SYNTHESIS OF CMI-977 AND ANALOGUE, OXINDOLE DERIVATIVE AND METATHESIS APPLICATIONS

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

TO
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BY

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DEDICATED

TO

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CERTIFICATE

The research work presented in thesis entitled " **Synthesis of CMI-977 and analogue, oxindole derivative and metathesis applications** " has been carried out under my supervision and is bonafide work of Mr. A. M. S. Murugaiah. This work is original and has not been submitted for any other degree or diploma of this or any other University.

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

23th, October, 2000 Research Guide

DECLARATION

The research work embodied in this thesis has been carried out at Indian Institute of Chemical Technology, Hyderabad, and National Chemical Laboratory, Pune under the supervision of **Dr. M. K. Gurjar**, Deputy director, and Head, Division of organic chemistry: Technology, National Chemical Laboratory, Pune-411008. This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

Pune-8 (A. M. S. Murugaiah)
23th, October, 2000

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
BnBr	-	Benzyl bromide
BF_3:OEt_2	-	Boron trifluoride diethyl etherate
BsCl	-	Benzenesulfonyl chloride
BTEAC	-	Benzyltriethylammonium chloride
CSA	-	Camphorsulfonic acid
CuHP	-	Cumene hydroperoxide
DCM	-	Dichloromethane
DEAD	-	Diethyl azodicarboxylate
DMA	-	*N*,*N'*-Dimethylacetamide
DMAP	-	*N*,*N'*-Dimethylaminoformamide
DMF	-	*N*,*N'*-Dimethylformamide
DMS	-	Dimethylsulphide
DMSO	-	Dimethyl sulfoxide
DIAD	-	Diisopropyl azodicarboxylate
DIBAL-H	-	Diisobutylaluminium hydride
DIPT	-	Diisopropyl tartrate
IBX	-	Iodoxybenzoic acid
LDA	-	Lithium diisopropylamide
MsCl	-	Methanesulfonyl chloride
*m*CPBA	-	*meta*-Chloroperbenzoic acid
PMB	-	*para*-methoxybenzyl
PTSA	-	*para*-Toluenesulfonic acid
TBAI	-	Tetra-*n*-butylammonium iodide
TBTH	-	Tri-*n*-butyltin hydride
TEA	-	Triethylamine
TIP	-	Titanium tetrakis(isopropoxide)
TPP	-	Triphenylphosphine
TsCl	-	*para*-Toluenesulfonyl chloride

GENERAL REMARKS

- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.

- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.

- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}

- Proton magnetic resonance spectra were recorded on Varian FT-200 MHZ (Gemini), AC-200 MHz, MSL-300 MHz, Bruker-500 MHz and Varian Unity-400 MHz spectrometer using tetramethyl 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 Varian FT-50 MHz (Gemini), AC-50 MHz, MSL-75 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 autospec 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 Molisch's reagent or Anisaldehyde reagent in ethanol as development reagents.

- All evaporation 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.

CONTENTS

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Last, thanks to my parents who shaped me to this status with their bluntless vision and selfless agenda. Special mention to my sisters for love.

A.M.S.Murugaiah

ABSTRACT

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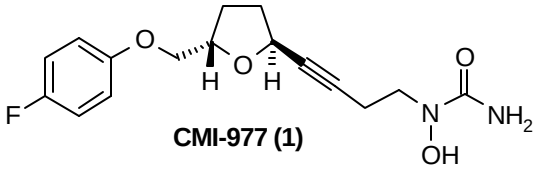
The thesis entitled "**synthesis of CMI-977 and analogue, oxindole derivative and metathesis applications**" is divided into three chapters. The first chapter deliberates the synthetic efforts towards anti-asthmatic lead candidate CMI-977 (section I) and AZA-CMI-977 (section II). The second chapter deals with the synthesis of oxindole part of schizophrenia drug Zeldox. The last chapter includes the application of ring closing metathesis in the synthesis of (*R*)-4-benzyloxycyclopent-2-en-1-one.

CHAPTER I

SECTION-I: Asymmetric synthesis of CMI-977.

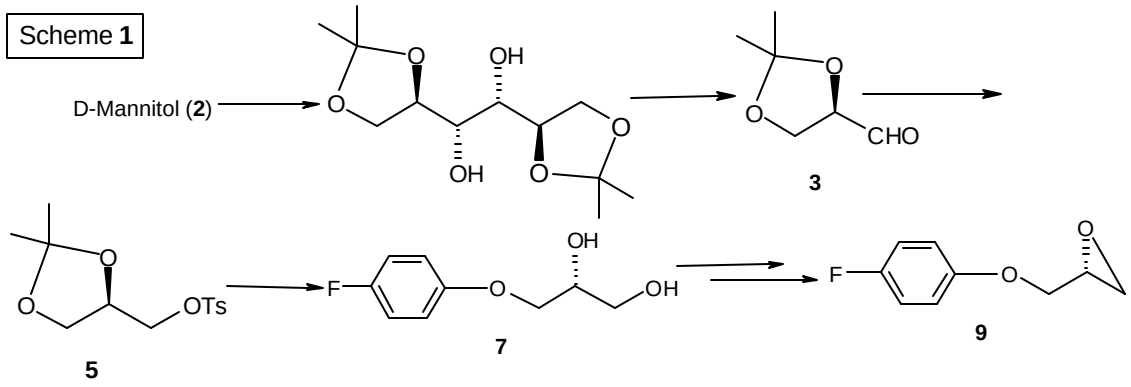
The alarming rise of asthma constitutes the biggest mystery in modern health care at the beginning of this century and the exact reasons still evade the researchers despite the advances in molecular biology and asthma chemotherapy. This has led to the worldwide intense search for safer and target-specific drugs for asthma. CMI-977, (2*S*,5*S*)-*trans*-5-(4-fluorophenoxy) methyl-2-(4-*N*-hydroxyureidyl-1-butynyl)tetrahydrofuran (**1**) is being currently developed by Millenium Pharmaceuticals, USA, as a promising candidate for chronic asthma.



CMI-977 (1)

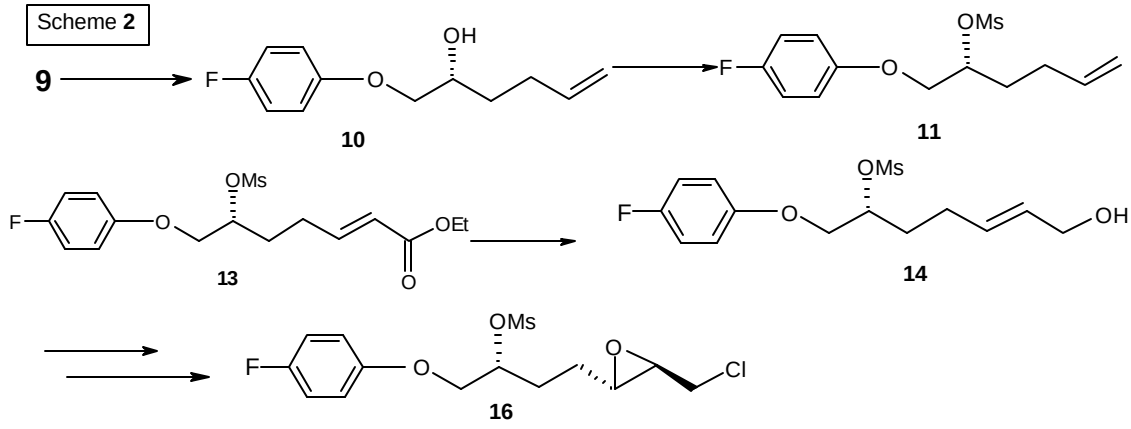
The unique structural ensemble, featured with diverse substitution and *trans*-juxtapositioned ring invited the proposal to undertake a 'single enantiomer synthesis' that would deliver the target molecule with relevant stereochemistry and functionalities. Accordingly, the journey began with D-mannitol (**2**), which was ketalized followed by oxidative cleavage to provide (D)-glyceraldehyde synthon (**3**), which was then converted to glycidyl ether (**9**) as described in the Scheme **1.**

Scheme **1**



The CuCN-coordinated opening of **9** with allylmagnesium bromide and subsequent mesylation of alcohol afforded **11**. The purpose behind the introduction of mesyl group at this stage was to utilize for dual role, as a protecting group for the next couple of steps and as a

Scheme **2**

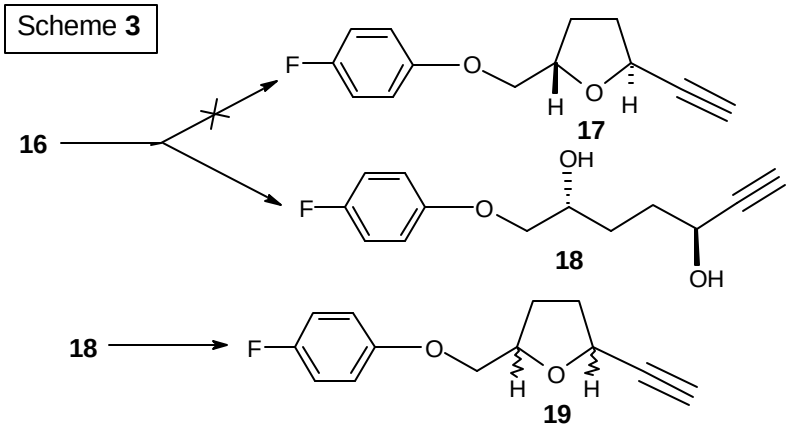


leaving group at the required last stage. Ozonolysis of **11**, followed by exposure to ethoxycarbonylmethylenetriphenylphosphorane provided (*E*)-α,β-unsaturated ester (**13**). Reductive chemistry of **13** with DIBAL-H provided the allyl alcohol (**14**) in 93% yield. This set the stage for Sharpless Asymmetric Epoxidation (SAE) that would install the second chiral centre relevant to the target.

Asymmetric epoxidation of **14** with CuHP and $Ti(O^iPr)_4$–[(+)-DIPT] complex gave the epoxy alcohol, which, in turn, was converted to **16.** The central transformation, base-induced double elimination-cum-intramolecular S_N2 ring annulation, was investigated next. The

compound **16** was exposed to *n*-BuLi at −78 ºC, followed by warming to room temperature. The product was found to be the undesired propargylic diol (**18**).

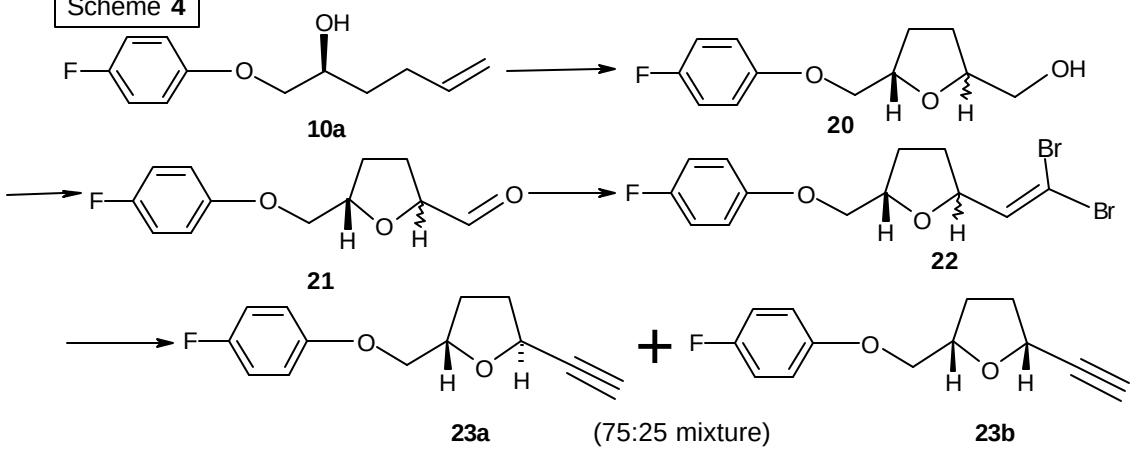
Scheme **3**



After this failure, an alternative approach was planned. The strategy was to generate the second stereogenic centre via diastereoselective substrate bias. The epoxidation of terminal alkene and ring closure by intramolecular oxygen nucleophile would result in hydroxymethyl tetrahydrofuran that can be further elaborated to our required destiny, through oxidation and Corey–Fuch's reaction to position terminal acetylene at G2. Accordingly, **10a** was exposed to *m*CPBA in CH_2Cl_2 and CSA to provide **20**, which was oxidized with IBX in DMSO followed by Wittig-type dibromomethylenation to afford **22**. This dibromoolefin (**22**) was treated with *n*-BuLi to get 2-ethynyltetrahydrofuran (**23**) [a mixture of **23a** and **23b**] in 70% yield. The mixture of diastereomers was found to be in 75:25 ratio, the predominant isomer being the required *trans*-THF isomer (**23a**). The moderate stereoselectivity and difficulty in the separation of diastereomers precluded us to advance further as there was no scope for derivatisation for want of functionalities and recrystallisation because of liquid state of product.

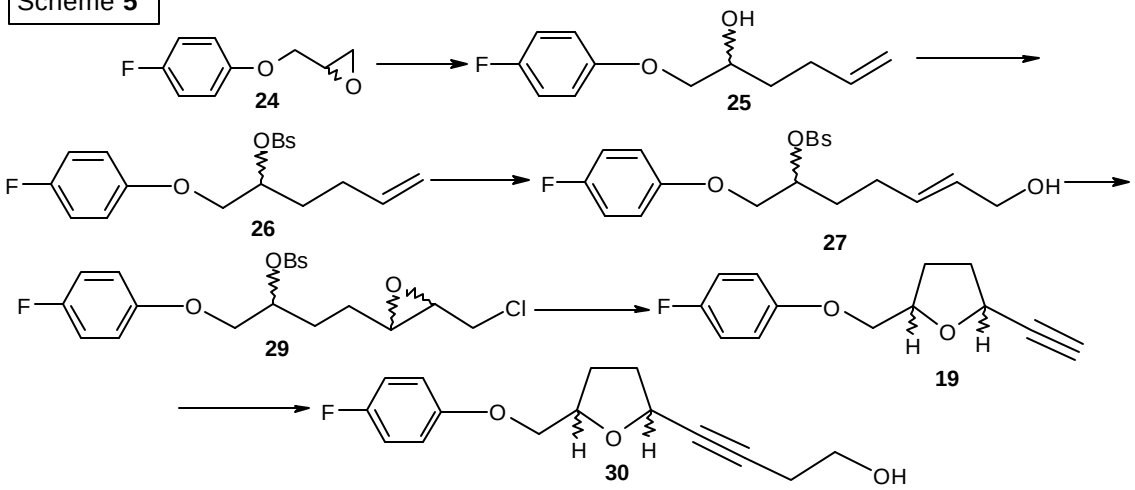
We returned to our primordial strategy. We sought to replace mesylate group with some leaving group that will withstand the basic conditions, to experiment with the racemic

Scheme **4**



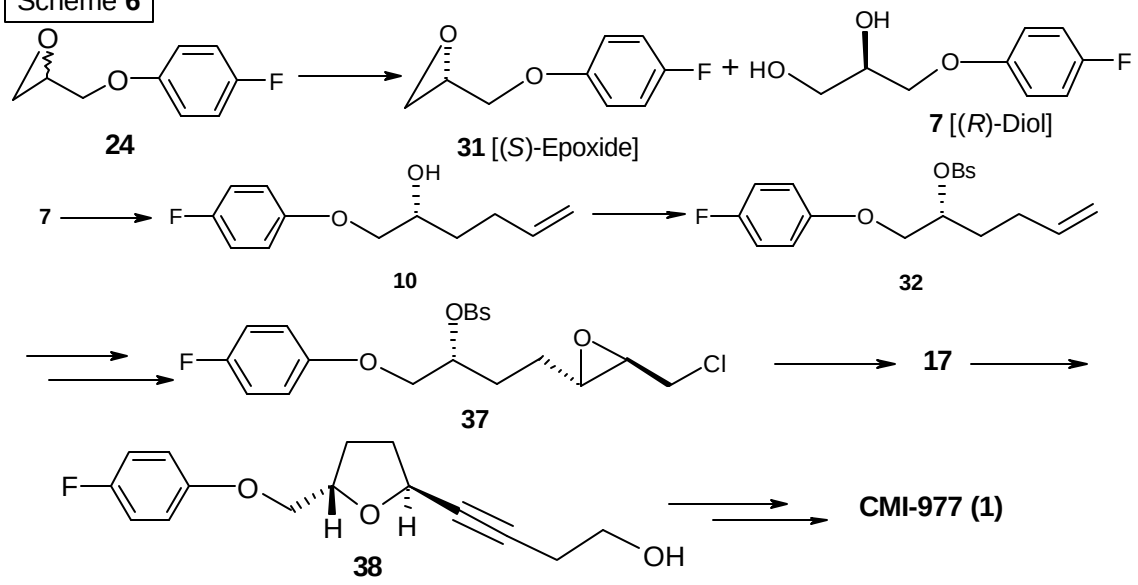
starting material (**25**), *e.g.* benzenesuphonyl group. Reaction of 4-fluorophenol with epichlorohydrin/K_2CO_3 gave *rac*-4-fluorophenyl glycidyl ether **24**, which was converted to (±)-benzenesulphonate ester (**26**) in two steps. The entire sequence, in parallel to mesylate ester scheme, was executed**.** The critical LDA-directed double elimination of epoxymethyl chloride (**29**) uneventfully gave the desired *rac*-2-ethynyltetrahydrofuran (**19**) and subsequent opening of ethylene oxide with acetylide anion made homopropargyl alcohol (**30**). Thus, this racemic model became the useful training ground providing the critical information before entering the real battlefield, i.e., asymmetric route.

Scheme **5**



The glycidyl ether (**24**) was subjected to HKR conditions to provide (*S*)-epoxide (**31**) and (*R*)-diol (**7**) in 46% yield each. The diol (**7**) was converted through cyclic orthoester technology of Sharpless *et al.* in one pot to the glycidyl ether (**9**) and then to **32** in two steps. The olefin (**32**) was converted to epoxymethyl chloride (**37**), through a sequence of steps. Double-elimination was effected by exposure of **37** to LDA to afford THF-acetylene derivative (**17**). 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 (**38**). Mitsunobu reaction of **38** with *N,O*-bis(phenoxycarbonyl) hydroxylamine/TPP/DIAD gave the urethane derivative followed by ammonolysis culminated in the total synthesis of target compound **1**, identical in all respects, *viz*., ^{1}H NMR, ^{13}C NMR, IR, EI, HRMS spectra, specific rotation and melting point with that of authentic sample.

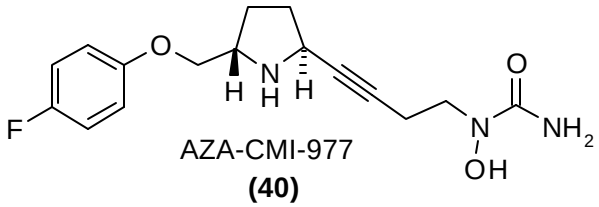
Scheme **6**



SECTION-II: Stereoselective synthesis of AZA-CMI-977

The advent of genomic sciences, 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. Genomic science, combined with bioinformatic tools, allow us to dissect the genetic basis of multifactorial diseases and to determine the most suitable points of attack for future medicines, thereby increasing the number of treatment options. The target-oriented synthesis has effectively been replaced by diversity-oriented synthesis in modern drug discovery. In the aftermath of completion of enantioselective synthesis of CMI-977, it was planned to synthesise a library of similar compounds, differing in ring size, heteroatom, side chain length/homologation etc. Our interest was to synthesise aza-variant of CMI-977 (**40**), since nitrogen is an indispensable part of many natural products, indulged in life-making process, mental control to energy production.



AZA-CMI-977

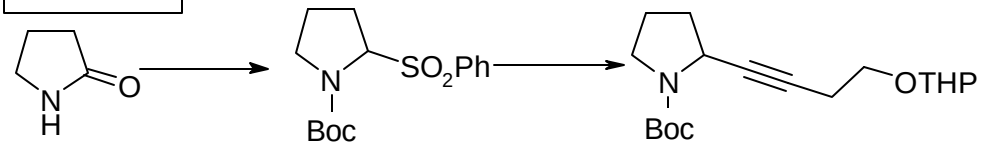
(40)

In the synthetic process, the homochiral allyl alcohol (**35**), a known intermediate, was converted to its azido derivative (**41**) with LiN_3. Asymmetric epoxidation of **41** with Ti(O-^{i}Pr)$_4$/(+)-DIPT/cumene hydroperoxide, followed by tosylation and subsequent exposure to LiCl in DMF gave epoxymethyl chloride (**44**). The compound **44** was then treated with LDA to obtain propargyl alcohol. However, the major isolated product didn't provide the clear image over the structure, as the ^{1}H NMR spectrum was complex and suggested mixture of compounds formed probably due to destructive decomposition of **44**. Hence, we stopped at this juncture and looked for alternative scheme.

With the failure of asymmetric route, the quest for conquering the synthesis of nitrogen mimic of CMI-977 solely rested on " chiron approach". Essentially, L-pyroglutamic acid poses as a replica of a segment of our target, i.e., as chiral template, indicating L-glutamic acid as the chiral progenitor. Before launching the synthesis, a model study was conducted to probe

the conceivability of the crux of the strategy, the C-C bond formation in the nucleophilic addition of N-acyliminium ion for destining the elusive side chain which was found successful (Scheme **7**).

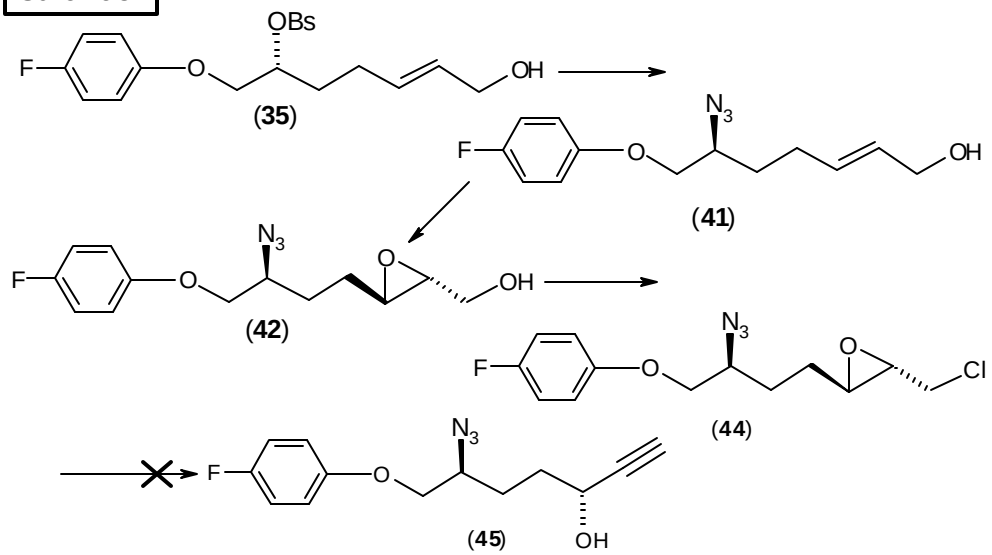
Scheme **7**



(**46**) (**49**) (**50**)

In the synthetic direction, L-glutamic acid (**51**) was converted to *N*-(4-methoxybenzyl)-2-oxoproline (**52**). Treatment of **52** with catalytic $SOCl_2$/methanol afforded methyl ester and subsequent reduction with $LiBH_4$ gave **54.** The compound **54** was converted to **59** through a multi-step sequence: tosylatation, substitution with sodio 4-fluorophenol, CAN-mediated unmasking of *N*-PMB group and protection with di-*tert*-butyldicarbonate and reduction with DIBAL-H. This precursor laid the situation to introduce the appendage at

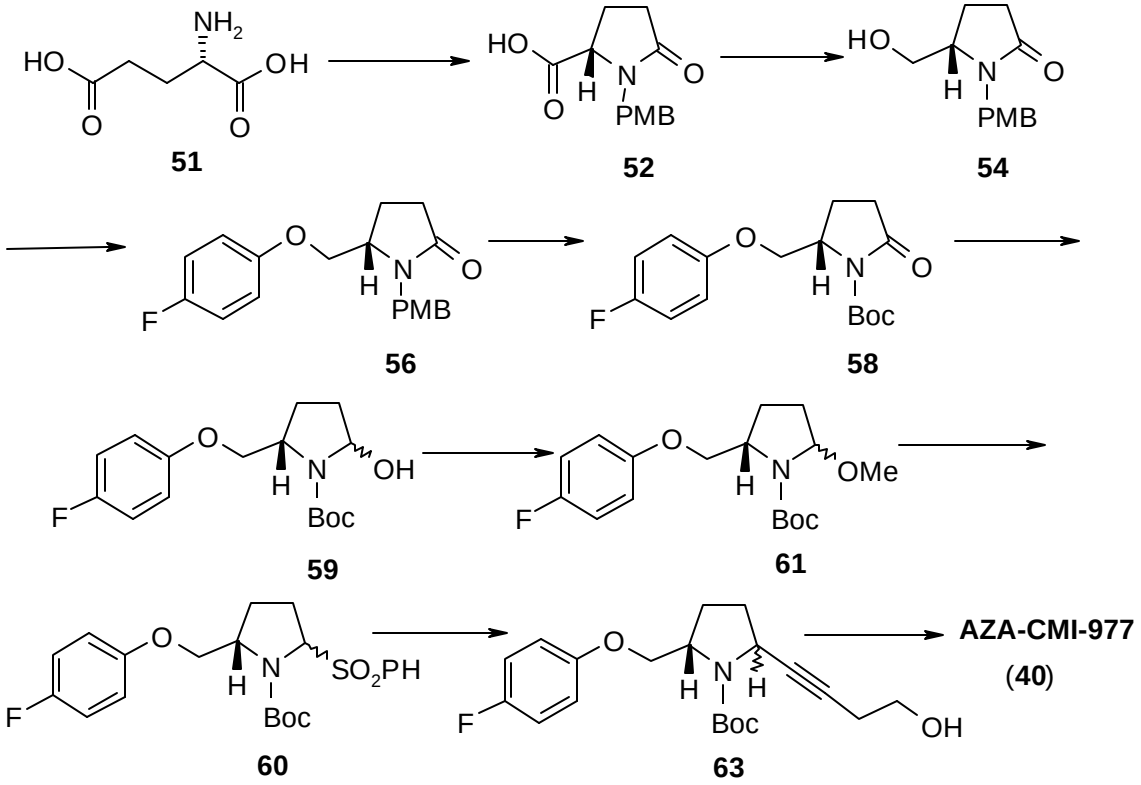
Scheme **8**



C_2 position via the Lewis acid mediated nucleophilic addition to N-acyliminium ion in diastereoselective fashion.

When we exposed hemiaminal (**59**) to $PhSO_2H$ in DCM as per the literature precedent, no product was imminent. Hence, we next investigated with **61**, obtained from **59** on exposure to PTSA in methanol, in accordance with the model studies. Exposure of 2-methoxypyrrolidine (**61**) to $PhSO_2H$ in CH_2Cl_2 in the presence of $CaCl_2$ gave the desired 2-benzenesulphonyl

Scheme **9**



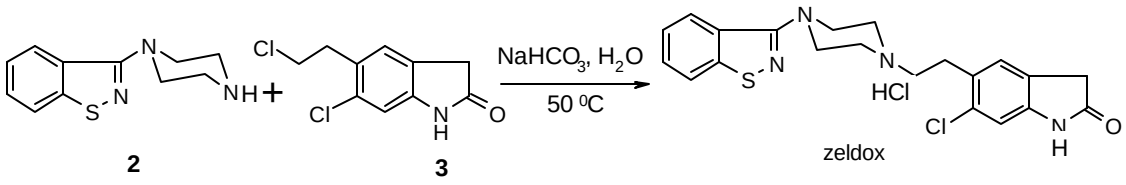
pyrrolidine (**60**). The compound **60** was reacted with the dialkylzinc nucleophile (4-tetrahydropyranyloxy-1-butynylmagnesium bromide + zinc bromide) to provide THP ether derivative, which was stirred with catalytic PPTS in methanol to retrieve the homopropargyl alcohol (**63**). The diastereomeric mixture was found to be in 87:13 ratio (analytical HPLC). Transformation of **63** into the target molecule **40** was carried out essentially by the same Scheme as reported for CMI-977 (**1**). The compound **40** was substantiated for its structure by the correlative information from ^{1}H NMR, ^{13}C NMR, FABMS and DEPT studies. It was

interesting that chiral HPLC indicated only one isomer, whose stereochemistry was established as *trans* by NOESY studies.

CHAPTER-II: **Synthesis of oxindole part (CP-88, 059) of antipsychotic drug 'Zeldox'.**

The world health organization has predicted that depression (schizophrenia) will be the world's largest ailment by 2010 after heart failures. There is a greater hope now than ever before for patients with schizophrenia, although there is presently no permanent cure for schizophrenia. The recent thrust in antipsychotic drug development has been to identify targets with clozapine-like efficacy without its serious toxicity. FDA, USA, has approved the antipsychotic drug Zeldox ® (Ziprasidone hydrochloride) in midst 2000, and recommended for first line therapy, developed by Pfizer Inc. USA. Zeldox is a serotonin and dopamine antagonist that is effective in treating the wide range of positive, negative and depressive symptoms associated with schizophrenia.

Scheme **1**



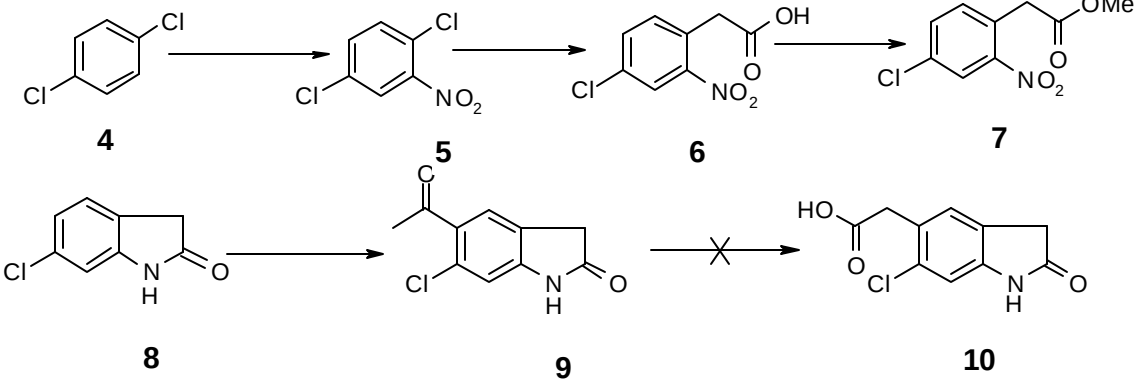
2 **3**

Hence, we embarked on a programme for a synthetic process under the aegis of Pfizer Inc. for the oxindole part (**3**) of ziprasidone as the discovery route to (**3**) involved the hazardous intermediates and expensive reagents. A three-pronged strategy was crafted for synthetic trails: 1) initial oxindole formation; second, the introduction of side chain; 2) preferential side chain introduction followed by the construction of oxindole; 3) simultaneous introduction of functional elements requisite for oxindole and side chain.

STRATEGY-I AND RESULTS

1,4-dichlorobenzene (**4**) was converted into 1,4-dichloro-2-nitrobenzene (**5**) on nitration with nitrating mixture. Subsequent S_NAr reaction of **5** with cyanoacetic ester and NaOH followed by decarboxylative hydrolysis with 6 N HCl/AcOH provided phenylacetic acid (**6**), which was later esterified with dimethyl sulphate and K_2CO_3 in 2-butanone to provide **7**. Reductive cyclisation of **7** was effected with H_2/Raney-Ni/AcOH to furnish oxindole (**8**). Friedel-Crafts acylation gave 5-acetyl-2-oxindole (**9**), which was then subjected to Willgerodt transformation (S/morpholine, reflux). Unfortunately, this reaction returned only tarry material. A series of modifications were tried, but nothing proved fruitful. The only other similar transformation, McKillop's protocol for the conversion of acetophenone into the methyl ester of phenylacetic acid with $Tl(NO_3)_3.3H_2O$, also miserably failed when we applied to our original substrate.

Scheme **2**

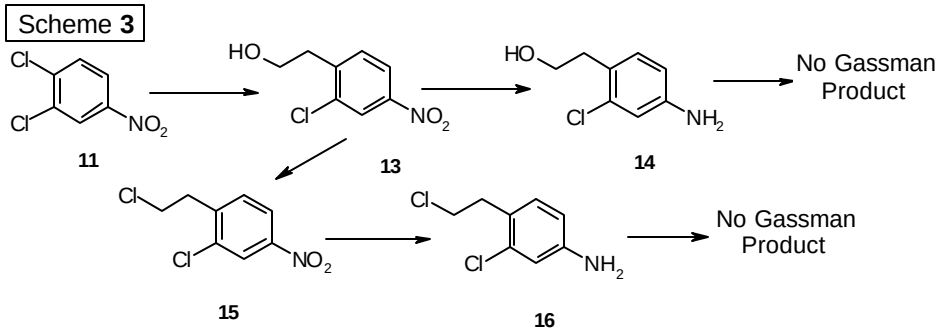


STRATEGY-II AND RESULTS

We examined our second strategy, keeping Gassmann reaction as a key transformation. The commercially available 1,2-dichloro-4-nitrobenzene (**11**) was converted to the corresponding phenylacetic acid followed by reduction with borane ($NaBH_4$ and I_2 in THF) to give **13**. Reduction of nitrobenzene (**13**) was accomplished with H_2/Raney-Ni/EtOAc/NH_4Cl.

With the acquisition of aniline (**14**) in hand, the stage was set for the introduction of oxindole moiety.

Although a plethora of methods are available for the aforesaid task, the popular among them is Gassman's protocol. Accordingly, the compound **14** was exposed to $CH_3SCH_2CO_2Me$/*t*-BuOCl/Et_3N/dilute HCl. But no product was obtained. The recent modifications 1) $MeS(=O)CH_2CO_2Et$, $(COCl)_2$, DMSO and 2) SO_2Cl_2/proton sponge in place of *t*-BuOCl/TEA also didn't deliver the product. Under the presumption that the presence of OH group would be fatal to the formation of azasulfonium ylide, the substrate **16** was prepared and exposed to Gassman conditions, which also failed to make any headway.

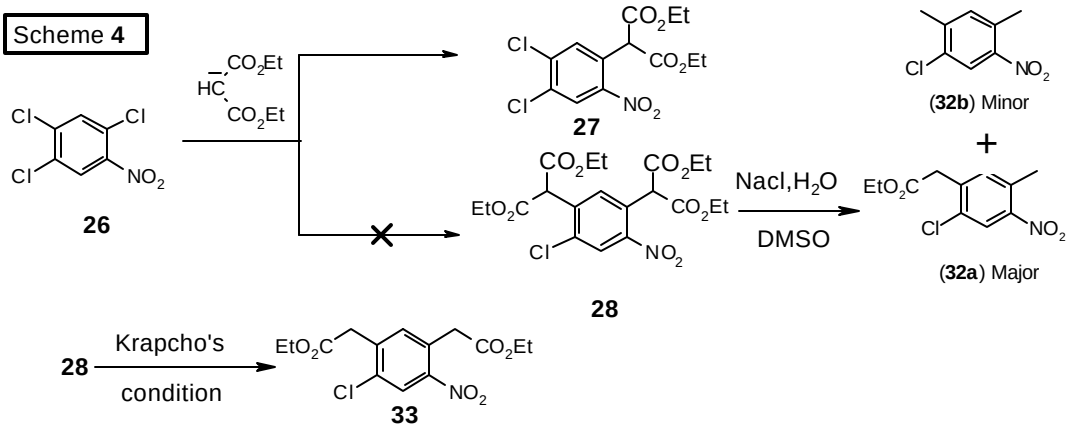


STRATEGY-III AND RESULTS:

Our final strategy was the dialkylation approach, which would eventually constitute the inexpensive route to the intermediate **3.** The starting material **26**, prepared from cheap 1,2,4-trichlorobenzene, was subjected to S_NAr reaction with diethylmalonate and NaH in DMF, resulting in the exclusive formation of monoalkylated product (**27**). The dialkylation was not achieved even under forceful conditions. Diethyl malonate and malononitrile were also examined as possible alkylating agents. In all cases, only the mono alkyl product formed. Therefore, alkylation of chlorodifluoronitrobenzene (**30**) was investigated next. After severe experimentation, the required **28** was obtained, after treating **30** with sodio diethyl malonate (4

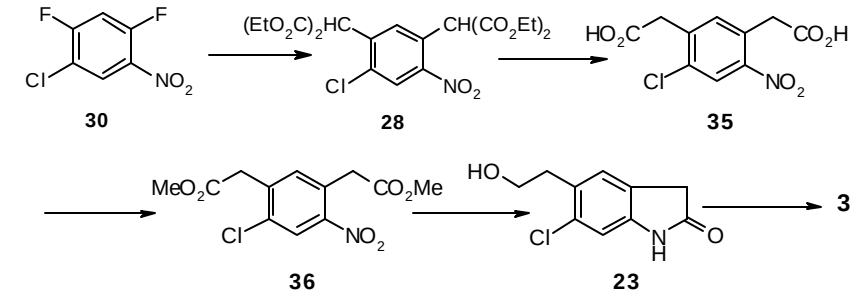
equiv.) in DMF. The compound **28** was then exposed to Krapcho's decarboxylation conditions resulting in an unexpected mixture of products **32a** and **32b**. This kind of bis(dealkoxycarbonylation) of aryl malonate to tolune has been observed for the first time under Krapcho's

Scheme **4**



protocol. The product **33** was predominantly obtained when the temperature was maintained between 100-120 ^{o}C. Reduction of **33** with H_2 and Raney-Ni in AcOH provided 2-oxindole (**34**). In an alternative route, the aryl dimalonate **33** was subjected to hydrolysis under acidic conditions to afford **35** which was derivatised to **36** with catalytic $SOCl_2$ in MeOH. Sucessive reduction with of **36** with H_2/Raney-Ni/AcOH and $LiBH_4$/$B(OMe)_3$ in THF gave **23**. The conversion of **23** into **3** was effected with TPP in refluxing CCl_4 in good yield. In alternative to these conditions, the phenylethanol **23** was converted to it tosylate ester followed by reaction with LiCl in DMF gave **3**.

Scheme **5**

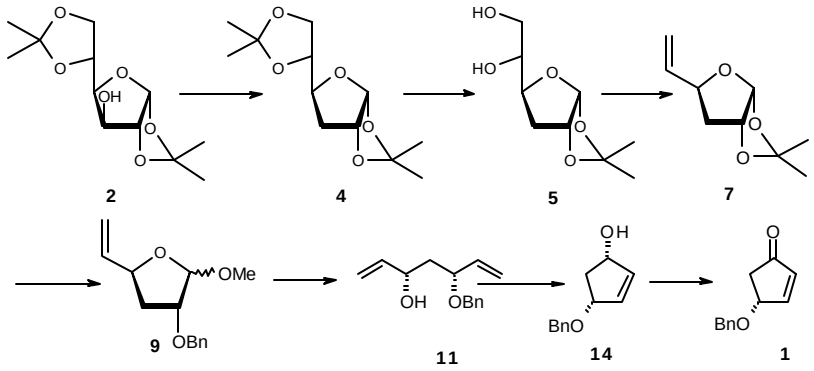


CHAPTER-III: Application of ring closing metathesis in the synthesis of (*R*)-4-benzyloxycyclopent-2-en-1-one.

The importance of hydroxycyclopent-2-en-1-one derivatives to synthesise compounds of medicinal significance and natural products, especially, carbocyclic nucleosides and prostaglandins should constitute the strong drive to undertake rapid and efficient synthesis to the value-added intermediate **1** by utilizing the new advances in synthetic methodologies, especially, for C-C bond formation. "Conversion of carbohydrates to carbocycles" has prevailed as one of the thematic strategies in organic synthesis. Accordingly, our synthetic strategy hinges on RCM as key transformation for carbocycle construction, while envisaging the required chiral diene precursor **11** to arise from the chiral source D-glucose through a series of manipulative transformations.

Diacetone-D-glucose (**2**) was deoxygenated under Barton-McCombie protocol to provide 3-deoxyglucose derivative **4**. Regioselective monohydrolysis of 5,6-*O*-isopropylidene group in **4** with 0.8% H_2SO_4 provided the diol (**5**) which was then converted to its dimesylate ester using $MeSO_2Cl$/TEA/DMAP in CH_2Cl_2 and exposure of ester to LiI in 2-butanone effected the elimination to give the desired ene (**7**). The next endeavour was to derive the second double bond of diene derivative in advance of ring closing metathesis.

Scheme **1**



Deprotection of 1,2-*O*-isopropylidene group in **7** with PTSA in MeOH afforded methyl furanoside in 75% yield which was benzylated at C-2 position to afford **9**. The hydrolysis of furanoside (**9**) with conc. H_2SO_4 in a mixture of 1,4-dioxane and water at 100-110 ^oC gave the glycal derivative **10**. Witting methylenation of **10** with incipient methylenetriphenyl phosphorane readied the substrate **11** for RCM.

Ring closing metathesis has emerged as an attractive tool among synthetic chemists for C=C bond formation. Exposure of **11** to Grubbs' catalyst (5 mol%) in CH_2Cl_2 gave the desired product cyclopentenol (**14**). The last step was the allylic oxidation of **14**, which was accomplished with Fetizone's reagent to afford **1** in 78% yield. The structure of **1** was substantiated by the ^1H NMR, EI and HRMS spectral analysis.

CHAPTER-1

SYNTHESIS OF CMI-977 AND ANALOGUE

PROLOGUE

According to the estimate of World Health Organisation, 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 industrialised 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	

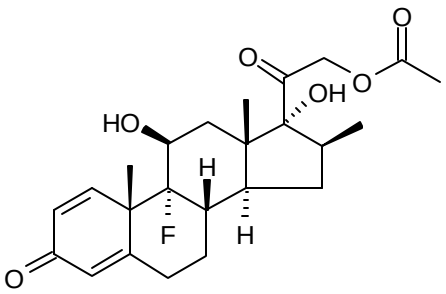
Abbreviations: GM-CSF - granulocyte-macrophage colony-stimulating factor; RANTES - regulated upon activation normal T-expressed secreted ligand.

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:

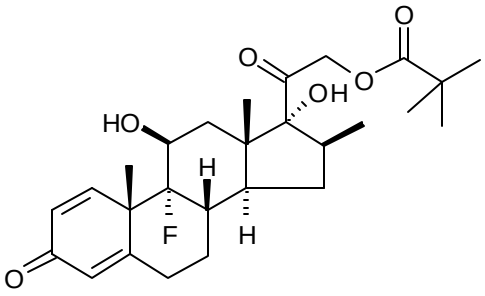
Glucocorticosteroides, â$_2$-adrenoreceptor agonists and theophylline:

Inhaled â$_2$-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

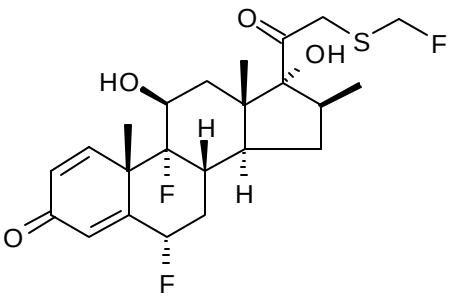
binds to a cytosotic glucocorticoid receptor (GR) and the resulting dimer translocates to the nucleus where it interacts with a glucocorticoid response element (GRE) to increase or decrease gene transcription (*trans*-activation and *trans*-repression respectively). Activated GR



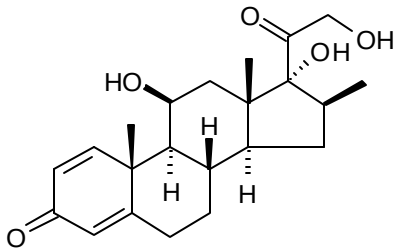
Betamethasone acetate (**1**)



Dexamethasone.pivalate (**2**)



Fluticasone.dipropionate (**3**)

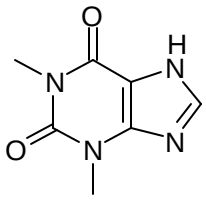


Cortisone (**4**)

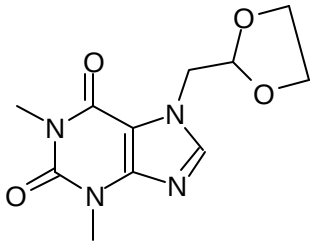
can also interact directly with cytoplasmic transcription factors such as activator protein 1 (AP-1), and nuclear factor êB (NF-êB), which alter gene transcription in response to inflammatory stimuli. Salbutamol (**5**) is a potent â$_2$-adrenergeric receptor antagonist. â$_2$-adrenergeric receptors are found on the smooth muscle lining airways of the lungs. The binding of salbutamol to â$_2$-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 dssociate 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.

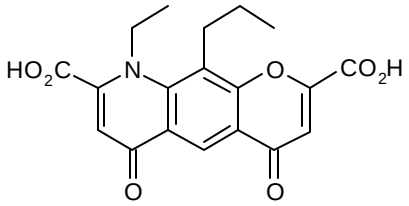
Theophylline (**6**) has a long historic background through its ability to bronchodilate asthmatic subjects. Although limited by side-effects profile, theophylline is effective in reducing the symptoms and improving lung function in patients with mild chronic asthma. Theophylline is believed to inhibit 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**)

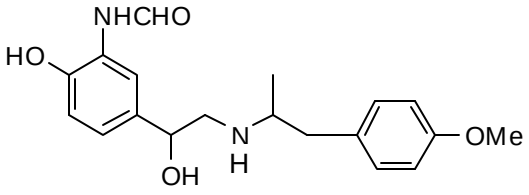


Doxophylline (**6a**)

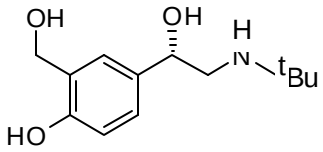


Nedocromil (**7**)

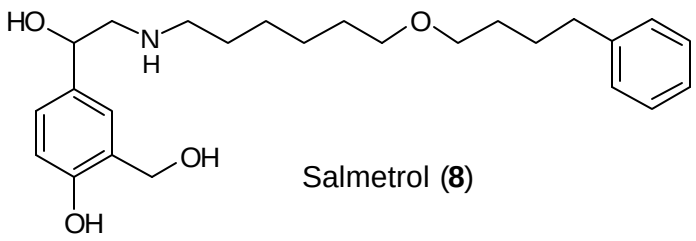
Long action of â$_2$-adrenoreceptor agonists can be achieved by exosite binding (e.g., salmeterol)[5] (**8**) and by alterations in pharmacokinetics (e.g., formoterol)[6] (**9**). Although highly lipophilic, the extended duration of action of salmeterol appears due to anchoring in the vicinity of the â$_2$-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 â$_2$-adrenoreceptor agonists with inhaled steroids, e.g., seretide (salmetrol and fluticasone) combined in a single formulation.



Formoterol (**9**)



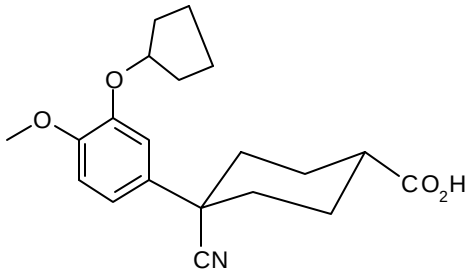
(R)-Salbutamol (**5**)



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]

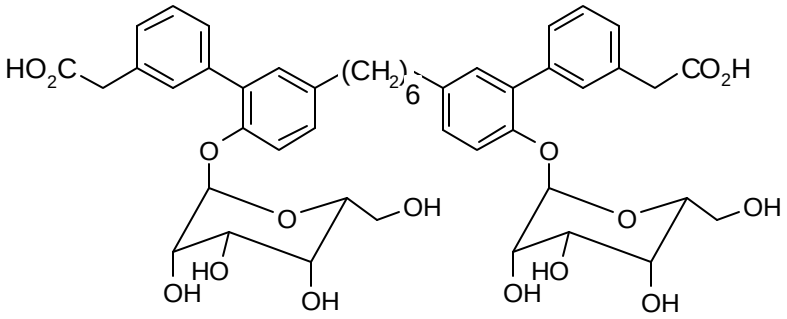
Mediators of T-lymphocyte–eosinophil interactions:

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-endothelium 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



TBC-1269 (**11**)

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.

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-êB. 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- êB/AP-1-dependant gene transcription.[11] In addition, SP100030 also inhibits transcription of IL-2, IL-8, TNF-á and GM-CS factor genes with similar IC_{50} – thus holding great promise in the treatment of asthma.

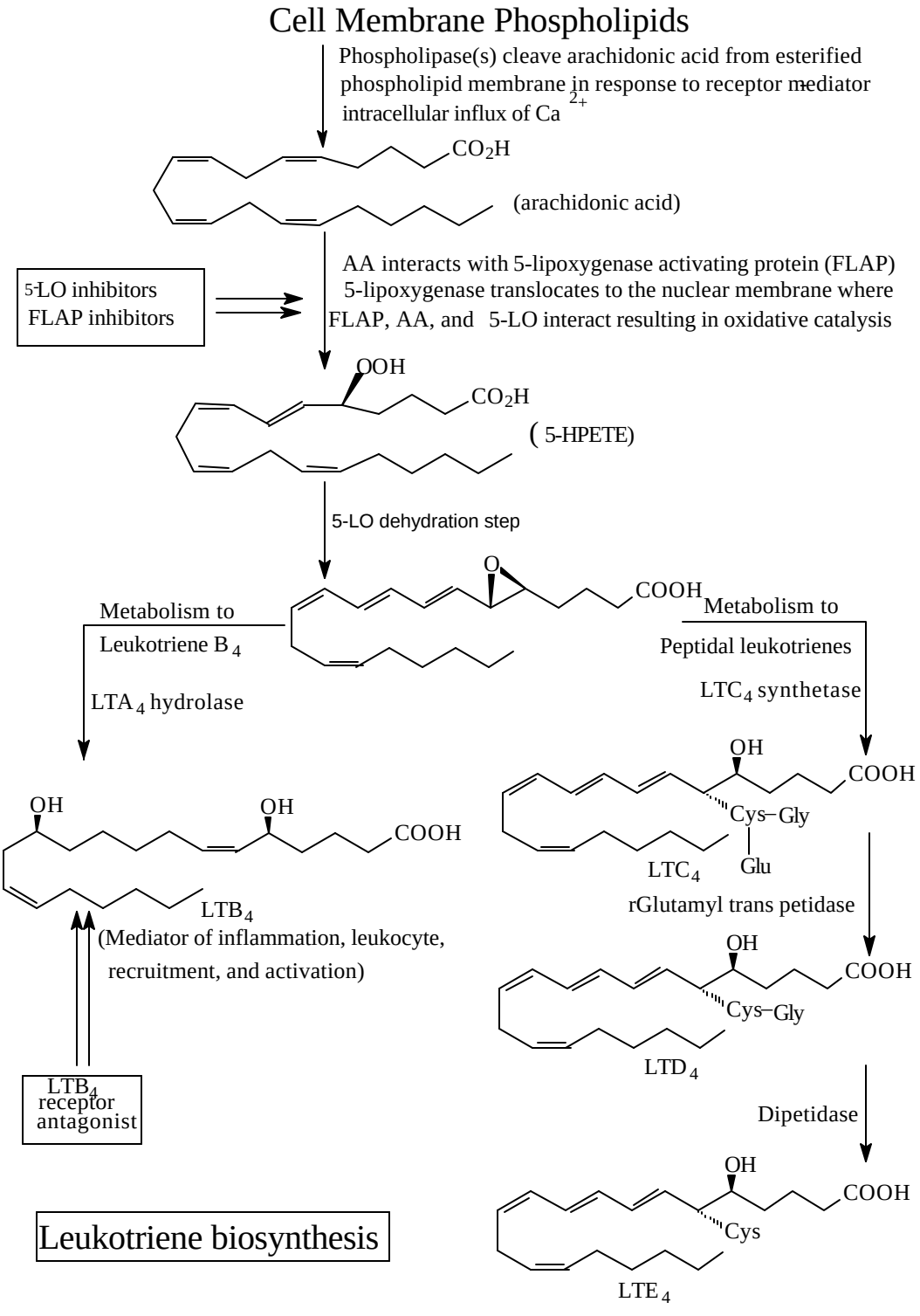
MAP kinase inhibition:

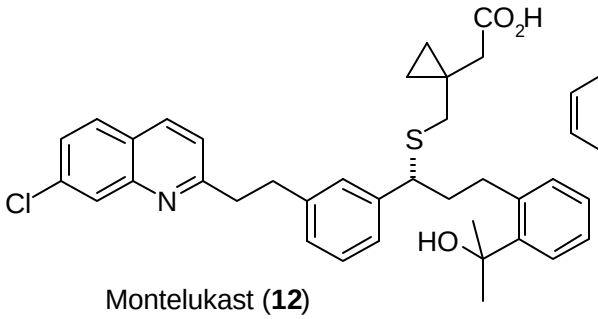
A novel family of mutagen activated protein kinases (P38 MAP kinases) are intimately involved in the generation of pro-inflammatory cytokines.[12] Pyridinyl imidazoles exemplified by SB 203580 and SB 202190 supress the generation of IL-1 and tumour necrosis factor (TNF) from human monocytes and IL-4-induced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

Inflammatory mediator receptor antagonists:

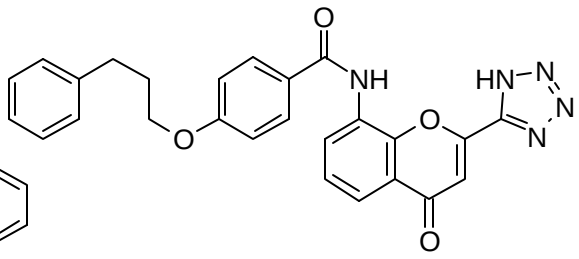
Small molecule receptor antagonists for a number of inflammatory mediators have been developed. Trailing for so long in the wake of other putative mediators, the cysteinyl leukotrienes have assumed a central role in asthma and in drug development with *Cys*T_1 receptor antagonists such as montelukast (**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] 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).



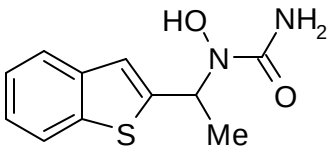


Montelukast (**12**)

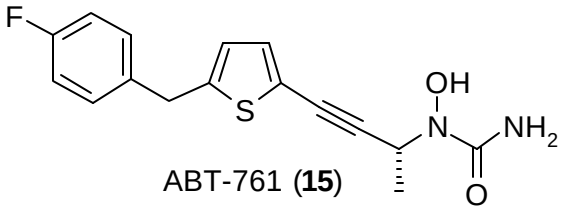


Pranulakast (**13**)

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

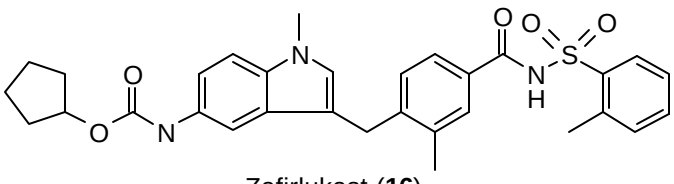


Zileuton (**14**)

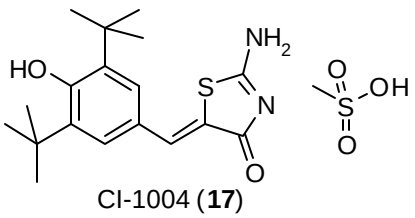


ABT-761 (**15**)

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 (**17**)

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)

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 prostaglandins. 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

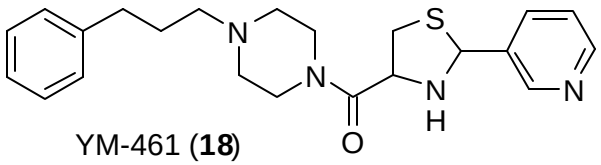
both children and adults in phase III clinical trails in double-blind, randomized, placebo-controlled studies.[18]

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

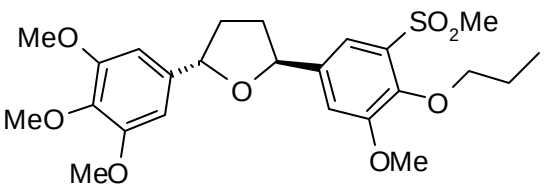
Platelet activating factor is a phospholipid, exhibiting potent pro-inflammatory effects. It is produced by a number of cells, including eosinophils, basophils, neutrophils, macrophages, and endothelial cells. YM-461 (**18**) is a selective, potent and orally active PAF antagonist.[20]



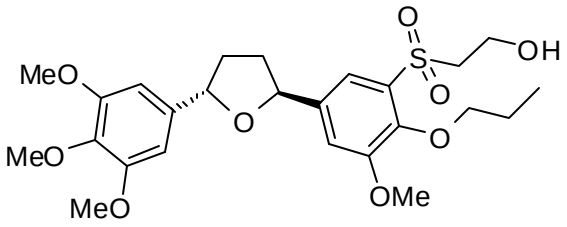
YM-461 (**18**)

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**)

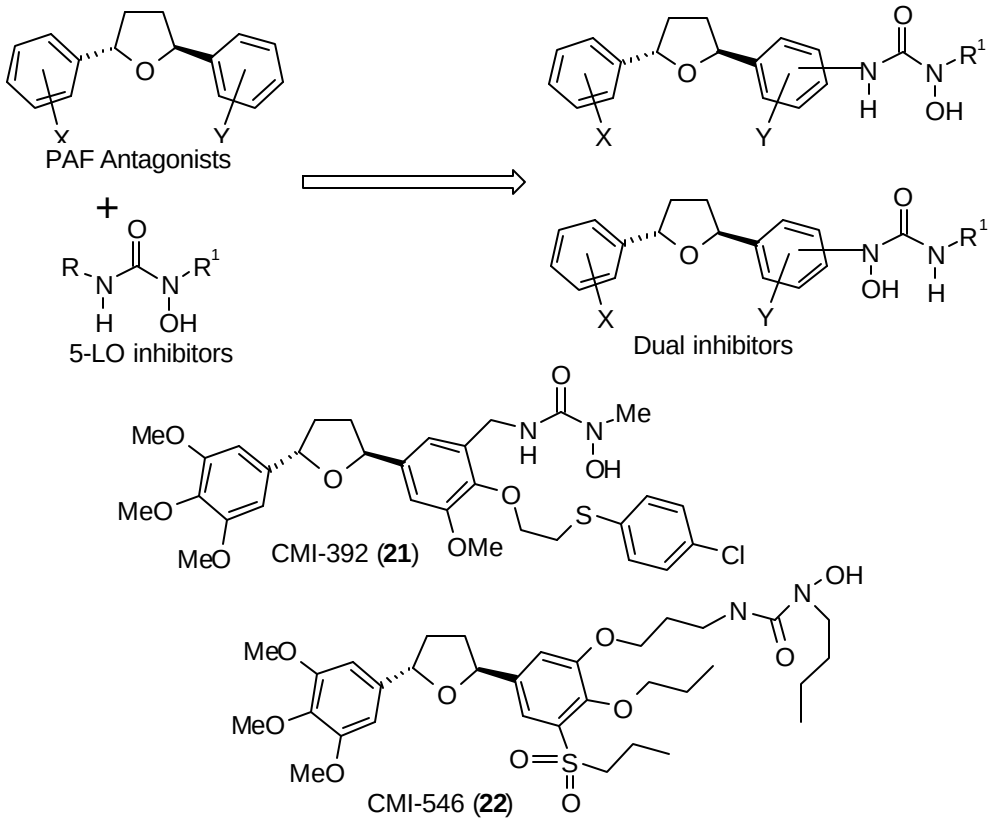


MK-287 (**20**)

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]

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]

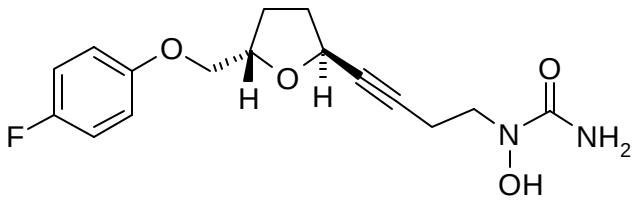


SECTION–I

ASYMMETRIC SYNTHESIS OF (2*S*,5*S*)-5-(4-FLUORO PHENOXY)METHYL-2-(4-*N*-HYDROXYUREIDYL) BUTYNYL)TETRAHYDROFURAN (CMI-977)

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)tetrahydrofuran (**1**) for final clinical trails for chronic asthma.[24]



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

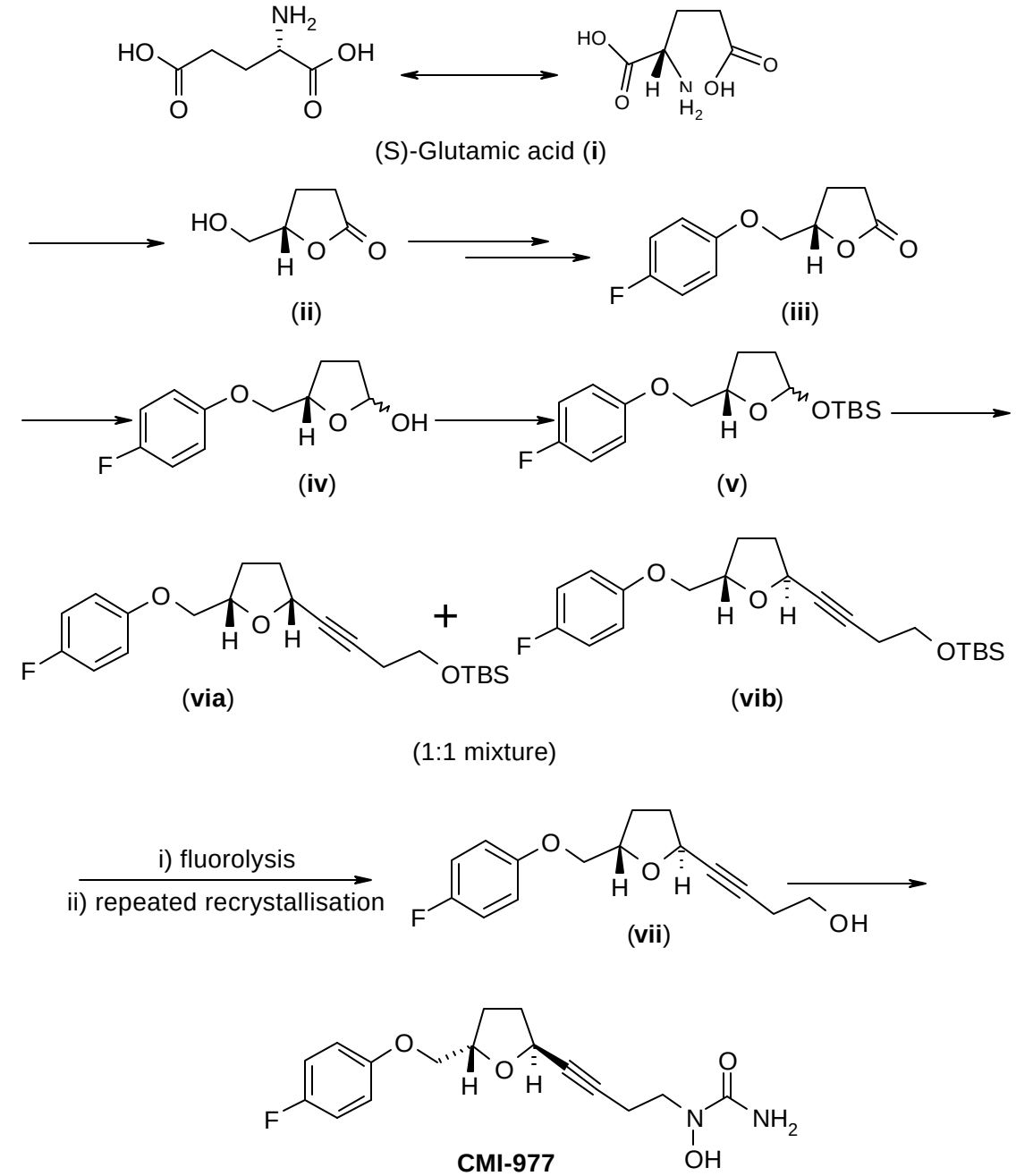
analysis to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of CMI-977 in normal subjects, showed that PK/PD profile is comparable with a single dose of zileuton, i.e., it may administered orally once or twice a day. Overall, CMI-977 has shown a high degree of potency, excellent oral bioavailability and exceptionally favourable safety profile.[25]

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.

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 (**ii**) as core chiral synthon, easily derivable from chiral pool L-glutamic acid (**i**).[26] Nucleophilic substitution with lithium 1-*tert*-butyldimethylsilyoxybutynide at the anomeric centre of intermediate (**iv**) after anomeric activation with TMSBr yielded a *cis*/*trans* mixture without any stereoselectivity (1:1 mixture). The desired *trans*-butynol (**vii**) 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. 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 numerousinstances. 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

Scheme **1**

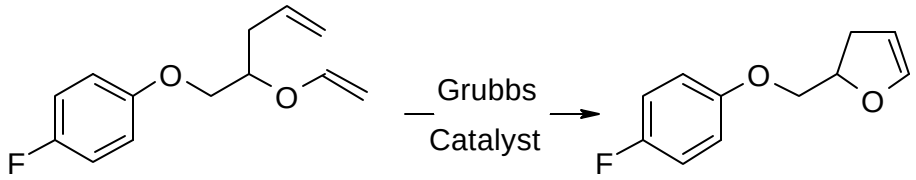


in 1:1 mixture of *cis*/*trans* isomers whose separation to furnish the *trans* material involved tedious column chromatography or repeated recrystallisation. Hence, the undesired formation of *cis*-isomer by half after several steps was a major concern.

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. Three routes were simultaneously developed in our laboratory that would effectively address the aforesaid problems. The two synthetic routes, developed by our colleagues[27] would essentially hang around the lactol (**iv** in scheme **1**) with adroit manipulation of pre- and post-steps of this intermediate, involving the key transformation as diastereoselective C-C bond formation *via* nucleophilic substitution of 2-benzenesulphonyltetrahydrofuran, as authored by S.V. Ley. These approaches adequately addressed all the concerns faced in the discovery route, but still suffer from the real Gordian Knot, the diastereoselective excess.

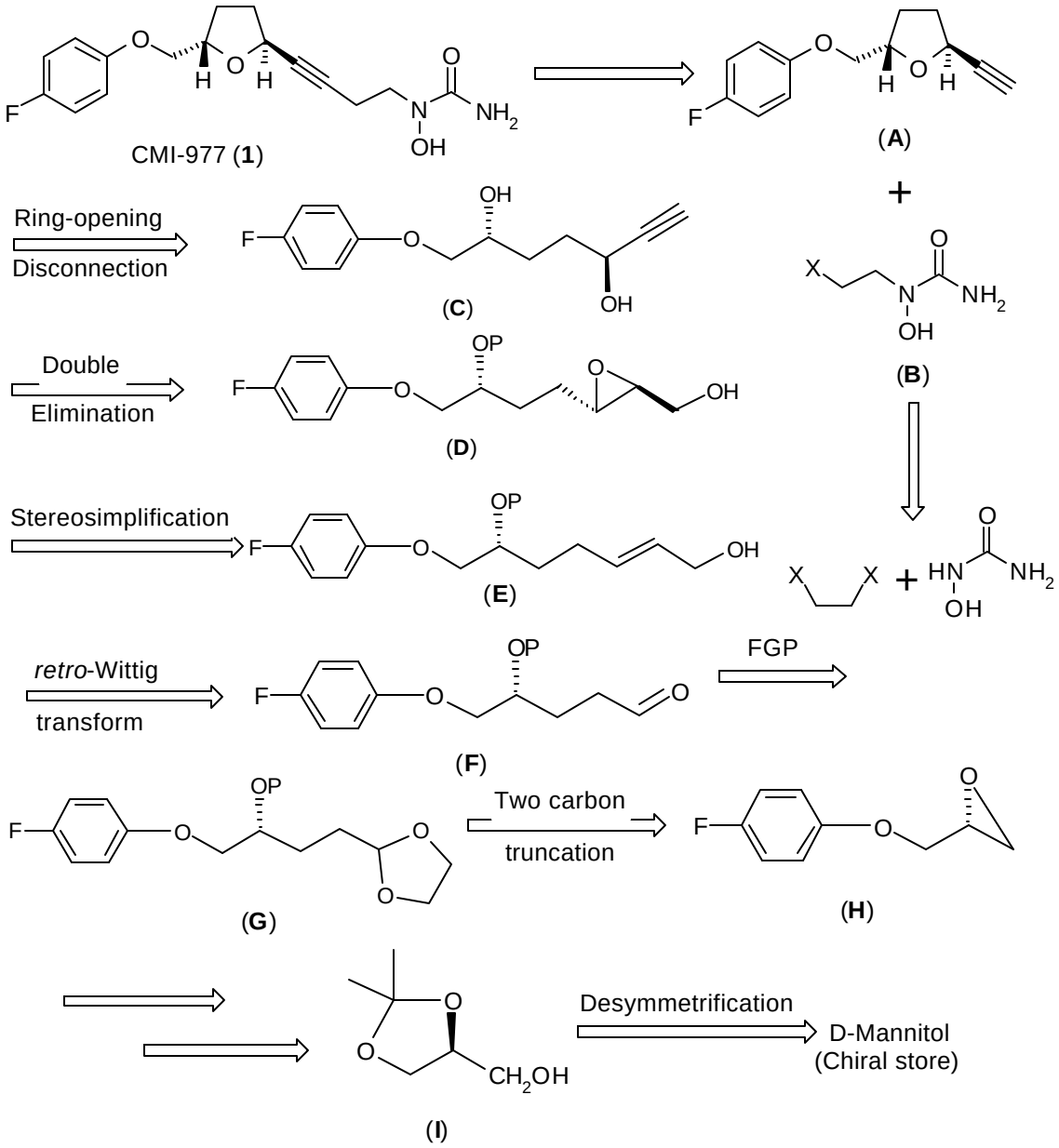
The fourth synthetic route, emerged recently form this laboratory was purely methodology-driven and cleverly orchestrated to arrive at the dihydrofuran (**ii** in schme **2**), a synthetically-equivalent intermediate of lactol (**iv** in scheme **1**) with striking resemblance of further elaboration, taking advantage of the exquisiteness of ring closing metathesis which has emerged as a superb tool in the versatile construction of rings via C-C bond formation.[28]

Scheme **2**



(**i**) (**ii**)

The retrosynthetic analysis for our synthetic endeavour was planned using a 'tactical combination of transforms' putting onus on T-goal approaches, as outlined in Scheme **3**.[29] The initial C-C disconnection of *N*-hydroxyureidyl moiety appended with ethyl chain would provide the precursors tetrahydrofuranylethyne (**A**) and ethyl *N*-ethyl-*N*-hydroxyurea (**B**). The latter fragment (**B**) would, on application of simplifying transform by dissecting ethyl chain,



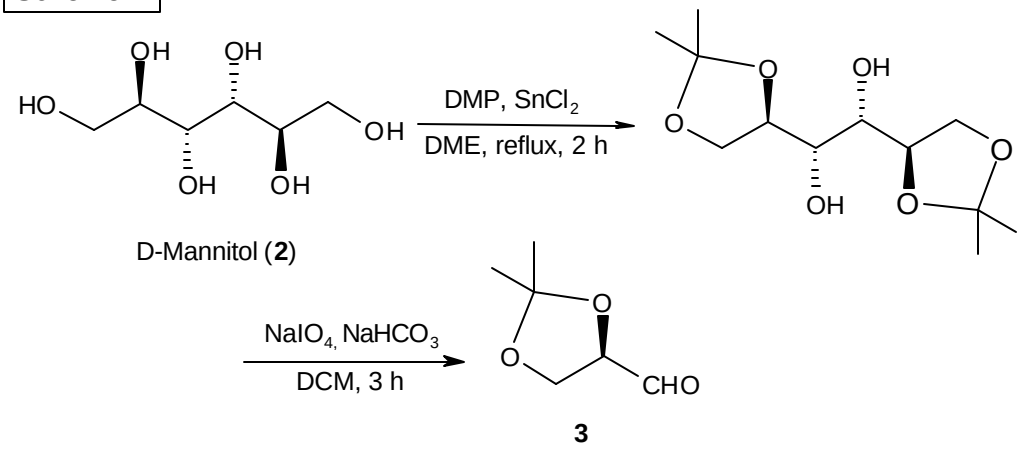
Scheme **3**: Retrosynthetic analysis

deliver epoxide synthetic equivalent and *N*-hydroxyurea. The second and key operation using heteroatom ring disconnective transform would reveal the diol intermediate (**C**). In the synthetic direction, the feasibility of this synthetic step (**C** to **A**) was more appealing, out of several strategies explored till now to construct tetrahydrofuran ring with appendages at 2nd and 5th positions, since the outcome of the reaction through internal S_N2 displacement in a pre-

organised substrate would be completely stereospecific with predictability of stereochemistry at the ring junctions. The propargyl alcohol (**C**), on the rightern side, was envisaged to arise from epoxymethanol through base-mediated double elimination of epoxymethyl chloride after simple FGT. The allyl alcohol (**E**) was thought to be the unambiguous retron for the epoxymethanol (**D**) under the application of stereoflexible and sterocontrolled transform. C=C Wittig disconnection would imply the aldehyde that can be judiciously protected for further refinement. The requisite synthon (**G**) can, in principle, be generated by adapting a prudent practice of generating 4-hydroxyaldehyde, *i.e.*, opening of epoxide (**H**) with nucleophilic synthetic equivalent, derivable from bromoacetaldehyde. The synthetic conversion of (**I**) to (**H**), *i.e.*, generalization of three carbon unit in glycidyl ether from three carbon synthon, *O*-isopropylidene-D-glycerol through conceivable transformations was assumed to be a reasonable proposition. In the ensuing section, we describe the implementation of this basic strategy and realization of stereocontrolled synthesis of CMI-977.

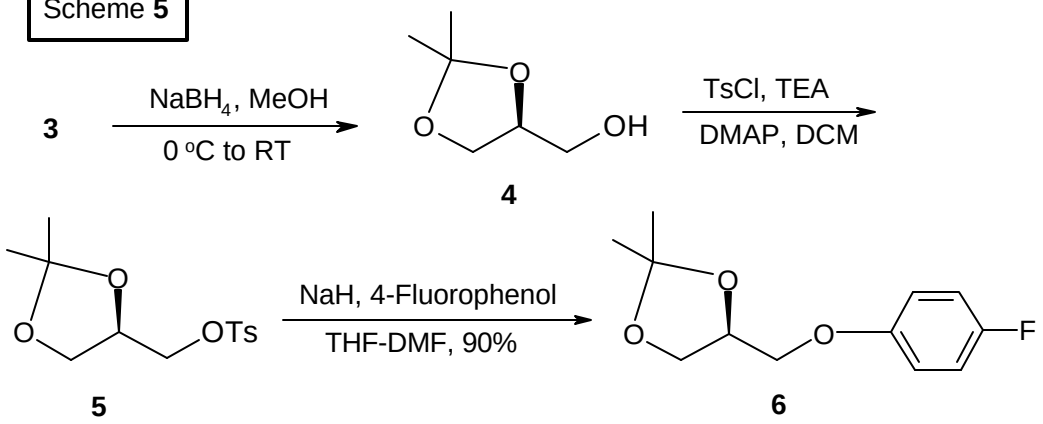
Accordingly, the journey began with D-mannitol (**2**), which was ketalized as 1,2:5,6-di-*O*-isopropylidene–(D)-mannitol followed by oxidative cleavage to provide (*R*)-2,3-*O*-isopropylidene-(D)-glyceraldehyde synthon (**3**), according to the established procedure.[30] The cheap and easy availability, high enantiomeric purity, and equivalence to double unit of chiral building block because of C_2 symmetry were the strong incentives for our interest to start with D-mannitol. Reduction was next carried out with $NaBH_4$ in methanol at 0 ^oC to provide the corresponding (D)-α,β-isopropylideneglycerol (**4**), which was unambiguously assigned the structure based on the ^1H NMR spectrum. Two CH_3 groups of isopropylidene moiety appeared as two singlets at 1.34 and 1.41 ppm, while the OH proton as a broad singlet at the region 1.80-2.10 ppm. The rest of the protons were identified at their appropriate positions in the region of 3.44 - 4.25 ppm. The compound **4** was treated with *p*-toluenesulphonyl chloride and TEA in CH_2Cl_2 to afford the tosylate (**5**) in 92 % yield, which was identified by the ^1H NMR spectrum.

Scheme **4**



A signal at δ 2.46 due to CH_3 group and two A_2B_2 doublets at 7.33 and 7.77 ppm confirmed the presence of *p*-toluenesulphonyl group. Subsequent nucleophilic *O*-alkylation with sodium salt of *p*-fluorophenol in a solvent mixture of DMF and THF at ambient temperature gave the exclusive product **6**. The conspicuous absence of peaks due to tosyl group and the appearance of a multiplet at 6.68–6.96 ppm, characteristic of *p*-fluorophenoxy group, indicated the product **6**. Deketalisation of **6** was effected with methanolic HCl at room temperature to obtain the propanediol (**7**) in 90% yield. The structural feature was unambiguously corroborated from the

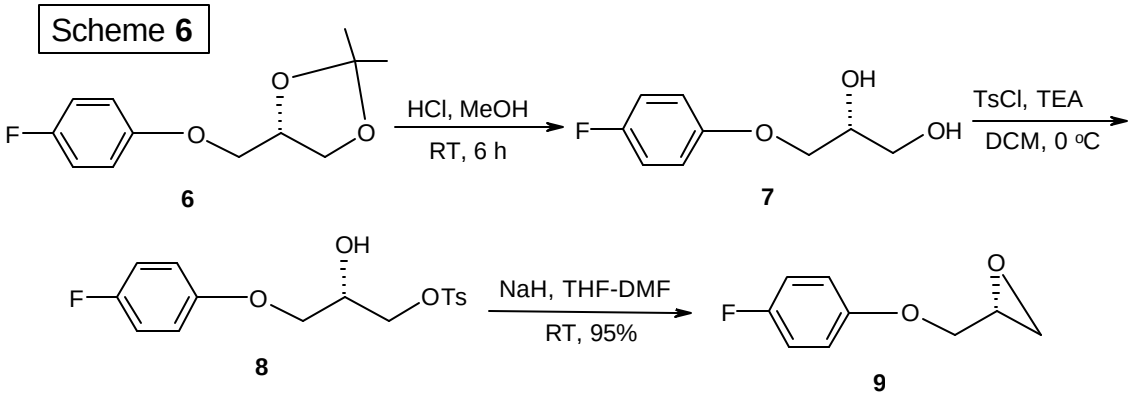
Scheme **5**



combined spectral data from ^{1}H NMR, ^{13}C NMR, IR, EI and HRMS. The peaks owing to isopropylidene group disappeared in the ^{1}H NMR spectrum. The EI mass spectrum gave a highest mass peak at (*m*/*z*) 186 [M^+] whose elemental composition was later identified by

HRMS as 186.0962 (Calcd. for [$C_9H_{11}FO$]: 182.0692). The next step of regioselective arenesulphonylation was conveniently achieved with TsCl and Et_3N in 0.4 M CH_2Cl_2 as per the Sharpless procedure.[31] The product **8** was confirmed by the presence of additional peaks in the ^{1}H NMR spectrum due to tosylate group, i.e., a singlet at 2.4 ppm for aryl methyl and two doublets at 7.20 and 7.82 ppm of A_2B_2 pattern. The epoxide (**9**) was derived out of **8** in 95% yield on exposure to NaH in a solvent mixture of THF and DMF at room temperature for 1 h.

Scheme **6**

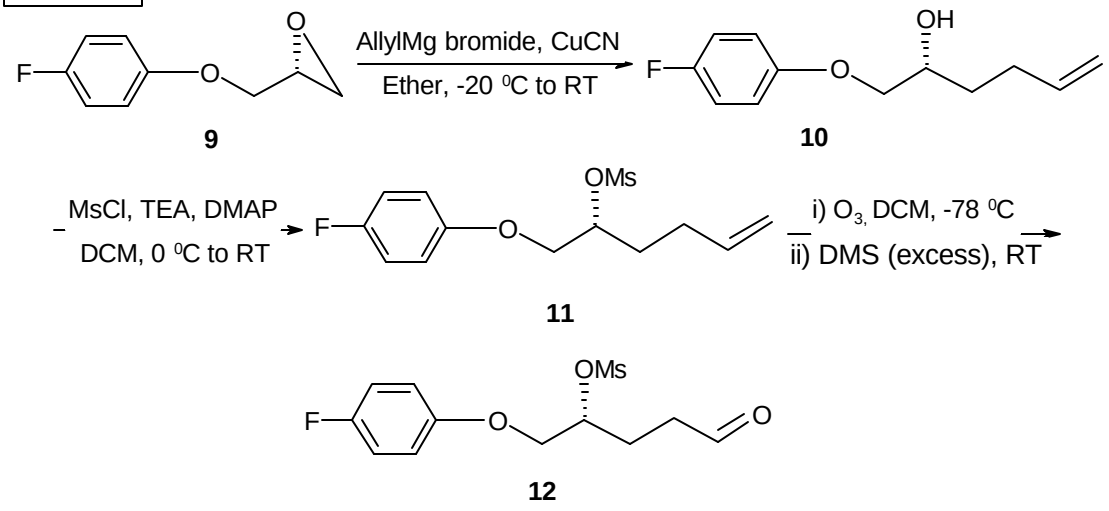


6 **7** **8** **9**

The product was readily confirmed by the ^{1}H NMR spectrum with substantial information from ^{13}C NMR, IR, EI Mass and HRMS spectral studies. While the protons specifying OTs group were no more, new peaks at the region of 2.7-3.00 ppm, characteristic of terminal epoxy protons were observed in the ^{1}H NMR spectrum. The EI mass spectrum gave a molecular ion peak at (*m*/*z*) 168, which was further substantiated by HRMS for elemental integrity (Calcd. for [$C_9H_9FO_2$-M^+]: 168.0586. Found: 168.0580). The epoxide (**9**) was subjected to CuCN-coordinated regioselective nucleophilic opening with allylmagnesium bromide to provide the alcohol **10** in 90% yield, which was adequately substantiated by spectral studies.[32] In the ^{1}H NMR spectrum, the olefinic protons gave peaks at 5.0 and 5.7 ppm [two doublets (J = 10.9 and 14.5 Hz) due to terminal protons] and 5.80–5.92 ppm (HC=). Two set of methylene protons, homoallylic and allylic, resonated as multiplets at the region δ 1.58–1.73 and 2.16–2.40 ppm respectively. The EI mass spectrum gave a molecular ion peak at (*m*/*z*) 210 while HRMS

confirmed it's elemental composition (Calcd. for [$C_{12}H_{15}O_2F$-M^+] 210.1056. Found 210.1067). The alcohol **10** was converted into its mesylate ester (**11**) using $MeSO_2Cl$, Et_3N and DMAP (catalytic) in CH_2Cl_2. The purpose behind the introduction of mesyl group at this stage was to utilize for dual role, as a protecting group for the next couple of steps and as a leaving group at the required last stage. Mesylation of **10** was confirmed by the presence of new resonance at 3.06 ppm as a singlet (CH_3SO_2) and downfield shift of methine proton carrying the mesylate group into 5.0 ppm (from 4.0 ppm) in the ^1H NMR spectrum. This was supported by a molecular ion peak at (*m*/*z*) 288 (M^+) in the EI spectrum. The subsequent oxidative fission of **11** on exposure to ozone in CH_2Cl_2 at –78 °C followed by reductive decomposition with dimethyl sulphide gave the aldehyde (**12**) in good yield. In fact, the reaction resulted in two products in 1:1 ratio. The first product was desired aldehyde itself. The second product, which

Scheme **7**



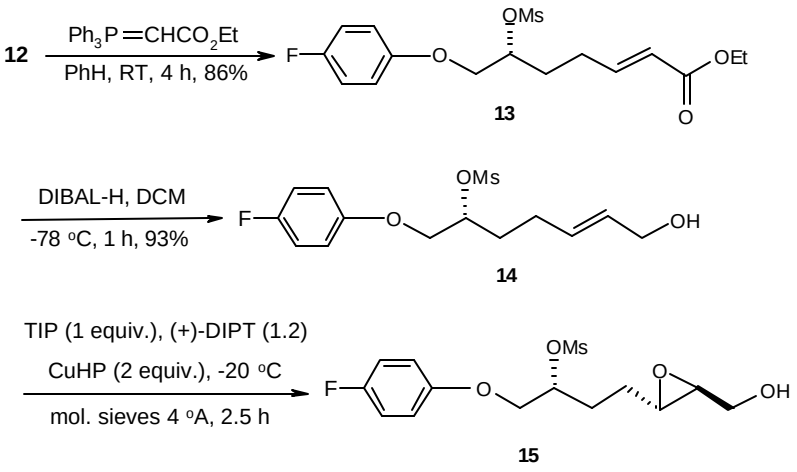
could not be characterized by its ^1H NMR spectrum, transformed to the desired aldehyde (**12**) on long standing. The absence of resonances due to olefinic protons between 5.0–6.0 ppm and the presence of aldehyde proton at 9.74 ppm as a singlet and methylene protons adjacent to aldehyde group at 2.69 ppm were the indications of product **12** in the ^1H NMR spectrum. The aldehyde **12** was quickly exposed to ethoxycarbonylmethylenetriphenylphosphorane in

benzene at ambient temperature to provide the corresponding α,β-unsaturated ester as a geometric mixture (9:1 by TLC). The minor (*Z*)-isomer was eliminated through column chromatography. The predominant (*E*)-isomer (**13)**, obtained in 86% yield, showed characteristic coupling constant (J = 16.0 Hz) for olefinic protons in the ^{1}H NMR spectrum. The relevant resonances due to alkene (a doublet at 5.89 and multiplet between 6.76- 7.06 ppm) and ester group $CO_2CH_2CH_3$ (1.30 and 4.18 ppm) were observed in the ^{1}H NMR spectrum. In the IR spectrum, the carbonyl stretching at 1712 cm^{-1}, characteristic of α,β-unsaturated ester was observed whereas the EI mass spectrum showed the molecular ion peak at (*m*/*z*) 360. Reductive chemistry was next undertaken with DIBAL-H to provide the corresponding allyl alcohol (**14**) in 93% yield. The structure was elucidated on the basis of ^{1}H NMR, IR and EI mass spectral analyses. In the ^{1}H NMR spectrum, the resonances due to olefinic protons moved upfield and were observed between 5.54–5.80 ppm and the CH_2 group of allyl alcohol was localized between 3.95–4.15 ppm. The molecular ion peak (M^+) at (*m*/*z*) 318 was recorded in the EI mass spectrum. This set the stage for Sharpless Asymmetric Epoxidation (SAE) that would install the second chiral centre relevant to the target. SAE figures prominently in modern asymmetric synthesis for external chiral induction for two contiguous chiral centers under passive substrate control because of the factors like (i) oxidation of wide spectrum of substrates with different substituent patterns including *meso* compounds (ii) inexpensive reagents (iii) compatibility of various functional groups (iv) excellent *ee*'s (v) feasibility of either enantiomeric product and (vi) predictability of product configuration by mnemonic device (scheme **8**).[33]

Asymmetric epoxidation of **14** was conducted at –20 °C in stoichiometric fashion in CH_2Cl_2 with cumene hydroperoxide as oxo donor and $Ti(O^iPr)_4$– [(+) -DIPT] complex as chiral adjuvanct. Overnight refrigeration of the reaction mixture resulted in the complete consumption of starting material. Surprisingly, the catalytic version of Sharpless epoxidation

also worked efficiently in our case with faster rate of reaction (1 h for consumption of substrate) and without any erosion in enantiomeric purity (when compared to the product obtained above). The epoxy alcohol (**15**) gave satisfactory spectral data. The ^{1}H NMR spectrum carried peaks between 2.87–3.03 ppm, characteristic of epoxy protons whereas other peaks resonated at their expected chemical shifts. This was further confirmed by appropriate molecular ion peak M^+ at (*m/z*) 334 in the EI mass spectrum. No quantitative study was undertaken to estimate the enantioselection in the epoxidation step, as it was thought that the

Scheme **8**



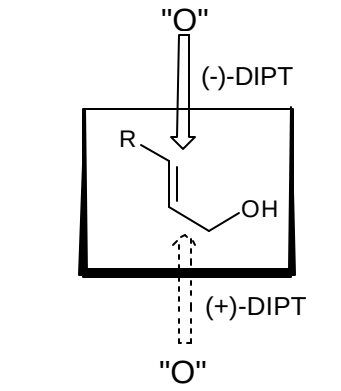


Fig. SAE mnemonic device

enantiopurity could be determined at later stage after two steps. Conversion of (**15**) to epoxymethylene chloride (**16**) was not a smooth affair, as the exposure to triphenylphosphine in refluxing CCl_4 resulted in a mixture of three chromatographically-separable products. The major product formed in 50% yield was the desired product. The other two products were probably the ring-opened products, as evident from the absence of epoxide protons at 3.0 ppm in their ^{1}H NMR spectra. Attempts to minimise the ring-opened products, by the addition of base, *viz*., pyridine and triethylamine, to the reaction medium were to no avail, as the starting material was quantitatively recovered in each case. The product (**16**) was reliably confirmed by the analysis of the ^{1}H NMR, IR and EI mass spectra. In the ^{1}H NMR spectrum of

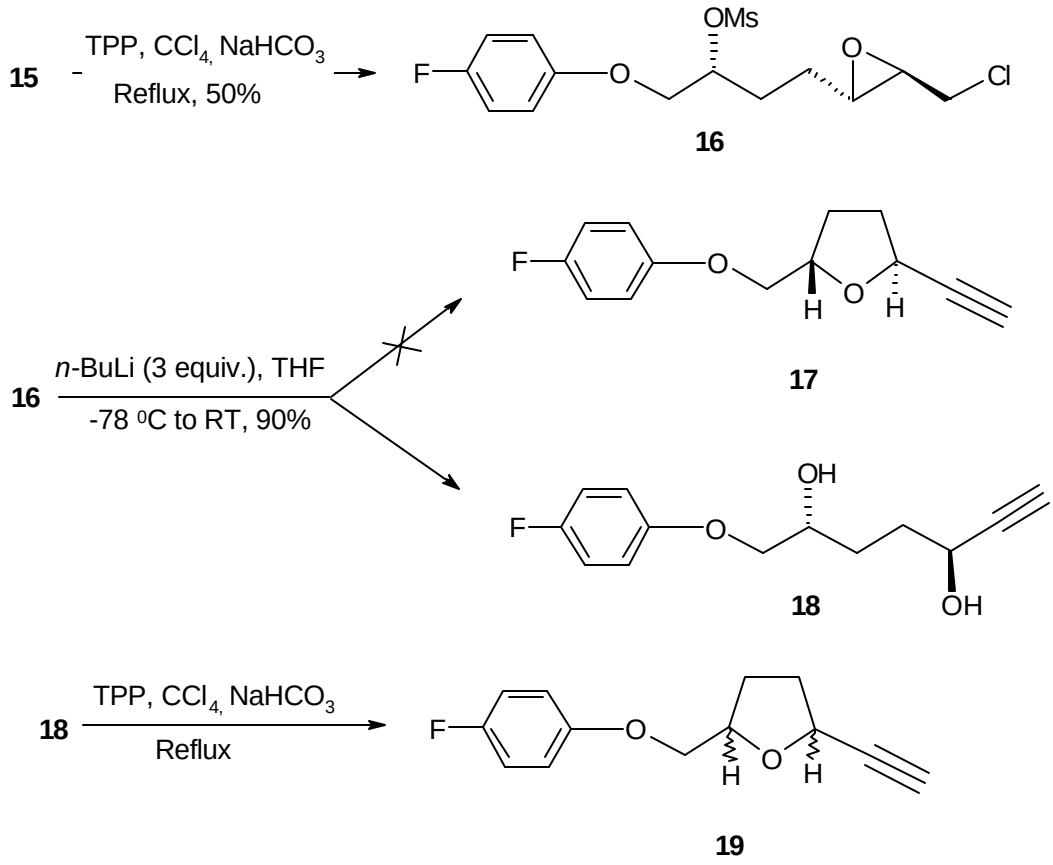
16, upfield shift of peaks belonging to methylene protons (CH_2Cl) compared to that of **15** was noticed. This was further confirmed by a molecular ion peak at (*m*/*z*) 352 in the EI mass spectrum. The central transformation of the synthetic sequence, i.e., formation of THF ring with appropriate stereochemistry, *trans*-fusion, through base-induced double elimination-cum-intramolecular S_N2 ring annulation was investigated next.

Accordingly, the epoxymethyl chloride (**16**) was exposed to 3 equiv. of *n*-BuLi at –78 ºC in dry THF, followed by warming to room temperature.[34] The higher polarity of the resultant product cast doubt over the formation of desired cyclised product, 2-ethynyltetrahydrofuran (**17**), which was supposed to be less polar than starting material. The presence of acetylenic group with its proton resonating at 2.36 ppm as a doublet in the ^1H NMR spectrum confirmed that the substrate had indeed undergone double elimination. Further

revelation was the absence of mesylate ester group and presence of a broad peak at 2.9-3.5 ppm (D_2O exchangeable) implicating the OH group in the product. This information, duly supported by other peaks in the ^1H NMR spectrum had suggested the formation of propargylic diol (**18**), which was subsequently confirmed by conversion into *rac*-ethynyltetrahydrofuran (**19**) on refluxing with TPP in CCl_4, which, *de facto*, is a mild method to convert 1,4-diol into the corresponding tetrahydrofuran.[35] Of course, this method could not serve our purpose, since the product was found to be racemic, loosing the asymmetric information of the starting material during the course of the reaction. This unfortunate development, the formation of undesired **18**, because of susceptibility of mesylate ester to basic conditions, leaving behind alcohol through the self-destruction via the formation of sulphene became the Damocles sword in synthesis – only one step need fail for the entire project to meet sudden death. Damage control experimentation, *viz*., change of base (LDA, Li/NH_3), performing the reaction at –78

C, and the controlled and stoichiometric addition of base didn't halt the susceptibility of mesylate ester.

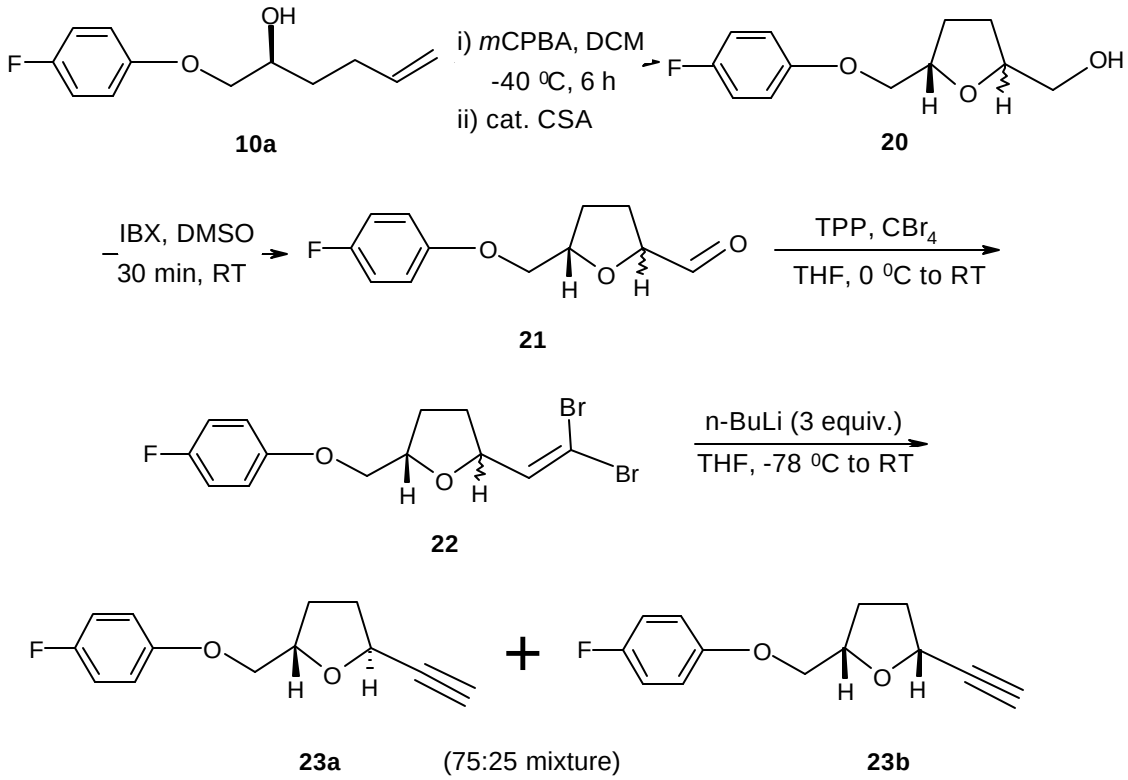
Scheme **9**



After this failure, an alternative yet simplified approach to reach the target was planned. The strategy was to generate the second stereogenic centre via diastereoselective substrate bias, taking advantage of existing centre. The conversion of suitably-posed alkenyl alcohols into tetrahydro-furanyl and pyranyl ethers via electrophilic oxidation of alkenes and subsequent capture by the adventurous nucleophile in an intramolecular fashion has been earmarked as one of the main synthetic strategies in the constructions of cyclic, polycyclic and fused ethers.[36] This transformation has notched up popularity in recent years with the advent of robust catalysts to enhance the diastereoselectivity. We envisaged that the sequential epoxidation of

terminal alkene and immediate ring closure by intramolecular oxygen nucleophile would be the ideal approach for our purpose since the resulting hydroxymethyltetrahydrofuran can be further elaborated to our required destiny, through oxidation of 1º alcohol followed by Corey–Fuch's reaction to position terminal acetylene at C-2. Since the required starting material alkenol **10a** was readily made available from epoxide **31** (*vide infra*), it was decided to advance without much fuss. Accordingly, **10a** was exposed to *m*CPBA in CH_2Cl_2 at –40 ºC for 6 h, followed by further stirring with catalytic CSA overnight to provide the required product (**20**) in 70% yield. The absence of signals due to olefinic protons and the presence of multiplets due to ring junction protons at C_5 and C_2 located between 4.07–4.44 ppm were the clear indication of THF-methanol (**20**) formation. The rest of the protons were localized at their expected regions. The compound (**20**) was efficiently oxidized with IBX in DMSO at ambient temperature with quantitative conversion to provide the aldehyde (**21**), which was quickly exposed for Wittig-type dibromomethylenation with the reagents TPP and CBr_4 to afford the corresponding product (**22**) in good yield.[37] The ^{1}H NMR spectrum of **22** showed a characteristic doublet at 6.52 ppm due to the olefinic proton (CH=). The ring junction protons at C_5 and C_2 appeared as two multiplets at the region 4.32 and 4.50–4.73 ppm. The rest of the protons were located as expected. This dibromoolefin **22** was then treated with 3 equivalent of *n*-BuLi for double elimination at –78 ºC, which gave 2-ethynyltetrahydrofuran (**23**) [a mixture of **23a** and **23b**] in 70% yield. The product was unambiguously supported by its ^{1}H NMR, EI and HRMS spectral data. In the ^{1}H NMR spectrum, the characteristic acetylenic proton appeared as a doublet (J = 2.15 Hz) at 2.42 ppm. The ring junction protons at C_5 and C_2 appeared as a set of multiplets at

Scheme **10**



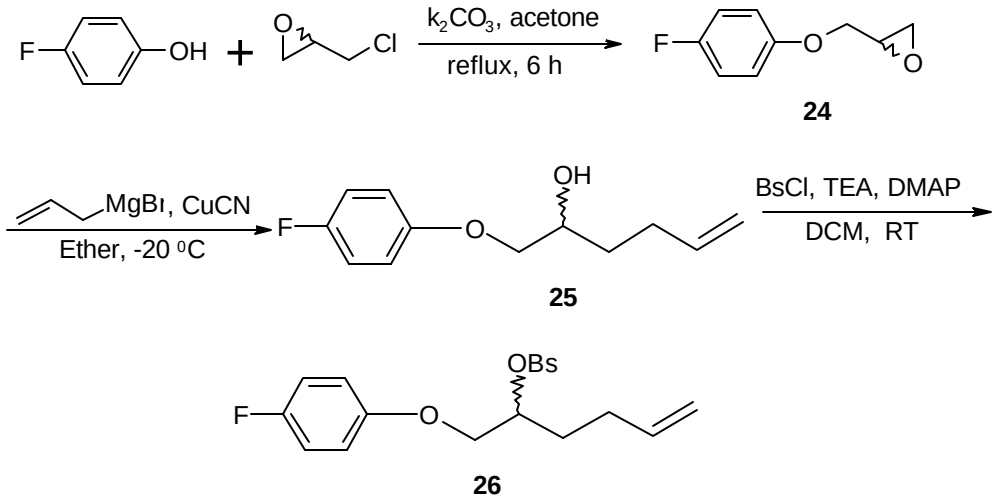
10a **20** **21** **22** **23a** (75:25 mixture) **23b**

4.60–4.80 and 4.24–4.54 ppm respectively, revealing the diasteroselective excess information during epoxidation step. The mixture of diastereomers was found to be in 75:25 ratio, the predominant isomer being the required *trans*-THF isomer (**23a**). The moderate stereoselectivity and difficulty encountered in separation of diastereomers at this stage precluded us to advance further as there was no scope for derivatisation for want of functionalities and recrystallisation because of liquid state of product.

We returned to our primordial strategy (Scheme **3**). The hindsight gained out of the failure indicated the replacement of mesylate ester group with some other stubborn leaving group that will withstand the basic conditions, i.e., *n*-BuLi and LDA. Thus, benzenesuphonyl group, which lacks acidic protons adjacent to SO_2 group was selected. To commence with this endeavour, we had to *de tour* a few steps back in the original scheme, i.e., till hexenol **10**. This time we were precautious to start with racemic starting material as a prelude before

implementing the chiral version because of strategic advantages: the racemic starting material can be made in bulk; to avoid costly chiral reagents requisite for chiral induction; and to bring forth deeper insight in the strategy to remedy any remaining inadequacies. Accordingly, the racemic hexenol **25** was accessed in two steps. Reaction of 4-fluorophenol with epichlorohydrin in the presence of K_2CO_3 in refluxing acetone gave *rac*-4-fluorophenyl glycidyl ether (**24**) in 95% yield, which on subsequent exposure to allylmagnesium bromide gave the alcohol **25** in excellent yield. The alcohol was then converted to (±)-benzenesulphonate ester (**26**) with bezenesulphonyl chloride and Et_3N.

Scheme **11**

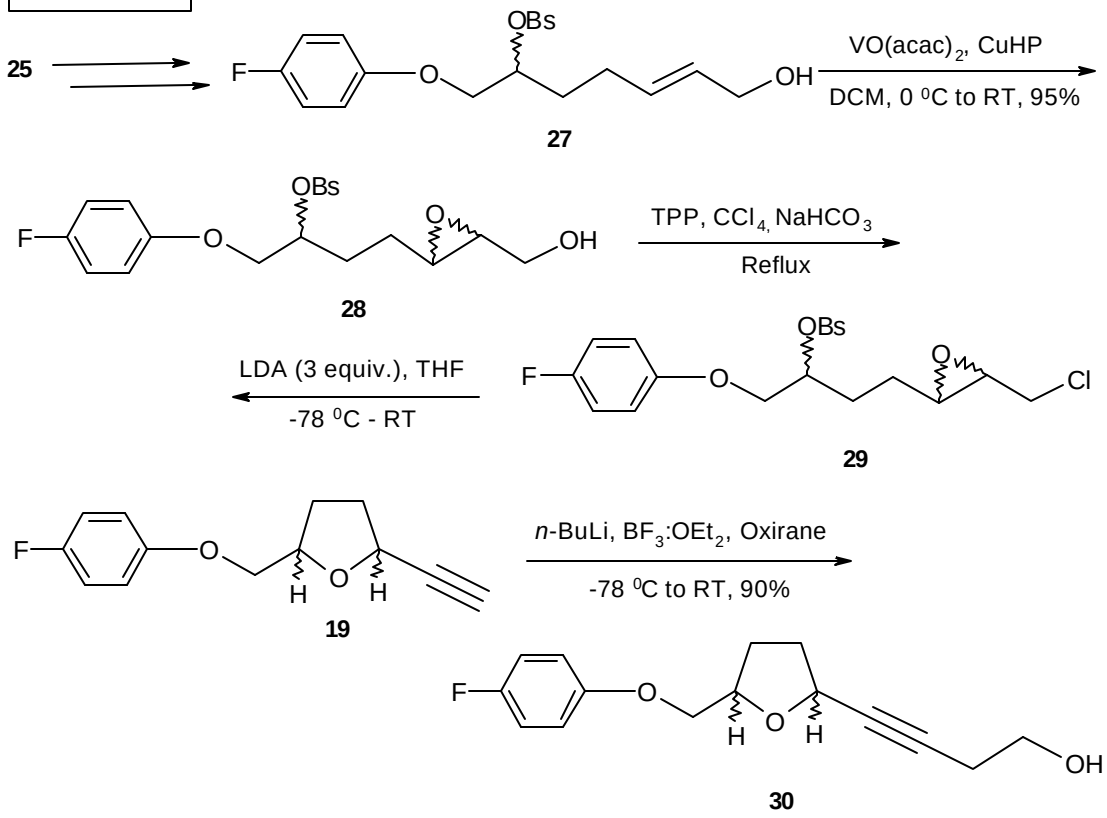


The entire sequence, in parallel to mesylate ester scheme, was executed, as described in scheme **12** with the only modification being the introduction of epoxy group with the reagents $VO(acac)_2$ as catalyst and CuHP as oxidant. The critical LDA-directed double elimination of epoxymethyl chloride (**29**) uneventfully gave the desired *rac*-2-ethynyltetrahydrofuran (**19**), albeit in moderate yield and subsequent opening of ethylene oxide with acetylide anion under Lewis acidic conditions made 2-carbon elongation to access the homopropargyl alcohol (**30**).[38]

Both the products **19** and **30** were unambiguously established by their ^1H NMR spectra. The comprehensive step-by-step explanation and characterization of each product are prescribed for

the corresponding chiral version in the adjoining pages. Thus, this racemic model became the useful training ground providing the critical information before entering the real battlefield, i.e., asymmetric route.

Scheme **12**



By the time we started to asymmetrify the racemic route, described above, we came across the diligent discovery by Jacobsen *et al.* of hydrolytic kinetic resolution (HKR) ofterminal epoxides with exceptional enantionselectivity.[39] This methodology was more appealing, because the chiral building block, (*R*)-4-fluorophenyl glycidyl ether which requires seven steps from D-mannitol can be prepared in only three steps by HKR approach. In fact, this HKR methodology has several beneficial factors like: i) many functional groups are relatively stable toward HKR reaction ii) low cost process for enantiopure terminal epoxides and diols, which otherwise require multistep synthesis from chiral pool or via costly high-volume biocatalytic processes iii) separation and purification of epoxide-diol through fractional

distillation taking advantage of volatality-bias iv) inexpensive starting materials and catalysts (both the enantiomers), producing either enantiomer of epoxide or diol v) high-volume efficiency vi) recovery and reuse of the catalyst, preferentially via catalyst immobilization.

Accordingly, the glycidyl ether (**24**) was subjected to HKR conditions with 0.55 equiv. of water in *t*-butyl methyl ether using the catalyst (*R*, *R*)-(salen)Co^{III}(OAc) (scheme **13**) to provide enantiomerically-pure (*S*)-epoxide (**31**) and (*R*)-diol (**7**) in 46% yield each. The homochiral salen ligand and the catalyst were prepared in this laboratory by a five-step sequence. The (*R*)-diol was identical in all respects (^{1}H NMR, optical rotation, etc.) with that of obtained from D-mannitol. The diol (**7**) was, this time, converted to the desired epoxide (**9**) through cyclic orthoester technology of Sharpless *et al.* in one pot, rather than cyclodehydration of monotosylate, which needs one extra step and tedious column chromatography.[40] Accordingly, **7** was treated with a slight excess of trimethyl orthoacetate in

Scheme **13**

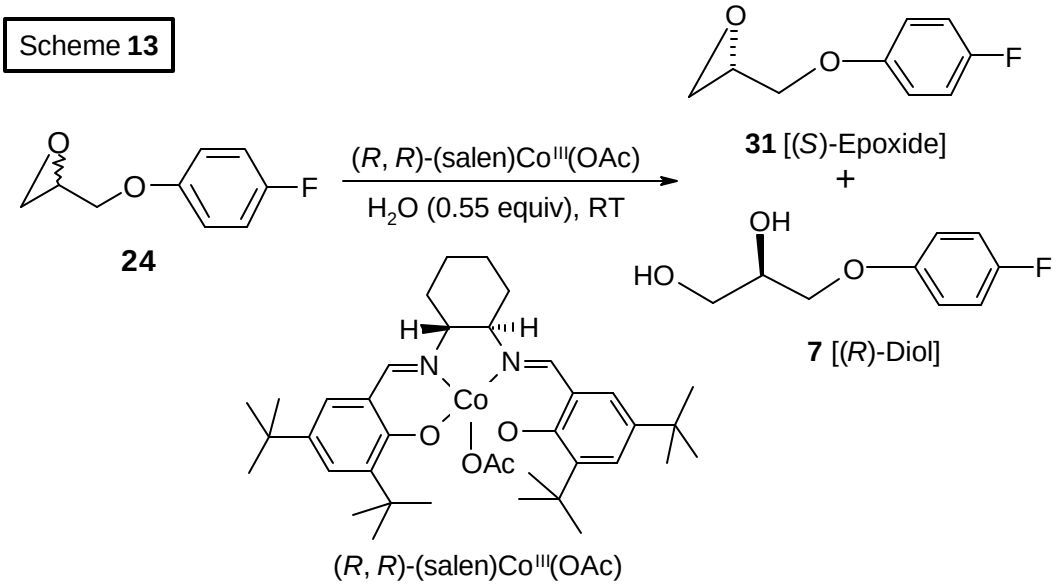
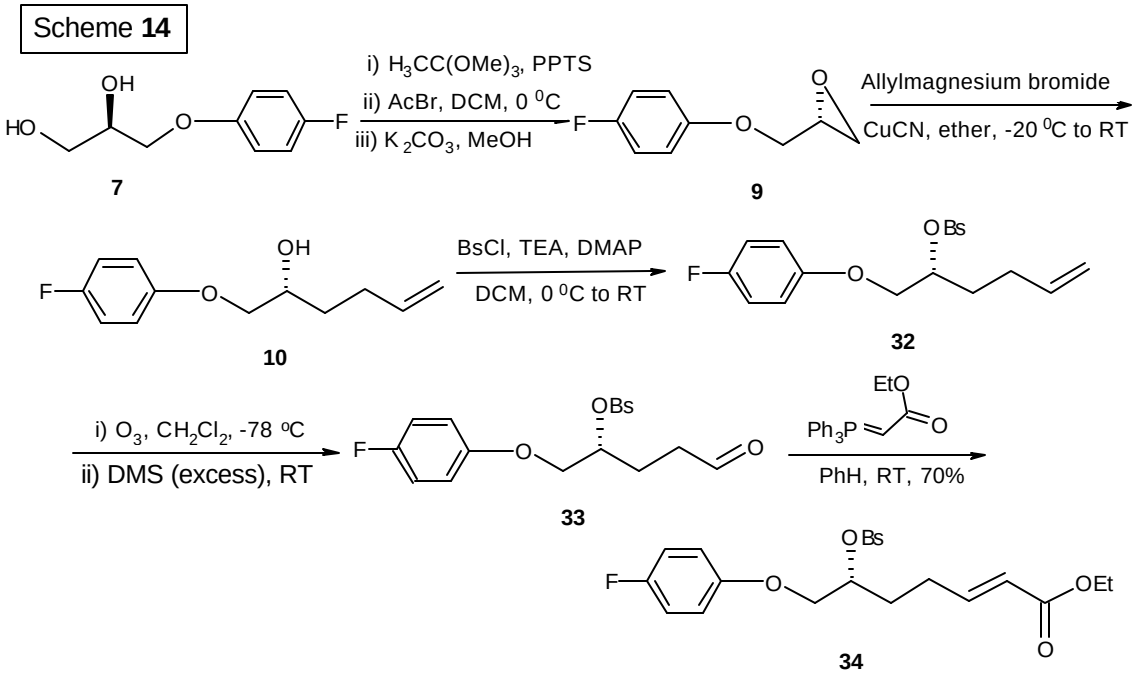


Fig. Jacobsen's HKR catalyst

the presence of catalytic PPTS to effect transesterification, which was then treated with acetyl bromide. The subsequent exposure of *vic*-bromoacetate to K_2CO_3 in methanol afforded the epoxide (**9**) in excellent yield. The product gave identical ^{1}H NMR spectrum and optical

rotation with that of obtained from D-mannitol source (*vide infra*). The glycidyl ether (**9**) was converted to bezenesulphonate ester (**32**), as described earlier. The product **32** was confirmed for its structure by the ^{1}H NMR spectrum with clinching evidences from ^{13}C NMR, IR, EI and HRMS spectral data. The chemical shift of methine proton bearing the sulphonate group shifted downfield (compared to **10**) and appeared at 4.82 ppm and whereas the protons in $PhSO_2$ group as two set of resonances between 7.44–7.91 ppm in the ^{1}H NMR spectrum. In the IR spectrum, two intense peaks at 1170 and 1339 cm^{-1} characteristic of sulphonyl group were observed. The EI mass spectrum gave a molecular ion peak at (*m/z*) 350, which was subsequently confirmed by HRMS (Calcd. for $[C_{18}H_{19}FO_4S]$: 350.0988. Found 350.0996). The olefin (**32**) was then submitted to reductive ozonolysis to provide the corresponding aldehyde (**33**), which was then elongated on reaction with stable Wittig ylide to provide the corresponding α,β-unsaturated ester (**34**). The predominant (*E*)-olefinic ester, obtained after chromatographic removal of minor (*Z*)-isomer, was thoroughly characterized by ^{1}H NMR, ^{13}C

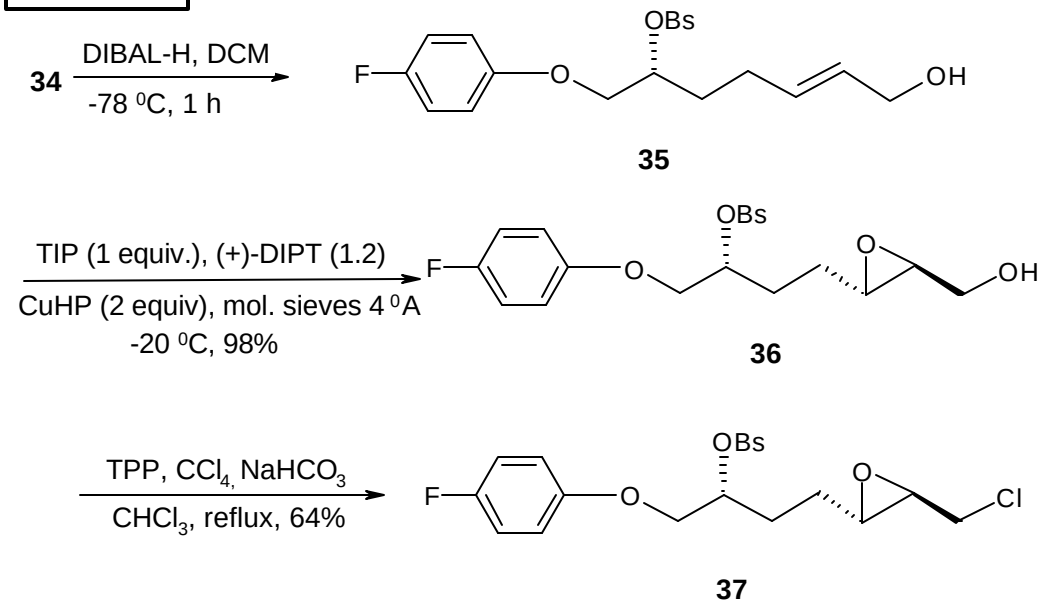
Scheme **14**



NMR, IR, EI and HRMS spectral data. The coupling constant values (J = 16.0 Hz) of olefinic protons confirmed the (*E*)-geometry of olefin. The signals due to methyl group of OCH_2CH_3 appeared at 1.30 ppm as triplet (J = 7.1 Hz) and the methylene at 4.17 ppm as a quartet whereas olefinic protons at 5.77 and 6.73–6.98 ppm. An intense IR adsorption at 1708 cm^{-1} was characteristic for α,β-unsaturated ester. The allyl alcohol (**35**) was secured in excellent yield through the reduction of ester **34** with DIBAL-H at −78 ^{o}C in advance of installing the second chiral centre. The structural identity was secured from the interpretation of ^{1}H NMR, ^{13}C NMR, IR, EI and HRMS spectral data. The methylene group of allyl alcohol resonated between 3.84-4.13 ppm in the ^{1}H NMR spectrum. The EI mass gave a molecular ion peak at (*m/z*) 380, further supported by HRMS (Calcd. for $[C_{19}H_{21}FO_5S]$: 380.1093. Found 380.1097).

The next phase of endeavour was Sharpless asymmetric epoxidation (SAE) of the allyl alcohol (**35**). The epoxidation was performed with $Ti(O^{i}Pr)_4$-(+)-DIPT chiral complex and cumene hydroperoxide. The product **36** was obtained after column chromatography in 90% yield. The spectral information from ^{1}H NMR, ^{13}C NMR, IR, EI and HRMS studies proved the structure of **36** beyond doubt. The multiplet between 2.84-3.01 ppm revealed the identity of the

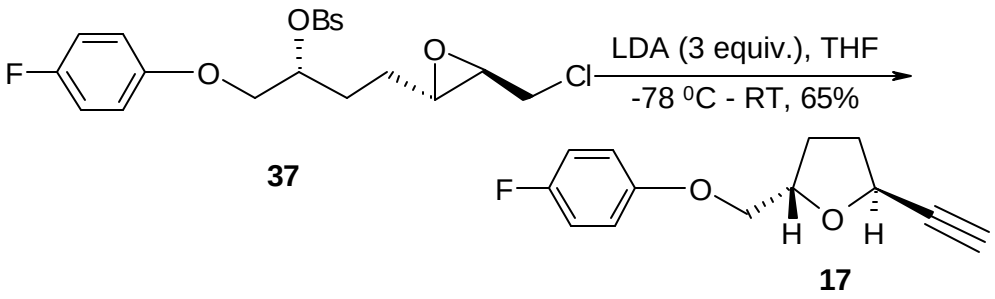
Scheme **15**



epoxy protons, whereas the two olefinic protons disappeared in the region of 5.5-6.5 ppm. The rest of the protons resonated at the expected chemical shift regions. The elemental composition was confirmed by a molecular ion peak at (*m*/*z*) 396.1043 (Calcd. for [$C_{19}H_{21}FO_{16}S$]: 396.1043) in HRMS(FAB) studies. Reaction of epoxymethanol (**36**) with TPP in refluxing CCl_4, not unexpectedly, gave the required epoxymethyl chloride (**37**) in poor yield, with the additional formation of ring-opened products in substantial ratio. The formation of side products was subdued considerably by addition of $CHCl_3$ to enable the solubility of starting material in reaction medium and the product was obtained in gratifying 64% yield. The methylene group (CH_2Cl) moved upfield and resonated as two doublets of doublet at 3.43 ppm (J = 5.5, 8.0 Hz) and 3.58 ppm in the ^{1}H NMR spectrum. The molecular ion peak (M^+, *m*/*z*) at 416 in the EI spectrum was an additional support.

The key transformation was next effected by exposure of **37** to 3 equiv. of LDA, which resulted in the generation of propargyl alcohol through double elimination followed by

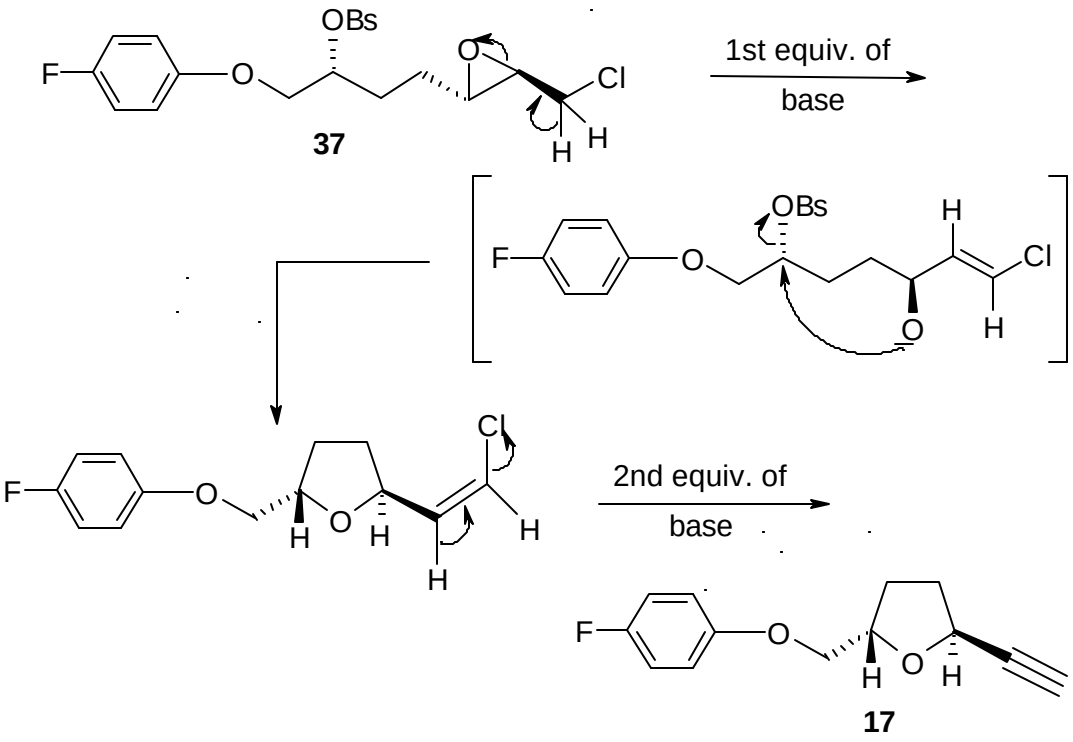
Scheme **16a**



concurrent intramolecular S_N2 cyclisation to provide the THF-acetylene derivative (**17**). This transformation was clearly verified by ^{1}H NMR, IR, EI and HRMS spectral data of the product. In the ^{1}H NMR spectrum, the resonances of two ring-junction protons at C_5 and C_2 appeared between ä 4.38– 4.53 and at δ 4.74 ppm respectively, the acetylenic proton as a doublet at 2.39 ppm and the rest of the protons at the relevant positions. This was further confirmed by a molecular ion peak at (*m*/*z*) 220 in the EI mass spectrum {HRMS: Calcd. for [$C_{13}H_{13}FO_2$]:

220.0899. Found 220.0899). The mechanistic detail of this key step is sketched in scheme **16b**. Thus, this central transformation uneventfully framed the main skeleton in one pot with appropriate substitution and crucial stereochemistry.

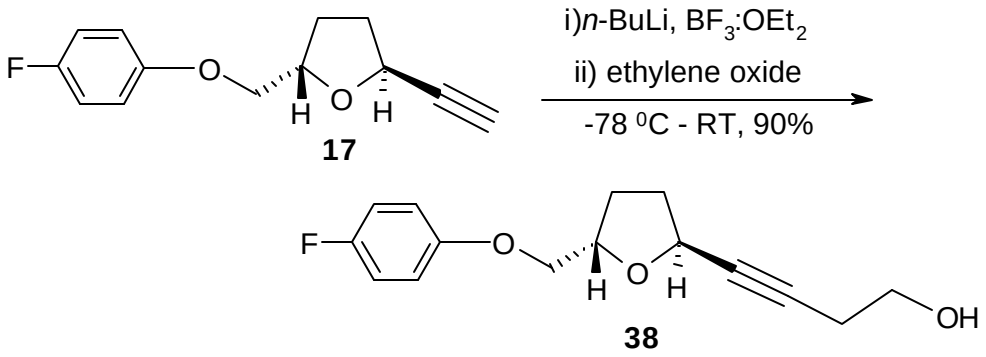
Scheme **16b**: mechanism:



Saito's protocol was next deployed to achieve two carbon homologation, apparently, through $F_3B{:}OEt_2$ facilitated opening of oxirane at $-78\ ^{o}C$ with incipient THF-ylacetylide generated from **17** with *n*-butyllithium.[41] The product, homoprqpargyl alcohol alcohol (**38**) was confirmed by dint of ^{1}H NMR, IR, EI and HRMS spectral studies. The induction of two new methylene groups were clearly displayed by the observed resonances at ä 2.52 ppm as a doublet of triplet and ä 3.74 ppm as a triplet with other features of signals remained intact. The M^{+} ion peak in the FAB mass spectrum at (*m/z*) 264 (HRMS: Calcd. for $[C_{15}H_{17}FO_3]$ 264.1161. Found: 264.1165) approved evidently the structure. The poor NOE enhancement observed during the double irradiation of protons at C-2 and C-5 suggested that these protons

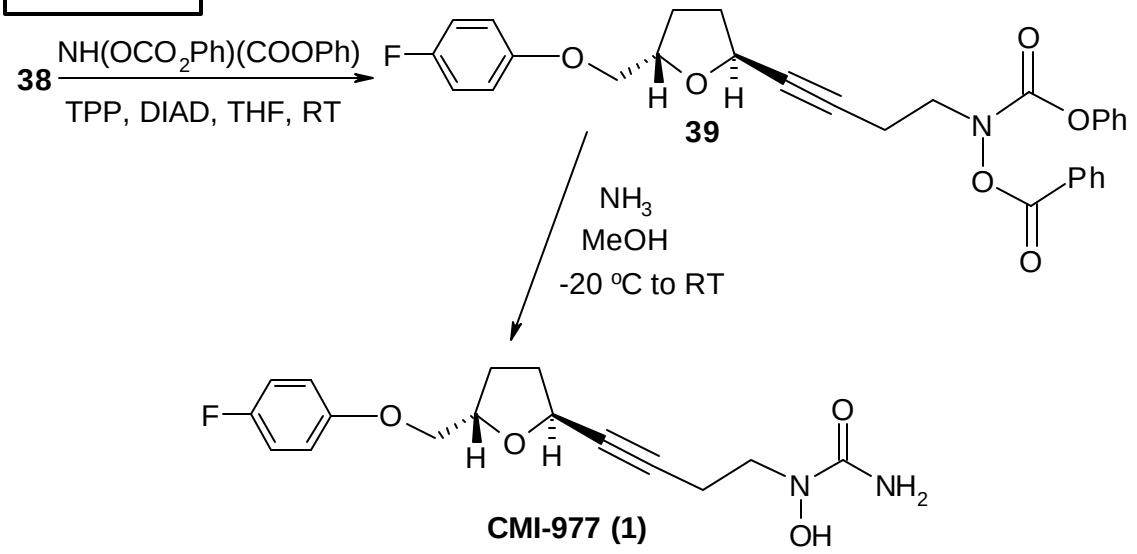
are not in close proximity, i.e., the relative stereochemistry of junction is probably *trans*, which was invariably established by single crystal X-ray crystallographic studies. The chiral homogenity of **38** was checked by matching specific rotation with the sample supplied by M/S Steroids, Chicago, USA {$[\alpha]_D$ -34.3º (c 1.4, $CHCl_3$), lit $[\alpha]_D$- 34º (c 1, $CHCl_3$)}.

Scheme **17a**



The final endeavour was appending of *N*-hydroxyuriedyl moiety to **38**, which was effectively accomplished through Abbott technology, using *N*-hydroxyurea equivalent *N*,*O*-bis (phenoxycarbonyl)hydroxylamine.[42] Thus, Mitsunobu reaction of (**38**) with Abbott reagent in the presence of TPP and DIAD gave the fully-protected derivative (**39**) whose structure was deduced from the ^{1}H NMR, FAB MS and HRMS spectral data. The surge in the integration values in the aromatic region (2 x Ph = 10H) and the downfield shifted resonances of CH_2NR_2 at 4.16 ppm (compared to CH_2OH) pinpointed the conversion, duly supported by FABMS [(M^++1) at (*m*/*z*) 520] and HRMS (Calcd. for [$C_{29}H_{27}FNO_7$]: 520.1771. Found: 520.1770). Ammonolysis of urethane derivative (**39**) on exposure to methanolic ammonia solution culminated in the total synthesis of target compound (**1**) which was identical in all respects, *viz*., ^{1}H NMR, ^{13}C NMR, IR, EI, HRMS spectra, specific rotation and melting point with that of authentic sample.

Scheme **17b**



EPILOGUE:

In conclusion, we have described a total synthesis of CMI-977 in a complete stereocontrolled fashion. 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. 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.[43] 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 SECTION

1,2-*O*-Isopropylidene-D-glycerol (4)[44]

$NaBH_4$ (4.35 g, 115 mol) was added to a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde **2** (15 g, 115 mmol) in methanol (100 mL) over a period of 5 min. at 0 ^{0}C. The reaction mixture was stirred for 1 h and quenched with dilute HCl. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate and water. The organic phase was washed with brine, dried (Na_2SO_4), concentrated and the residue purified by silica gel chromatography (40% ethyl acetate in hexane) to provide **4** (7.62 g, 50%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): ä 1.34, 1.41 (2s, 6H, 2 x CH_3), 1.80-2.10 (br s, 1H, OH), 3.44-3.81 (m, 3H), 3.99 (t, *J* = 7 Hz, 1H), 4.18 (q, *J* = 7 Hz, 1H, H-2)

1,2-*O*-Isopropylidene-3-*O*-*p*-toluenesulphonyl-D-glycerol (5)

To a stirred solution of **4** (7.62 g, 58 mmol), triethylamine (16.13 ml, 116 mmol) and DMAP (61 mg) in dry CH_2Cl_2 (125 mL) was added *p*-toluenesulphonyl chloride (12.08 g, 64 mmol) under N_2 atmosphere at 0 ^{0}C. The reaction mixture was stirred at room temperature for 6 h, washed with sodium bicarbonate solution and brine, dried (Na_2SO_4) and concentrated to afford the residue, which on silica gel purification (20% ethyl acetate in hexane as eluent) gave **5** (15.2 g, 92%).

^{1}H NMR ($CDCl_3$, 200 MHz): ä 1.28, 1.32 (2s, 6H, 2 x CH_3), 2.46 (s, 3H, CH_3 of tosyl), 3.74 (dd, *J* = 5.6, 9.0 Hz, 1H, H-3), 3.84-4.04 (m, 3H, H-3', H-1, 1'), 4.23 (qui, *J* = 5.6 Hz, 1H, H-2), 7.33 (AB d, *J* = 8.1 Hz, 2H, aromatic), 7.77 (AB d, *J* = 8.1 Hz, 2H, aromatic)

(*S*)-3-*O*-(4-Fluorophenyl)-1,2-*O*-isopropylideneglycerol (6)

Sodium hydride (1.9 g, 80 mmol) was added slowly to a solution of 4-fluorophenol (6.54 g, 58 mmol) in a mixture of THF and DMF (4:1, 60 mL) at 0 ^{0}C. After being stirred for 30 minutes, a solution of **5** (15.5 g, 54 mmol) in THF (40 mL) was added at room temperature. The reaction mixture was stirred overnight and quenched with water. After the removal of

solvent, the residue was partitioned between ether (200 mL) and water (200 mL). The organic layer was dried (Na_2SO_4), concentrated, and the residue purified by silica gel chromatography (10% ethyl acetate in hexane) to give **6** (10.8 g, 90%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): ä 1.32, 1.38 (2s, 6H, 2 x CH_3), 3.73-3.88 (m, 2H, H-3, 3'), 3.95 (dd, *J* = 5.0, 10.0 Hz, 1H, H-1), 4.06 (t, *J* = 10.0 Hz, 1H, H-1'), 4.33 (qui, *J* = 6.0 Hz, 1H), 6.68-6.81 (m, 2H, aromatic), 6.89 (t, *J* = 8.8 Hz, 2H, aromatic).

(2*R*)-1-(4-Fluorophe noxy)propane-2,3-diol (7)

A solution of **6** (4.26 g, 18.8 mmol) in methanolic HCl (10%, 25mL) was stirred overnight, quenched with solid $NaHCO_3$, filtered and evaporated. The residue on silica gel chromatographic purification (50% ethyl acetate in hexane) gave **7** (3.2 g, 90%) as a solid.

M.p.: 58– 59 °C

$[\alpha]_D$ –10^o (c 1.0, $CHCl_3$)

IR ($CHCl_3$): 3200 (br), 3020, 1493, 1044, 846 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.09 (br s, 1H, OH, D_2O exchangeable), 2.65 (d, 1H, *J* = 3.4 Hz, OH), 3.60– 3.87 (m, 2H), 3.91– 4.12 (m, 3H), 6.73 – 7.03 (m, 4H, aromatic)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 63.6, 69.6, 70.4, 115.4, 115.6, 116.1, 154.4 and 155.0, 159.8

EI MS at (*m*/*z*): 43 (21), 57 (34), 83 (34), 95 (21), 112 (100), 186 (9) [M^+]

HRMS: Calcd. for ($C_9H_{11}FO_3$): 186.0962. Found 186.0693

(2*S*)-3-(4-Fluorophenoxy)-1-*p*-toluenesulphonyloxypropan-2-ol (8)

The compound **7** (5.0 g, 26.8 mmol) and pyridine (4.5 mL) in CH_2Cl_2 (60 mL) were cooled to 0 °C, followed by the addition of *p*-toluenesulphonyl chloride (5.0 g, 26.8 mmol) portionwise. The mixture was stirred at room temperature overnight. The solvent was removed by co-distillation with toluene and the residue poured on silica gel and eluted (2:3 ethyl acetate and hexane) to afford **8** (7.7 g, 85%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.4 (s, 3H, CH_3 of tosyl), 2.94 (br s, 1H, OH), 3.85 (s, 2H, CH_2O), 3.97– 4.28 (m, 3H, CH_2-OTs + CH-O), 6.70 (m, 2H, aromatic), 6.88 (t, *J* = 8.0 Hz, 2H, aromatic), 7.25 (AB d, *J* = 8.1 Hz, 2H, tosyl), 7.74 (AB d, *J* = 8.1 Hz, 2H, tosyl)

(2*R*)-2,3-Epoxy-1-(4-fluorophenoxy)propane (9)

The compound **8** (5.0 g, 14.7 mmol) was taken in a solvent mixture of THF and DMF (100 mL, 4:1 ratio) and cooled to 0 °C. Sodium hydride (0.75 g, 19.2 mmol) was then added in several lots. After being stirred for 1 h at ambient temperature, THF was removed. The residue was partitioned between ether (100 mL) and water (100 mL). The ether extract was successively washed with water and brine, dried (Na_2SO_4) and concentrated to afford **9** (2.53 g, 95%) as a colourless oil, directly used in the next step.

B.p.: 100 ^{o}C at 4 mm/Hg.

$[\alpha]_D$ – 5.2° (c 1.1, $CHCl_3$)

IR (neat): 831, 1215, 1493, 2892 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.73 (m, 1H, H-3), 2.88 (t, *J* = 4.5 Hz, 1H, H-3'), 3.30 (m, 1H, H-2), 3.92 (dd, *J* = 6.7, 15.7 Hz, 1H, H-1), 4.16 (dd, *J* = 4.5, 15.7 Hz, 1H, H-1'), 6.78-7.09 (m, 4H, aromatic).

EI MS (*m*/*z*): 51 (100), 75 (23), 83 (80), 95 (31), 112 (98), 125 (20), 168 (54) [M^+]

HRMS: Calcd. for [$C_9H_9FO_2$-M^+]: 168.0586. Found 168.0580

(2*R*)-1-(4-Fluorophenoxy)hex-5-en-2-ol (10)

To a mixture of magnesium (0.89 g, 36.6 mmol) and iodine (a crystal) in ether (15 mL), a solution of allyl bromide (3.0 g, 24.4 mmol) in ether (10 mL) was slowly added. After stirring for 30 min. at room temperature, cuprous cyanide (22 mg) was then added at once, resulting in immediate colour change of reaction mixture into dark brown. After cooling to –22 °C, epoxide **9** (2.05 g, 12.2 mmol) in ether (25 mL) was added dropwise. The reaction mixture was stirred for 30 minutes at –22 ^{o}C, quenched with saturated NH_4Cl solution and the resulting

suspension stirred for another 30 minutes. Inorganic solid material was filtered off and washed with ether. The pooled ether layer was dried (Na_2SO_4) and concentrated to furnish the residue, which on filtration over silica gel column (20% ethyl acetate in hexane) gave **10** (2.3 g, 90%) as a colourless oil.

$[\alpha]_D$ –16.3° (c 1.5, $CHCl_3$)

IR ($CHCl_3$): 3400, 2930, 1530, 1215, 830 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz): δ 1.58–1.73 (m, 2H, H-3, 3'), 2.16–2.40 (m, 2H, CH_2-C), 3.80 (t, *J* = 8.4 Hz, 1H, H-1), 3.91 (d, *J* = 11.0 Hz, 1H, H-1'), 3.96 – 4.03 (m, 1H), 5.0 (d, *J* = 10.2 Hz, 1H, one of CH_2=), 5.07 (d, *J* = 17.4 Hz, 1H, one of CH_2=), 5.76– 5.91 (m, 1H, CH=), 6.78–6.88 (m, 2H, aromatic), 6.98 (t, *J* = 9.0, 2H, aromatic)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.6, 32.1, 69.4, 72.7, 115.0, 115.5, 115.6, 116.0, 138.0, 154.6 and 154.9, 159.7

EI MS (*m*/*z*): 43 (34), 57 (22), 112 (110), 210 (12) [M^+]

HRMS: Calcd. for ($C_{12}H_{15}FO_2$-M^+): 211.1089. Found 211.1086.

(2*R*)-1-(4-Fluorophenoxy)-2-methanesulphonyloxy-5-hexene (11)

To a solution of alcohol (**10**) (2.39 g, 10.9 mmol), triethylamine (1.65 g, 16.35 mmol) and DMAP (0.13 g, 1.09 mmol) at 0 °C in CH_2Cl_2, methanesulphonyl chloride (1.5 g, 13.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred for 45 minutes, washed successively with aqueous sodium bicarbonate and water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel (10% ethyl acetate in hexane) to afford **11** (3.15 g, 97%) as a colourless oil.

$[\alpha]_D$ – 8.8° (c 1.4, $CHCl_3$)

IR (neat): 2950, 1650, 1500, 1350, 1200, 1175, 900 cm^{-1} ^1H NMR ($CDCl_3$, 200 MHz): ä 1.8 – 2.0 (m, 2H, H-3, 3'), 2.12–2.34 (m, 2H, H-4, 4'), 3.06 (s, 3H, CH_3SO_2), 3.99- 4.16 (m, 2H, H-1, 1'), 4.88–5.18 (m, 3H, H-2, CH_2=), 5.68–5.92 (m, 1H, CH=), 6.73– 7.05 (m, 4H, aromatic).

EI MS (*m*/*z*): 41 (22), 81 (100), 112 (35), 125 (13), 151 (9), 288 (25) [M^+]

(4*R*)-5-(4-Fluorophenoxy)-4-(methanesulphonyloxy)pentan-1-al (12)

Ozonated oxygen was purged in a solution of olefin **11** (2.85 g, 9.5 mmol) in CH_2Cl_2 (30 mL) at −78 °C, until the medium turned blue. After the removal of excess ozone by bubbling N_2 gas, dimethyl sulphide (5.6 g, 90.5 mmol) was added. The reaction mixture was brought to RT, stirred overnight, concentrated and purified by silica gel column chromatography to afford **12** (2.85 g, 96%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): ä 1.81 – 2.20 (m, 2H, H-3, 3'), 2.69 (q, *J* = 6.9 Hz, 2H, H-2, 2'), 3.0 (s, 3H, CH_3SO_2), 4.0 (d, *J* = 5.6 Hz, 2H, H-5, 5'), 4.8- 4.96 (m, 1H, H-4), 6.67–6.98 (m, 4H, aromatic), 9.74 (s, 1H, aldehydic)

Ethyl (2*E*, 6*R*)-7-(4-fluorophenoxy)-6-(methanesulphonyloxy)hept-2-en-1-oate (13)

A mixture of aldehyde (**12**) (7.0 g, 23.0 mmol) and ethoxycarbonylmethylenetri phenylphosphorane (9.75 g, 28.0 mmol) in benzene (100 mL) was stirred at room temperature for 4 h. Removal of solvent and residue purification by silica gel chromatography (30% ethyl acetate in hexane) gave **13** (7.2 g, 86%) as a colourless oil.

$[\alpha]_D$ – 6.4° (c 1.9, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz): ä 1.30 (t, *J* = 8.0 Hz, 3H, CH_3), 1.89 – 2.08 (m, 2H, H-5, 5'), 2.34–2.53 (m, 2H, H-4, 4'), 3.08 (s, 3H, Me of mesyl), 3.99-4.12 (m, 2H, H-7, 7'), 4.18 (q, *J* = 8.0 Hz, 2H, OCH_2), 4.97 (qui, *J* = 6.0 Hz, 1H, H-6), 5.89 (d, *J* = 16.0 Hz, 1H, H-3), 6.76–7.07 (m, 5H, aromatic and H-2)

IR (neat): 2952, 1712, 1504, 1312, 1175, 1048, 920, 528 cm^{-1}

EI MS (*m*/*z*): 43 (66), 55 (39), 67 (46), 79 (100), 97 (57), 112 (93), 125 (85), 151 (57), 360 (34) [M^+].

(2*E*,6*R*)-7-(4-Fluorophenoxy)-6-(methanesulphonyloxy)hept-2-en-1-ol (14)

DIBAL-H (4.89 g, 17ml {2 M in hexane}, 34.3 mmol) was dropwise added to a solution of **13** (5.62 g, 15.6 mmol) at −78 °C under N_2 atm. After being vigorously stirred for 1 h at −78 °C, the reaction mixture was quenched with aqueous NH_4Cl solution and then stirred at room temperature for 2 h. The solid was filtered, and the filtrate concentrated to afford the crude product, which was purified by silica gel chromatography (60% ethyl acetate in hexane) gave **14** (4.61 g, 93%) as amorphous solid.

$[\alpha]_D$ −10.8° (c 1.9, $CHCl_3$)

IR (neat): 3384, 2936, 1488, 1344, 1210, 1168, 928, 536 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): ä 1.78-2.0 (m, 2H, H-5, 5'), 2.17-2.33 (m, 2H, H-4, 4'), 3.04 (s, 3H, CH_3SO_2), 3.95-4.15 (m, 4H, H-1, 1', 7, 7'), 4.95 (qui, *J* = 6.8 Hz, 1H, H-6), 5.54-5.8 (m, 2H, olefinic), 6.73-7.03 (m, 4H, aromatic)

EI MS (*m*/*z*): 41 (43), 55 (34), 67 (60), 81 (16), 94 (100), 112 (90), 125 (16), 152 (19), 318 (9) $[M^+]$

(2*S*,3*S*,6*R*)-2,3-Epoxy-7-(4-fluorophenoxy)-6-(methanesulphonyloxy)heptan-1-ol (15)

To a solution of titanium tetrakis(isopropoxide) (1.11 g, 3.9 mmol) and (+)-DIPT (0.8 mL, 4.7 mmol) in CH_2Cl_2 (5 mL) carrying activated molecular sieves (4 °A, 0.5 g) at −22 °C, was added cumene hydroperoxide (1.19 g, 7.8 mmol) dropwise. After 15 minutes, a solution of allyl alcohol **14** (1.25 g, 3.9 mmol) in CH_2Cl_2 (15 mL) was added dropwise. The reaction flask was kept in refrigerator for 16 h at −15 °C. Aqueous tartaric acid (10%) was added followed by stirring for 1 h. The reaction mixture was filtered and the filtrate concentrated. The residue was passed through a short silica gel pad (60% ethyl acetate in hexane) to afford **15** (1.13 g, 86%) as a colourless solid.

$[\alpha]_D$ −23.2° (c 1.8, $CHCl_3$)

IR (neat): 3444, 2944, 1520, 1360, 1216, 1170, 920, 560 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): ä 1.5-1.74 (m, 1H, H-5), 1.8-2.04 (br s, 3H, H-5' and H-4, 4'), 2.87-3.03 (m, 2H, H-2, 3), 3.06 (s, 3H, CH_3SO_2), 3.52-3.71 (m, 1H, H-1), 3.76-3.92 (m, 1H, H-1), 3.98-4.17 (m, 2H, H-7, 7'), 4.97 (qui, *J* = 3.2 Hz, 1H, H-6), 6.73-7.04 (m, 4H, aromatic)

EI MS (*m*/*z*): 41 (53), 43 (71), 55 (56), 67 (49), 95 (42), 112 (62), 125 (33), 152 (31), 334 (13) [M^+]

(2*R*,3*S*,6*R*)-1-Chloro-2,3-epoxy-7-(4-fluorophenoxy)-6-(methanesulphonyloxy)heptane (16)

A solution of **15** (1.03 g, 3.08 mmol) and triphenylphosphine (1.62 g, 6.16 mmol) containing sodium bicarbonate (0.5 g) was refluxed in CCl_4 (10 mL) for 2 h. Removal of solvent and residue purification by silica gel column chromatography (30% ethyl acetate in hexane) gave **16** (0.54 g, 50%) as a colourless solid.

$[\alpha]_D$ -21^o (c 0.6, $CHCl_3$)

IR (neat): 1504, 1532, 1216, 1170, 928, 544 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.57-1.7 (m, 1H), 1.91-2.12 (m, 3H), 2.89-3.07 (m, 2H, H-2, 3), 3.09 (s, 3H, CH_3SO_2), 3.47 (dd, *J* = 5.3, 12.0 Hz, 1H, H-1), 3.62 (dd, *J* = 5.3, 12.0 Hz, 1H, H-1'), 4.03-4.17 (m, 2H, H-7, 7'), 4.95- 5.02 (m, 1H, H-6), 6.79-7.04 (m, 4H, aromatic)

EI MS (*m*/*z*): 41(42), 43 (100), 55 (46), 95 (36), 112 (33), 149 (43), 195 (12), 274 (9), 352 (5) [M^+]

(2*R*,5*S*)-1-(4-Fluorophenoxy)-6-heptyne-2,5-diol (18)

n-Butyllithium (0.16 mL, 2.6 mmol, 1.6 M solution in hexane) was added dropwise to a solution of **16** (0.3 g, 1.02 mmol) in dry THF (7 mL) at −78 °C under nitrogen atm. After stirring for 1 h at −78 °C, the reaction mixture was gradually warmed to room temperature over a period of 1 h, quenched with aqueous NH_4Cl solution, and concentrated. The residue was taken in ethyl acetate, washed with water and brine, dried (Na_2SO_4), concentrated. The crude

product was purified on silica gel by eluting with 40% ethyl acetate in hexane to afford **18** (0.15 g, 85%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.52-2.0 (m, 4H, H-4, 4' and H-5, 5'), 2.36 (d, *J* = 1.8 Hz, 1H, acetylenic), 2.9-3.5 (br s, 2H, 2 x OH), 3.7-4.1 (m, 3H, H-3 and H-7, 7'), 4.3-4.48 (m, 1H, H-3), 6.83 (m, 2H, aromatic), 7.02 (t, *J* = 8.1 Hz, 2H, aromatic)

(2*R*, 5*RS*)-2-[(4-Fluorophenoxy)methyl]-5-hydroxymethyltetrahydrofuran (20)

The compound **10a** (3.0 g, 14.3 mmol), and *m*CPBA (4.94 g, 28.6 mmol, 50% by purity) were taken in CH_2Cl_2 (60 mL), cooled at −40 ^{0}C under N_2 atm. The reaction mixture was stirred at −40 ^{o}C for 6 h. CSA (100 mg) was then added to the suspension and the reaction allowed to stir overnight at room temperature, washed with saturated $NaHCO_3$ solution, saturated $Na_2S_2O_3$ solution, water, and brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (40% ethyl acetate in hexane) to afford **20** (2.3 g, 70%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.7-2.3 (m, 4H, H-3, 3' and H-4, 4'), 3.51 (dd, *J* = 5.1, 12.0 Hz, 1H, one of CH_2O), 3.73 (dt, *J* = 3.0, 12.0 Hz, 1H, one of CH_2O), 3.88-4.02 (m, 2H), 4.07-4.24 (m, 1H), 4.25-4.44 (m, 1H), 6.77-7.04 (m, 4H, aromatic)

(2*RS*, 5*R*)-2-(2,2'-Dibromoethenyl)-5-[(4-fluorophenoxy)methyl]tetrahydrofuran (22)

IBX (4.1 g, 14.68 mmol) was added slowly to a solution of **19** (2.76 g, 12.28 mmol) in DMSO (15 mL). The reaction mixture was stirred for 1 h, the precipitated solid filtered and washed with ether and water. The organic extract was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude aldehyde (21), which was dissolved in dry CH_2Cl_2 (50 mL). Triphenylphosphine (3.93 g, 14.68 mmol) and carbon tetrabromide (4.9 g, 14.68 mmol) were successively added at 0 ^{0}C under N_2 atm. The reaction mixture was stirred for 1 h at room temperature, evaporated *in vacuo*, and the residue chromatographed on silica gel (5% ethyl acetate in hexane) to afford **22** (2.9 g, 65%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.7-2.01 (m, 2H, H-4, 4'), 2.01-2.40 (m, 2H, H-3, 3'), 3.92 (d, *J* = 4.5 Hz, 2H, CH_2O), 4.32 (dt, *J* = 7.0, 17.8 Hz, 1H, H-5), 4.5-4.73 (m, 1H, H-2), 6.52 (d, *J* = 7.8 Hz, 1H, olefinic), 6.76-7.03 (m, 4H, aromatic)

(2*RS*,5*R*)-2-Ethynyl-5-[(4-fluorophenoxy)methyl]tetrahydrofuran (23)

To a solution of **22** (0.65 g, 2.32 mmol) in THF (10 mL) under N_2 blanket, *n*-butyllithium (3 mL, 4.6 mmol, 1.6 M solution in hexane) was added dropwise for 10 minutes at –78 ^{0}C and gradually warmed to room temperature over 45 min. Quenching with aqueous NH_4Cl solution (0.5 mL), evaporation of the solvent, partition of the residue between ethyl acetate and water, drying of organic extract (Na_2SO_4), and concentration *in vacuo*. The residue was subjected to silica gel chromatography (5% ethyl acetate in hexane) to afford a mixture of diastereomers **23a** and **23b** (0.27 g, 70%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.81-2.37 (m, 4H, H-3, 3' and H-4, 4'), 2.42 (d, *J* = 2.8 Hz, 1H, acetylenic), 3.91 (dd, *J* = 5.6, 9.7 Hz, 1H, one of CH_2O), 4.07 (dd, *J* = 5.6, 9.7 Hz, 1H, one of CH_2O), 4.24-4.38 and 4.41-4.54 (set of multiplets, 1H, H-5, diasteromeric), 4.60-4.69 and 4.71-4.80 (set of multiplets, 1H, H-2, diasteromeric), 6.78-7.03 (m, 4H, aromatic)

(±)-2,3-Epoxy-1-(4-fluorophenoxy)propane (24)

A mixture of *p*-fluorophenol (5.0 g, 44.6 mmol), epichlorohydrin (16.5 g, 178.4 mmol) and K_2CO_3 (24.0 g, 178.4 mmol) in anhydrous acetone (100 mL) was heated under reflux for 6 h with vigorous stirring. The reaction mixture was filtered and the filtrate evaporated on rotavapor. After distilling out the excess of epichlorohydrin at 120-130 ^{o}C, the residue was distilled under reduced pressure (b.p. 100 ^{o}C at 4 mm/Hg) to give **24** (8.5 g, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.68 (dd, *J* = 2.2, 4.5 Hz, 1H, H-3), 2.85 (t, *J* = 4.5 Hz, 1H, H-3'), 3.27 (m, 1H, H-2), 3.89 (dd, *J* = 6.7, 15.7 Hz, 1H, H-1), 4.11 (dd, *J* = 4.5, 15.7 Hz, 1H, H-1'), 6.74–7.02 (m, 4H, aromatic).

EI MS at (*m*/*z*): 57 (100), 73 (23), 83 (80), 95 (31), 112 (98), 125 (20), 168 (54).

HRMS: Anal. calcd. for [$C_9H_9FO_2$-M^+]: 168.0586. Found 168.0581.

(2*R*)-1-(4-Fluorophenoxy)propane-2, 3-diol (7) and

(2*S*)-2,3-Epoxy-1-(4-fluorophenoxy)propane (31)

The compound **24** (10 g, 59.5 mmol) and (*R*,*R*)-(salen)Co^{III}(OAc) catalyst (215 mg, 0.29 mmol) were taken in *t*-butyl methyl ether (20 mL) and cooled to 0 °C. Conducting water (0.6 mL, 32.7 mmol) was then added dropwise for one hour and stirred for additional 5 hours at room temperature (monitored by HPLC). The reaction mixture was eluted through a short silica gel column to obtain epoxide **31** (4.36 g, 46%, 1:9 ethyl acetate: hexane) and diol **7** (5.06 g, 46%, 1:1 ethyl acetate: hexane).

Physical data of **31**:

The characterization data from ^{1}H NMR, IR, EI and HRMS spectra were identical in all respects with that of **9**, except for the sign of the specific rotation.

$[\alpha]_D$ -5.0^o (c 1.0, $CHCl_3$)

Physical data of **7**:

M.p.: 58-59 ^{o}C

$[\alpha]_D$ -10^o (c 1.5, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.09 (br s, 1H, OH, D_2O exchangeable), 2.65 (d, 1H, J = 3.4 Hz, OH), 3.60– 3.87 (m, 2H), 3.91– 4.12 (m, 3H), 6.73 – 7.03 (m, 4H, aromatic)

(2*R*)-2-Benzenesulphonyloxy-1-(4-fluorophenoxy)-5-hexene (32)

The compound **10** (7.4 g, 35.2 mmol), triethylamine (10 mL, 70.4 mmol) and 4-*N*,*N*'-dimethylaminopyridine (0.43 g) were dissolved in dry CH_2Cl_2 (50 mL) and cooled to 0 ^{o}C. Benzenesulphonyl chloride (5 mL, 38.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring at room temperature for 6 h, the solvent was stripped off on rotary evaporator, and the

residue passed through short silica gel column (1:4 ethyl acetate and hexane) to afford **32** (11.3 g, 92% yield) as a colourless solid.

M.p.: 63-64 °C

$[\alpha]_D$ 5.4° (c 2.6, $CHCl_3$)

IR ($CHCl_3$): 3415 (br), 1493, 1339, 1170, 923 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ 1.88 (q, *J* = 7.7 Hz, 2H, H-3, 3'), 2.0–2.23 (m, 2H, H-4, 4'), 3.88 – 4.08 (m, 2H, OCH_2), 4.82 (qui, *J* = 6.4 Hz, 1H, H-5), 4.90– 5.05 (m, 2H, CH_2=), 5.59–5.82 (m, 1H, CH=), 6.64 (m, 2H, aromatic), 6.90 (t, *J* = 9.1 Hz, 2H, aromatic), 7.44– 7.68 (m, 3H, $PhSO_2$), 7.91 (d, *J* = 6.4 Hz, 2H, $PhSO_2$)

^{13}C NMR ($CDCl_3$, 50 MHz): 28.7, 30.6, 69.1, 80.2, 115.4, 115.5, 115.7 and 116.0, 127.7, 129.1, 133.6, 136.6, 137.0, 154.1, 155.1, 159.8

EI MS (*m*/*z*): 77 (100), 112(16), 141 (48), 162 (12), 234 (12), 350 (10) [M^+]

HRMS: Calcd. for [$C_{18}H_{19}FO_4S$]: 350.0988. Found: 350.0996.

Ethyl (2*E*,6*R*)-6-benzenesulphonyloxy-7-(4-fluorophenoxy)hept-2-en-1-oate (34)

Ozone was purged through a solution of **32** (11.3 g, 32.5 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C, until the blue colour persisted (~ 30 minutes). The reaction mixture was brought to room temperature and then a stream of N_2 gas passed to remove excess of ozone. After cooling again to −78 °C, dimethyl sulfide (13.9 mL, 32. 5 mmol) was added. The reaction mixture was brought to room temperature, stirred further for 12 h, washed with water and brine, and concentrated to afford the crude aldehyde **33** (10.8 g, 95%), which was immediately dissolved in benzene (100 mL). Ethoxycarbonyl methylenetriphenylphosphorane (11.5 g, 33 mmol) was introduced. After being stirred for 5 h at ambient temperature, the reaction mixture was concentrated and the residue chromatographed on silica gel (1:3 ethyl acetate: hexane) to afford **34** (8.8 g, 70%) as a colourless oil.

$[\alpha]_D$ 5.8° (c 1.5, $CHCl_3$)

IR ($CHCl_3$): 2923, 1708, 1493, 1339, 1170, 830 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 1.30 (t, *J* = 7.1 Hz, 3H, CH_3), 1.94 (q, *J* = 6.6 Hz, 2H, H-5, 5'), 2.10-2.40 (m, 2H, H-4, 4'), 3.89– 4.10 (m, 2H, CH_2O), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.82 (qui, *J* = 6.6 Hz, 1H, H-6), 5.77 (d, *J* = 16.0 Hz, 1H, H-3), 6.60-6.90 (m, 5H, aromatic and H-2), 7.47–7.98 (m, 5H, aromatic).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0, 27.0, 29.8, 60.1, 69.0, 79.5, 115.4, 115.5, 116.0, 122.3, 127.7, 129.1, 133.7, 136.7, 146.4, 153.9, 155.1, 160.0, 166.1

EI MS (*m*/*z*): 41 (34), 43 (52), 55 (30), 57 (36), 77 (100), 96 (28), 125 (40), 142 (37), 152(21), 422 (3) [M^+]

HRMS: Calcd. for [$C_{21}H_{23}FO_6S$]: 422.1199. Found: 422.1180.

(2*E*,6*R*)-6-Benzenesulphonyloxy-7-(4-fluorophenoxy)hept-2-en-1-ol (35)

DIBAL-H (14.2 mL, 14.2 mmol, 1 M solution in toluene) was added dropwise over 5 minutes to a solution of **34** (3 g, 7.1 mmol) in CH_2Cl_2 (30 mL) under N_2 blanket at –78 °C. The solution was stirred at the same temperature for 45 minutes, quenched with saturated NH_4Cl solution. The reaction mixture was filtered through a pad of celite, dried (Na_2SO_4) and concentrated. The residue was eluted through a column of short silica gel (50% ethyl acetate in hexane) to obtain **35** (2.2 g, 82%) as a colourless solid.

M.p.: 76-77 ^oC

$[\alpha]_D$ 19.5^o (c 0.6, $CHCl_3$)

IR ($CHCl_3$): 3562, 2923, 1493, 1323, 1177, 1170, 923 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 1.30-1.46 (br s, 1H, OH), 1.82-2.0 (m, 4H, H-4, 4', 5, 5'), 3.84-4.13 (m, 4H, H-1, 1', 7, 7'), 4.88 (qui, *J* = 5.6 Hz, 1H, H-6), 5.5-5.73 (m, 2H, H-2 & H-3), 6.57-6.72 (m, 2H, aromatic), 6.92 (t, *J* = 8.1 Hz, 2H, aromatic), 7.46-7.70 (m, 3H, aromatic), 7.88-8.01 (d, *J* = 7.7 Hz, 2H, aromatic)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.3, 30.8, 63.2, 69.1, 80.3, 115.4, 115.5, 115.6, 116.0, 127.8, 129.1, 130.4, 133.7, 137.0, 154.0, 155.1, 160.1

EI MS (*m*/*z*): 41 (40), 55 (25), 67 (46), 77 (100), 93 (91), 112 (52), 141 (22), 152 (16), 380 (3) [M^+]

HRMS: Calcd. for [$C_{19}H_{21}FO_5S$]: 380.1093. Found: 380.1098.

(2*S*,3*S*,6*R*)-6-Benzenesulphonyloxy-2,3-epoxy-7-(4-fluorophenoxy)heptan-1-ol (36)

Titanium tetrakis(isopropoxide) (1.62 g, 5.47 mmol) and (+)-diisopropyl tartrate (1.07 mL, 6.56 mmol) were sucessively added to a suspension of powdered molecular sieves (4 °A, 3 g), in CH_2Cl_2 (15 mL). After stirring for 5 minutes, cumene hydroperoxide (22.1 mL, 10.94 mmol, 80% solution in cumene) was added dropwise. After stirring for 15 minutes, the allyl alcohol **35** (2.0 g, 5.47 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred for 2.5 h at –20 °C, left refrigerated overnight, quenched with 10% tartaric acid solution (1 mL) at –20 °C, and allowed to warm to room temperature. After filtration of the reaction mixture over celite pad, the filtrate was dried (anhydrous sodium sulphate), and concentrated. The chromatographic purification of the residue on silica gel (1:1 ethyl acetate and hexane) afforded pure epoxy alcohol **36** (2.4 g, 98%) as a colourless solid.

M.p.: 109-110 °C

$[\alpha]_D$ 2.13° (c 1.0, $CHCl_3$)

IR ($CHCl_3$): 3546, 2923, 1508, 1360, 1170, 908, 831, 754 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.39-2.07 (m, 4H, H-4, 4', 5, 5'), 2.84-3.01 (m, 2H, H-2, 3), 3.54-3.72 (m, 1H, H-1), 3.82-4.08 (m, 3H, H-1, 7, 7'), 4.88 (qui, *J* = 6.0 Hz, 1H, H-6), 6.63 (dd, *J* = 4.0, 9.0 Hz, 2H, aromatic) and 6.92 (t, *J* = 9.0 Hz, 2H, aromatic), 7.47-7.72 (m, 3H, aromatic) and 7.93 (d, *J* = 7.5 Hz, 2H, aromatic)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.0, 28.1, 55.1 and 58.2, 61.4, 69.1, 80.3, 115.45, 115.54, 116.0, 127.7, 129.1, 133.7, 136.9, 154.0, 155.1, 160.0

EI MS (*m*/*z*): 41 (28), 43 (40), 67 (43), 77 (100), 84 (39), 96 (39), 114 (42), 142 (27), 152 (34), 196 (13), 272 (9), 396 (8) [M^+]

HRMS: Calcd. for [$C_{19}H_{21}FO_6S$]: 396.1043. Found: 396.1024.

(2*R*,3*S*,6*R*)-6-Benzenesulphonyloxy-1-chloro-2,3-epoxy-7-(4-fluorophenoxy)heptane (37):

A solution of **36** (2.25 g, 5.7 mmol) and triphenylphosphine (1.5 g, 5.7 mmol) in a solvent mixture of $CHCl_3$ and CCl_4 (40 mL, 1:1 ratio) containing $NaHCO_3$ (0.3 g) was refluxed for 3 h. Removal of the solvent and subsequent purification of the residue by silica gel column chromatography (1:4 ethyl acetate and hexane) afforded **37** (1.5 g, 64%) as a colourless solid.

M.p.: 59-60 ^oC

$[\alpha]_D$ -5.5^o (c 0.6, $CHCl_3$)

IR ($CHCl_3$): 2939, 1493, 1369, 1185, 923 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 1.53 (q, *J* = 6.8 Hz, 1H, H-5), 1.72-2.09 (m, 3H, H-4, 5, 5'), 2.83 (td, *J* = 2.3, 5.5 Hz, 1H, H-3), 2.92 (td, *J* = 2.3, 5.5 Hz, 1H, H-2), 3.43 (dd, *J* = 5.5, 8.0 Hz, 1H, H-1), 3.58 (dd, *J* = 5.5, 8.0 Hz, 1H, H-1'), 3.87-4.10 (m, 2H, H-7, 7'), 4.86 (q, *J* = 6.8 Hz, 1H, H-6), 6.58-6.74 (m, 2H, aromatic), 6.92 (t, *J* = 9.0 Hz, 2H, aromatic), 7.47-7.73 (m, 3H, aromatic) and 7.92 (d, *J* = 7.3 Hz, 2H, $PhSO_2$)

EI MS (*m*/*z*): 41 (19), 67(31), 77 (100), 81 (24), 83 (31), 95 (25), 125 (25), 141 (55), 145 (55), 414 (10) [M^+]

HRMS: Calcd. for [$C_{19}H_{20}ClFO_5S$]: 414.0704. Found: 414.0721.

(2*S*,5*S*)-2-Ethynyl-5-[(4-fluorophenoxy)methyl]tetrahydrofuran (17)

A solution of **37** (1.0 g, 2.42 mmol) in dry THF (8 mL) was added to lithium diisopropylamide (7.2 mmol) {generated *in situ* by the addition of n-BuLi (7.2 mL, 7.2 mmol) to a solution of diisopropylamine (1.12 mL, 8.6 mmol) in dry THF (6 mL) at -40 °C and aftermath stirring for 15 minutes} at -40 °C. The reaction was stirred for 1 h at -40 ^oC, gradually warmed to RT and quenched with aqueous NH_4Cl (1 mL). The solvent was stripped

off and the residue taken in ethyl acetate, washed with water and brine, dried (anhydrous sodium sulphate) and concentrated. The residue on silica gel chromatographic purification (1:9 ethyl acetate) afforded **17** (0.32 g, 60 %) as a colorless liquid.

$[\alpha]_D$ −23.0° (c 0.7, $CHCl_3$)

IR ($CHCl_3$): 3308, 2923, 2123, 1600, 1493, 1212, 1046, 838 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 1.81-2.37 (m, 4H, H-3, 3', 4, 4'), 2.39 (d, *J* = 2.3 Hz, acetylenic), 3.86-4.01 (m, 2H, OCH_2), 4.38-4.53 (m, 1H, H-5), 4.74 (dt, *J* = 3.0, 5.6 Hz, 1H, H-2), 6.76-7.02 (m, 4H, aromatic).

EI MS (*m*/*z*): 43 (37), 55 (19), 81 (65), 95 (100), 112 (32), 125 (11), 220 (35) [M^+].

HRMS: Calcd. for [$C_{13}H_{13}FO_2$]: 220.0899. Found: 220.0899.

(2*S*,5*S*)-2-(4-Hydroxyl-1-butynyl)-5-[(4-fluorophenoxy)methyl]tetrahydrofuran (38)

n-BuLi (5 mL, 1M solution in hexane) was added to a solution of **17** (0.8 g, 3.6 mmol) in THF (15 mL) at −78 °C. Freshly distilled BF_3:OEt_2 (1.4 mL, 11.0 mmol) in THF (2 mL) was then added followed by excess of ethylene oxide in THF (5 mL). The reaction mixture was allowed to stir at -78 °C for 30 minutes, quenched with aqueous NH_4Cl solution, and concentrated on rotary evaporator. The residue was taken in ethyl acetate, washed with water and brine, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography to afford **38** (0.87 g, 90% yield) as a colorless solid.

M.p.: 72-73 °C; lit. 77-79 °C

$[\alpha]_D$ −34.3° (c 1.8, $CHCl_3$); lit. $[\alpha]_D$ −34.0 (c 1.8, $CHCl_3$)

^1H NMR ($CDCl_3$, 200 MHz): δ 1.67-1.77 (br s, 1H, OH), 1.78-2.37 (m, 4H, H-3, 4, 4'), 2.52 (dt, *J* = 1.7, 6.4 Hz, 2H, $\equiv CH_2$), 3.74 (t, *J* = 6.4 Hz, 2H, CH_2OH), 3.94 (d, *J* = 5.0 Hz, 2H, $ArOCH_2$), 4.40-4.54 (m, 1H, H-5), 4.72-4.83 (m, 1H, H-2), 6.80-7.06 (m, 4H, aromatic)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.0, 17.7, 33.3, 60.7, 68.9, 70.6, 76.8, 81.1, 82.1, 115.4,115.6, 115.8, 154.8, 159.6

EI MS (*m*/*z*): 65 (33), 67 (42), 69 (92), 77 (100), 79 (84), 81 (48), 83 (48), 111 (46), 112 (67), 121 (45), 125 (28), 139 (55), 152 912), 264 (8) (M^++1)

HRMS: Calcd. for [$C_{12}H_{13}FO_3$-M^+]: 264.1161. Found: 264.1165.

(2*S*,5*S*)-5-[(4-Fluorophenoxyl)methyl]-2-(4-*N*,*O*-bis(phenoxycarbonyl)hydroxylamino) -1-butynyl]tetrahydrofuran (39)

To a solution of **38** (1.0 g, 3.8 mmol), triphenylphosphine (1.17 g, 4.05 mmol) and *N*,*O*-bis(phenoxycarbonyl)hydroxylamine (1.24 g, 4.05 mmol) in THF (15 mL), was added diisopropylazodicarboxylate (0.82 g, 4.05 mmol) dropwise at 0 °C for 5 min. The reaction mixture was stirred at 0 °C for 30 min. and at room temperature for 6 h. The solvent was stripped off and the residue chromatographically purified on silica gel (1:7 ethyl acetate and hexane) to provide **39** (1.6 g, 80%)

$[\alpha]_D$ −18.4° (c 0.9, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.76 (m, 1H), 1.95 (m, 1H), 2.13 (m, 2H), 2.64 (t, *J* = 6.8 Hz, 2H, CH_2N), 3.79 (dd, *J* = 2.0, 4.5 Hz), 3.95 (t, 2H, *J* = 6.8 Hz, ≡-CH_2), 4.33 (m, 1H), 4.63 (m, 1H, H-2), 6.63-6.93 (m, 4H, aromatic), 7.13-7.50 (m, 10 H, aromatic)

FABMS at (*m*/*z*): 520

HRMS: Calcd. for [$C_{29}H_{27}FNO_7$- M^++1]: 520.1771. Found: 520.1770

(2S,5S)-*trans*-5[(4-fluorophenoxy)methyl]-2-(4-*N*-hydroxyureid-1-butynyl)tetrahydro furan (CMI-977) (1)[45]

Ammonia gas was purged into a solution of **39** (1.0 g, 1.93 mmol) in methanol (10 mL) at 0 °C for 30 minutes. The reaction mixture was allowed to stir at ambient temperature for 1 h. Rotary evaporation of the solvent, followed by purification of the residue on elution through a short silica gel pad ($CHCl_3$:MeOH, 20:1) afforded **1** (1.3 g, 70%) as a colourless solid.

M.p.: 106 – 107 °C; lit. 113-114 °C

$[\alpha]_D$ –46.8° (c 1.1, MeOH) lit., $[\alpha]_D$ –47.8 ° (c 0.3, CD_3OD)

^1H NMR ($CDCl_3$, 200 MHz): δ 1.83 (m, 1H, H-4), 2.01 (m, 1H, H-4') 2.22 (m, 2H, H-3, 3'), 2.54 (t, *J* = 7.8 Hz, 2H, **o**-CH_2), 3.68 (t, *J* = 7.8 Hz, 2H, CH_2N), 3.91 (m, 2H, CH_2O), 4.46 (m, 1H, H-5), 4.73 (m, 1H, H-2), 5.68 (br s, 2H, NH_2), 6.78 - 7.02 (m, 4H, aromatic), 8.95 (s, 1H, N-OH)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.13, 27.66, 33.28, 48.62, 69.08, 70.72, 76.36, 80.72, 82.80, 115.50, 115.63, 115.97, 154.98, 159.70,161.84

FABMS at (*m/z*): 137 (42), 154 (54), 280 (11), 324 (100) [M^++1]

HRMS: Calcd. for [$C_{16}H_{19}FN_2O_4$-M^++1]: 323.1407. Found: 323.1424.

SECTION–II

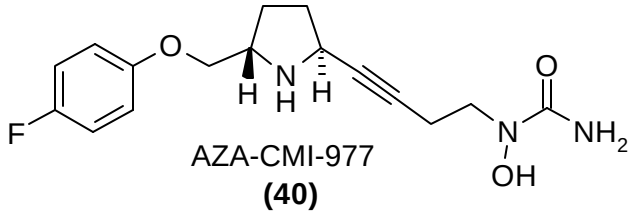
STEREOSELECTIVE SYNTHESIS OF (2*S*,5*S*)-5-(4-FLUOROPHENOXY)METHYL-2-(4-*N*-HYDROXYUREIDYL)-1-BUTYNYL)PYRROLIDINE (AZA ANALOGUE)

PRESENT WORK

The advent of genomic sciences, 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.[46] Recombinant proteins and monoclonal antibodies under the charm "biopharmaceuticals" have greatly enriched our therapeutic armamentarium. Genomic science, combined with bioinformatic tools, allow us to dissect the genetic basis of multifactorial diseases and to determine the most suitable points of attack for future medicines, thereby 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.[47]

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 these laboratories to synthesise 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



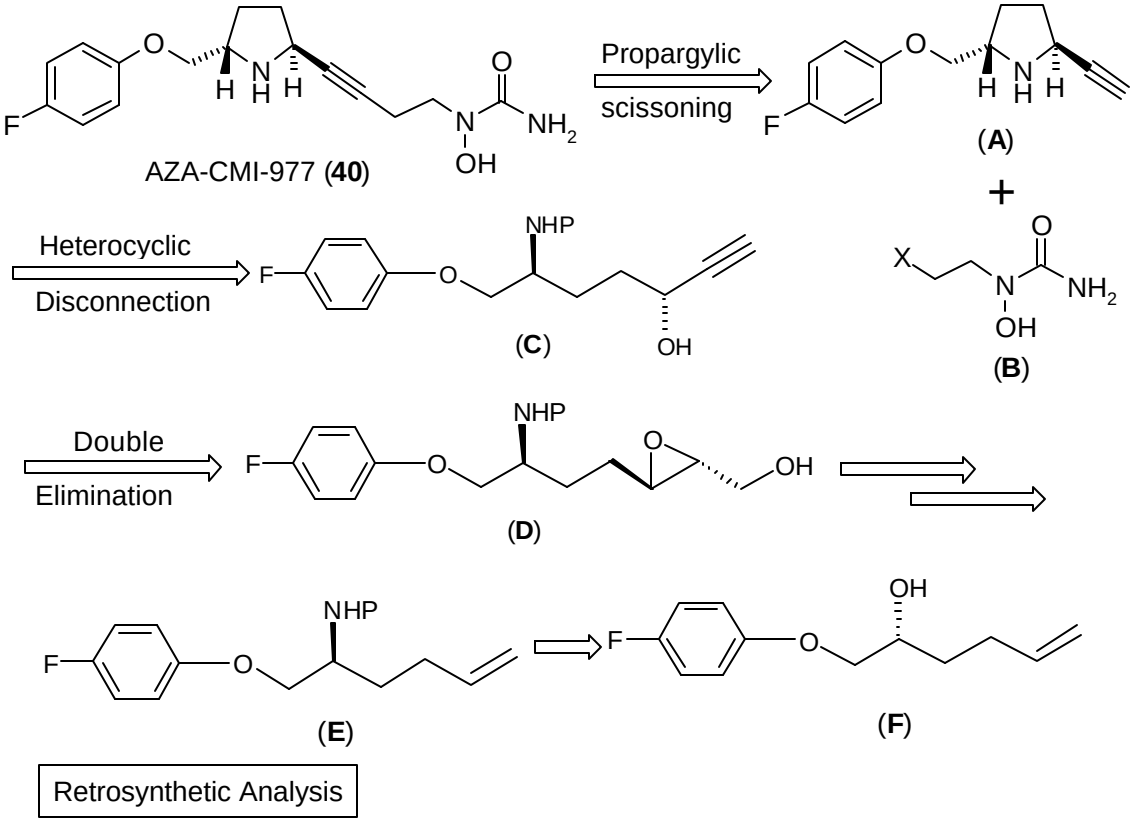
AZA-CMI-977

(40)

structure-activity relationship. Out of the core group formed for analogues making, we were interested in the aza derivative of CMI-977 (**40**) since nitrogen is an indispensable part of many compounds including alkaloids, amino acids, azacarbohydrates and macromolecules (including proteins, glycopeptides, DNA, RNA and other aza supramolecules) available in nature's store. These compounds indulge in various physiological functions, right from life-making process to behavioural control and photosynthesis. These type compounds play dubious role of distinction while one type of molecules have been implicated in several human disorders like cancer-inducing, hallucinogenic property, inflammation, etc., the other kind including several of synthetic origin serve to cure and control these debilitating diseases like asthma, schizophrenia, HIV (AZT) and other infectious ailments.[48] Out of compendium of excellent strategies for the construction of *trans*-fused pyrrolidine rings available in literature, 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 antithetic analysis (scheme **18).** The initial C-C disconnection involved the separation

of *N*-ethyl-*N*-hydroxyurea (**B**) from the acetylenic fragment (**A**). Ring disconnection of ethynylpyrrolidine was made based on intramolecular S_N2 Mitsunobu transformation, resulting in aminoalcohol (**C**). The rightern-part, propargyl alcohol in (**C**) could be equated equitably to epoxymethanol (**D**). Further simplification of stereochemical and functional group based complexity will generate the offspring synthon alkenyl amine (**E**), which was expected to arise from the corresponding alcohol (**F**) available already in our hand.

Scheme (**18**)

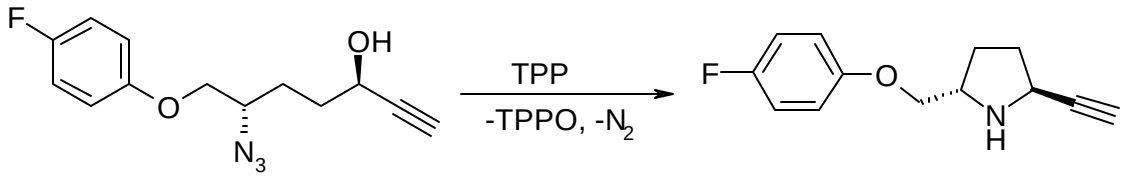


Retrosynthetic Analysis

It is instructive to preface the discussion on the key transformation (**C**→**A**). The suitably-framed 1,4-azidoalcohol (**G**) was expected to be an acyclic equivalent of pyrrolidine (**H**), as the reaction of 1,4-azidoalcohol with TPP would deliver the corresponding pyrrolidine derivative. The elctrophilic azaphosphorane, which forms first, would be trapped by internal

OH group to form putative cyclic phosphoxazapane intermediate that will lead to pyrrolidine with the extrusion of TPPO (scheme **19**).[49]

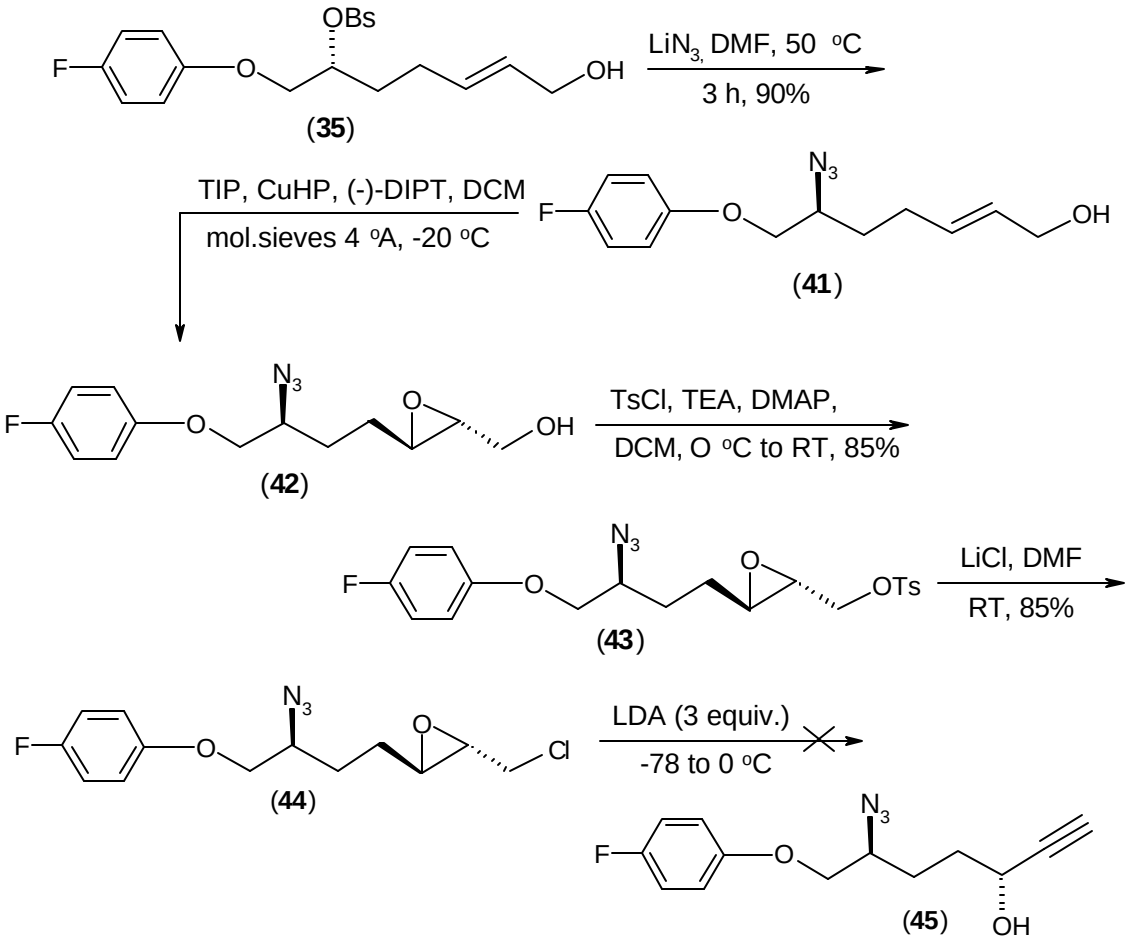
Scheme **19**



G **F**

In the synthetic process, the homochiral allyl alcohol (**35**), a known intermediate (described in the previous section), was converted to its azido derivative (**41**) in the presence of LiN_3 in DMF at 50 °C. In the ^{1}H NMR spectrum of **41,** the proton at azide bearing carbon gave a multiplet at 3.60– 3.76 ppm. The IR spectrum possessed a strong signal at 2100 cm^{-1}, characteristic of azide group. The next step would pave the way for creation of second chiral centre through Sharpless epoxidation. Asymmetric epoxidation of (**41**) with stoichiometric amount of reagents $Ti(O\text{-}^iPr)_4$/(+)-DIPT/cumene hydroperoxide in the presence of 4 °A molecular sieves gave the 2,3-epoxymethanol (**42**) in moderate yield, in addition to the formation of a highly polar product which could not be isolated for characterization. In the ^{1}H NMR spectrum of **42**, peaks corresponding to epoxy protons appeared at 2.86–3.06 ppm as multiplets, while no change was encountered with rest of the protons. The succeeding step was the conversion of epoxymethanol to epoxymethyl chloride. Since the one-pot transformation with TPP in refluxing CCl_4 was observed as a low-yielding process in the synthesis of CMI-977, a two-step procedure was followed. Accordingly, (**42**) was converted to glycidol tosylate (**43**) on treating with *p*-toluenesulphonyl chloride, Et_3N and catalytic DMAP in CH_2Cl_2 in 85% yield. The conversion was confirmed by the ^{1}H NMR spectrum, with new peaks owing to toluenesulphonyl group (a singlet at 2.45 ppm and two doublets $\{A_2B_2\}$ between 7.28– 7.82 ppm). This was uneventfully transformed into 2,3-epoxymethyl chloride (**44**) by treating with

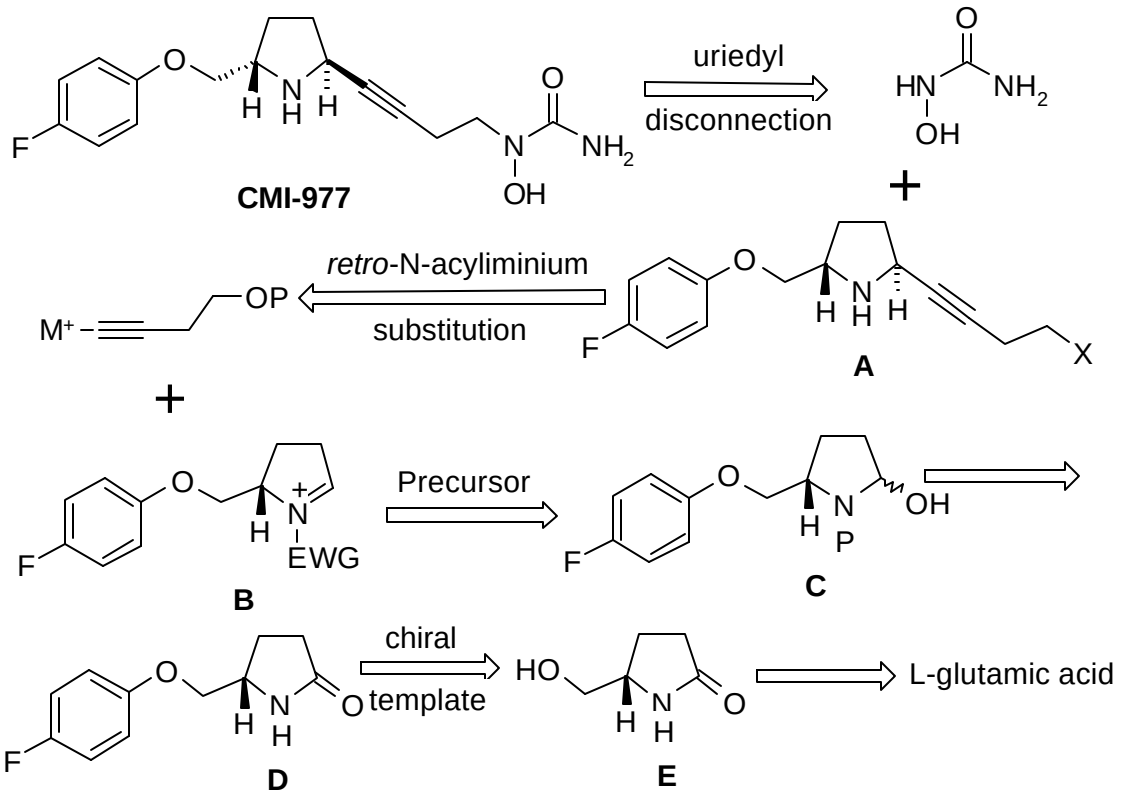
Scheme **20**



LiCl in DMF at ambient temperature in excellent yield. In ^{1}H NMR spectrum of **44**, the characteristic signals due to CH_2 of CH_2Cl were observed at ä 3.36–3.70 ppm, whereas the remaining signals were in complete agreement with the assigned structure. The compound **44** was then treated with 3 equiv. of LDA at −78 °C to obtain propargyl alcohol. However, the major isolated product didn't provide the clear image over the structure, as the ^{1}H NMR spectrum was complex and suggested mixture of compounds formed probably due to destructive decomposition of **44**. Hence, we stopped at this juncture and looked for alternative.

With the failure of asymmetric route, the quest for conquering the synthesis of nitrogen mimic of CMI-977 solely rested on the prospects of " chiron approach" which over the years

has been nurtured by the synthetic chemists to manoeuver chemically and stereochemically with obvious operational and practical advantages to realize the asymmetric targets.[50] Readily available chiral starting materials such as amino acids have their unique place in the practice of art of synthetic design, particularly when one or two chiral centers are sought. The scrutinization of the molecular architecture of our target to locate the elements of symmetry, chirality and functionality, decoding such information and transposing it onto the carbon framework of suitable synthetic precursors (chirons) should imply L-pyroglutamic acid by systematic functionalization. Essentially, L-pyroglutamic acid poses as a replica of a segment



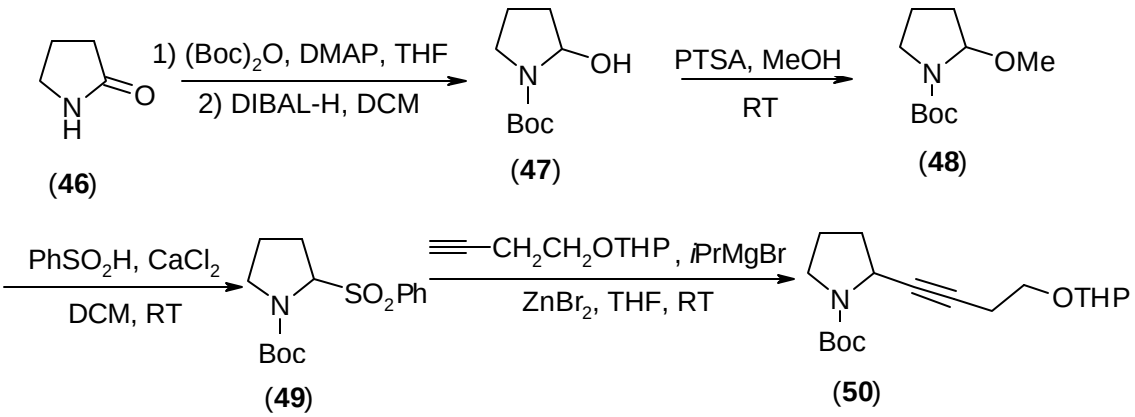
Scheme **21**: Retrosynthetic analysis

of our target, i.e., as chiral template. The overall chiron strategy is described in scheme **21**. The pivotal step in this strategy is the C-C bond formation to affix the side chain at C-2 position, i.e., at the prevailing carbonyl position of lactam (**D**) with control of stereochemistry

taking advantage of natural inherent chirality. This precarious planning should reveal L-glutamic acid, the acyclic precursor of L-pyroglutamic acid as the chiron progenitor to start with.

Before launching the synthesis, as planned in the preceding lines, a model study was conducted to probe the conceivability of the crux of the strategy, the GC bond formation in the nucleophilic addition of N-acyliminium ion for destining the elusive side chain. In accordance with, simple 2-pyrrolidinone (**46**) was chosen that is reminiscent of the compound used to access the target molecule. The compound **46** was converted to its corresponding lactol (**47**) through protection as the carbamate derivative followed by reduction with DIBAL-H in good yield. Since the ^{1}H NMR spectrum of the compound (**47**) was short of clarity, it was further converted to (2)-methoxypyrrolidine (48) on exposure to PTSA in methanol, which was readily confirmed by the ^{1}H NMR spectrum. Replacement of methoxy group with benzenesulphonyl group was easily accomplished on treatment with freshly prepared $PhSO_2H$ in CH_2Cl_2 to afford the corresponding derivat**ive (49).** The dialkyl zinc reagent, derived *in situ* from $ZnBr_2$ and

Scheme **22**



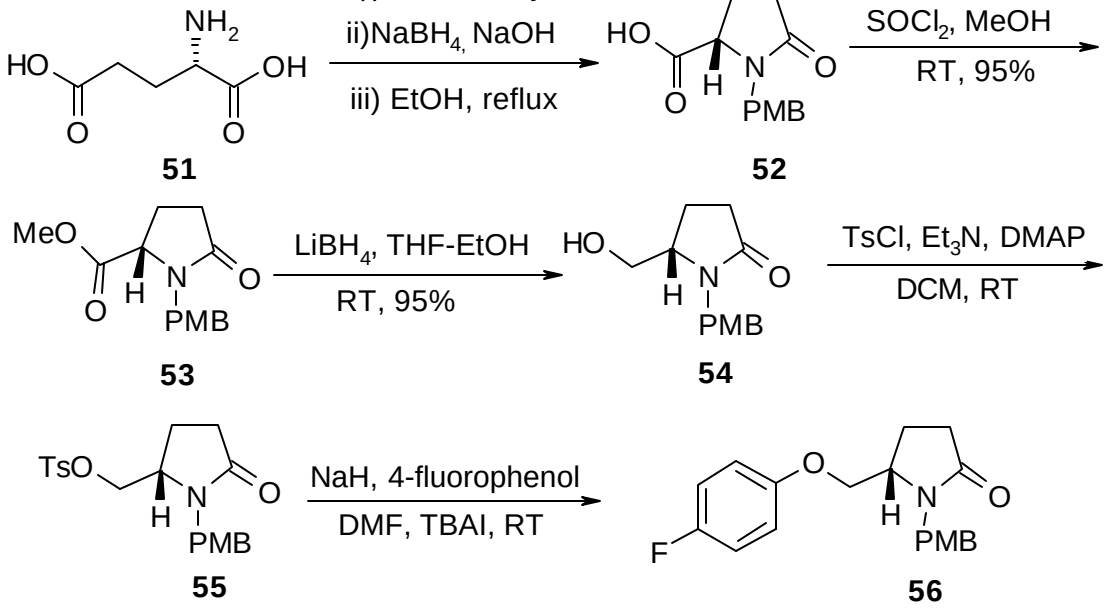
(**46**) (**47**) (**48**)

(**49**) (**50**)

4-tetrahydropyranyloxy-1-butynylmagnesium bromide smoothly reacted with the substrate to provide the C-C coupled product, homopropargylpyrrolidine derivative (**50**). The PMR spectra of both the compounds (**49**) and (**50**) highlighted the major structural features evidently.

The euphoria generated in the model studies seemed suffice to carry forward *en route* to the promised target. In the synthetic direction, L-glutamic acid (**51**) was converted to *N*-(4-methoxybenzyl)-2-oxoproline (**52**) in 24% yield, according to Decroix protocol,[51] which involved the treatment with *p*-anisaldehyde and $NaBH_4$ under basic pH. Esterification was next performed with catalytic $SOCl_2$ in methanol to afford the methyl ester (**53**) in 95% yield. The product was confirmed by the relevant signals in the ^1H NMR spectrum. Reduction of **53** was conveniently accomplished with $LiBH_4$ {generated *in situ* from $NaBH_4$ and LiCl in a solvent mixture of THF and EtOH} to obtain hydroxymethylpyrrolidinone (**54**) in 95% yield.[52]

Scheme **23**

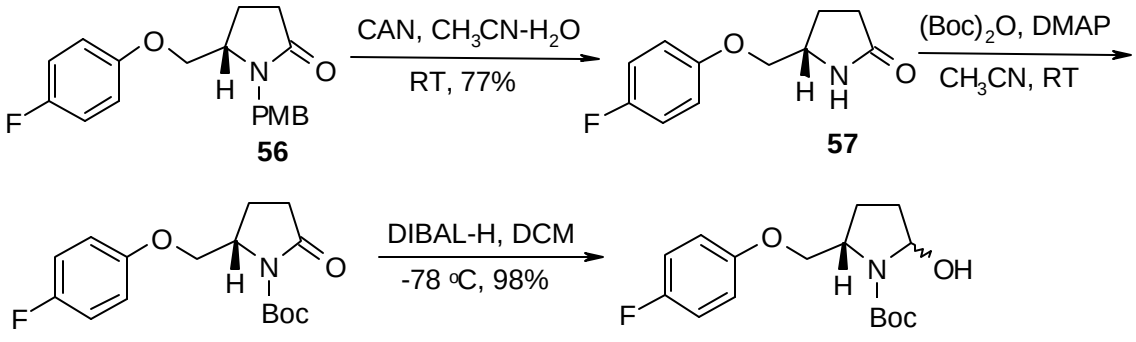


The PMB group was identified by a singlet at δ 3.75 ppm due to OCH_3 group, two doublets at 4.08 and 4.78 ppm due to benzylic methylene group and another two doublets at 6.79 and 7.14 ppm. The methylene protons of CH_2OH resonated in the region of 3.37-3.52 ppm. The corresponding tosylate derivative (**55**) was obtained in good yield from **54** using TsCl and Et_3N and DMAP in CH_2Cl_2. The new signals at 2.80 ppm due to CH_3 group and 7.38 and 7.76 ppm (A_2B_2 doublets) due to tosyl group in the ^1H NMR spectrum confirmed the product. Substitution of tosylate ester in **55** with sodium salt of 4-fluorophenol was achieved at ambient

temperature in the presence of catalytic *n*-$Bu_4N^+I^-$ in DMF in 89% yield. The product (4-fluorophenoxy)methylpyrrolidinone (**56**) was confirmed by spectral studies such as ^1H NMR, ^{13}C NMR, IR, EI and HRMS. The ^1H NMR spectrum of **56** revealed the charecteristic peaks due to 4-fluorophenoxy group and absence of peaks owing to tosyl group. The observations in ^{13}C NMR, a doublet at δ 154.4 and 154.6 ppm due to aromatic C-F and a singlet at 159.0 ppm claiming of aromatic C-O was characteristic of 4-fluorophenoxy group. The molecular formula was confirmed by EI MS through the molecular ion peak at (*m*/*z*) 330 and readily by HRMS (Calcd. for [$C_{19}H_{21}FNO_3$]: 330.1505. Found: 330.1520).

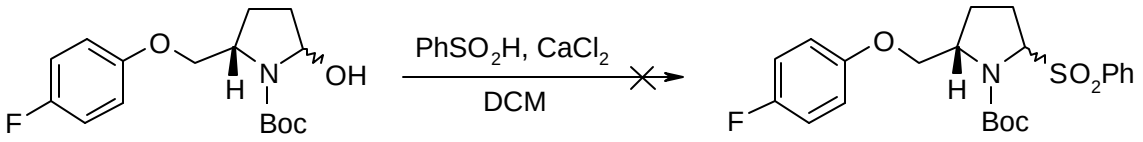
Unmasking of *N*-PMB group in **56** was accomplished with CAN to provide the free pyrrolidinone (**57**) in 77% yield.[53] This deprotection was supported by the ^1H NMR spectrum by the disappearance of peaks due to *N*-PMB group. The ^{13}C NMR, IR, EI MS [(M^++1) at (*m*/*z*) 210] and HRMS (Calcd. for [$C_{11}H_{13}FNO_2$]: 210.0930. Found: 209.0850) spectral studies also supported the structure. Protection of lactam (**57**) as its carbamate (**58**) was effected with di-*tert*-butyldicarbonate and stiochiometric DMAP in THF at room temperature to afford **60** in 86% yield. The ^1H NMR, ^{13}C NMR, IR, EI, and HRMS spectral data scrupulously indicated the carbamate protection. In the ^1H NMR spectrum of **58**, a singlet at 1.53 ppm due to *t*-butyl group (N-Boc) was appeared, whereas the rest of the protons were in complete agreement with the assigned sructure. The EI spectrum with the molecular ion peak at (*m*/*z*) 310 and HRMS data (Calcd. for [$C_{16}H_{21}FNO_4$]: 309.1376. Found: 309.1365) were also in favour of the structure. Reduction of **58** with DIBAL-H at $-78\ ^0C$ in CH_2Cl_2 provided the corresponding 2-hydroxypyrrolidine (**59**) as a diastereomeric mixture in quantitative yield. The diasteromeric nature in concert with rotameric population due to *N*-Boc group gave the broad peaks in ^1H NMR spectrum although the peaks accounted for the overall number and environment of protons. This precursor laid the situation to introduce the appendage at C_2 position via the Lewis acid mediated nucleophilic addition to N-acyliminium ion in diastereoselective fashion.

Scheme **24**



Though hemiaminal compounds have been reported to undergo nucleophilic substitution in the presence of various Lewis acids, especially BF_3:OEt_2, $TiCl_4$, $SnCl_4$, etc., this method is flawed with several factors: only countable strength of nucleophiles like allylTMS, TMSCN, $TMSN_3$, etc., inferior yield and stereoselectivity, and Lewis-acid dependency.[54] A modified version, enacted by S.V. Ley, has scored popularity in recent years to accomplish the same job devoid of aforesaid factors.[55] This method replaces the less stable iminal with stable electrophilic counterpart 2-arenesulphonylpyrrolidine. The attractive features of this methodology include the stability and crystalline nature of most sulphone derivatives paving for easy purification by recrystallisation, amenability to broad range of nucleophiles, easy-to-perform and work up, good stereoselectivity and no requirement for external Lewis acid additive. Accordingly, when we exposed hemiaminal (**59**) to $PhSO_2H$ in DCM at ambient temperature as per the literature precedent, no product was imminent from the reaction. When the reaction was conducted with refluxing $CHCl_3$, no change was observed in TLC. Raising the temperature of the reaction medium further (110 ^oC) with refluxing toluene resulted in the deterioration of starting material **59**. The addition of H_2SO_4/PTSA that will facilitate the formation of putative intermediate N-acyliminium ion because of their superior acidity to $PhSO_2H$ didn't cause any improvement.

Scheme **25**



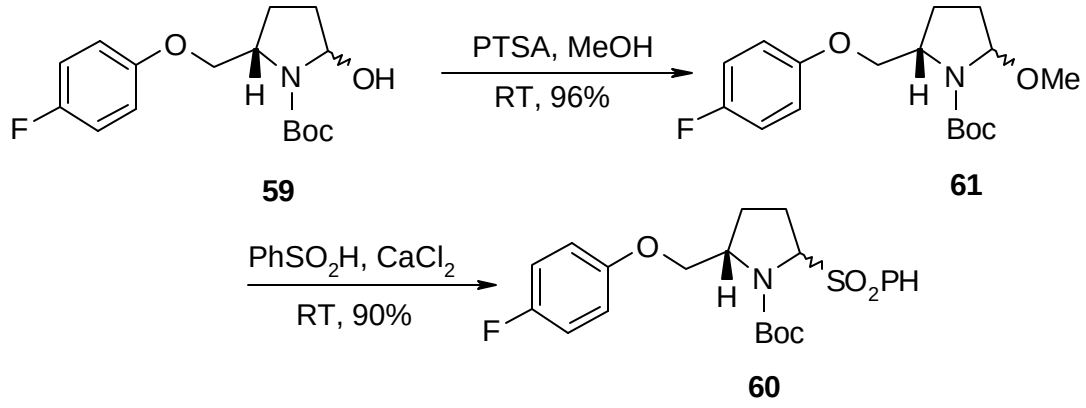
59 **60**

Hence, we next investigated this reaction with the intermediate **61**, which was easily obtained from **59** on exposure to PTSA in methanol, in accordance with the model studies (scheme **23**). The product (**61**) was found to be a diastereomeric mixture, as it was evident from each set of distinct signals for OMe group (two singlets in the region of δ 3.29-3.53 ppm), C-1 proton (two broad multiplets between δ 5.10-5.57 ppm) and *t*-butyl protons (two singlets between δ 1.4-1.6 ppm) in the ^{1}H NMR spectrum.

Exposure of 2-methoxypyrrolidine (**61**) to $PhSO_2H$ in CH_2Cl_2 in the presence of $CaCl_2$ at ambient temperature afforded the desired 2-benzenesulphonylpyrrolidine (**60**) in a spot-to-spot conversion to much of our satisfaction. The feasibility of this reaction at the minuscule difference at the reaction site, i.e., from hemiaminal to aminal invites some mechanistic explanation since the same reaction has been reported to proceed at equal tenor in the case of glycal and its methylated derivative glycoside.[56] The probable explanation that will account for this stereoelectronic bias relies on the better leaving nature of OMe group as MeOH compared to the OH group as H_2O, after initial protonation with $PhSO_2H$. The salient features of structure (**60**) were clearly corroborated from the spectral data in ^{1}H NMR, IR, FAB MS {(M+1) at (*m*/*z*) 436} and HRMS (Calcd for [$C_{22}H_{27}FNO_4S$]: 436.1593. Found: 436.1624). The induction of SO_2Ph was clearly visible through the multiple peaks between δ 7.49-7.97 ppm in the ^{1}H NMR spectrum.

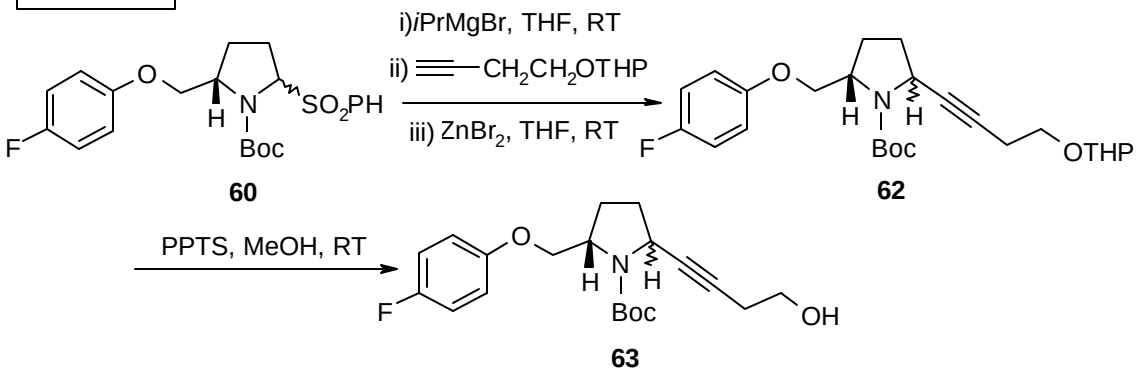
The sulphone intermediate (**60**) was reacted with the dialkylzinc nucleophile {generated *in situ* by the addition of 4-tetrahydropyranyloxy-1-butynylmagnesium bromide to

Scheme **26**



zinc bromide in THF at ambient temperature} in THF for 10 h at ambient temperature. The THP ether derivative (**62**), which was identified by its ^{1}H NMR spectrum, was subsequently stirred with catalytic PPTS in methanol to retrieve the homopropargyl alcohol (**63**) {in 80% yield for overall two steps}. The structure was unambiguously derived from the relevant chemical shifts in the ^{1}H NMR spectrum. The two CH_2 groups of homopropargylic part appeared at 2.44 (CH_2-C) and 3.70 ppm (CH_2-O). The diasteromeric excess information could

Scheme **27**

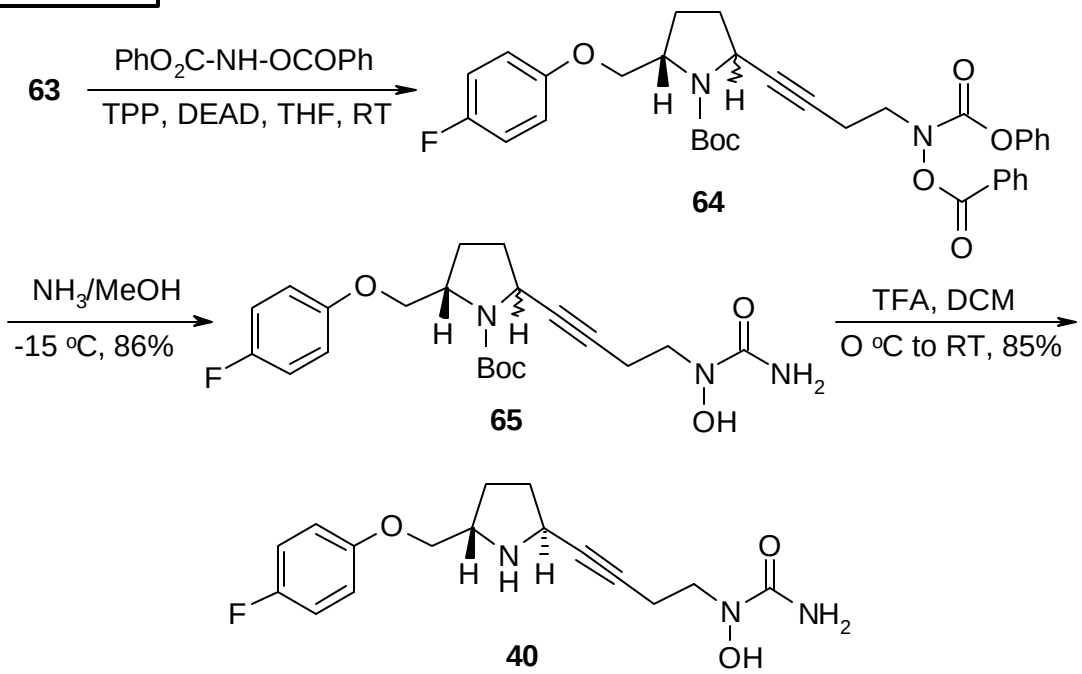


not be quantified from the ^{1}H NMR spectrum, probably, because of the rotameric distortion of signals.[57] The diastereomers were not separable by flash chromatography. However, the mixture was found to be in 87:13 ratio through analytical HPLC (ODS column, mobile phase: 40% acetonitrile+20% water+40% methanol; retention times: 20.5 and 24.2). The structure of **63** was also supported by ^{13}C NMR and DEPT, FAB MS [(M^++1) at 364] and HRMS (Calcd.

for [$C_{20}H_{26}FNO_4$]: 364.1924. Found: 364.1917) spectral data. Transformation of **63** into the target molecule **40** was carried out essentially by the same scheme as reported for CMI-977.

The compound **63** was converted to fully protected urethane derivative (**64**) via Mitsunobu reaction on treatment with the reagents TPP/DEAD/*N*,*O*-bis(phenoxycarbonyl) hydroxylamine. The structure was established with the assistance of ^{1}H NMR spectrum. Exposure of (**64**) to methanolic solution of NH_3 released the *N*-hydroxyurea derivative (**65**) in 80% yield through ammonolysis. The structure was fully secured on the basis of information from ^{1}H NMR, ^{13}C NMR, DEPT, IR and FAB MS spectral data. The last endeavour, treatment with trifluoroacetic acid in CH_2Cl_2 at room temperature conveniently resulted in the removal of Boc group to reach, after purification of the impure product by column chromatography, the target molecule (**40**), which was substantiated for its structure by the correlative information

Scheme **28**



from ^{1}H NMR, ^{13}C NMR, FABMS and DEPT studies. It was interesting to note that when we subjected the final compound to HPLC analysis, only one peak was observed with both reverse phase and chiral columns, indicating that the minor cis isomer might have been removed from

the mixture during purification. Accordingly, the *trans*-stereochemistry of **40** was established by the extensive NOE and NOESY studies.

Conclusion:

In summary, a concise and expedient synthesis of nitrogen variant of CMI-477 (**40**) has been conceptualized in stereocontrolled manner under active control of substrate from the natural realm of L-glutamic acid with amiability for large-scale manufacture. The compound has been submitted to Cytomed Inc. USA for evaluating pharmacological profile (PK/PD) in the treatment of asthma, especially for 5-lipoxygenase inhibition. This compound joins the almara of compounds available to medicinal chemist to test for asthma in addition to other anti-inflammatory diseases. The future will envision that synergism between the combinatorial and synthetic chemists (diversity oriented) will outgrow, thriving upon such small molecule inhibitors and potential analogues to hammer out asthma and enhance the human life for new world order.

EXPERIMENTAL SECTION

(6*S*)-6-Azido-7-(4-fluorophenoxy)hept-2-en-1-ol (41)

A mixture of sulphonate **35** (7.02 g, 184.7 mmol) and LiN_3 (0.9 g, 184.7 mmol) in DMF (35 mL) was stirred for 3 h at 50 ^oC. The reaction mixture was diluted with ether (100 mL) and water (200 mL) and the organic extract washed with water and brine, dried (Na_2SO_4), and evaporated. The residue on silica gel column purification (30% ethyl acetate in hexane) afforded **41** (3.70 g, 75%) as a colourless oil.

^1H NMR ($CDCl_3$, 200 MHz): δ 1.51-1.73 (m, 2H, H-5, 5'), 2.1-2.5 (m, 3H, OH, H-4, 4'), 3.59-3.76 (m, 1H, H-6), 3.8-4.13 (m, 4H, H-1, 1', 7, 7'), 5.54-5.78 (m, 2H, H-2, 3), 6.74-7.02 (m, 4H, aromatic).

(2*R*,3*R*,6*S*)-6-Azido-2,3-epoxy-7-(4-fluorophenoxy)-1-(*p*-tolunesulphonyloxy)heptane (43)

$Ti(OiPr)_4$ (1.1 mL, 3.77 mmol) and (+)-DIPT (1.1 mL, 3.77 mmol) were added to a suspension of molecular sieves (4 ^oA, 1 g) in CH_2Cl_2 (10 mL). After cooling the mixture to –20 ^oC, CuHP (1.15 g, 7.54 mmol) was added. After a gap of 15 minutes, a solution of **41** (1.1 g, 3.75 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture, after being stirred at –20 ^oC for 3 h, was quenched with 10% tartaric acid solution, filtered and the filtrate concentrated. The residue was purified by silica gel chromatography (40% ethyl acetate in hexane) to afford **42** (0.64 g, 60%) as an oil.

^1H NMR ($CDCl_3$, 200 MHz): δ 1.47-2.2 (m, 5H, OH, H-4, 4', 5, 5'), 2.88-3.07 (m, 2H, H-2, 3), 3.53-3.83 (m, 2H, H-1, 6), 3.84-4.10 (m, 3H, H-1', 7, 7'), 6.78-7.07 (m, 4H, aromatic)

p-Toluenesulphonyl chloride (0.4 g, 2.08 mmol) was added to a mixture of compound **42** (0.5 g, 1.9 mmol), triethylamine (0.5 mL, 3.8 mmol), and DMAP (16 mg) in CH_2Cl_2 (20 mL). The reaction mixture was washed with aqueous $NaHCO_3$ solution, water and brine, dried (Na_2SO_4), concentrated, and the residue chromatographically purified on silica gel (20% ethyl acetate in hexane) to afford **43** (0.7 g, 85%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.57-1.82 (m, 4H, H-4, 4', 5, 5'), 2.45 (s, 3H, CH_3), 2.80-2.90 (m, 1H, H-3), 2.93-3.02 (m, 1H, H-2), 3.63-3.79 (m, 1H, H-6), 3.76-4.19 (m, 4H, H-1, 1', 7, 7'), 6.76-7.02 (m, 4H, aromatic), 7.33 (d, *J* =7.9 Hz, 2H, aromatic), 7.78 (d, *J* =7.9 Hz, 2H, aromatic).

$[\alpha]_D$ 23.4 (c 0.7, $CHCl_3$)

(2*R*,3*R*,6*S*)-6-Azido-1-chloro-2,3-epoxy-7-(4-fluorophenoxy)heptane (44)

A mixture of **43** (0.7 g, 1.6 mmol) and LiCl (81 mg, 1.9 mmol) in DMF (5 mL) was stirred at room temperature for 3 h, and diluted with ether (25 mL) and water (25 mL). The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography to give **44** (0.4 g, 85%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.52-2.04 (m, 4H, H-4, 4', 5, 5'), 2.83-2.94 (m, 1H, H-3), 3.02 (dt, *J* = 1.4, 5.8 Hz, 1H, H-2), 3.43 (dd, *J* = 5.6, 12.0 Hz, 1H, H-1), 3.64 (dd, *J* = 5.6, 12.0 Hz, 1H, H-1'), 3.7-3.84 (m, 1H, H-6), 3.9-4.10 (m, 2H, H-7, 7'), 6.78-7.04 (m, 4H, aromatic)

(*S*)-5-Methoxycarbonyl-1-(4-methoxybenzyl)-2-pyrrolidinone (53)

To a solution of (S)-glutamic acid **51** (50 g, 340 mmol) in 2 M NaOH (300 mL), was added a solution of *p*-anisaldehyde (46.3 g, 340 mmol) in ethanol (50 mL). Following stirring for 30 min., the reaction mixture was cooled to 0 °C and sodium borohydride (3.8 g, 0.1 mmol) was added in portions. After being stirred for 2 h at room temperature, an additional amount of *p*-anisaldehyde (4.6 g, 33 mmol) was added. After a gap of 30 min., $NaBH_4$ (0.25 g, 0.006 mmol) was added. The reaction mixture was stirred for 1 h, and extracted with ether (3 x 300 mL). The pH of the aqueous layer was adjusted to ~ 3 by dropwise addition of conc. HCl at 0 °C. The precipitated solid was filtered off, dried and then dissolved in ethanol (700 mL). After refluxing for 5 h, the solution was concentrated and the residue taken in CH_2Cl_2. Filtration of the undissolved material and evaporation of the filtrate gave the crude product **52** (20 g, 24%) as a colourless solid

To a solution of **52** (20 g) in dry methanol (500 mL), thionyl chloride (2 mL) was added for 2 min. After being stirred for 12 h at room temperature, the reaction mixture was neutralized with saturated $NaHCO_3$ solution, evaporated *in vacuo,* and the residue dissolved in ethyl acetate, washed with water and brine, dried (anhydrous sodium sulphate), and concentrated. The residue on purification by silica gel chromatography (20% ethyl acetate in hexane) gave **53** (20 g, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.93– 2.63 (m, 4H, H-3, 3', 4, 4'), 3.66 (s, 3H, CO_2CH_3), 3.76 (s, 3H, OCH_3), 3.82-3.99 (m + d, 2H, H-5, one of NCH_2), 4.90 (d, *J* = 10.0 Hz, 1H, one of NCH_2), 6.78 (d, *J* = 8.2 Hz, 2H, aromatic), 7.09 (d, *J* = 8.2 Hz, 2H, aromatic).

(*S*)-5-Hydroxymethyl-1-(4-methoxybenzyl)-2-pyrrolidinone (54)

Lithium chloride (8.17 g, 190 mmol) and sodium borohydride (7.2 g, 190 mmol) were taken in a solvent mixture of ethanol (100 mL) and THF (60 mL) at 0 °C. After vigorous stirring for 1 h at room temperature, to the resulting suspension, a solution of **53** (20 g, 76 mmol) in THF (40 mL) was added. The reaction mixture was stirred for 6 h at room temperature, the solid filtered off, and the filtrate neutralised to pH ~ 7 by dropwise addition of saturated NH_4Cl solution at 0 °C. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic extract was washed with brine, dried (anhydrous Na_2SO_4) and concentrated on rotavapor to afford the crude product **54** (17 g, 95%) as a colourless oil, which was directly used in the next reaction.

$[\alpha]_D$ 74.0 ^{o} (c 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.9 – 2.16 (q, *J* = 7.7 Hz, 2H, H-4, 4'), 2.22– 2.64 (m, 3H, OH, H-3, 3'), 3.37-3.52 (m, 2H, CH_2O), 3.71-3.83 (m + s, 4H, H-5, $ArOCH_3$), 4.08 (d, *J* = 10.5 Hz, 2H, one of NCH_2), 4.78 (d, *J* = 10.5 Hz, 2H, one of NCH_2), 6.79 (d, *J* = 8.2 Hz, 2H, aromatic), 7.14 (d, *J* = 8.2 Hz, 2H, aromatic).

(*S*)-1-(4-Methoxybenzyl)-5-(*p*-toluenesulphonyloxy)methyl-2-pyrrolidinone (55):

A mixture of **54** (5 g, 21.28 mmol), *p*-toluenesulphonyl chloride (4.46 g, 23.5 mmol), triethylamine (4.3 g, 42.56 mmol) and DMAP (100 mg) in CH_2Cl_2 (75 mL) was stirred for 12 h at room temperature. The reaction mixture was washed with saturated $NaHCO_3$ solution, water and brine, dried (anhydrous Na_2SO_4) and concentrated to afford the crude product, which was filtered through a silica gel column (50% ethyl acetate in hexane) to afford **55** (7.5 g, 90%) as a colorless solid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1. 74-1.93 (m, 1H, H-4), 1.96– 2.18 (m, 1H, H-4'), 2.26 – 2.57 (m + s, 5H, H-3, 3', CH_3), 3.56- 3.68 (m, 1H, H-5), 3.75 (d, *J* = 10.2 Hz, 1H, one of NCH_2), 3.80 (s, 3H, OCH_3), 3.90– 4.10 (m, 2H, CH_2O), 4.86 (d, *J* = 10.2 Hz, 1H, one of NCH_2), 6.82 (d, *J* = 9.0, Hz, 2H, *N*-PMB aromatic), 7.07 (d, *J* = 9.0, Hz, 2H, *N*-PMB aromatic) 7.38 (d, *J* = 8.3 Hz, 2H, tosyl aromatic), 7.76 (d, *J* = 8.3 Hz, 2H, tosyl aromatic)

(*S*)-5-(4-Fluorophenoxy)methyl-1-(4-methoxybenzyl)-2-pyrrolidinone (56)

To a solution of 4-fluorophenol (8.6 g, 77 mmol) in dry DMF (50 mL), sodium hydride (3.08 g, 77 mmol) was added spanning 5 min. at 0 °C under N_2 atm. After stirring for 15 minutes at room temperature, a solution of **55** in dry DMF (100 mL) was introduced followed by TBAI (0.33 g, 9 mmol). The reaction was stirred for 3 h, diluted with ice-cold water and extracted with ether (3 x). The pooled extract was washed with water and brine, dried (anhydrous Na_2SO_4), and concentrated to give the residue, which was purified by silica gel column chromatography (50% ethyl acetate in hexane) to afford **56** (16 g, 89%) as a colorless solid.

M.p.: 62-63 °C

$[\alpha]_D$ 5.51° (c 6.0, $CHCl_3$)

IR ($CHCl_3$): 2904, 1688, 1504, 1440, 1248, 1040, 840 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.8– 2.20 (m, 2H, H-4, 4'), 2.24– 2.63 (m, 2H, H-3, 3'), 3.64-3.83 (m, 6H, H-5, OCH_2, OCH_3), 4.01 (d, *J* = 9.9 Hz, 1H, one of NCH_2), 4.77 (d, *J* = 9.9 Hz,

1H, one of NCH_2) 6.59– 6.75 (m, 4H, aromatic), 6.80- 6.91 (t, *J* = 8.1 Hz, 2H, aromatic), 7.08 (d, *J* = 9.0 Hz, 2H, aromatic).

^{13}C NMR ($CDCl_3$, 50MHz): δ 21.68, 30.16, 44.27, 55.14, 56.39, 69.15, 113.96, 115.34, 115.54, 116.0, 128.81, 129.24, 154.4, 154.6, 158.97, 159.77, 175.25

FAB MS (*m*/*z*): 121(100), 204 (26), 222 (16), 330 (37) (M^++1)

HRMS: Calcd. for [$C_{19}H_{21}FNO_3$]: 330.1505. Found: 330.1520

(*S*)-5-(4-Fluorophenoxy)methyl-2-pyrrolidinone (57)

A mixture of **56** (11 g, 54.4 mmol) and ceric ammonium nitrate (89.5 g, 163.2 mmol) in a solvent mixture of acetonitrile (160 mL) and water (16 mL) was stirred for 2 h. The solvent was evaporated *in vacuo*. Ethyl acetate was added and the insoluble material filtered off. The filtrate was washed with water and brine, dried (anhydrous sodium sulphate), and concentrated to leave the brown residue, which was purified on silica gel chromatography (pure ethyl acetate) to obtain **57** (8.74 g, 77%) as a colourless solid.

M.p.: 90–91 °C

$[\alpha]_D$ 59.4 ^{o} (c 0.9, $CHCl_3$)

IR (neat): 820, 1204, 1352, 1648, 2876, 3212 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 1.08– 2.07 (m, 1H, H-4), 2.22– 2.5 (m, 3H, H-3, 3', 4), 3.7– 3.80 (t, *J* = 8.4 Hz, 1H, one of OCH_2), 3.95 (dd, *J* = 4.2, 9.3 Hz, 1H, one of OCH_2), 4.0– 4.15 (m, 1H, H-5), 6.33 (br s, 1H, CONH), 6.75– 6.88 (m, 2H, aromatic), 6.97 (t, *J* = 8.4 Hz, 2H, aromatic)

^{13}C NMR ($CDCl_3$, 50MHz): δ 23.13, 29.59, 53.33, 71.90, 115.51, 115.63, 116.10, 154.45, 155.13, 159.89, 178.10

EI MS (*m*/*z*): 210 (92) [M^++1], 117 (59), 101 (100), 84 (49), 73 (30), 60.

HRMS: Calcd. for [$C_{11}H_{13}FNO_2$]: 210.0939. Found: 209.0850

(5*S*)-1-*tert*-Butyloxycarbonyl-5-(4-fluorophenoxy)methyl-2-pyrrolidinone (58)

To a stirred mixture of **57** (8.24 g, 39.8 mmol) and DMAP (4.86 g, 39.8 mmol) in dry THF (100 mL) under N_2 atmosphere, di-*tert*-butyl dicarbonate (17.4 g, 79.6 mmol) was added. After a period of 5 h, the solvent was removed under vacuum, the residue triturated with a mixture of ethyl acetate and ligtht petroleum (1:3 ratio, 200 mL) and the precipitated material filtered off. The filtrate was washed with water and brine, dried (anhydrous sodium sulphate) and concentrated to afford the residue, which was purified by column chromatography on silica gel (5% ethyl acetate in hexane) providing **58** (10.5 g, 86%) as a colourless solid.

M.p.: 75 – 76 °C

$[\alpha]_D$ -71.4 ^{o} (C 3.1, $CHCl_3$)

IR (neat): 2992, 1792, 1712, 1504, 1472, 1376, 1312, 1264, 1200, 1152, 1024, 832 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.53 (s, 9H, *t*-Bu), 2.13-2.36 (m, 2H, H-4, 4'), 2.46 (ddd, *J* = 2.4, 8.1, 17.8 Hz, 1H, H-3), 2.8 (dt, *J* = 6.1, 17.8 Hz, 1H, H-3'), 4.02– 4.22 (m, 2H, OCH_2), 4.38- 4.52 (m, 1H, H-5), 6.75- 6.89 (m, 2H, aromatic), and 6.96 (t, *J* = 9.0 Hz, 2H, aromatic)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.13, 28.05, 31.87, 56.63, 69.15, 83.10, 96.11, 115.49, 115.65, 116.12, 160.0, 174.0

EI MS (*m*/*z*): 107 (8), 142 (15), 154 (20), 179 (18), 210 (100), 254 (78), 310 (22) [M^++1].

HRMS: Calcd for [$C_{16}H_{20}FNO_4$]: 309.1376. Found: 309.1365

(2*RS*,5*S*)-1-*tert*-Butyloxycarbonyl-5-(4-fluorophenoxy)methyl-2-methoxypyrrolidine (61)

To a stirred solution of **58** (10.0 g, 32.3 mmol) in dry CH_2Cl_2 (100 mL) at –78 °C under N_2 blanket, was added DIBAL-H (1 M solution in toluene, 34 ml, 32.3 mmol) dropwise. The reaction mixture was stirred for 1 h, and decomposed with aqueous Rochelle's salt solution. After stirring for further1 h, the precipitated solid was filtered off and washed well with CH_2Cl_2. The filtrate was dried (anhydrous sodium sulphate) and concentrated to afford the crude product **59** (10 g, 98%) as a colourless oil, used as such for next reaction.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.50 (s, 9H, *t*-butyl), 1.80– 2.42 (m, 4H, H-3, 3', 4, 4'), 3.6–4.27 (m, 3H, H-5, OCH_2), 5.32–5.58 (m, 1H, H-5, diastereotopic), 6.77– 7.02 (m, 4H, aromatic).

A mixture of **59** (10.0 g, 32.15 mmol) and PPTS (0.8 g, 3.2 mmol) in methanol (100 mL) was stirred for 18 h at room temperature and evaporated on rotavapor to give the residue, which on purification by silica gel column chromatography (10% ethyl acetate in hexane) afforded **61** (10.0 g, 96%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.49 and 1.55 (2s, 9H, *t*-butyl), 1.74– 2.25 (m, 4H, H-3, 3', 4, 4'), 3.29 (s, 3H, OCH_3), 3.70– 4.39 (m, 3H, H-5, CH_2O), 5.1– 5.57 (m, 1H, H-1, diastereotopic), 6.78– 7.01 (m, 4H, aromatic).

IR (neat): 2976, 2944, 1696, 1504, 1392, 1208, 1186, 1078, 824 cm^{-1}.

(2*RS*,5*S*)-2-Benzenesulfonyl-1-*tert*-butyloxycarbonyl-5-(4-fluorophenoxy)methylpyrrolidine (60)

To a solution of **61** (9.8 g, 30.15 mmol) in dry CH_2Cl_2 (100 mL) containing powdered $CaCl_2$ (5.0 g) at 0 °C, freshly prepared benzenesulfinic acid (4.3 g, 30.15 mmol) was added. The reaction mixture, after being stirred for 2 h at ambient temperature, was cooled to 0 °C, and neutralized with aqueous sodium bicarbonate solution. The suspension was filtered over celite pad and the filtrate washed with water and brine, dried (anhydrous sodium sulphate) and concentrated to afford **60** (11.8 g, 90%) as a colourless solid.

M.p.: 113-114 ^{o}C

IR (neat): 2976, 1752, 1504, 1488, 1368, 1312, 1216, 1152, 1088, 1040, 832, 768, 688 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.20 (s, 9H, *t*-Bu, diastereotopic), 2.1– 2.56 (m, 3H, H-3, 4, 4'), 2.7 – 2.83 (m, 1H, H-3'), 4.08- 4.52 (m, 3H, OCH_2, H-5), 5.1– 5.25 (m, 1H, H-1), 6.85– 7.06 (m, 4H, aromatic), 7.49 – 7.76 (m, 3H, $PhSO_2$), 7.85 – 7.97 (m, 2H, $PhSO_2$)

FAB MS (*m*/*z*): 125 (6), 154 (6), 194 (100), 195 (24), 434 (15), 436 (34) [M^++1]

HRMS: Calcd. for [$C_{22}H_{27}FNO_5S$]: 436.1593. Found: 436.1624

(5*S*,2*RS*)-1-*tert*-Butyloxycarbonyl-5-(4-fluorophenoxy)methyl-2-(4-hydroxy-1-butynyl) pyrrolidine (63)

To a stirred solution of 4-tetrahydropyranyloxy-1-butynylmagnesium bromide in THF {prepared *in situ* by the addition of isopropylmagnesium bromide (1.1 g, 7.1 mmol) in THF to 2-(3-butynyl-1-oxy)tetrahydropyran (1.078 g, 7 mmol)}, was added a solution of zinc bromide in THF (0.78 g, 3.5 mmol, 2 M solution) at ambient temperature. After a gap of 30 minutes, to the resulting suspension, was introduced the compound **60** (1.5 g, 3.5 mmol) in THF (12 mL). The reaction mixture was stirred for 10 h, quenched with aqueous NH_4Cl solution and partitioned between ether and water. The organic part was washed with brine, dried (anhydrous sodium sulphate) and concentrated to afford the crude product 62, which was dissolved in methanol (15 mL) containing pyridinium toluene-*p*-sulphonate (66 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 10 h, evaporated *in vacuo* and the residue purified by column chromatography on silica gel (30% ethyl acetate in hexane) to afford **63** (1.0 g, 86%) as a colourless oil.

HPLC Analysis: 1st peak (area, 87.2%; time, 24.2), 2nd peak (area, 10.0; time 20.6){mobile phase = 40% acetonitrile + 20% water + 40% methanol; column = ODS; flow rate = 1.0 mL/min.; UV detection = 225 nm}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (s, 9H, *t*-Bu), 1.66 (br s, 1H, OH), 1.89– 2.34 (m, 4H, H-3, 3', 4, 4'), 2.44 (t, J = 6.74 Hz, 2H, ≡-CH_2), 3.70 (t, J = 4.0 Hz, 2H, CH_2OH), 3.74 (t, J = 8.0 Hz, 0.5H) and 3.86 (t, J = 8.0 Hz, 0.5H), 4.02 (d, J = 8.0 Hz, 0.5H) and 4.09 (d, J = 8.0 Hz, 0.5H), 4.12– 4.24 (m, 1H), 4.41-4.58 (m, 1H), 6.80 – 7.0 (m, 4H, aromatic).

^{13}C NMR ($CDCl_3$, 50 MHz): 22.62, 26.30, 28.17, 31.33, 49.23, 55.5, 60.66, 69.79, 79.78, 82.5, 115.21, 115.69, 153.78, 153.90, 154.58, 159.50

FAB MS (*m*/*z*): 107 (27), 120 (18), 138 (70), 194 (25), 264 (48), 290 (7.5), 364 (22) (M^++1)

HRMS: Calcd. for [$C_{20}H_{27}FNO_4$]: 364.1924. Found: 364.1917

(2*RS*,5*S*)-1-*tert*-Butyloxycarbonyl-5-(4-fluorophenoxy)methyl-2-[4-*N*,*O*-bis(phenoxycarbonylhydroxylamino-1-butynyl)pyrrolidine (64)

To a solution of **63** (0.82 g, 2.26 mmol), triphenylphosphine (0.71 g, 2.7 mmol) and *N*,*O*-bis(phenoxycarbonylhydroxylamine) (0.7 g, 2.7 mmol), was added diethyl azodicarboxylate (0.47 g, 2.7 mmol) dropwise at 0 ^{o}C. The reaction mixture was stirred at 0 °C for 30 min., and for 6 h at room temperature. The solvent was stripped off and the residue on purification by silica gel column chromatography (30% ethyl acetate in hexane) afforded **64** (1.12 g, 80%) as a colorless semi-solid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.52 (s, 9H, *t*-butyl), 1.94 (t, *J* = 5.64 Hz, 1H, H-3), 2.0-2.4 (m, 3H, H-3', 4, 4'), 2.70 (t, *J* = 7.0 Hz, 2H, ≡-CH_2), 3.65-3.93 (m, 1H), 3.93-4.29 (m + t [3.93-4.05, J = 7.0 Hz, 2H, CH_2N], overall 4H), 4.40- 4.60 (m, 1H, H-5), 6.76-7.02 (m, 4H, aromatic), 7.12-7.49 (m, 10H, aromatic)

(2*RS*,5*S*)-1-*tert*-Butyloxycarbonyl-5-(4-fluorophenoxy)-2-(4-*N*-hydroxyureidyl-1-butynyl) pyrrolidine (65)

Ammonia gas was purged into a solution of **64** (1.4 g, 2.26 mmol) in a solvent mixture of methanol (30 mL) and THF (10 mL) at 0 °C for 15 minutes. The reaction mixture was stirred for 6 h at room temperature, evaporated *in vacuo* and the residue purified by column chromatography on silica gel (30% ethyl acetate in hexane) to afford **65** (0.81g, 85%) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45 (s, 9H, *t*-butyl), 1.85– 2.50 (m, 6H, H-3, 3', 4, 4', ≡-CH_2), 3.5– 3.68 (m, 1H), 3.70– 3.91 (m, 2H), 3.94– 4.03 (dd, *J* = 8.8, 3.8 Hz, 1H, one of OCH_2), 4.07- 4.2 (m, 1H, H-5), 4.36– 4.55 (m, 1H, H-2), 5.1– 5.35 (br s, 2H, NH_2), 6.73– 7.0 (m, 4H, aromatic), 8.45 (s, 1H, N-OH)

IR (neat): 3504, 3450-3000 (br.), 1688, 1512, 1392, 1208, 1160, 760 cm^{-1}.

FABMS (*m/z*): 106 (7), 120 (7), 153 (11), 194 (17), 233 (5.5), 244 (5.5), 274 (40), 322 (100), 388 (5.5), 422 (7)(M^++1)

(2*S*,5*S*)-5-(4-Fluorophenoxy)methyl-2-(4-*N*-hydroxyureidyl-1-butynyl)pyrrolidine (40)

Trifluoroacetic acid (0.5 mL, 5.49 mmol) was added to a solution of **65** (0.8 g, 1.83 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred for 10 minutes at this temperature, the reaction mixture was additionally stirred for 3 h at room temperature, cooled to 0 ^oC, neutralized with dilute aqueous $NaHCO_3$. The organic layer was separated, washed with water and brine, dried (anhydrous sodium sulphate) and concentrated to afford the brown residue which was purified by column chromatography (10% methanol in ethyl acetate) to afford **40** (0.55 g, 86%) the colorless highly-hygroscopic solid. The compound was stored as its hydrochloride salt which was obtained on treatment with dilute hydrochloric acid followed by extraction with ethyl acetate. Removal of solvent gave the colourless foam.

HPLC: Peak-(retention time: 1.9, area: 99.2%); stationary phase-chiral column (OJ); Mobile phase-10% isopropanol in hexane; flow rate-1 mL/min.; UV detection-254 nm.

^{1}H NMR ($CDCl_3$, 500 MHz): δ1.65-1.9 (m, 1H, H-4), 2.0-2.2 (m, 1H, H-4'), 2.25-2.40 (m, 2H, H-3, 3'), 2.50-2.54 (dt, J = 2.0, 6.35 Hz, 2H, ≡-CH_2), 3.56-3.6 (t, *J* = 6.36 Hz, 2H, CH_2N), 4.0-4.03 (dd, *J* = 3.17, 10.7 Hz, 1H, one of OCH_2), 4.09-4.16 (dq, *J* = 3.18, 7.55 Hz, 1H, H-5), 4.18-4.23 (dd, *J* = 3.18, 10.73 Hz, 1H, one of OCH_2), 4.38-4.43 (dt, *J* = 2.0, 6.0 Hz, 1H, H-2), 6.89-6.92 (m, 2H, aromatic), 6.98-7.04 (t, *J* = 8.75 Hz, 2H, aromatic)

^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.22, 25.15, 31.36, 46.91, 50.20, 57.86, 66.65, 74.39, 86.17, 115.68, 115.78, 115.86, 153.42, 156.38, 158.27, 162.33

FABMS (*m/z*): 107 (18), 120 (15), 136 (54), 154 (55), 167 (4.5), 176 (15), 194 (14), 210 (6), 233 (8), 268 (26), 279 (23), 321 (16) [M^+], 322 (100) [M^++1], 323 (19) [M^++2]

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57. Extensive line broadening and doubling of signals in the ^{1}H NMR due to the rotameric nature of carbamtes have been frequently observed (ref. 52).

CHAPTER-2

SYNTHESIS OF OXINDOLE PART (CP-88,059) OF ANTIPSYCHOTIC DRUG 'ZELDOX'.

PROLOGUE

The world health organization has predicted that depression will be the world's largest ailment by 2010 after heart failures. Depression or schizophrenia is the most common form of psychiatric disorder. Schizophrenia affects approximately 1% of world population.[1] It is a common, tragic and devastating mental illness that typically strikes young people just when they are maturing into adulthood.[2] This disease translates into enormous burden as well as the strain on financial and health care resources. Also, schizophrenia leads to social and psychological anguish for patients and families.[3] This primordial account will outline the genetic basis of disorder, existing medication plus prodrugs undergoing clinical trails in advance of our synthetic description to the oxindole part of latest antipsychotic drug Zeldox ® (Ziprasidone hydrochloride).

Schizophrenia is a disease of brain. Both its symptoms and signs and associated cognitive abnormalities are too diverse to permit its localization in a single region of brain. In other words, it is a disease of neural connectivity caused by multiple factors that affect brain development. The disease probably occurs because of the combination of genetic and non-genetic factors that affect the regulation and expression of genes governing brain function or injure the brain directly. Some people may have a genetic predisposition that requires a convergence of additional factors to produce the expression of disorder. This convergence leads to abnormalities in brain development and maturation, the process ongoing in the first two decades of life. These abnormalities involve typically distributed neural circuits and neurotransmitters. When the connectivity and communication with neural circuit is disrupted, patients have a variety of symptoms and impairments in cognition.

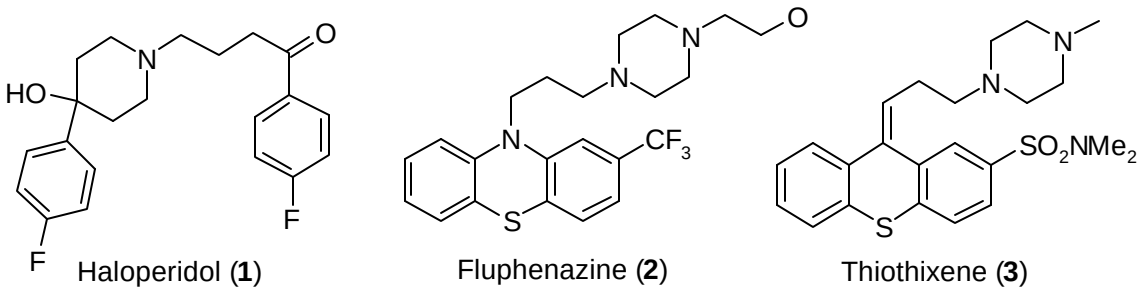
The symptoms and signs of schizophrenia are very diverse and encompass the entire range of human mental activity. However, they can be classified into three kinds: 1) positive symptoms (are characteristics that are present but should be absent), e.g., hallucinations and

delusions, suspiciousness, and distorted perceptions) 2) negative symptoms (refer to the absence of expected behaviour) e.g., lack of facial expression, speech deficiencies and inattentiveness 3) affective symptoms (own feelings, inappropriate emotions), e.g., depression, guilt, anxiety.

Since neuroleptic drugs were introduced in the 1950's, they have become the primary mode of psychoses.[4] Traditionally, antipsychotic medications were shown to be effective because of their ability to antagonize dopamine receptors. Non-selectivity of this antagonism, however has led to undesirable side effects, especially extrapyramidal symptoms (EPS) which commonly manifest as muscle rigidity, akathesia (motor restlessness), and tremors or other abnormal muscle movements. In the past decade, several new agents have become available, generally termed atypical antipsychotics because of their more diffuse receptor affinities and lack of extrapyramidal symptoms. These medications are characterized by a potentially greater efficacy, especially for negative syndromes, and a better clinical response in patients thought to be refractory to treatment. In general, antipsychotic drugs are thought to exhibit their activity due to selective or multiple receptor interactions including, mainly, dopaminergic, serotonergic, and to the lesser extent, adrenergic, histaminergic and muscarinic receptor interactions.

Haloperidol, fluphenazine, thiothixene, and chlorpromazine all belong to typical or classical neuroleptics. These drugs treat only positive symptoms and not other kinds, negative and cognitive. They enable most patients to remain out of hospital and function well in the community. However, these drugs often produce serious side effects leading to non-compliance of the patient. Promazine, chlorpromazine, chlorprothixene, thioridazine and mesoriadazines are low potency typical antipsychotics, whereas doperidol, loxapine, molidone, perphenazine and prochlorperazine exert medium potency and, trifuoperazine, haloperidol (**1**), fluphenazine (**2**), thiothixene (**3**) and pimozide belong to the high potency type.[5]

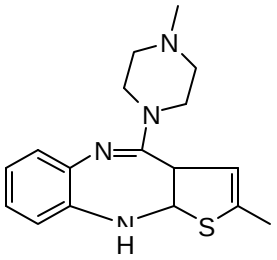
Scheme **1**: typical antipsychotics



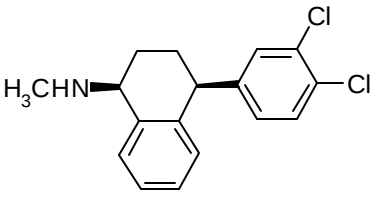
Haloperidol (**1**) Fluphenazine (**2**) Thiothixene (**3**)

Examples of atypical antipsychotics include risperidone (**4**), olanzapine (**5**), sertindole (**6**), sertraline (**7**), clozapine (**8**), fluoxetin (**9**), Iloperidone (**10**), and zeldox. Clozapine has been long regarded as the holy grail of antipsychotic drugs.[6] It displays atypical profile showing little or no neurological side effects either acutely or on long-term treatment. Clozapine also shows exceptional efficacy and has been used in the treatment of patients who don't respond to traditional agents such as haloperidol. Clozapine is a second line therapy due to its small potential for agranulocytocis. The drug binds to a variety of different receptors including dopmine D_1, D_2, serotinin 5-HT_{2A} and 5-HT_{2C}, α-1-adrenergic receptors. Iloperidone, another atypical antipsychotic with its mode of action as serotonin/dopamine receptor antagonist is effective in reducing the symptoms of schizophrenia and schizoeffective disorder with excellent tolerability profile including the lack of EPS. Risperidone is another antipsychotic drug with narrow receptor affinity as dopamine D_2 and serotonin 5-hydroxytryptamine receptor antagonist. Risperidone, which is more effective than haloperidol may be of more benefit to new-onset and elderly patients because of its lower side effect profile, which leads to greater tolerance and compliance. Olanzapine has wide receptor affinity with the exception of 5-HT_{1A} and α-2 adrenergic receptors. Clinical evidence suggests that olanzapine is more effective than haloperidol in reducing negative symptoms and doesn't induce extrapyramidal symptoms when used in therapeutic doses.

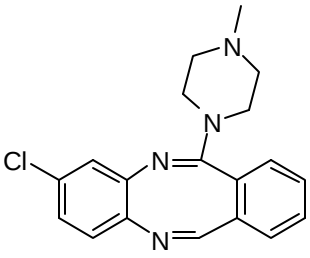
Scheme **2**: atypical psychotics



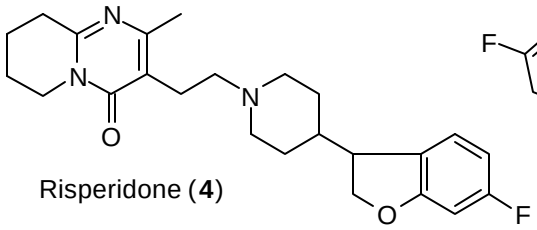
Olanzapine (**5**)



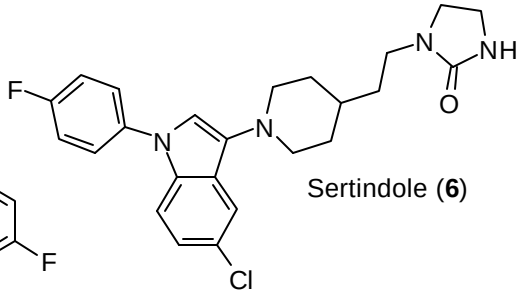
Sertralin (**7**)



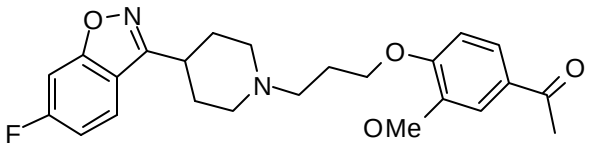
Clozapine (**8**)



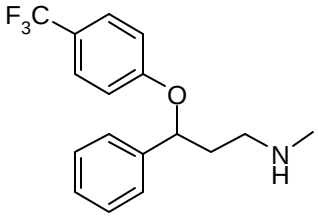
Risperidone (**4**)



Sertindole (**6**)



Iloperidone (**10**)



Fluoxetin (**9**)

Conventional antipsychotics (typical)	Atypical antipsychotics
Haloperidol Thiothiexene Fluphenazine	Riperidone Olanzapine Iloperidone Sertraline Sertindole

Sertindole is a potent antagonist at D_2, $5HT_2$ and α-1 receptors without activity histaminic, muscarinic or α-2 receptors. This selectivity suggests that Serlect or sertindole mitigates both the positive and negative symptoms of schizophrenia, but should not produce sedative effects or anticholinergic effects (such as constipation and dry mouth) related to those

receptors. Sertindole at a dose of 20 mg/day reduced negative symptoms, as measured by PANSS Negative Symptom Subscale and total Scale for the Assessment of Negative Symptoms (SANS). The antidepressant effect of sertraline is presumed to be linked to its ability to inhibit the neuronal reuptake of serotonin. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. Like most clinically effective antidepressants, sertraline downregulates brain norepinephrine and serotonin receptors in animals. In receptor binding studies, sertraline has no significant affinity for adrenergic (α-(1), α-(2) and β), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_2) or benzodiazepine binding sites. In placebo-controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. A placebo-controlled European study carried out over 44 weeks, in patients who were responders to sertraline has indicated that sertraline may be useful in continuation treatment, suppressing reemergence of depressive symptoms. Flouxetine is the widely-used antipsychotic drug with 35 million people using in 100 countries today. This drug is a selective serotonin antagonist with fewer side effects. The antidepressant, antiobsessional, and antibulimic actions of fluoxetine are presumed to be linked to its ability to inhibit the neuronal reuptake of serotonin. Fluoxetine preferentially inhibited the reuptake of serotonin into brain synaptosomes and platelets in rats and humans. In receptor binding studies, fluoxetine was shown to have only weak affinity for various receptor systems, namely opiate, serotonergic 5HT(1), dopaminergic, β-adrenergic, α-(2)-adrenergic, histaminergic, α-(1)-adrenergic, muscarinic, and serotonergic 5HT(2) receptors. Unlike most clinically effective antidepressants, fluoxetine did not down-regulate beta-adrenergic receptors; however like all tested antidepressants, it caused up-regulation of GABA-B receptors. Mixed effects have been observed on serotonergic receptor sensitivity.

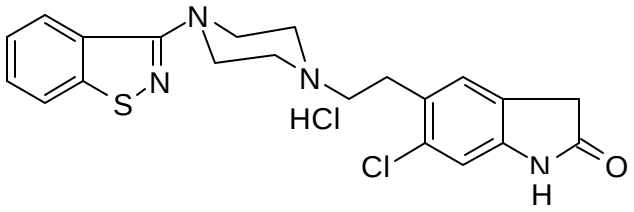
Table: World-wide intense survey of antipsychotic drugs under clinical development:

Drug	Company	Mechanism	Phase
(*S*)-Amisulpride	Sanofi-synthelabo	D_2/D_3 antagonist	Phase II
Ampalex	Cortex	AMPA receptor antagonist	Phase II
Aripiprazole	Otsuka	D_2 antagonist, Dopamine autoreceptor agonist	Phase III
Belaperidone	Knoll	$D_2/5HT_{2A}$ receptor antagonist	Phase II
Blonanserin	Dainippon	$D_4/5HT_{2A}$ receptor antagonist	Phase III
E-5842	Esteve	σ-receptor antagonist	Phase I
Mazapertine	Janssen	D_2 antagonist	Phase II
Perospirone.HCl	Sumitomo	$5HT_{2A}/D_2$ antagonist	Phase II
Sonepiperazole.mesilate	Pharmacia & Upjohn	D_4 antagonist	Phase II

In conclusion, the causation of schizophrenia is clearly a complicated matter. As our understanding of it progresses, however, our hope for improving the lives of patients with the disease increases. We can also potentially improve the treatment of schizophrenia, which currently focuses on reversing abnormal neural communication by blocking dopamine or serotonin receptors. Although newer treatments such as the recently developed atypical neuroleptic drugs have already substantially improved the outcome of schizophrenia, they remain blunt instruments that have relatively generalized effects on neurotransmitter systems. As we identify more precisely the cascade of events leading to schizophrenia--neurodevelopmental abnormalities that lead to neural misconnections that lead, in turn, to impaired cognitive processing -- we will also identify better and more specific targets for future treatment.

PRESENT WORK

There is a greater hope now than ever before for patients with schizophrenia, although there is presently no permanent cure for schizophrenia. With the availability of better and newer treatments, there is a brighter future for those affected by this most debilitating ailment. Although all clinically available drugs for schizophrenia are dopamine D_2 antagonists, there are wide variations in individual responsiveness to drugs and liability to side effect suggesting that other receptors and/or mechanisms are involved. The recent thrust in antipsychotic drug development has been to identify targets with clozapine-like efficacy without its serious toxicity. clozapine is unusual among antipsychotic drugs, *ut supra* in that it is effective not only against positive symptoms of schizophrenia but also against more debilitating negative and deficit symptoms. Interestingly, Clozapine has this unusual efficacy profile without producing motor side effects, associated with conventional agents. However, clozapine's use is restricted by a potentially fatal blood dyscrasia. [8]

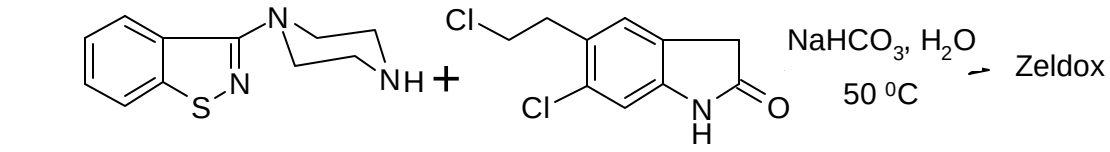


Zeldox (Ziprasidone.hydrochloride) **1**

Food Drug Administration, USA, has approved the antipsychotic drug Zeldox ® (Ziprasidone hydrochloride) in midst 2000, and recommended for first line therapy, discovered and developed by Pfizer Inc. USA.[9] Zeldox is a serotonin and dopamine antagonist that is effective in treating the wide range of positive, negative and depressive symptoms associated with schizophrenia. Positive symptoms include visual and auditory hallucinations and delusions. The harder-to-treat negative symptoms include blunted effect, social withdrawal and lack of motivation. The 4,500 patient worldwide clinical trails program was

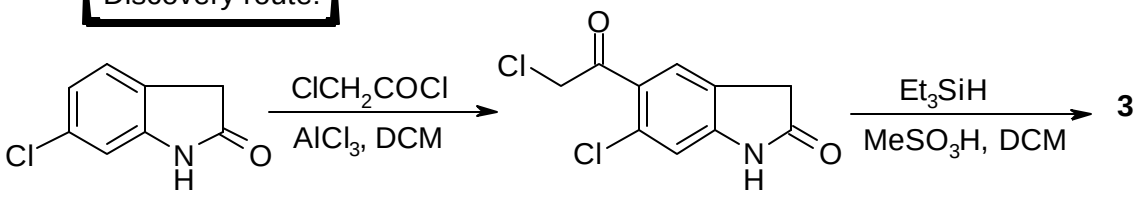
the largest ever conducted for a novel antipsychotic medicine, prior to launch. In addition to its demonstrated efficacy in treating schizophrenia, Zeldox was shown to be weight neutral, a feature that distinguishes it from all marketed antipsychotics. Significant weight gain associated with many currently available antipsychotic medicines are distressing and stigmatizing to patients and often results in non-compliance. Patients who gain weight may also be at increased risk for cardiovascular complications such as increased lipid levels and poor glycemic control. Furthermore, the therapy showed a low incidence of abnormal movement and sexual dysfunction. The most common side effects reported in persons treated with zeldox in clinical trails included head ache, nausea, somnolence, constipation and dyspepsia. These side effects are of mild to moderate severity and rarely, led to the discontinuation of the drug.

Scheme **1**



2 **3** **1**

Discovery route:



4 **5**

Hence, we embarked on a programme for a new and robust synthetic process under the aegis of Pfizer. Inc. for the rightern hemisphere of ziprasidone (CP-88, 059) , the oxindole part (**3**). The discovery route to the oxindole (**3**), which was disclosed to us, involved essentially the intermediate (**5**), which posed major health problem. This intermediate was lachrymatory and the chemists exposed to this intermediate developed severe allergy symptoms. Due to this

health hazard coupled with the employment of higly-expensive Et_3SiH for reduction of benzylic ketone, the discovery route was abandoned.

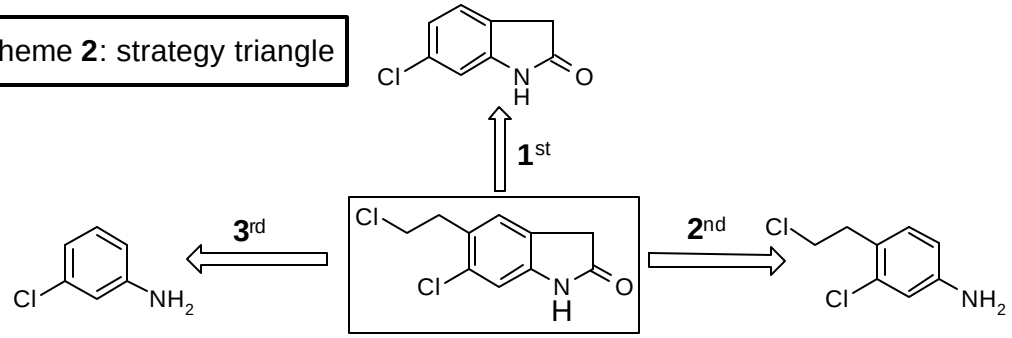
In view of the above problems, it was apparent that any new route discovery should not involve the intermediate **5**. Based on the retrosynthetic analysis and literature precedence,[7] a three-pronged strategy was crafted for synthetic trails as delineated below:

1) Initial oxindole formation; second, the introduction of side chain.

2) Preferential side chain introduction followed by the construction of oxindole

3) Simultaneous introduction of functional elements requisite for oxindole and side chain.

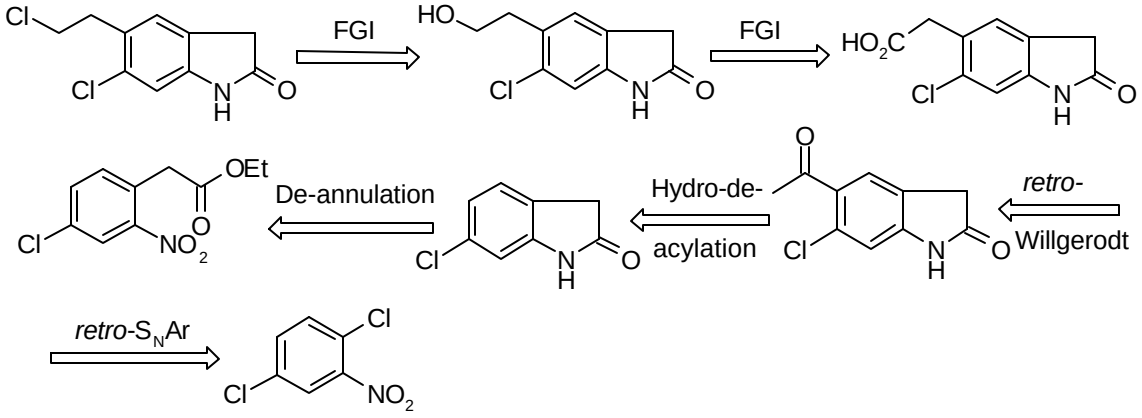
Scheme **2**: strategy triangle



STRATEGY I AND RESULTS

The retrosynthetic analysis was evolved under the precints of strategy **1** (scheme 3)**,** which involves the foremost disconnection of 5-chloroethyl side chain. The disconnection of

Scheme **3:** antithetic analysis



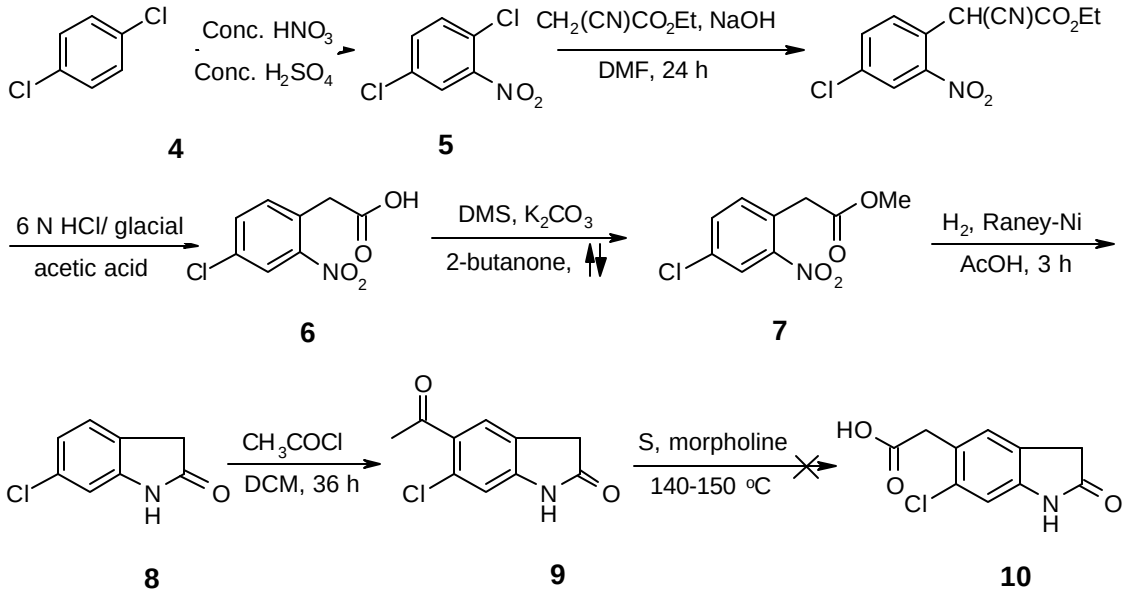
lactam ring would reveal the arene precursor containing NH_2 and CH_2CO_2Et bearing *ortho* relationship. Further simplification, based on *retro*-S_NAr, should reveal the starting material. In the synthetic direction, the acquisition of side chain was envisaged from Friedel-Crafts and Willgerodt reactions.

In the merit of aforesaid analysis, 1,4-dichlorobenzene (**4**) was converted into 1,4-dichloro-2-nitrobenzene (**5**) on nitration with nitrating mixture (prepared from conc. HNO_3 and conc. H_2SO_4) in 86% yield. Subsequent S_NAr reaction of **5** with cyanoacetic ester in the presence of sodium hydroxide at room temperature gave the aryl substituted cyanoacetic ester which was without purification subjected to decarboxylative hydrolysis with 6 N HCl and glacial acetic acid to provide (4-chloro-2-nitro)phenylacetic acid (**6**) in 71% yield. The product was unambiguously established by the ^1H NMR spectrum with benzylic protons resonating at δ 3.90 ppm while the aromatic protons at the region of δ 7.42-8.02 ppm. Arylacetic acid **6** was then esterified with dimethyl sulphate and K_2CO_3 in boiling 2-butanone to provide methyl arylacetate (**7**) in 95% yield. A singlet at δ 3.75 due to ester methyl group and another at δ 4.00 ppm (upfield shifted) due to benzylic methylene group in the ^1H NMR spectrum were the indications of the product **7**. Reductive cyclisation of *o*-nitrophenyl acetate (**7**) was effected with H_2 and Raney-Ni catalyst in acetic acid medium for 3 h to furnish the oxindole derivative (**8**) in 89% yield. Absence of resonance due to methyl ester (CO_2Me), upfield shift of resonances due to benzylic protons from δ 4.0 to 2.69 ppm, and appearance of NH proton (CONH) at δ 9.69 ppm as a broad singlet indicated the product. The IR spectrum showed an adsorption at 1699 cm^{-1} due to lactam carbonyl. The preliminary preceding to attach the side chain was Fridel-Crafts acylation.[10] For this task, oxindole (**8**) was heated under reflux in CH_2Cl_2 with acetyl chloride and $AlCl_3$ to afford 5-acetyl-2-oxindole (**9**) in 85% yield. The induction of acetyl group was revealed in the ^1H NMR spectrum by a singlet at δ 2.65 ppm and

the disappearence of signal due to H-5 (aromatic). Acetophenone (**9**) was then subjected to Willgerodt transformation, on treatment with sulphur powder under refluxing morpholine followed by hydrolysis with H_2SO_4 and AcOH.[11] Unfortunately, this reaction returned only tarry material with limited solubility in organic solvents and water. A series of modifications were unfolded to win over this decisive step. When the temperature was lowered to 100-110 °C, the starting material was recovered as such. Performing the reaction in different solvent medium, like DMF, DMSO, *m*-xylene and 1,4-dioxane was virtually of no use and resulted in only complex mixture of products, difficult to isolate. The innocuous substituents across the aryl ring might be the cause of this failure, as the Willgerodt conversion of simple acetophenone to phenylacetic acid worked well in our hand.[12, 13]

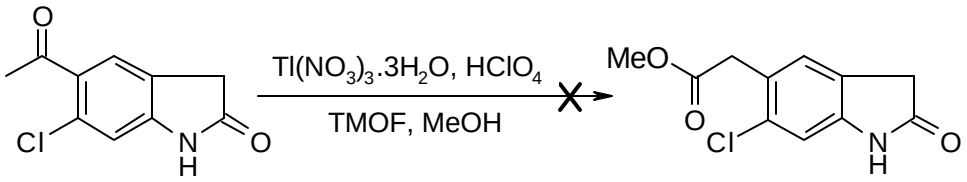
The only other similar transformation documented in the literature, was the conversion of acetophenone into the methyl ester of phenylacetic acid with $Tl(NO_3)_3.3H_2O$, as pioneered by McKillop *et al.*[14] This method also miserably failed when we applied to our original substrate. This methodology has evolved suitable modifications along the years, to cover good yield and wider substrate applicability, which include change of solvent from MeOH to TMOF

Scheme **4**



$HClO_4$ to H_2SO_4, PTSA and zeolites.[15] These modifications were also found to be ineffective with our substrate. Another recent version was the utility of iodine/silver nitrate/PTSA vice $Tl(NO_3)_3.3H_2O$ in methanol.[16] This reaction produced only inextricable mixture of products.

Scheme **5**



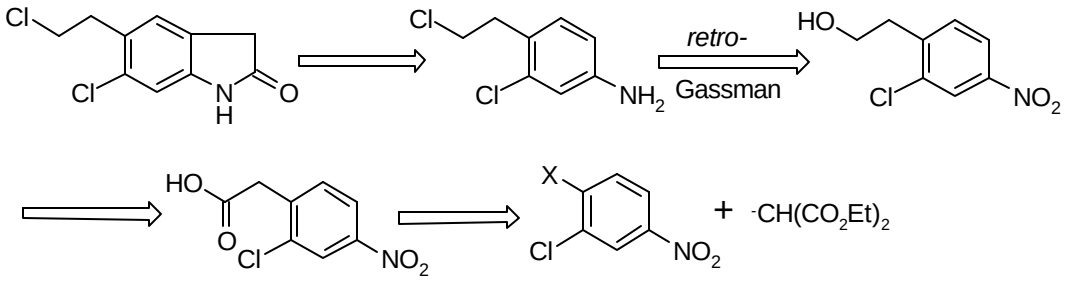
9

STRATEGY II AND RESULTS

After all of these foregoing failed efforts, we tried to examine our second strategy which involves the installation of side chain beforehand and thereafter to construct the oxindole moiety in the required direction, bearing in mind, Gassmann reaction[17] as a key transformation. The retrosynthetic analysis is delineated in scheme **6**

As per this disconnective approach, we started with the commercially available and inexpensive 1,2-dichloro-4-nitrobenzene (**11**) which was converted to the corresponding phenylacetic acid (**12**) following two-step procedure i.e., the initial S_NAr reaction of **11** with the anion of ethyl cyanoacetate (excess) followed by decarboxylative hydrolysis with 6 N HCl/glacial AcOH in 70% yield. The product was confirmed by the presence of relevant reson

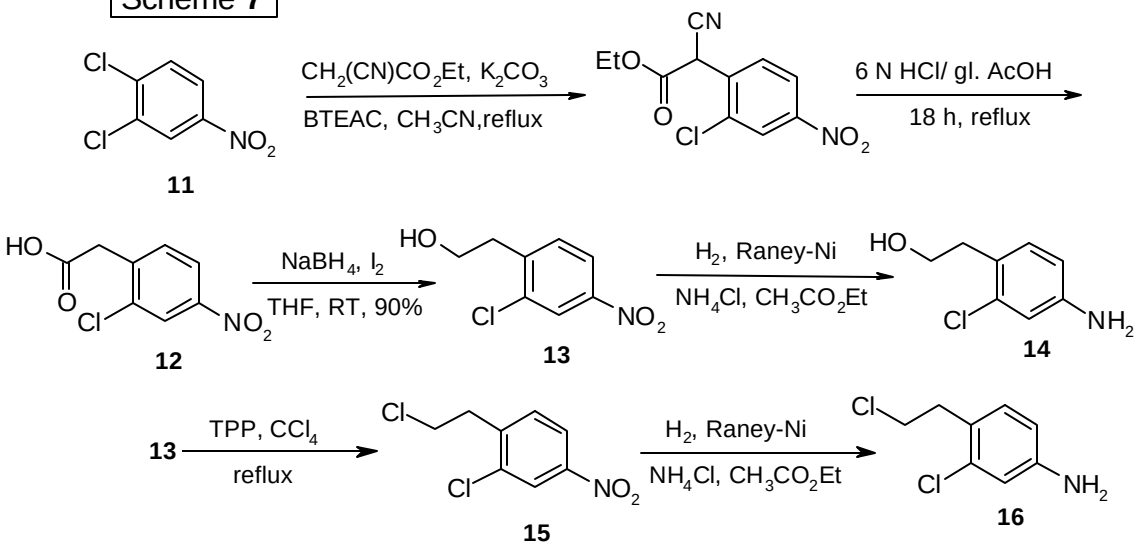
Scheme **6**



ances in the ^1H NMR spectrum in which the benzylic group (CH_2) resonated at δ 3.73 ppm. Conversion of phenylacetic acid to phenylethanol (**13**) was transacted with *in situ* borane generated from $NaBH_4$ and I_2 in THF.[18] The adherence to the literature protocol, i.e., performing the reaction at 70 ^oC (refluxing THF) resulted in a mixture of products, along with the required product in poor yield. The reaction was gleaned to provide the single product **13** in 90% yield by mere room temperature stirring of the reaction. In the ^1H NMR spectrum, the presence of CH_2CH_2OH group was characterized by the chemical shifts, one triplet at δ 3.10 due to $PhCH_2$, another at δ 3.95 due to CH_2O and a broad singlet at δ 1.6-1.85 ppm due to OH group.

Reduction of nitrobenzene (**13**) to aniline (**14**) was found to be problematic. When (**13**) was subjected to reduction with $SnCl_2$. $2H_2O$ in refluxing ethanol, the product was obtained in poor yield (40%). The reduction performed with Raney-Ni catalyst under positive pressure of H_2 in ethanol resulted in the formation of undesired dehalogenated amine product. Mixture of products (with and without halogen) was the result, when hydrazine hydrate was employed as

Scheme 7

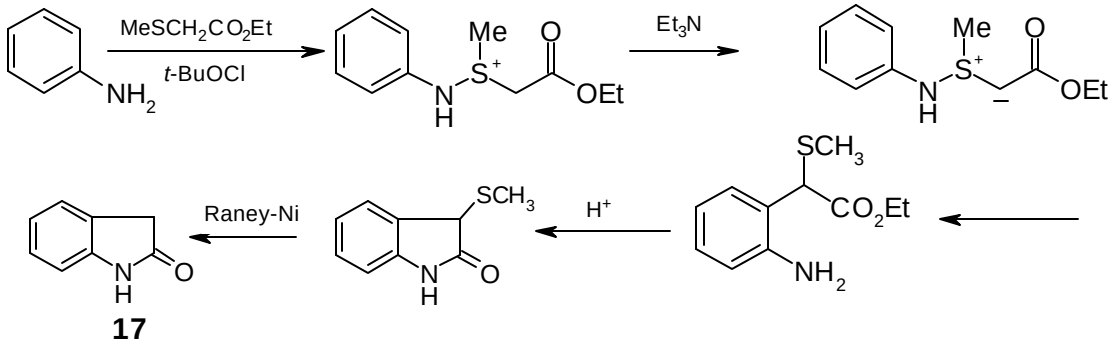


the reducing source in the presence of Raney-Ni. The reaction didn't proceed under the conditions H_2/Raney-Ni/AcOH. However, the required product **14** was exclusively obtained

with no loss of halogen and in good yield, after the modified condition was employed, i.e., H_2/Raney-Ni/ethanol in the presence of additive NH_4Cl. The structural proof of (**14**) was codified from the ^1H NMR and IR spectra. With the acquisition of aniline (**14**) in hand, the stage was set for the introduction of oxindole moiety.

A plethora of methods are available for the preparation of indolin-2-ones in the literature. The classical approaches include reduction of isatin derivatives, oxidation of indole intermediates, Lewis acid mediated Friedel-Crafts cyclisation of *N*-substituted chloroacetanilides, etc. These methods are limited to use, because of the required harsh conditions, pre-substituted acetanilides, etc. The recent methodologies include pummerer rearrangements, carbenoid insertion of β-diazoacetanilides, thermal Rh(II) catalysed Wolff rearrangement of diazoquinolines[19] and palladium catalysed cyclisation of *ortho*-iodophenyethylamines and intramolecular amide arylation of 2-haloanilides.[20] These approaches need *N*-substitution as a prerequisite. The seminal contributions of Gassman *et al.* to oxindole chemistry have led to the conversion of anilines to 3-(methylthio)indolin-2-ones via a Sommelet-Hauser type rearrangement . This involves the transformation of aniline into an aza-sulphonium salt followed by deprotonation to form the ylide, which then undergoes Sommelet-Hauser type rearrangement to an *o*-aminophenylacetic ester. Acidic annulation then

Scheme **8**

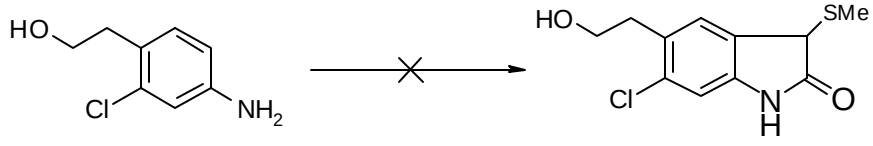


17

affords the 3-(methylthio)indolin-2-ones from which the 3-methylthio group can be knocked off by reductive desulfurisation (scheme **8**) to afford **17**. This method is frequently used for the synthesis of indolin-2-ones of agrochemical and pharmaceutical interest.

Accordingly, the compound **14** was exposed to $CH_3SCH_2CO_2Me$ and *t*-BuOCl followed by successive treatment with Et_3N and dilute HCl. However, no product was spotted after the work up and the initial enthusiasm faded away with the recovery of the starting material. The recent implementations of Gassman technology include the modified conditions for the critical azasulphonium ylide formation via 1) Swern-type intermediate [$MeS(=O)CH_2CO_2Et$, $(COCl)_2$, DMSO] and 2) the reagents SO_2Cl_2/proton sponge in place of *t*-BuOCl/TEA (scheme **9**).[21] These conditions also emulated the path of original version without delivering the product. It might be argued that the presence of OH group would be fatal to the formation of azasulfonium ylide at this stage. The substrate (**16**), which was essentially prepared for this purpose (scheme **7)** was then exposed to Gassman conditions, which also failed to make any headway with no sight of product (**19**). The starting material was recovered as such.

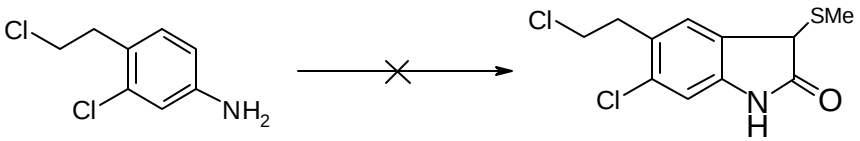
Scheme **9**



14 **18**

Conditions:

1)*t*-BuOCl, $H_3CSCH_2CO_2Me$, TEA, dil. HCl 2) $H_3CS(=O)CH_2CO_2Me$, $(COCl)_2$, TEA, dil. HCl
3) SO_2Cl_2, proton sponge, $H_3CSCH_2CO_2Me$, TEA, dil. HCl

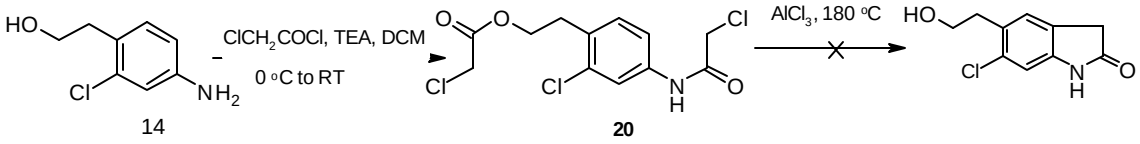


16 **19**

Conditions: as described above

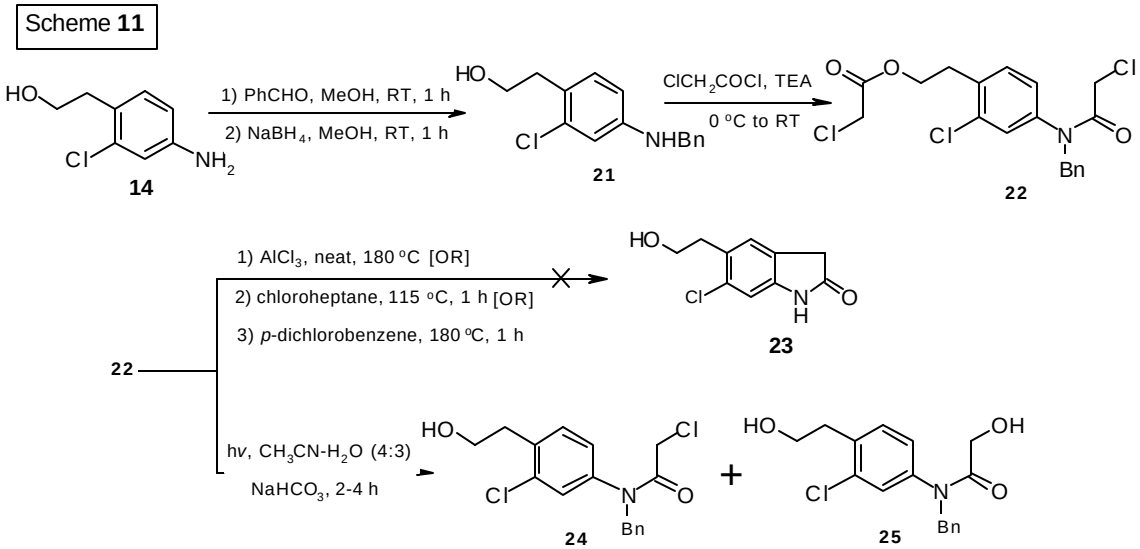
The failure of milder Gassman rearrangement forced us to opt for harsher conditions, notably, Lewis acid mediated Friedel-Crafts reaction of *N*-chloroacetanilides. Accordingly, aniline **14** was, on treatment with $ClCH_2COCl$/TEA, converted to bis(*N*,*O*-chloroacetyl)aniline derivative (**20**), which was structurally consistent with the ^1H NMR spectrum. The compound was then heated neat with $AlCl_3$ at 180 ^oC. But, no product was evident from the reaction.

Scheme **10**



Another substrategy was to try the same Friedel-Crafts annulation with substituted *N*-chloroacetanilides which have been known as superior substrates with cisoid amide conformation favourable for ring closure since such arrangement is not conducive in unsubstituted *N*-chloroacetanilides.[22] In this regard, aniline **14** was converted into *N*-benzyl derivative **21** via the formation of schiff's base with PhCHO and immediate reduction with $NaBH_4$. *N*-Benzylation was revealed in the ^1H NMR spectrum by the presence of peaks at δ 4.25 and 7.00-7.40 ppm. The aniline **21** was then converted into bis(*N*,*O*-chloroacetyl)aniline

Scheme **11**



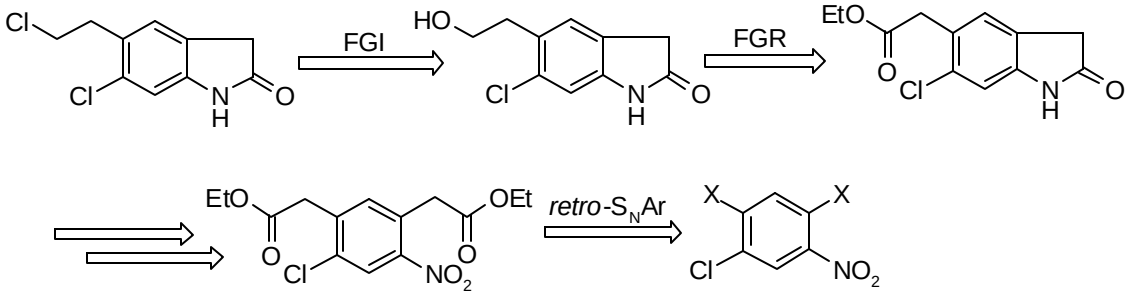
derivative (**22**) on treatment with chloroacetyl chloride and Et_3N in CH_2Cl_2 at 0 ^oC, whose structure was confirmed by the ^1H NMR spectrum. Even this substrate **22** succumbed to the same failure, unrelenting to variety of conditions including photochemical means (scheme **11**).[22, 23] While $AlCl_3$ mediated route resulted in the decomposition of the substrate, the photochemical exposure hydrolysed *O*-acetyl group and effected chloro-substitution in *N*-$COCH_2Cl$ to provide a mixture of **24** and **25** under aqueous conditions.

Hence, the time arrived here to decide that the electrophilic oxindole annulation whether Gassman approach or Friedel-Crafts method was impractical with the substrate of like-substitution. This laid the ground for switching over to our only last hope, third strategy.

STRATEGY III AND RESULTS:

Our final strategy was the dialkylation approach, which would eventually constitute the shortest and inexpensive route to the intermediate **3**. It was known in the literature that disubstitution of nitropolyhaloaromatics (S_NAr, halo groups *o*- and *p*- to the NO_2 group) was possible with S and N nucleophile. But, only one report has been reported with C-based nucleophiles in the literature with the transition metal complex elegantly promulgating the double alkylation event, even though it is not lucrative from practical perspective because of poor yield (20-40%), restriction to bromo/iodo aromatics and pronucleophile-specificity[24]. The disconnection approach, keeping in mind, the concurrent introduction of the FG elements is outlined below:

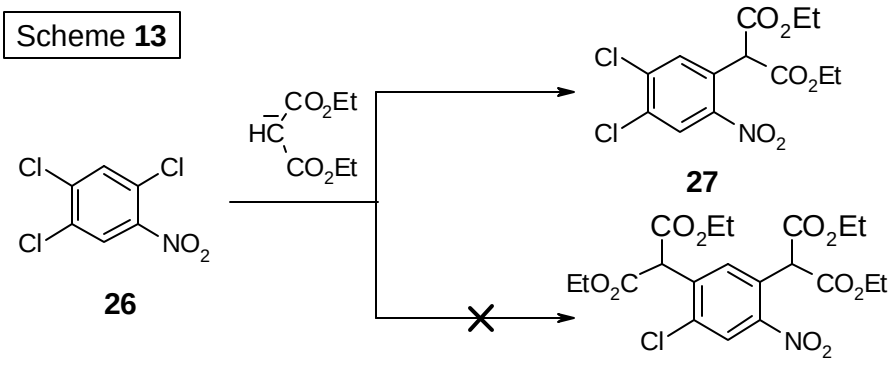
Scheme **12**



By contemplating that the hydroxyethyl side chain could be derived from CH_2CO_2Et group on one side, the disconnection of oxindole ring, on the other side, would generate the synthon, nitrophenyl diacetate (scheme **12**), which could meld the way for double disconnection of ArC-C bonding in *retro*-S_NAr fashion, taking advantage of pseudosymmetry. Since dialkyl malonates are synthetic equivalents of CH_2CO_2Et, the nitrophenyl diacetate can be disassembled to provide the starting material, 1,2,4,-trihalo-5-nitrobenzene.

Accordingly, 1,2,4,-trichloro-5-nitrobenzene **26** was chosen as our starting material, which was prepared from cheap 1,2,4-trichlorobenzene, an inexpensive by-product of lindane manufacture, by nitration with nitrating mixture, according to the literature protocol.[25] The compound **26** was subjected to S_NAr reaction with diethylmalonate and NaH in DMF at ambient temperature, resulting in the exclusive formation of monoalkylated product (**27**). The dialkylation was not achieved even under forceful conditions. Diethyl malonate and malononitrile were also examined as possible alkylating agents. In all cases, only the mono alkyl product formed. The various modifications in S_NAr conditions are detailed in table **1**.

Scheme **13**

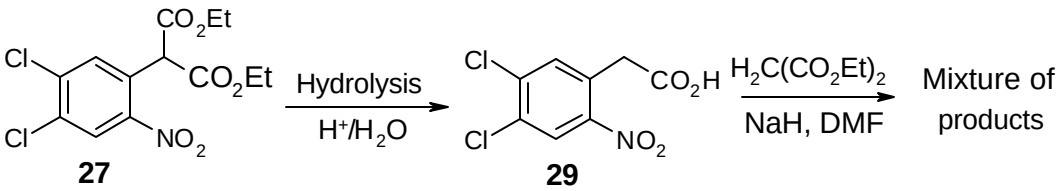


It was decided at this stage to subject the monoalkyated product to decarboxylation and then resulting phenylacetic acid 29 to further alkylation. Unfortunately, all the conditions, as described above, gave invariably the intractable mixture of products.

Table 1: reaction conditions for scheme 13

Pronucleophile	Quantity	Conditions	Temperature
$CH_2(COOEt)_2$			
i)	2 equiv.	K_2CO_3 , DMF	RT
ii)	2 equiv.	$Pd(PPh_3)_2Cl_2$, K_2CO_3 , DMF	120°C
iii)	4 equiv	K_2CO_3, CH_3CN, BTEAC	reflux
iv)	excess	NaH, THF	60°C
$CH_2(CN)COOEt$			
i)	2 equiv.	NaOH, DMF	RT
ii)	2 equiv.	K_2CO_3, CH_3CN, BTEAC	RT
iii)	2 equiv.	$Pd(PPh_3)_2Cl_2$, K_2CO_3 , DMF	reflux
iv)	2 equiv.	NaOH, DMF	120°C
$CH_2(CN)_2$			
i)	5 equiv.	K_2CO_3, DMF	reflux
ii)	2 equiv	$Pd(PPh_3)_2Cl_2$, K_2CO_3 , DMF	120°C

Scheme **14**

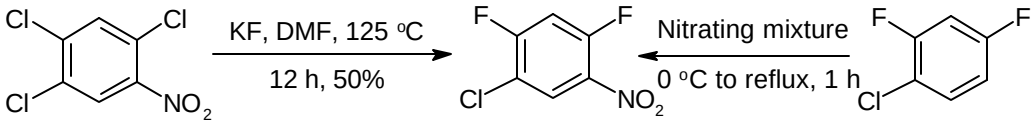


27 **29**

Therefore, alkylation of chlorodifluoronitrobenzene (**30**) was investigated next. It has been observed that that fluoro group is by far the best leaving group with C, N, or O

nucleophiles provided F group is activated by the electron withdrawing substituents in the aromatic ring such as NO_2, CN, CHO, etc. Accordingly, the requisite starting material 5-chloro-2,4-difluoronitrobenzene (**30**) was prepared by two different procedures (scheme **15**). The first procedure involved double halex reaction of 1,2,4-trichloronitrobenzene with F^- ion. The reaction was performed by heating the precursor **26** with activated KF at 125 ^oC for 12 h in DMF affording the required product **30** in moderate yield (50%).[26] The alternative procedure involving the nitration of 1-chloro-2,4-difluorobenzene was carried out which was very successful to give **29** in 95% yield. However, the high cost of 2,4-difluoro-1-chlorobenzene was to be noted in this case. The product was identified by the ^1H NMR resonances at δ 7.1-7.25 and 8.2-8.3 ppm.

Scheme **15**

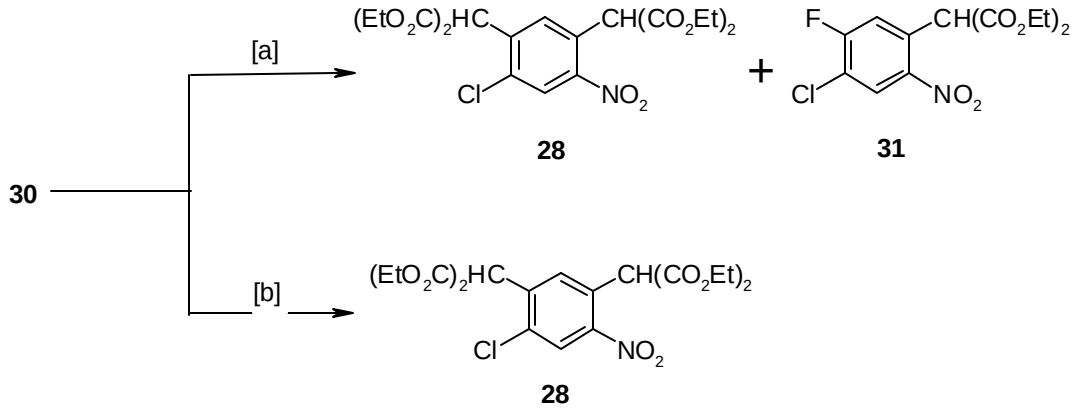


26 **30**

The compound **30** was then exposed to $CH_2(CN)CO_2Me$ and OH^- as base in DMF at room temperature. The result was the usual monoalkyated product, as if that the activated substrate **30** behaved like its mentor **26** in reactivity. Though disappointed with this outcome, we screened this substrate further with different pronucleophiles and conditions, as tabulated previously. At the last, reprieve was realized after **30** was treated with sodium salt of diethyl malonate (4 equiv.) [prepared from sodium sand and diethyl malonate] in DMF at RT. In fact, the reaction gave a mixture of two products, which were separated by column chromatography and identified individually by the ^1H NMR spectrum as mono- (**31,** major) and di-akylated (**28,** minor) products. The product (**31**) gave characteristic ^1H NMR resonances due to ethyl group at δ 1.3 and 4.32 ppm. The active methine proton was observed at δ 5.2-5.40 as two singlets

while aromatic protons resonated between δ 7.30-7.40 ppm (two doublets). The appearance of two singlets at δ 7.7 and 8.1 ppm in aromatic region assured the total displacement of fluorine, which was known to couple with the adjacent protons (I = ½), whereas double-the-integration in the non-aromatic region of monoalkylated product confirmed the double alkylation event in the ^{1}H NMR spectrum of **28**. Both the compounds gave the intense peak at 1715 cm^{-1} in the IR spectrum, thus signaling the presence of ester. Our next move was to get the dialkylated product exclusively. This would be either accomplished by adding the excess of the malonate anion reagent or increasing the reaction temperature. After several tribulations, it was found that the optimized condition was to stir the substrate with 2.75 equiv. of sodium salt of diethyl malonate at 100 °C for 12h. The increased reactivity of carbanion generated from $CH_2(CO_2Et)_2$ over that of unreactive nucleophiles $CH_2(CN)CO_2Et$ and $CH_2(CN)_2$ can be accounted to the difference in the acidic strength of their corresponding conjugate acids (pKa = 13, 11, 9).

Scheme **16**



Conditions: [a] diethyl malonate (4 equiv.), NaH, DMF, RT

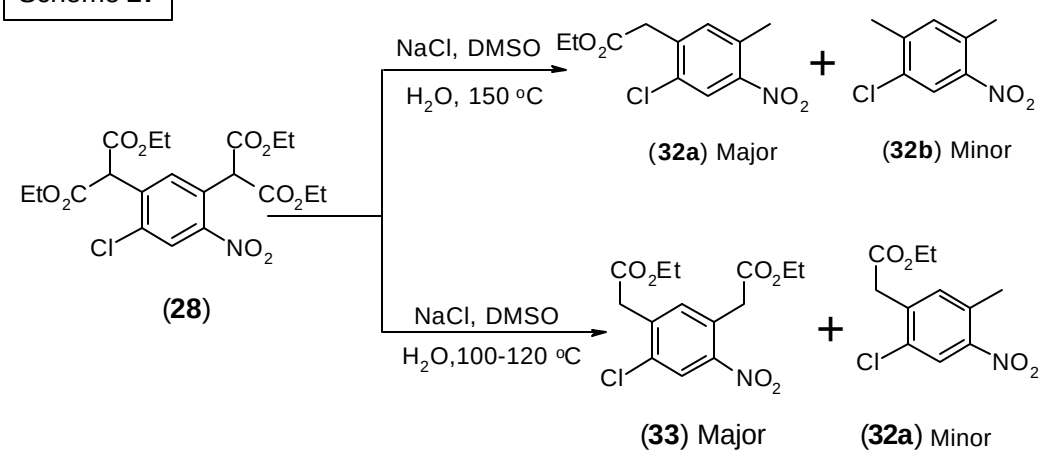
[b] diethyl malonate (2.75 equiv.), NaH, DMF, 100 °C, 12 h

The product **28** was then exposed to Krapcho's decarboxylation conditions (NaCl, H_2O, DMSO, 150 °C, 15 h), resulting in an unexpected mixture of products **32a** and **32b** in 67% yield.[27] The minor product was assigned structure **32b** based on the ^{1}H NMR spectral analysis, which showed characteristic two singlets at δ 2.45 and 2.6 ppm owing to methyl protons. The

major product **32a** was assigned the corresponding structure by the ample resonances in the ^1H NMR spectrum: singlet at δ 2.45 ppm for CH_3 group; singlet at δ 3.9 for benzylic protons; triplet at δ 1.28 and quartet at δ 4.17 ppm showing the presence of ethoxy group. The compound also gave intense adsorption at 1738 cm^{-1} pertaining to 'ester carbonyl' in the IR spectrum. Both the compounds were checked for their elemental integrity too.

This kind of bis(dealkoxycarbonylation) of aryl malonate to tolune or xylene has been observed for the first time under Krapcho's protocol in nitroaryl malonates. Simple aryl malonates (without electron-withdrawing NO_2 group) are known at first decarboxylation itself providing the respective phenylacetates.[27] Hence, one can emphasize that the NO_2 group present because of its electron-withdrawing nature, may accelerate the second decarboxylation by stabilizing the transition states/intermediate across the pathway. The probable mechanism

Scheme **17**

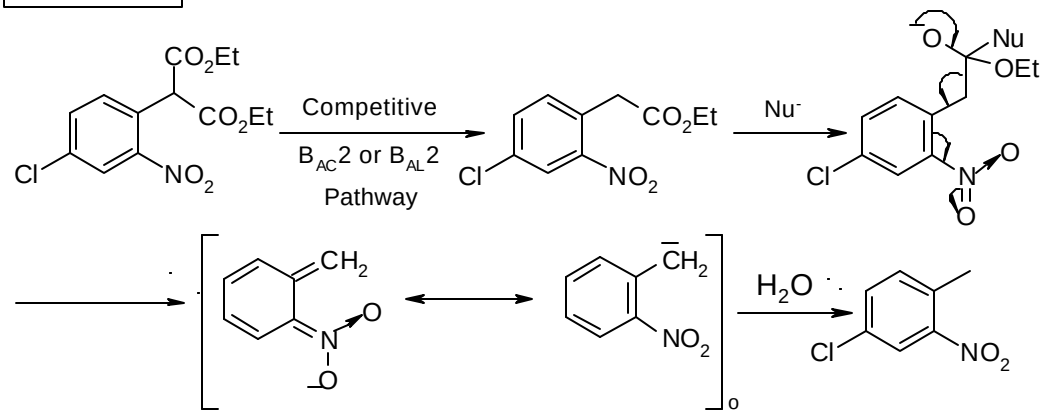


may proceed in two steps: the initial decarboxylation of aryl malonates via competitive $B_{AC}2$ or $B_{AL}2$ pathway to give nitrophenyl acetate; the nucleophilic counterpart of the added salt in the second step might attack the ester carbonyl to form the tetrahedral intermediate which then undergoes elimination to provide the corresponding benzyl carbanion which is mesomerically stabilized by NO_2 group at *o*- and/or *p*-position, the phenomenon called, captodative effect.[28] The formation of **33** and **32a** as major and minor products unambiguously indicate that the

ester group *ortho* to nitro group undergoes facile decarboxylation than that one at *p*-position because of the better stabilization of *o*-nitrobenzyl carbanion than its *para* counterpart. This serendipitous observation, which forms as the subject of our recent communication, has astutely been exploited to synthesise various alkylated nitroaromatics, which are otherwise difficult to prepare from the halonitrobenzenes using inexpensive reagents.

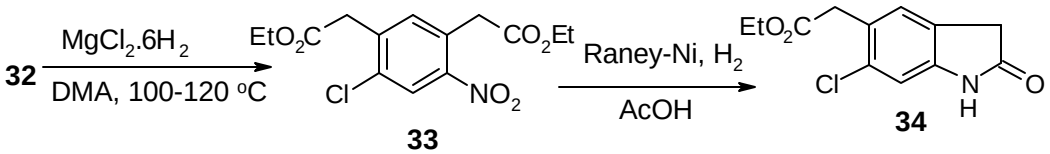
However, our original goal was to excavate the procedure for exclusively getting the product (**33**) without the products of double decarboxylation. The optimized condition was to maintain the temperature of the reaction mixture (**31**, NaCl, DMSO, H_2O) in between 100-120 ^oC for 24 h. The increased yield and shorter reaction timings were observed

Scheme **18**



when the modified Kracho's condition was employed, i.e., $MgCl_2.6H_2O$ in DMA.[29] The desired product **33** was predominant one with little formation of the by-product **32a**. The structure of the product was fully consistent with the ^1H NMR spectrum: two methylene protons showed two singlets at δ 3.8 and 4.0 ppm, ethyl ester protons resonated at routine

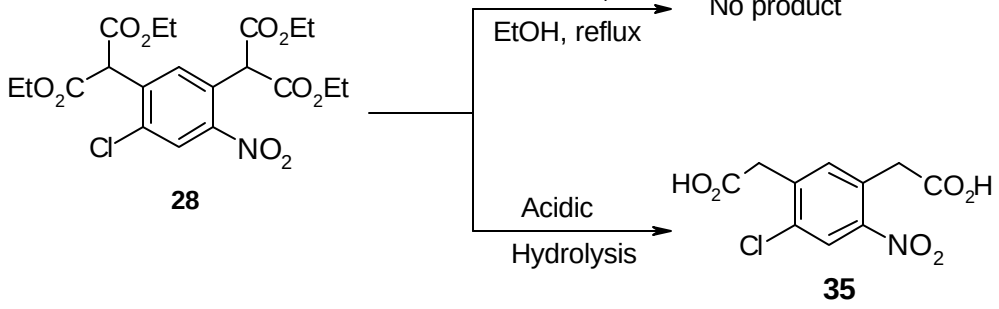
Scheme **19**



positions and aromatic protons at δ 7.30 and 8.15 ppm. The compound (**33**) was then subjected to the reduction of NO_2 group with concomitant cyclisation with H_2 and Raney-Ni in acidic medium to provide 2-oxindole **34** in quantitative yield. The structure was elucidated through the ^1H NMR spectrum. The appearance of CH_2 protons of lactam at δ 3.8 ppm (moved upfield compared to **33**) as singlet and lactam NH proton at 8.15 ppm unambiguously supported the structure. Other protons staked claim at the required positions.

The formation of side product **32a** was unwarranted to develop the process on multigram scale. Hence, the scheme was modified to avoid this step. Accordingly, the aryl dimalonate **33** was subjected to hydrolysis under basic conditions (NaOH/EtOH/H_2O/reflux, H^+/H_2O). To much of our surprise, this reaction gave only dark-brownish solid compose beyond characterization. This might be due to the general concept that nitroarenes are less compatible to basic conditions. Hence, the solution was to perform the hydrolysis under acidic conditions. Accordingly, the solution of **28** in 6 N HCl and glacial acetic acid was refluxed for 18 h, which gave the clean product, the diacid (**35**) without any deterioration and in excellent yield. Hydrolytic product **35** was characterized by the ^1H NMR spectrum. The peaks due to ester groups disappeared. Two set of methylene protons gave resonances at δ 3.9 (*p*- to nitro) and 4.1 ppm (*o*- to nitro), whilst the two aromatic protons remained unchanged in the scheduled positions. The presence of acid group was identified by the IR frequency at 1685

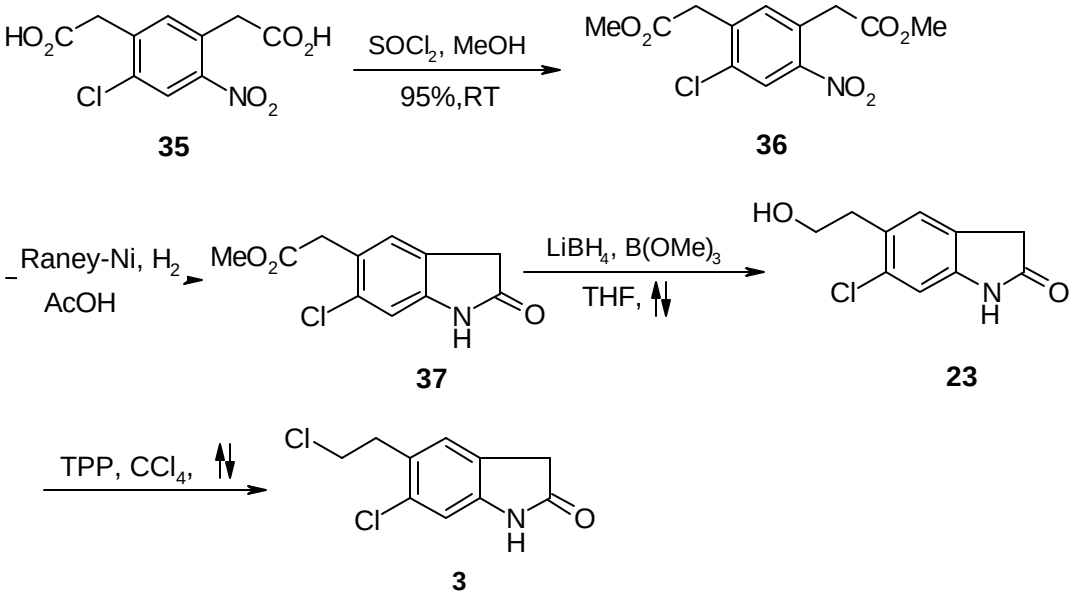
Scheme **20**



cm^{-1}. The next endeavour was the methylation of the diacid. Accordingly, the substrate was refluxed with dimethyl sulphate and K_2CO_3 in 2-butanone. The reaction resulted in a mixture of two products none of which belonged to the desired category, as evident from the ^1H NMR spectra. We then resorted to acid mediated esterification. Thus, the treatment of diacid (**35**) with catalytic $SOCl_2$ in MeOH provided its corresponding dimethyl ester (**36**) as a single product in 95% yield. The structure was confirmed by the ^1H NMR spectrum with ancillary information from IR spectral and combustion analysis. The ^1H NMR spectrum contained two additional signals at δ 3.7 and 3.75 ppm as singlets loyal to two OMe groups compared to that of starting material. Other protons resonated at proper positions. The IR spectrum gave an intense adsorption at 1725 cm^{-1} characteristic of 'ester carbonyl'. Domino reduction and cyclisation of nitrophenylacetate precursor **36** with H_2 and Raney-Ni in AcOH at 45 psi afforded the corresponding 2-oxindole derivative (**37**). The structure was derived from the ^1H NMR, IR spectral and combustion data. The ^1H NMR spectrum showed the disappearance of one of the two OMe groups and the upfield shift of one of the two methylenes because of the conversion from ester to amide. The IR spectrum gave an intense peak at 1722 cm^{-1} specific for 2-oxindole ring.

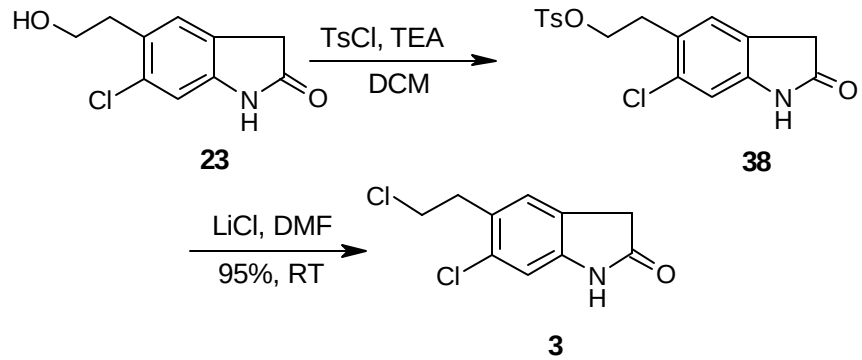
Reduction of **37** with $LiBH_4$ generated *in situ* by mixing the reagents $NaBH_4$ and LiCl in a solvent mixture of ethanol and THF gave a mixture of products with the major recovery of starting material even after prolonged exposure. Surprisingly, the reduction of ester with LAH in THF at 0 ^oC afforded the desired product (**23**), although in moderate yield. Fortunatley, LAH didn't saturate reductively the lactam to provide the corresponding pyrrolidine. The better procedure for the reduction of ester was to employ the reagents $LiBH_4$ and $B(OMe)_3$ in THF under refluxing conditions in 75% yield where the $LiBH_4$ was generated *in situ* in accordance with an improved protocol reported by H.C.Brown *et al.*[30] The structure was elucidated from the IR, ^1H NMR, EI spectral and elemental analysis. The ^1H NMR spectrum of

Scheme **21**



23 acknowledged the reduction by displaying two sets of peaks at δ 2.70-2.90 and 3.60-3.77 ppm due to two methylene groups. The highest mass peak in EI spectrum at 211 (M^+) was observed. It is gracefully noted that the yield and completion of the reaction depends upon the efficient formation of $LiBH_4$. Hence, the reaction stands further to be optimized or performed with commercially available reagent. The conversion of **23** into **3** was easily effected with TPP in refluxing CCl_4 in good yield.

Scheme **22**



However, both TPP and CCl_4 are proclaimed toxic to the environment, an alternative two-step procedure was also developed. Accordingly, the phenylethanol **23** was converted to it tosylate ester (**38**) with TsCl, TEA, DMAP and refluxing CH_2Cl_2. Subsequent reaction of **38** with LiCl in DMF at 50 ^oC gave **3**. The structural verification was performed with ^1H NMR,IR, EI spectral and elemental analyses. The methylene protons of lactam ring appeared as a singlet at δ 3.45 ppm. The side-chain methylene groups were located at δ 3.15 and 3.77 ppm. Aromatic protons appeared at expected regions. The IR spectrum gave intense peak at 1716 cm^{-1} owing to 2-oxindole moiety. The EI spectrum gave a molecular ion peak at (*m*/*z*) 211 supporting the molecular formula.

CONCLUSION:

In thumbnail, this route constitutes a formal synthesis of CP-88, 059, the current drug for schizophrenia. This synthetic technology can be fine-tuned as the practical and economically viable process, suitable for multigram scale. The existing substituents would have negated the feasibility of Willgerodt rearrangement in strategy I, the same contenders could have thwarted our attempt in ring forming step in strategy II. It is heartening these these dead ends rendered as stepping-stones to execute the last scheme strategy III that went all right culminating the important derivative to everybody's delight.

EXPERIMENTAL SECTION:

(4-Chloro-2-nitro)phenylacetic acid (6)

Sodium hydroxide (9.6 g, 0.24 mol.) was added to an ice-cold solution of ethyl cyanoacetate (26.6 mL, 0.24 mol) in DMF (100 mL). After stirring for 30 minutes to dissolve NaOH, the compound **5** (20 g, 0.1 mol) was added for 10 minutes portionwise at 0 ^oC. The reaction mixture was stirred for 24 h at room temperature, cooled to 0 ^oC and neutralized with dropwise addition of dilute HCl followed by extraction with ether. The organic part was

washed with water and brine, dried (anhydrous sodium sulphate) and concentrated to afford the crude product as brownish syrup (35 g).

The crude material was refluxed for 12 h in a mixture of 6 N HCl (150 mL) and glacial AcOH (150 mL). The reaction was poured into ice (1.5 kg). The solid was filtered off and dried to furnish **6** (16 g, 71%) as a yellowish solid.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.90 (s, 2H, $PhCH_2$), 7.4 (dd, J = 4.54, 9.1 Hz, 1H, H-6), 7.52-7.65 (m, 1H, H-5), 7.95-8.02 (m, 1H,H-3)

Methyl (4-chloro-2-nitro)phenylacetate (7)

A mixture of phenylacetic acid **6** (15 g, 69.4 mmol), dimethyl sulphate (10.5 g, 69.4 mmol), and potassium carbonate (14.4 g, 104 mmol) in 2-butanone (75 mL) was taken in a 500 mL RB flask. The mixture was refluxed for 3 h, filtered through a celite pad, and concentrated. The residue was dissolved in dichloroethane, washed with water, dried (Na_2SO_4) and concentrated to afford **7** (16 g, 95%) as colorless oil, directly used in the next reaction.

M.P.: 75-76 °C

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.75 (s, 3H, CO_2Me), 4.0 (s, 2H, CH_2), 7.25-7.40 (m, 1H, H-6), 7.5-7.65 (m, 1H, H-5), 8.10 (s, 1H, H-3)

6-Chloroindol-2(3H)-one (8)

A solution of ester **7** (2 g, 8.69 mmol) in acetic acid (10 mL) containing Raney-Ni catalyst (0.4 g) was stirred under hydrogen atmosphere (15 psi) for 3 h. The catalyst was filtered off and washed with methanol. The solvent was evaporated and the crude solid recrstallised from EtOH to afford **8** (1.3 g, 89%) as light-yellowish solid.

M.p.: 165-167 °C

IR (nujol): 3134, 2922, 2854, 1699, 1401 cm^{-1}

^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.69 (s, 2H, CH_2), 6.11 (s, 1H, H-6), 6.18 (d, J = 8.0 Hz, H-4), 6.40 (d, J = 8.0 Hz, H-4), 9.69 (br s, 1H, CONH)

5-Acetyl-6-chloro-2-oxindole (9)

Acetyl chloride (2.1 mL, 29.4 mmol) was added dropwise to a slurry of aluminium chloride (8.0 g, 60.0 mmol) at 0 ^{o}C under N_2 blanket. After being stirred for 5 minutes, oxindole **8** (3.3 g, 19.6 mmol) was added at once. The reaction mixture was refluxed for 36 h with vigorous stirring and quenched at 0 ^{o}C with dilute HCl. The precipitated solid was filtered off and dried to afford **9** (3.5 g, 85%) as a colourless solid, which was directly used in the next reaction.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.65 (s, 3H, $COCH_3$), 3.45 (s, 2H, lactam CH_2), 6.95 (s, 1H, H-7), 7.53 (s, 1H, H-4), 10.20-10.35 (br s. 1H, CONH)

(2-Chloro-4-nitro)phenylacetic acid (12)

A mixture of **11** (25 g, 130 mmol), ethyl cyanoacetate (16.6 mL, 156 mmol), potassium carbonate (54 g, 390 mmol) and BTEAC (1.48 g, 6.5 mmol) in acetonitrile (500 mL) was refluxed for 24 h. Dilute HCl (6 N) was tipped in at 0 ^{o}C until the solution turned colourless. After the evaporation of the solvent, the residue was partitioned between water (500 mL) and ether (500 mL), the organic phase washed with water and brine, dried (anhydrous Na_2SO_4) and concentrated. The residue was next dissolved in 6 N HCl (300 mL) and glacial AcOH (300 mL) and refluxed for 12 h. The reaction was poured into crushed ice, the solid filtered at the pump, and purified by dissolving in 20% NaOH solution followed by acidification to afford **12** (19.8 g, 70%) as a yellowish solid.

^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.73 (s, 2H, $PhCH_2$), 7.5 (t, J = 6.7 Hz, 1H, H-6), 8.0 (dd, J = 1.7, 8.4 Hz, 1H, H-5), 8.20 (s, 1H, H-3).

(2-Chloro-4-nitro)phenylethanol (13)

To a stirred solution of **12** (3 g, 12 mmol) in THF (30 mL), $NaBH_4$ (0.9 g, 24 mmol) was added portionwise at 0 ^{o}C . A solution of iodine (3.01 g, 12.0 mmol) in THF (20 mL) was then introduced dropwise. The resultant mixture was stirred for 6 h at room temperature,

cooled at 0 ^{o}C, and quenched with dilute HCl. The solvent was evaporated, and the residue taken in ether, washed with water, aqueous Na_2SO_3 solution and brine, dried (anhydrous Na_2SO_4) and concentrated to afford **13** (2.53 g, 90%) as a colourless oil, directly used in the next step.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.6-1.85 (br s, 1H, -OH), 3.10 (t, *J* = 6.7 Hz, 2H, $PhCH_2$), 3.95 (t, *J* = 6.7 Hz, 2H, CH_2O), 7.5 (d, *J* = 8.5 Hz, 1H, H-6), 8.05 (dd, *J* = 6.7, 2.0 Hz, 1H, H-5), 8.25 (d, *J* = 2.0 Hz, 1H, H-3)

(4-Amino-2-chloro)phenylethanol (14)

A solution of **13** (1.4 g, 6.9 mmol) in ethyl acetate (10 mL) containing the suspension of Raney-Ni catalyst (0.15 g) and solid NH_4Cl (1.4 g, 12.96 mmol) was stirred under positive H_2 atmosphere overnight. Removal of the catalyst by filtration, and the solvent by evaporation gave the residue, which on acid-base (1 N NaOH/dilute HCl) purification gave **14** (1.2 g, 75%) as a light-yellowish liquid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.77 (t, *J* = 6.73 Hz, 2H, $PhCH_2$), 2.95-3.20 (br s, 1H, OH), 3.67 (t, *J* = 6.73 Hz, 2H, CH_2O), 6.40 (dd, *J* = 2.9, 8.6 Hz, 1H, H-4), 6.58 (d, *J* = 1.92 Hz, 1H, H-6), 6.90 (d, *J* = 8.6 Hz, 1H, H-3)

IR (nujol): 3200-3600 (br. band), 2936, 2872, 1614, 1492, 1420, 1037, 849 cm^{-1}

1-Chloro-2-(2-chloroethyl)-4-nitrobenzene (15)

A solution of **13** (2 .0 g, 9.9 mmol) and triphenylphosphine (2.85 g, 10.9 mmol) in a solvent mixture of $CHCl_3$ and CCl_4 (5 mL each) was refluxed for 3 h. The solvent was stripped off and the residue purified by silica gel column chromatography (15% ethyl acetate in hexane) to afford **15** (1.5 g, 70%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.79 (t, *J* = 7.9 Hz, 2H, $PhCH_2$), 2.93 (t, *J* = 7.9 Hz, 2H, CH_2Cl), 7.47 (d, *J* = 9.0 Hz, 1H, H-3), 8.13 (dd, *J* = 9.0, 2.0 Hz, H-4), 8.25 (d, *J* = 2.0 Hz, 1H, H-6).

1-Chloro-2-(2-chloroethyl)-4-aniline (16)

Raney Ni catalyst (100 mg), was carefully added to a solution of **15** (1.0 g, 4.5 mmol) in ethyl acetate containing ammonium chloride (1.0 g). The resulting suspension was stirred under hydrogen atmosphere (approximately 15 psi) for 12 h, filtered at the pump and the filtrate concentrated. The residue was purified by treating with dilute HCl, washed with ethyl acetate, treated with aqueous sodium bicarbonate till basic pH, extracted with ethyl acetate. The organic extract was dried (anhydrous sodium sulphate), and evaporated to afford pure **16** (0.78 g, 90 %) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.10 (d, *J* = 8.1 Hz, 2H, $PhCH_2$), 3.7 (d, *J* = 8.1 Hz, 2H, CH_2Cl), 6.57 (dd, *J* = 1.9, 7.4 Hz, 2H, H-4), 6.73 (d, *J* = 1.9 Hz, H-6), 7.06 (d, *J* = 7.4 Hz, 1H, H-3).

2-{2-chloro-4-[(chloroacetyl)amino]phenyl}ethyl chloroacetate (20)

Chloroacetyl chloride (1.4 g, 12.5 mmol) was dropwise added to a solution of aniline **14** (1 g, 5 mmol) and triethylamine (2.8 mL, 62 mmol) in CH_2Cl_2 at 0 ^{o}C. After stirring for overnight at room temperature, the reaction was washed with dilute $NaHCO_3$ solution, water and brine, dried (anhydrous sodium sulphate), and concentrated to afford **20** (1.45 g, 90%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.11 (t, *J* = 6.5 Hz, 2H, $PhCH_2$), 4.03 (s, 2H, $NHCOCH_2Cl$), 4.20 (s, 2H, $OCOCH_2Cl$), 4.40 (t, *J* = 6.6 Hz, 2H, CH_2O), 7.25 (d, *J* = 4.9 Hz, 1H, H-6), 7.40 (dd, *J* = 1.65, 8.0 Hz, 1H, H-5), 7.70 (d, *J* = 1.65 Hz, 1H, H-3), 8.23 (br s, 1H, NHCO)

[4-(*N*-Benzyl)amino-2-chloro]phenylethanol (21) and 1-Chloro-2-(chloroethylacetyloxy)-5-(*N*-benzyl)chloroacetamide (22)

A solution of aniline **14** (2 g, 9.9 mmol) and benzaldehyde (1.17 g, 11.0 mmol) in methanol were stirred for 30 min. $NaBH_4$ (0.4 g, 9.9 mmol) was then added at 0 ^{o}C and the stirring continued for 30 minutes. The solvent was stripped off and the residue taken in dilute

HCl, washed with chloroform, neutralized with aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated to afford **21** (2.75 g, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.85 (t, *J* = 6.3 Hz, $PhCH_2$), 3.78 (t, *J* = 6.3 Hz, 2H, CH_2O), 4.25 (s, 2H, NCH_2), 6.45 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.64 (d, *J* = 2.0 Hz, 1H, H-3), 7.0-7.4 (m, 6H).

To a stirred mixture of **21** (2.7g, 9.25 mmol) and triethylamine (3.8 g, 37.5 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC, chloroacetyl chloride (2.3 g, 20.3 mmol) was added dropwise. The reaction, after being stirred overnight, was worked up as described for the compound **20** to afford **22** (2.7 g, 71%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.14 (t, *J* = 6.9 Hz, 2H, CH_2Ph), 3.85 (s, 2H, $NCOCH_2$), 4.02 (s, 2H, $OCOCH_2$), 4.43 (t, *J* = 6.9 Hz, 2H, CH_2O), 4.85 (s, 2H, CH_2N), 6.8-7.40 (m, 8H, aromatic).

[4-(*N*-benzyl,*N*-chloroacetyl)amino-2-chloro]phenylethanol (24) and [4-(*N*-benzyl,*N*-hydroxyacetyl)amino-2-chloro]phenylethanol (25)

A mixture of **22** (1.5 g, 3.6 mmol) and sodium bicarbonate (0.5 g) in a solvent mixture of CH_3CN: H_2O (90+120 mL) was irradiated with 500 W bulb for 2 h. Acetonitrile was stripped off and the remains extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and purified by column chromatography to afford **24** (0.73 g, 60%), (30% ethyl acetate in hexane as eluent) as a colourless liquid and **25** (0.23 g, 20%), (40% ethyl acetate in hexane) as a colourless liquid.

Physical data of **24**

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.0 (t, *J* = 5.2 Hz, 2H, CH_2Ph), 3.84 (s, 2H, $COCH_2Ci$), 3.9 (t, *J* = 5.2 Hz, 2H, CH_2O), 4.85 (s, 2H, CH_2N), 6.8 – 7.35 (m, 8H, aromatic).

EI MS (*m*/*z*): 82 (14), 91 (100), 117 (50), 180 (5), 302 (14), 337 (10), 339 (M^++1).

IR ($CHCl_3$): 3100– 3600 (br.), 1656 cm^{-1}

Physical data of **25**

^1H NMR ($CDCl_3$, 200 MHz): δ 1.95 (br s, 1H, OH), 2.95 (t, *J* = 7.2 Hz, 2H, CH_2Ph), 3.41 (br s, 1H, OH), 3.87 (s, 2H, $COCH_2O$), 3.9 (t, *J* = 7.2 Hz, 2H, CH_2O), 4.87 (s, 2H, CH_2N), 6.75 – 7.35 (m, 8H, aromatic).

EI MS (*m*/*z*): 91 (100), 230 (8), 319 (19), 321 (8) [M^++1].

Diethyl (2,5-dichloro-4-nitro)phenylmalonate (27) and (2,5-dichloro-4-nitro)phenylacetic acid (29)

A mixture of **26** (5 g, 22 mmol), diethyl malonate (6.7 mL, 43.8 mmol), potassium carbonate (12.1 g, 87.6 mmol), BTEAC (0.25 g, 1.1 mmol) in acetonitrile (50 mL) was refluxed for 12 h, cooled to 0 ^oC and neutralized with dilute HCl. The solvent was stripped off and the residue extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude product **27** (7.5 g), which was refluxed in a mixture of 6 N HCl (10 mL) and glacial AcOH (10 mL) for 15 h. The solvent was removed *in vacuo*. The residue was dissolved in 1 N NaOH solution, washed with ethyl acetate, neutralized with dilute HCl and extracted with ethyl acetate. The solvent was evaporated to afford **29** (5.4 g. 70%) as a colourless oil.

^1H NMR of **27** ($CDCl_3$, 200 MHz): δ 1.25 (t, *J* = 5.9 Hz, 6H, two CH_3), 4.25 (q, *J* = 5.9 Hz, 4H, two CH_2), 5.15 and 5.2 (2s, 1H, active methine H), 7.64 (s, 1H, H-6), 8.15 (s, 1H, H-3)

^1H NMR of **29** ($CDCl_3$, 200 MHz): δ 3.99 (s, 2H, CH_2CO), 7.55 (s, 1H, H-6), 8.24 (s, 1H, H-3)

IR (nujol): 2800-3300 (br), 2731, 1705, 1529, 1460, 1340, 946 cm^{-1}

1-Chloro-2,4-difluoro-5-nitrobenzene (30)

Method A: To a solution of nitrating mixture {prepared *in situ* by dropwise addition of conc. H_2SO_4 (35.4 mL, 650 mmol) to conc. HNO_3 (34.6 mL, 770 mmol) at 0 C for 5 minutes}, was added 1-chloro-2,4-difluorobenzene (25 g, 168.3 mmol) dropwise for 20

minutes with vigorous stirring and occasional cooling. The biphasic mixture was heated to 80-100 C for 1 h (consumption of starting material was checked by GC), cooled down to ambient temperature, and partitioned between water (400 mL) and ether (400 mL). The organic extract was successively washed with water and brine, dried (anhydrous sodium sulphate) and concentrated *in vacuo* to afford the crude material, which was distilled off at reduced pressure to provide **30** (30 g, 92 % yield) as a light-yellowish oil.

Method B: A mixture of potassium fluoride (19.1 g, 329 mmol), cetrimide (3.21 g, 8.8 mmol) and DMF (125 mL), charged in a 500 mL RB flask, was dried by the addition of toluene (50 mL) followed by azeotropic distillation through Dean-Stark apparatus. 1,2,4-trichloro-5-nitrobenzene **26** (25 g, 110 mmol) was then added in single phase. The resultant stirred mixture was heated to 125 C for 12 h under N_2 blanket. The brownish-turned reaction mixture was brought to room temperature, diluted with water (750 mL) and a mixture of ethyl acetate & petroleum ether (3: 7 ratio, 750 mL). Separation of organic phase followed by washing with water and brine, drying (anhydrous sodium sulphate) and rotary evaporation gave the residue, which was submitted to distillation at reduced pressure to provide **30** (9.73g, 55%) as a light-yellowish oil.

^{1}H NMR ($CDCl_3$, 200 MHz): ä 7.18 (t, *J* = 9.25 Hz, 1H, H-6), 8.24 (t, *J* = 7.4 Hz, 1H, H-3)

1-Chloro-2,4-bis(diethylcarboxymethyl)-5-nitrobenzene (28)

Method A: To a solution of sodio diethylmalonate (52 g, 284 mmol) in DMF (125 mL), was added 1-chloro-2,4-difluoro-5-nitrobenzene **30** (20 g, 103 mmol) in several lots at 0 C for 5 minutes under N_2 atmosphere. The brick-red solution was gradually heated to 100 C and stirred at this temperature for 12 h. (TLC: 20% ethyl acetate in hexane). The reaction mixture was cooled to 0 C, acidified by dropwise addition of dilute HCl, until the solution turned colourless and diluted with water (1 L) and ethyl acetate-petroleum ether mixture (3: 7 ratio, 1 L). The organic phase was washed with water (3 x 1 L) and brine, dried (anhydrous

sodium sulphate) and concentrated *in vacuo*. The crude product **28** (62 g) was telescoped to the next step.

Method B: Sodium hydride (11.34 g, 283.5 mmol) was added to an ice-cold solution of diethyl malonate (45.4 g, 283.5 mmol) in dry DMF (200 mL) for 30 minutes. The temperature was slowly elevated to 100 C. After stirring for 1 h at 100 C, the solution was cooled to 0 ^{o}C. 1-Chloro-2,4-difluoro-5-nitrobenzene **30** (20 g, 103.1 mmol) was added at various intervals for 15 minutes. Heating the reaction mixture for 12 h at 100 C, followed by work up, as described above, gave the crude product **28** (60-62 g)

Note: A small amount of the crude product was chromatographically purified by passage over silica gel column (20 % ethyl acetate in petroleum ether) for analytical purpose.

^{1}H NMR ($CDCl_3$, 200 MHz): ä 1.31 (t, *J* = 7.27 Hz, 12H, 4 x CH_3), 4.28 (m, 8H, 4 x OCH_2), 5.21 (s, 1H, CH), 5.27(s, 1H, CH), 7.70 (s, 1H, H-6), 8.10 (s, 1H, H-3)

IR (nujol): 2957, 1715, 1505, 1323, 1271, 1202, 1005 cm^{-1}

Ethyl (2-chloro-5-methyl-4-nitro)phenylacetate (32a) and 1-Chloro-2,4-dimethyl-5-nitro benzene (32b)

A mixture of aryl dimalonate **28** (1.6 g, 3.6 mmol) and $MgCl_2.6H_20$ (0.73 g, 3.6 mmol) were taken in *N,N*'-dimethylacetamide (20 mL) and heated to 100-120 ^{o}C overnight with vigorous stirring. The mixture was partitioned between ether and water (100 mL each). The organic phase was successively washed with water and brine, dried (sodium sulphate) and evaporated. The crude was chromatographed on silica gel with gradual elevation of solvent polarity to afford **32b** (0.52 g, 60%) {2% ethyl aceate in hexane as eluent} as yellowish oil and **32a** (0.12 g, 20%) {10% ethyl aceate in hexane as eluent}as yellowish solid**.**

Physical data of **32a:**

IR ($CHCl_3$): 760, 1344, 1522, 1768 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): ä 1.28 (t, 3H, J = 7.4 Hz, CH_3), 2.45 (s, 3H, CH_3 at C-5), 3.9 (s, 2H, CH_2CO), 4.17 (q, *J* = 7.4 Hz, 2H, OCH_2), 7.2 (s, 1H, H-3), 8.1 (s, 1H, H-6).

Physical data of **32b:**

^{1}H NMR ($CDCl_3$, 200 MHz): ä 2.4 (s, 3H, CH_3 at C-2), 2.65 (s, 3H, CH_3 at C-4), 7.20 (s, 1H, H-3), 8.05 (s, 1H, H-6)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.37, 26.96, 121.71, 124.34, 129.74, 134.50, 146.49, 149.06

IR ($CHCl_3$): 764, 1364, 1568 cm^{-1}

Anal. calcd. for C 51.6, H 4.3, N 7.5; found C 52.0, H 4.93, N 7.58

(2-Chloro-4-nitro)phenyl-1,5-diacetic acid (35)

The foregoing crude aryldimalonate **28** (62 g) was taken in a mixture of 6 N hydrochloric acid (125 mL) and glacial acetic acid (125 mL). The reaction mixture was refluxed for 18 h, cooled to ambient temperature and evaporated *in vacuo* to provide the crude solid, which was recrystallised from ethyl acetate-light petroleum to provide **35** (24 g, 85%) as a light-yellowish solid. [The yield refers to overall yield for two steps]

M.p.: 193-194 C

^{1}H NMR (acetone-d_6, 200 MHz): ä 3.9 (s, 2H, CH_2 at C-2), 4.10(s, 2H, CH_2 at C-4), 7.60 (s, 1H, H-3), 8.15 (s, 1H, H-6).

IR (nujol): 2907, 1685, 1500 cm^{-1}

Anal. calcd. for C 43.87, H 2.93, N 5.12; found C 44.90, H 2.92, N 4.94

1-Chloro-(2,4-dimethoxycarbonylmethylene)-5-nitrobenzene (36)

Thionyl chloride (3 mL, 5.5 mmol) was added dropwise at 0 C to a solution of phenyl diacetic acid **35** (15 g, 55 mmol) in methanol (150 mL) for 5 minutes. The reaction mixture was stirred at room temperature for 4 h. The pure precipitated diester was filtered off. The solution was cooled to 0 °C, neutralized with saturated sodium bicarbonate solution, and concentrated *in vacuo.* The residue was taken in ethyl acetate (50 mL), washed with brine,

dried (anhydrous Na_2SO_4) and evaporated to leave the crude solid, which was recrystallised from methanol. The combined crystalline product gave **36** (15.7 g, 95%) as a light yellowish solid.

M.p.: 107-108 C

^{1}H NMR ($CDCl_3$, 200 MHz): ä 3.70 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.85 (s, 2H), 3.95 (s, 2H), 7.30 (s, 1H, H-3), 8.20 (s, 1H, H-6).

IR (nujol): 1724, 1521, 1420, 1339, 1200, 1164 cm^{-1}

Anal. calcd. for C 47.64, H 3.9, N 4.6; found C 47.64, H 3.9, N 4.6

6-Chloro-5-methoxycarbonylmethylene-2-oxindole (37)

A solution of diester **36** (8 g, 26.5 mmol) in acetic acid (40mL) containing 0.8 g of Raney-nickel was hydrogenated under positive pressure of H_2 (45 psi) for 3 h. Following the catalyst filtration, acetic acid was removed on rotary evaporator to afford the crude solid which was recrystallised from isopropanol to afford **37** (6 g, 94 %) as an orange-tinged solid.

M.p.: 191-192 C

^{1}H NMR (acetone-d_6, 200 MHz): ä 3.70 (s, 2H, lactam CH_2), 3.85 (s, 3H, OMe), 3.95 (s, 2H, CH_2CO), 7.07 (s, 1H, H-4), 7.45 (s, 1H, H-7), 10.72 (s, 1H, NHCO).

IR (nujol): 3100-3250 (br. band), 2907, 2841, 1722, 1676, 1629, 1338, 1319 cm^{-1}

Anal. calcd. for C 55.0, H 4.18, N 5.85; found C 55.08, H 4.63, N 5.64

6-Chloro-5-(2-hydroxyethyl)-2-oxindole (23)

A mixture of sodium borohydride (0.48 g, 12.63 mmol) and lithium bromide (1.1 g, 12.63 mmol) in THF (15 mL) was refluxed for 16 h with vigorous stirring. Oxindole ester **37** (1.5 g, 6.25 mmol) was then added in one lot. The reaction mixture was refluxed for few minutes and then $B(OMe)_3$ (0.06 mL, 0.62 mmol) was added. The reflux was continued for 18 h. The solvent was stripped off and the residue acidified with 3 N sulphuric acid. The

precipitated solid was filtered, and dried to afford **23** (1 g, 75%) as a colourless solid, which was homogeneous by TLC.

M.p.: 178-179 C

IR (nujol): 3300-3350 (br. band), 3158, 2954, 1716, 1631 cm^{-1}

^1H NMR (acetone-d_6, 200 MHz): ä 2.70-2.90 (m, 2H, $PhCH_2$), 3.40 (s, 2H, CH_2CON), 3.60-3.77 (m, 2H, CH_2O), 6.85 (s, 1H, H-4), 7.17 (s, 1H, H-7), 9.3 (br s, 1H, CONH).

EI MS (*m*/*z*): 117 (20), 125 (14), 146 (8), 152 (65), 180 (100), 211 (24) [M^+]

Anal calcd. for C 56.6, H 4.7, N 6.6; found C 56.3, H 5.0, N 6.29

6-Chloro-5-(2-chloroethyl)-2-oxindole (3)

Phenylethanol **23** (1.4 g, 6.6 mmol), triphenylphosphine (2.6 g, 10 mmol) were taken in a mixture of THF (17 ml) and CCl_4 (3 ml). The reaction mixture was refluxed for 3 h. Vacuum evaporation of the solvent and purification of the residue by silica gel column chromatography (50% ethyl acetate in petroleum ether, 60-120 mesh) afforded **3** (1.48 g, 96%) as a light yellowish solid.

M.p.: 222-223 C

IR (nujol): 3226, 2953, 2923, 2853, 1716, 1626, 1480, 1316 cm^{-1}

^1H NMR (acetone-d_6, 200MHz): ä 3.15 (t, J = 7.14 Hz, 2H, $PhCH_2$), 3.45 (s, 2H, CH_2CON), 3.77 (t, 2H, J = 7.14 Hz, CH_2Cl), 6.90 (s, 1H, H-4), 7.10 (s, 1H, H-7), 9.95 (br s, 1H, CONH)

EI MS (*m*/*z*): 89 (4), 117 (11), 152 (57), 180 (100), 183 (42), 229 (18), 231 (11) [M^++1]

6-Chloro-5-(2-touenesulphonyloxyethyl)-2-oxidole (38)

A mixture of phenylethanol **23** (2.7 g, 10.3 mmol), TsCl (2.9 g, 15 mmol), triethylamine (4 mL) and DMAP (50 mg) in CH_2Cl_2 (50 mL) was refluxed for 5 h, concentrated and the residue passed through a silica gel pad (30% ethyl acetate in hexane) to obtain **38** (4.0 g, 85%) as a colourless oil.

^{1}H NMR ($CHCl_3$, 200MHz): δ 2.43 (s, 3H, tosyl CH_3), 3.02 (t, *J* = 4.3 Hz, 2H, CH_2), 3.43 (s, 2H, CH_2CON), 4.22 (t, *J* = 4.3 Hz, CH_2OTs), 6.83 (s, 1H, H-4), 7.1 (s, 1H, H-7), 7.26 (d, *J* = 6.5 Hz, 2H, aromatic), 7.67 (d, *J* = 6.5 Hz, 2H, aromatic) 9.10 (s, 1H, CONH)

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CHAPTER - 3

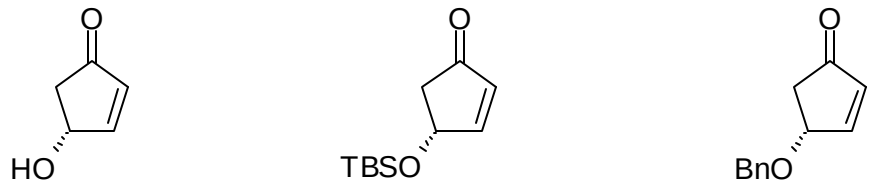
RING CLOSING METATHESIS IN THE SYNTHESIS OF (4*R*)-4-BENZYLOXYCYCLOPENT-2-EN-1-ONE.

INTRODUCTION:

Prostaglandins (PGs) and carbocyclic nucleosides have been regarded as important cyclopentanoid compounds in the arena of chemical biology and medicinal chemistry.[1] PGs exhibit diverse activities in body tissues and cells such as smooth muscle contraction of relaxation, blood platelet aggregation or inhibition of such aggregation, stimulation of uterine activity, inhibition of gastric secretion, and enhancement of secretion of cytoprotective mucous and are now recognized as local harmones for maintaining homeostatis of the circulatory, respiratory, and digestive organs, etc. Several natural PGs and synthetic analogues are now being used as drugs.[2] Some difficulties involved in their therapeutic application include scarce natural productivity, chemical instability, rapid inactivation by enzymatic degradation and non-selective widespread action on most tissues and cells. Biosynthesis does not meet the increasing demand and is also inappropriate for production of medicinally-more cultivated compounds possessing the desired tissue selectivity and higher metabolic stability. A supply of sufficient quantities of natural PGs and artificial analogues relies on efficient and flexible chemical synthesis.

4-Hydroxycyclopent-2-enone and its derivatives (Scheme **1**) are the universal chiral building blocks for prostaglandins and carbocyclic nucleosides to make available in multigram

Scheme **1**

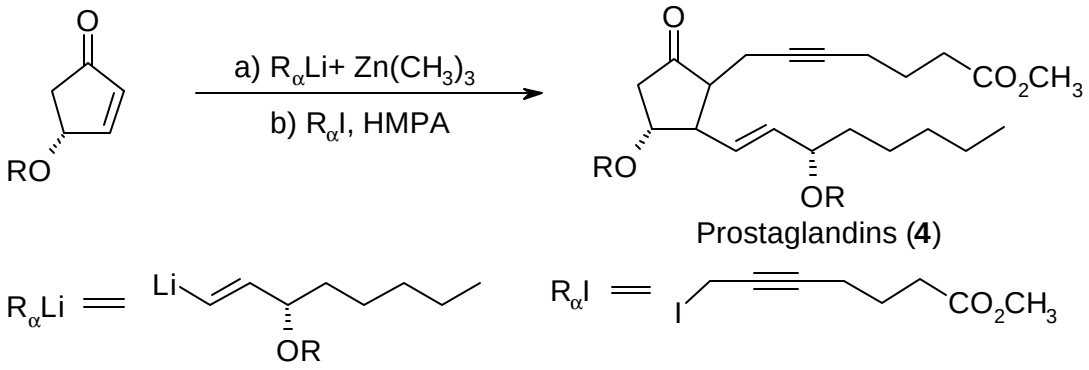


1 **2** **3**

quantities. Out of several synthetic approaches to PGs including the early pioneering efforts of Corey *et al*., three component coupling strategy developed by Noyori is considered the landmark route because of its directness, convergence, flexibility, and amenability to large

scale.[3] This involves the one-pot organometallic-aided initial conjugate addition of an ω-side chain unit to an *O*-protected (*R*)-4-hydroxycyclopenten-2-one followed by the electrophilic trapping of an enolate intermediate by an α-chain organic halide, leading to the whole PG frame work. This tandem conjugate addition/alkylation sequence is a very short route and the desired *trans*, *trans* relative configuration is generated by the internal asymmetric induction. This route serves as a common platform for the synthesis of naturally occuring PGs including PGD1, PGE1, PGE2, $PGF_{1\alpha}$, $PGF_{2\alpha}$ and also therapeutically useful unnatural prostaglandin and prostacyclin analogues, e.g., misoprostol used for the prevention of gastroduodenal ulcer.

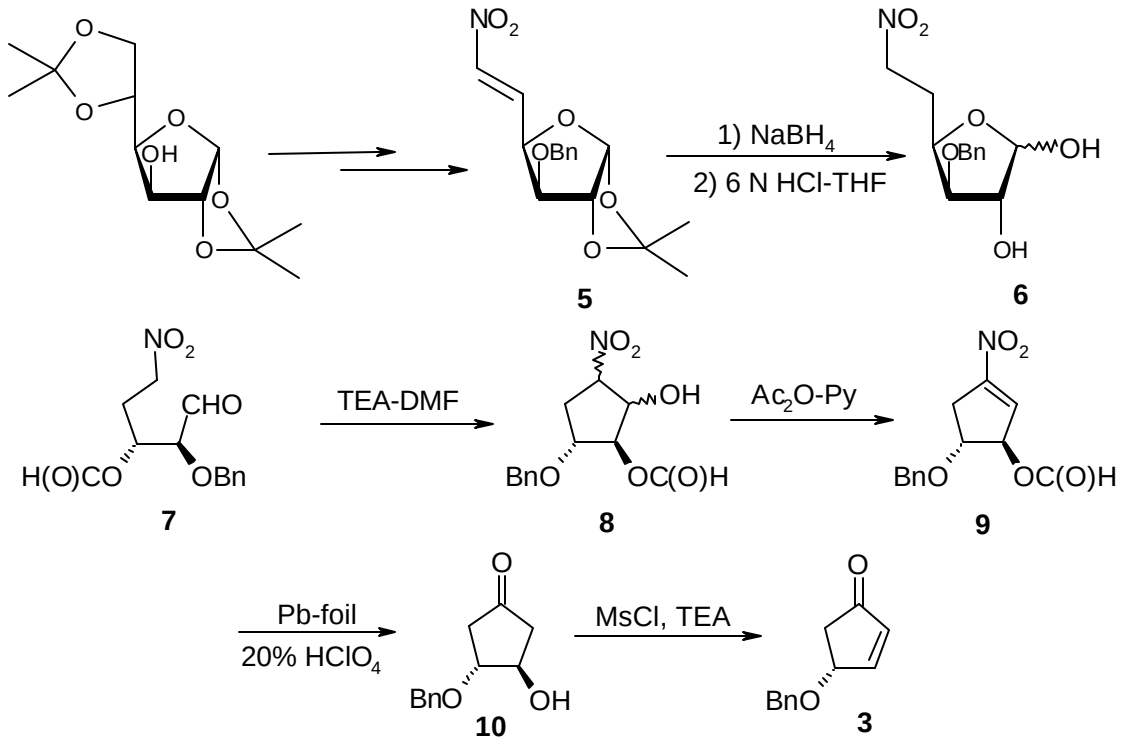
Scheme **2**



As a result, several synthetic routes have been put forward to secure the important building blocks, cyclopentanones (scheme **1**), known for either methodology-specificity or economical feasibility. Initial efforts to obtain these compounds in enantiomerically pure form involved the chemical modification of D-tartaric acid, degradation of fungal metabolite terrain, ring contraction of 2,4,6-trichlorophenol with resolution, chromatography of diastereomers of chiral chromatography of racemic 4-hydroxy derivatives and a multi-step conversion from glucose.[4] The lattest method is to desymmetrise the meso epoxide through hydrolytic kinetic resolution of meso epoxides.[5] However, the enzymatic desymmetrisation of *cis*-3,5-diacetoxycyclopent-1-ene is by far the most efficient method in case of both economic viability and suitability for multigram scale with high enantioselectivity.[6]

Two synthetic processes have been reported for the enone (**1**) till date. The first synthesis aims at chiron approach for asymmetry with nitro-aldol reaction as key step.[7] Thus, the known nitroalkene (**5**), accessible from diacetone-D-glucose was subjected to reduction with $NaBH_4$ followed by deprotection of acetonide with dilute HCl to provide the intermediate (**6**). Oxidative fission of **6** with $NaIO_4$ generated the desired aldehyde (**7**), which on nitro-aldol condensation with triethylamine in DMF afforded nitrocyclopentanol (**8**). Dehydration of **8**

Scheme **3**

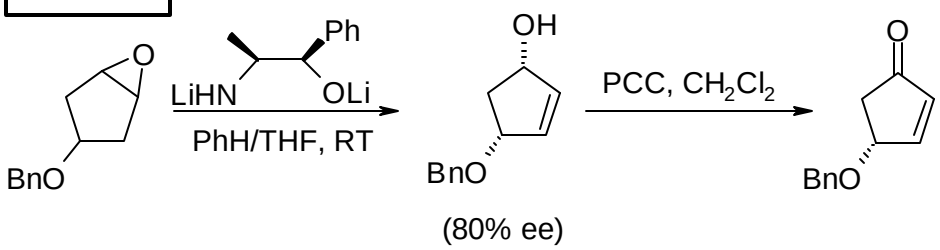


with Ac_2O in pyridine gave the nitro-olefin (**9**), which on stirring with 20% $HClO_4$ in the presence of Pb coil gave the hydroxycyclopentanone derivative (**10**). The required enone (**3**) was obtained on dehydration with $MeSO_2Cl$ and TEA.

The second strategy capitulates on the asymmetric deprotonation/rearrangement of 4-substituted cyclopentene oxides to cyclopentenols (Scheme **4**).[8] Thus, 4-benzyloxy-1,2-cyclopentene oxide (**11**) was treated with dilithiated (1*R*,2*S*)-norephedrine at 0 ^oC to provide

the rearranged allyl alcohol (**12)** (*ee* 80%). The allyl alcohol was then oxidized with PCC in CH_2Cl_2 to give the target enone **3**. This route is concise, although there is scope to improve the enantioselectivity during the aymmetric protonation step.

Scheme **4**

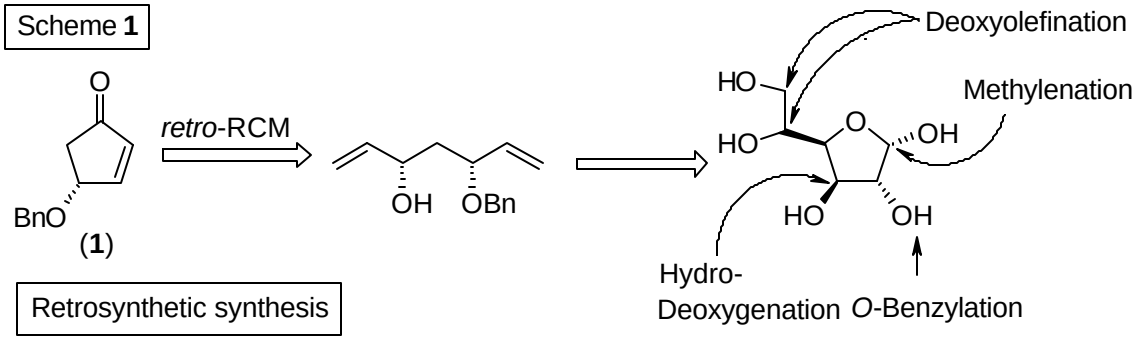


(80% ee)

11 **12** **3**

PRESENT TEXT

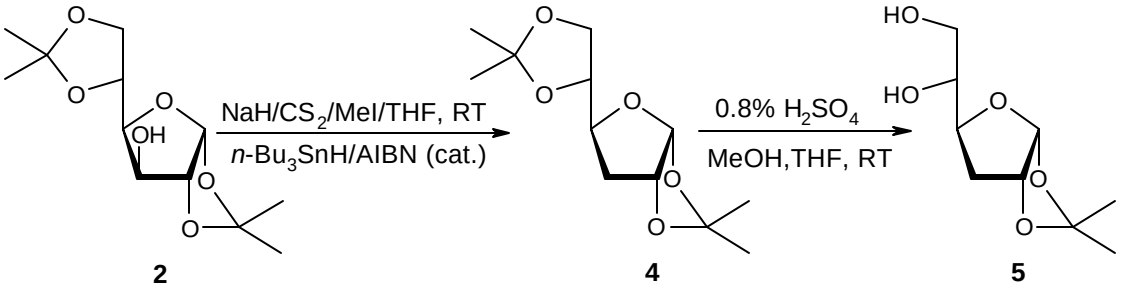
The importance of hydroxycyclopent-2-en-1-one derivatives to synthesise compounds of medicinal significance and natural products, as deliberated in the preceding section, should constitute the strong drive to undertake rapid and efficient synthesis to the value-added intermediate (**1**) by utilizing the new advances in synthetic methodologies, especially, for C-C bond formation. "Conversion of carbohydrates to carbocycles" has prevailed as one of the thematic strategies in organic synthesis. Accordingly, our synthetic strategy for this intermediate hinges on the RCM as key transformation for carbocycle construction, while envisaging the required chiral diene precursor to arise from the chiral source D-glucose through a series of manipulative transformations as depicted in scheme **1**.



In the relevance of disconnection program, pointing D-glucose out as the starting material, diacetone-D-glucose (**2**) was converted to its corresponding xanthate derivative with $NaH/CS_2/MeI$ in THF at ambient temperature in 92% yield. The ^1H NMR spectrum confirmed the presence of xanthate group (a singlet at δ 2.62 ppm due to SCH_3) and the other features, *viz*., the isopropylidene groups (singlets at the region of δ 1.3-1.59 accounting for four CH_3 groups) and H-1 (doublet at 5.90 ppm). The xanthate was then deoxygenated under Barton-McCombie protocol (*n*-Bu_3SnH/AIBN (catalytic)/toluene, reflux) to provide the 3-deoxyglucose derivative (**4**) in 94% yield.[9] This was clearly conveyed in the

^{1}H NMR spectrum by the resonances due to methylene group (a multiplet between δ 1.64-1.8 and a doublet of doublet between 2.12-2.26 ppm). Regioselective monohydrolysis of 5,6-*O*-isopropylidene group in **4** with 0.8% H_2SO_4 in a mixture of MeOH and THF at ambient temperature provided the diol (**5**) in 75% yield. The ^{1}H NMR spectrum indicated the presence of only one acetonide (two singlets, two CH_3) and two free hydroxyl groups (2 br s, between δ 2.42-2.56 and 2.7-2.9 ppm).

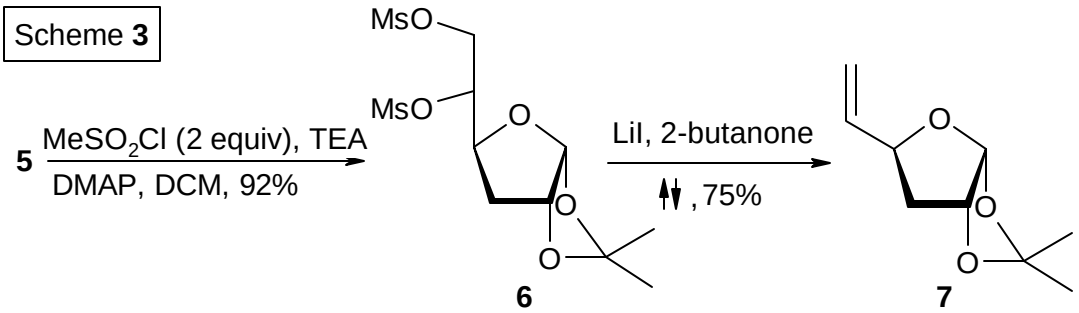
Scheme **2**



2 **4** **5**

The compound **5** was then transformed to 5,6-ene derivative (**7**) following the two-step procedure reported by Jones *et al.*[10] Thus, the diol was converted to its dimesylate ester (**6**) under routine conditions using $MeSO_2Cl$ (2 equiv.)/TEA/DMAP (catalytic) in CH_2Cl_2 at ambient temperature in 92% yield. This dimesylation was confirmed by the ^{1}H NMR spectrum in which the resonances due to CH_3SO_2 groups (two singlets at δ 3.06 and 3.1 ppm, two CH_3)

Scheme **3**



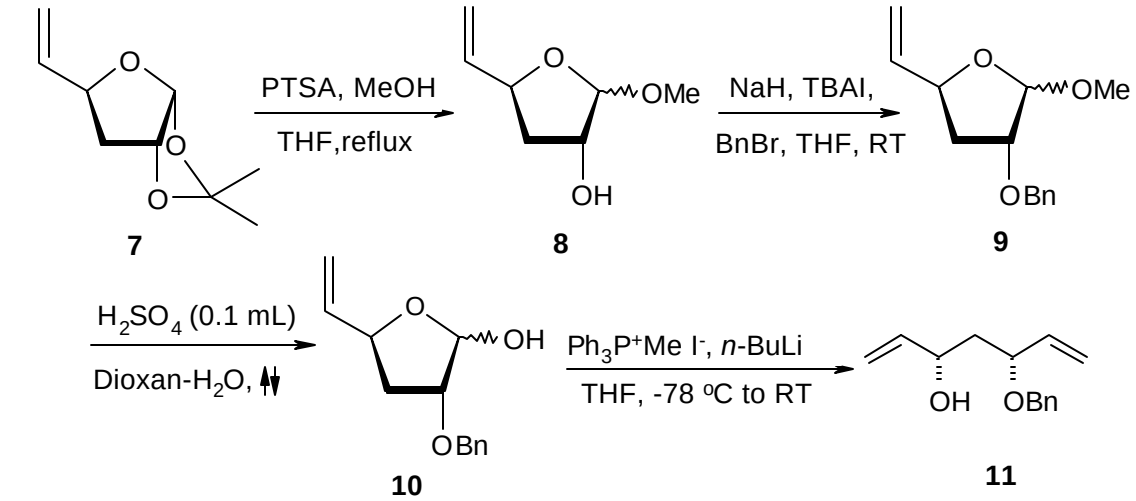
6 **7**

and downfield shift of peaks due to H-5 and H-6 protons, compared to that of starting material were observed. Exposure of **6** to excess of LiI in boiling 2-butanone smoothly effected the elimination to give the desired ene (**7**) in 70% yield. The chemical shifts at the region of 5.12-

5.4 (multiplet due to CH_2=) and 5.72-5.92 (multiplet due to CH=) were the strong evidences for terminal olefin in product **7**. The next endeavour was to derive the second double bond of diene derivative in advance of ring closing metathesis.

Deprotection of 1,2-*O*-isopropylidene group in **7** with catalytic PTSA in a solvent mixture of MeOH and THF under reflux conditions afforded the anomeric mixture of methyl furanoside (**8**) in 75% yield. The disappearance of peaks due to isopropylidene group and a new peak at 3.4 ppm (singlet, OMe group) in the ^{1}H NMR spectrum evidently indicated the product formation. The free hydroxyl group at C-2 position in **8** was then protected as its benzyl derivative (**9**) on treatment with benzyl bromide, NaH, and *n*-$Bu_4N^+I^-$ (catalytic) in THF at ambient temperature in 88% yield. The ^{1}H NMR spectrum showed the peaks pertaining to benzylic protons at the region of δ 4.5-5.0 ppm whereas the aromatic protons between 7.2- ppm, indicating the *O*-benzyl group. The hydrolysis of furanoside **9** with catalytic H_2SO_4 in a

Scheme **4**

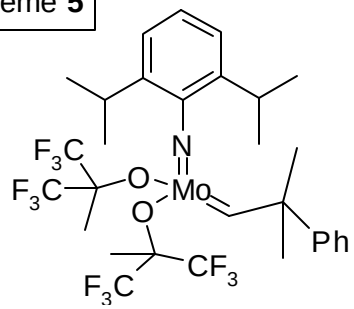


solvent mixture of 1,4-dioxane and water at 100-110 ^oC gave the glycal derivative (**10**) as a mixture of anomers in 87% yield. The ^{1}H NMR spectrum indicated the absence of OMe groupwhereas the other relevant signals remained intact at the expected chemical shifts. Witting methylenation of **10** with incipient methylenetriphenylphosphorane generated *in situ*

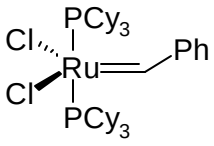
from $CH_3P^+Ph_3I^-$ and *n*-BuLi in THF at −78 °C to RT gave the requisite heptadiene intermediate (**11**) in moderate yield. This readied the substrate for RCM. The structure of acyclic diene was elucidated from the ^1H NMR and mass spectral analysis. The ^1H NMR spectrum indicated presence of two olefinic groups at the region of δ 5.05-5.45 (two CH_2=) and 5.65-5.95 (two CH=), while the EI mass recorded the highest mass peak at 219 (M^+).

Ring closing metathesis has emerged as an attractive tool among synthetic chemists for C=C bond formation.[11] The field has reached to the matured level because of the steadfast advances in recent years. The exotic reasons attributable to this are: i) well defined, stable and highly active catalysts ii) very high TON in the catalytic reaction iii) efficacy in medium to macro-ring cyclisation iv) its superiority over other cyclisations like Diels-Alder, macrolactonisation, etc., because of favourable thermodynamic profile v) adaptability for both

Scheme **5**



Schrock catalyst (**12**)



Grubbs' catalyst (**13**)

solution phase and solid phase reactions vi) availability of polymer bound catalysts vii) water soluble catalysts enabling the metathesis in water and methanol viii) applicability to broad scope of substrates like ene-yne and yne-yne metathesis, in addition to tri- and tetra-substituted systems ix) ecosafety profile including viability in solvents like $ScCO_2$ and x) compatibility to various functional groups xi) combinatorial RCM libraries. The pioneering efforts of Schrock and Grubbs led to the introduction of their respective catalysts (**12**) and (**13**) which find widespread use now-a-days, although the discovery and development of new and robust catalysts is presently a hot-pursuit.[12] This reaction has changed the strategy of synthetic

chemists and it is very common to find RCM as key transformation in the recent total syntheses of natural products, esp., for ring construction.

The postulated mechanism involves an iterative process of [2+2] cycloaddition and cycloreversion between the olefins, metal alkylidene and metallocyclobutane species (scheme **6**). The initial retro-type intermolecular [2+2] cycloaddition between the catalyst and one of

Scheme **6**

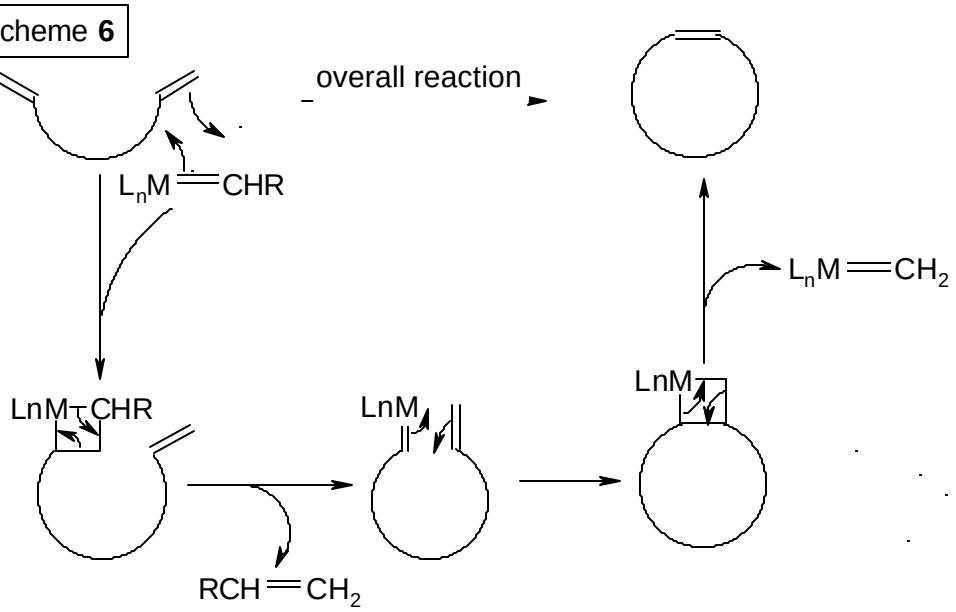


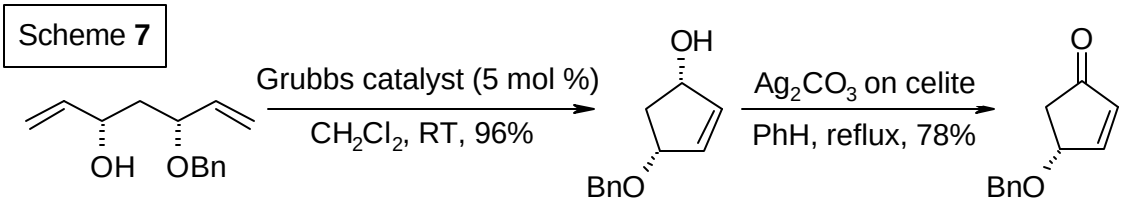
Fig. Ring Closing Metathesis Mechanism

the olefins of diene leads to the incorporation of the metal alkylidene in the substrate. The second cycloaddition takes place in a facile intramolecular fashion and ring opening of resulting metallocyclobutane leads to the cycloalkene and regeneration of the catalyst. In the first turn of the cycle, the volatile nature of the alkene by-product (the gaseous ethene in most cases) tends the reaction to proceed forward thermodynamically.

Ring closing metathesis of **11** on exposure to Grubbs' catalyst (5 mol%) in CH_2Cl_2 at ambient temperature uneventfully gave the desired product cyclopentenol (**14**) in 96% yield. The ^1H NMR spectrum indicated the signals accounting for only two internal olefinic protons and the absence of peaks belonging to terminal olefinic protons, thereby confirming the ring closure. It is interesting to note that no allylic isomerisation was observed

in this RCM step though allyl alcohols are prone to such transformation via intramolecular redox hydrogen transfer leading to ethyl ketones.[13] It is pertinent to mention that the cyclopentenol (**14**) itself has served as chiral building block to many natural products, including cyclopentanoids (taking advantage of oraganopalladium chemistry).[14] The last step was the allylic oxidation of **14**, which was conveniently accomplished with Fetizone's reagent (Ag_2CO_3 in celite) in boiling benzene to afford **1** in 78% yield.[15] The structure of **1** was substantiated by the ^1H NMR, EI and HRMS spectral analysis. The characteristic features in the ^1H NMR spectrum, the absence of signals due to H-5, downfield shift of peaks due to methylene protons to the region of δ 2.3-2.78 ppm and relocation of olefinic protons (H-1 at δ

Scheme **7**



11 **14** **1**

7.25 as doublet and H-2 at 7.6 ppm as a doublet of doublet)-all confirmed the structure. The highest mass peak in FABMS was recorded at (*m/z*) 189 indicating the molecular ion. (HRMS: Calcd for [$C_{12}H_{13}O_2$-M^+]: 189.0915. Found: 189.0911).[16]

SUMMARY:

In conclusion, a stereospecific route to (*R*)-4-benzyloxy-2-cyclopenten-1-one, an important chiral progenitor for prostaglandin and carbocyclic nucleosides has been demonstrated taking advantage of chiral pool to inherit the chirality and ring closing metathesis to construct the carbocycle. Undoubtedly, this synthesis articulates the versatility of RCM in the C-C bond formation. The limitations of the scheme include multi-step synthesis and non-viability to large scale.

EXPERIMENTAL SECTION

3-Deoxy-1,2:5,6-*O*-isopropylidene-a -D-glucofuranoside (4)

To a solution of diacetone-D-glucose **2** (2.0 g, 7.7 mmol) in THF (30 mL) at 0 ^{o}C, NaH (0.3 g, 7.7 mmol) was added. After being stirred for 30 minutes, carbon disulphide (0.5 mL, 7.7 mmol) was added. After an interval for 30 minutes, MeI (0.5 mL, 7.7 mmol) was added. The reaction mixture was stirred for 1 h [TLC: 30% ethyl acetate in hexane], quenched with water and evaporated to leave the residue, which was taken in ethyl acetate. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated to afford the crude, which on column silica gel chromatography (20% ethyl acetate in hexane) gave **3** (2.5 g, 92%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3-1.6 (3s, 12H, 4 x CH_3), 2.62 (s, 3H, SCH_3), 4.0-4.44 (m, 2H), 4.26 (m, 2H), 4.64 (d, *J* = 4.1 Hz, 1H), 5.9 (s, 2H, H-1, H-3)

To a solution of xanthate **2** (2.5 g, 7.01 mmol) and AIBN (40 mg) in toluene (25 mL), TBTH (2.23 mL, 7.01 mmol) was added dropwise. The reaction mixture was refluxed for 24 h, concentrated *in vacuo* and purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford **4** (1.64 g, 94% yield) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.34, 1.42, and 1.5 (4s, 12H, 4 x CH_3), 1.64-1.82 (m, 1H, H-3), 2.19 (dd, *J* = 3.6, 12.5 Hz, 1H, H-3'), 3.73-3.9 (m, 1H), 3.98-4.2 (m, 3H), 4.72 (t, *J* = 4.5 Hz, 1H), 5.78 (d, *J* = 4.1 Hz, H-1).

$[\alpha]_D$ –7.4^{o} (c 1.2, $CHCl_3$); lit.[17] $[\alpha]_D$ –7.5^{o} (c 1.0, $CHCl_3$)

3-Deoxy-1,2-*O*-isopropylidene-a -D-glucofuranoside (5)[17]

The compound **4** (1.6 g, 6.5 mmol) was stirred with 0.8% H_2SO_4 (1 mL) in methanol (16 mL) at ambient temperature for 10 h. After neutralization with solid $NaHCO_3$, the reaction

mixture was filtered, concentrated and the residue purified by silica gel column chromatography (10% methanol in chloroform) to afford **5** (1 g, 75%) as a colourless solid.

M.p.: 81-82 ^{o}C; lit.[17] 84 ^{o}C

$[\alpha]_D$ −14.0^{o} (c 1.2, $CHCl_3$); lit.[17] $[\alpha]_D$ −15.3^{o} (c 1.5, EtOH)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.3 and 1.5 (2s, 6H, 2 x CH_3), 1.73-1.96 (m, 1H, H-3), 2.06 (dd, *J* = 4.3, 13.8 Hz, 1H, H-3'), 2.43-2.6 and 2.72-2.90 (2 br s, 2H, 2 x OH), 3.5-3.78 (m, 2H), 3.82-3.95 (m, 1H), 4.13-4.27 (m, 1H), 4.73 (t, *J* = 3.4 Hz, 1H), 5.79 (d, *J* = 3.4 Hz, 1H, H-1)

3-Deoxy-5,6-di-*O*-methanesulphonyl-1,2-*O*-isopropylidene-α-D-glucofuranoside (6)

To a solution of **5** (2.7 g, 13.1 mmol), triethylamine (3.65 mL, 26.2 mmol), and DMAP (0.16 g, 1.31 mmol) in CH_2Cl_2 (20 mL) was added a solution of methanesulphonyl chloride (1.12 mL, 14.5 mmol) in CH_2Cl_2 (5 mL) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 1 h [TLC: 40% ethyl acetate in hexane], washed with water and brine, dried (Na_2SO_4), and concentrated on rotavapor. The residue on purification by silical gel chromatography (30% ethyl acetate in hexane) gave **6** (4.7 g, 92%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31 and 1.5 (2s, 6H, 2 x CH_3), 1.85-1.98 (m, 1H, H-3), 2.38 (dd, *J* = 4.3, 13.8 Hz, 1H, H-3'), 3.06 and 3.10 (2s, 6H, 2 x CH_3SO_2), 4.24-4.39 (m, 2H, H-2), 4.51 (dd, *J* = 3.2, 11.7 Hz, 1H), 4.74 (t, J = 4.3 Hz, 1H), 4.8-4.9 (m, 1H), 5.77 (d, J = 3.2 Hz, 1H, H-1)

3-Deoxy-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-ribohex-5-enofuranoside (7)

A mixture of compound **6** (4.75 g, 13.1 mmol) and LiI (8.8 g, 65.7 mmol) in dry 2-butanone (50 mL) was refluxed for 8 h. The dark brownish solution was concentrated. The residue was diluted with ethyl acetate washed successively with saturated sodium thiosulphate solution, water and brine, dried (Na_2SO_4), and concentrated. The crude was purified by silica gel column chromatography (5% ethyl acetate in hexane) to give **7** (1.54 g, 70%) as a colourless oil.

$[\alpha]_D$ -18.4 (c 5.9, $CHCl_3$)

^1H NMR ($CDCl_3$, 200 MHz): δ 1.31 and 1.52 (2s, 6H, 2 x CH_3), 1.55-1.68 (m, 1H, H-3), 2.17 (dd, *J* = 4.7, 14.0 Hz, 1H, H-3'), 4.6 (qui, *J* = 5.8 Hz, 1H, H-4), 4.71 (t, *J* = 4.2 Hz, 1H, H-2), 5.12-5.4 (m, 2H, CH_2=), 5.72-5.92 (m, 2H, H-1, CH=)

Methyl 3-deoxy-5,6-dideoxy-D-ribohex-5-enofuranoside (8)

A solution of compound **7** (1.23 g, 7.2 mmol), PTSA (catalytic) in a solvent mixture of MeOH and THF (10 mL each) was heated to reflux overnight. Triethylamine (excess) was added to neutralize PTSA and the stirring continued for 30 minutes. Evaporation of the solvent and purification of the crude by silica gel column chromatography (30% ethyl acetate in hexane) afforded **8** (0.8 g, 75%) as an oil.

^1H NMR ($CDCl_3$, 200 MHz): δ 1.76-1.9 (br s, 1H, OH), 1.9-2.2 (m, 2H, H-3, 3'), 3.41 (s, 3H, OMe), 4.3 (d, J = 5.7 Hz, 1H, H-2), 4.7-4.9 (m, 2H, H-1, H-4), 5.1-5.4 (m, 2H, CH_2=), 5.76-5.97 (m, 1H, CH=).

Methyl 2-*O*-benzyl-3-dexoy-5,6-dideoxyribo-D-hex-5-enofuranoside (9)

Sodium hydride (0.23 g, 5.7 mmol) was added to a solution of **8** (0.7 g, 4.8 mmol) in THF (20 mL) at 0 ºC. After being stirred for 30 minutes, benzyl bromide (0.63 mL, 5.28 mmol) and *n*-$Bu_4N^+I^-$ (0.18g, 0.48 mmol) were successively added to the resulting suspension. The reaction was stirred for 6 h. The solvent was evaporated *in vacuo* and the residue taken in ethyl acetate (50 mL). The organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated. The residue on purification by silica gel chromatography (10% ethyl acetate in hexane) gave **9** (0.82 g, 88%) as an oil.

^1H NMR ($CDCl_3$, 200 MHz): δ 1.78-1.95 (m, 1H, H-3 [β]), 2.16 (dd, *J* = 6.8, 13.7 Hz, 1H, H-3' [α]), 3.33 (s, 3H, OMe), 3.97 (d, *J* = 4.54 Hz, 1H, H-2), 4.50-4.80 (m, 3H, H-4, OCH_2Ph), 5.04-5.3 (m, 3H, H-1, CH_2=), 5.7-5.9 (m, 1H, CH=), 7.2-7.4 (m, 5H, aromatic)

2-*O*-Benzyl-3-deoxy-5,6-dideoxyribohex-5-eno-D-furanoside (10)

A solution of **9** (0.9 g, 3.97 mmol) and concentrated H_2SO_4 (2 drops) in a solvent mixture of water (1.5 mL) and dioxane (15 mL) was refluxed for 12 h. After the evaporation of the solvent, the residue was taken in ethyl acetate (25 mL), washed with aqueous $NaHCO_3$ solution, water and brine, dried (anhydrous Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (15% ethyl acetate in hexane) to afford **10** (0.7g, 87%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.7-2.28 (m, 2H, H-3, 3'), 2.9-3.4 (br s, 1H, OH), 3.52-3.7 (br s, 1H, OH), 3.9-4.1 (m, 1H, H-2), 4.46-4.8 (m, 3H, OCH_2Ph, H-4), 5.06-5.46 (m, 3H, CH_2=, H-1), 5.68-5.97 (m, 1H, CH=), 7.2-7.4 (m, 5H, aromatic)

(3*S*,5*R*)-5-*O*-Benzyl-1,6-heptadien-3-ol (11)

n-BuLi (4.6 mL, 6.8 mmol, 1.5 M solution in hexane) was added at 0 °C to methylenetriphenylphosphonium iodide (2.8 g, 6.8 mmol) in THF (20 mL). The resultant yellowish solution was stirred for 10 min and cooled to -78 °C. A solution of **10** (0.5 g, 2.3 mmol) in THF (9.5 mL) was then added. After being stirred at −78 °C for 1 h, the reaction mixture was gradually warmed to room temperature. After quenching with saturated NH_4Cl solution, the solvent was evaporated and the residue taken in ethyl acetate. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue on silica gel chromatography purification gave **11** (0.3 g, 60%) as a colourless oil.

$[\alpha]_D$ +26.4° (c 1.2, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.6-1.98 (m, 2H, H-4, H-4'), 3.4 (br s, 1H, OH), 4.06 (dt, *J* = 4.5, 9.1 Hz, 1H, H-5), 4.26-4.35 (m, 1H, H-3), 4.38 (d, J = 11.2 Hz, 1H, one of CH_2Ph) 4.64 (d, *J* = 11.2 Hz, 1H, one of CH_2Ph), 5.02-5.35 (m, 4H, 2 x CH_2=), 5.67-5.94 (m, 2H, 2x CH=), 7.29-7.4 (m, 5H, aromatic)

(1*R*, 4*S*)-4-benzyloxycyclopent-2-en-1-ol (14)

A solution of diene **11** (0.24 g, 1.1 mmol) and Grubbs' catalyst (90 mg, 0.11 mmol) in CH_2Cl_2 (100 mL) was stirred for 6 h at ambient temperature. The solvent was evaporated *in vacuo* and the residue purified on silica gel column chromatography (20% ethyl acetate in hexane) to give **14** (0.29, 96%) as oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.68 (dt, *J* = 4.54 Hz, 19.3 Hz, 1H, H-5 [β]), 1.95-2.09 (br s, 1H, OH), 2.57-2.75 (m, 1H, H-5' [α]), 4.4-4.7 (m, 4H, H-1, H-4, CH_2O), 6.05 (s, 2H, olefinic), 7.28-7.4 (m, 5H, aromatic).

(*R*)-4-Benzyloxycyclopent-2-en-1-one (1)

A mixture of **14** (0.6 g, 3.2 mmol) and Ag_2CO_3 on celite (2.8 g, 0.6g ~ 1 mmol) in benzene (20 mL) was heated to reflux for 6 h. Filtration over celite pad, evaporation of the filtrate and subsequent purification of the residue by silica gel chromatography (10% ethyl acetate in hexane) gave **1** (0.46 g, 78%) as an oil.

$[\alpha]_D$ +77.0 (c 1.1, $CHCl_3$); lit. $[\alpha]_D$ +42.0 (c 0.9, $CHCl_3$) and $[\alpha]_D$ +22.0 (c 0.9, $CHCl_3$) for 80% ee.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.36 (dd, *J* = 3.75, 17.5 Hz, 1H, H-5 [β]), 2.7 (dd, *J* = 6.3, 17.5 Hz, 1H, H-5 [α]), 4.55-4.70 (m, 2H, OCH_2Ph), 4.75-4.85 (m, 1H, H-4), 6.25 (d, *J* = 6.3 Hz, 1H, H-2), 7.35 (m, 5H, aromatic), 7.6 (dd, *J* = 1.25, 6.25 Hz, 1H, H-3)

FAB MS (m/z): 27 (56), 41 (77), 55 (81), 69 (53), 91 (100), 107 (33), 123 (15), 154 (11), 189 (15) (M^+)

HRMS: Calcd. for ($C_{12}H_{13}O$-M^+): 189.0916. Found: 189.0911.

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List of Publications and Patents:

- **Synthesis of (4R)-4-benzyloxycycopent-2-en-1-one and 2,7-Dioxabicyclo [4.3.0] non-4-enes by ring closing metathesis of carbohydrate precursors.**
  Gurjar, M. K.; **Murugaiah, A. M. S.**; Cherian, J.; Chorghade, M. S.
  Carbohydrate Letters 1999, 3(5), 343
- **Synthesis of (2S,5S)-trans- 5- (4-fluorophenoxymethyl)-2-(1- N- hydroxyureidyl-3-butyn-4-yl)tetrahydrofuran–(CMI-977)**
  Chorghade, M. S.; Gurjar, M. K.; Adhikari, S.; Sadalpure, K.; Lalitha, S. V. S.; **Murugaiah, A. M. S.**; Radhakrishna, P.
  Pure Appl. Chem. 1999, 71(6), 1071
- **A carbohydrate route to CMI-977: A potent 5-Lipoxygenase inhibitor**
  Chorghade, M.S.; Sadalpure, K.; Adhikari, S.; Lalitha, S.V.S.; **Murugaiah, A. M. S.**; Radhakrishna, P.; Reddy, B. S.; Gurjar, M. K.
  Carbohydrate Letters,1999 (In Press)
- **Methods for the synthesis of substituted tetrahydrofuran compounds .**
  Chorghade, M .S.; Gurjar, M. K; Adhikari, S; Sadalapure, K.; Lalitha, S.V.S; **Murugaiah, A. M. S.** ; Radhakrishna, P.
  U S Patent application No. 60/091,709, July 3, 1998.
- **Substituted Oxygen alicyclic compounds, including methods for synthesis thereof :**
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  US Patent application No. 60/091,694, July 3, 1998.
- **Bis dealkoxycarbonylation of nitroaryl malonates: A facile entry to alkylated nitroaromatics.** Gurjar, M. K. ; Reddy, D. P. S. ; **Murugaiah, A. M. S.**
  Synthesis ,2000,0000.
- **Applications of catalytic organic reactions in fine chemicals and pharmaceuticals**. Gurjar, M. K.; Hotha, S.; **Murugaiah, A. M. S.**
  La Industria Chimica. (Communicated as review)