3$



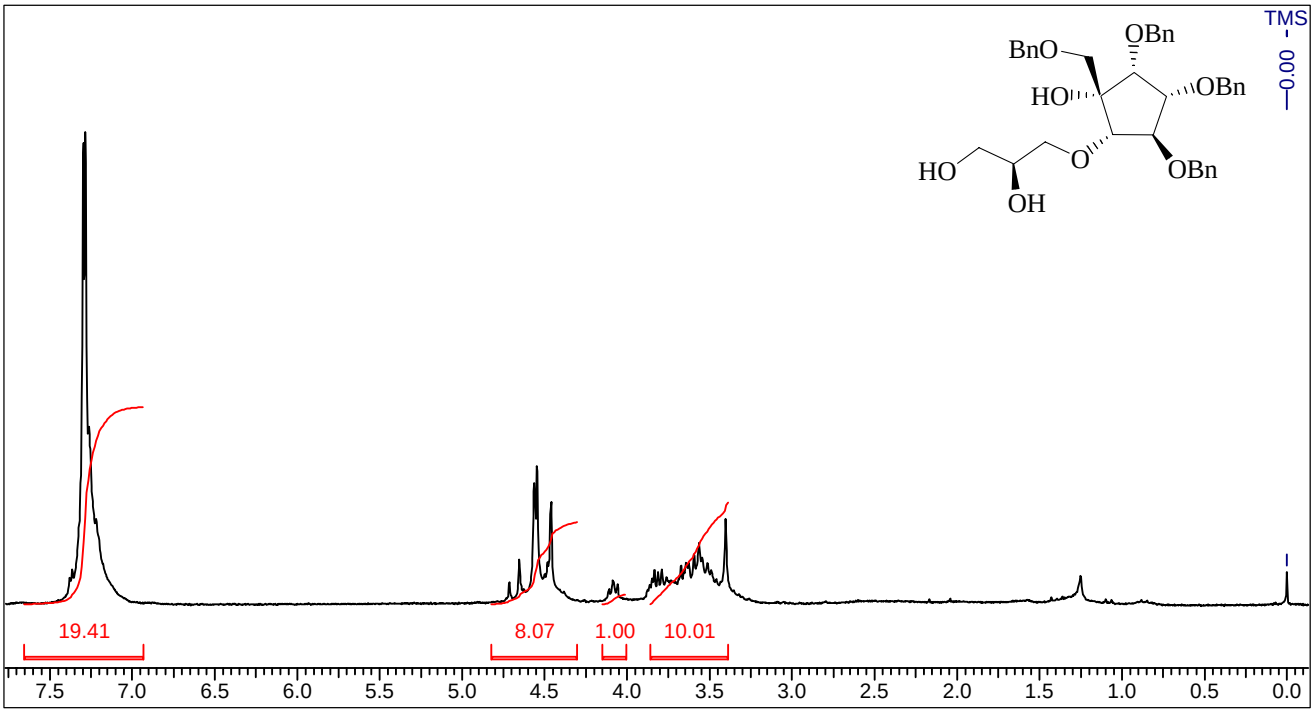
^{1}H NMR Spectrum of compound 20 in $CDCl_3$



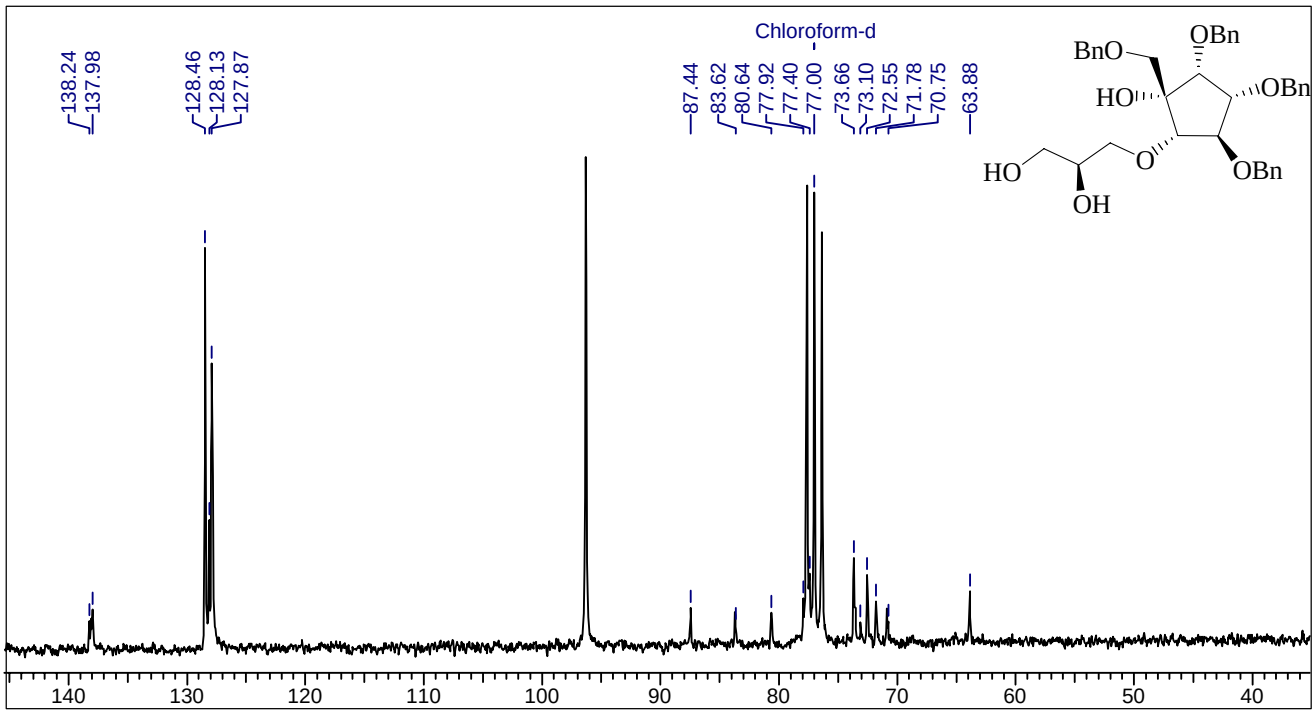
^{13}C NMR Spectrum of compound 20 in $CDCl_3$



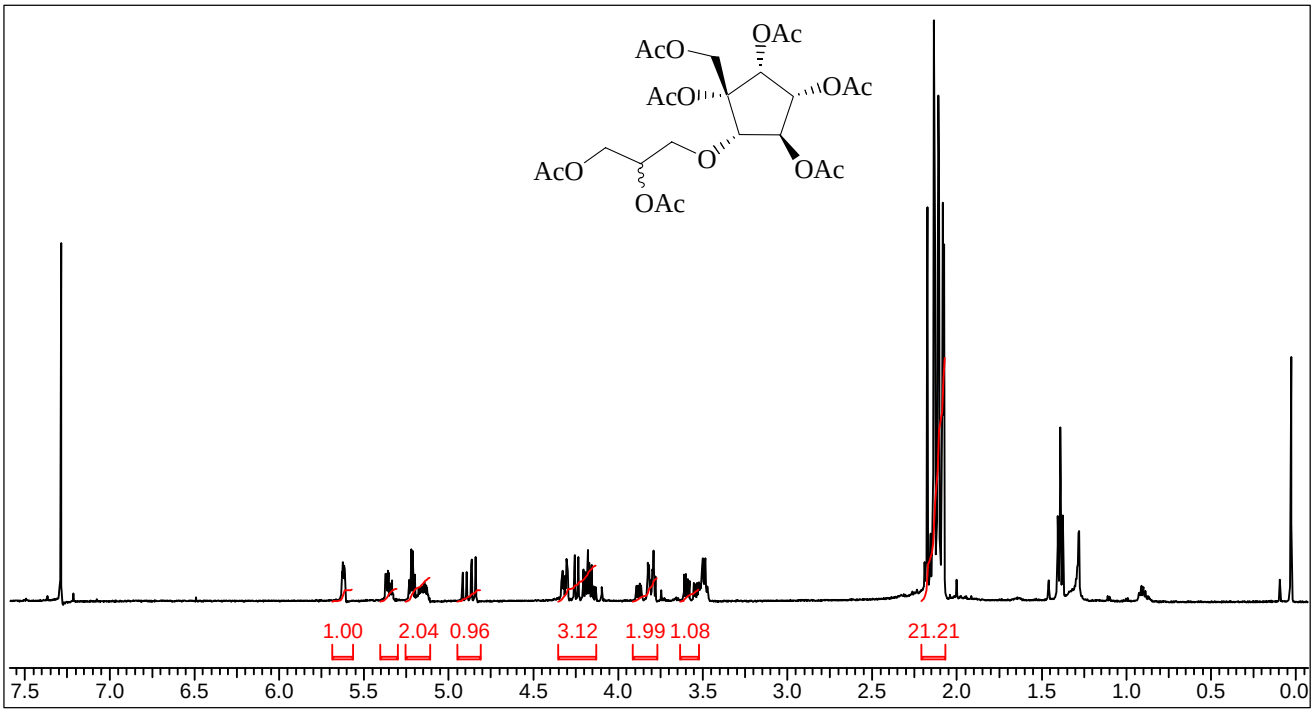
^{1}H NMR Spectrum of compound 21 in $CDCl_3$



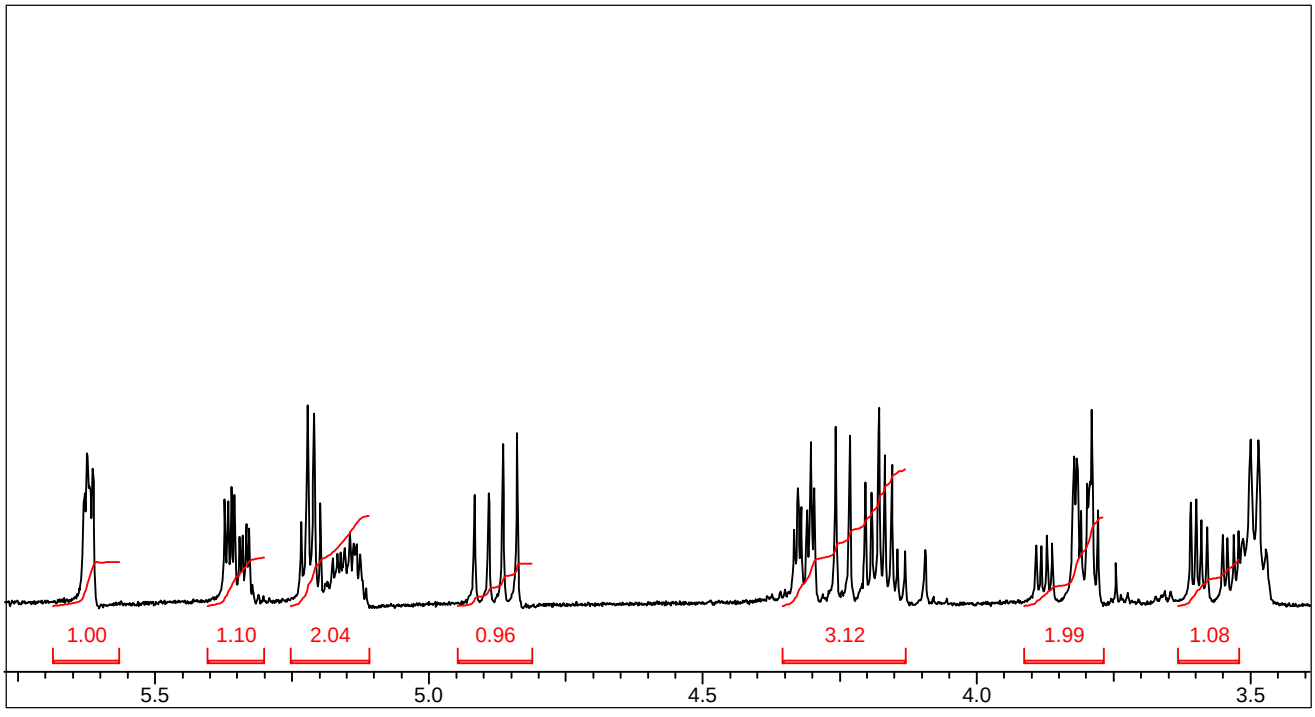
^{1}H NMR Spectrum of compound 22 in $CDCl_3$



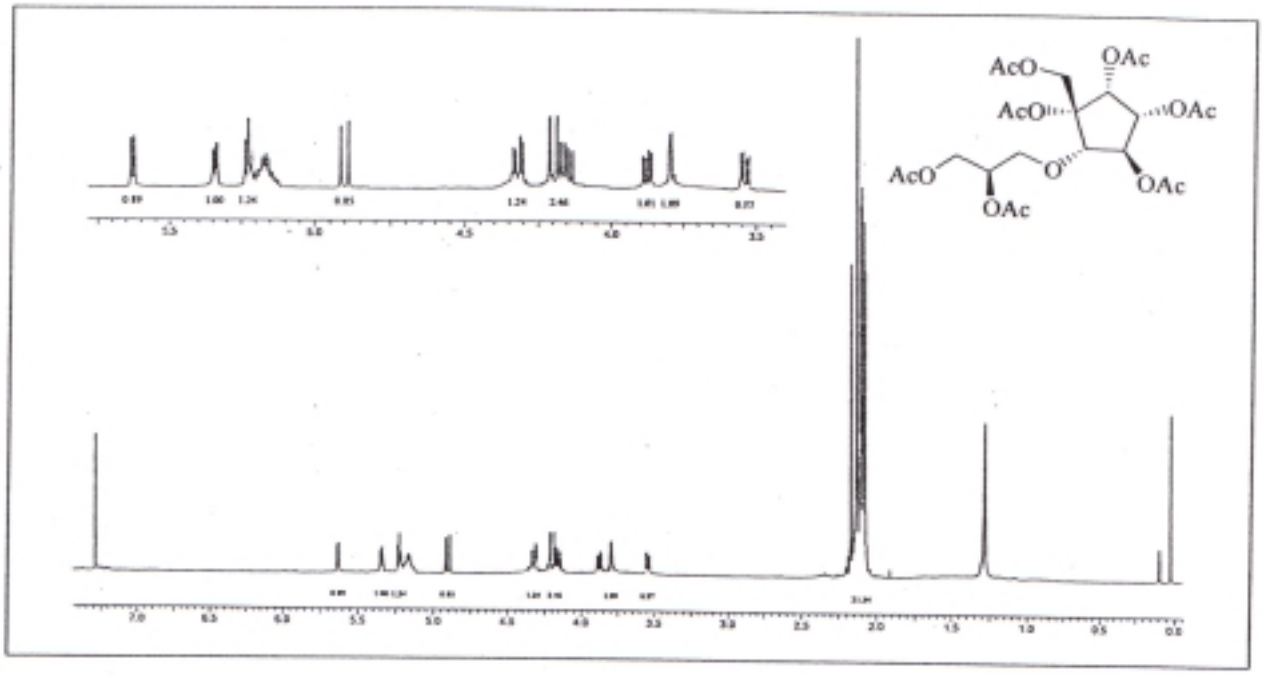
^{13}C NMR Spectrum of compound 22 in $CDCl_3$



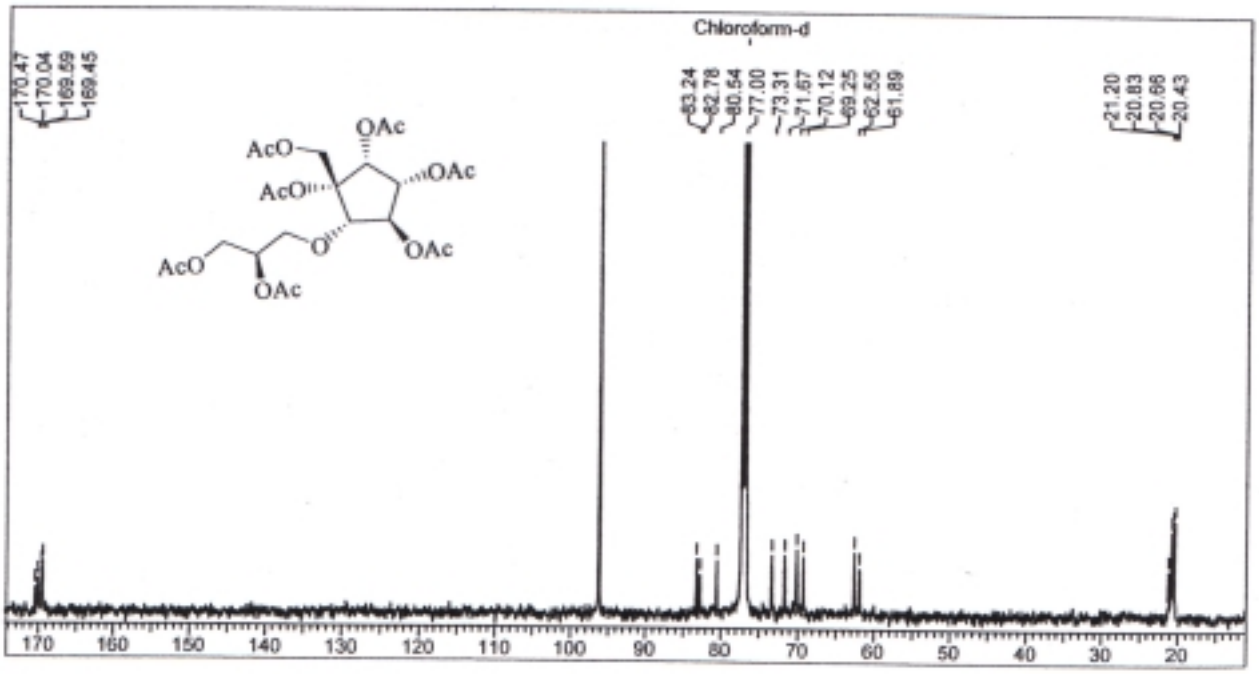
^{1}H NMR Spectrum of compound 23 in $CDCl_3$ (mixture)



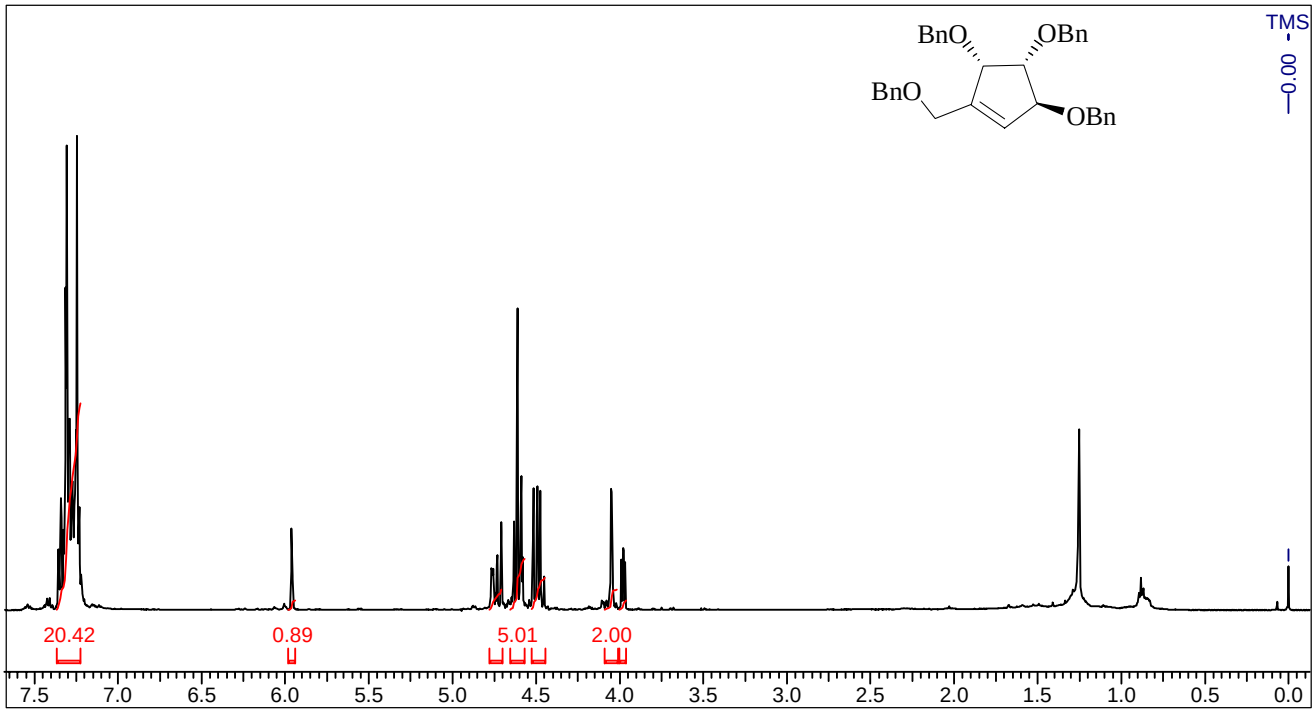
Expansion



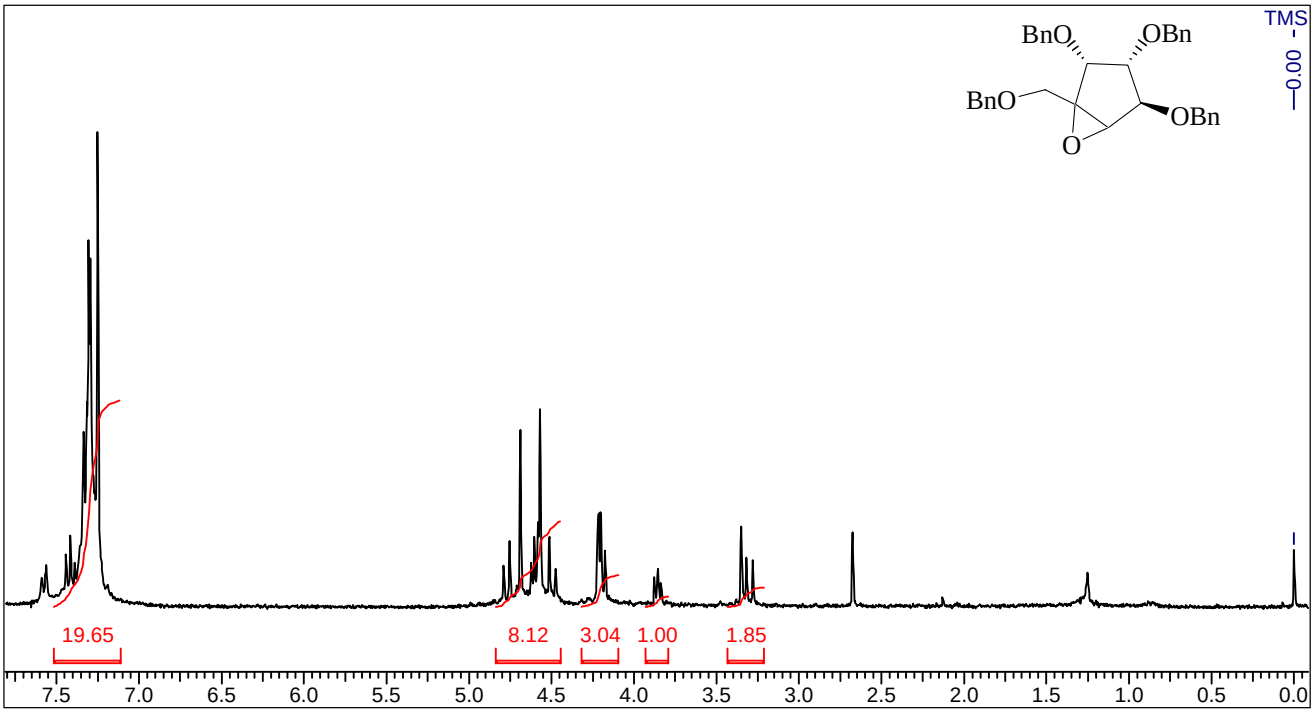
^{1}H NMR Spectrum of compound 23 in $CDCl_3$



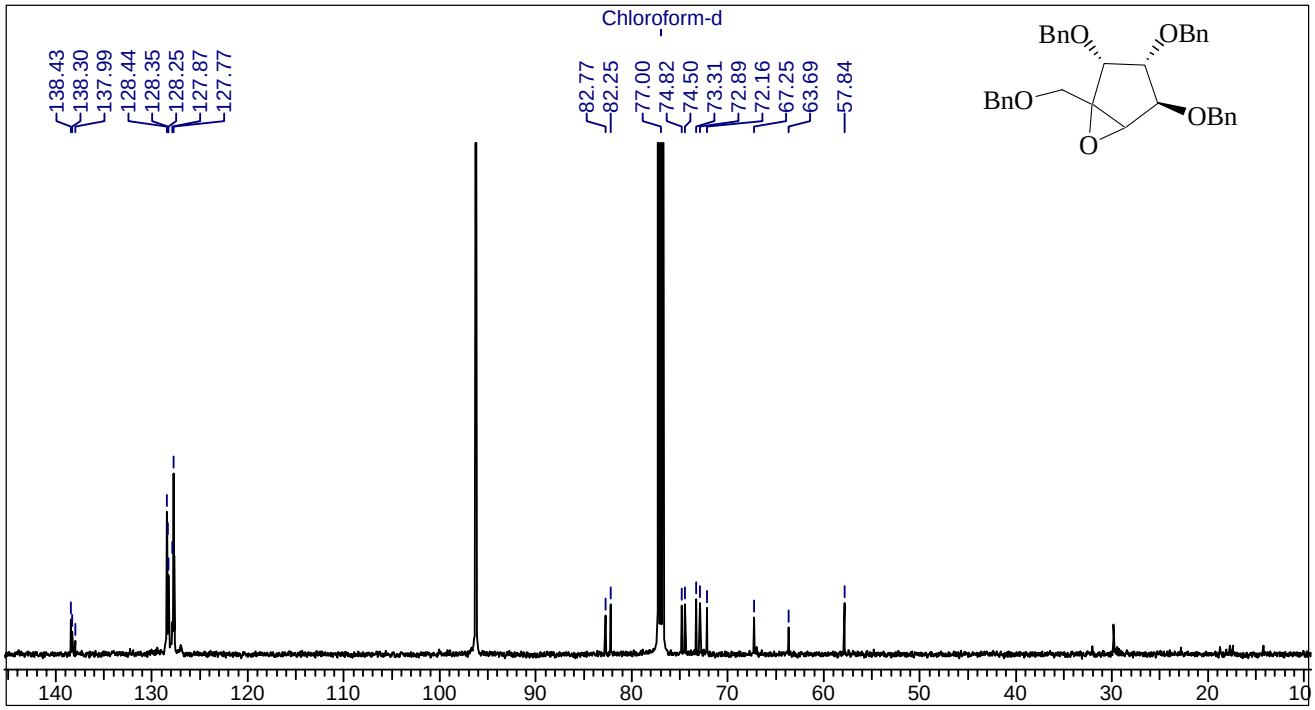
^{13}C NMR Spectrum of compound 23 in $CDCl_3$



^{1}H NMR Spectrum of compound 27 in $CDCl_3$



^{1}H NMR Spectrum of compound 28 in $CDCl_3$



^{13}C NMR Spectrum of compound 28 in $CDCl_3$

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Chapter III

Synthetic studies towards Carba calanolide

Introduction

Introduction

Human health care is facing one of the biggest challenges of the 21st century in the form of Acquired Immuno Deficiency Syndrome (AIDS). AIDS is a devastating progressive syndrome caused by Human Immunodeficiency Virus (HIV) and its condition leads destruction of immune system and subsequent susceptibility to opportunistic infections. Stopping the epidemic is of paramount importance. The virus has spread rapidly through human population and was recently designated to come third on the World Health Organisation's list of global causes of death by the middle of this decade.

Since the first case of AIDS was reported in 1981, the virus has spread rapidly through the human population and an estimated 46 million people are now infected with HIV over the world and as many 3 million people were dieing in each year. HIV is spreading especially quickly in sub-Saharan Africa and in south Asia. The region below sub-Sahara Africa houses two thirds of global HIV-infected population.

The search for therapies to treat HIV/AIDS and related opportunistic infections remains among the highest priorities of present day research in the world.[1] Formulating a right therapy could be achieved only by having a clear understanding of the causative agent at cellular and molecular level. This introduction is aimed at presenting birds eye view of what is an AIDS virus, how does it infect and different therapeutic methods followed to contain it.

Symptoms of AIDS:

AIDS patients usually exhibit one or more of these symptoms[2] such as reduced appetite and malabsorption, increased excretion of nutrients, endocrine and neurological abnormalities, metabolic and immune derangement, severe malnutrition as evidenced by progressive weight loss, lymphadenopathy, opportunistic infections, neoplasms e,g. Kaposi's sarcoma (KS), malignant lymphoma.

HIV Life Cycle - How HIV Harms:

After the nearly twenty-five years of HIV-AIDS research, significant understanding of HIV has been gained. Main targets of HIV are two types of white blood cells, the CD4 T lymphocytes and macrophage lineage such as the dendritic cells of lymphoid tissue and skin and microglia of the central nervous system. The hallmark of AIDS is depletion of the CD4 T lymphocytes population.

At the molecular level[3] scientists gained full understanding of how HIV invades and destroys CD4 T lymphocytes. Initially virus gains access to the interior of these cells (and certain other cell types) by binding to the CD4 itself and to molecule, a co-receptor on the cell surface. Such binding enables HIV to fuse with the cell membrane and to release its contents in to the cytoplasm. These contents include various enzymes and two strands of RNA that each carry the entire HIV genome: the genetic blueprint for making new HIV particles.[4]

One of the enzymes, reverse transcriptase (RT), copies HIV RNA into double strand DNA. Then a second enzyme, integrase (IN), helps to splice the HIV DNA permanently in to a chromosome in the host cell. When a T cell that harbors this integrated DNA becomes activated against HIV or other microbes, the cell replicates and also unwittingly begins to produce new copies of both the viral genome and viral proteins. Now another HIV enzyme, protease (PR) cuts the new protein molecules into forms that are packed with the virus's RNA genome in new viral particles. These particles bud from the cell and infect other cells. If enough particles form, they can overwhelm and kill the cell that produced them.

At the start of the infection, hefty viral replication and the killing of CD4 T cells are manifested by high levels of HIV in the blood and by a dramatic drop in CD4 T concentrations from the normal level of atleast 800 cells per cubic millimeter of blood. About three weeks in to this acute phase, many people display symptoms reminiscent of mononucleosis, such as fever, enlarged lymph nodes, rash, muscle aches and headaches. These maladies resolve with in another

one to three weeks, as the immune system starts to gain some control over the virus. that is , the CD4 T cell population responds in ways that spur other immune cells CD8, or cytotoxic T lymphocytes to increase their killing of infected, virus producing cells. The body also produces antibody molecules in an effort to contain the virus; they bind to free HIV particles and assist in their removal.

Despite all these activities, the immune system rarely, if ever, fully eliminates the virus. by about six months the rate of viral replication reaches a lower, but relatively steady state that is reflected in the maintainance of viral levels at a kind of set point. This set point varies greatly from patient to patient and dictates the subsequent rate of disease progression; on average 8 to 10 years pass before the major HIV related complications develop. In the prolonged, cronic stage, patients feel good and show few if any symptoms.

Their apparent good health continuous because CD4 T cell levels remain high enough to preserve defensive response to other pathogens. But over time, CD4 T cell concentration gradually falls. When the level drops below 200 cells per cubic millimeter of blood, people are said to have AIDS.

Anti AIDS therapies:

The advent of molecular biology has permitted the study of the individual stages with in the life cycle of HIV and identification of steps without which the virons cannot replicate. A vaccine would certainly be ideal for preventing infection by HIV, at the near-term prospects for a vaccine are poor, and people who contract the virus need care. For the immediate future many scientists are concentrating mainly on improved chemotherapy.

Chemotherapy

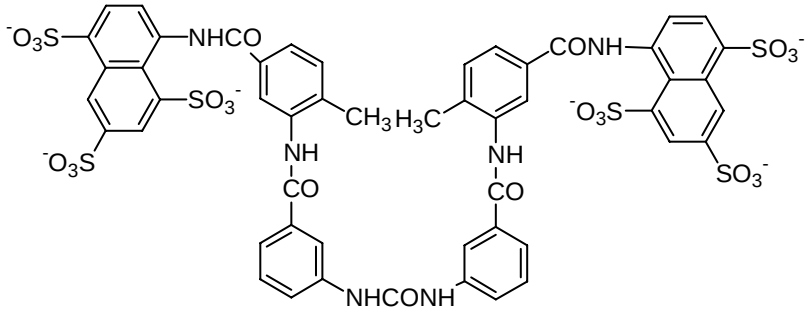
Since HIV was identified as the etiological cause of AIDS, chemotherapy of AIDS has been one of the most challenging scientific projects. Successful anti retroviral drugs, in theory, exert their effects by interacting with viral receptors, virally encoded enzymes, viral structural

components, viral genes or their transcripts or cellular factors required for replicating cycle can serve as a site for chemotherapeutic attack. Only some of them have been identified and investigated with significant success. Notable among these are the inhibitors of viral entry, the reverse transcriptase (RT), the integrase (IN), *tat*, *rev* and *nef* gene and the protease (PR).

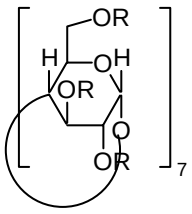
1.Viral entry inhibitors:

The HIV viral entry in to its target cells is generally accompanied by virus binding, adsorption on the cell surface, virus cell fusion and un coating of its contents into the cell.

The binding of viral gp 120 to cellular CD4 is the first step of viral entry in to the cell. According to one plausible model,[1] the binding of gp 120 to cellular CD4 induces a change in conformation of the envelope, unmasking a specific site, the fusogenic domain in the hydrophobic gp 41 transmembrane portion of the viral envelope. This hydrophobic site is assumed to be normally hidden under the gp 120 molecule. Once it is unmasked, the hydrophobic domain interacts with the adjacent cell membrane and induces viron-cell or cell-cell fusion. Antibodies or drugs that interfere with these fusogenic domain function could theoretically block HIV replication. Many agents have been identified as potential drugs, though none of them have been approved yet.



Suramin (1)



β-Cyclodextrin sulfate (2)

Polyanionic compounds act as virus adsorption inhibitors. Infact anti-HIV chemotherapy era started more than a decade ago when a poly anionic compound Suramin was found to protect human T lymphocytes against HIV infectivity.[5] However it was withdrawn later due to its high

toxicity. The other polyanionic compounds include heparin dextran sulfate, β-cyclodextrin sulfate, aurintricarboxylic acid, polyvinyl alcohol sulfate *etc.*

2. Reverse transcriptase inhibitors:

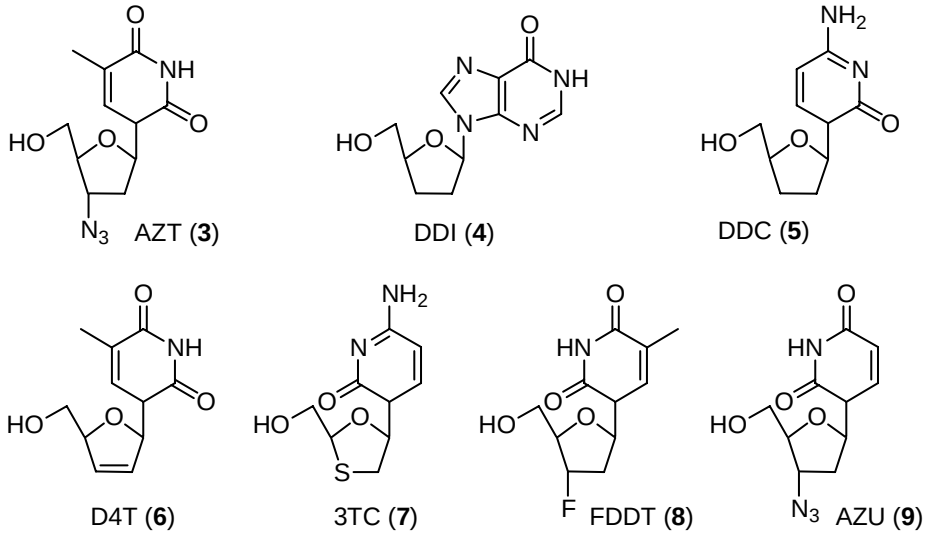
Reverse transcriptase (RT) is a multifunctional enzyme having both RNA-dependent DNA polymerase and DNA-dependent DNA polymerase activities as well as a inherent RNase-H activity.[6] It initiates DNA synthesis *in vivo* from the 3'-OH end of the host primer which partially attached to a complementary region of the viral RNA called "the primer binding site". Following the formation of the (-) DNA strand, it is RNase-H activity that is necessary to specifically degrade the RNA in the RNA-DNA heteroduplex. This inherent RNase-H function is vital for the viral function and cannot be substituted by host cellular RNase-H. A short polypurine sequence remains uncleaved during this process and serves as a specific primer in the initiation of (+) strand synthesis. At some stage, the primers both the (–) and (+) strands are removed, presumably by RNase-H to produce the double strand DNA. RT has been found to be a successful target for the devolepment of anti retroviral agents. RT inhibitors can be broadly classified in to nucleoside, non-nucleoside inhibitors and inhibitors selective for RNase-H.

a) Nucleoside reverse transcriptase inhibitors:

The majority of the nucleoside inhibitors belong to the family of 2',3'- dideoxy-nucleosides. Clinically approved anti-AIDS drugs belonging to this class include AZT (Zidovudine **3**, Retrovir), DDI (Didanosine, Videx), DDC (HIVID, Zalcitabine), D4T (Stavudine, Zerit), 3TC (Lamividine, Epivir). The other nucleoside analogues under study include[5] FDDT (**8**), AZU (**9**), several acyclic nucleoside phosphonates such as PMEA, PMEDAP, FPMP, DAP and PMPDAP.

Nucleoside inhibitors have been the most widely studied class of anti HIV agents and a great deal of knowledge regarding the phosphorylation, mechanism of action and structure activity relations emerged.[1] The nucleoside analogues are designed to disrupt a normal

polymerase function of HIV-RT. Each drug that inhibits RT, must first be activated to a 5'- tri-phosphate form by the biochemical machinery of the target cell. It is triphosphate form that is active against HIV. The activation process called anabolic phosphorylation involves a series of enzymes which are specific for each nucleoside.

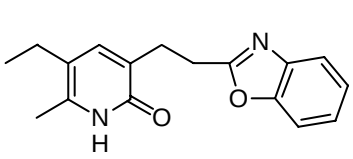


Zidovudine or AZT[6] was the first approved antiviral drug for HIV infection. Although AZT is efficacious, the most serious side effect associated with it is bone marrow suppression resulting in anemia and neutropenia, probably resulting from the toxic effect of AZT on bone marrow progentier cells. A particular advantage of AZT is its ability to penetrate the blood-brain barrier, since HIV infects cells in CNS causing dementia. It has been shown that D4T [7] (**6**) is less toxic than AZT in mice and human bone marrow cells. Following the discovery of the anti-HIV activity of AZT search for superior analogues resulted in the discovery of DDA and DDI.[8]

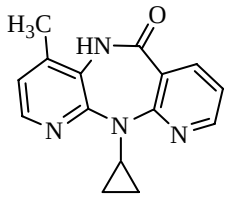
b) Non-nucleoside reverse transcriptase inhibitors: (NNRTIs)

The NNRTIs represent a group of highly potent and specific inhibitors of HIV-1 replication that interact non competitively with the enzyme at an allosteric nonsubstrate binding site that is distinct from, but functionally and also spatially associated with the substrate binding site.[5] This particular site corresponds to a flexible highly hydrophobic pocket that is exclusively

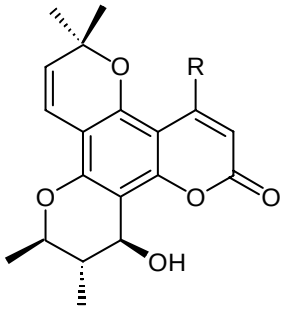
found in the RT of HIV-1 and hence, NNRTI are only inhibitory to HIV-1 and not HIV-2 or other retroviruses.



Pyridinone series (l-696229 (10)



Nevirapine (11)



(+)-Calanolide A (R = *n*-propyl) (12)
(+)-Inophyluum B (R = phenyl) (13)
(+)-Cordatolide A (R = methyl) (14)

Well known NNRTI include[9] 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (HEPT), tetrahydroimazo[4,5,1-*jk*][14]benzodiepin-2-(1H)-thione (TIBO) derivatives R82150, R82913 pyridinone derivatives, TSAO derivatives,[10] delaviridine, nevirapine[11] (**11**), bis-(heteroaryl)-piperizine (BHAP) and α-anilino phenylacetamide derivatives. Among NNRTIs, TSAO derivatives represent a particular and peculiar group of specific RT inhibitors that are able to interfere at the interface between the p51 and p66 RT subunits. TSAO-T was the first sugar derivative found to be specifically inhibit HIV-1 RT. Delaviridin and Navirapine were the first two drugs to be approved under this class. The investigational NNRTI efavirnez[12] holds promise because of potency and possibility for once daily dosing. Certain coumarin derivatives isolated form several tropical plants of *Calophyllum* were recently identified as HIV-1 specific NNRTIs, amongst which (+) calanolide-A (**12**), (+) cordatolide-A (**13**) and inophyllum-B (**14**) are the most potent.[13] Since these compounds are active not only against AZT-resistant strains of HIV-1 but also against the pyridinone-resistant strain A-17 they belong to a second generation of HIV-1 specific NNRTIs.

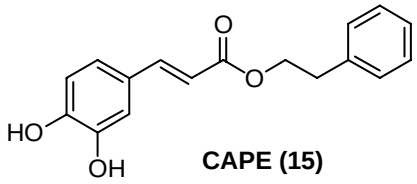
RNase-H inhibitors

RNase-H plays crucial role in preparing a DNA template for (+) strand synthesis and hence is an alternate target for drugs designed to combat HIV replication. In contrast to the

inhibitors of the polymerase activity, relatively little is known about RNase-H ligands. Illimaquinanone[14] has been shown to have a differential effect on the RNase-H and polymerase activities of the RT.

3. Integrase inhibitors:

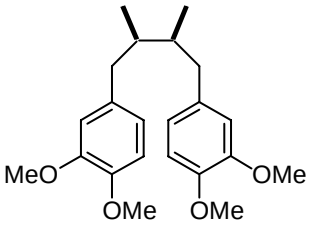
In addition to RT and PR, another target potentially amenable target to a selective chemo therapeutic intervention is the HIV-1 integrase (IN), an enzyme which has no counterparts in the host cell and catalyses an essential step in the retroviral life cycle.[15] In fact, following reverse transcription of the viral DNA genome into a double-stranded DNA, IN catalyses integration of the later into the host chromosome through coordinated reactions of processing and joining. Many different classes of compounds have been reported to inhibit the HIV-1 IN in enzyme assays, and among them, natural and synthetic polyhydroxyated molecules have emerged as potent IN inhibitors. They include flavones such as quercetin, caffeic acid phenethyl ester (CAPE **15**) and related amides, bis-catechols, curcumin, a tyrphostin and its potent 6,7-dihydroxy naptho-2-yl derivative. However very few of the above compounds have shown specific anti IN activity and still fewer proved active in cell based assays.



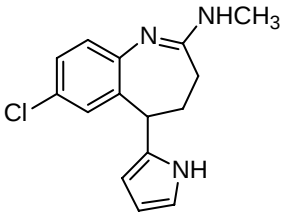
CAPE (15)

4. Transcription and translation inhibitors:

After integration of the HIV genome in to the host cell genome and a variable latency period, the proviral DNA is transcribed into mRNA by host RNA polymerase. Subsequently the viral mRNA is translated to form viral proteins, again by the biochemical apparatus of the host cell. Flouroquinoline class of compounds,[16] K12, was found to be not only potentially inhibit HIV-1 transcription, but also enhances the activity of clinically available anti retroviral agents in cell culture.



Tetramethylnordihydro guaiaretic acid (**16**)

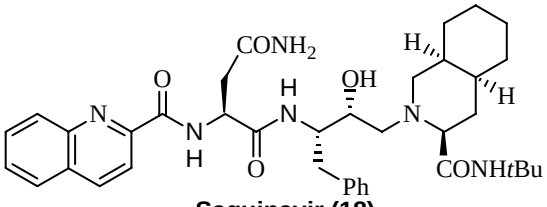


RO-24-7429 (**17**)

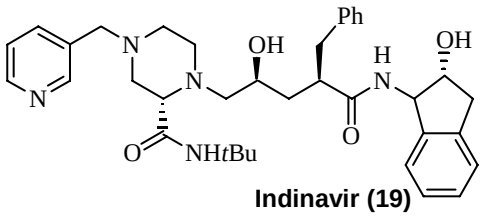
The HIV regulatory proteins *tat* and *rev* play and important role in the expression of the HIV genes; *tat* by stimulating transcription from viral long terminal repeat (LTR) and *rev* by increasing the transport stability of the late mRNAs encoding the structural proteins of the virus. Two important compounds studied as anti-*tat* agents were tetramethyl nordihydroguaiaretic acid[17] (**16**), RO-24-7429[5] (**17**) HIV resistant strains were not observed with anti-*tat* agents.

5. Protease inhibitors:

After the transcription and translation of the viral genes into the proteins, the poly protein precursors have to be processed in to matured structural proteins and enzymes during particle assembly and maturation. This is carried out by the viral enzyme-HIV protease (PR) that process the viral *gag* and *gag*-pol polyproteins. Inhibition of HIV-PR *in vitro* results in the production of progeny virons which are immature and non infectious.



Saquinavir (18)



Indinavir (19)

In designing HIV protease inhibitors, the transcription state peptidomimetic principle was followed, which means that in the inhibitors the hydrolysable peptide linkage was replaced by non-hydrolysable transition state isostere. Well known examples are saquinavir (**18**) RO 31-8959), U-81749, norstatine and C_2 symmetric compound A-74704, retronavir.

6. Other prominent targets for Chemothearaputic inhibition:

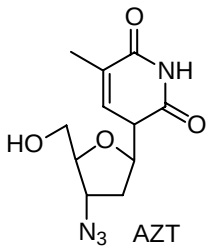
In addition to the viral protease, cellular enzymes such as myristoylating and glycosylating enzymes also involved in the formation of infectious viral particles. myristoylation inhibitors such as 13-oxatetradecanoic acid and 12 azidodecanoic acid are targeted at protein N-myristoyl transferase.[5] Although myristoylation inhibitors are found to inhibit HIV-1 infection in both acutely and chronically infected cells, they may not be therapeutically useful as these inhibitors are expected to interfere with viral cellular processes. Glycosylation inhibitors such as castenospermine, 1-deoxynojirimycin are targeted at protein α-glycosidase. These compounds are neither very potent nor very useful, a drug candidate is yet to be designed from this category.

As the global HIV pandemic continues to spiral out of control, the need for an effective vaccine becomes even more pressing. At present however, there is no proof that vaccination against HIV is possible but there is hope. As the pathogenesis of HIV infection has become better understood, investigators realized that if the virus can be kept at low concentrations in blood, the infected person may never progress to AIDS. With a vaccine still years away, the only broadly applicable way to prevent new HIV infections is to change behaviors that enable transmission of those infections especially behaviors relating to sex and drug infection.

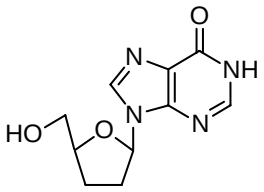
Presentwork

Present Work

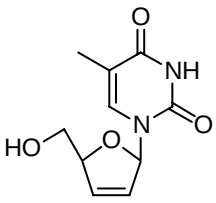
The human immunodeficiency virus (HIV), first identified in 1983, is a human retrovirus commonly accepted as the causative agent of acquired immune deficiency syndrome (AIDS), a condition which leads to destruction of the immune system and subsequent susceptibility to opportunistic infections. Since the first case of AIDS was reported in 1981, the virus has spread rapidly through the human population and an estimated 46 million people are now infected with HIV over the world and as many 3 million people were dieing in each year. Efforts to develop a vaccine to protect against infection have been disappointing, and to date, nine "small molecule" drugs have been approved for use in the treatment of AIDS and AIDS-related complex: the nucleoside reverse transcriptase (RT) inhibitors[6-8] AZT, ddI, ddC, d4T, and 3TC; the non-nucleoside reverse transcriptase inhibitor,[9] nevirapine;[11] and the HIV protease inhibitors, indinavir, ritonavir, and saquinavir. Although the four antiviral nucleoside agents can extend the life of AIDS patients, none are capable of curing the disease, and serious side effects are induced. For example, treatment with AZT leads to a suppression of bone-marrow formation, which often causes anemia and leukopenia, resulting in the need for frequent blood transfusions. The use of ddI, ddC, and d4T is associated with painful sensory-motor peripheral neuropathy, as well as acute pancreatitis and hepatotoxicity in some cases. More importantly, long-term treatment of patients with all these drugs has led to emergence of drug-resistant HIV strains, primary infections have also been found with AZT-resistant HIV strains.



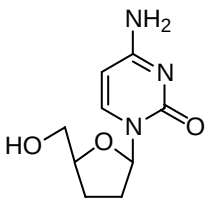
AZT



DDI

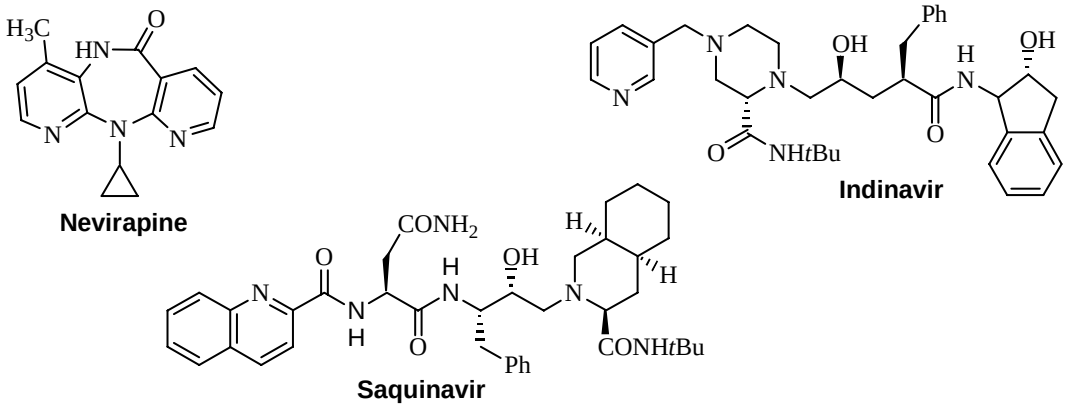


D4T



ddC

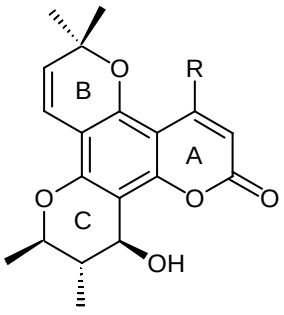
The need for other promising AIDS drug candidates having improved selectivity, and activity against HIV is extremely urgent. Several approaches, including chemical synthesis, natural products screening, and biotechnology, have been utilized to identify compounds targeting different stages of HIV replication for therapeutic intervention. As with other retroviruses, the genetic information of HIV is encoded in RNA and must be converted into DNA in the infected host cell. Only then can the viral genes be transcribed and translated into proteins in the usual sequence. The virally encoded reverse transcriptase is the sole enzyme responsible for the catalytic formation of unintegrated viral DNA from the single-stranded RNA viral genome and, accordingly, plays a key role in the life cycle of HIV. It is therefore logical to focus on this enzyme, which is not required for normal cellular processes, as a target for the development of anti-HIV drugs.



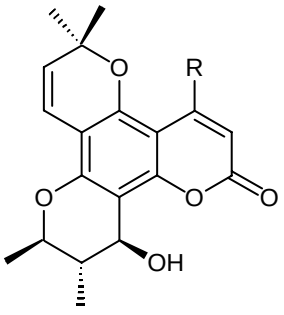
The development of additional anti-HIV drugs having novel structures is of critical importance for overcoming the problems of drug resistance, arising from both drug promoted selection and natural random genetic mutations. Exposure of HIV-infected cells, either in vitro or in vivo, to drugs targeting RT leads to rapid selection for resistant viral strains, mediated by mutations of the RT enzyme. All of the RT inhibitors approved to date have been reported to select for drug resistant mutants, and several mutant viral strains exhibit cross-resistance to more than one nucleoside analogue. Similar problems of wide spectrum drug resistance have been observed for the protease inhibitors as well. One area of intensive research has been the

development of non-nucleoside reverse transcriptase inhibitors (NNRTIs), which inhibit RT by occupying a binding site different than that targeted by the nucleoside analogues, and thus offer the possibility of overcoming drug resistance associated with the nucleoside analogues. Even though a variety of structurally unrelated NNRTIs have been identified which inhibit RT, all of these also lead to rapid emergence of resistant strains.

Unique among the recently described non-nucleoside compounds are the natural products, (+)-calanolide A and inophyllum B. The calanolide compounds were originally derived from the tropical plant genus *Calophyllum* and have now been identified as effective inhibitors of HIV-1 replication.[13] They have the added advantage of non-cross-resistance with both the AZT- and the pyridonone-resistant strains of HIV. Due to the fact that combinations of non-nucleoside and nucleoside compounds and/or novel protease inhibitors have been shown to be clearly superior to single agents, the future of HIV treatment clearly involves multiple agent therapies. Because (+)-calanolide A and AZT have recently been demonstrated to synergistically inhibit HIV strain A17, the use of active nucleoside agents together with effective non-nucleoside natural products, such as the calanolide compounds, may also offer improved therapeutic results against this difficult disease.



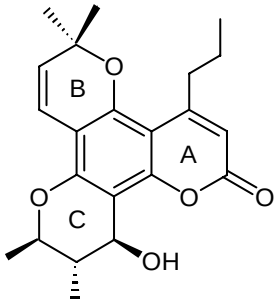
(+)-Calanolide A (R = *n*-propyl) (**1**)
(+)-Inophyluum B (R = phenyl) (**2**)



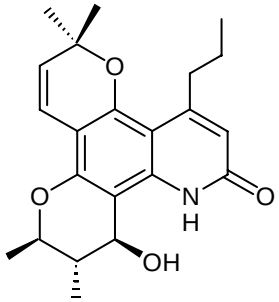
(-)-Calanolide B (R = *n*-propyl) (**3**)
(-)-Inophyluum P (R = phenyl) (**4**)

Supplies of the compound from plant material are extremely limited and difficult to obtain, since the original natural source of (+)-calanolide A was destroyed and other nearby members of the same species did not contain the same compound. Further pharmacological

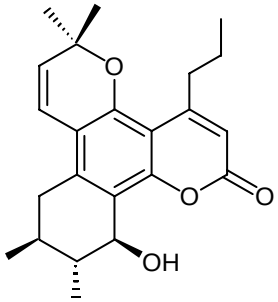
investigation of this class of compounds, as well as related analogues, is dependent upon the ready availability of significant amounts of material. In an effort to identify structural features necessary for antiviral activity, we initiated the synthesis and evaluation of a series of compounds modified on ring A and C. It has been observed that the trans relationship between 10- and 11-methyl groups in ring C was crucial for activity. All of the natural calanolide compounds exhibiting significant anti-HIV activity possess a hydroxy group at the 12-position, suggesting this feature is critical for activity.



Calanolide A (**1**)



Aza-Calanolide (**5**)

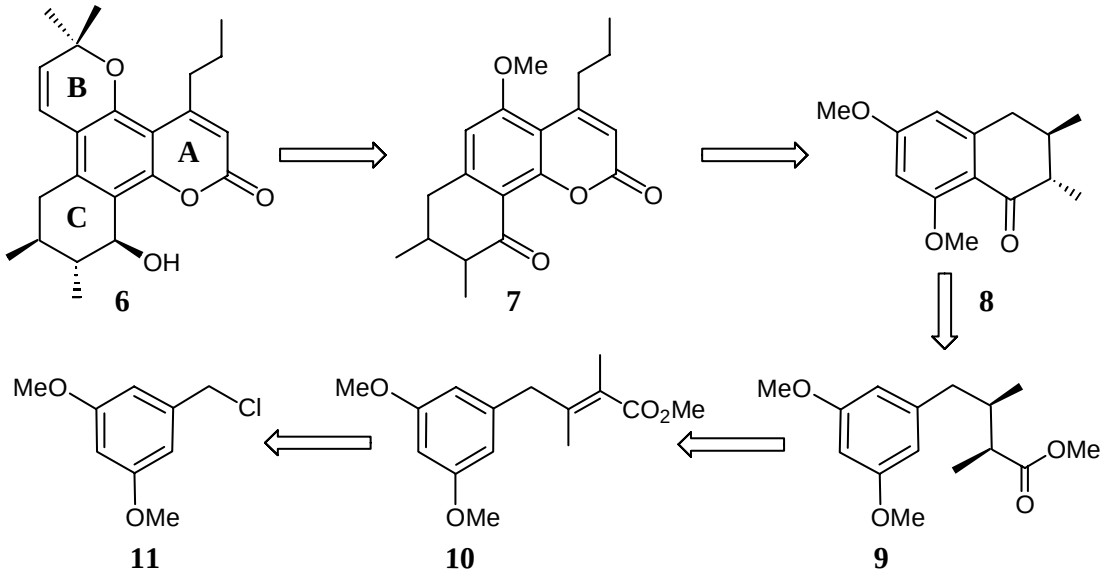


9-Carba-Calanolide (**6**)

Inspired by its activity we initiated a program for the synthesis of various calanolide analogues by changing the heteroatom in A ring with nitrogen (**5**), by replacing the hetero atom of ring C with carbon (**6**) and without altering the relative stereochemistry in ring C. The racemic aza-analogue (**5**), which was previously synthesized in our laboratory, has shown the enhanced anti-HIV activity when compared to the natural product calanolide A.[18] This section describes the synthetic studies toward the 9-carba-calanolide (**6**).

As presented in the scheme 1 the retrosynthetic analysis of carba-calanolide involves the construction of A, B, C rings. We intended to used established literature procedures[19,20] for the construction of A and B rings at a later stage in our synthetic scheme. Our devised strategy involves the construction of Ring C first and then Ring B and finally Ring A. We have planned to construct Ring C by the Intramolecular Friedal Craft's acylation of **9**, which intern was planned to prepare by Heck-type reaction between the benzylchloride **11** and methyl tiglate.

Scheme 1

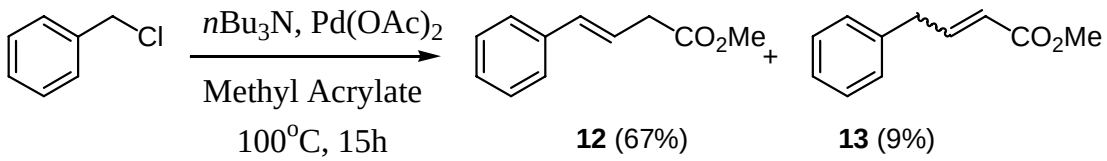


Retrosynthetic Analysis

As this later reaction is one of the key reaction in our synthetic strategy it is pertinent to brief about this relatively unexplored reaction.

Heck Reactions Using Benzyl Halides: In 1972, Heck reported[21] the coupling of benzyl chloride to methyl acrylate, promoted by $Pd(OAc)_2$, leading to the formation of 4-phenyl-3-butenoate **12** (69%) and 4-pheynyl-2-butenoate **13** (9%). Since that time, relatively little interest has been shown in this reaction. Reports concerning the use of benzyl halides in Heck-type couplings are handful.

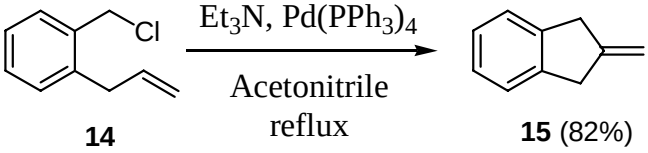
Scheme 2



After its inception in 1972, the next report concerning benzylpalladation of alkenes was by Negishi and co-workers[22] was in 1989, where they have unveiled an intramolecular verion (cyclic benzylpalladation of alkenes) of this reaction for the synthesis of indene derivatives. They

have also examined the effects of leaving groups on the conversion of **14** to **15**. The following order of reactivity has been given Cl>Br>OMs>I>….>OAc.

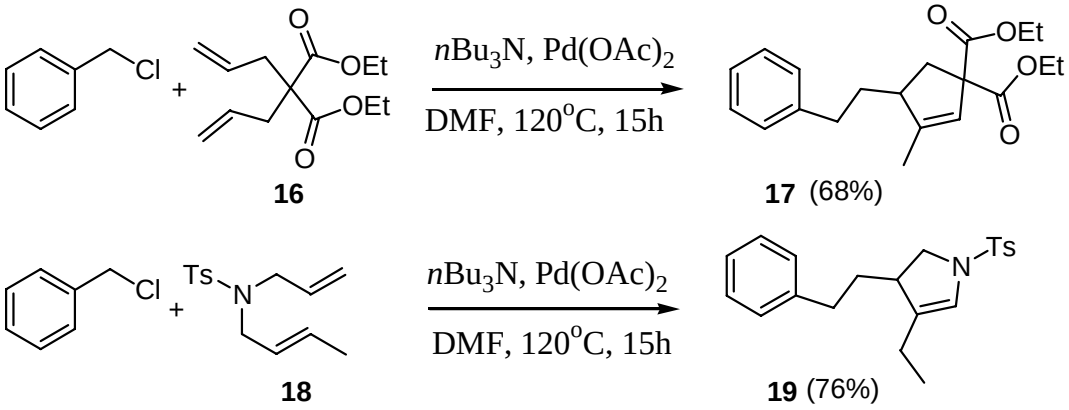
Scheme 3



14 **15** (82%)

Very recently, Pan and co-workers[23] have explored the potential of this benzylpalladation reaction and reported very interesting observations.

Scheme 4

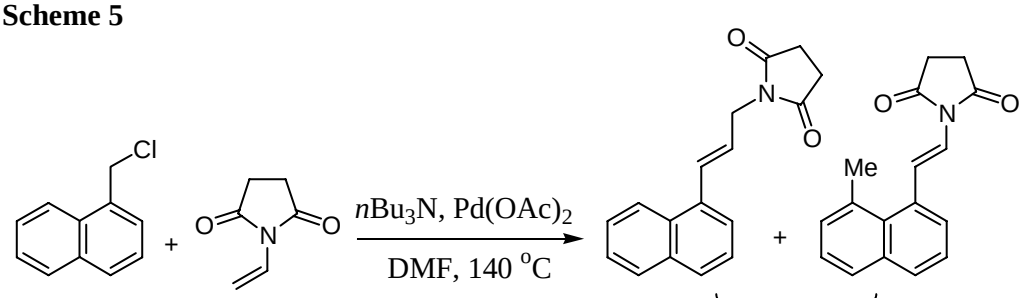


16 **17** (68%)

18 **19** (76%)

With α-naphthylmethylene halides, along with the expected regioisomers, they have also found the formation of a product resulting from peri-alkylation of naphtyl ring via cyclopalladation.[24]

Scheme 5

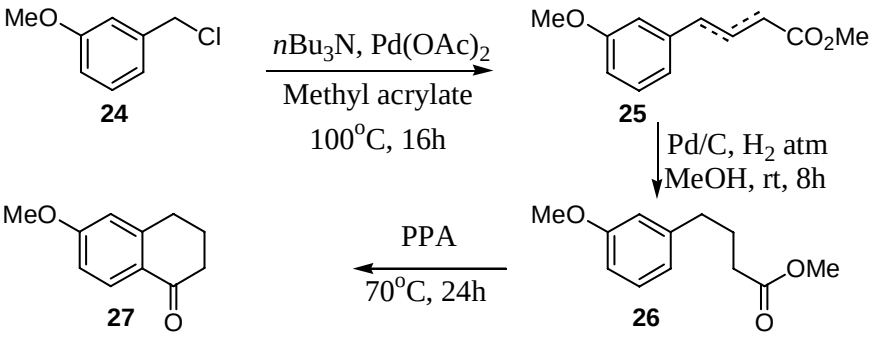


20 **21** **22** **23**

45%
1 :1.2

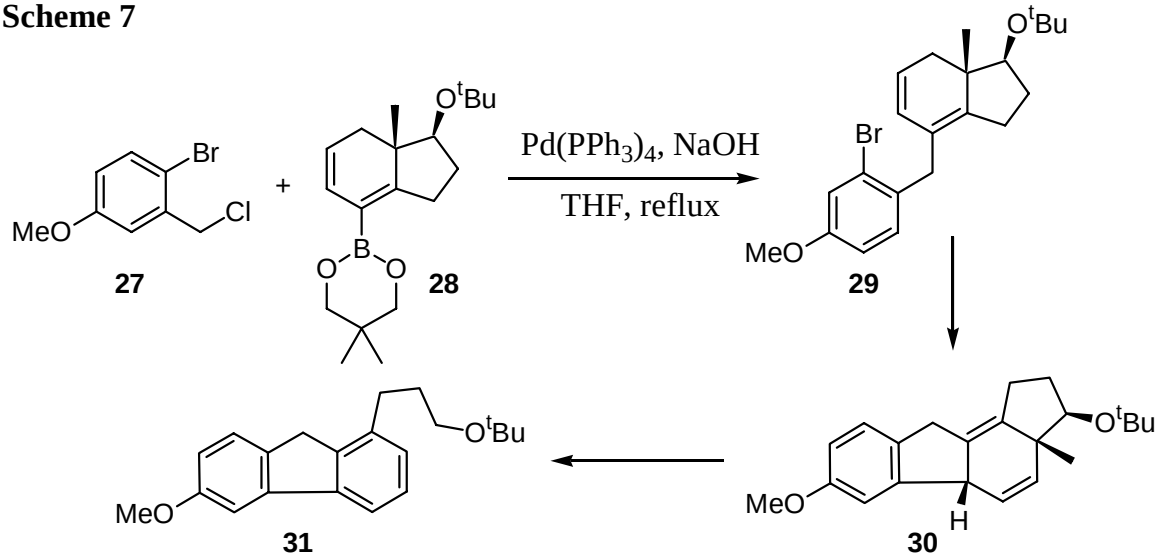
Punit[25] has explored the potential of these acrylate benzylpalladation products for the synthesis of substituted 1-tetralones using some simple chemical transformations such as hydrogenation and intramolecular Friedelcraft's acylation.

Scheme 6



Tietze *et al*[26] have recently reported an elegant application of this benzylpalldation reaction in combination with Suzuki reaction for the total synthesis of enantiopure B-nor-steroids.

Scheme 7

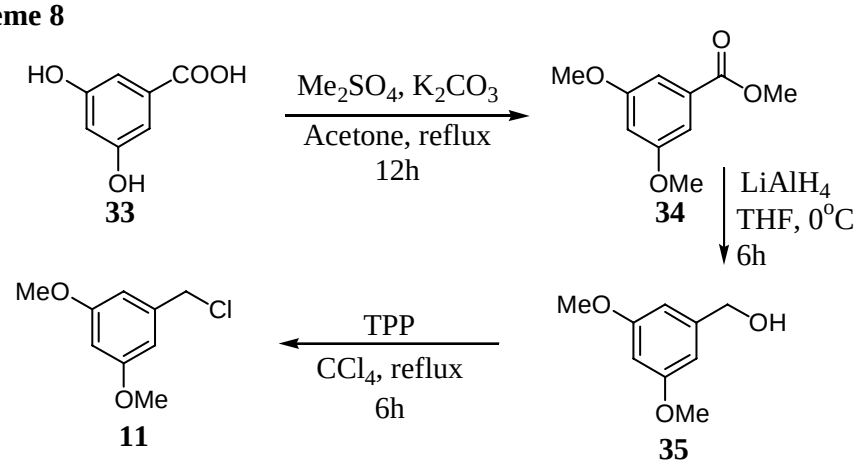


Synthetic Approach:

The synthetic endeavor begins with the synthesis of a suitable derivative for the Heck-type reaction. Accordingly, 3,5-dihydroxybenzoic acid was transformed into 3,5-dimethoxy-

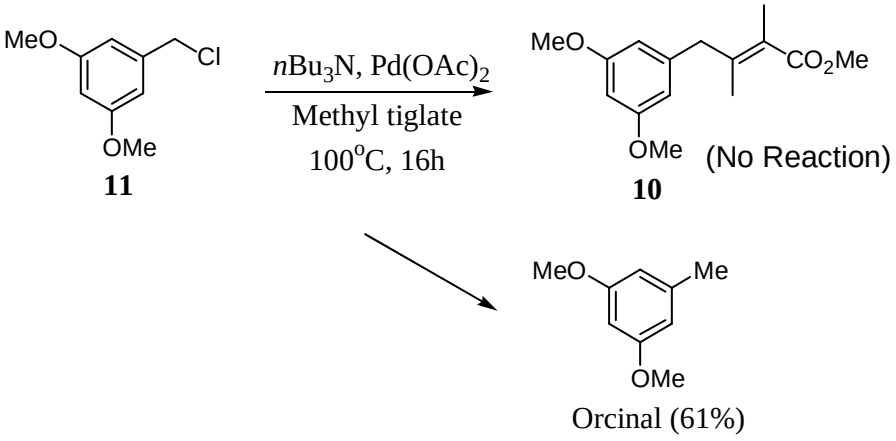
benzyl chloride (**10**) as shown in the Scheme 8 by standard procedures. Compound **10** was characterized by comparing its melting point with that of literature values.

Scheme 8



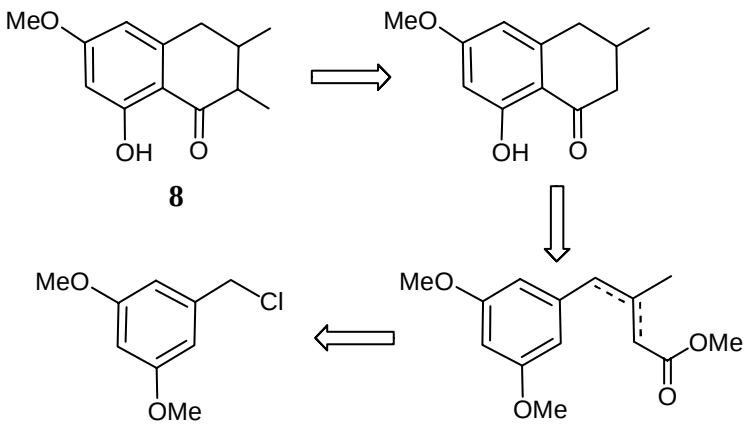
After having an easy access for the benzyl chloride **11**, we next focused our attention on Heck like coupling between **26** and methyl tiglate. Although, there are no reports in the literature on Heck coupling of benzyl halides with a trisubstituted olefin, however considering the examples provided by Punit[25] (Heck coupling with Methyl methacrylate), by Pan and co-workers[23] (1,2-disubstituted olefins) we anticipated a smooth coupling with methyl tiglate. However, when we carried out the coupling reaction of benzyl chloride **11** with methyl tiglate, we isolated orcinal resulting from the dehalogenation of **11** along with some minor unidentified products. Changing the catalyst or solvent systems was also found to be resulting the same.

Scheme 9



After being encountered the problem with Heck coupling between **11** and methyl tiglate, we intended to change the strategy for the preparation of **8** by using methyl crotonate as a coupling partner with **11** and the introduction of methyl at C-3 of the tetralone ring at a later stage either by alkylation or by crossed aldol reaction with formaldehyde and hydrogenation (Scheme 10).

Scheme 10

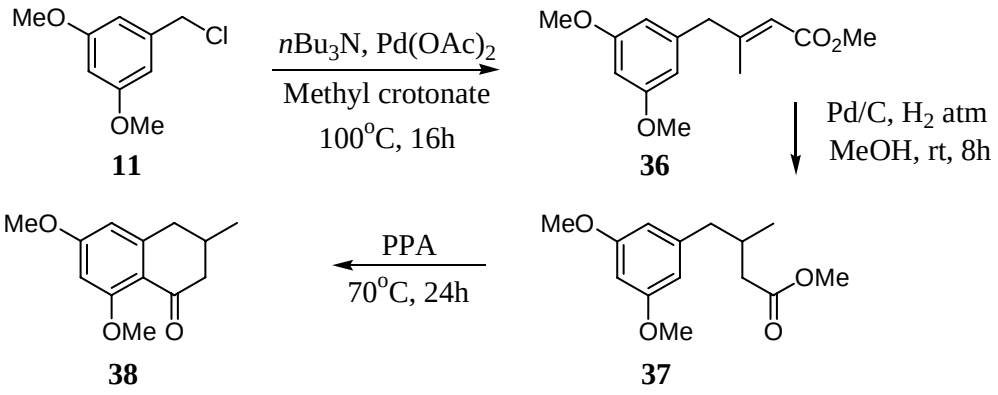


Accordingly, compound **26** was subjected to Heck like coupling with methyl crotonate under the original conditions reported by Heck (5 mol% $Pd(OAc)_2$ and tri-*n*-butyl amine and heating at 120 °C for 15h) and to afford the mixture of regioisomeric mixture **36a** and **36b**. The formation of coupled products was confirmed by its ^{1}H NMR spectrum, in which a singlet was appeared at 2.05 ppm due to the vinylic methyl protons.

The two regioisomers formed in the Heck-type reaction were then subjected to hydrogenation conditions using Pd/C under H_2 atmosphere to afford the compound **37**. The structure of compound **37** was confirmed by its ^{1}H NMR spectrum, in which peaks due to the alkyl side chain appeared between 2.1-2.65 ppm and the methyl protons resonated as a clear doublet at 0.95 ppm. In the ^{13}C NMR spectrum, presence of four carbon signals between 19.4-43.0 ppm due to alkyl chain carbons further confirmed the assigned structure. Compound **37** was treated with polyphosphoric acid (Friedal Craft's acylation conditions)[27] to give the tetralone **38**.

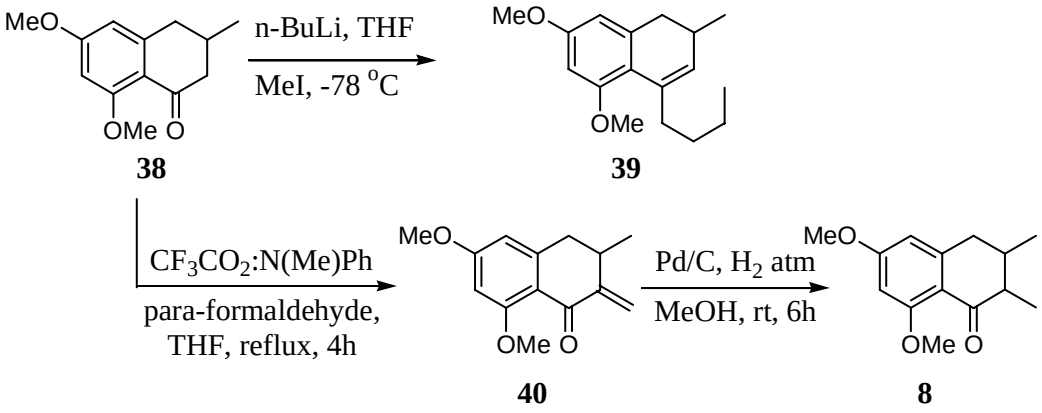
In the ^{1}H NMR spectrum of compound **38** absence of signals corresponding to the $-CO_2CH_3$ protons and in ^{13}C NMR, appearance of carbon signal due to C=O at 195.1 confirmed the assigned tetralone structure.

Scheme 11



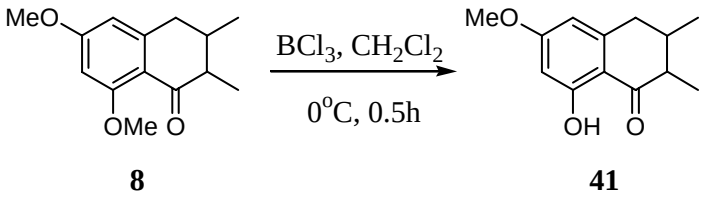
The attempted α-methylation of **38** with MeI using *n*-BuLi resulted exclusively with the addition elimination product **39**. In order to over come this problem we have chosen the other alternatione *i.e*. crossed aldol reaction with formaldehyde and hydrogenation. As expected the crossed aldol reaction between **38** and para-formaldehyde (excess) in the presence of *N*-methylanilinium.trifluoroacetate occurred smoothly and the resulting *exo*-methylene derivative **40** was subjected to hydrogenation (as the removal of excess paraformaldehyde was found to be problematic by chromatingraphy/removal by cracking resulted in the recovery of **38** because of retro-aldol) with out any characterization/purification using Pd/C to afford the dimethyl tetralone **8** as a mixture of *cis*-*trans* ratio (1:1) (Scheme 12). The appearance of conspicuous doublet due to the newly formed methyl protons at 1.24 ppm in ^{1}H NMR spectrum confirmed the assigned structure of compound **8**.

Scheme 12



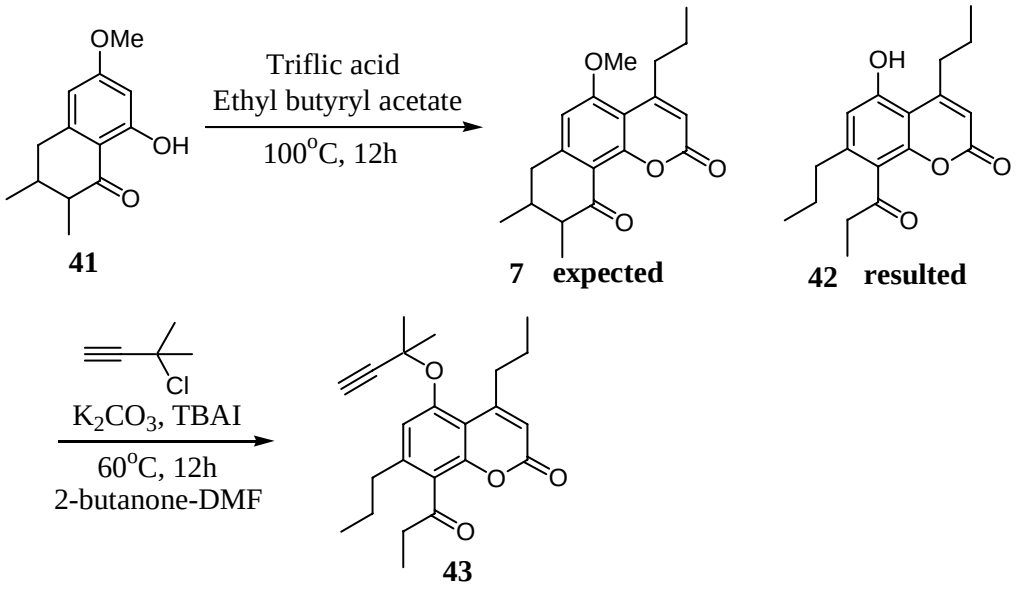
Selective demethylation of **8** was achieved by treatment with boron trichloride to afford the phenol **41** (Scheme 13). The structure of compound **41** was confirmed by its ^{1}H NMR spectrum, in which a doublet due to Ar-OH was appeared at 12.95 ppm. In the ^{13}C NMR spectrum, the absence of methoxy carbon signal at 55.4 ppm further supported the assigned structure.

Scheme 13



For the construction of coumarin ring **A**, phenol **41** was treated with ethyl butyryl acetate in triflic acid. Surprisingly, under these conditions, we have noticed the fragmentation of the tetralone ring affording the compound **42** instead of **7**. In the ^{1}H NMR spectrum, characteristic coumarin olefin proton was resonated at 6.86 ppm as a singlet confirming the formation of coumarin ring. At the same time the splitting pattern of methyl protons in ring **C** were changed from doublets to triplets and also the methoxy proton signal disappeared. Initially we presumed that along with the coumarine ring formation only demethylation has occurred and the observed two triplets in the ^{1}H –NMR spectrum are due to the overlap of the methyl signals of *cis* and *trans* isomers (in the case of **8**, these methyls appeared as 3 doublets).

Scheme 14



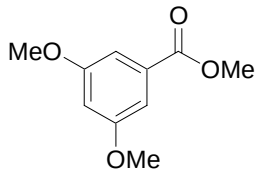
However, when a similar two triplets encountered with **43** resulting from the alkylation of **42** with 3-chloro-3-methyl-1-butyne in presence of K_2CO_3 and catalytic TBAI, we have analysed the structure of this compound cautiously. In the ^{1}H NMR spectrum of **43**, in which three triplets due to nine methyl protons at 1.03, 1.06, 1.18 ppm and a singlet due to acetylene proton at 2.71 ppm appeared. In the ^{13}C NMR spectrum, among the 13 aliphatic carbons appeared, 5 are found to be methylene, 3 methyl carbons, 1 methine and 3 quartenary carbons (DEPT). Further studies with the help of COSY spectrum we came to a conclusion that the ring cleavage occurred between C(2) – C(3).

In conclusion, we have successfully synthesized the dimethyl tetralone intermediate required for the synthesis of *Cabra*-Calanolide-A using Heck-type reaction as one of the key reaction. We were unable to complete the total synthesis of 9-carba calanolide because of the C-C bond cleavage during the coumarin ring construction. Although we are sure about the ring cleavage of tetralone by heating with triflic acid, however at this stage we have no plausible mechanism to explain this observation. Presently, we are working on the construction of coumarin ring using Pd-based methodologies.

Experimental

Experimental

Methyl-3,5-dimethoxy benzoate (34):



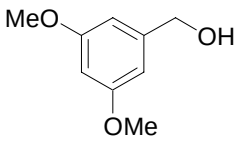
a suspension of 3,5-dihydroxy benzoic acid **33** (20 g, 0.11 mol) and K_2CO_3 (60.6 g, 0.44 mol) in dry acetone (300 ml) was treated with dimethyl sulfate (41.6 ml, 0.44 mol) and then refluxed for 12 h. The reaction mixture was filtered, the precipitate was washed repeatedly with acetone, concentrated and partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4), concentrated and purified over a silica gel column using ethyl acetate-light petroleum (1:9) as an eluent to afford **34** (19.4 g, 90%) as white solid.

Melting point : 44 °C [lit mp: 42-43 °C]

^{1}HNMR ($CDCl_3$, 500 MHz) : δ 3.80 (s, 6H), 3.9 (s, 3H), 6.6 (t, *J* = 2.4 Hz, 2H), 7.15 (d, *J* = 2.4 Hz, 1H).

Anal: Calcd for $C_{10}H_{12}O_4$: C, 61.22, H, 6.12. Found: C, 60.85, H, 6.2

3,5-Dimethoxy benzyl alcohol (35):



At 0 °C, a solution of **34** (19 g, 0.1 mol) in dry THF (150 ml) was treated with $LiAlH_4$ (4.42 g, 0.11 mol) over a period of 1 h and the stirring was continued for 5 h at the same temperature. Then the reaction mixture was quenched with aqueous KOH (5 ml), water (14 ml), stirred for 1 h and filtered through a pad of celite. The filtrate was dried (Na_2SO_4), concentrated

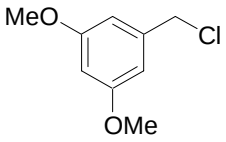
and purified by column chromatography (ethyl acetate-light petroleum, 3:7) to obtain **35** (14.3 g, 88%) as a white solid.

Melting point : 52 °C [lit mp: 47-50 °C]

^{1}HNMR ($CDCl_3$, 200MHz) : δ 1.97 (bs, 1H), 3.79 (s, 6H), 4.6 (s, 2H), 6.35 (t, *J* = 2.4 Hz, 1H), 6.5 (d, *J* = 2.4 Hz, 2H).

Anal: Calcd for $C_9H_{12}O_3$: C, 64.28, H, 7.14. Found: C, 64.52, H, 6.86.

3,5-Dimethoxy benzyl chloride (11):



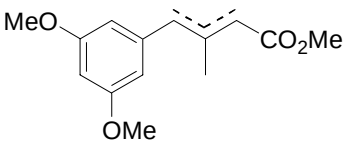
A solution of alcohol **35** (14 g, 83.3 mmol) and triphenyl phosphine (26.2 g, 0.1 mol) in CCl_4 (150 ml) was refluxed for 6 h. After the complete disappearance of starting material, the reaction mixture was filtered, concentrated and purified over a silica gel column using ethyl acetate-light petroleum (1:9) as eluent to afford **11** (14 g, 90%) as a white solid.

Melting point : 46 °C [lit mp: 46-48 °C]

^{1}HMNR ($CDCl_3$, 200MHz) : δ 3.82 (s, 6H), 4.53 (s, 2H), 6.4 (t, *J* = 2.4 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 2H).

Anal: Calcd for $C_9H_{11}ClO_2$: C, 57.9, H, 5.89. Found: C, 58.12, H, 6.16.

Heck Reaction:



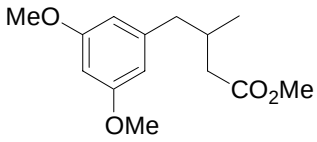
A thick suspension of **11** (5 g, 26.8 mmol), *n*-Bu_3N (12.7 ml, 53.6 mmol) and methyl crotonate (5.6 ml, 53.6 mmol) were de-gassed for 30 min with argon, then $Pd(OAc)_2$ (0.18 g, 0.8 mmol) was added and the contents were stirred at 100 °C, under argon for 16h. The reaction mixture was poured into ice, extracted with ethyl acetate and washed with dilute HCl and water.

The organic layer was dried (Na_2SO_4), concentrated and purified by column chromatography (ethyl acetate- light petroleum, 1:9) to afford **36** (4.35 g, 65%) as a pale yellow oil.

^{1}HNMR ($CDCl_3$, 200 MHz) : δ 2.05 (s, 3H), 3.25 (m, 1H), 3.65 (m, 1H), 3.75 (s, 9H), 5.0 (s, 1H), 6.35 (t, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 2H).

Anal: Calcd for $C_{14}H_{18}O_4$: C, 67.18, H, 7.25. Found C, 67.34, H, 7.36.

4-(3,5-Dimethoxy-phenyl)-3-methyl-butyric acid methyl ester (37):



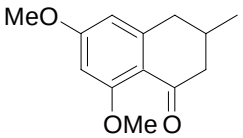
A suspension of **36** (4.2 g, 16.8 mmol) and Pd/C (0.4 g) in MeOH (20 ml) was stirred vigorously under H_2 atmosphere for 8 h. The reaction mixture was filtered through a pad of celite, concentrated, dried (Na_2SO_4), and purified over a silica gel column using ethyl acetate-light petroleum (1:9) as an eluent to procure **37** (3.4 g, 80%) as a colorless oil.

^{1}HNMR ($CDCl_3$, 200 MHz) : δ 0.95 (d, *J* = 5.8 Hz, 3H), 2.1-2.65 (m, 5H), 3.65 (s, 3H), 3.8 (s, 6H), 6.3 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 19.47, 31.82, 40.50, 43.07, 50.94, 54.80, 97.88, 106.99, 142.25, 160.55, 172.90.

Anal: Calcd for $C_{14}H_{20}O_4$: C, 66.65, H, 7.99. Found: C, 66. 42, H, 8.14.

6,8-Dimethoxy-3-methyl-3,4-dihydro-2*H*-naphthalen-1-one (38):



A mixture of **37** (3.2 g, 12.7 mmol) and poly phosphoric acid (17 g, 5 g per 1 g of compound) was stirred at 70 °C for 24 h. Then ice-cooled water was added and the reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4),

concentrated and purified by column chromatography (ethyl acetate-light petroleum,1:2) to afford **38** (1.95 g, 70%) as pale yellow crystalline.

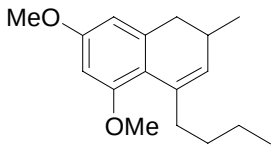
Melting point : 136 °C.

^{1}HNMR ($CDCl_3$, 200 MHz) : δ 1.05 (d, *J* = 5.8 Hz, 3H), 2.2 (m, 2H), 2.6 (m, 2H), 2.85 (m, 1H), 3.81 (s, 3H), 3.85 (s, 6H), 6.3 (d, *J* = 2.4 Hz, 2H)..

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.73, 29.41, 39.33, 48.49, 54.88, 55.40, 96.75, 104.43, 115.57, 147.99, 162.10, 163.50, 195.11.

Anal: Calcd for $C_{13}H_{16}O_3$: C, 70.89, H, 7.32. Found: C, 71.02, H, 7.42.

4-Butyl-5,7-dimethoxy-2-methyl-1,2-dihydro-naphthalene (39):



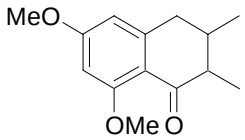
To a solution of **38** (0.2 g, 0.9 mmol) in THF (5 ml) was added 1.6 M *n*-BuLi (0.7 ml, 1.1 mmol) at –78 °C. After 20 min, MeI (0.1 ml, 1.8 mmol) was added and stirred for 1 h at –78 °C. The reaction was quenched with sat NH_4Cl, concentrated and partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4), concentrated and purified on silica gel using ethyl acetate-light petroleum (1:4) as eluent to afford **39** (0.4 g, 86%) as colourless liquid.

^{1}HNMR ($CDCl_3$, 200 MHz) : δ 0.95 (t, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 5.8 Hz, 3H), 1.35 (m, 4H), 2.25- 2.50 (m, 3H), 2.55-2.95 (m, 2H), 3.80 (s, 3H), 3. 85 (s, 3H), 5.55 (s, 1H), 6.37 (d, *J* = 2.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ14.1, 19.9, 22.6, 28.5, 31.7, 36.1, 39.4, 54.9, 55.1, 97.2, 105.4, 117.1, 130.5, 136.5, 140.8, 157.2, 158.9.

Anal: Calcd for $C_{17}H_{24}O_2$: C, 78.42, H, 9.29. Found: C, 78.27, H, 9.38.

6,8-Dimethoxy-2,3-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (8):



A mixture of **38** (1 g, 4.5 mmol), para formaldehyde (0.6 g, 20 mmol) and CF_3CO_2:N(Me)Ph salt (1.5 g, 6.8 mmol) in THF (15 ml) were refluxed for 4 h (The aniline salt was insoluble at initial stage of the reactions and dissolves after 1 h of reflux). The resulting red solution was cooled to room temperature, diethyl ether was added drop wise with efficient stirring, the ether layer was decanted and washed with half saturated bicarbonate. The ether layer was dried (Na_2SO_4) and concentrated to afford crude methylene product **40** (0.9 g)**,** which was used as such for next reaction. A suspension of compound **40** (0.9 g, 3.9 mmol) and Pd/C (0.1 g) in MeOH (5 ml) was stirred under H_2 atmosphere for 6 h. The reaction mixture was filtered through a pad of celite, concentrated and purified over a silica gel column using ethyl acetate-light petroleum (1:2) as an eluent to afford **8** (0.8 g, 75% overall) as white solid.

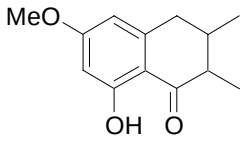
Melting point : 150 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.95 (d, *J* = 7.0 Hz, 0.6H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 2.4H), 1.90 (m, 1H), 2.16 (m, 1H), 2.57-2.98 (m, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 6.24 (s, 1H), 6.29 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.20, 13.34, 14.95, 19.84, 33.11, 35.39, 36.64, 38.55, 47.85, 50.31, 54.87, 55.42, 96.81, 104.02, 104.61, 115.34, 146.69, 147.13, 159.52, 162.13, 163.38, 197.68, 198.34.

Anal: Calcd for $C_{14}H_{18}O_3$: C, 71.77, H, 7.74. Found: C, 71.89, H, 7.65.

8-Hydroxy-6-methoxy-2,3-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one (41):



An ice-cooled solution of **8** (0.5 g, 2.1 mmol) in CH_2Cl_2 (10 ml) was treated with BCl_3 (4.3 ml, 1M solution in CH_2Cl_2, 4.3 mmol) slowly and stirred for 30 min. The reaction mixture was quenched with water, diluted with CH_2Cl_2 and washed repeatedly with water. The organic layer was dried (Na_2SO_4), concentrated and purified by column chromatography (ethyl acetate-light petroleum, 1:9) to afford **41** (0.4 g, 86%) as a pale yellow solid.

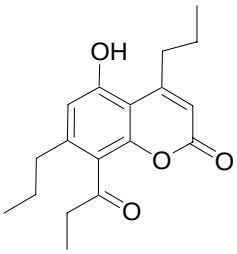
Melting point : 195 °C.

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.15 (d, *J* = 6.6 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.97 (m, 1H), 2.26 (m, 1H), 2.62 (d, *J* = 10.7 Hz, 1/2H), 2.66 (d, *J* = 10.7 Hz, 1/2H), 2.90 (d, *J* = 3.9 Hz, 1/2H), 2.92 (d, *J* = 3.9 Hz, 1/2H), 3.84 (s, 3H), 6.24 (m, 1H), 6.29 (d, *J* = 2.1Hz, 1H), 12.95 (d, *J* = 13.9 Hz, OH).

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 12.52, 15.19, 19.81, 35.07, 37.25, 48.47, 55.10, 98.53, 106.09, 145.64, 165.43, 204.71.

Anal: Calcd for $C_{13}H_{16}O_3$: C, 70.89, H, 7.32. Found: C, 71.08, H, 7.38.

5-Hydroxy-8-propionyl-4,7-dipropyl-chromen-2-one (42):



A solution of **41** (0.2 g, 0.9 mmol), triflic acid (2 ml) and ethyl butyryl acetate (0.3 ml, 1.8 mmol) was stirred at 100 °C for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and purified

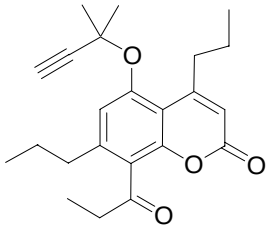
over a silica gel column using ethyl acetate-light petroleum (1:4) as an eluent gave **42** (0.16 g, 60%) as colourless liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.97 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.59-1.85 (m, 4H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.88 (q, *J* = 7.5 Hz, 2H), 3.18 (t, *J* = 7.5 Hz, 2H), 6.11 (s, 1H), 6.86 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.56, 14.14, 16.53, 20.21, 24.66, 29.69, 35.79, 37.19, 96.22, 109.97, 114.68, 115.96, 116.22, 143.94, 157.90, 158.75, 159.78, 167.31, 181.02.

Anal: Calcd for $C_{18}H_{22}O_4$: C, 71.50, H, 7.33. Found C, 71.34, H, 7.25.

5-(1,1-Dimethyl-prop-2-ynyloxy)-8-propionyl-4,7-dipropyl-chromen-2-one (43):

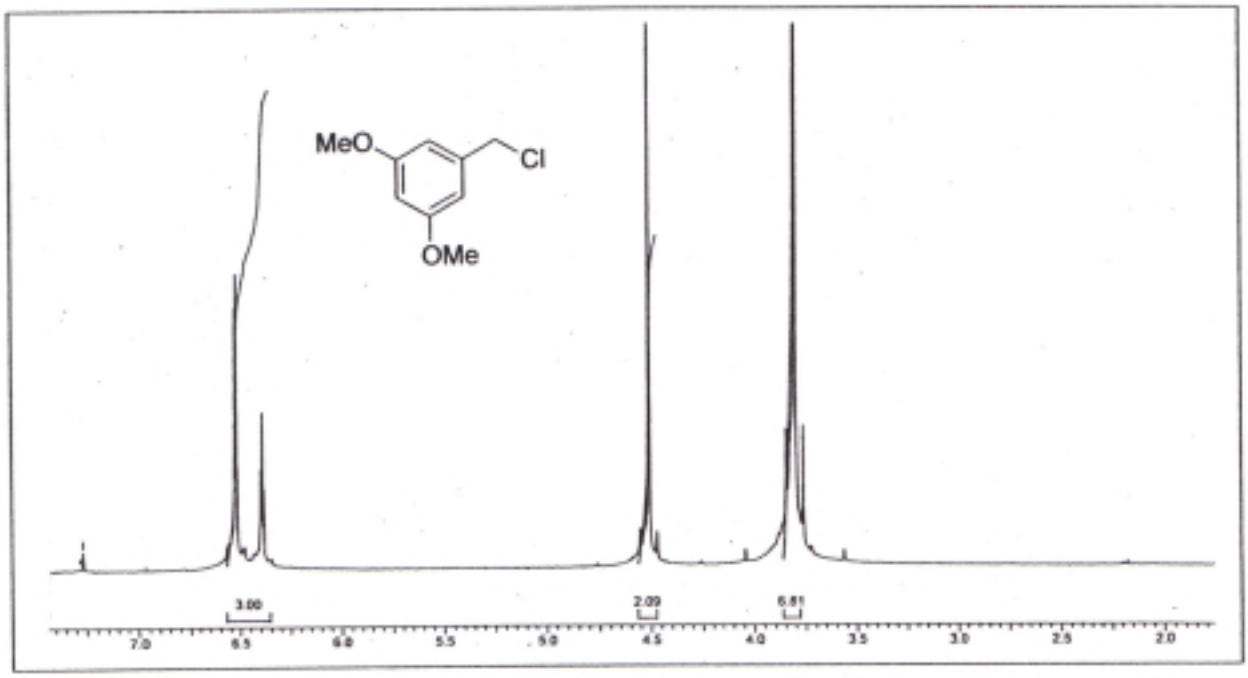


A suspension of **42** (0.15 g, 0.5 mmol) and K_2CO_3 (0.17 g, 1.25 mmol) in 2-butanone (65 ml) and dry DMF (65 ml) was treated with 3-chloro-3-methyl-1-butyne (0.25 g, 2.5 mmol) and TBAI (0.18 g, 0.5 mmol) and the contents were stirred for 12 h at 60 °C. The reaction mixture was filtered and the filtrate was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4), concentrated and purified by column chromatography (ethyl acetate-light petroleum as eluent, 1:3) to obtain **43** (0.13g, 72%) as colorless syrup.

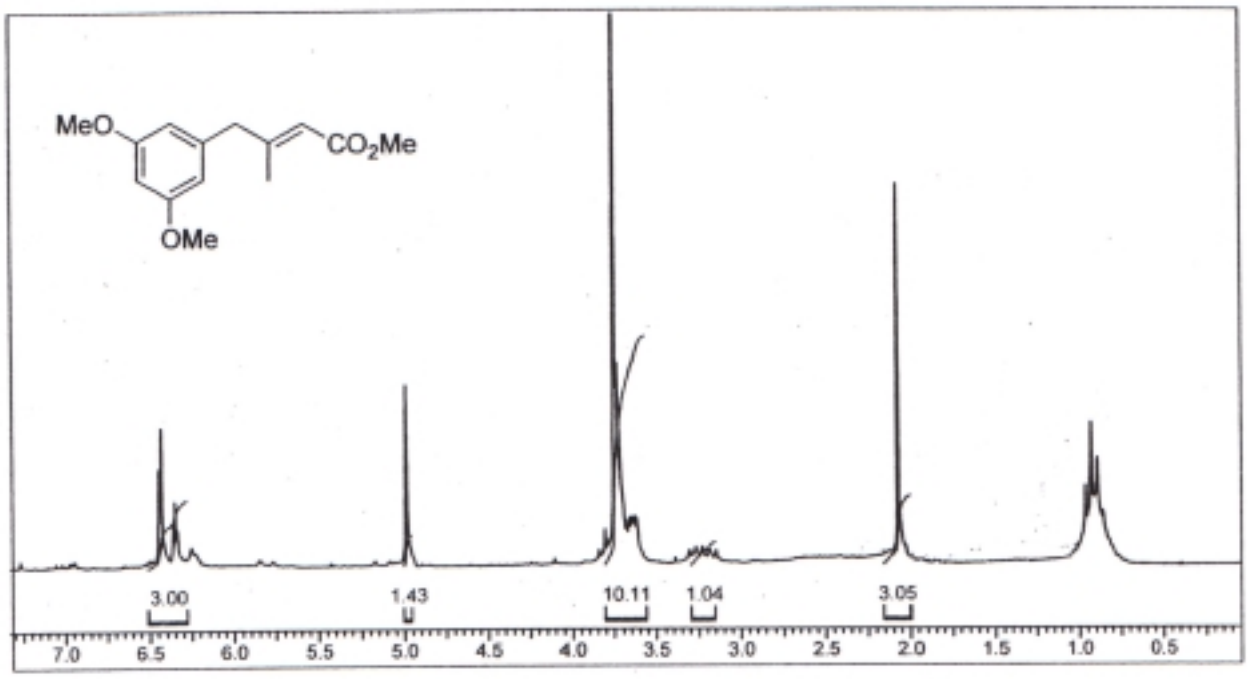
^{1}H NMR ($CDCl_3$, 500 MHz) : δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.06 (t, *J* = 7.3 Hz, 3H), 1.18 (t, *J* = 7.3 Hz, 3H), 1.70 (m, 2H), 1.79 (s, 6H), 1.83 (m, 2H), 2.69 (t, *J* = 7.45 Hz, 2H), 2.71 (s, 1H), 2.85 (q, *J* = 7.45 Hz, 2H), 3.25 (t, *J* = 7.7 Hz, 2H), 6.69 (s, 1H), 7.55 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 13.54, 13.63, 14.04, 16.94, 20.27, 24.36, 29.91, 35.97, 37.41, 72.71, 74.91, 85.33, 96.17, 109.4, 113.4, 117.7, 120.9, 143.3, 157.4, 180.2.

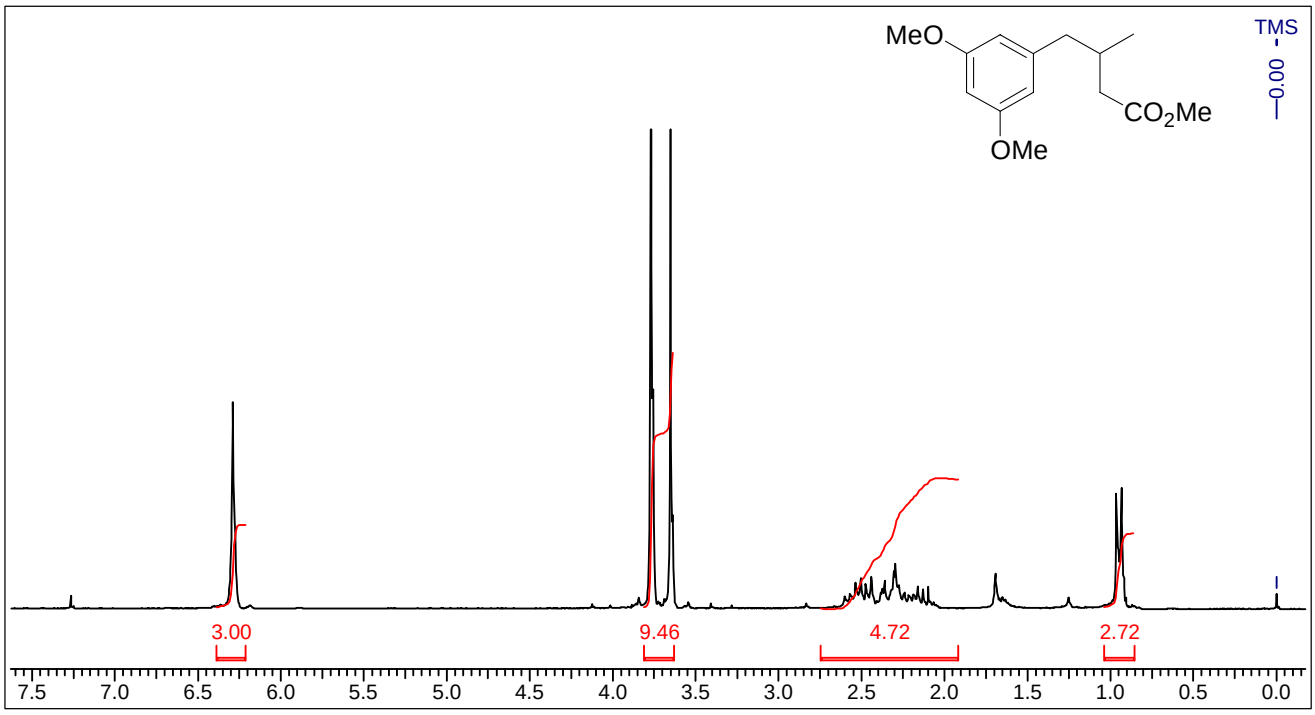
Anal: Calcd for $C_{23}H_{28}O_4$: C, 74.97, H, 7.66. Found: C, 75.32, H, 7.52



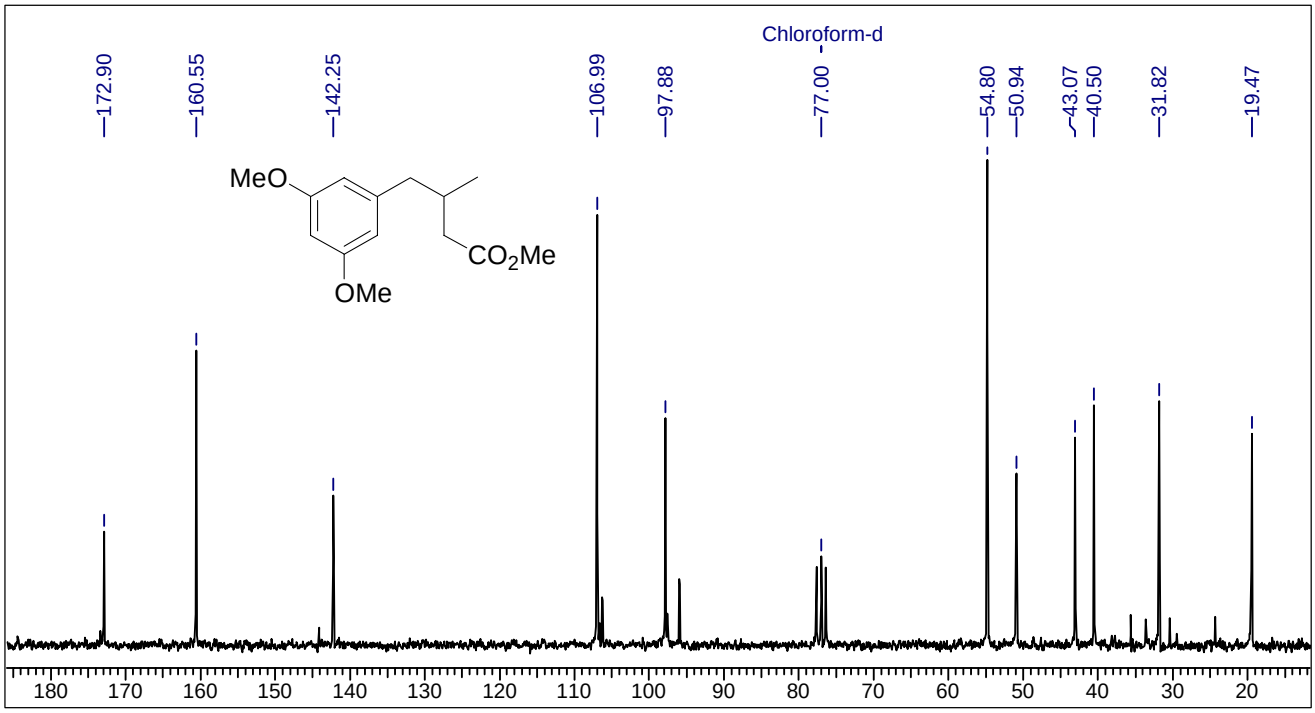
^{1}H NMR Spectrum of compound 11 in $CDCl_3$



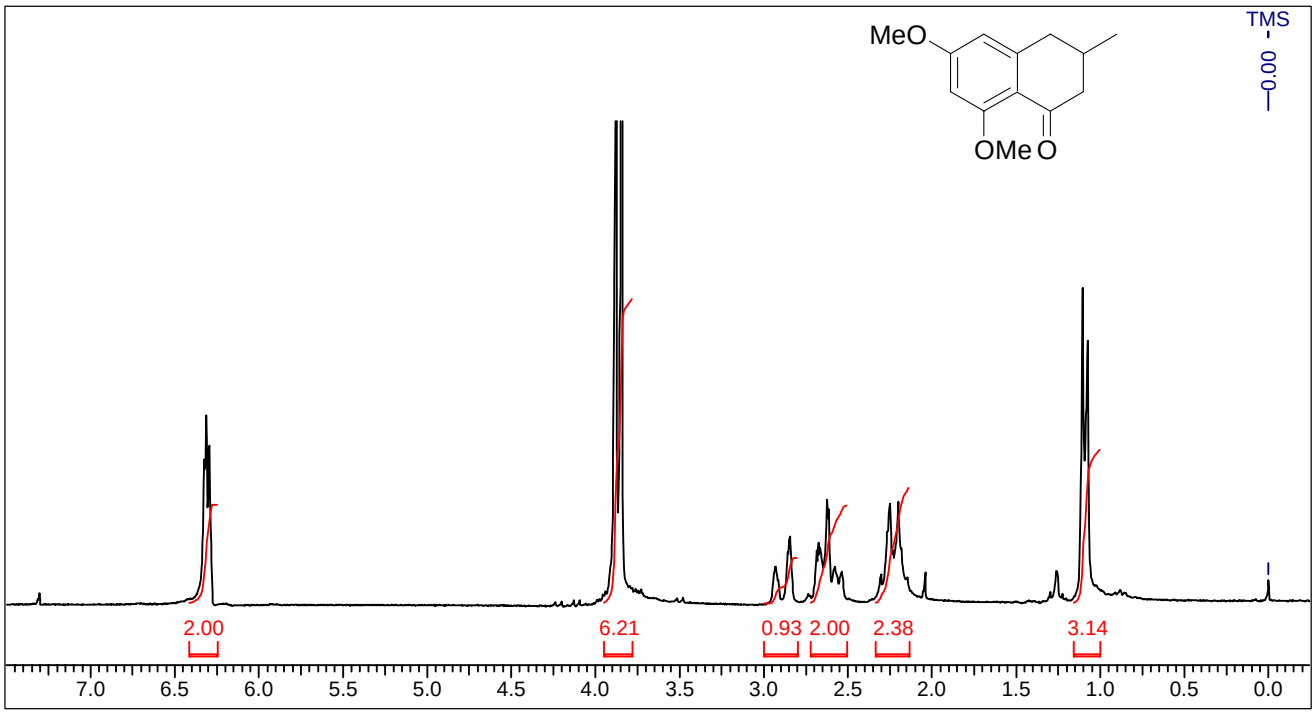
^{1}H NMR Spectrum of compound 36 in $CDCl_3$



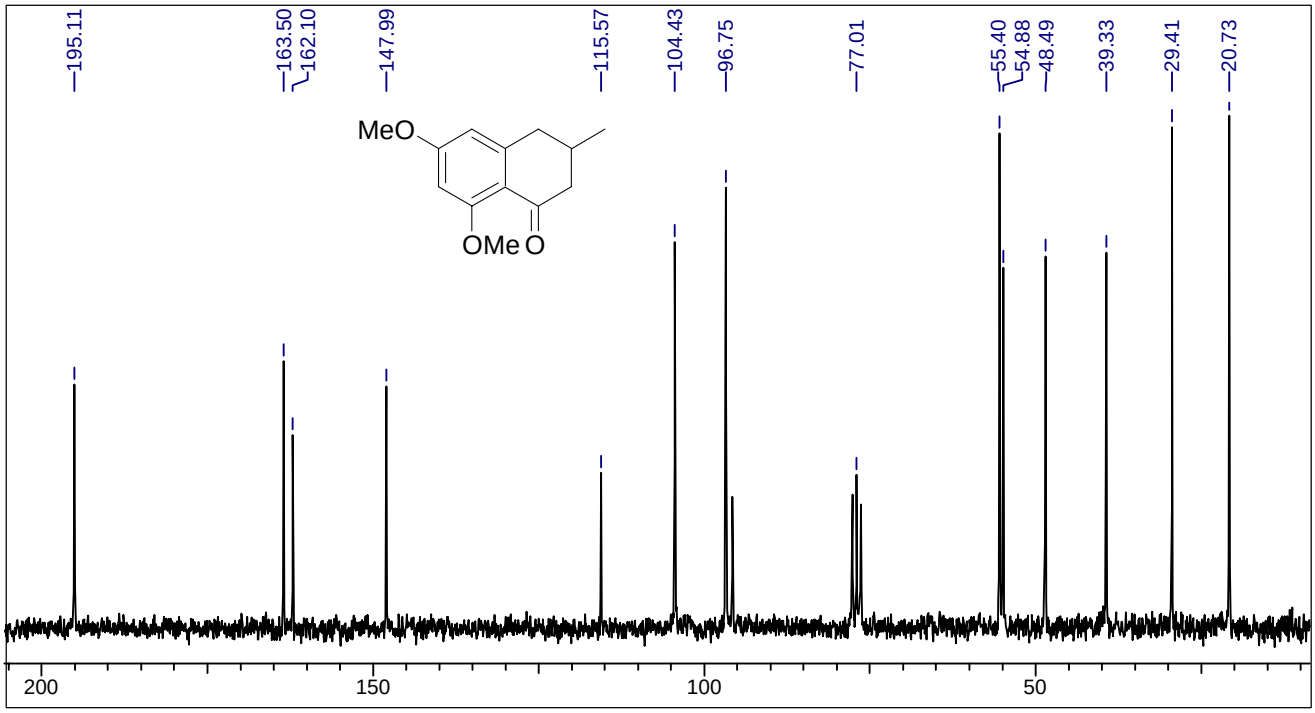
^{1}H NMR Spectrum of compound 37 in $CDCl_3$



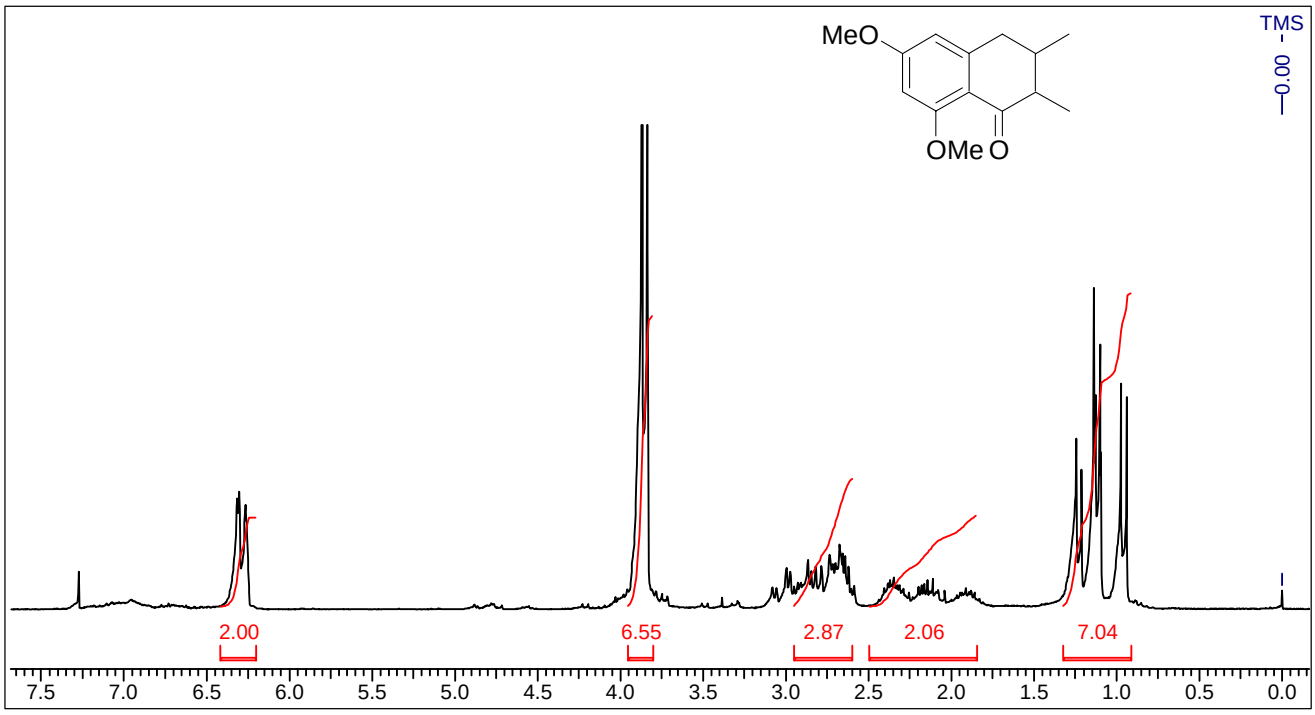
^{13}C NMR Spectrum of compound 37 in $CDCl_3$



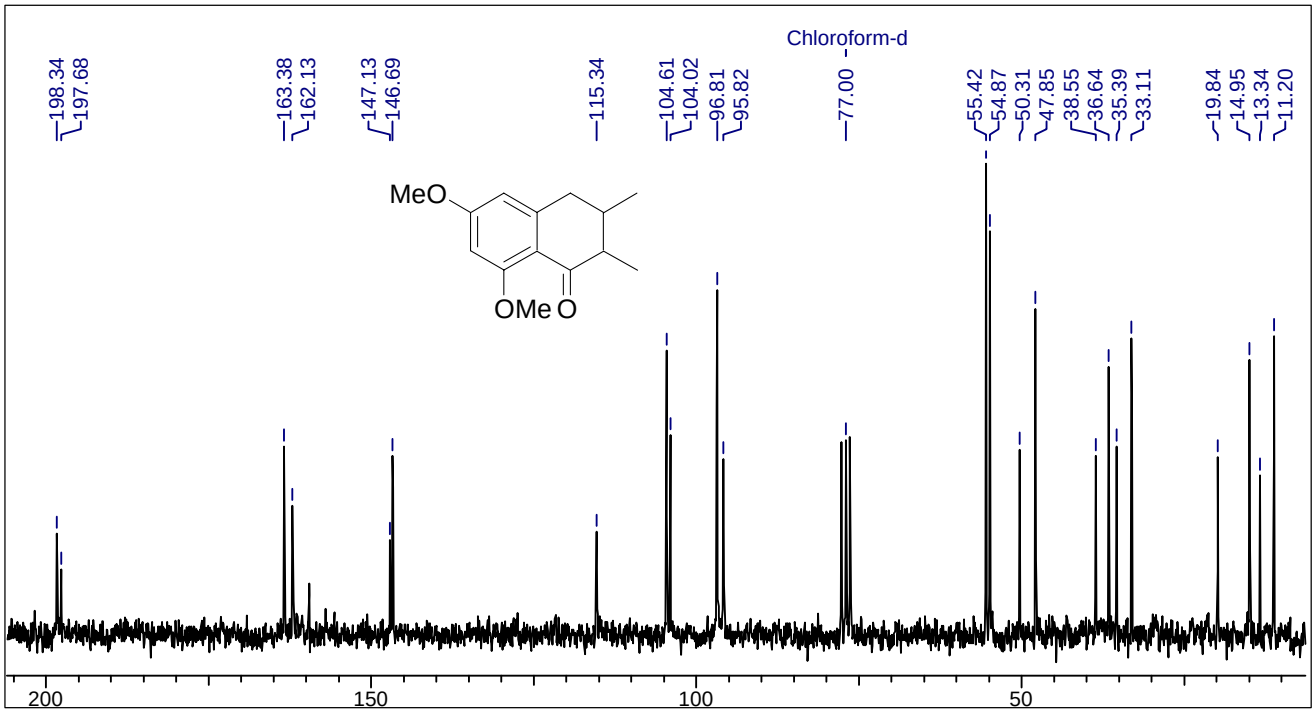
^{1}H NMR Spectrum of compound 38 in $CDCl_3$



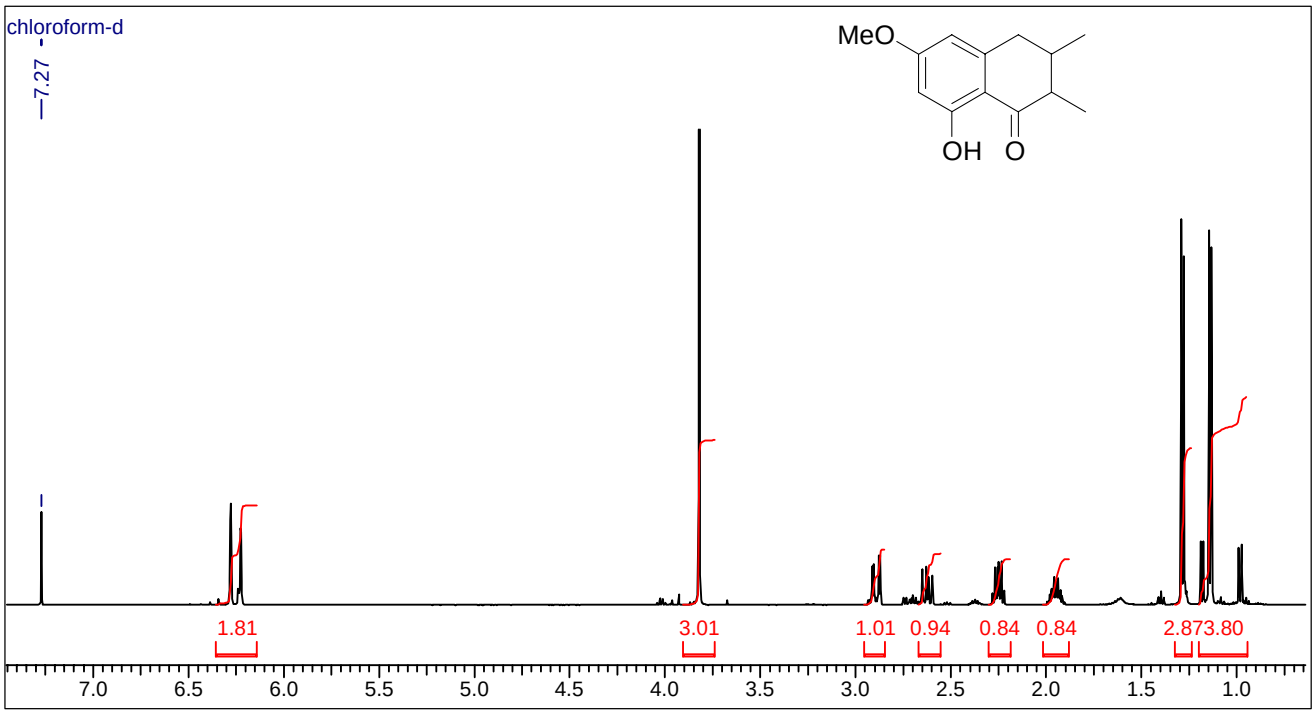
^{13}C NMR Spectrum of compound 38 in $CDCl_3$



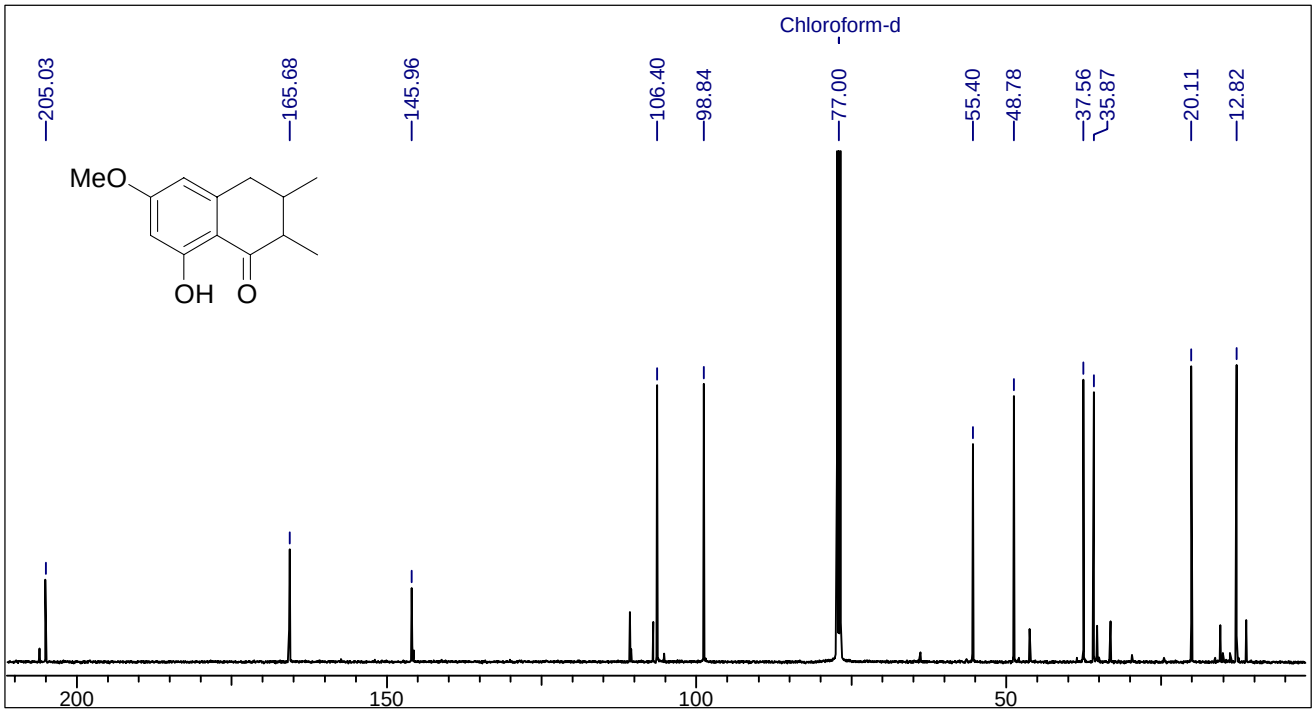
^{1}H NMR Spectrum of compound 8 in $CDCl_3$



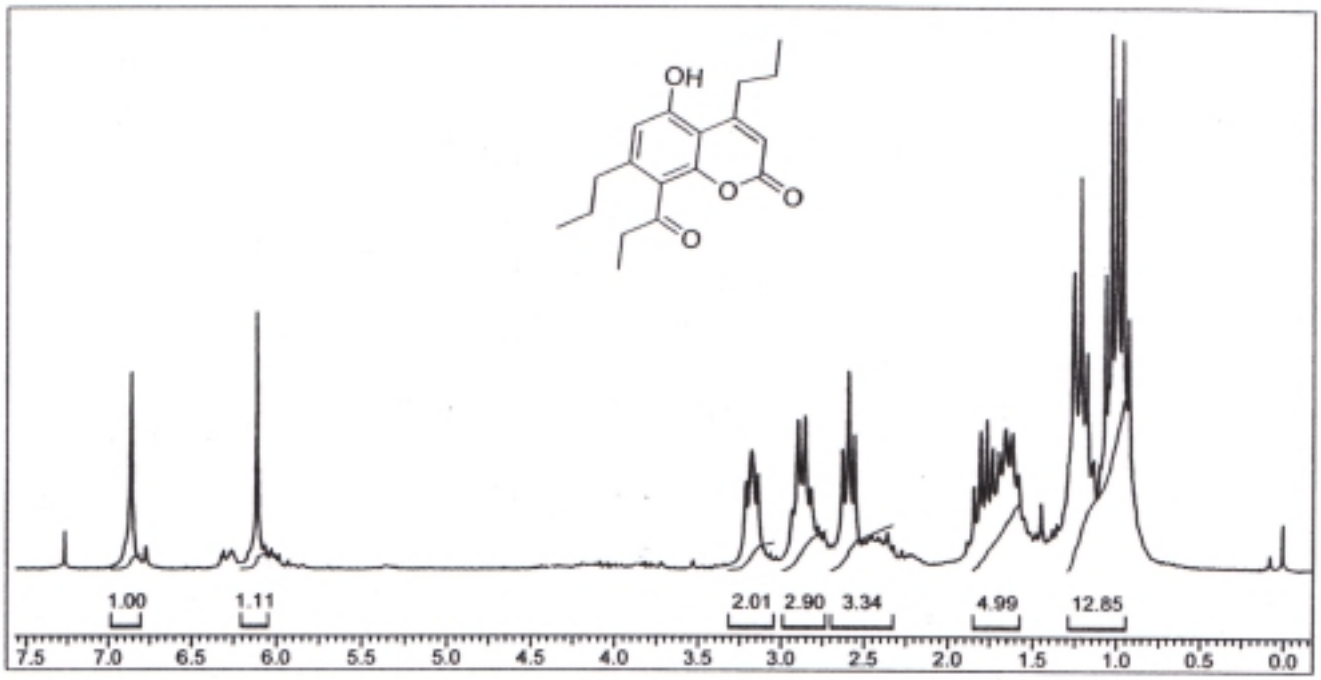
^{13}C NMR Spectrum of compound 8 in $CDCl_3$



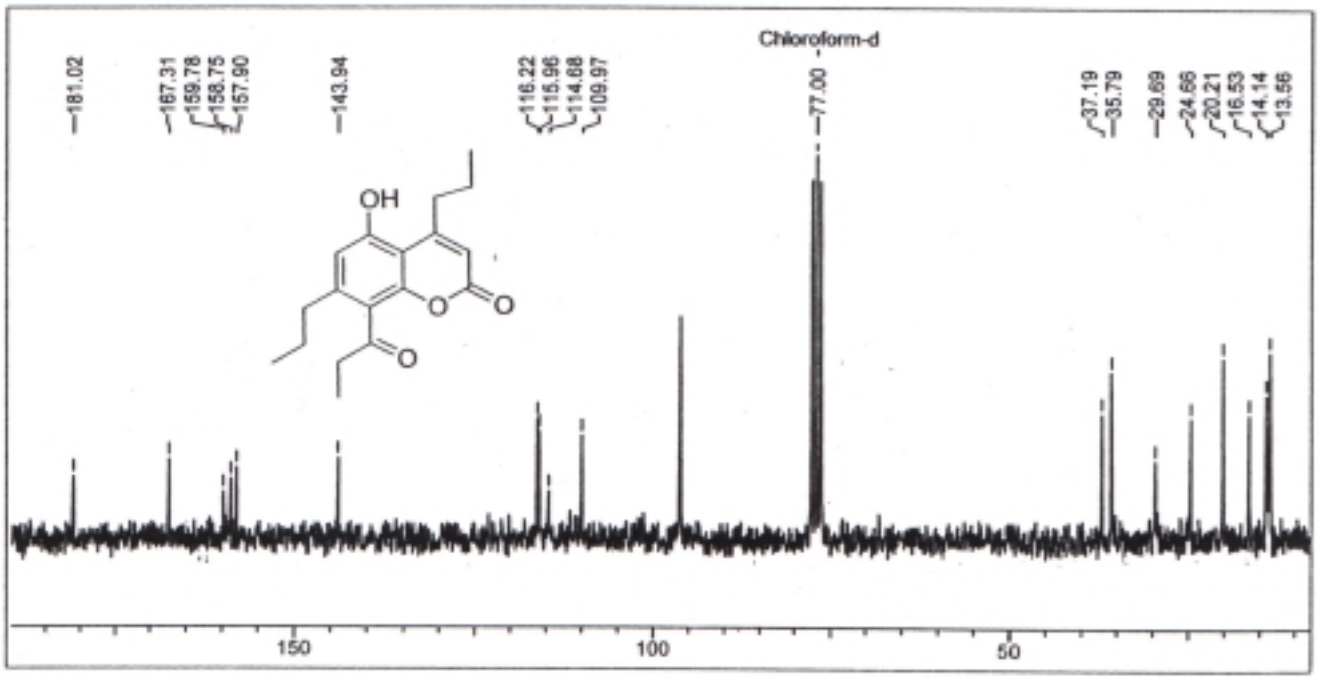
^{1}H NMR Spectrum of compound 41 in $CDCl_3$



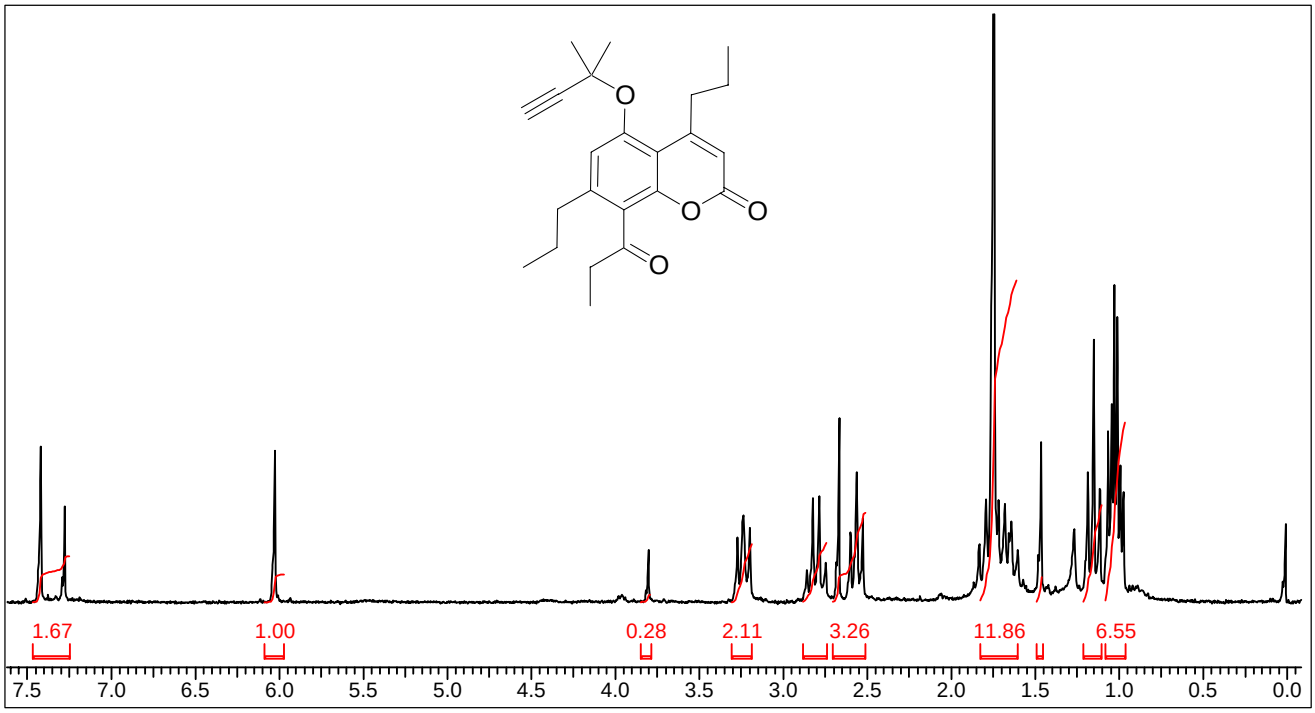
^{13}C NMR Spectrum of compound 41 in $CDCl_3$



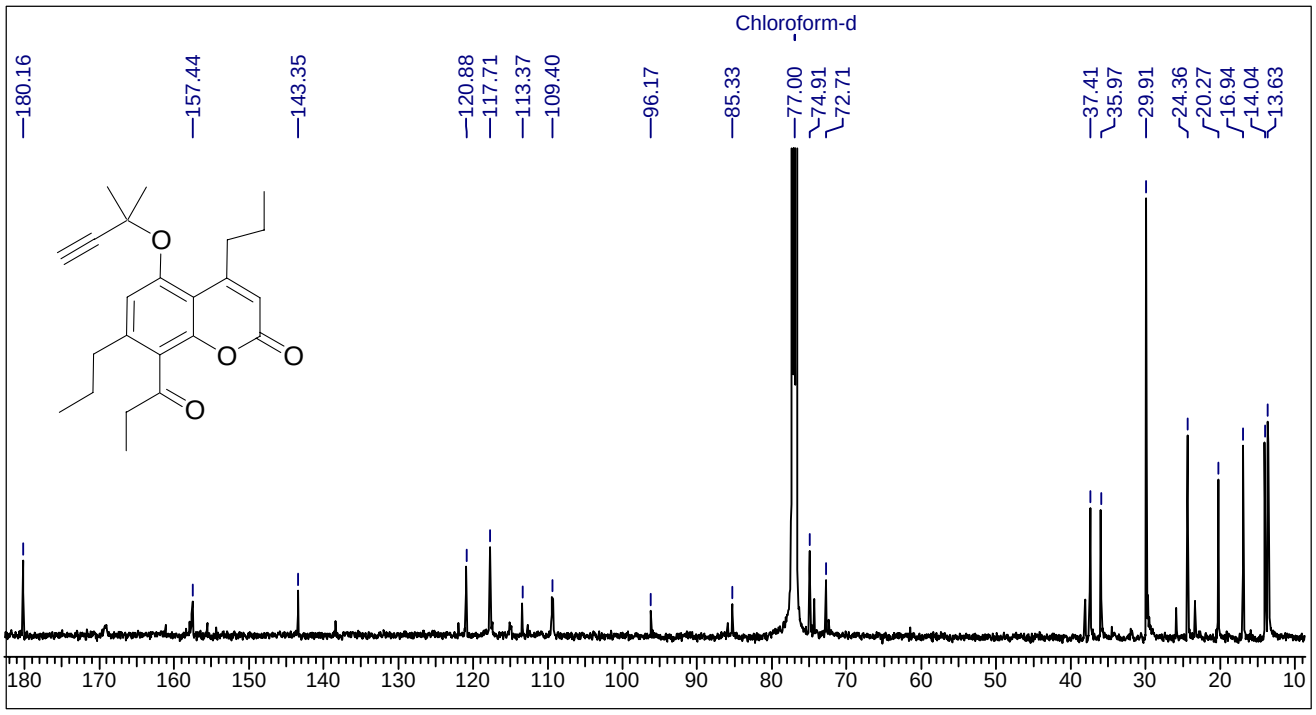
^{1}H NMR Spectrum of compound 42 in $CDCl_3$



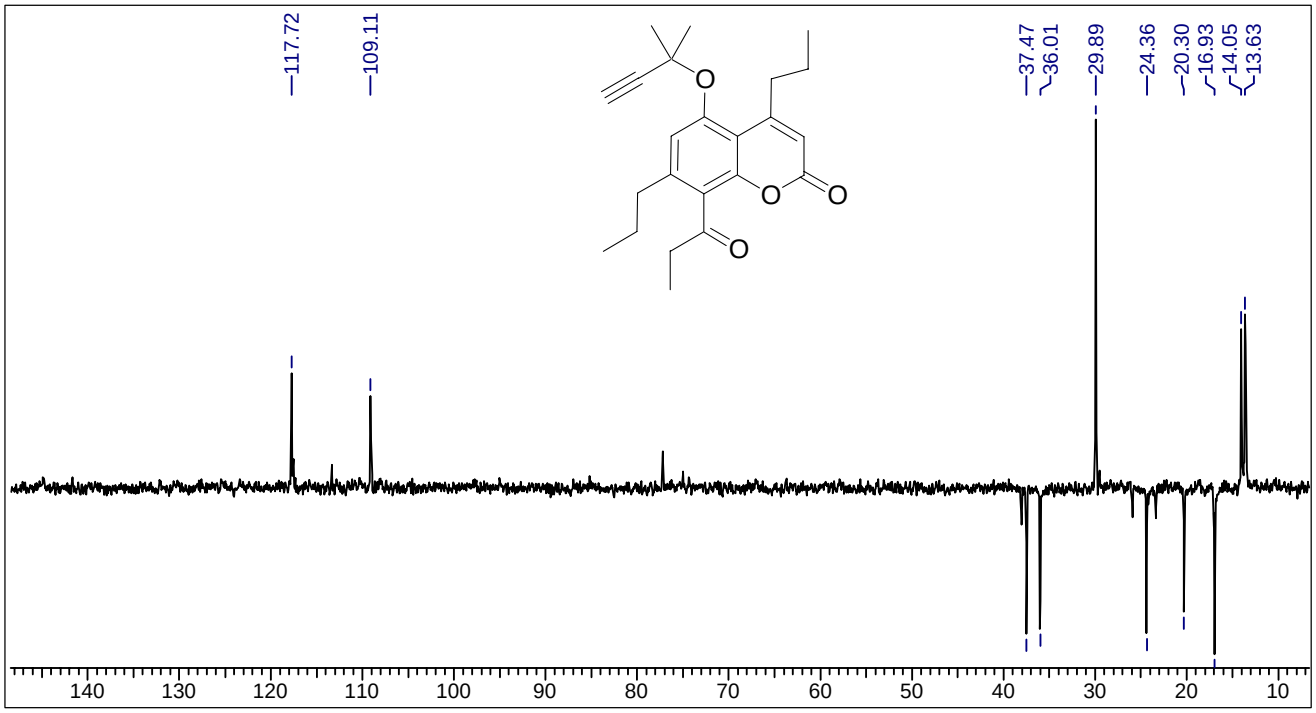
^{13}C NMR Spectrum of compound 42 in $CDCl_3$



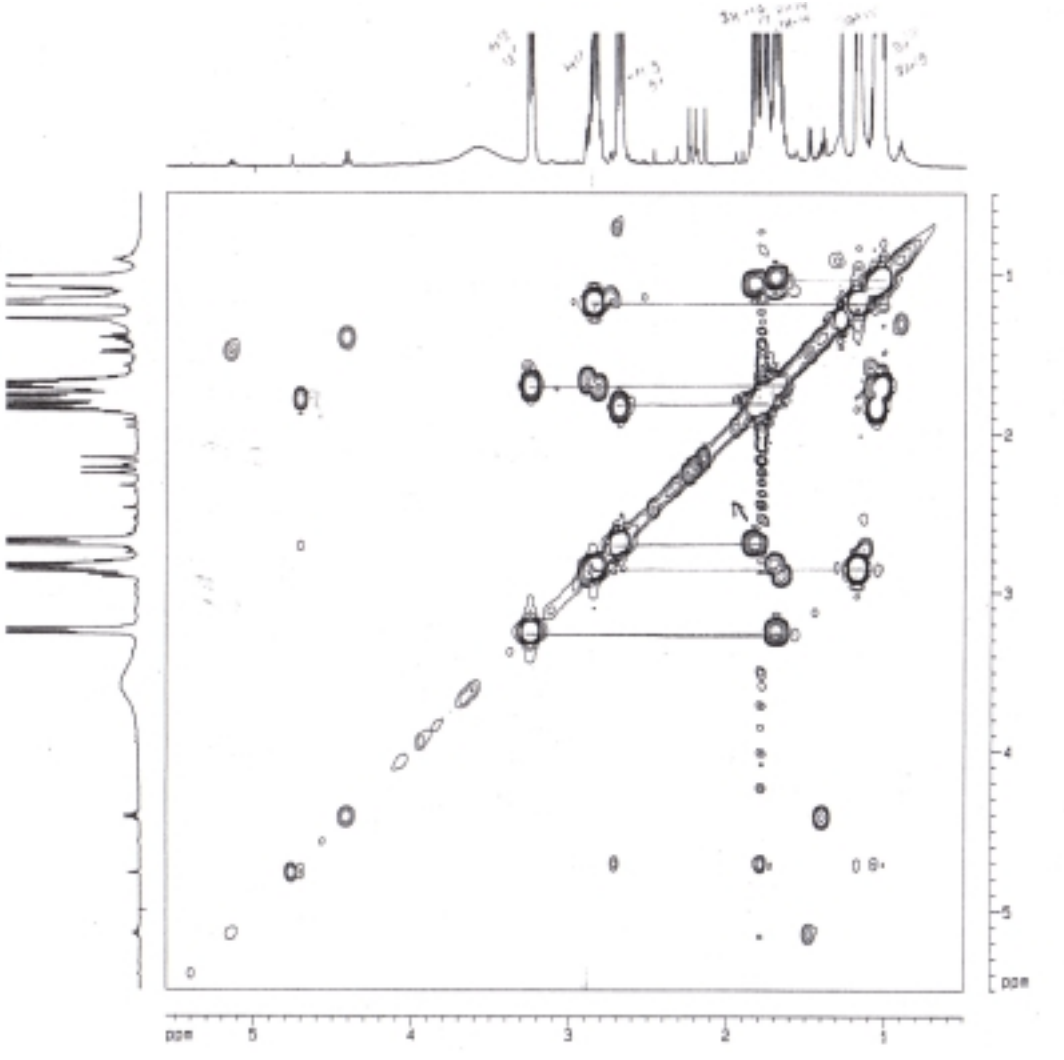
^{1}H NMR Spectrum of compound 43 in $CDCl_3$



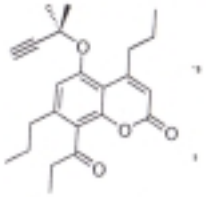
^{13}C NMR Spectrum of compound 43 in $CDCl_3$



DEPT Spectrum of compound 43 in $CDCl_3$



B.S.Reddy;
B.Galon;Cosy90 in cdcl3



COSY of compound 43

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List of Publications

1. *A carbohydrate route to CMI-977: A potent 5-lipoxygenase inhibitor*" M. S. Chorghade, K. Sadalpure, S. Adhikari, S.V.S. Lalitha, A. M. S. Murugaiah, P. Radha Krishna, **B. S. Reddy**, M. K. Gurjar, *Carbohydrate Letters*, **2000**, 3, 405-410.

2. "*A versatile approach to anti-asthmatic compound CMI-977 and it's six membered analogue*" M. K Gurjar, L. M. Krishna, **B. S. Reddy**, Mukund S. Chorghade, *Synthesis*, **2000**, 4, 557-560.

3. "*Substituted oxygen alicyclic compounds, including methods for synthesis there of*" M. S. Chorghade, M. K. Gurjar, **B. S. Reddy**, et al, USP- 6,433,197: **2002** and WIPO, WO-00/01381 A1, **2000**.

4. *"Synthesis of differentially protected cyclopentitol: its application towards the stereoselective synthesis of 5-epi-calditol*" C. V. Ramana, **B. S. Reddy**, M. K. Gurjar (*Tetrahedron Letters* **2004**, *in press*).