STUDIES ON THE SYNTHESIS OF SOME BIOLOGICALLY ACTIVE HETEROCYCLIC COMPOUNDS

「生物活性を持つ複素環化合物の合成研究」

5

A DISSERTATION

SUBMITTED TO THE UNIVERSITY OF TOKYO IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DOCTOR OF PHILOSOPHY.

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DEPARTMENT OF APPLIED BIOLOGICAL CHEMISTRY

THE UNIVERSITY OF TOKYO

BALARAM ROY

DEDICATED

TO

MY SWEET DAUGHTER

BARNINI ROY

ACKNOWLEDGEMENTS

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With great respect in this moment, I memorized my two grand fathers Late Jogendra Lal Roy and Late Rebati Mohon Saha for their great interest and encouragement about higher study from my boyhood education.

At the end all praise goes to the almighty, the most magnificient and merciful.

CONTENTS

ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
An	acetone
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Bz	benzoyl
CAN	cerium ammonium nitrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminium hydride
DEAD	diethyl azidodicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
Gal	galactose
Glu	glucose
IR	infra red
KHMDS	potassium hexamethyldisilazide
K-Selectride	potassium tri-*sec*-butylborohydride
LAH	lithium aluminium hydride
L-Selectride	lithium tri-*sec*-butylborohydride
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Ms	methanesulfonyl

NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine N-oxide
NMP	*N*-methylphthalimide/N-methylpyrrolidine
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
Super Hydride	lithium triethylborohydride
TBS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetyl
TFSA	trifluorosulfonic acid
THF	tetrahydrofuran
TIPSCl	1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
TMS	trimethylsilyl
tol	toluene
p-TsOH	*p*-toluenesulfonic acid

GENERAL INTRODUCTION

Depending on the isolation technique, a lot of naturally occurring compounds have been already isolated from the different plants, animals or microbial sources due to their greater biological interest. Our conclusion is that synthetic chemistry is one of the most efficient way to know the proper chemistry of those naturally occurring compounds. That's why, R.B.Woodward[1] commented that there are excitement, adventure and challenge and there can be great art in organic synthesis. The ultimate goal of organic synthesis is to assemble a given organic compound, i.e a target molecule, usually via a combination of atoms from the following group of elements; C, H, O, N, S, P and halogens and from readily available starting materials and reagents in the most efficient way. Thus, science of organic synthesis is constantly enriched by new inventions and discoveries pursued deliberately for their own sake or as subgoals within a program directed towards the synthesis of a target molecule. Organic chemistry has a long history that can be traced back to anicent times, although at first it was not recognized as such, because it was practiced randomly and heuristically. As a science, organic synthesis is relatively young, its beginning being marked by the rational synthesis of urea (**1**) by Wöhler[2] in 1828. This synthesis was followed by other milestones, such as the synthesis of acetic acid (**2**) by Kolbe[3] in 1845, glucose (**3**) by Fischer[4] in 1890, α-terpineol (**4**) by Perkin[5] in 1904, camphor (**5**) by Komppa[6,7] in 1903 and in 1909, pyridoxin hydrochloride (**6**) by Folkers[8] in 1939 and quinine (**7**) by Woodward and Doering[9] in 1944.

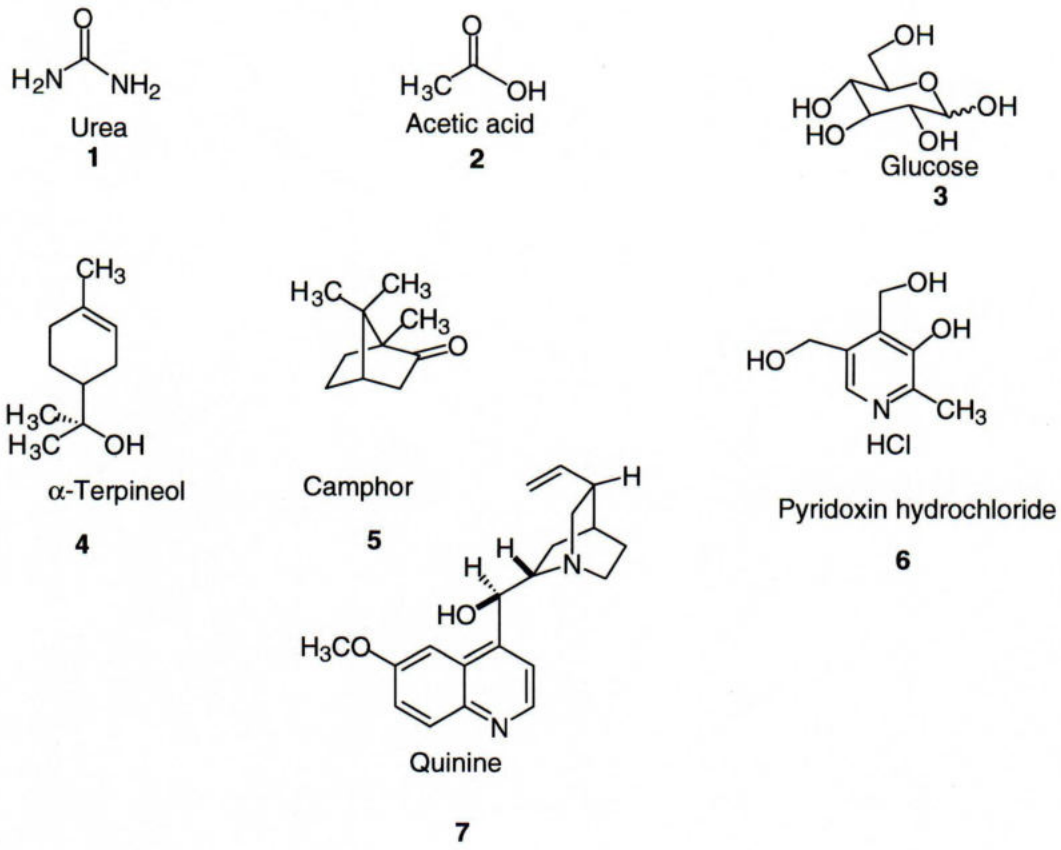


Fig-1: Selected landmark total synthesis of natural products from 1828 to 1944.

In true sense, synthetic organic chemistry deals with the following criteria;

1) Invention of an efficient new synthetic route.

2) Synthesis of molecules which are biologically active having medicinal, pharmacological or also agricultural importance.

3) Preparation of biologically active compounds by low cost and also by shorter way.

4) Discovery and creation of new artificial substances having significant role compared with natural substances.

5) To find out a effective method and also suggest for industrial scale preparation of that compound.

6) To know the biological phenomena or physiological functions at molecular level.

7) To know the proper stereochemistry and also to determine the absolute configurations of the

synthetic compounds.

In this connection, my research interest has grown in synthetic organic chemistry and I chose my research area for " Studies on the synthesis of some biologically active heterocyclic compounds".

In the way of study, my manuscript is devided into two chapters:

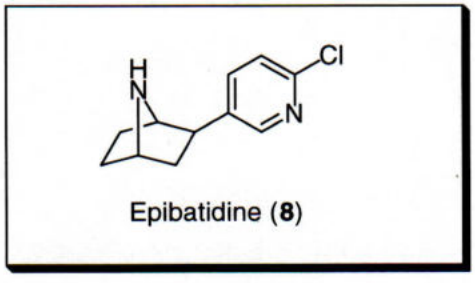
Chapter 1: Studies on the Synthesis of Epibatidine and its Analogs.

Chapter 2: Attempt for Studies on the Synthesis of Allosamidin Analogs.

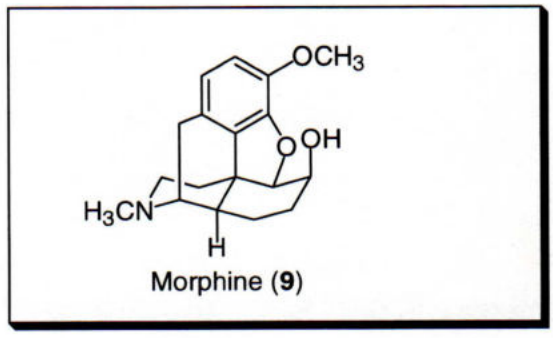
CHAPTER - 1: STUDIES ON THE SYNTHESIS OF EPIBATIDINE AND ITS ANALOGS

1-1. INTRODUCTION

Epibatidine (**8**), a new class of amphibian alkaloid, was islotated by Daily and co-workers[10] in 1992 in a trace amount (ca. 1 mg from 750 frogs) from the skin extract of the Ecuadorian poison frog (Fig-2), *Epipedobates tricolor,* the family Dendrobatidae. This alkaloid contains 7-azabicyclo[2.2.1]-heptane skeleton and has been reported to be a highly potent non-opioid analgesic. In preliminary test on mice, epibatidine proved to be 200 to 500 times as effective as morphine (**9**) in analgesic effect.[11] Subsequent studies showed that the analgesic activity of epibatidine is attributed to its distinctive property as an extremely potent agonist of the nicotinic acetylcholine receptor.[12-14] Although the substance is toxic,[15] it does serve as a lead compound in the development of drugs[16] for pain relief as well as for treatment of disorders whose pathogenesis involves[17] nicotonic receptors. The unique feature of this alkaloid is the presence of a strained nitrogen bridged six-membered carbon ring system (7-azabicyclo[2.2.1]heptane) with an *exo*-oriented 3-(6-chloropyridyl) substituent, which was first recognized as a component of the natural product.



Epibatidine (**8**)



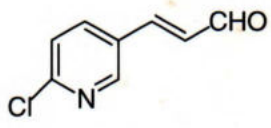
Morphine (**9**)

Fig-2 : Ecudorian poison frog (picture was taken from internet)

Due to its unique structure, outstanding pharmacological action and also related biological interest and scarcity in nature, the alkaloid (**8**) has prompted to extensive synthetic efforts towards its total synthesis. A number of syntheses of epibatidine have already been reported in the previous years in both racemic and also enantiomeric forms.

Broka et al.[17] first reported the total synthesis of epibatidine using 6-chloronicotinaldehyde as a starting material. According to their strategy, 6-chloronicotinaldehyde was reacted with (triphenylphosphoranyldiene)acetaldehyde gave enal (**10**) with complete stereoselectivity. Then,

reaction of the enal (**10**) with 2-trimethylsilyloxy-1,3-butadiene (6 eq, neat, 150°C 10h) and treatment of enol silyl ether with dilute HCl in H_2O-THF-MeOH gave (**11**) in 75% yield as a single stereoisomer.



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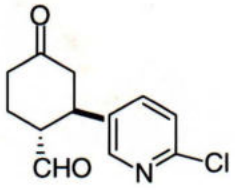

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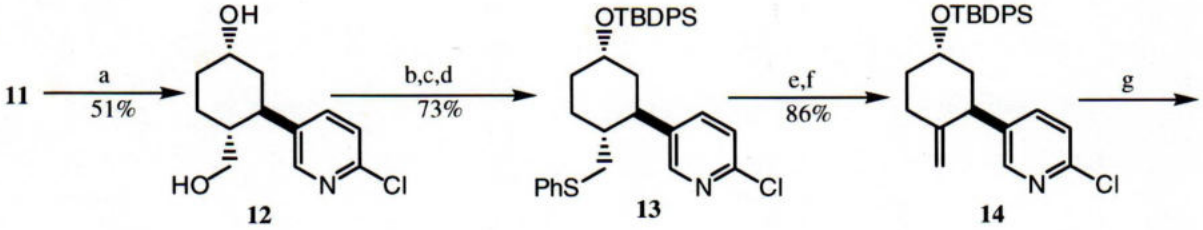
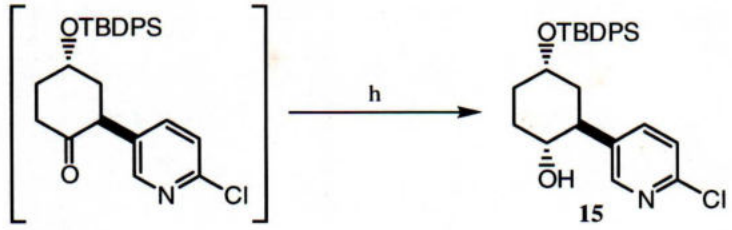
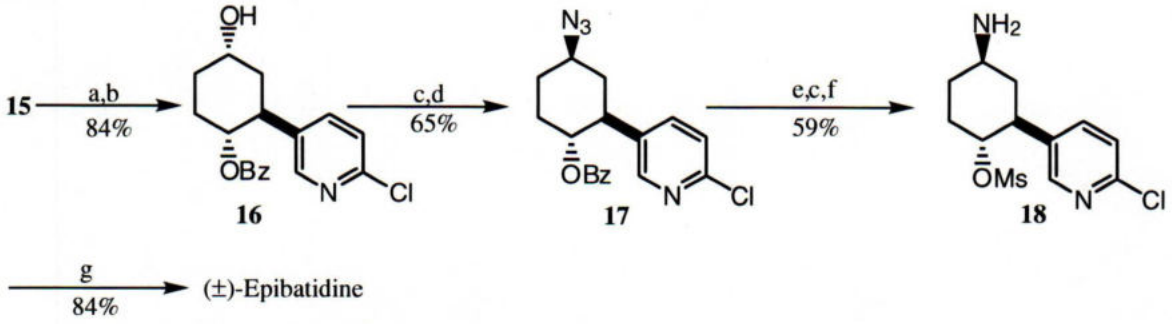




Reagents: a) L-Selectride, THF, -78°C to -20°C, 2h, 51%. b) TsCl, pyridine, 20°C, 2h . c) PhSK, DMF/THF(1:1), 20°C, 30 min. d) TBDPSCl, imidazole, DMF, 20°C, 1day. e) MCPBA, CH_2Cl_2, 20°C, 15 min. f) 0.02M Xylene, 200°C, 2h. g) OsO_4, NMO, acetone/H_2O(9:1) then $Pb(OAc)_4$, C_6H_6. h) $NaBH_4$, MeOH, 0°C, 30 min.

Scheme- 1

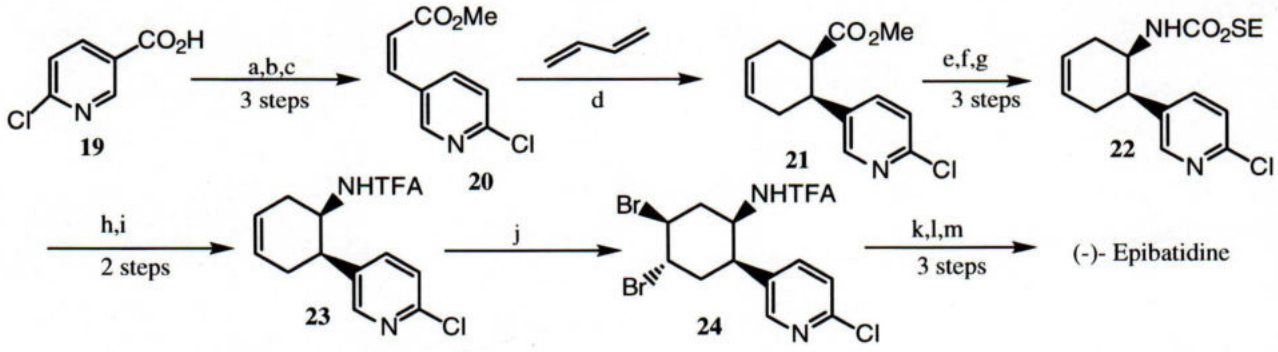


Reagents: a) BzCl, pyridine. b) TBAF, THF. c) MsCl, Et_3N, CH_2Cl_2, 0°C, 45 min. d) LiN_3(excess), DMF,55°C, 12h. e) 0.3 M NaOH, H_2O/THF/MeOH(1:2:4), 20°C, 3.5h. f) $SnCl_2$(excess), MeOH/THF(1:1), 20°C, 1h. g) $CHCl_3$, 55°C, 4days.

Scheme-2

Scheme - 1 & 2 : Synthesis of Epibatidine by Broka et al.

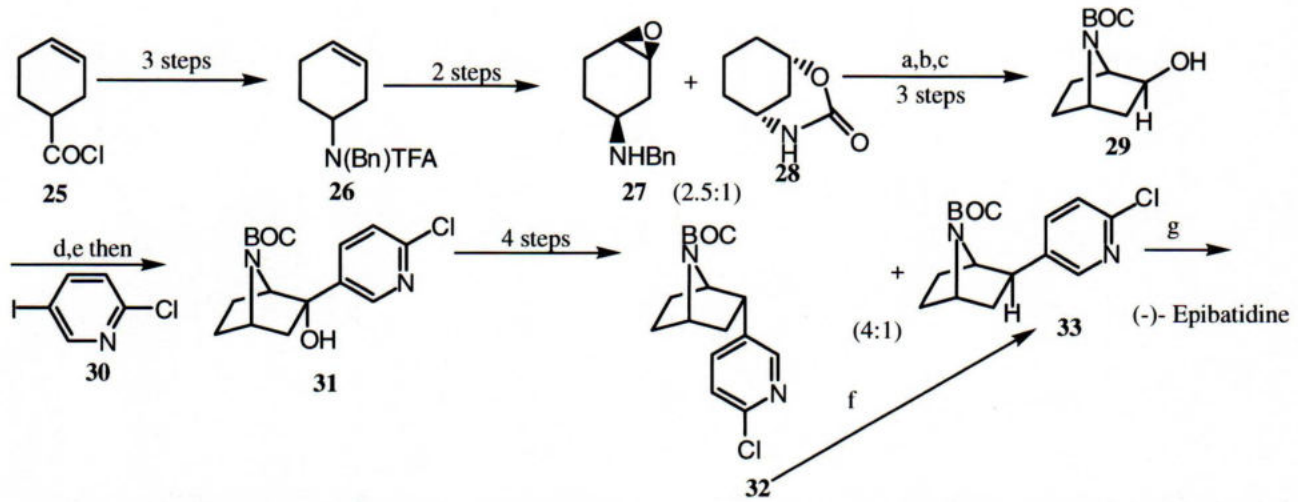
Corey et al.[18] reported the synthesis of (-)-epibatidine from the same starting material (**19**) like Broka et al. and their key intermediate was (**21**) also based on the Diels-Alder reaction and completed the synthesis through 13 steps by the following scheme:



Reagents: a) $LiAlH_4$. b) PCC. c) Still's Wittig reagent (3 steps,47%). d) toluene, 190°C, 95%. e) LiOH, THF. f) DPPA, Et_3N, toluene. g) TMS-CH_2CH_2OH (3 steps,95%). h) TBAF, THF. i) TFA_2O, Et_3N (2 steps,80%). j) $Et_4N^+Br^-$, Br_2, CH_2Cl_2, 96%. k) $KOBu^t$, THF, 75%. l) $^nBu_3SnH$, AIBN, PhH. m) NaOMe/MeOH (2 steps,91%).

Scheme - 3: Synthesis of (-)-Epibatidine by Corey et al.

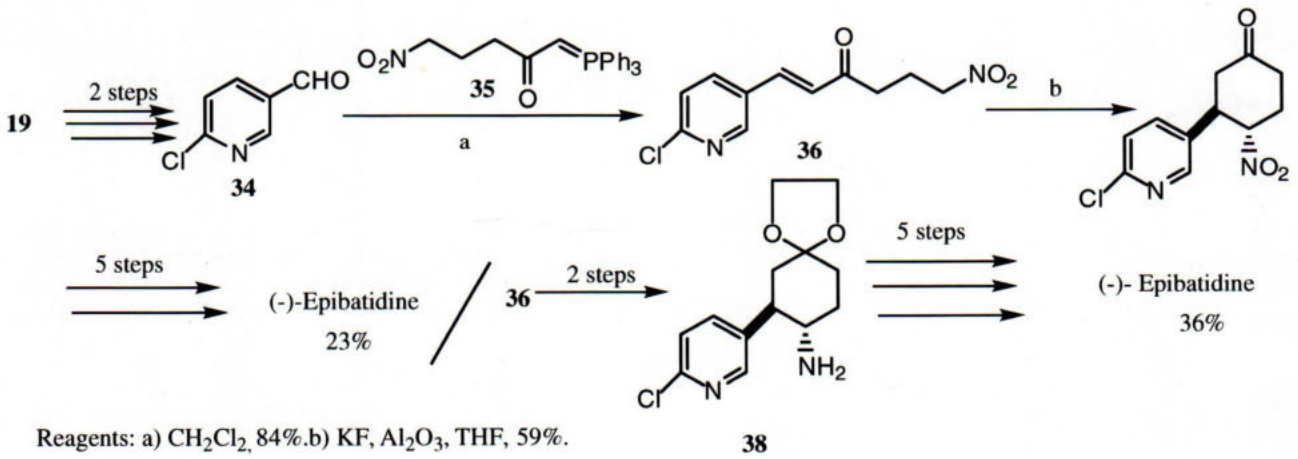
In 1994 Fletcher et al.[19] reported the synthesis of (-)-epibatidine involving the reaction of 5-lithio-2-chloropyridine with *N-tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-one as the critical step.



Reagents: a) 1-methyl-2-pyrrolidone,180°C, 16h, 61%. b) $Pd(OH)_2$, EtOH, HCl, H_2. c) BOC_2O, dioxane, NaOH (2 steps, 79%) d) Swern oxidation. e) $^nBuLi,Et_2O$, THF. f) Bu^tOH, $KOBu^t$. g) HCl, EtOAc (quantitative yield).

Scheme - 4: Synthesis of (-)-Epibatidine by Fletcher et al.

Szantay et al.[20] synthesized epibatidine from compound (**19**) within 9 steps as shown in the following scheme:

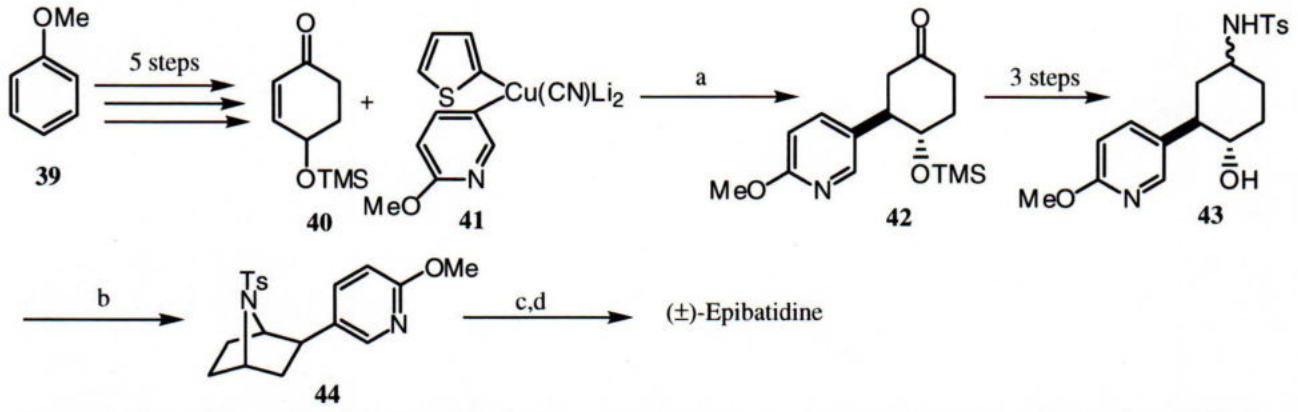


Reagents: a) CH_2Cl_2, 84%.b) KF, Al_2O_3, THF, 59%.

Scheme - 5: Synthesis of (-)-Epibatidine by Szantay et al.

Starting from anisole (**39**), Sestanj et al.[21] reported the synthesis of (±)-epibatidine via the conjugate

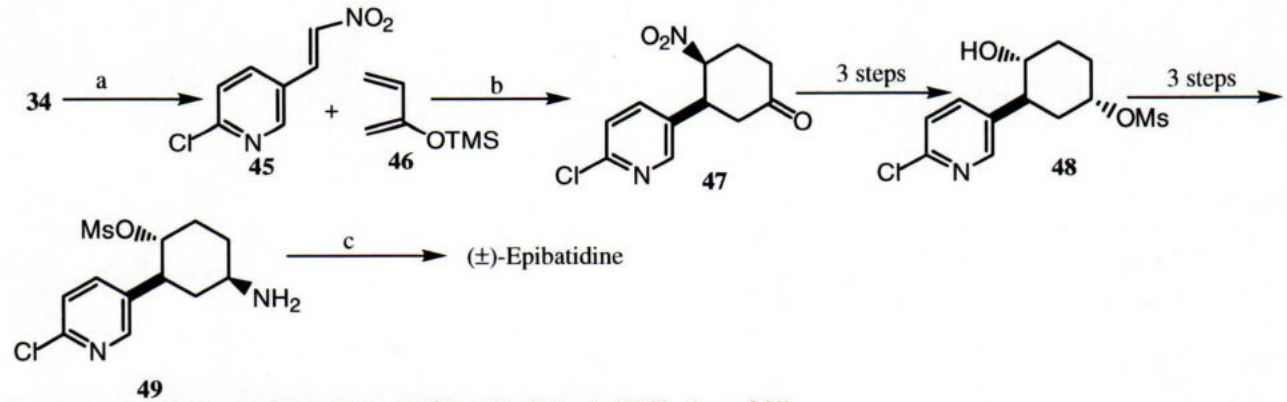
addition of the cuprate (**41**) to the enone (**40**) to isolate the ketone (**42**) as the key intermediate.



Reagents: a) Et_2O, THF, NH_4Cl, 60%. b) DEAD, PPh_3, THF. c) Na/Hg, Na_2HPO_4, Et_2O, HCl. d) $POCl_3/PCl_5$, Et_2O, HCl, (2steps,16%)

Scheme - 6: Synthesis of (±)-Epibatidine by Sestanj et al.

Based on the Diels-Alder reaction between nitroethylene (**45**) and silyloxy diene (**46**), Albertini et al[22] reported the synthesis of the (±)-epibatidine by the following scheme:

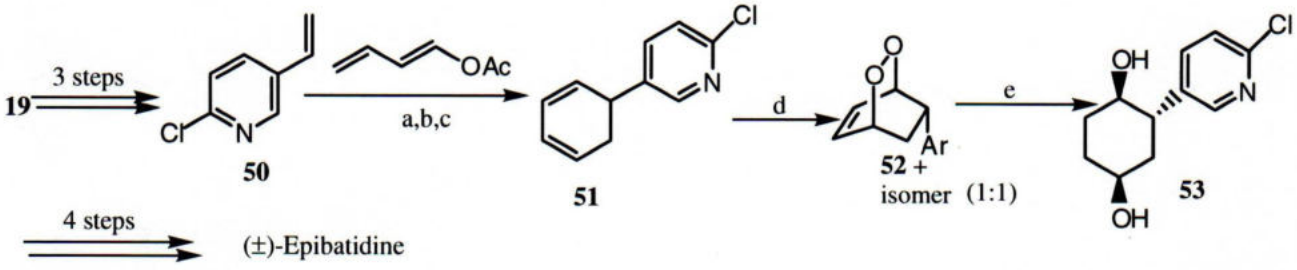


Reagents: a) $MeNO_2$, MsCl, Et_3N. b) 120°C, HCl, 68%. c) $CHCl_3$, heat, 84%.

Scheme - 7: Synthesis of (±)-Epibatidine by Albertini et al.

Ko et al.[23] reported the synthesis of (±)-epibatidine within 12 steps employing the [4+2] addition reaction of 1-(2-chloro-5-pyridyl)cyclohexa-2,4-diene (**51**) with singlet oxygen, forming the bicyclic

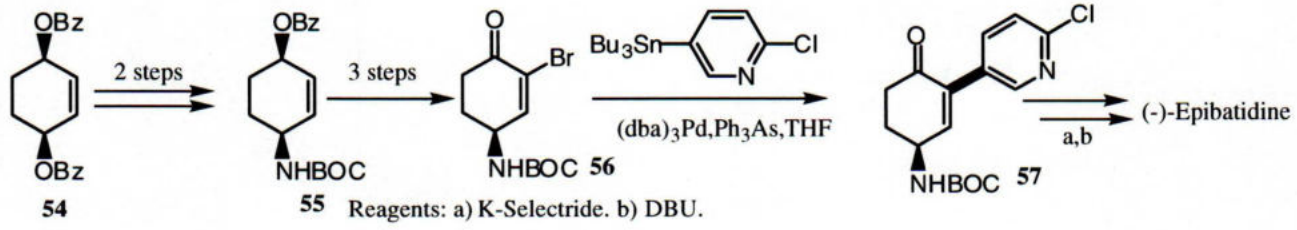
peroxide (**52**) as a key intermediate as shown below.



Reagents: a) Xylene, 140°C 50%. b) K_2CO_3, aqMeOH. c) 2,4-dinitrophenylsulfonyl chloride, Et_3N, $ClCH_2CH_2Cl$ (<81 %). d) O_2, 5,10,15,20-tetraphenyl-21H,23H-porphine, CCl_4, Hg lamp, 80%. e) H_2, Rh/Al_2O_3, MeOH, 70%.

Scheme - 8: Synthesis of (±)-Epibatidine by Ko et al.

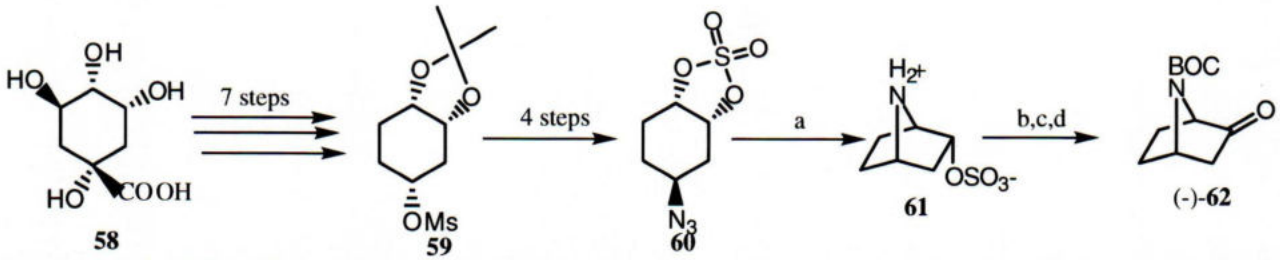
Pd-catalyzed desymmetrization of *cis*-3,6-dibenzoyloxy-2-cyclohexene (**54**) and a Pd catalyzed cross-coupling as the key reactions in a synthesis of (-)-epibatidine were reported by Trost et al.[24]



Reagents: a) K-Selectride. b) DBU.

Scheme - 9: Synthesis of (-)-Epibatidine by B.M.Trost et al.

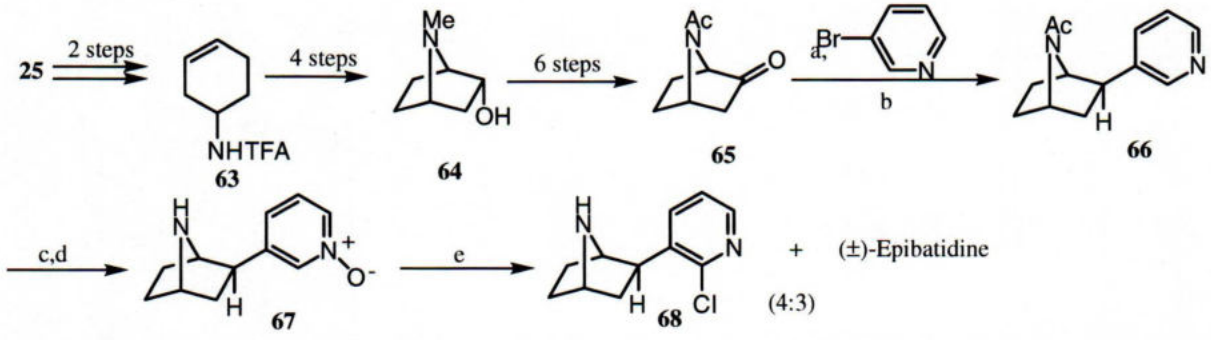
Albertini et al.[25] again reported the synthesis of (+)-epibatidine by utilizing (-)-quinic acid as the chiral source to give the optically pure 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-one, (**62**) as an advanced intermediate through a facile and regioselective intramolecular nucleophilic ring opening of cyclic sulfate moiety as shown by the following scheme:



Reagents: a) H_2, Pd/C, THF-H_2O, 78%. b) conc.H_2SO_4, H_2O, THF, Na_2CO_3. c) BOC_2O, CH_2Cl_2. d) Swern oxidation (3 steps 69%).

Scheme - 10: Synthesis of Epibatidine precursor by Albertini et al

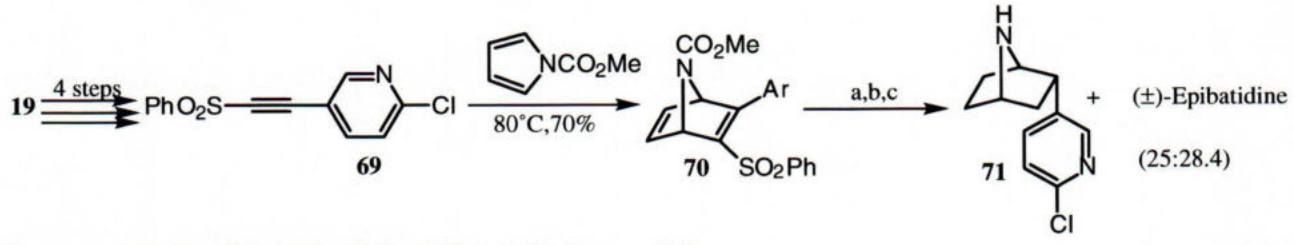
Starting from compound (**25**), Nakai et al.[26]reported the synthesis of (±)-epibatidine via reductive elimination of hydroxy function as a key step shown:



Reagents: a) ^{n}BuLi, Et_2O-THF. b) Ra-Ni, EtOH-H_2O (2 steps,18%). c) MCPBA. d) 2N HCl (2 steps,quantitative yield). e) $POCl_3$, 21%.

Scheme - 11: Synthesis of (±)-Epibatidine by Nakai et al.

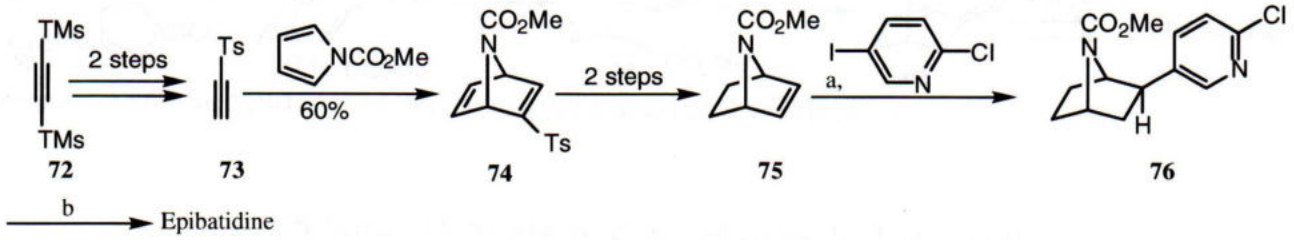
Using the key step based on a Diels-Alder reaction of N-carbomethoxypyrrole and 6-chloro-3-pyridyl phenylsulfonyl acetylene (**69**), followed by desulfonation, hydrogeneation and deprotection of amino group, Shen et al.[27] also reported the synthesis of (±)-epibatidine.



Reagents: a) Na-Hg, 42%. b) H_2, Pd/C. c) HBr/AcOH, (2 steps, 49%).

Scheme - 12: Synthesis of (±)-Epibatidine by Shen et al.

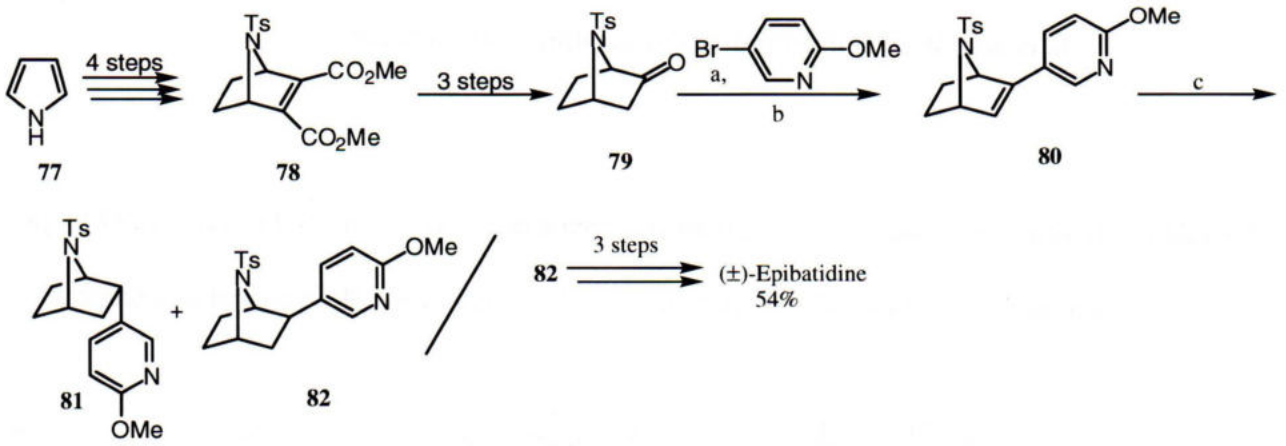
Regan et al.[28] reported the synthesis of (±) epibatidine via palladium-catalyzed Heck-type coupling as key step by the following scheme:



Reagents: a) $(Ph_3P)_2Pd(OAc)_2$ DMF, piperidine, HCOOH, 22%. b) HBr-AcOH, 74%.

Scheme - 13: Synthesis of (±)-Epibatidine by Regan et al.

Starting from pyrrole (**78**), Natsume et al.[29] reported the synthesis of (±)-epibatidine in 13 steps by the following scheme:

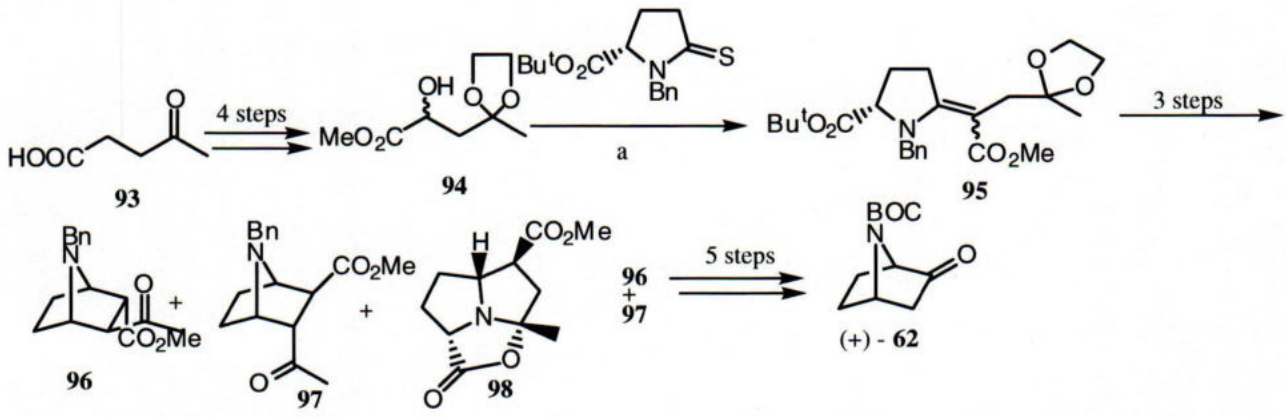


Reagents : a) ^{n}BuLi. b) Burgess reagent, (2 steps 60%). c) Pd-C, HCl, Pr^{i}OH.

Scheme - 14: Synthesis of (±)-epibatidine by Natsume et al.

Scheme - 17: Synthesis of (±)-epibatidine by Pandey et al.

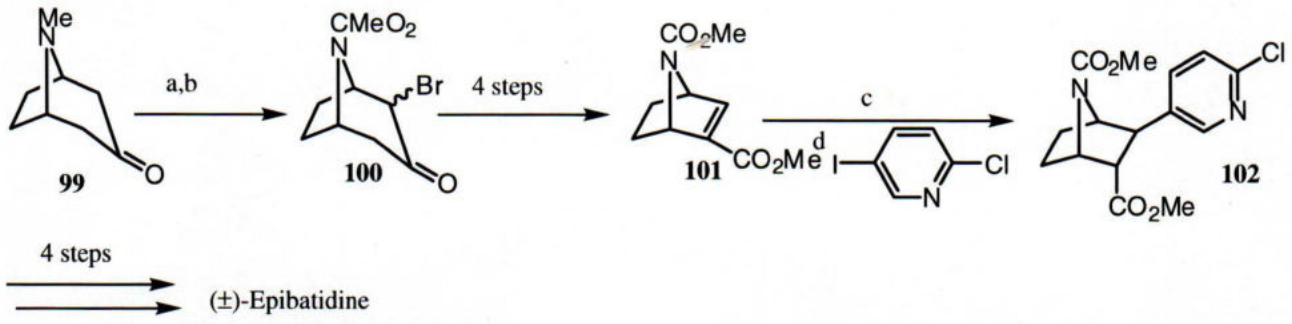
Starting from l-glutamic acid and levulinic acid both of (+)-and (-)-N-BOC-7-azabicyclo[2.2.1]heptan-2-one (**62**) were prepared by selective formation of *trans*-2,3-disubstituted-7-azabicyclo[2.2.1]heptanes from (1'-methoxycarbonyl-3'-oxobutyl)proline via a decarbonylation/iminium ion cyclization process. This versatile intermediate (**62**) was used for the synthesis of epibatidine by Rapoport et al.[33]



Reagents: a) Tf_2O, PPh_3, NMP, 68%.

Scheme - 18: Synthesis of Epibatidine by Rapoport et al.

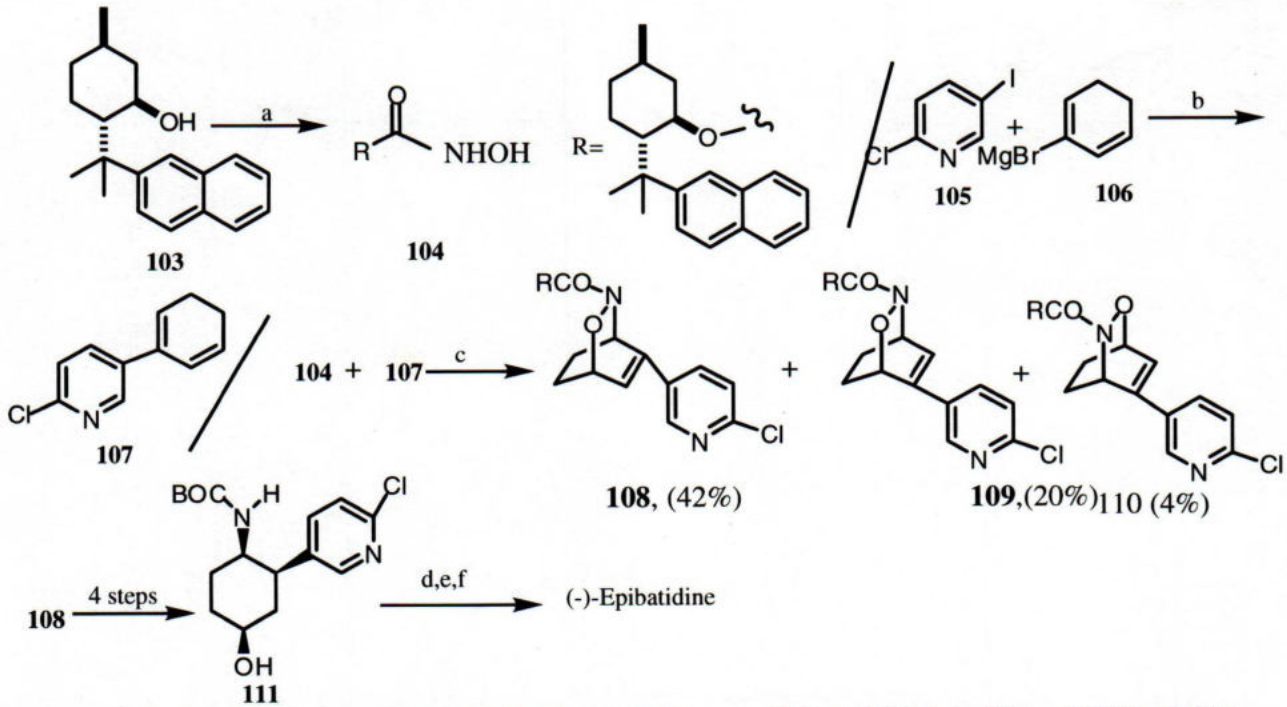
Bai et al.[34]also reported the synthesis of (±)-epibatidine via the construction of the 7-azabicyclo[2.2.1]heptane ring system (**101**) through contraction of the tropinone skeleton by Favorskii rearrangement :



Reagents: a) $(Ph_3P)_2Pd(OAc)_2$, piperidine, HCOOH, DMF, Et_3N, 56%.

Scheme - 19: Synthesis of (±)-Epibatidine by Bai et al.

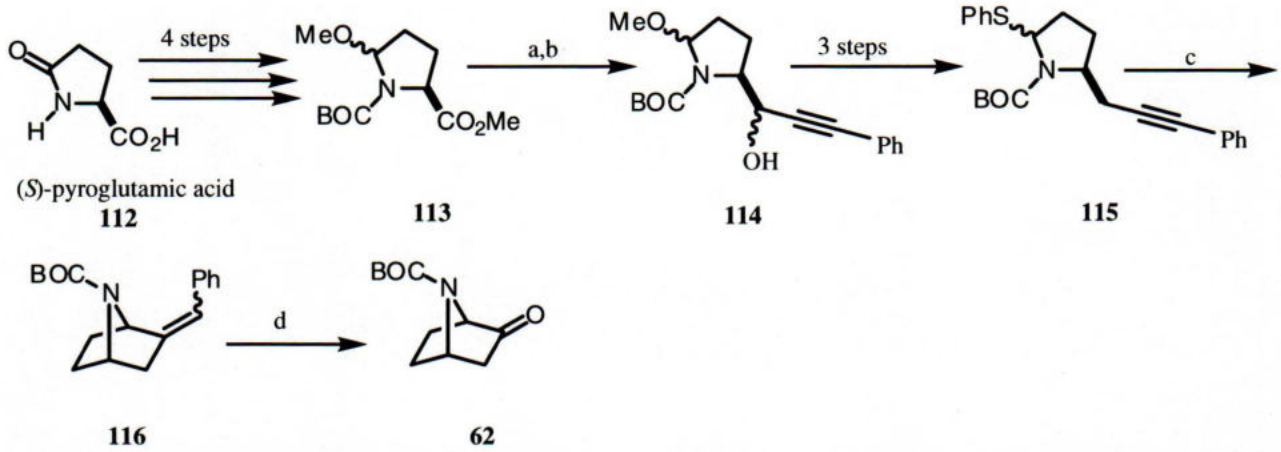
More recently Kibayashi et al.[35] reported the synthesis of (-)-epibatidine based on asymmetric hetero Diels-Alder cycloaddition with an N-acylnitroso dienophile bearing 8-(2-naphthyl)menthol as a chiral source.



Reagents: a) $(Cl_3CO)_2CO$, pyridine, thenTMSNHOTMS, then HCl (one pot,88%). b) $Pd(PPh_3)_4$, 50%. c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C. d) PPh_3, CBr_4, MeCN. e) CF_3CO_2H, CH_2Cl_2, 40%. f) $CHCl_3$, reflux, 3days, 97%.

Scheme - 20: Synthesis of (-)-Epibatidine by Kibayashi et al.

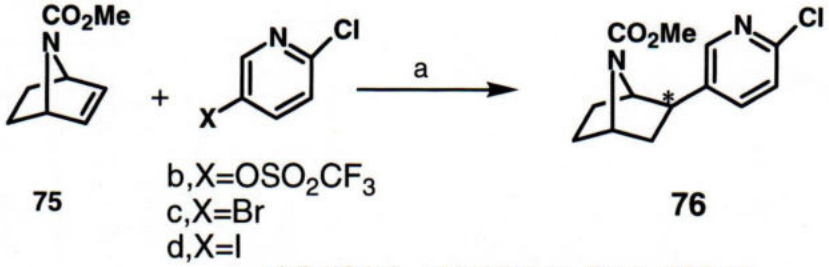
Later in the same year, Clive et al.[36] reported the synthesis of 7-azabicyclo[2.2.1]heptane (**11 6**) via radical cyclization and conversion to the ketone (**6 2**) as a synthetic precursor of (-)-epibatidine.



Reagents: a) DIBAL-H, CH_2Cl_2, -78°C, 73%. b) PhCCLi, THF, -78°C, 90%. c) Bu_3SnH, AIBN, PhMe, 110°C, slowaddition, 76%. d) O_3, CH_2Cl_2, MeOH, -78°C, Me_2S, 95%.

Scheme - 21: Synthesis of (-)-Epibatidine by Clive et al.

Most recently Kaufmann et al.[37] reported asymmetric synthesis of both enantiomers of N-protected epibatidine via reductive Heck-type arylation of the azabicycles (**75**) using the optically active ligands as shown:



75 b,X=OSO_2CF_3 c,X=Br d,X=I **76**

a) $Pd(OAc)_2$, chiral ligand, Et_3N, HCO_2H.

Scheme - 22: Synthesis of N-protected epibatidine by Kaufmann et al.

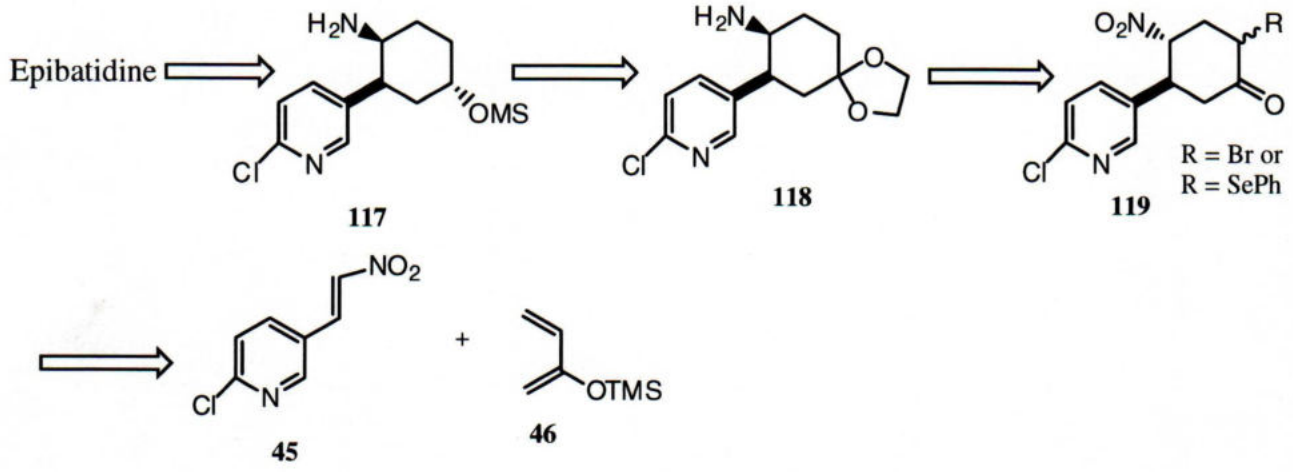
1-2: **RESULTS AND DISCUSSION.**

After reviewing previous works for the synthesis of epibatidine and also due to its unique structure and excellent pharmacological action, I am interested in establishing a completely new route for the synthesis of epibatidine using 2-chloro-5-cyanopyridine (**125**) as the starting precursor, which is available from Mitsubishi Chemical Company, Japan in large quantity.

1-2-1: **INITIAL STRATEGY:**

Initially, to furnish the synthesis, I adopted two strategies described below respectively:

Strategy - 1:



Strategy - 2:

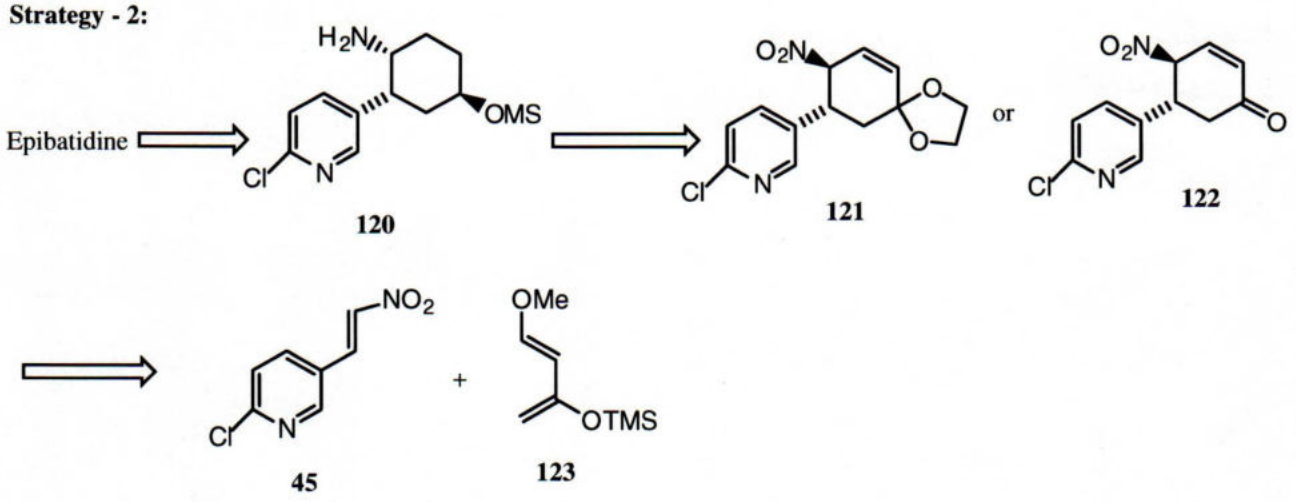
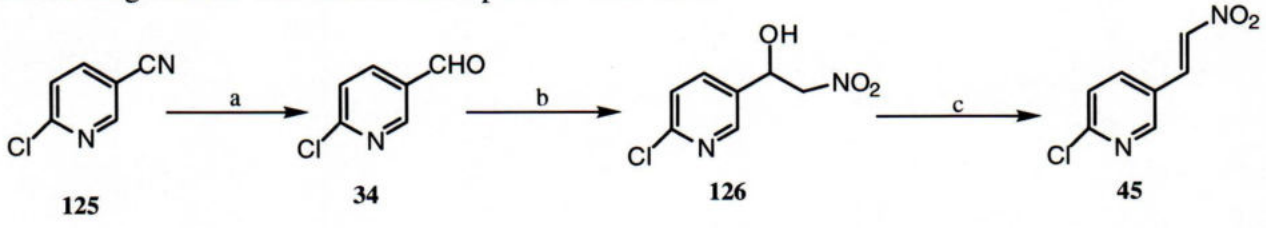


Fig - 2 Strategies 1 and 2

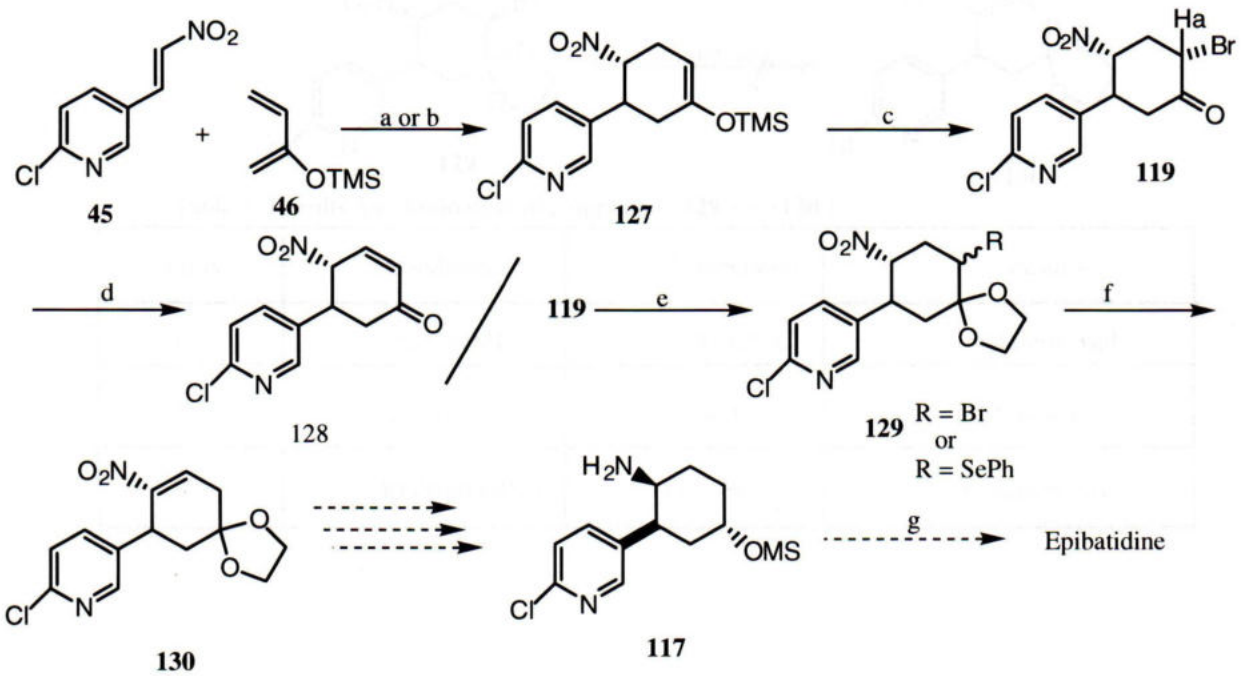
Strategy 1 and 2 are based on Diels-Alder reaction,and nitroethylene (**45**) which was synthesized by the following scheme was used as dienophile in both cases:



Reagents: a) DIBAL-H, toluene, -78°C, 62%. b) $MeNO_2$, MeOH/MeONa, 0-5°C, then 1eq. CH_3COOH, quantitative yield. c) MsCl, CH_2Cl_2, Et_3N(excess), reflux, 50%.

Scheme - 23 Synthesis of nitroethylene

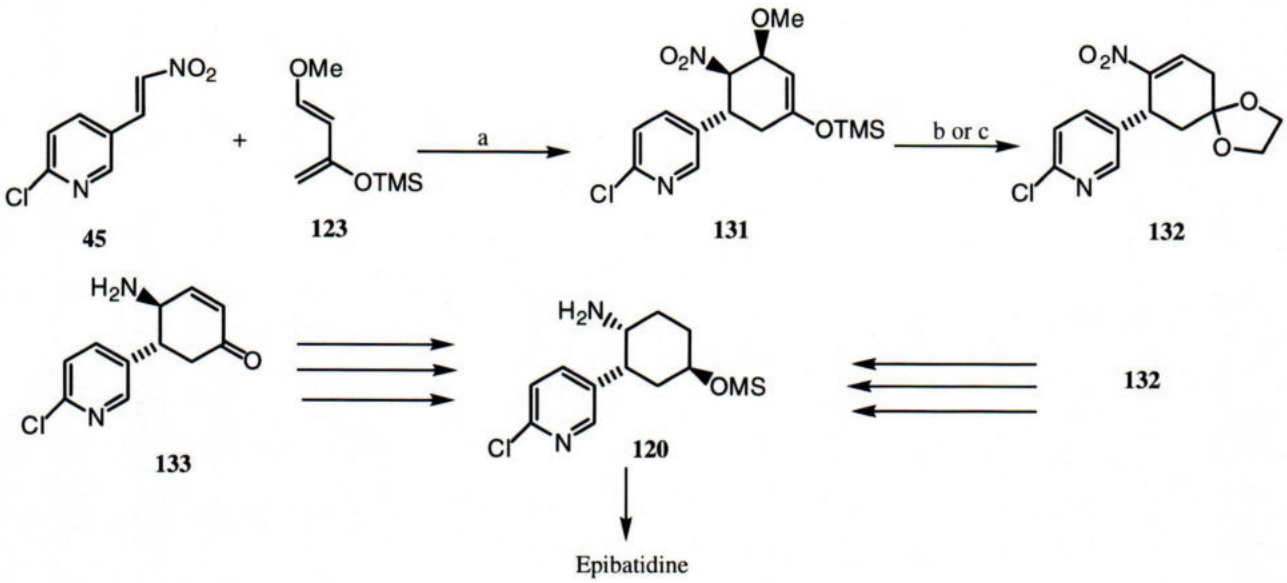
2-Chloro-5-cyanopyridine was subjected to DIBAL-H reduction in toluene at -78°C to give aldehyde (**34**) in 62% yield, which was treated with nitromethane in MeOH/MeONa at 0-5°C for overnight by the method of Barco et al.,[38] and then treated with 1 eq of CH_3COOH to give quantitative yield of nitro alcohol (**126**) . Treatment of nitro alcohol (**126**) with MsCl in the presence of excess Et_3N afforded the desired nitroethylene (**45**) in about 50%.



Reagents: a) sealed tube, 48h, 120°C. b) neat,120°C,4 8h. c) Br_2/CCl_4, 0°C-rt,1h, 30%. d) Li_2CO_3/LiBr, DMF, 120°C. e) ethylene- glycol, C_6H_6, p-TsOH, reflux. f) elimination. g) cyclisation

Scheme - 24: Expected scheme for synthesis of epibatidine by strategy 1.

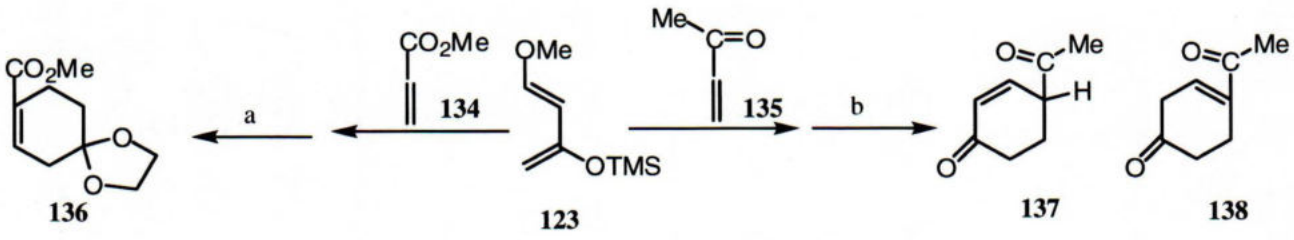
According to the strategy-1 (Scheme-24), Diels-Alder reaction between nitroethylene (**45**) and silyloxydiene (**46**) was performed by heating in sealed tube for 48 h or heating without solvent at 120°C for 48 h and successively, each reaction mixture was treated with Br_2 in CCl_4 by the method of Jung et al.[39] to give bromoketone (**119**). Although it was difficult to purify completely, it was



Reagents: a) C_6H_6, reflux. b) ethylene glycol, p-TsOH, C_6H_6, reflux. c) THF-0.1N HCl, rt

Scheme -25: Expected scheme for the synthesis of Epibatidine by strategy-2.

In 1979, Danishefsky and Kitahara[43] reported Diels-Alder Reactions of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**123**) and they mentioned that cycloaddition of (**123**) with methyl acrylate (**134**) and the successive direct treatment with ethylene glycol in refluxing benzene in the presence of *p*-toluenesulfonic acid gave ketal (**136**) in high yield. On the other hand, the diene (**123**) with methyl vinyl ketone (**135**) gave the adduct which was successively treated with THF - 0.1N HCl to give compound (**137**) and (**138**) .

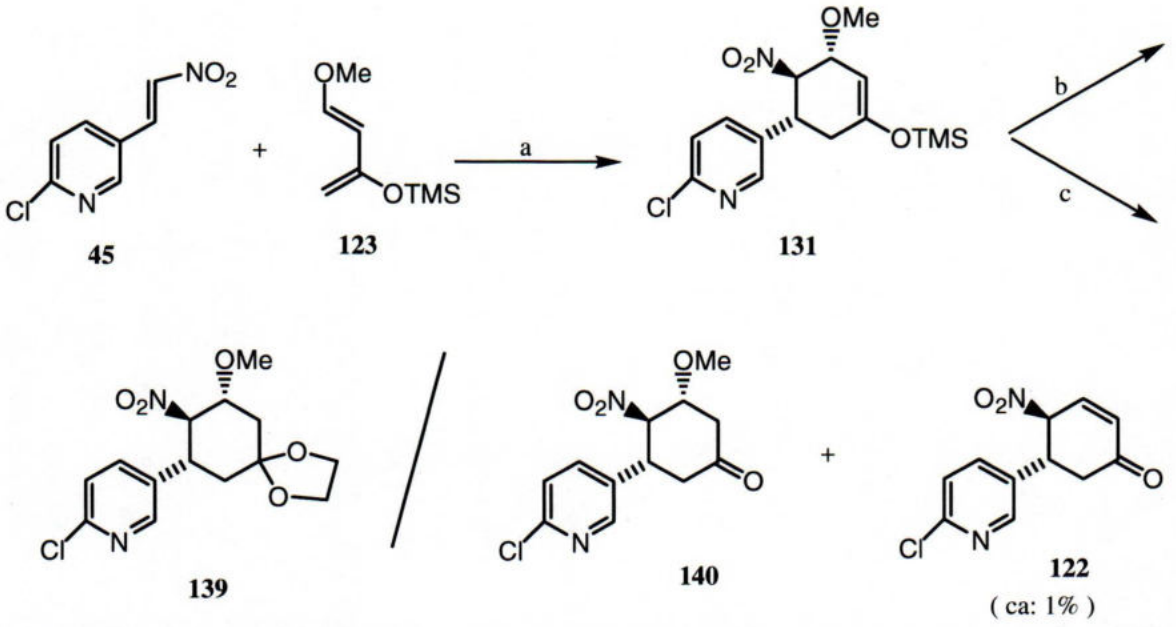


Reagents: a) ethylene glycol, *p*-TsOH, C_6H_6, reflux, 85%. b) THF -0.1N HCl, rt ,71%.

Scheme - 26: Diels - Alder reactions by Danishefsky and Kitahara et al.

According to this procedure, a mixture of nitroethylene (**45**) and *trans*-1-methoxy-3-

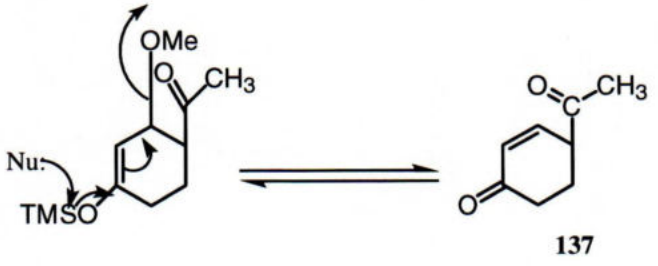
trimethylsilyloxy-1,3-butadiene (**123**) was refluxed in benzene for 24 h and then, was treated either with ethylene glycol in the presence of *p*-TsOH for 6 h or with THF-0.1 N HCl gave methoxy ketal (**139**) or methoxy ketone (**140**) together with very little amount of enone (**122**, ca.~1%), respectively.



Reagents: a) C_6H_6, reflux. b) ethylene glycol, *p*-TsOH, C_6H_6, reflux, 6h, 45%. c) THF-0.1N HCl, rt,30 min, 75%.

Scheme - 27

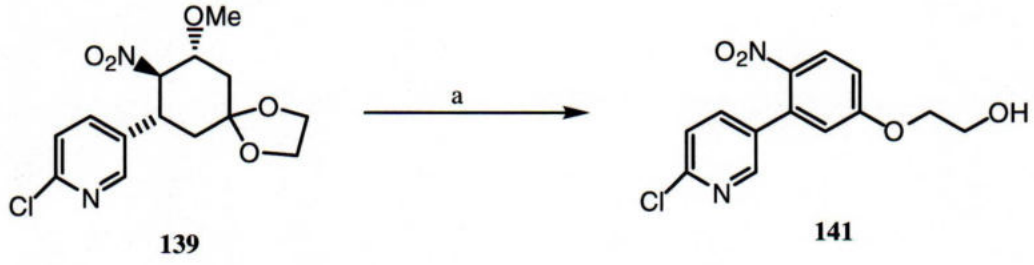
Structure of the compounds (**139**), (**140**) and also the enone (**122**) was determined by ^{1}H NMR and IR. The mechanism for the formation of the enone was proposed by Danishefsky and Kitahara[43] as shown below .



137

Fig - 3

As to the acid treatment of the adduct (**131**), the concentration of the acid was varied to promote β-elimination, but in most cases, only methoxy ketone (**140**) was isolated and only in the case of 0.1 N HCl, tiny amount of the enone (**122**, ca.~1%) was obtained. In order to furnish the enone, I attempted to use base for elimination of OMe group from methoxy ketal (**139**) and methoxy ketone (**140**). But unfortunately, treatment of methoxy ketal (**139**) with DBU in benzene gave only aromatized product (**141**) .

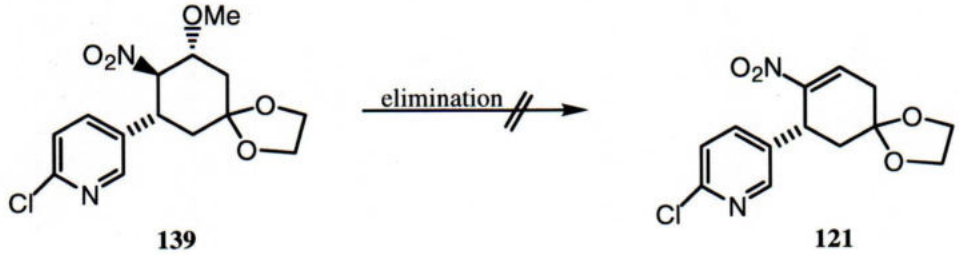


139 **141**

a) DBU, C_6H_6, rt- reflux

Scheme - 28

Other unsuccessful attempts for the elimination of OMe group from (**139**) were summarized in Table 2.

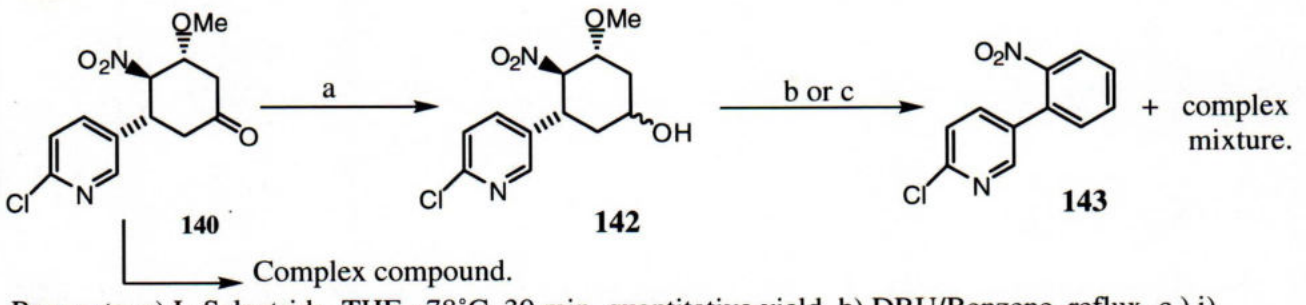


139 **121**

Table 2: Attempt for elimination of OMe group from (**139**) under different condition.

Entry	Reagent	Solvent	Conditions	Product obtained
1	DBU	Benzene	Reflux,2h	Aromatized
2	DBU	THF	50-55°C Reflux,	No reaction Aromatized
3	DABCO	Benzene	rt- reflux	No reaction
4	$^{i}Pr_2NEt$	Benzene	Reflux	No reaction
5	Li_2CO_3/LiBr	DMF	90-120°C	No reaction
6	DBN	Benzene	Reflux	Aromatized
7	KO^{t}Bu	Benzene	Reflux,20min.	Epimerization

From ^{1}H NMR study of methoxy ketal (**139**), it was observed that the Diels-Alder reaction took place via *exo*-addition and -NO_2 and methoxy group are located at stable 1,2-*trans*-diequatorial. Therefore, it might resist to eliminate. So I examined to employ methoxy ketone (**140**) as a substrate for the elimination process.

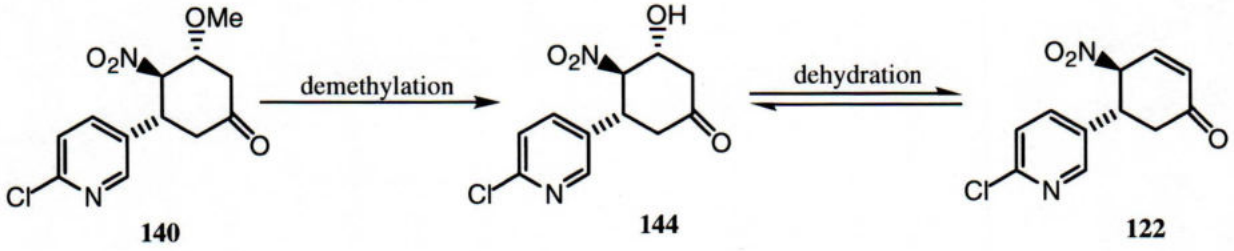


Reagents: a) L-Selectride, THF, -78°C, 30 min. quantitative yield. b) DBU/Benzene, reflux. c) i) NaH/THF, 0°C-rt .ii) DBU (1eq.), 40°C- reflux. d) TMSOTf/CH_2Cl_2, 0°C.

Scheme - 29

(**142**) as a mixture in quantitative yield. In order to obtain α,β-unsaturated nitro-derivative, the mixture was treated with DBU in benzene under reflux. But only complex mixture with small amount of aromatized product (**143**) was obtained. In order to suppress dehydration, the alcohol (**142**) was treated with 1 eq. of NaH in THF to form hydroxide in situ but unfortunately, successive treatment with DBU gave only aromatized product (**143**) .

Thus, I tried to cleave methyl ether of the methoxy ketone (**140**) to get the desired enone (**122**) via dehydration in the following way:



140 **144** **122**

Scheme - 30

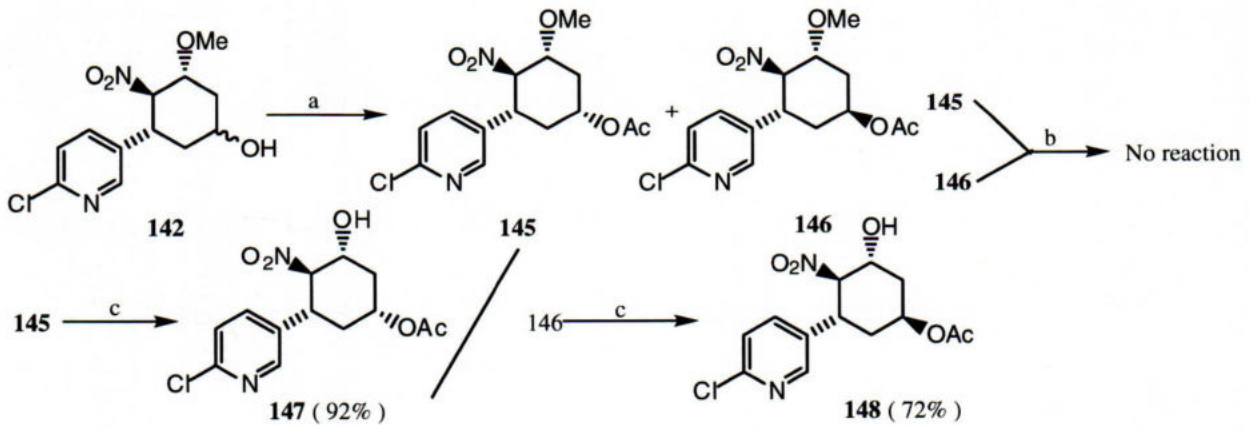
Demethylation was attempted under several conditions as in Table 3:

Table 3: Attempted for demethylation from compound (**140**)to (**144**).

Entry	Reagent	Conditions	Result
1	BBr_3(neat)/CH_2Cl_2	-20 to 0°C	No reaction
2	$BF_3.OEt_2$ $(n\text{-}C_4H_9)_4N^+I^-,CHCl_3$	rt- reflux	SM destroyed
3	TMSCl/NaI,CH_3CN	rt- reflux	No reaction
4	BBr_3-NaI-15Crown-5	-10 to 0°C	Complex mix.

Unfortunately, every attempt failed to afford the desired product (**122**).

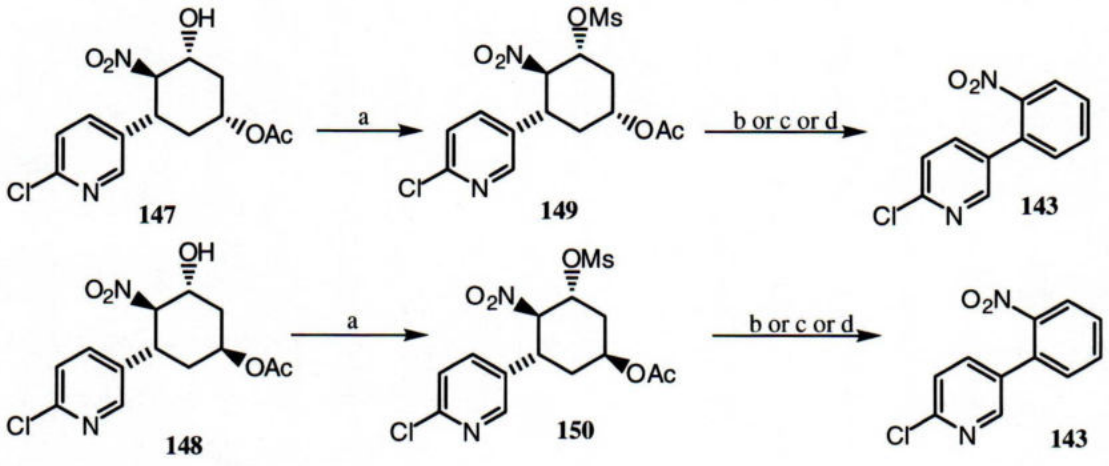
Again demethylation was tried starting from previous intermediate methoxy alcohol (**142**), which was first acylated under usual condition to give α and β–acetate **145** and **146** (1:1) . Then, treatment of ether **145** or **146** with BBr_3 (1 M solution in CH_2Cl_2) at 0°C within 30 min afforded the desired hydroxy α–acetate (**147**, 92%) or hydroxy β–acetate (**148**, 72%).



Reagents : a) Ac_2O, pyridine, over night (quantitative yield). b) BBr_3-NaI-15-crown-5, CH_2Cl_2. c) BBr_3 (1M solution in CH_2Cl_2), CH_2Cl_2, 0°C, 30 minute.

Scheme - 31

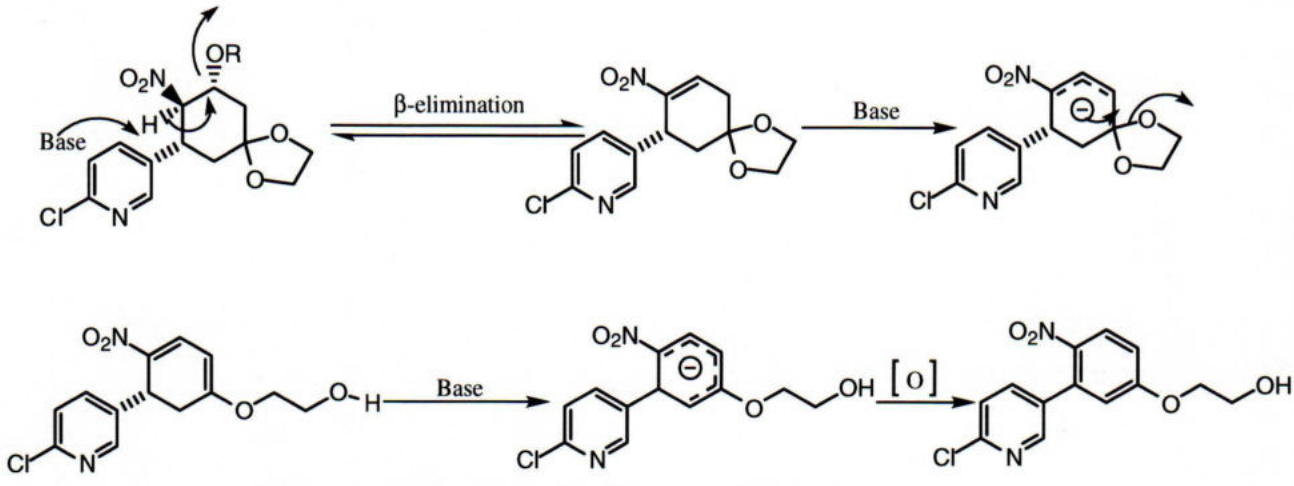
When hydroxy α–acetate (**147**) and hydroxy β–acetate (**148**) were treated with MsCl in CH_2Cl_2 in the presence of excess Et_3N, mesyloxy α–acetate (**149**) and mesyloxy β–acetate (**150**) were obtained in ca. 80% yield, respectively. The mesyloxy acetates were treated with excess base, such as Et_3N,DBU or MeONa/MeOH, but in all cases only aromatized product (**143**) was obtained.



Reagents: a) MsCl, Et_3N(excess), CH_2Cl_2. b) Et_3N(excess), reflux, 81%. c) DBU/THF, rt, 73%. d) MeONa/MeOH, rt, 60%.

Scheme - 32

Thus, Diels-Alder routes via strategies 1 and 2 were unsuccessful due to undesired aromatization. I suggested the following mechanism for aromatization, and therefore I decided to use this intermediates for the preparation of epibatidine analogues to investigate structure-activity relationship.



Scheme - 33: Probable idea for aromatization.

1-2-2: **Strategy - 3**

After failure to furnish the synthesis of epibatidine via strategies 1 & 2, again persued via strategy-3 shown below:

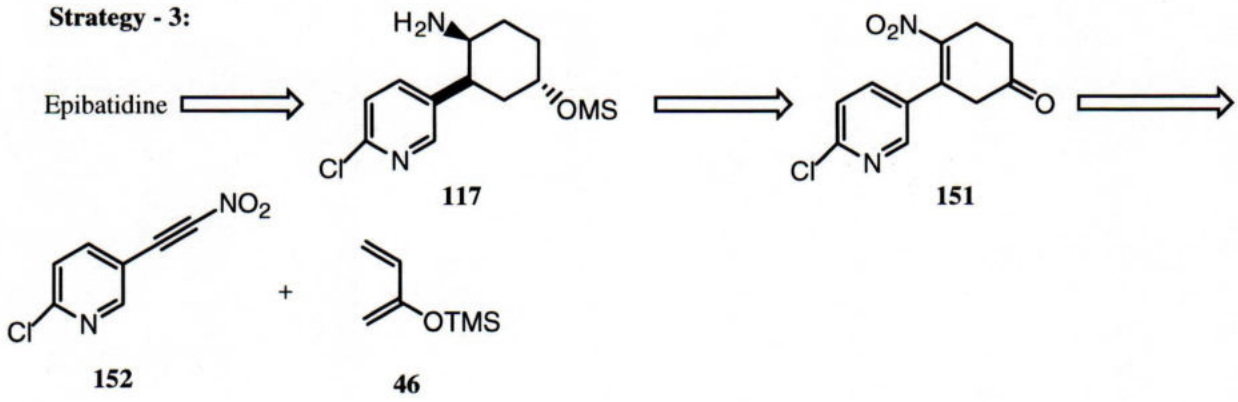
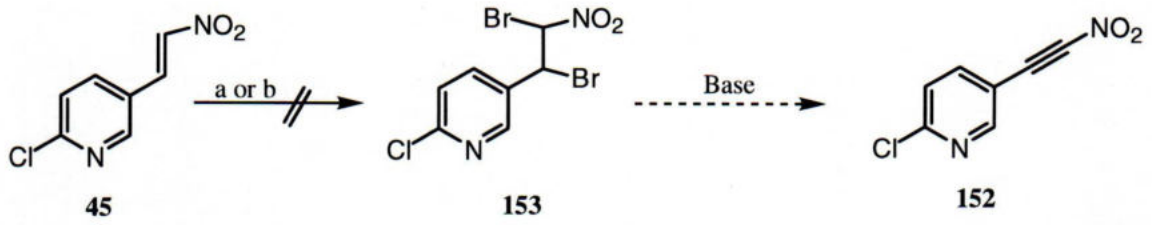


Fig - 4

Strategy - 3 also based on Diels-Alder reaction, in which the diene was the same as strategy 1 & 2, but dienophile was nitroacetylene (**152**) instead of nitroethylene (**45**).

In order to furnish the synthesis of epibatidine, I attempted to prepare the nitroacetylene (**152**) from nitroethylene (**45**) by the following scheme, but bromination could not be achieved, because of electron deficiency of the olefin.

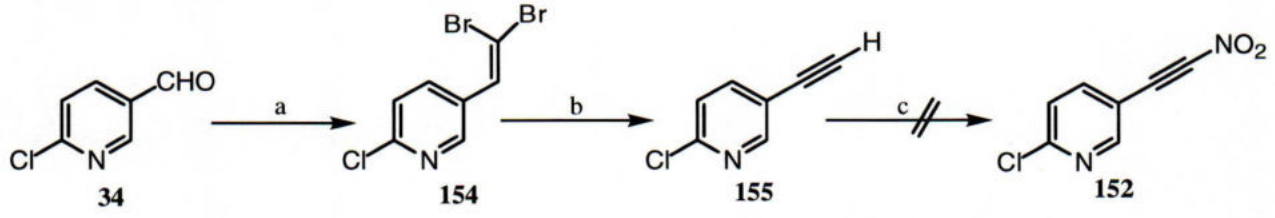


45 **153** **152**

Reagents: a) Br_2/CCl_4,0°C-rt. b) $Br_2/CHCl_3$,Et_3N,0°C.

Scheme -34: Attempted scheme for synthesis of nitro acetylene

Thus, the aldehyde (**34**), was first converted to acetylene (**155**) in two steps. The Wittig olefination of (**34**) with PPh_3/CBr_4 in CH_2Cl_2 afforded dibromide (**154**,~quantitative yield) by the method of Floss et al.,[44] whose structure was clearly confirmed by ^1H NMR. The dibromide (**154**) was treated with *n*-BuLi in THF at -78°C to give the acetylene (**155**), which on treatment with $NO_2^+BF_4^-$ at -78°C to room temperature did not give the desired (**152**).



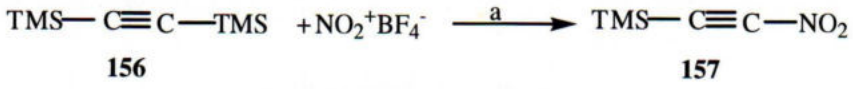
34 **154** **155** **152**

Reagents: a) $PPh_3/CBr_4,CH_2Cl_2$,0°C,quantitative yield. b) ^nBuLi/THF,-78°C. c) $NO_2^+BF_4^-$,-78°C - rt.

Scheme - 35 : Expected scheme for synthesis of nitro acetylene.

In 1986 Schmitt et al.[45] reported the synthesis of a nitroacetylene (**157**) from TMS acetylene (**156**)

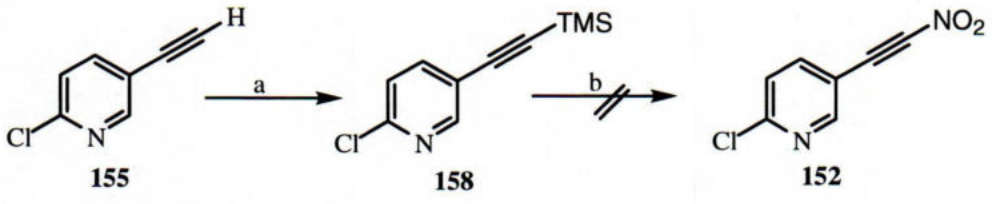
by the following way.



a) CsF/(n-C_4H_9)$_4N^+BF_4^-$,CH_2Cl_2,rt,2h,70%.

Scheme - 36 : Synthesis of nitro acetylene by Schmitt et al.

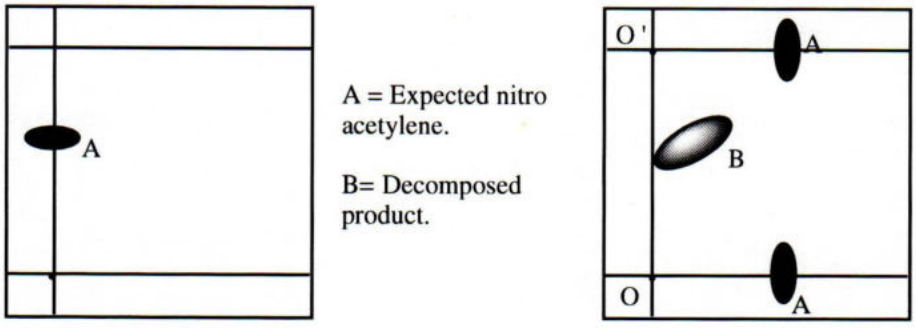
Therefore, TMS-acetylene was prepared from the acetylene (**155**) and the preparation of nitroacetylene (**152**) was attepmted.



Reagents: a) ^{n}BuLi(1.2eq)/THF,-78°C,then TMSCl/Et_3N,60%.b) $NO_2^+BF_4^-$,CsF/(n-C_4H_9)$_4N^+BF_4^-$,dry CH_2Cl_2,

Scheme - 37 :Attempted scheme for the synthesis of nitro acetylene.

Acetylene (**155**) was first treated with n-BuLi (1.2 eq) in THF at -78°C and then successively with TMSCl/Et_3N for 1 h gave 60% of TMS-acetylene (**158**). Then TMS-acetylene (**158**) was treated with $NO_2^+BF_4^-$ in the presence of CSF/(n-C_4H_9)$_4N^+BF_4^-$ in dry CH_2Cl_2 according to the method of Schmitt et al.[45] Starting material disappeared, the crude nitroacetylene was obtained and it was confirmed by ^{1}H-NMR and IR. But unfortunately, purification of crude nitroacetylene decomposed very quickly and it was confirmed by two dimensional TLC.



Develope just after spotting at Hexane :Ethylacetate,1:1

Develope after one hour of first developement.(crude - mixture was spotted on O and O ' just before second development)

Fig - 5 : Two dimensional TLC of Crude Nitro acetylene.

Because of this instability of the nitroacetylene (**152**), it was concluded that the nitroacetylene (**152**) is not suitable dienophile for the Diels-Alder reaction.

1-2-3: **Strategy - 4 (Robinson Annelation route)**

After failure to furnish the synthesis of epibatidine by previous strategies 1-3, I reached strategy-4, based on Robinson annulation for the construction of the skeleton as shown below.

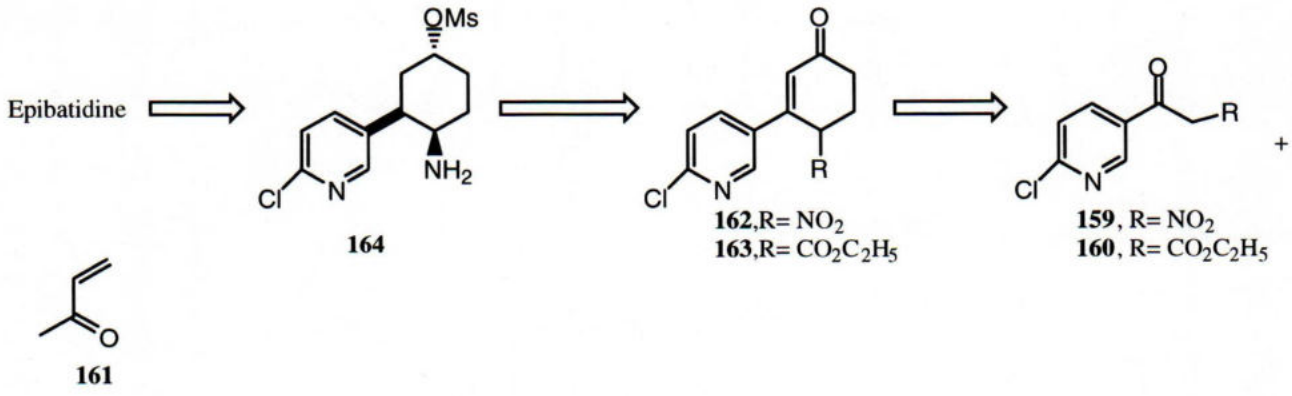
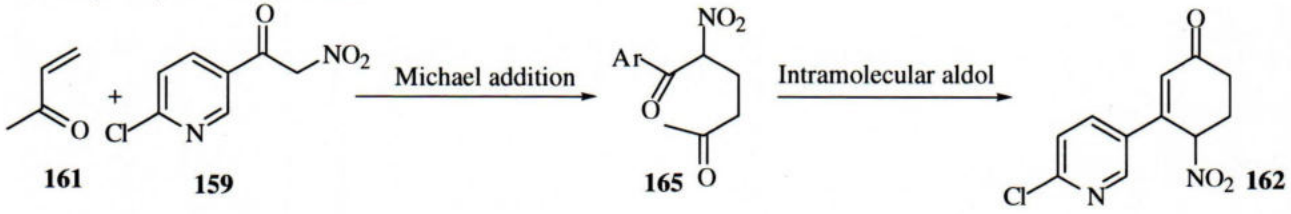


Fig : - 6: Strategy - 4

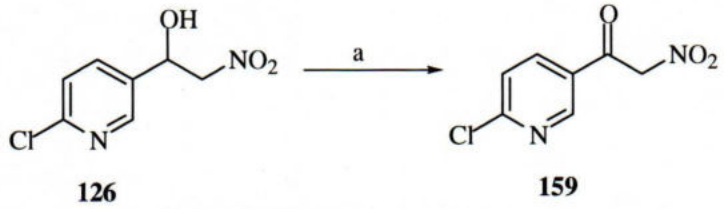
According to the strategy-4, Robinson annulation between nitro ketone (**159**) and methyl vinyl ketone (**161**) was examined.



161 **159** **165** **162**

Scheme - 38 : Expected scheme for skeleton construction by Robinson annulation.

The nitro alcohol (**126**) was oxidized with pyridinium chlorochromate (PCC) in CH_2Cl_2 in the presence of MS-3A, but unfortunately it was very difficult to isolate the desired nitroketone (**159**) because of instability.

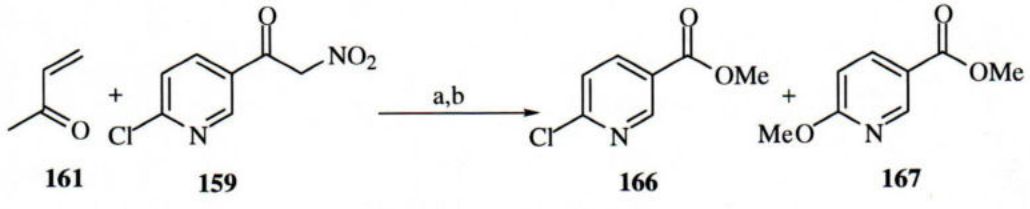


126 **159**

a) PCC, CH_2Cl_2, MS-3A (powder)

Scheme - 39

When the crude nitroketone (**159**) was subjected to Robinson annulation with methyl vinyl ketone (**161**) by the method of Heathcock et al.,[46] the following unwanted compounds were isolated via retro-Claisen type reaction.



161 **159** **166** **167**

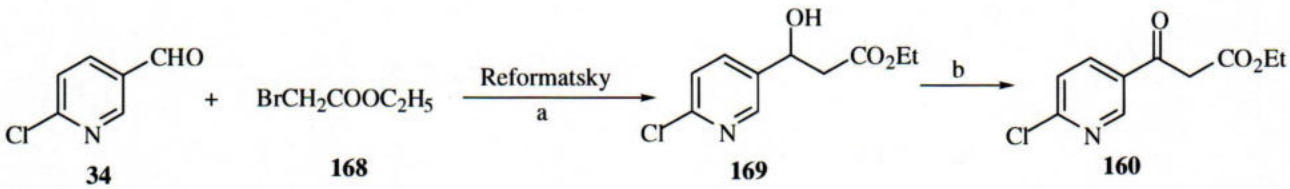
Reagents: a) KOH, MeOH. b) pyrrolidine, benzene, reflux.

Scheme - 40 : Attempted Robinson annulation between compound (**159**) and (**161**).

Thus, it was planned to introduce amino group via Curtius Rearrengement after the construction of the skeleton by employing β–keto ester (**160**).

1-2-3-1: **Synthesis of β–keto ester (160):**

The aldehyde (**34**) was subjected to the Reformatsky reaction with ethyl bromoacetate (**168**) by the method of White et al.[47] to give alcohol (**169**,~80%), which upon oxidation with PCC in CH_2Cl_2 in the presence of MS-3A by the method of Corey et al.[48] at room temperature gave the desired β–keto ester (**160**, 52%) .



34 **168** **169** **160**

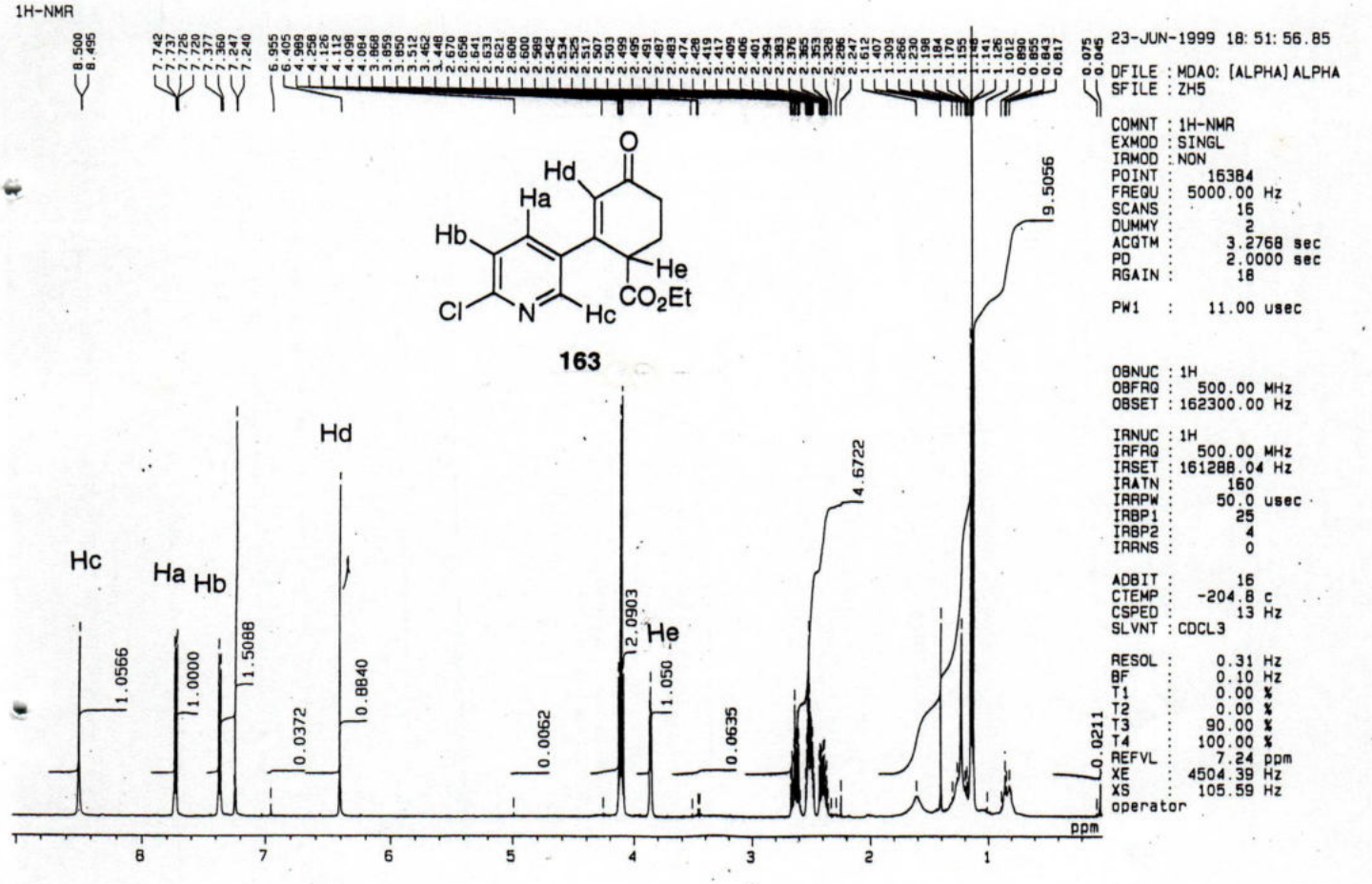
Reagents: a) Zn, benzene, reflux , 80%. b) PCC, CH_2Cl_2 MS-3A (powder), 52% .

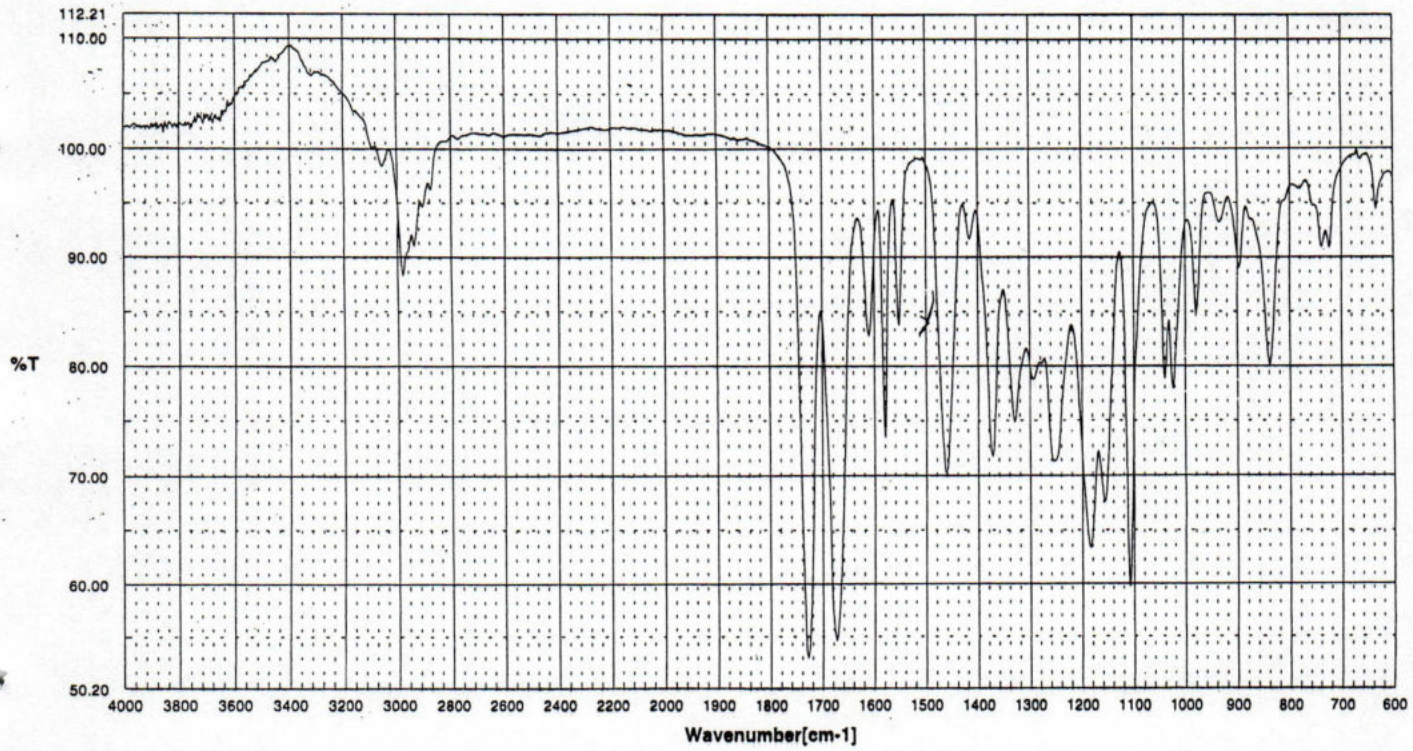
Scheme - 41 : Synthesis of β–keto ester.

1-2-3-2: **Robinson Annulation (For the construction of the key intermediate) .**

Michael addition of the β–keto ester (**160**) with methyl vinyl ketone (**161**) in NaOEt/EtOH by the method of Watt et al.[49] gave diketone (**170**) in 60% yield and then intramolecular aldol reaction was first persued using the same base under reflux to give aromatized product (**171**). Intramolecular aldol reaction was also persued under acidic condition refluxing with conc. H_2SO_4 in acetic acid[50] to afford the desired enone (**163**) in only poor yield. But aldol reaction proceeded very smoothly by refluxing with pyrrolidine by the method of Heathcock et al.[46] to afford the desired enone (**163**) (the key intermediate) in excellent yield as shown in the following scheme:

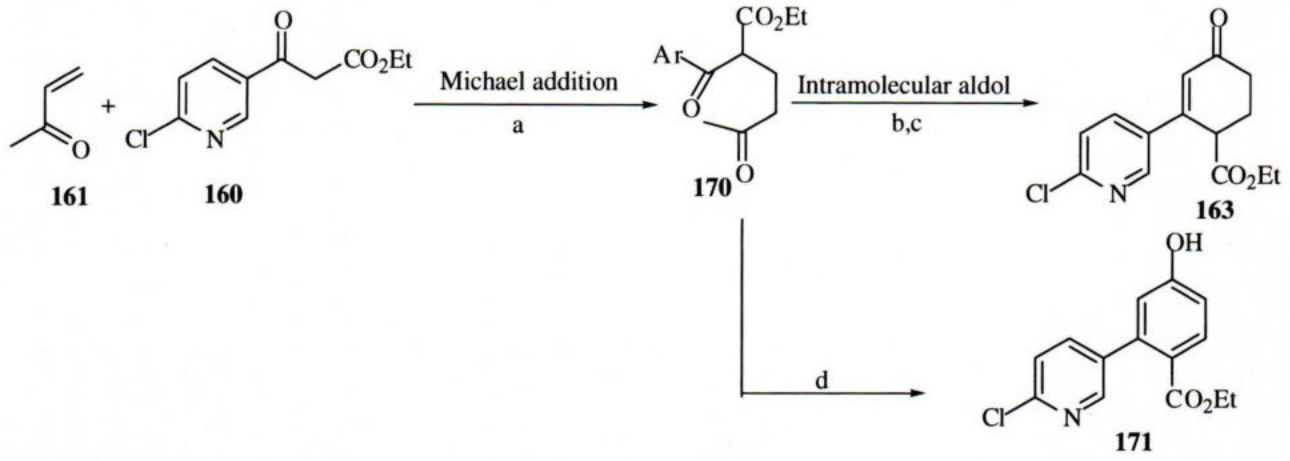
1H-NMR





サンプル名: film
分解: 4 cm-1
アポダイゼーション: Cosine

26
12/10/99 11:39AM

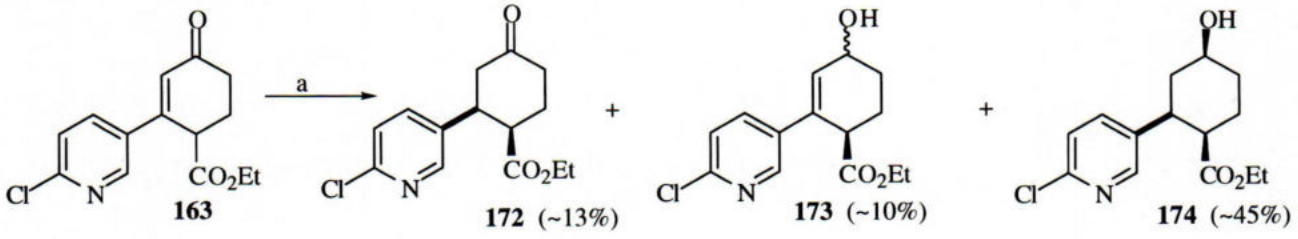


Reagents: a) NaOEt, EtOH, rt, 2.5h, 60% . b) conc.H_2SO_4, CH_3COOH, Reflux, very low yield . c) pyrrolidine, benzene, reflux, 6h, 85% . d) NaOEt, reflux .

Scheme - 42 : Construction of the skeleton of the key intermediate (**163**).

1-2-3-3: **Completion of the Synthesis**

In order to finish the synthesis of epibatidine, the next step was the reduction of enone (**163**) Catalytic hydrogenation of the enone with excess amount of Rh/Al_2O_3 by the method of Barrett et al.[51] gave a mixture of ketone (**172**), allylic alcohol (**173**) and in this case, the undesired *cis*-alcohol (**174**) was obtained as a major product .



a) H_2, Rh/Al_2O_3, EtOH, rt .

Scheme - 43

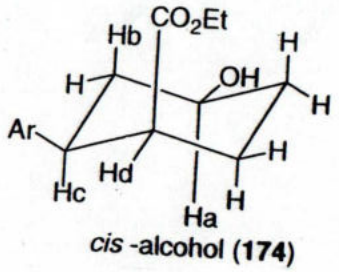
Selective hydrogenation of the double bond, however, was acheived by using the limited amount of catalyst as summarized in table 4.

1H-NMR

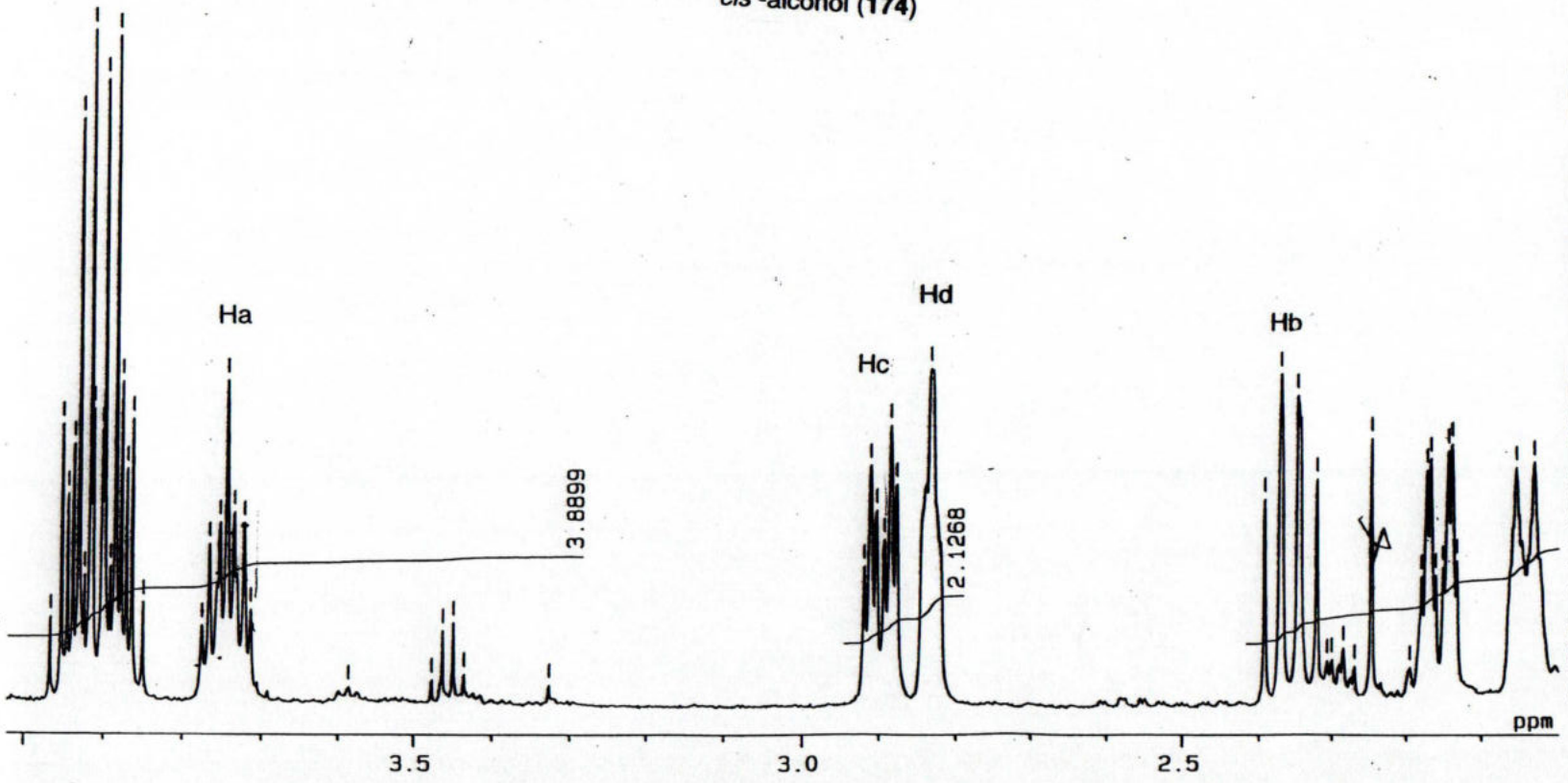
3.968 3.954 3.946 3.939 3.932 3.925 3.918 3.915 3.904 3.901 3.893 3.886 3.879 3.872 3.865 3.850 3.776 3.768 3.755 3.746 3.736 3.724 3.715 3.587 3.477 3.463 3.449 3.435 3.327

2.920 2.912 2.904 2.894 2.885 2.878 2.833

2.392 2.369 2.347 2.320 2.307 2.301 2.286 2.270 2.247 2.196 2.180 2.173 2.168 2.162 2.152 2.145 2.140 2.134 2.054 2.030



cis -alcohol (**174**)



3-JUL-1999 20: 52: 04.30

DFILE : MDA0: [ALPHA] ALPHA
SFILE : ZH5

COMNT : 1H-NMR
EXMOD : SINGL
IRMOD : NON
POINT : 16384
FREQU : 5000.00 Hz
SCANS : 16
DUMMY : 2
ACQTM : 3.2768 sec
PD : 2.0000 sec
RGAIN : 16

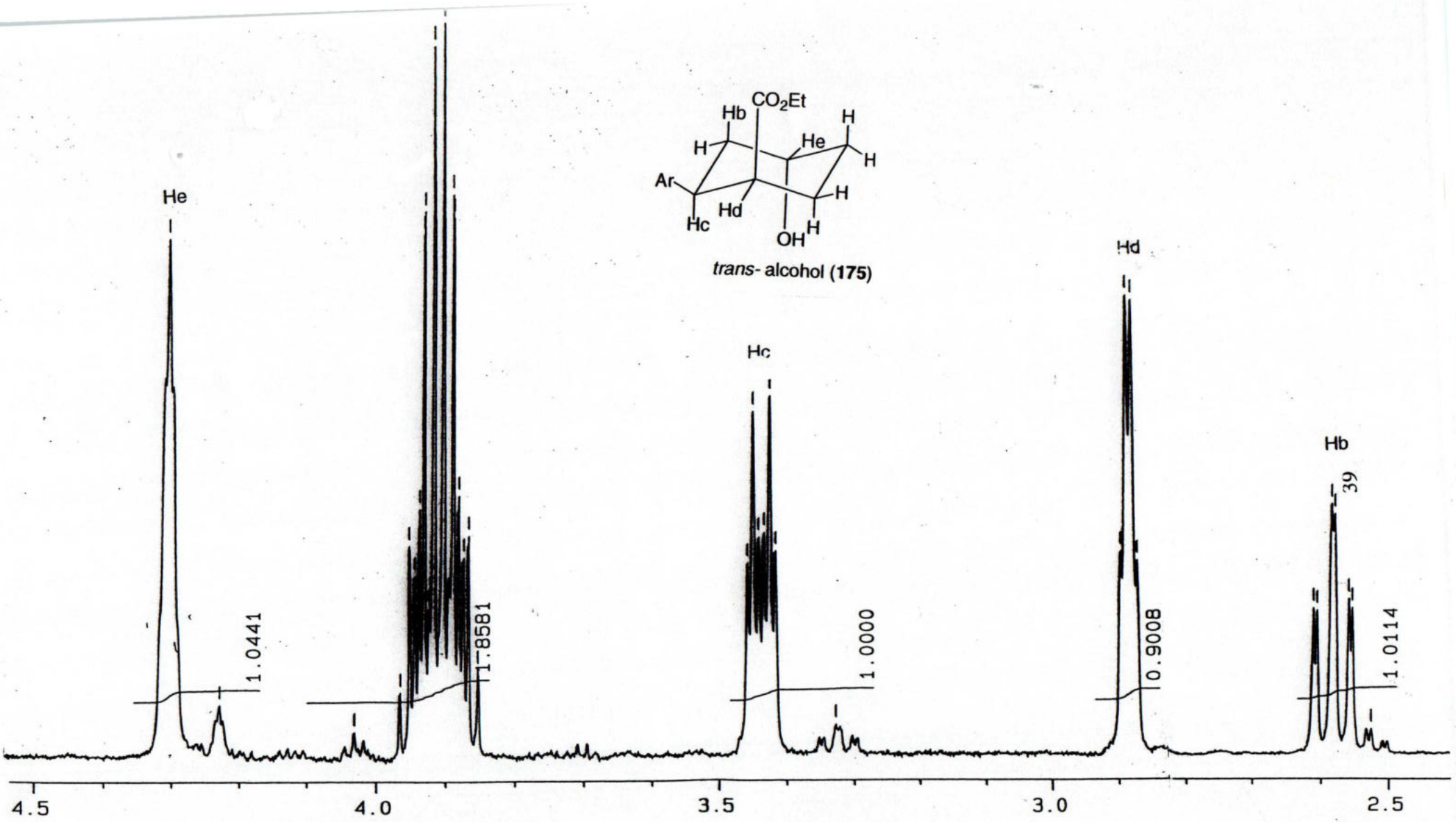
PW1 : 11.00 usec

OBNUC : 1H
OBFRQ : 500.00 MHz
OBSET : 162300.00 H

IRNUC : 1H
IRFRQ : 500.00 M
IRSET : 161288.04
IRATN : 160
IRRPW : 50.0 u
IRBP1 : 25
IRBP2 : 4
IRRNS : 0

ADBIT : 16
CTEMP : 21.9 c
CSPED : 11 Hz
SLVNT : CDCL3

RESOL : 0.31 Hz
BF : 0.10 Hz
T1 : 0.00 %
T2 : 0.00 %
T3 : 90.00 %
T4 : 100.00 %
REFVL : 7.24 ppm
XE : 1012.57 Hz
XS : 866.39 Hz
operator


CO2Et
Hb
H
He
H
H
Ar
Hd
H
Hc
OH
H
trans- alcohol (175)
He
Hc
Hd
Hb
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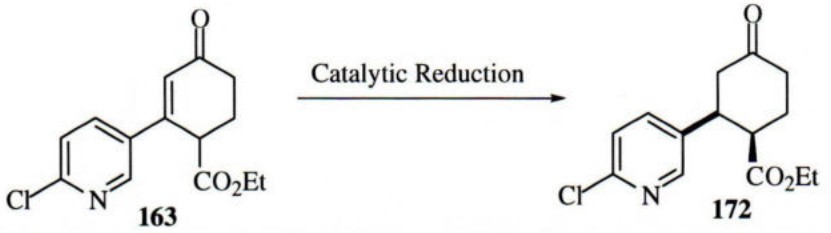
1.8581
1.0000
0.9008
1.0114
39
4.5
4.0
3.5
3.0
2.5

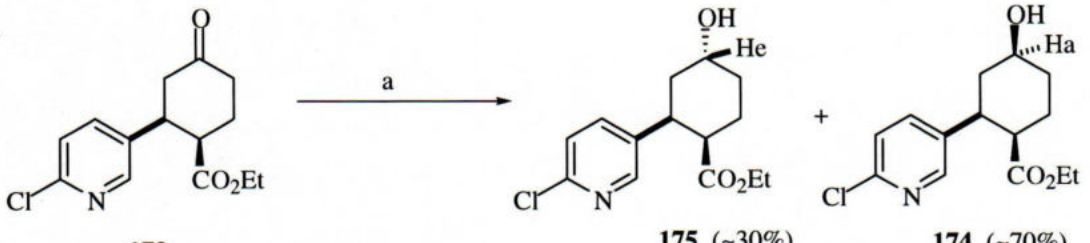


163 **172**

Table-4: Screening for amoumt of catalyst for reduction of compound (**163**) to (**172**)

Entry	Rh/Al_2O_3	Solvent	Temp	Time	% of yield
1	10%	EtOH	rt	over night	76
2	20%	EtOH	rt	6h	76
3	30%	EtOH	rt	3h	85

In order to obtain the desired *trans*-alcohol (**175**), the ketone (**172**) was initially reduced with L-Selectride in THF at -78°C to give a mixture of (**175**) and (**174**)l in a ratio of 3 to 7.



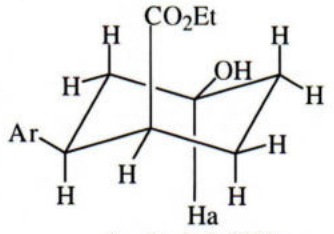
172

175 (~30%) (3:7) **174** (~70%)

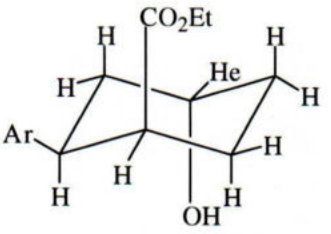
a) L-Selectride, THF, -78°C

Scheme - 44 : Reduction of compound (**172**)

Stereochemistry of the product was easily determined from ^{1}H-NMR because Ha of (**174**) showed large coupling constant comparison with He of (**175**): Ha (3.75 ppm, tt, J = 4.0, 10.5, 15.0 Hz), He (4.31 ppm, br t, $W_{1/2}$ = 10.5 Hz) .



cis -alcohol (**174**)



trans- alcohol (**175**)

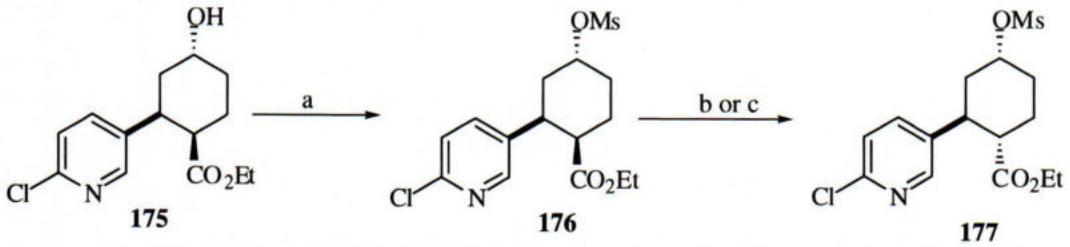
Fig - 7 : *cis*-alcohol and *trans*-alcohol

Therefore, the reduction of the ketone (**172**) with other reducing agents were also examined and the results are summarized in Table 5:

Table 5: Screening for reduction of the ketone (**172**) under different conditions.

Entry	Reagent	Conditions	Time	Trans alcohol : Cis alcohol
1	L-Selectride/THF	-78°C	30 min.	3 : 7
2	$NaBH_4$/EtOH	0°C	30 min.	- : only cis
3	$LiAlH(O^tBu)_3$/THF	0°C-rt	2h	No reaction
4	DIBAL-H/CH_2Cl_2	-78°C	1h	5 : 5
5	Spuer Hydride/THF	-78°C	30 min.	- : only cis
6	K-Selectride/THF	-78°C	30 min.	8 : 2

Finally, I observed that K-Selectride reduction of the ketone (**172**) in THF at -78°C gave the desired *trans*-alcohol (**175**, 80%) as a major product. The *trans*-alcohol (**175**) was treated with MsCl in pyridine/CH_2Cl_2 to give mesyloxy ester (**176**). Then, hydrolysis was executed with 1 M LiOH or 1 M NaOH in THF at 60°C, but unfortunately, in both cases epimerization took place to give compound (**177**).



Reagents: a) MsCl, pyridine, CH_2Cl_2, 0°C to rt, overnight, >80% . b) 1M LiOH, THF, rt to 60°C . c) 1M NaOH, THF, rt to 60°C .

Scheme - 45

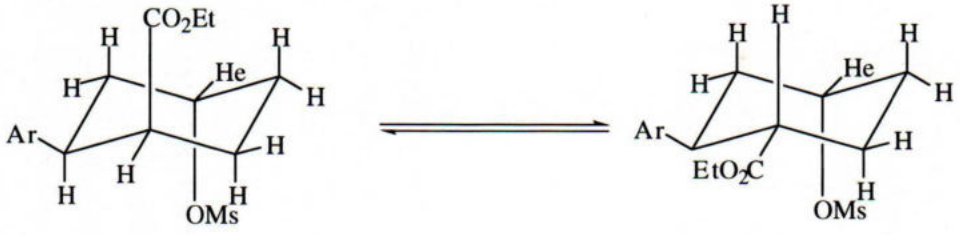
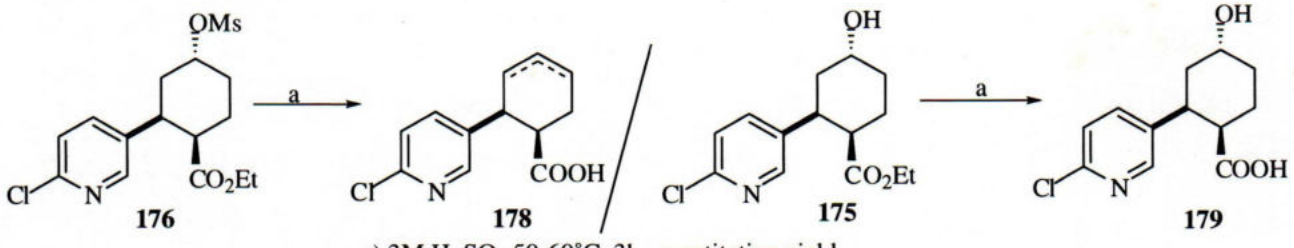


Fig - 8: Isomerization of the mesylate (**176**)

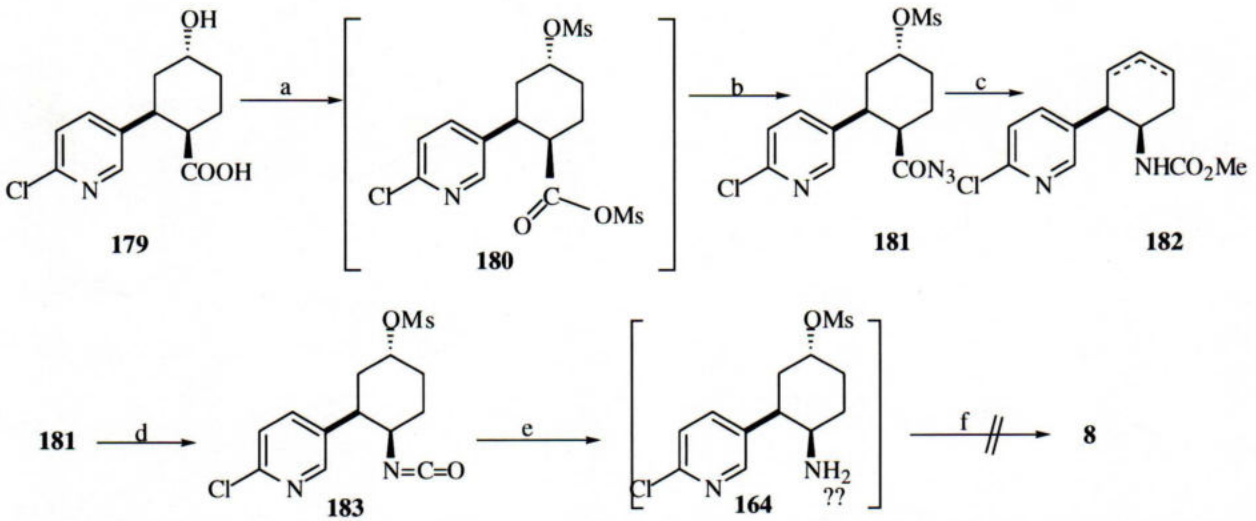
When the mesyloxyester (**176**) was subjected to acid hydrolysis by heating with 3 M H_2SO_4 at 50-60°C concomitant eliminatiom of mesyloxy group occurred to afford a mixture of olefinic acid (**178**) but in this case, epimerization of ester was not observed. So,the *trans*-hydroxyester (**175**) was hydrolyzed under acidic condition to give the desired *trans*-hydroxyacid (**179**, quantitative yield) as shown below.



a) 3M H_2SO_4,50-60°C, 3h, quantitative yield

Scheme - 46

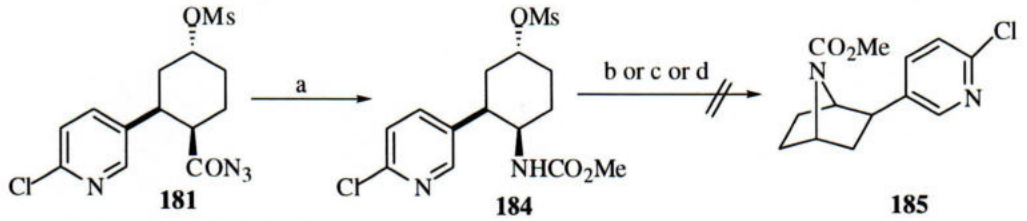
In order to complete the synthesis, the next step was the introduction of amino group via Curtius rearrangement. The hydroxy acid (**179**) was treated with $MsCl/Et_3N$ in acetone at 0°C and successively treated with NaN_3 by the method of Poulter et al.[52] to give crude acyl azide (**181**). When the crude azide (**181**) was heated in toluene at 80-100°C in the presence of MeOH, methylcarbamate (**182**) was formed with concomitant elimination of -OMs group. While, heating the azide (**181**) in dry toluene at 70°C gave isocyanate (**183**), which was identified by IR, but the isocyanate (**183**) was very unstable, and the desired cyclized product (**8**) was not obtained through refluxing in $CHCl_3$



Reagents: a) MsCl, Et_3N, acetone, 0°C . b) NaN_3 . c) toluene, MeOH, 80-100°C . d) toluene, 70°C . e) SiO_2 . f) $CHCl_3$, reflux, 3 days .

Scheme -47

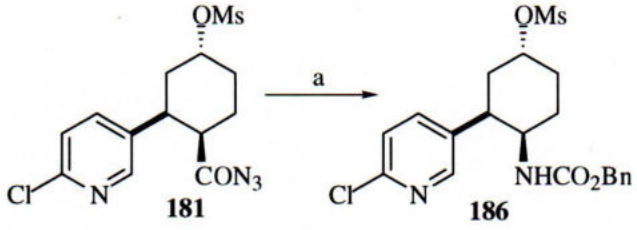
Thus, I turned to obtain protected aminomesylate under milder treatment. Heating the azide (**181**) in benzene-MeOH (1:1) at 70°C for 1 h gave methylcarbamate (**184**, 45% from **179**). Treatment of the methylcarbamate (**184**) neither with potassium *tert*-butoxide nor with KHMDS gave the desired bicyclic carbamate (**185**) .



Reagents: a) C_6H_6:MeOH(1:1), 70°C,1h, (45% from 192) . b) KO^{t}Bu, THF, -78°-4°C, over night . c) KO^{t}Bu(1M solution in THF), -78-4°C . d) KHMDS, THF, -78°C, 1h .

Scheme - 48

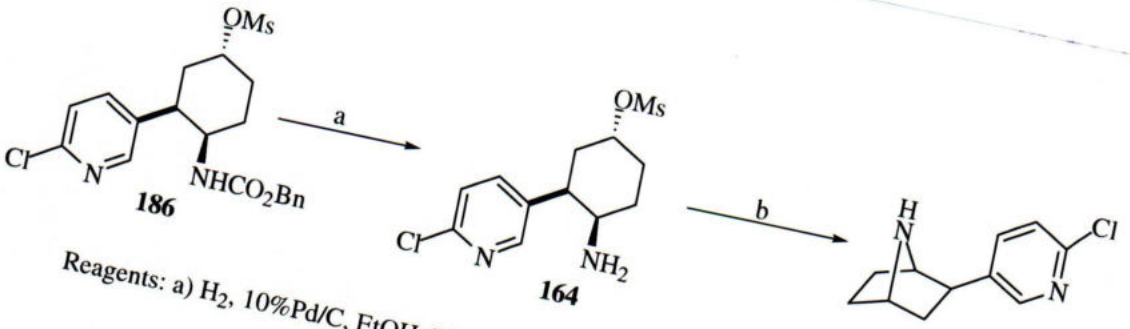
To overcome this problem, benzylcarbamate (**186**) was prepared from azido-compound (**181**) by heating in benzene in the presence of benzyl alcohol.



a) BnOH, C_6H_6, 70°C, over night, 81% from **179**).

Scheme - 49

Finally, debenzylation and the following cyclization of aminomesylate (**164**) to afford the target molecule, (±)-epibatidine (**8**, 78%).

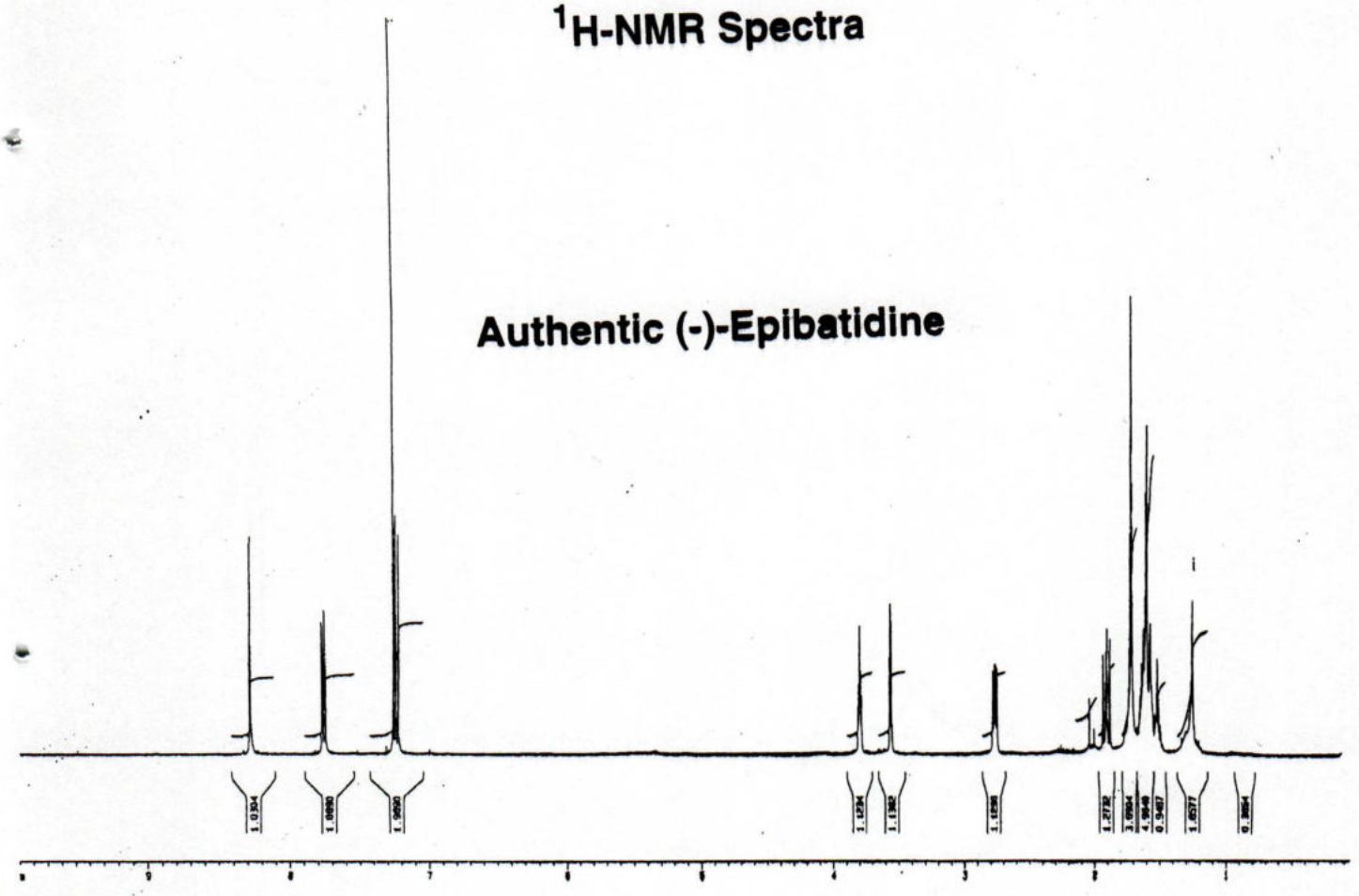


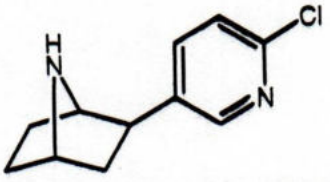
Reagents: a) H_2, 10%Pd/C, EtOH, HCl, 30% . b) $CHCl_3$, reflux, 30h, 78% .

Scheme - 50 : Last key step for synthesis of (±)-epibatidine.

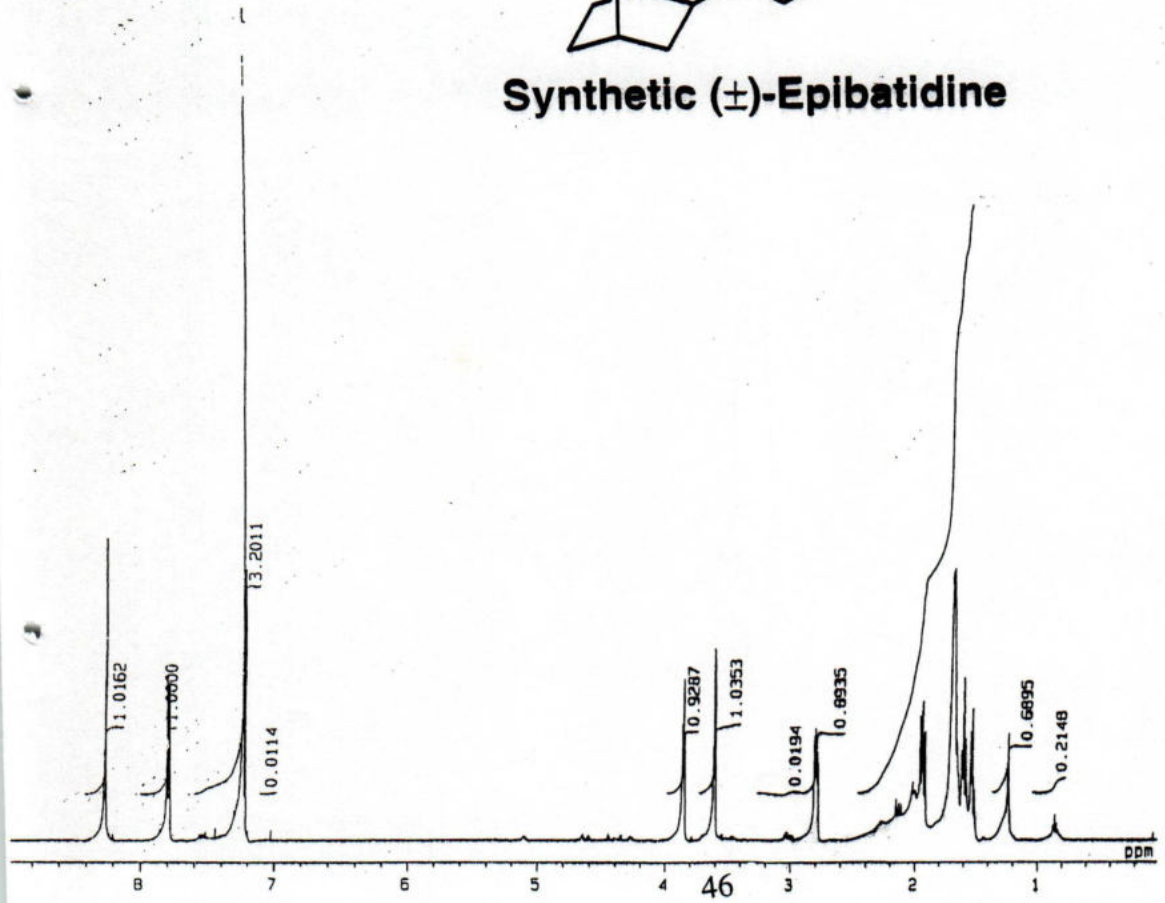
^{1}H-NMR Spectra

Authentic (-)-Epibatidine





Synthetic (±)-Epibatidine



1-3: STUDIES ON THE SYNTHESIS OF SOME ANALOGS AND HETEROCYCLIC MOIETY OF EPIBATIDINE

2-1. INTRODUCTION:

Due to high toxicity of epibatidine (causing death in mice at 10µl/kg scale), the therapeutic development of epibatidine has become a major impediment.[53] Hence, there has been a renewed interest toward searching for a pharmacophore related to the structure of (**8**) that exhibits pharmacological and toxicological activity. In this context, various groups have begun perceiving analogues to (**8**) by combining structural features of the known alkaloids having high affinity toward nicotinic receptors with that of (**8**) and study on their activity as well as toxicity. These studies have led to the design and synthesis of various newer analogues such as **187**,[54a-b] **188**,[55] and UB 165 (**189**) [56].

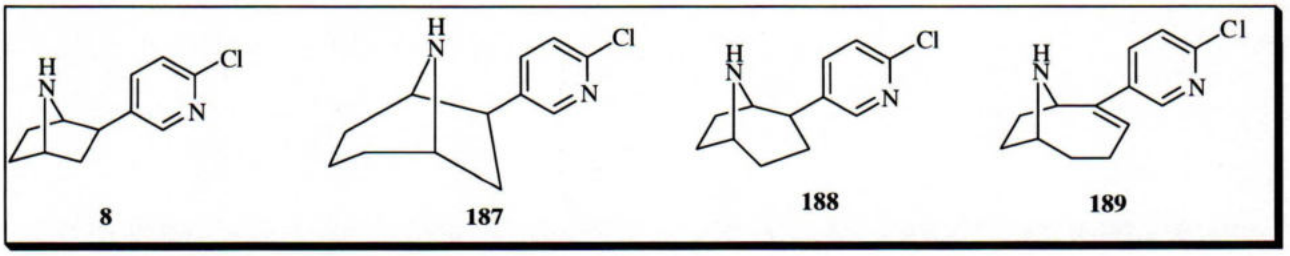
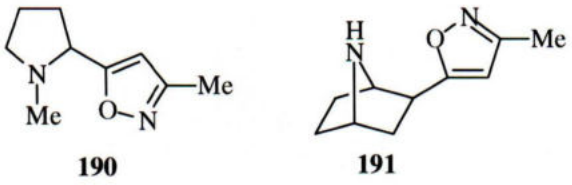


Fig - 9 : Structure of Epibatidine and its newer analogues.

Daly et al.[10] designed a pharmacophore by combining the structural features of the known nicotinic receptor antagonist ABT 418(**190**) [57a-b] and (**8**) and named it epiboxidine (**191**) . Compound (**191**) was shown to be a potent nicotinic receptor agonist and 10-fold less potent antinociceptive agent with 20-fold less toxicity than (**8**)[10].



190 **191**

Fig - 10 : Structure of Epiboxidine

2-2. **RESULTS AND DISCUSSION:**

In the present study, I am interested in synthesizing an methoxy-*epi* epibatidine **192** (a newer analogs of epibatidine) designing a strategy based on Diels-Alder reaction shown below :

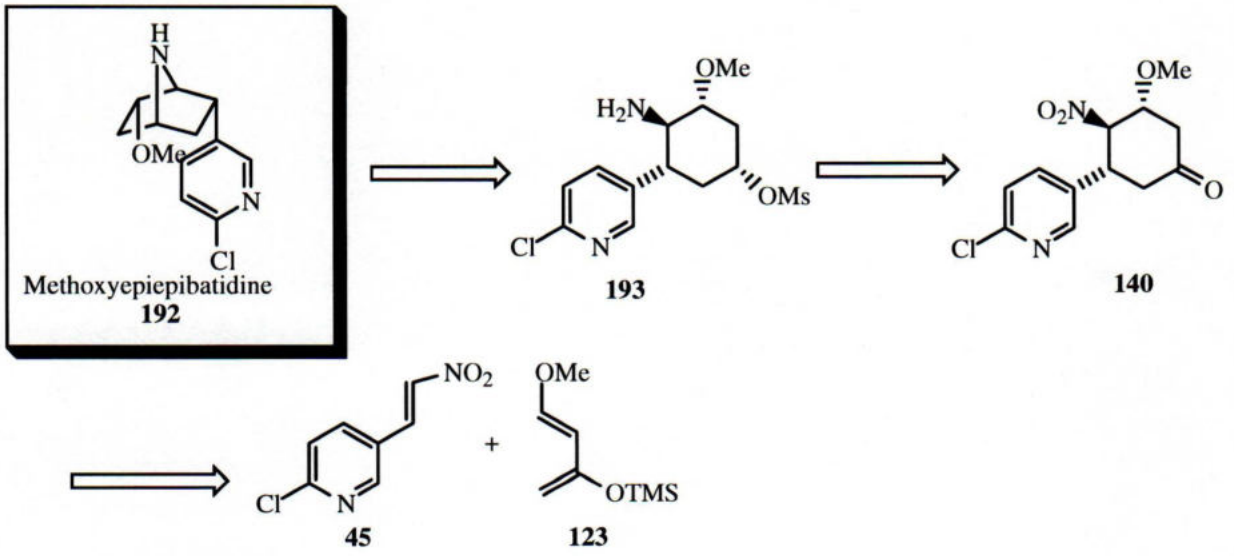
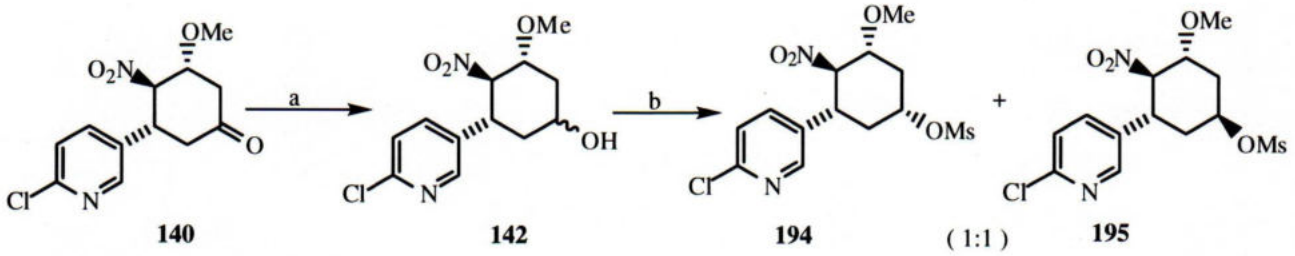


Fig -11: A new strategy for synthesis of methoxy-*epi*-epibatidine.

On the basis of above strategy, using the previous intermediate, methoxy ketone (**140**), a product of Diels-Alder adduct, it was attempted to establish a new and efficient route for the synthesis of methoxy-*epi* epibatidine.

The methoxy ketone (**140**) was first reduced with L-Selectride in THF to give alcohol (**142**,

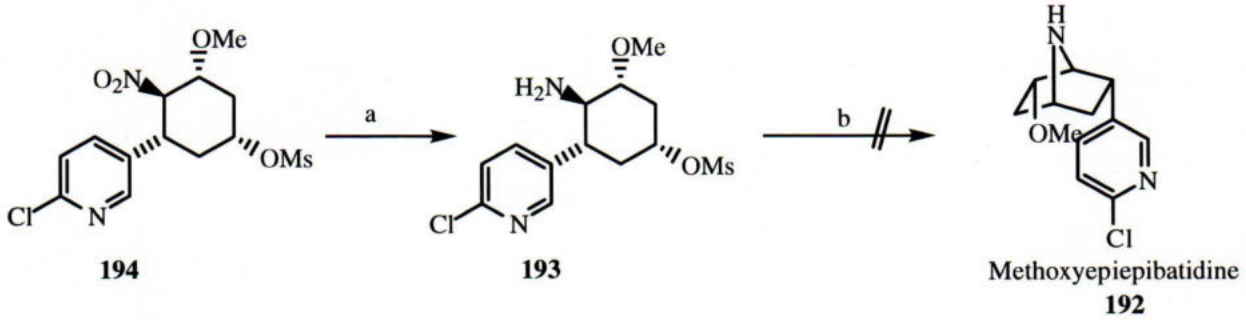
~quantitative yield), which was then mesylated with MsCl/pyridine in CH_2Cl_2 at room temperature for over night by the method of Szantay et al.[13] to afford separable α and β–mesylate in a ratio of 1:1 in quantitative yield.



Reagents: a) L-Selectride/THF, -78°C, 30 min, quantitative yield . b) MsCl/pyridine, CH_2Cl_2, rt, over night, quantitative yield.

Scheme - 51

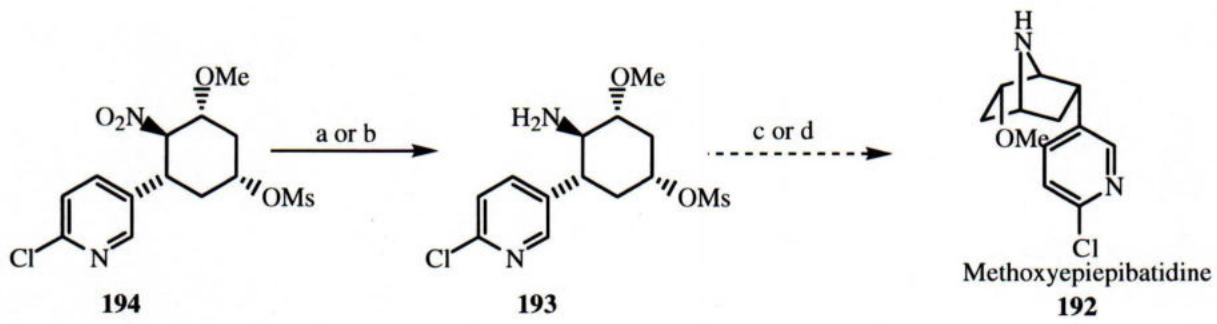
Then reduction of nitro group was first pursued with $SnCl_2.2H_2O$ in refluxing EtOH by the method of Szantay et al.[13] and then the crude mixture was subjected for cyclization under toluene reflux, but it gave complex mixture .



Reagents: a) $SnCl_2.2H_2O$(excess), EtOH, reflux. b) Toluene, reflux, over night.

Scheme -52

Because the reduction with $SnCl_2$ was not clear, reduction of the nitro group was then attempted under catalytic condition in the presence of 10% Pd/C or Pd/Black in MeOH in acidic medium to give a polar amino mesylate. The final cyclization is now under investigation .



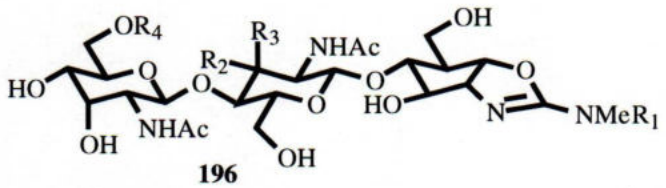
Reagents: a) 10%Pd/C, MeOH, conc.HCl, H_2 atm. b) Pd/Black, MeOH, conc.HCl, H_2 atm. c) $CHCl_3$, reflux, 3days. d) toluene, reflux, over night.

Scheme - 53: Attempted scheme for synthesis of Epibatidine analogs.

CHAPTER - 2: STUDIES ON THE SYNTHESIS OF ALLOSAMIDIN ANALOGS.

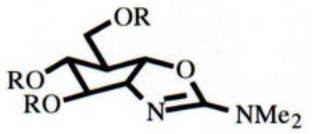
3 - 1: **INTRODUCTION:**

Chitin is widely known as one of the main skeletal components of insect cuticles[58] and microbial cell walls.[59] As its turnover during metamorphoses of insects is controlled by two different types of chitinases and is essential steps for regulating their lifecycles, much attention has been focussed on discovering substances that interact with its biosynthesis and metabolism. Allosamidin (**196a**) and its congeners (**196b-f**) are the first example of endo-chitinase inhibitors. They were isolated from the mycelial extract of *Streptomyces* sp. No.1713 and related Actinomycete by Sakuda et al.[60,61] and Somers et al.(culture A 82516).[62] Structural studies[63-67] revaled that **196a** produced two eqivalents of D-allosamine and one equivalent of an aminocyclitol (**197a**) named allosamizoline with an unusual cyclopentane ring under acid hydrolysis. Milder acid hydrolysis gave a disaccharide composed of D-allosamine and (**197a**). Interestingly, this disaccharide still possessed inhibitory activity, and thus, essential structure for the bioactivity was involved in this molecule.



196

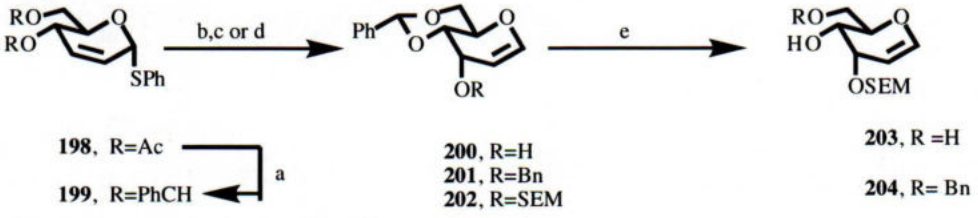
a R_1=Me, R_2=R_4=H,R_3=OH Allosamidin
b R_1=R_2=R_4=H, R_3=OH Demethylallosamidin
c R_1=R_4=Me,R_2=H,R_3=OH Methylallosamidin
d R_1=R_2=H, R_3=OH, R_4=Me Methyl N-demethylallosamidin
e R_1=R_4=Me, R_2=OH,R_3=H Glucoallosamidin A
f R_1=R_3=H, R_2=OH, R_4=Me Glucoallosamidin B



197a R =H Allosamizoline
b R= Ac

Fig - 12 : Structure of Allosamidin.

Its remarkable bioactivity[60-62,64-68] has made this trisaccharide an attractive target for the synthetic chemists and the first synthesis was reported by Griffith and Danishefsky[69] et al. They embarked on a program directed toward its total synthesis. The key feature of their effort was, 1) expeditious syntheses of axial glycal derivatives(**201**) and (**204**) via their recently disclosed [2,3]-sigmatropic rearrangement of anomeric phenylsulfinylpseudoglycals,[70] 2) Use of an enzyme-mediated hydrolysis of prochiral diacetate to provide an enantiospecific route to the properly protected aglycon (**209**) and 3) the application of their sulfonamido-glycosylation methodology for the construction of (**210**) and (**212**). Ferrier type rearrangement of tri-O-acetyl-D-glucal with thiophenol afforded glycal (**198**) (scheme-54). The 4,6-diol obtained from the methanolysis of (**198**) was converted to benzylidene derivative (**199**). The later upon oxidation with 2,2-dimethyldioxirane followed by exposure to diethylamine provided a 96% yield of 4,6-O-benzylidine-D-allal (**200**).

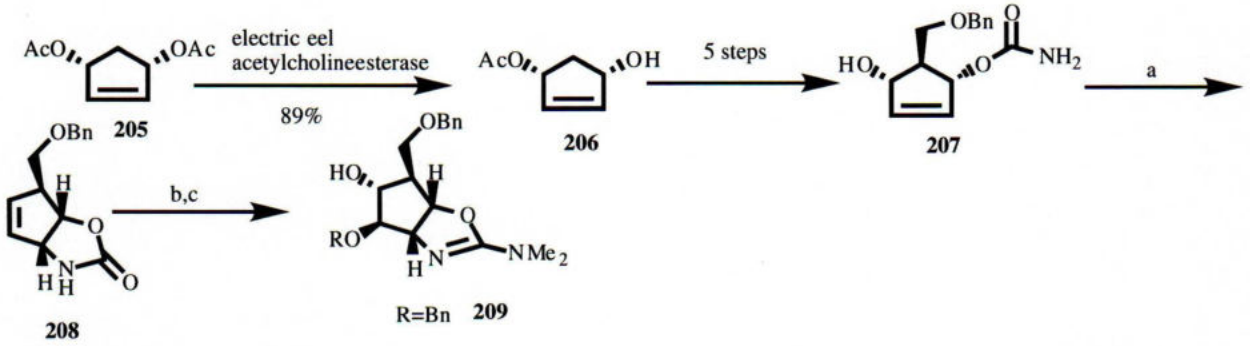


Reagents : a) NaOMe, MeOH, then $PhCH(OMe)_2$, TsOH, DMF, 71% . b) 2,2-dimethyldioxirane, CH_2Cl_2, -78°C, Et_2NH, THF, 96% . c) NaH, THF, BnBr, Bu_4NI, 96% . d) SEMCl, $^iPr_2NEt$, CH_2Cl_2, 100% . e) Na, NH_3, then Bn_2SnO, MeOH, reflux, CsF, BnBr, DMF, 69% .

Scheme - 54

Benzylation under standard condition gave glycal (**201**). Alternatively, the axial alcohol of allal derivative (**200**) was protected as its SEM derivative. Then reaction of (**202**) with sodium in ammonia liberated diol (**203**) , which was directly protected at C6 via its stannylene derivative to gave glycal (**204**) . They completed the synthesis of dibenzylated allosamizoline (**209**) from the compound (**205**). The compound (**205**) was converted to (**206**) by the reaction of electric eel

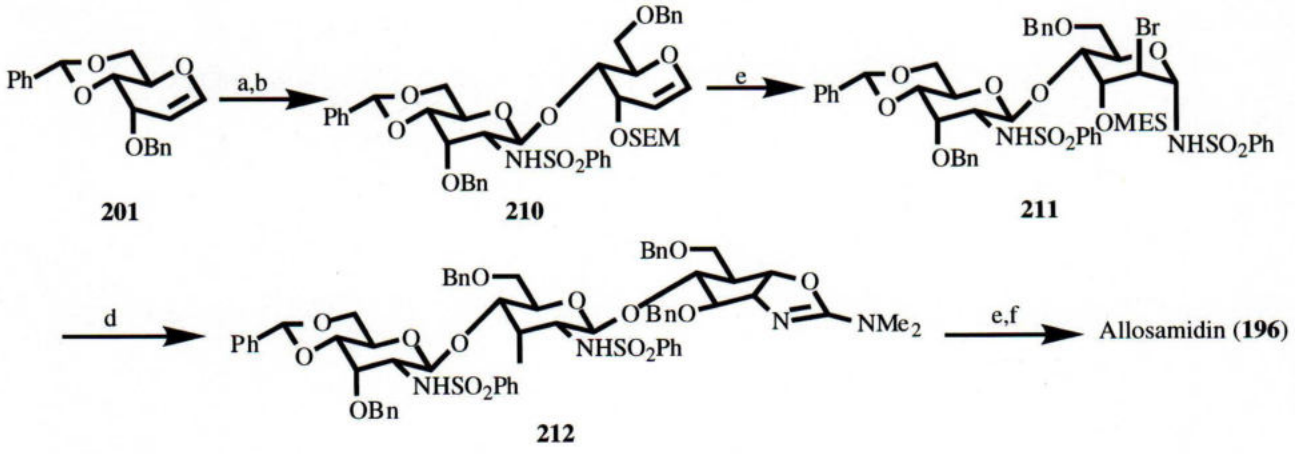
acetylcholineesterase, which after 5 steps gave monocarbamate (**207**). Treatment of (**207**) with trifluoroacetic anhydride-triethylamine gave oxazolidone (**208**), which after 2 steps gave compound (**209**).



Reagents : a) Et_3N, TFAA, THF, -78°C to rt, 63% . b) MeOTf, CH_2Cl_2, Me_2NH, 87% , CF_3CO_3H, TFA, H_2O, 44% . c) Bu_2SnO, MeOH, reflux, BnBr, CsF, DMF, 46% .

Scheme - 55.

With building blocks (**201**), (**204**) and (**209**) in hand, they completed the synthesis of their target by repeating sulfonamido-glycosylation method.



Reagents : a) Br_2NSO_2Ph, CH_2Cl_2, 0°C, NH_4I, EtOH, 63% . b) **204**, KHMDS, DMF, - 40°C to rt, 81% . c) Br_2NSO_2Ph, CH_2Cl_2, 0°C, NH_4I, EtOH, 57% . d) **209**, KHMDS, - 40°C to rt, 30% . e) 5% aq HCl-MeOH, Na, NH_3, Ac_2O, pyridine, 23% .f) NH_3, MeOH, 74% .

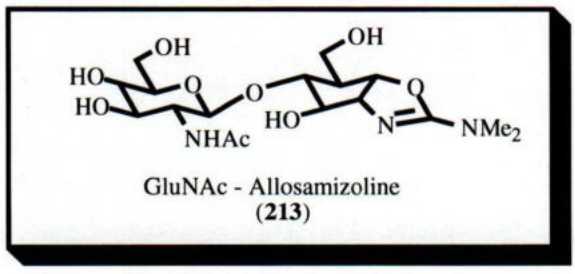
Scheme - 56

More recently, several other syntheses of allosamidin (**196a**) and allosamizoline (**197a**) starting from

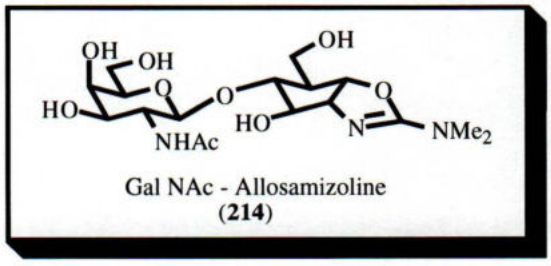
D-glucosamine and from other precursors already have been reported.[71,72]

3 - 2: **RESULTS AND DISCUSSION**

In the present investigation, I am interested in the synthesis of disaccharide analogs of allosamidin (**196a**), i.e some pseudodisaccharides which are the component of allosamidin, not only for developing an efficient route but also for making a precise biological evaluation of this unique bioregulator. On view of this, my initial target was to synthesize Glu-N-Ac-allosamizoline (**213**) and Gal-N-Ac-allosamizoline (**214**) using mono TBS-allosamizoline (**230**) as an acceptor and glycosyl imidiates (**234**) as donor prepared from commercially available D-glucosamine (**215**) as the starting source.



GluNAc - Allosamizoline
(**213**)



Gal NAc - Allosamizoline
(**214**)

Fig - 13: Glu & GalNAc-Allosamizoline.

According to my initial synthetic plan, first synthesized free allosamizoline (**197a**) by modification of the known method of Kitahara et al.[73]by the following scheme.

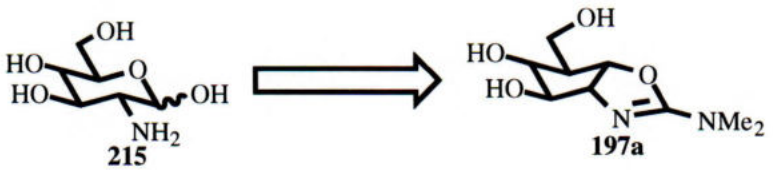
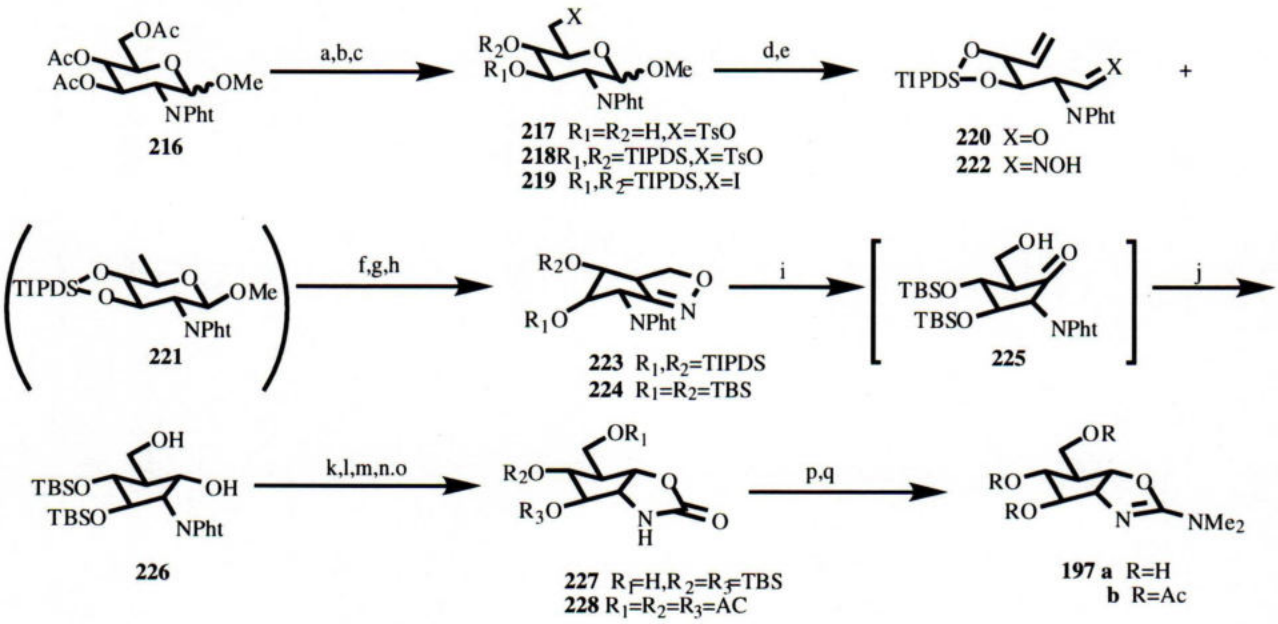


Fig- 14: Synthetic plan of allosamizoline by Kitahara et al.

Treatment of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranoside (**216**)[74] with sodium methoxide in methanol and subsequent selective monotosylation (*p*-TsCl, pyridine, 0-5°C) gave 6-*O*-tosylate (**217**) in a 73% yield. The reaction of (**217**) with dichlorotetraisopropyldisiloxane (TIPDSCl) and imidazole in dry DMF gave TIPDS ether (**218**) in a high yield, which was converted to iodide (**219**) by displacement with sodium iodide in hot DMF (69% from **217**). Reductive ring cleavage, the first key step , was effected by heating (**219**) with freshly activated zinc powder in THF containing 1.5% water for 30 min. under vigorous stirring to give the expected vinyl aldehyde (**220**) and 6-deoxy sugar (**221**). The resultant mixture was treated with hydroxylamine hydrochloride and anhydrous sodium acetate in MeOH to give oxime (**222**), the precursor for cyclization. In this step, the choice of protective group for the C-3 hydroxyl function was very important to afford (**220**) in a better yield via this ring cleavage. When the benzyl group was employed, only a degradation product via the β-elimination of benzylalcohol was obtained. The use of TIPDS ether , however, remarkably improved the yield of desired aldehyde (**220**), possibly because the cyclic TIPDS ether linkage fixed the conformation of (**219**) and (**220**) to prevent further β-elimination.

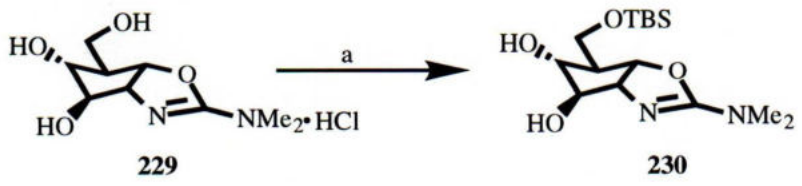


Reagents: a) TsCl, Pyridine, 0-5°C, 20h. b) $TIPDSCl_2$, imidazole/DMF, 45°C,18h. c) NaI, $NaHCO_3$/DMF, 70°C, 18h. d) Zn/THFaq, reflux, 40 min. e) $NH_2OH.HCl$, NaOAc/MeOH, rt,18h. f) 2.5% NaClOaq./CH_2Cl_2, 0°C- rt,10h. g)1M TBAF/THF, rt, 20min. h) TBSCl, imidazole/DMF, 40°C, 4days. i) O_3/CH_2Cl_2.MeOH, -30°C,12h, then Me_2S, -30°C-rt. j) $Zn(BH_4)_2$/THF-ether, 0°C, 2h. k) $NH_2NH_2.H_2O$/EtOH, 70°C, 4h. l) BnOCOCl, Na_2CO_3/CH_2Cl_2-H_2O, 0°C,100 min. m) NaH/THF, rt, 30 min. n) HCl-MeOH, rt, 2.5h. o) Ac_2O, pyridine, rt, 16h. p) Et_3OBF_4/CH_2Cl_2, rt, 20h, then Me_2NH(toluene solution), rt, 48h. q) 1M HCl.

Scheme - 57

When oxime (**222**) was exposed to excess aq. 2.5% sodium hypochlorite in methylene chloride, crystalline isoxazoline (**223**) was obtained as the sole product (91%). Untill this step, I followed the method reported by Kitahara et al,[73] but I improved the following several steps for the synthesis of allosamizoline in better yield and as more practical process. I found that the TIPDS group was too bulky to effect hydrolysis of the phthalimido group at a later stage, so it was converted to the bis-TBS ether. Treatment of **223** with tetra-*n*-butylammonium fluoride (TBAF) in THF gave a crude diol, which was silylated with excess *tert*-butyldimethylsilylchloride (TBDMSCl) and imidazole in DMF at 40℃ for 4 days to give bis-TBS ether (**224**, 87%) with better yield than that of Kitahara's method (60%) . Ozonolysis of compound (**224**) and the successive reductive work-up gave labile β-ketol (**225**), which was immidiately reduced with zinc borohydride in THF and ether at 0℃ to afford diol

(**226**, 52%). Removal of phthaloyl group with hydrazine, benzyloxycarbonylation and successive cyclization with NaH yielded cyclic carbamate (**227**) as a crystalline product (89% from **226**). Desilylation and subsequent acetylation of compound (**227**) gave triacetoxy carbamate (**228**) as a thick syrup (~quantitative yield). Then, triacetoxy carbamate (**228**) was treated with triethyloxonium tetrafluoroborate in methylene chloride and then dimethylamine in toluene at rt for 48h to give allosamizoline triacetate (**197b**, quantitative yield based on the recovery of the starting material), which is the slight modification of Kitahara's method. In my study, I observed that a solution of Me_2NH in CH_2Cl_2 was not suitable, because using freshly prepared Me_2NH solution in CH_2Cl_2 the product was obtained in better yield than using stocked solution. Fortunately, in the case of Me_2NH solution in toluene, it was always obtained in the same yield (~quantitative yield) for all times. Acidic hydrolysis of triacetoxy allosamizoline (**197b**) with 1M HCl at 50℃ for 4.5h afforded allosamizoline hydrochloride (**229**, quantitative yield). In order to provide mono-TBS-allosamizoline (**230**) as acceptor, allsamizoline hydrochloride (**229**) was treated with TBDMSCl/ imidazole in DMF for overnight at room temp to give the desired mono TBS-allosamizoline (**230**, 63%), the structure of which was confirmed by its ^1H NMR.



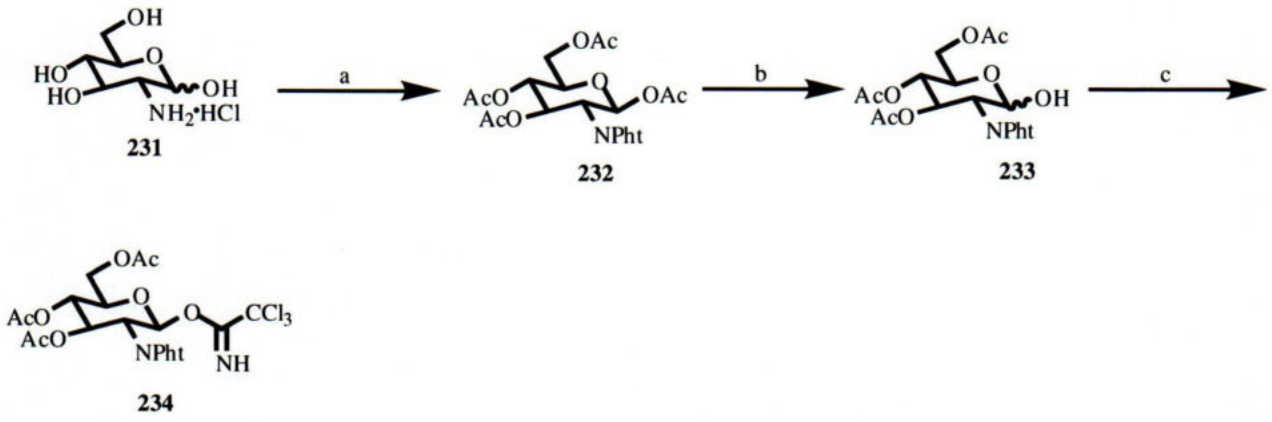
229 **230**

a : TBDMSCl, imidazole/DMF ,rt, over night, 63%

Scheme - 58

The donor was synthesized from D-glucosamine hydrochloride (**231**) by the following scheme . D-Glucosamine hydrochloride was first converted into its phthalimidotetraacetate derivative (**232**),

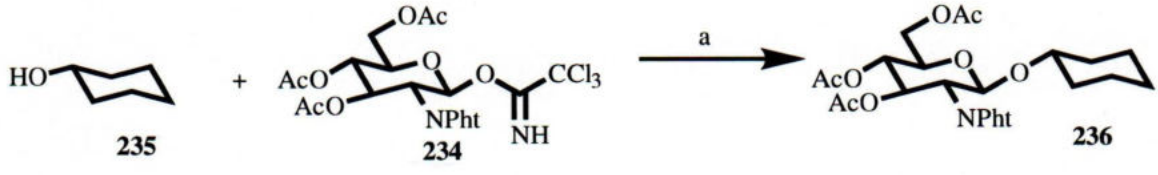
which was then treated with hydrazine acetate in DMF to give hemiacetal (**233**, 86%). The compound (**233**) was treated with CCl_3CN in CH_2Cl_2 in the presence of DBU at 0℃ to give the desired trichloroimidiate (**234**) as a donor (86%) by the method of Schmidt et al.[75].



Reagents: a) i) Na/MeOH, Et_3N, $(C_6H_4CO)_2O$, rt, over night. ii) Ac_2O, pyridine,16h,rt . b) $NH_2NH_2 \cdot AcOH$, DMF, 50°C, 86%. c) CCl_3CN, CH_2Cl_2, DBU, 0°C, 86%.

Scheme - 59

To establish the glycosylation method using trichloroimidate donor, first it was pursued with cyclohexanol (**235**) as an acceptor using TMSOTf as promotor by the method of Ogawa et al.[76]to give the desired glycosylated product (**236**, quantitative yield), the structure of which was confirmed by its ^1H NMR (90 MHz).

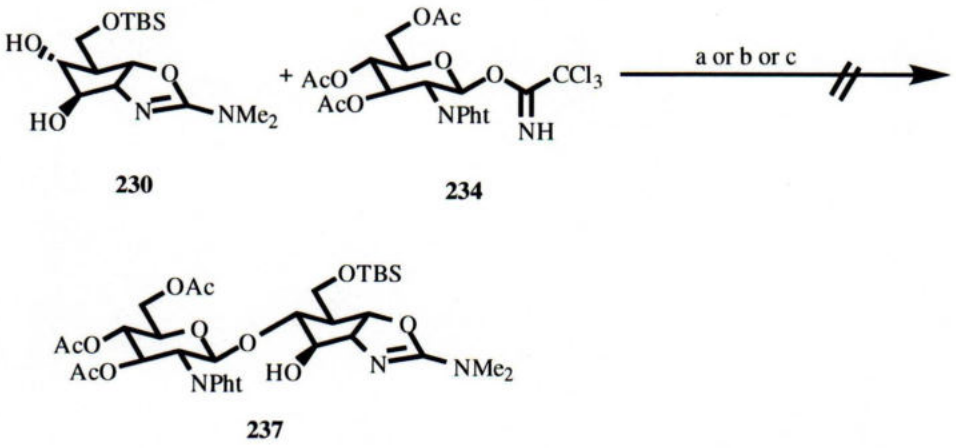


a : MS-AW - 300, CH_2Cl_2, TMSOTf, -78°C.

Scheme - 60

Then, I wanted to adopt this method to synthesize Glu and Gal N-acetyl allosamizoline using mono-

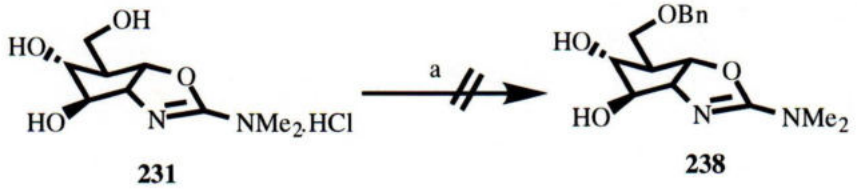
TBS-allosamizoline (**230**) as an acceptor by the following scheme.



Reagents: a) TMSOTf, MS AW-300/DCE . b) TMSOTf, MSAW-300, CH_2Cl_2,-78°C . c) BF_3 Et_2O, MSAW-300, CH_2Cl_2, -78°C.

Scheme - 61

But unfortunately, it was failed to obtain the desired protected disaccharide (**237**), probably because labile protecting TBS group might be deprotected before glycosylation and it caused the formation of complex mixtures of products. In this situation, it was decided to change the acceptor from mono-TBS allosamizoline to monobenzyl allosamizoline (**238**) . Monobenzyl allosamizoline (**238**) is a good acceptor for glycosylation which was synthesized previously by different workers.[77,78] In this case, it was first tried to synthesize monobenzyl allosamizoline (**238**) from allosamizoline hydrochloride directly by benzylation by the method of Roush et al.,[79] and allosamizoline hydrochloride was treated with BnBr in DMF at -50°C, but it gave complex mixture which was difficult for isolation.

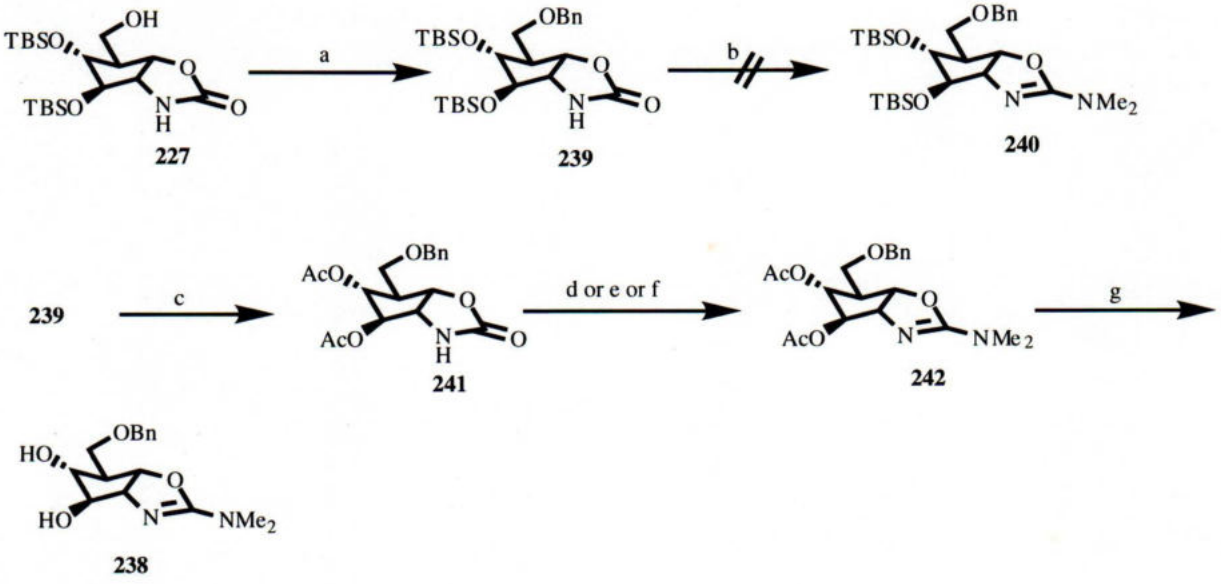


231 **238**

a) BnBr, NaH, DMF, -50°C .

Scheme - 62

Then, the synthetic scheme for the synthesis of monobenzyl allosamizoline (**238**) was changed using my previous intermidiate, bis-TBS carbamate (**227**), and was established a completely new synthetic route to mono benzyl allosamizoline (**238**) as shown in the the following scheme :

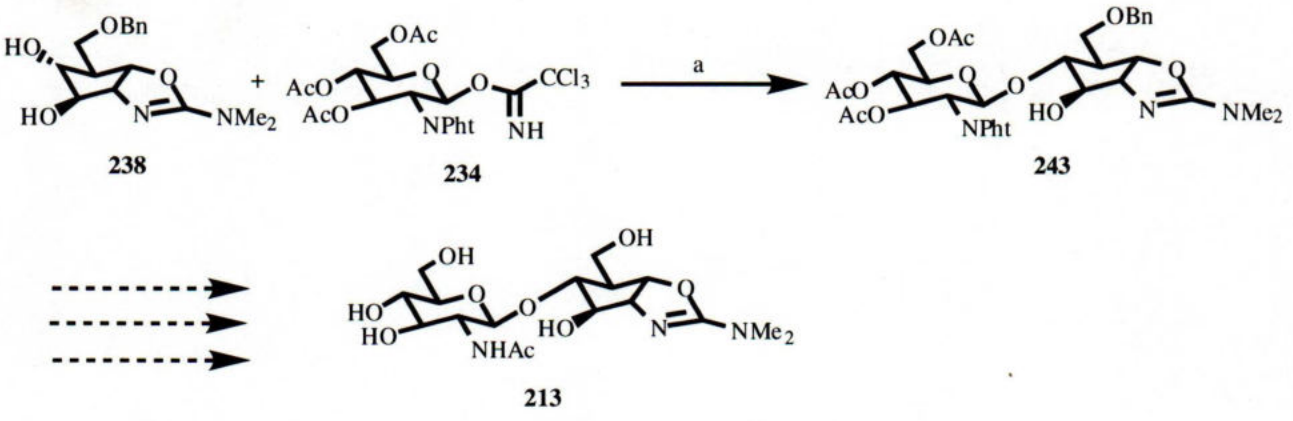


Reagents : a) $CCl_3C(=NH)OCH_2C_6H_5$, CH_2Cl_2-cyclohexane, ca.TFSA, rt, 5h, 100%. b) Et_3OBF_4/CH_2Cl_2, 20h, rt, then Me_2NH(toluene solution), 24h, rt. c) i) conc.HCl/MeOH, rt, 2.5h . ii) Ac_2O, pyridine, DMAP, over night, 2 steps, 70%. d) i) Et_3OBF_4/CH_2Cl_2, 24h, rt, then Me_2NH (toluene solution), rt, 48h. e) MeOTf/CH_2Cl_2, rt, 24h, then Me_2NH (toluene-solution), rt, 48h . f) MS-4A, Et_3OBF_4/CH_2Cl_2, rt, 24h, then Me_2NH (toluene solution), rt, 48h, 45% (90% based on recovered **241**). g) NaOMe/MeOH, rt, over night, 85% .

Scheme - 63

In the novel route, benzylation was performed under acid-catalised condition.[80] Thus, bis-TBS carbamate was treated with benzyl trichloroacetimidiate in CH_2Cl_2-cyclohexane in the presence of catalytic amount of TFSA afforded quantitative yield of benzyloxy bis-TBS carbamate (**239**) by the slight modification of Bundle et al. When the substrate (**227**) was treated with excess amount of TFSA according to the method of Bundle et al. one of the TBSO group was deprotected to give a mixture of monobenzylated product together with some extent of dibenzylated product. In order to obtain monobenzyl allosamizoline (**238**) as an acceptor , the compound (**239**) was treated with triethyloxonium tetrafluoroborate in CH_2Cl_2 for 48h and successively with Me_2NH in toluene for another 48h in one pot with concomitant deprotection of bis TBS group to afford only poor yield of mono benzyl allosamizoline (**238**) . Therefore, the compound (**239**) was treated with conc. HCl in MeOH to give diol, which was then acetylated with acetic anhydride in pyridine in the presence of DMAP for overnight to yield monobenzyl diacetylated carbamate (**241**, 70%). In order to afford the acetylated monobenzyl allosamizoline, the carbamate (**241**) was treated with triethyloxonium tetrafluoroborate in CH_2Cl_2 for 48h and then with Me_2NH toluene solution by the method of Kitahara et al.[73] It was observed benzyl group was deprotected during the reaction. When the carbamate (**241**) was treated with MeOTf/CH_2Cl_2 and then with Me_2NH tolune solution by the method of Griffith and Danishefsky et al.[69] cocomitant deprotection of -OBn & OAc groups were observed. It is very difficult to explain above situation but probably due to small scale reaction, it was not possible to remove moisture completely from the reaction mixture which caused the deprotection of both -OBn and OAc group. Interestingly, addition of MS-4A (powder form) to the reaction medium was extremely effective to circumvent this difficulty and the desired protected monobenzyl allosamizoline (**242**, 90%) was obtained in excellent yield. Finally, deprotection of acyl group with NaOMe in MeOH stirring overnight at room temperature afforded monobenzyl allosamizoline (**238**, 85%).

In order to furnish the synthesis of pseudo disaccharide, GluNAc allosamizoline (**213**), mono-benzyl allosamizoline (**238**) acceptor underwent glycosylation with imidiate donor (**234**) using TMSOTf as promotor by the method of Ferrier et al.[77] to give protected GluNAc-allosamizoline (**243**, 48%). The formation of a β–glycosidic bond between the anomeric carbon of glycolsyl imidate (**234**) and the C-7 hydroxyl of monobenzyl allosamizoline was confirmed by ^{1}H NMR. The regioselectivity of the glycosylation almost coincides with the result of glycosylation reported by Vasella et al.[81]

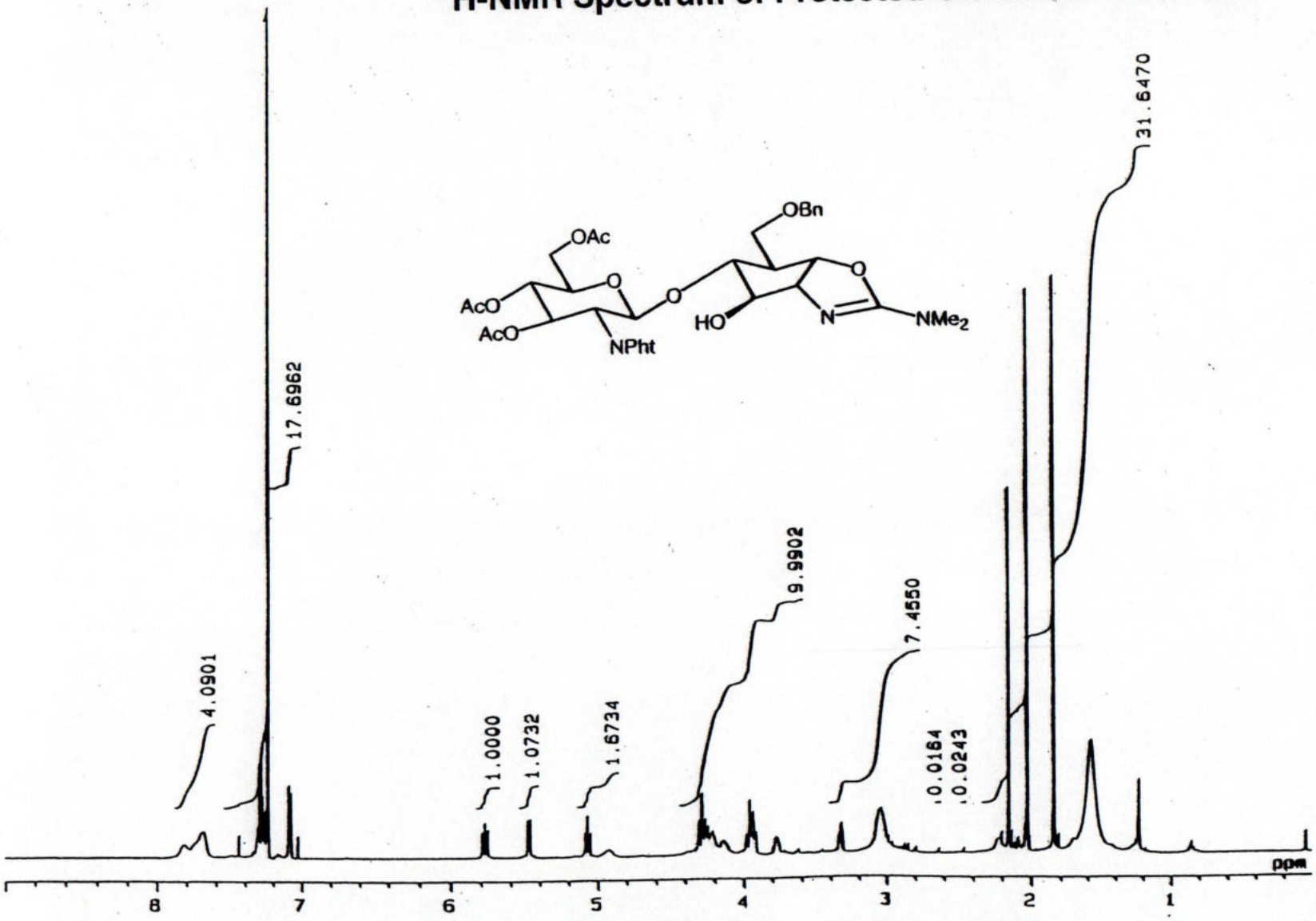


a) MS-AW300, CH_2Cl_2, TMSOTf, 0°C, 30 min, 48% .

Scheme - 64

From the compound (**243**) after 4 steps, I might be able to get the desired pseuodo disaccharide i.e GluNAc- allosamizoline (**213**), and similarly using galactosylimidiate donor I may also be able to get GalNAc- allosamizoline (**214**). So, after large scale preparation of mono benzyl allosamizoline as donor I will further proceed for synthesis of some disaccharide and also allosamidin (**196**) for their greater biological interest, which will be reported in due course.

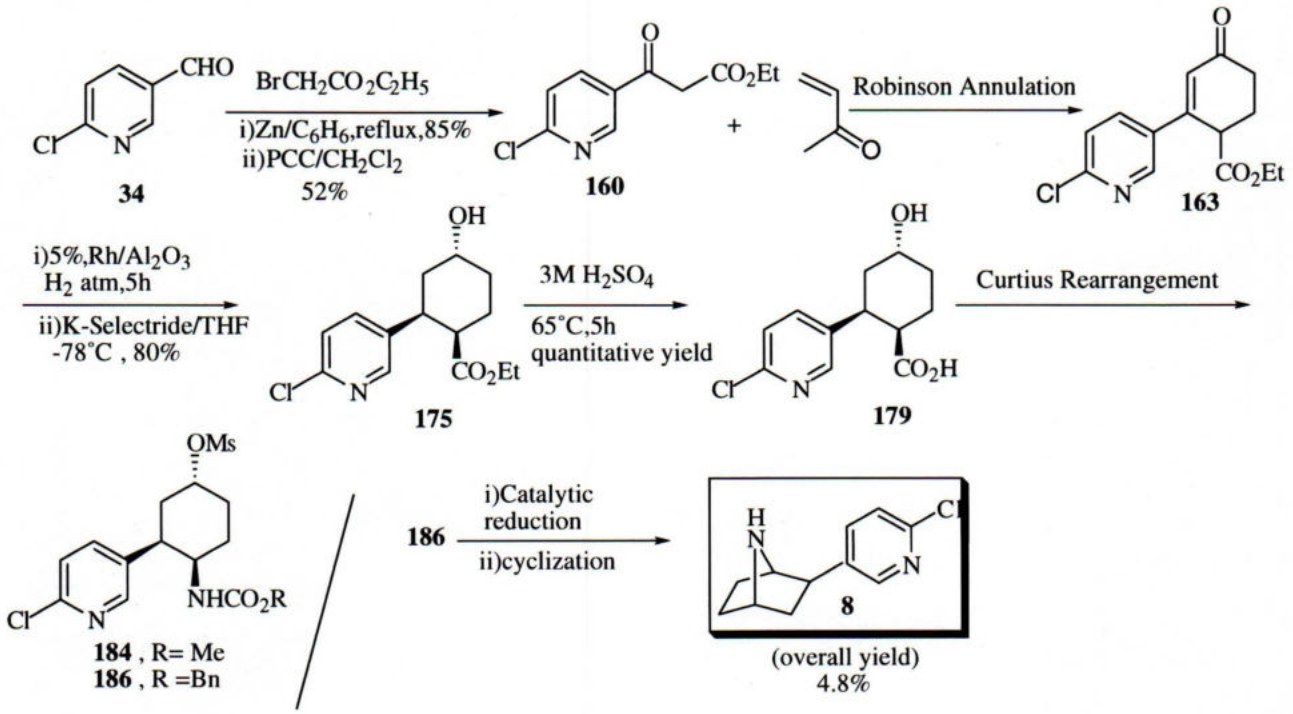
^{1}H-NMR Spectrum of Protected GlcNAc-allosamizoline



In conclusion, I established the novel and more efficient route to the protected allosamizoline derivatives useful for the synthesis of analogs and the preparation of disaccharide derivatives.

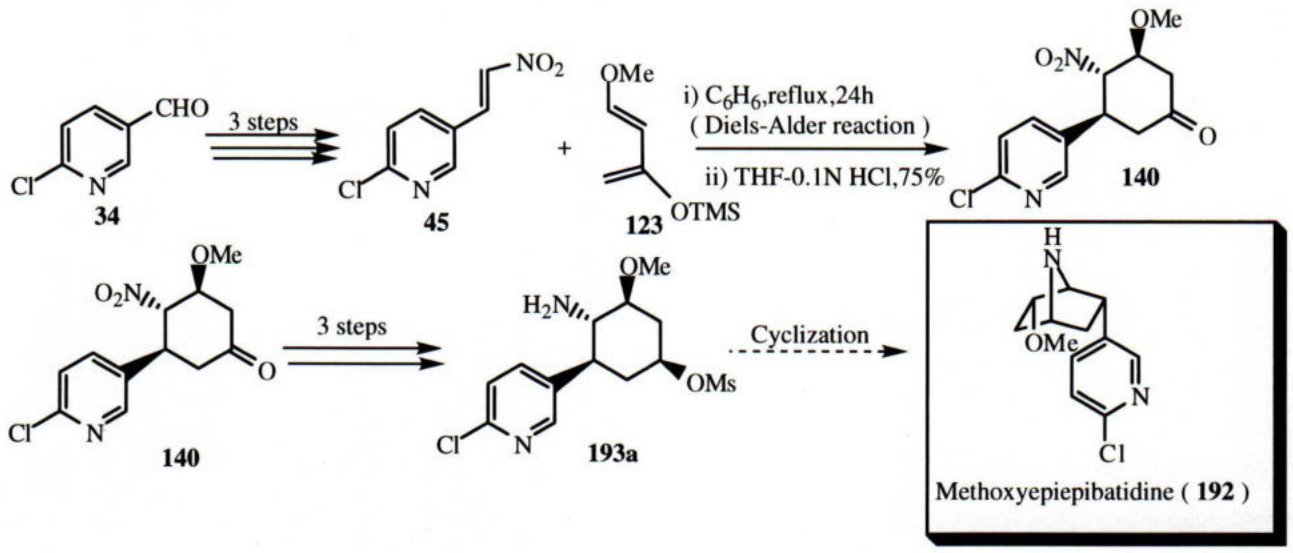
SUMMARY

In Chapter-1, I developed a completely new route for the synthesis of (±)-epibatidine using 6-chloropyridine-3-carbaldehyde (**34**). The strategy was basically based on Robinson Annulation for the construction of skeleton key intermediate (**163**), introduction of -NH_2 group via Curtius Rearrangement and then cyclization, I finished the synthesis of (±)-epibatidine within 10 steps.



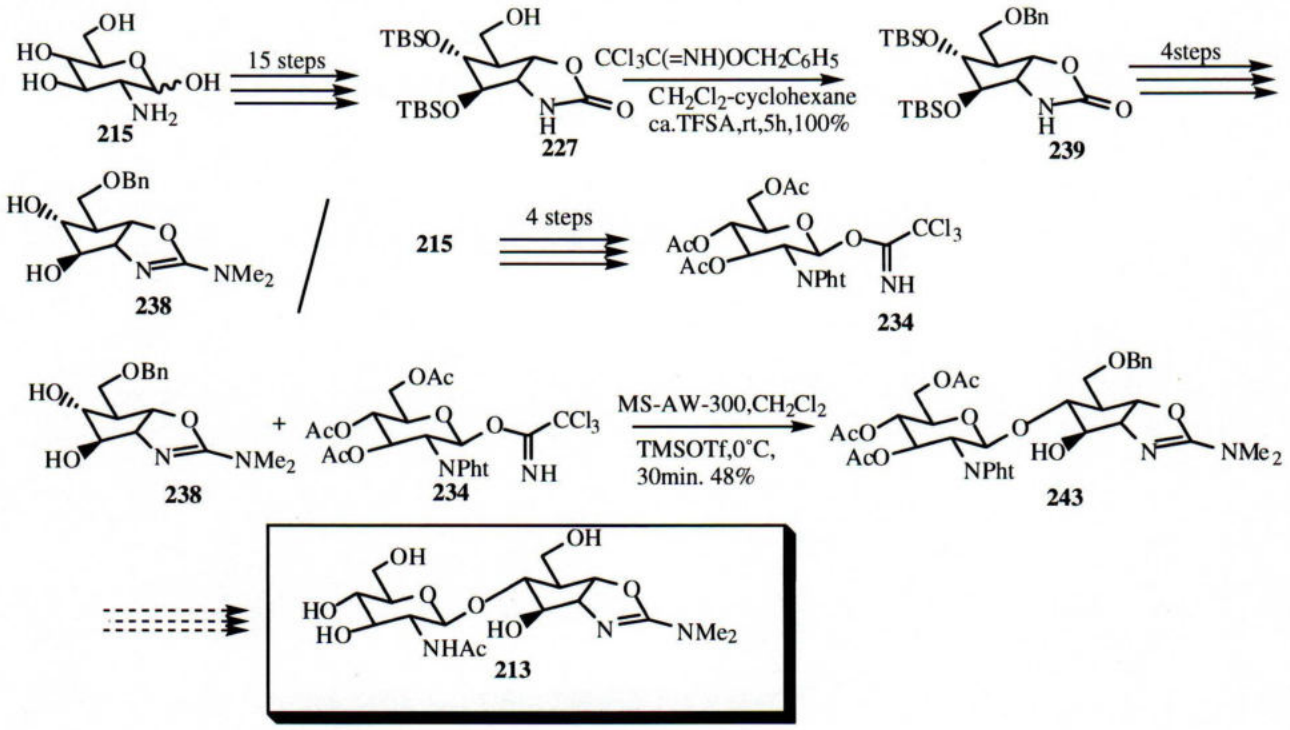
Scheme - 65 : A new route for the synthesis of (±)-epibatidine.

In section 1-3, I attempted to develope a new route for the synthesis of epibatidine analogs based on Diels-Alder reaction for the construction of the key intermediate (**140**) using Danishefsky diene (**123**) and nitroethylene (**45**) as a dienophile.



Scheme - 66 : Attempted new route for the synthesis of Epibatidine analogs.

In Chapter-2, I developed a novel route for the synthesis of monobenzylallosamizoline (**238**), which was shown to be a good acceptor for the synthesis of allosamidin (**196**) and its analogs. Using monobenzylallosamizoline (**238**) and trichlorimidiate (**234**) as donor, I also developed the synthesis of protected GluNAc-Allosamizoline (**243**) as shown:



Scheme - 67: A novel route for the synthesis of monobenzyl allosamizoline and protected disaccharide.

EXPERIMENTAL SECTION

General methods:

Tetrahydrofuran, benzene and toluene were distilled from Na/benzophenone. Methylene chloride was distilled from P_2O_5. All reactions involving oxygen or moisture sensitive compounds were performed under argon atmosphere. Organic extracts were dried with anhydrous magnesium sulfate/sodium sulfate and concentrated with a rotary evaporator under reduced pressure. Melting point (m.p) data were determined with Yanagimoto micro-melting point apparatus and are uncorrected. IR Spectra were measured with a Jasco A-102, Jasco FT/IR-230 IR Spectrometer. ^{1}H and ^{13}C NMR spectra were measured with Jeol JNMEX - 90 (90 MHz), Bruker AC - 300 (300 MHz), and Jeol JNM - A 500 (500 MHz) spectrometer. Optical rotation values were determined with a JASCO DIP 370 Polarimeter at 20 ± 3°C. Silicagel column chromatography was performed on Merck Kiselgel 60, art No.7734, while thin layer chromatography (TLC) was performed with silicagel 60 F254 (Merck).

2-Trimethylsilyloxy-1,3-butadiene (**46**).

An oven-dried, 300 ml three-necked, round-bottomed flask was fitted with two oven-dried dropping funnels and a glass stopper, and placed in an 80 - 90°C oil bath. Under an inert atmosphere, methyl vinyl ketone (10g, 142.67mmol) in 10 ml of dimethylformamide (DMF) and chlorotrimethylsilane (23.1g, 212.72mmol) in 13.3 ml of DMF were added over 30 min to a magnetically stirred solution of triethylamine (22.5g,222.35mmol) in 111 ml of DMF. The reaction mixture gradually darkened from colouress to yellow or dark brown, and yielded a white precipitate of triethylamine hydrochloride. The reaction mixture was allowed to stand overnight, cooled to room temperature and filtered. The filtrate was transferred to a 1-L separatory funnel containing 120 ml pentane. To this was added 400 ml of cold 5% sodium bicarbonate solution to facilitate the separation of phases and removal of DMF. The pentane layer was separated and the aqueous layer was extracted twice more with 200 ml of pentane. The combined pentane extract was washed with 100 ml of cold distilled water, and dried over anhydrous magnesium sulfate. The pentane and other volatiles were removed by fractional distillation with a 2-in. steel-wool packed column in a 70°C oil bath. Using an aspirator vaccuum, (6.09g, 30%) of the product **46** was obtained as a colourless oil, bp 50-55°C (50 mm Hg).

IR (solution of CCl_4): ν_{max} = 3050 cm^{-1}, 2950, 1620, 1560, 1400, 1360, 1300, 1250, 1060, 1000, 960, 920, 880, 850, 750;

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.00 - 4.82 (3H, m, 12 line, s. ABC vinylic pattern), 4.12 (2H, br s,), 0.33 (9H, s).

6-Chloropyridine-3-carbaldehyde (**34**)

To a solution of compound **125** (12g, 86.64mmol) in dry toluene (300ml) at -78°C was added diisobutylaluminium hydride (DIBAL-H, toluene solution, 1.01M, 96 ml, 96 mmol) dropwise under argon atmosphere. After stirring the mixture at the same temperature for 1h, excess amount of methanol was added to it slowly and the reaction mixture was warmed up to room temperature. Saturated potassium-sodium tartrate tetrahydrate aq. solution was added and the mixture was stirred for another 3h at room temperature. The aqueous layer was extracted with Et_2O (3 x 500ml). The combined extract was dried over anhydrous $MgSO_4$ and concetrated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane-ethylacetate (7:1) to give compound **34** (7.3g, 60%) as white solid.

^{1}H-NMR (90 MHz, $CDCl_3$): δ = 10.0 (1H, s, -CHO), 8.86 (1H, d, J = 2.7 Hz),8.18 (1H, dd, J = 2.7 Hz, 8.4 Hz), 7.56 (1H, d, J = 8.46 Hz)

6-Chloro-3-(2-nitro-1-hydroxyethyl)pyridine (**126**)

To a solution of the aldehyde **34** (5g,35.33mmol) in dry methanol (125 ml), nitromethane (2.6g, 42.47 mmol) was added. Then at 0°C, powdered NaOMe (2.3g, 42.58mmol) was added to it under argon atmosphere and the mixture was stirred at 0-5°C for 18h. Acetic acid (2.79g,46.46 mmol) was added and the mixture was stirred for another 2h at room temperature. Solvent was evaporated under reduced pressure to give solid residue, which was chromatographed on silica gel eluting with hexane-ethylacetate (1:1) to give compound **126** (6.65g, quantitative yield) as light brown oil.

IR (Solution of $CDCl_3$) : ν_{max} = 3250 cm^{-1},(br), 1570 (s), 1460 (s), 1380 (s), 1100 (m), 1025 (s), 910 (s), 840 (s).

^{1}H-NMR (500MHz, $CDCl_3$) : δ = 8.39 (1H, d, J = 2.0 Hz), 7.74 (1H, dd, J = 2.0 Hz, 8.5 Hz), 7.37 (1H, d, J = 8.5 Hz), 5.52 (1H, dd, J = 3.5 Hz, 9.5 Hz), 4.79 (1H, m), 4.59 (1H, dd, J = 9.5Hz, 13.5 Hz), 4.53 (1H,dd, J = 3.5Hz, 13.5 Hz).

(*E*)-2-Chloro-5-(2-nitrovinyl)pyridine (**45**)

To a solution of the compound **126** (5g, 24.91mmol) in dry CH_2Cl_2 (125 ml), excess amount of triethylamine (Et_3N) was added. Then methanesulfonyl chloride (6.0g, 52.38 mmol) was added and the mixture was refluxed for 1h . The reaction mixture was cooled to room temperature and diluted with Et_2O. Organic layer was separated and the aqueous layer was extracted with Et_2O (3l x 50ml). The combined ether extract was washed with 1N HCl, saturated sodium bicarbonate solution and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give crude brown solid, which on crystallisation from ether-hexane gave yellow crystal of compound **45** (2.3g, 50%).

IR (Nujol) : ν_{max} = 1635 cm^{-1} (s), 1460 (s), 1380 (s), 1155 (s), 1100 (s), 970 (s).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.58 (1H, d, J = 2.0 Hz), 7.94 (1H, d, J = 14.0 Hz), 7.79 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.59 (1H, d, J = 13.5 Hz), 7.43 (1H, d, J = 8.5 Hz).

$C_7H_5O_2N_2Cl$ Calc. : C, 45.55 H, 2.73 N, 15.1

Found : C, 45.03 H, 3.03 N, 14.75

(2*RS*,4*R**,5*S**)-2-Bromo-5-[3-(6-chloropyridyl)]-4-nitro-cyclohexan-1-one (**119**)

(Sealed tube reaction) :

A solution of the nitroethylene **45** (0.3g, 1.626 mmol) in dry toluene (20 ml) and 2-trimethylsilyloxy-1,3-butadiene **46** (0.9g, 6.338 mmol) in a sealed tube was heated in oil-bath at

120-130°C for 48h. Toluene was evaporated completely to dryness.

To a solution of above crude mixture in CCl_4 (30 ml) at 0°C, was added bromine (0.09 ml, 1.746 mmol) and the mixture was stirred for 1h at room temperature. The reaction mixture was poured into aqueous sodium bicarbonate solution and the aqueous layer was extracted with $CHCl_3$ (3 x 50ml). The organic layer was washed with aqueous $Na_2S_2O_3$ solution and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane-ethyl acetate (7:1) to give colourless oil **119** (0.147g, 27%).

Neat reaction :

A mixture of the nitroethylene **45** (0.2g, 1.084mmol) and the silyloxy diene **46** (1g, 7.042 mmol) in the presence of triethylamine and catalytic amount of BHT was heated at 120°C for 48h under argon. The reaction mixture was cooled to room temperature and solvent was evaporated to dryness. To a solution of the crude product in CCl_4 (20 ml) at 0°C, was added bromine (0.06 ml,1.164 mmol) and the mixture was stirred for 1h at room temperature. The reaction mixture was poured into aqueous sodium-bicarbonate solution and extracted with $CHCl_3$ (3 x 50ml). The organic layer was washed with aqueous $Na_2S_2O_3$ solution, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*, which was chromatographed on silica gel eluting with hexane-ethyl acetate (7:1) to give colourless oil of compound **119** (0.243g, 67%).

IR (Solution of $CDCl_3$) : ν_{max} = 1715 cm^{-1} (s), 1580 (s), 1560 (s), 1460 (s), 1370 (br), 950 (s), 730 (s).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.29 (1H, d, J = 2.0 Hz), 7.54 (1H, dd, J = 2.0 Hz, 8.0 Hz),7.35 (1H, d, J = 8.5 Hz), 4.66 (1H, dd, J = 6.0 Hz, 12.5 Hz, for Ha proton α to Br), 4.10 (1H, q), 3.68 (1H, m)

(4*R**,5*S*)-5β-[3-(6-chloropyridyl)]-4α-nitro-2-cyclohexen-1-one (**128**)

To a solution of bromoketone **119** (0.11g, 0.33 mmol) in DMF was added Li_2CO_3 (0.66g,0.8932 mmol) and LiBr (0.0495g, 0.5712 mmol). The mixture was heated at 120-130°C for 3.5h under argon atmosphere. The reaction mixture was cooled to room temperature and poured into aqueous saturated ammonium chloride solution . The aqueous layer was extracted with ethyl acetate (3 x 50ml). The combined extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (4:1) to give the expected compound **128** (0.052g, 63%) as a colourless oil.

IR (Solution of $CDCl_3$) : ν_{max} = 1740 cm^{-1} (s), 1670 (s), 1590 (s), 1540 (s), 1460 (s), 1365 (s), 1260 (m), 1170 (s), 1105 (s), 1025 (s) .

(2*RS*,4*R**,5*S**)-2-Bromo-5-[3-(6-chloropyridyl)]-4-nitro-1,1-ethylenedioxycyclohexane (**129**)

To a solution of bromo ketone **119** (0.05g,0.1499 mmol) in dry benzene (2 ml) was added ethylene glycol (0.055g,0.8965 mmol) and catalytic amount of *p*-toluenesulphonic acid (*p*-TsOH). The mixture was refluxed under argon with continuous removal of water for 6h. The reaction mixture was then cooled to room temperature and poured into aqueous saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3 x 20ml). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give crude compound **129** (0.026g, 48%) as oil.

(3*R**,4*R**,5*R**)-5-[3-(6-chloropyridyl)]-3-methoxy-4-nitro-1,1-ethylenedioxycyclohexane (**139**)

A solution of diene **123** (0.22g,1.284 mmol) and the nitroethylene **45** (0.2g,1.084 mmol) in 2ml

of dry benzene was heated under reflux for 24h. To this was added a solution of ethylene glycol (0.445g,7.169 mmol) and *p*-toluenesulfonic acid (0 05g) in 3ml of dry benzene. The resultant mixture was heated under reflux for another 6h with continuous separation of water. The benzene solution was washed with 5% aqueous sodium bicarbonate solution and then with brine. Evaporation of the volatiles from the dried ($MgSO_4$)organic phase left a residue, which was chromatographed on 10g of silica gel. Elution with hexane-ethyl acetate (5:1) afforded compound **139** (0.136g, 40%) as yellow oil .

IR (Solution of $CDCl_3$) : ν_{max} = 1560 cm^{-1} (s), 1460 (s), 1380 (s), 1360-1340 (br), 1160 (s), 1100-1080 (br), 1010 (br), 940 (s), 840 (s)

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.21 (1H, d, J = 3.0 Hz), 7.47 (1H, dd, J = 2.0 Hz, 8.5 Hz), 7.28 (1H, d, J = 8.5 Hz), 4.52 (1H, dd, J = 10.0 Hz, 12.0 Hz), 4.01 (4H, and also aryl proton overlapped here, m), 3.45 (1H, dd, J = 4.5 Hz, 12.5 Hz), 3.33 (3H, s), 2.36(1H, ddd, J = 4.5 Hz, 7.0 Hz, 14.0 Hz), 1.91-1.68 (3H,m).

(3*R**,4*R**,5*R**)-5-[3-(6-chloropyridyl)]-3-methoxy-4-nitrocyclohexan-1-one (**140**)

A solution of the diene **123** (0.22g, 1.284 mmol) and the nitroethylene **45** (0.2g,1.084 mmol) in 2 ml of dry benzene was heated under reflux for 24h. After cooling to room temperature, the solution was stirred rapidly with 5.6 ml of 4:1 THF-0.1N aqueous HCl for 30 min at room temperature. The mixture was poured into 5% aqueous sodium bicarbonate and extracted with 3 x 20 ml of chloroform. Evaporation of the volatiles from the dried ($MgSO_4$) organic phase afforded a residue, which was chromatographed on 10g silica gel. Elution with hexane-ethyl acetate (5:1) afforded compound **140** (0.175g, 75%) as a colourless oil along with compound **122** (ca.1%) .

IR (Solution of $CDCl_3$) : ν_{max} = 1725 cm^{-1} (s), 1560 (s), 1460 (s), 1380-1365 (s), 1340 (s), 1265 (s), 1230 (s), 1100 (s), 1020 (s), 1000 (s), 840 (w), 740 (w).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.26 (1H, d, J = 2.5 Hz), 7.51 (1H, dd, J = 2.5 Hz, 8.5 Hz), 7.34 (1H, d, J = 8.0 Hz), 4.93 (1H, H-4, dd, J = 9.5 Hz, 12.5 Hz), 4.09 (1H, H-5, dddd, J = 2.0 Hz, 5.0 Hz, 9.0 Hz, 14.0 Hz), 3.48 (1H, H-3, ddd, J = 5.5 Hz, 12.5 Hz, 17.0 Hz), 3.37(3H, s), 3.09 (1H, dddd, J = 1.5 Hz, 5.0 Hz, 14.5 Hz, 16.5 Hz), 2.65 (2H, ddd, J = 1.5 Hz,9.5 Hz 13.0 Hz), 2.57 (1H, dd ,J = 11.0 Hz, 14.5 Hz).

$C_{12}H_{13}O_4N_2Cl$ Calc. : C, 50.6 H, 4.6 N, 9.84

Found: C, 51.33 H, 4.7 N, 9.49

IR and ^{1}H-NMR of compound **122** :

IR (Solution of $CDCl_3$) : ν_{max} = 1670 cm^{-1} (s), 1590 (s), 1560 (s), 1460 (s), 1380 (br), 1270 (br), 1235 (s), 1215 (s), 1100 (s), 1040 (m), 930 (s), 840 (s), 800 (m.)

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.43 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.46(1H, d, J = 6.0 Hz), 7.39 (1H, d, J = 8.5 Hz), 5.56 (1H, dd, J = 1.5 Hz, 6.5 Hz), 5.46 (1H, dd, J = 3.5 Hz, 14.5 Hz), 2.85 (1H, dd, J = 14.0 Hz , 16.5 Hz), 2.69 (1H ,dd,J = 1.5 Hz, 4.0 Hz), 2.66 (1H, dd, J = 1.0 Hz, 3.5 Hz)

3-[3-(6-Chloropyridyl)]-4-nitro-(2-hydroxyethoxy)benzene (**141**)

To a solution of the methoxyketal **139** (0.03g, 0.0913 mmol) in 1 ml of dry THF, was added DBU (0.0213g,0.1404 mmol) was added .The resultant mixture was heated under reflux for 2h .The reaction mixture was then poured into ice-cold water . The aqueous phase was extracted with ethyl

acetate (3 x 10ml) and the combined organic layer was washed with dilute HCl, aqueous sodium bicarbonate solution and brine, and dried over anhydrous $MgSO_4$. Evaporation of the volatiles gave a residue, which was chromatographed on silica gel, eluting with hexane-ethyl acetate (2:1) to give aromatized product **141** (0.0042g, 28%) as yellow solid along with recovery of starting material .

IR (Nujol) : ν_{max} = 3360 cm^{-1} (br), 1590 (s), 1515 (s), 1460 (s), 1340 (s), 1310 (s), 1220 (br), 1100 (s), 1040 (s), 935 (s), 840 (s), 760 (s).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.32 (1H, d, J = 2.0 Hz), 8.11 (1H, d, J = 9.5 Hz), 7.56 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.38(1H, d, J = 8.5 Hz), 7.03 (1H, dd, J = 3.0 Hz, 9.5 Hz), 6.82 (1H, d, J = 2.5 Hz), 4.18 (2H, t, J = 4.5 Hz), 4.01 (2H, t, J = 5.0 Hz).

(3*R**,4*R**,5*R**)-5-[3-(6-Chloropyridyl)]-3-methoxy-4-nitro-cyclohexane-1-ol (**142**)

To a stirred solution of methoxy ketone **140** (0.02g, 0.0702 mmol) in dry THF (1 ml) at -78°C was added L-selectride (0.85 ml of a 1.0 M solution in THF,0.085 mmol) dropwise. The reaction mixture was then diluted with water and warmed up to room temperature. The aqueous layer was extracted with Et_2O (10 ml x 3). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* . The residue was chromatographed on silica gel, eluting with hexane-ethyl acetate (1:1) to afford diastereoisomeric mixture of alcohol **142** (0.02g, quantitative yield) as a colourless oil .

IR (Solution of $CDCl_3$) : ν_{max} = 3380 cm^{-1} (br), 1560 (s), 1460 (s), 1380 (br), 1340 (s), 1100 (s), 1060 (s), 1030 (s), 1000 (s), 990 (s), 915 (s), 840 (s), 740 (br) .

2-[3-(6-chloropyridyl)]-nitrobenzene (**143**)

To a solution of methoxyalcohol **142** (0.016g, 0.0558 mmol) in 1 ml of dry THF, DBU (0.01g, 0.0668 mmol) was added. The resultant mixture was heated under reflux for 75 minutes. The reaction mixture was then poured into ice-cold water.. The aqueous phase was extracted with ethyl acetate (3 x 10ml) and the combined organic layer was washed with dilute HCl, aqueous saturated sodium bicarbonate solution and then brine and dried over anhydrous $MgSO_4$ Evaporation of the volatiles gave a residue, which was purified by preparative TLC eluting with hexane-ethyl acetate (1:2) to give aromatized product **143** (0.005g, 42%) as a yellow solid .

IR (Nujol) : ν_{max} = 1520 cm^{-1} (s), 1460 (s, 1380 (s), 1260 (s).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.29 (1H, d, J = 2.5 Hz), 7.95 (1H, d, J = 8.0 Hz), 7.63 (1H, t,), 7.53 (1H, dd, J = 2.5 Hz, 8.5 Hz), 7.34 (2H, dd, J = 4.5 Hz, 7.5 Hz)

(1*R**,3*R**,4*R**,5*R**)-5-[3-(6-chloropyridyl)]-3-methoxy-4-nitrocyclohexyl-acetate (**145**) and (1*S**,3*R**,4*R**,5*R**)-5-[3-(6-chloropyridyl)]-3-methoxy-4-nitrocyclohexyl-acetate (**146**)

To a solution of the methoxyalcohol **142** (0.09g, 0.3141 mmol) in dry pyridine (2 ml) was added acetic anhydride (0.097g, 0.9538 mmol). The mixture was stirred for overnight at room temperature. The reaction mixture was then poured into ice-cold water and extracted with ethyl acetate (3 x 50ml). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporation of the volatiles left a residue, which was chromatographed on silica gel (4g). Elution with hexane-ethyl acetate (5:1) gave **145** (0.0515g, 50%) and **146** (0.0515g, 50%) in a ratio of 1:1 as colourless oil .

^{1}H-NMR (500 MHz, $CDCl_3$) of compound **145** :

δ = 8.21 (1H, d, J = 2.5 Hz), 7.46 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.29 (1H ,d, J = 8.5 Hz), 4.91 (1H, H-1, tt, J = 4.5 Hz, 11.5 Hz, 16.0 Hz), 4.51 (1H, H-4, dd, J = 10.0 Hz, 11.5 Hz), 3.88 (1H, H-3, dddd, J = 4.5 Hz, 9.5 Hz, 11.5 Hz, 14.0 Hz), 3.35 (3H, s), 3.22 (1H, H-5, ddd, J = 3.5 Hz, 13,5 Hz, 15.5 Hz), 2.67 (1H, dq, J = 4.0 Hz, 10.0 Hz), 2.23 (1H, dq, J = 5.5 Hz, 13.0 Hz), 2.04 (3H, OAc, s), 1.71 (1H, q, J = 13.5 Hz), 1.51 (1H, q, J = 12.0 Hz) .

^{1}H-NMR (500 MHz, $CDCl_3$) of compound **146** :

δ = 8.17 (1H, d, J = 2.0 Hz), 7.43 (1H, dd, J = 3.0 Hz, 8.5 Hz), 7.25 (1H, d, J = 8.5 Hz), 5.24 (1H, H-1, t, J = 3.0 Hz,6.0 Hz), 4.50 (1H, H-4, dd, J = 10.0 Hz, 11.0 Hz), 4.04 (1H, H-3, ddd, J = 5.0 Hz, 12.0 Hz, 16.5 Hz), 3.48 (1H, H-5, ddd, J = 4.0 Hz, 12.5 Hz, 16.5 Hz), 3.30 (3H, s), 2.50 (1H, dq, J = 14.0 Hz), 2.12 (3H, OAc, s), 2.07 (1H, dq, J = 2.5 Hz, 15.0 Hz), 1.77(1H, ddd, J = 2.5 Hz, 15.0 Hz), 1.53 (1H, ddd, J = 2.5 Hz, 14.0 Hz) .

(1*R**,3*R**,4*R**,5*R**)-5-[3-(6-chloropyridyl)]-3-hydroxy-4-nitrocyclohexyl-acetate (**147**)

To a solution of compound **145** (0.015g, 0.0456 mmol) in dry CH_2Cl_2 (2 ml), at 0°C was added boron tribromide (1M solution in CH_2Cl_2, 0.141 ml, 0.141 mmol) under argon atmosphere. The mixture was stirred for 30 min at the same temperature, then poured into aq.sat. $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC and elution with hexane-ethylacetate (1:1) gave compound **147** (0.013g, 92%) as colourless oil.

IR (solution of $CHCl_3$) : ν_{max} = 3420 cm^{-1}(br), 1730(s), 1555(s), 1460(s), 1370(s), 1240(s), 1150(s), 1100(s), 1035(s), 840(s), 740(s).

^{1}H-NMR (500MHz, $CDCl_3$): δ = 8.23 (1H, d, J = 2.5 Hz), 7.48 (1H, dd, J = 2.5 Hz, 8.5 Hz),

7.30 (1H, d, J = 8.5 Hz), 4.94 (1H, H-1, tt, J = 4.5 Hz, 11.5 Hz, 16.0 Hz), 4.52 (1H, H-4, dd, J = 9.5 Hz, 11.5 Hz), 4.33 (1H, H-3, ddd, J = 4.5 Hz, 9.0 Hz, 12.0 Hz), 3.24 (1H, H-5, ddt, J = 3.5 Hz, 13.0 Hz, 15.0 Hz), 2.51 (1H, dq, J = 4.5 Hz, 12.5 Hz), 2.26 (1H, dq, J = 4.0 Hz, 13.0 Hz), 2.04 (3H, -OAc, s), 1.71 (2H, q, J = 11.0 Hz).

(1*S**,3*R**,4*R**,5*R**)-5-[3-(6-chloropyridyl)]-3-hydroxy-4-nitrocyclohexyl-acetate (**148**)

Compound **148** was also prepared from **146** as like **147**.

IR (solution of $CHCl_3$) : ν_{max} = 3390 cm^{-1}(br), 1730(s), 1555(s), 1460(s), 1370(s), 1240(s), 1105(s), 1070(s), 1020(s), 980(s), 840(s), 730(s).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.24 (1H ,d, J = 3.0 Hz), 7.50 (1H, dd, J = 2.5 Hz, 8.5 Hz), 7.31 (1H, d, J = 8.5 Hz), 5.26 (1H, H-1, t, J = 3.0 Hz), 4.56 (2H, H-3 and H-4, m), 3.54 (1H, H-5, ddt, J = 4.0 Hz, 13.5 Hz), 2.43 (1H, dt, J = 4.5 Hz, 15.0 Hz), 2.15 (3H, -OAc, s), 2.11 (1H, dt), 1.84 (1H, ddd, J = 3.0 Hz, 11.5 Hz, 15.0 Hz), 1.76 (1H, ddd, J = 2.5 Hz, 11.0 Hz, 14.0 Hz).

5-(2,2-Dibromovinyl)-2-chloropyridine (**154**)

To a stirred solution of the aldehyde **34**(1g, 7.07 mmol) in dry CH_2Cl_2(200 ml) under a nitrogen atmosphere at ice-salt bath temperature was added triphenylphosphine(11.5g, 43.84 mmol). To this was added carbon tetrabromide(7.3g, 22.01 mmol). After being stirred for 30 min, the resulting pale brown solution was washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous Na_2SO_4. Evaporation of the volatiles left a residue, which was chromatographed on silicagel(~600g). Elution with hexane-ethyl acetate (1:1) gave compound **154** (2.1g, quantitative yield) as white solid .

^{1}H-NMR(500MHz, $CDCl_3$) : δ= 8.44 (1H, d, J = 2.0 Hz), 7.92 (1H, dd, J = 2.5 Hz, 8.5 Hz), 7.41 (1H, s), 7.34 (1H, d, J = 8.5 Hz) .

2-Chloro-5-ethynylpyridine (**155**)

To a solution compound **154**(1.5g, 5.045 mmol) in dry THF(55 ml) at -78°C under an argon atmosphere was added *n*-BuLi(1.54 M solution in hexane, 11.6 ml, 17.86 mmol). The reaction mixture was stirred for 1h saturated aqueous NH_4Cl solution was added at -78°C and the resulting mixture was allowed to warm up to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel(70g) eluting with hexane-ethyl acetate (60:1) to afford compound **155**(0.347g, 50%) as colourless oil.

IR (film) : ν_{max} = 3400 cm^{-1}(br), 2200(s), 1460(s), 1360 (m), 1260 (s), 1100 (s), 1020 (s), 925 (s), 835 (s).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.64 (1H, d, J = 2.0 Hz), 7.85 (1H, dd ,J = 2.0 Hz, 8.5 Hz), 7.45 (1H, d, J = 8.0 Hz), 3.40 (1H, acetylenic proton, s).

2-Chloro-5-(2-trimethylsilylethynyl)pyridine (**158**)

To a solution of the compound **155**(0.39g, 2.84 mmol) in dry THF(16 ml) at -78°C under an argon atmosphere was added *n*-BuLi (1.54 M in hexane, 2.4 ml, 3.696 mmol). Then at same temperature, triethylamine(0.944g, 9.33 mmol) and trimethylsilylchloride(1.02g, 9.455 mmol) was added. After stirring for 30 minutes, the reaction mixture was poured into cold aqueous saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate. The combined extract was

washed with cold brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on neutral alumina eluting with hexane to give compound **158** (0.289g, 60%) as a white crystal.

^{1}H-NMR (600 MHz, $CDCl_3$) : δ = 8.47 (1H, d, J =1.8 Hz), 7.69 (1H, dd, J = 2.4 Hz, 7.8Hz), 7.28 (1H, d, J = 8.4 Hz), 0.22 (9H, s).

2-Chloro-5-(2-nitroethynyl)pyridine (**152**)

Nitronium tetrafluoroborate (0.13g, 0.978 mmol), *tetra-n*-butyl ammonium tetrafluoroborate(0.323g, 0.98 mmol) and cesium fluoride (0.149g, 0.980 mmol) were added to a stirred solution of trimethylsilylacetylene **158**(0.1g, 0.477 mmol) in dry CH_2Cl_2 (5 ml). After stirring overnight, the reaction mixrure was filtered and the residue was washed with CH_2Cl_2. The combined filtrate was poured into cold aqueous sodium bicarbonate solution. The organic layer was separated and washed with water and dried over anhydrous $MgSO_4$. Evaporation of the volatiles left a crude solid **152**.

IR and ^{1}H-NMR of crude compound **152**.

IR (Nujol) : ν_{max} = 2260 cm^{-1}(s), 1820(s), 1660(s), 1580(s), 1520(s), 1470(br), 1380(s), 1350(s), 1280(s), 1050(br), 920(m), 730(s), 645(s).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.68 (1H, d, J = 2.5 Hz), 8.01 (1H, dd, 2.5 Hz, 8.5 Hz), 7.50 (1H, d, J =8.5 Hz).

2-Chloro-5-(2-ethoxycarbonyl-1-hydroxyethyl)pyridine (**169**)

A 50 ml three necked round bottomed flask containing slurry of Zn powder(1.1g) in 5 ml of dry benzene equipped with condenser under argon atmosphere was heated untill reflux starts. To this a

solution of aldehyde **34** (1.5g, 10.6 mmol) and ethyl bromoacetate **168** (1.96g, 11.72 mmol) in 20 ml of dry benzene was added dropwise at ca.1ml/min. After the addition was complete, the reflux was continued for another 2h. The resulting pale yellow solution was poured into 80 ml of ice-cold 20% sulfuric acid and the mixture was shaken untill the colourless precipitate dissolved. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (150 ml x 3). The combined organic layer was washed with saturated sodium bicarbonate solution and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure *in vacuo* and the residue was chromatographed on silica gel (63g). Elution with hexane-ethyl acetate (4:1) afforded compound **169** (1.93g, 80%) as a colourless oil.

IR (film) : ν_{max} = 3360 cm^{-1}(br), 1730(s), 1590(s), 1570(s), 1460(s), 1380(s), 1280(s), 1160(br), 1100(s), 840(s), 740(m).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.36 (1H, d, J = 2.5 Hz), 7.71 (1H, dd, J = 3.0 Hz,8.5 Hz), 7.32 (1H, d, J = 8.0 Hz), 5.15 (1H, br t,), 4.14 (2H, q, J = 7.0 Hz), 3.61 (1H, d, J = 3.5 Hz), 2.69 (2H, d), 1.25 (3H, t, J = 7.5 Hz).

2-Chloro-5-(2-ethoxycarbonyl-1-oxoethyl)pyridine (**160**)

To a solution of compound **169** (0.5g,2.18 mmol) in dry CH_2Cl_2 (15 ml) were added MS-3A powder (1g) and pyridinium chlorochromate (1g, 4.639 mmol) and the mixture was stirred at room temperature for 3h. The reaction mixture was filtered through silica gel (20g) and washed with ethyl acetate. Evaporation of the volatiles left a residue, which was chromatographed on silicagel (15g). Elution with hexane-ethyl acetate (7:1) gave β-keto ester **160** (0.255g, 52%) as a white solid.

IR (solution of $CDCl_3$) : ν_{max} = 1740 cm^{-1}(s), 1695(s), 1630(br), 1580(s), 1460(s), 1420(s),

1360(s), 1265(s), 1200(s), 1110(s), 1020(m), 800(s).

^{1}H-NMR of keto form:

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.85 (1H, d, J = 2.5 Hz), 8.13 (1H, dd, J = 2.5 Hz, 8.5 Hz), 7.41 (1H, d, J = 8.5 Hz), 4.15 (2H, q, J = 7.5 Hz), 3.91 (2H, s), 1.19 (3H, t, 7.5 Hz).

^{1}H NMR of enol form:

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.69 (1H, d, J = 2.5 Hz), 7.93 (1H, dd, J = 2.5 Hz, 8.5 Hz), 7.34 (1H, d, J = 8.5 Hz), 5.61 (1H, s), 4.21 (2H, q, J = 7.5 Hz), 1.28 (3H, t, J = 7.0 Hz).

2-Chloro-5-(2-ethoxycarbonyl-1,4-dioxopentyl)pyridine (**170**)

To a 2.5 ml of 2M solution of sodium ethoxide in ethanol at 0°C under argon atmosphere was added the keto ester **160** (1g, 4.393 mmol) in 5 ml of ethanol over a 5 min. followed by (0.631g, 9.009 mmol) of methyl vinyl ketone in 5 ml of ethanol over a 15 min. The resulting mixture was stirred at room temperature for 2.5h and acidified to pH 2~3 by adding conc. HCl. Evaporation of the solvent left a residue, which was diluted with water and extracted with Et_2O (100 ml x 3). The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. The organic layer was concentarted *in vauco*, and the residue was chromatographed on silica gel (60g) eluting with hexane-ethyl acetate (5:1) to afford compound **170** (0.773g, 60%) as a colourless oil .

IR (neat) : ν_{max} = 3500 cm^{-1}(br), 1720(s), 1690(s), 1690(s), 1580(s), 1460(s), 1360(m), 1245(s), 1190-1180(s), 1110(s), 1040(s), 920(s), 860(m).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.95 (1H, d, J = 2.5 Hz), 8.21 (1H, dd, J = 2.5 Hz,8.5 Hz), 7.41 (1H, d, J = 8.5 Hz), 4.31 (1H, dd, J = 6.5 Hz, 8.0 Hz), 4.09 (2H, q, J = 7.0 Hz), 2.55 (2H, q), 2.18 (2H, q), 2.08 (3H, s), 1.12 (3H, t, J = 7.5 Hz).

(±)-2-[3-(6-chloropyridyl)]-4-oxo-2-cyclohexene-1-carboxylate (**163**)

To a solution of the compound **170** (0.43g, 1.444 mmol) in dry benzene (10 ml) pyrrolidine (0.11g, 1.557 mmol) was added. The mixture was allowed to reflux under argon atmosphere with continuous removal of water . After 5h ,solvent was concentrated *in vacuo* and the residue was chromatographed on silica gel (20g). Elution with hexane-ethyl acetate (5:1) to give compound **163** (0.343g, 85%) as a colourless oil .

IR (neat) : ν_{max} = 1730 cm^{-1}(s), 1675(s), 1610(s), 1580(s), 1555(s), 1460(s), 1375(s), 1330(s), 1250 (br), 1180(s), 1155(s), 1110(s), 1040(s), 1025(s), 980(s), 900(m), 840(m).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.49 (1H, d, J = 2.5 Hz), 7.72 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.38 (1H, d, J = 8.5 Hz), 6.41 (1H, s), 4.09 (2H, q,J = 7.0 Hz), 3.86 (1H, t, J = 4.5 Hz), 2.67-2.35(4H, m), 1.14 (3H, t, J = 7.0 Hz).

(1*R**,2*S**)-2-[3-(6-chloropyridyl)]-4-oxocyclohexanecarboxylate (**172**)

A solution o the compound **163** (0.099g, 0.3539 mmol) in 5 ml of EtOH was stirred with 30% Rh/Al_2O_3 under hydrogen atmosphere for 3h. The reaction mixture was filtered through celite and the filter cake was washed with ethyl acetate. The combined filtrate was evaporated and the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (5:1) to afford **172** (0.084g, 85%) and **174** (~10%) as a colourless oil .

IR and ^{1}H-NMR of the compound (**172**)

IR (neat) : ν_{max} = 1720 cm^{-1}(s), 1460(s), 1380(s), 1235(s), 1180(s), 1100(s), 1020(s), 840(s), 740(s)

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.21 (1H, d, J = 2.5 Hz), 7.46 (1H, dd, J = 2.5 Hz, 8.5 Hz), 7.27 (1H, d, J = 8.0 Hz), 4.02 (2H, q), 3.47 (1H, H-2, dt, J = 4.5 Hz, 11.0 Hz), 3.25 (1H, H-3, dd,J = 11.0 Hz, J = 14.5 Hz), 3.08 (1H, H-1,q, J = 5.0 Hz), 2.72 (1H, ,H-5a, ddd, J=5.5 Hz, J=11.0 Hz, J= 15.5 Hz), 2.58 (1H, H-3e, dd, J=5.0 Hz, J=14.5 Hz), 2.44 (1H, H-5e, ddd, J=5.5 Hz, J=11.5 Hz, J=14.5 Hz), 2.26 (1H, H-6e, dt, J=5.5 Hz, J=11.0 Hz, J=14.0 Hz), 2.13 (1H, H-6a, ddt, J=5.0 Hz, J=11.0 Hz, J=15.0 Hz), 1.11 (3H, t, J = 7.5 Hz) .

(1*R**,2*S**,4*S**)-2-[3-(6-Chloropyridyl)]-4-hydroxycyclohexanecarboxylate (**175**)

A solution of compound **172** (0.037g, 0.1313 mmol) in dry THF (2 ml) was cooled to -78°C under argon atmosphere. To this K-selectride (1M solution inTHF ,0.242g, 0.265 mmol) was added and the resulting mixture was stirred at the same temperature for 1h. Water was added to the reaction mixture and the whole was warmed up to room temperature. The aqueous layer was extracted with Et_2O (4 x 25 ml). The combined extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the volatiles left a residue, which was chromatographed on silica gel (1.2g). Elution with hexane-ethyl acetate (4:1) gave compound **175** (0.03g, 80%) and also compound **174** (0.007g, 20%) as oil .

IR and ^{1}H-NMR of the compound **175** :

IR (solution of $CDCl_3$) : ν_{max} = 3380 cm^{-1}(br), 1725(s), 1580(s), 1560(s), 1460(s), 1380(s), 1235(s), 1180(s), 1105(s), 1060(s), 1020(s), 960(m), 740(m).

^{1}H-NMR (500 MHz,$CDCl_3$) : δ = 8.25 (1H, d, J = 2.5 Hz), 7.53 (1H, dd, J = 3.0 Hz, 8.5 Hz), 7.23 (1H, d, J = 8.5 Hz), 4.31 (1H, H-4e, br t), 3.903 (2H, q), 3.43 (1H, H-2, dt, J = 4.0 Hz, 12.5 Hz), 2.89 (1H, H-1, q,J = 4.5 Hz), 2.58 (1H, H-3a, ddd, J = 3.0 Hz, 13.0 Hz, 15.5 Hz),

2.22 (1H, dt, J = 4.5 Hz, 13.5 Hz), 1.94 (1H, dt, J = 4.0 Hz, 14.0 Hz), 1.88 (2H, ddd, J = 6.0 Hz, 13.0 Hz, 16.5 Hz), 1.66(1H, dd, J = 3.5 Hz, 13.0 Hz), 1.02 (3H, t, J = 7.5 Hz) .

^{1}H-NMR of compound **174** :

^{1}H-NMR (500 MHz,$CDCl_3$) : δ = 8.23 (1H, d, J = 2.5 Hz), 7.55 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.23 (1H, d, J = 8.5 Hz), 3.93 (2H, q), 3.75 (1H, H4a, tt, J = 4.0 Hz, 10.5 Hz, 15.0 Hz), 2.89 (1H, H2a, dt, J = 4.0 Hz, 13.5 Hz), 2.83 (1H, H1e, br t), 2.37 (1H, H3a ,q, J = 11.5 Hz), 2.16 (1H, dq, J = 6.0 Hz, 14.0 Hz), 2.04 (1H, br dt, J = 12.0 Hz), 1.91 (1H, dd, J = 2.5 Hz, 12.5 Hz), 1.77 (1H, ddd,J = 3.5 Hz, 14.0 Hz, 15.5 Hz), 1.59 (1H, m,), 1.03 (3H, t, J = 7.5 Hz) .

(1*R**,2*S**,4*S**)-2-[3-(6-Chloropyridyl)]-4-methanesulfonyloxycyclohexane-1-carboxylate (**176**)

The alcohol **175**(0.02g, 0.0704 mmol) was dissolved in a mixture of dry CH_2Cl_2 (0.4 ml) and dry pyridine (1.6 ml), and then methanesulfonylchloride (0.018 ml,0.2325 mmol) was added dropwise at 0°C. The resulting mixture was stirred for overnight at room temperature. Solvent was evaporated under reduced pressure and the residue was purified by preparative TLC. Elution with hexane-EtOAc (1:1) gave compound **176** (0.0197g, 82%) as colourless oil .

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.24 (1H, d, J = 2.0 Hz), 7.49 (1H, dd, J = 2.5 Hz, 8.5 Hz), 7.25(1H, d, J = 8.0 Hz), 5.21 (1H, H-4, br s), 3.91 (2H, q), 3.32 (1H, H-2a, dt,J = 4.5 Hz, 13.0 Hz,), 3.02 (3H, s), 2.94 (1H, H-1, q), 2.76 (1H, ddd, J = 2.5 Hz, 14.0 Hz, 16.0 Hz), 2.18-1.97 (5H, m), 1.03 (3H, t, J = 7.0 Hz) .

(1*R**,2*S**,4*S**)-2-[3-(6-Chloropyridyl)]-4-hydroxycyclohexanecarboxylic acid (**179**)

A solution of the compound **175** (0.036g, 0.1268 mmol) in 3M H_2SO_4 was heated at 60-65°C for

4h. The resulting mixture was cooled to room temperature and pH was adjusted to~7.0 by slow addition of solid sodium bicarbonate. It was then poured into saturated ammonium sulfate solution. The aqueous layer was extracted with Et_2O (5 x 50 ml). The combined extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude compound was chromatographed on silica gel (1.7g). Elution with 100% ethyl acetate to afford compound **179** (0.0324g, quantitative yield) as a colourless oil .

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.25 (1H, d, J = 2.0 Hz), 7.49 (1H, dd, J = 2.5 Hz,8.0 Hz), 7.18 (1H, d, J = 8.5 Hz), 4.25 (1H, H-4e, br s), 3.39 (1H, H-2a, dt, J = 4.0 Hz, 12.0 Hz), 2.89 (1H, H-1e, q, J = 4.5 Hz), 2.54 (1H, ddd, J = 2.5 Hz, 13.5 Hz, 15.5 Hz), 2.26 (1H, m,), 1.88 (2H, m), 1.78 (1H, br dt, J = 14.0 Hz), 1.64 (1H, br dt, J = 14.5 Hz).

(1*R**,2*S**,4*S**)-1-Azido-2-[3-(6-Chloropyridyl)]-4-methanesulfonyloxycyclohexane (**181**)

To the hydroxy acid **179** (0.025g, 0.0977 mmol) in 1 ml of freshly distilled acetone (0.124g, 1.22 mmol) of triethylamine was added under argon atmosphere .To this at 0°C was added dropwise methanesulfonyl chloride (0.074g, 0.646 mmol) and the mixture was stirred for 30 min at the same temperature. To this was added sodium azide (0.042g, 0.646 mmol) in 0.3 ml of water and stirring was continued for another 15 minutes. The mixture was quenched by adding water and diluted with Et_2O. The ethereal layer was separated and the aqueous layer was extracted with Et_2O (25ml x 3). The combined organic layer was dried over anhydrous $MgSO_4$. Evaporation of the volatiles left a crude compound **181** (0.035g), which was used for the next step without further purification.

IR (solution of $CDCl_3$) : ν_{max} = 2140 cm-1(s), 1720(s), 1460(s), 1380(s), 1105(s), 1010(s), 980(s).

IR of crude compound (**183**)

IR (solution of $CDCl_3$) : ν_{max} = 2260 cm^{-1}(s), 1725(s), 1460(s), 1380(s), 1260(s), 1170(br), 1100(s), 910(s), 800(s), 735(s).

(1R*, 2S*, 4S*)-1-*N*-Methoxycarbonyll-2-[3-(6-chloropyridyl)]-4-methanesulfonyloxycyclohexylamine (**184**)

A solution of crude azide **181** (0.0175g, 0.0487 mmol) in a mixture of benzene:methanol(1/1, 1.5 ml) was heated at 70°C under argon atmosphere for 1h. Solvent was evaporated and the residue was purified by preparative TLC. Elution with hexane-ethyl acetate (1:1) afforded compound **184** (0.008g, 46% from compound **179**) as an oil.

IR (neat) : ν_{max} = 3380 cm^{-1}(br), 1700(s), 1530(br), 1460(s), 1340(br), 1250(s), 1170(s), 1105(s), 1000(s), 965(s), 900(br), 840(s), 780(s), 735(s).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.19 (1H, d, J = 2.5 Hz), 7.47 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.28 (1H, d, J = 8.5 Hz), 5.17 (1H, H-4e, br s), 4.73 (1H, br, -NH), 4.14 (1H, H-1e, br q), 3.48 (3H, br s), 3.37 (1H, H-2a, br.dt, J = 13.0 Hz), 3.04 (3H, s), 2.19-1.76 (6H, m).

(1*R**, 2*S**, 4*S**)-1-*N*-Benzyloxycarbonyl-2-[3-(6-chloropyridyl)]-4-methanesulfonyloxycyclohexylamine (**186**)

To a solution of the crude azide **181** (0.0175g, 0.0487 mmol) in benzene (1.5 ml), was added benzyl alcohol (0.0114g,1.06 mmol) . The resulting mixture was heated at 70°C under argon atmosphere for overnight. Solvent was evaporated and the residue was chromatographed on silica gel (2.4g). Elution with hexane-ethyl acetate (6:1) afforded compound **186** (0.016g, 81% from **179**) as an oil.

IR (neat) : ν_{max} = 3380 cm^{-1}(br), 1700(s), 1530(s), 1460(s), 1340(s), 1240(s), 1175(s), 1105(s), 1000(s), 910(s), 840(s), 740(s), 700(m).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.18 (1H ,d, J=2.5 Hz), 7.32 (6H, m), 7.19(1H, d, J = 8.0 Hz), 5.15 (1H, H-4,,br s), 4.91 (2H, -CH_2, and overlapped with -NH proton), 4.19 (1H, H-1e, br t), 3.35 (1H, H-2, br q), 3.03 (3H, s), 2.13 (2H, m), 2.07 (1H, br t), 2,04 (1H, br t), 1.91 (1H, br t), 1.73 (1H, t).

(1R*,2S*,4R*)-1-Amino-2-[3-(6-chloropyridyl)]-4-methanesulfonyloxycyclohexane (**164**)

To a solution of compound **186** (0.025g, 0.00569 mmol) in EtOH (2.5 ml) containing trace amount of conc. HCl, was added 0.005g of 10% Pd/C. The resulting mixture was stirred under H_2 atmosphere at room temperature for 7h. The reaction mixture was then filtered through celite in the presence of solid sodium bi-carbonate. Evaporation of the volatiles left a residue, which was chromatographed on silica gel (1.5g). Elution with chloroform-methanol-ammonia (10:1:0.1) afforded compound **164** (0.0047g, 30%) as oil.

(±)-Epibatidine (**8**)

A solution of compound **164** (0.0047g, 0.0154 mmol) in chloroform (1.5 ml) was refluxed under argon atmosphere for 30h. The reaction mixture was diluted with chloroform and washed with aqueous sodium bicarbonate solution. The aqueous layer extracted with chloroform. The combined organic layer was dried over anhydrous K_2CO_3 and concentrated. The residue was chromatographed on silica gel (0.5g) eluting with chloroform-methanol-ammonia (10:1:0.1) afforded (±)-epibatidine **8** (0.0025g, 78%) as colourless oil.

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.26 (1H, d, J = 2.5 Hz), 7.80 (1H, dd, J = 2.0 Hz, 8.5 Hz), 7.23 (1H, d, J = 8.5 Hz), 3.86 (1H, H-4, br t), 3.61 (1H, H-1, br s), 2.80 (1H, H-2, dd, J = 5.5 Hz, 9.0 Hz), 1.94 (1H, H-3α, dd, J = 9.5 Hz, 12.5 Hz), 1.68-1.50 (6H, m, H-3β, H-5(2H), H-6(2H), and NH).

(1R*,3R*,4R*,5R*)-5-[3-(6-Chloropyridyl)]-3-methoxy-4-nitro-methanesulfonyloxycyclohexane (**194**) and

(1S*,3R*,4R*,5R*)-5-[3-(6-Chloropyridyl)]-3-methoxy-4-nitro-methanesulfonyloxycyclohexane (**195**)

To a solution of the compound **142** (0.08g, 0.28 mmol) in pyridine and dry CH_2Cl_2 (4:1,8 ml) at 0°C was added methanesulfonyl chloride (0.072 ml, 0.93 mmol). The resulting mixture was stirred at room temperature for over night. Solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (5g). Elution with hexane-EtOAc (7:1) afforded compound **194** (0.05g, 50%) and compound **195** (0.05g, 50%) as colourless oil.

^{1}H-NMR of the compound **194**.

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.22 (1H, d, J = 3.0 Hz), 7.47 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.31 (1H, d, J = 8.5 Hz), 4.82 (1H, H-1, tt, J = 4.0 Hz, 11.0 Hz, 15.5 Hz), 4.51 (1H, H-4, dd, J = 9.5 Hz, 11.0 Hz), 3.89 (1H, H-3, dddd, J = 4.0 Hz, 10.0 Hz, 11.0 Hz, 14.0 Hz), 3.36 (3H, -OMe, s), 3.22 (1H, H-5, ddd, J =3.0 Hz, 13.0 Hz, 15.5 Hz), 3.05 (3H, -OMs, s), 2.80 (1H, dq, J = 2.0 Hz, 12.5 Hz), 2.40 (1H, dq), 1.91 (1H, q,J = 13.0 Hz), 1.72 (1H, q, 12.0 Hz).

^{1}H-NMR of compound **195**.

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 8.24 (1H, d, J = 2.0 Hz), 7.48 (1H, dd, J = 3.0 Hz, 8.0 Hz), 7.31 (1H, d, J = 8.5 Hz), 5.20 (1H, H-1, t, J =2.5 Hz), 4.57 (1H, H-4, dd, J = 10.0 Hz, 11.5 Hz), 4.17 (1H, H-3, dddd, J = 4.5 Hz, 9.5 Hz, 11.5 Hz, 14.5 Hz), 3.61 (1H, H-5, ddd, J = 4.0 Hz, 13.5 Hz, 15.5 Hz), 3.36 (3H, -OAc, s), 3.13 (3H, -OMe, s), 2.76 (1H, dq, J = 7.0 Hz, 15.5 Hz), 2.33 (1H, dq, J = 7.5 Hz, 15.5 Hz), 1.90 (1H, ddd, J = 2.5 Hz, 13.5 Hz, 15.0 Hz), 1.67 (1H, ddd, J = 3.0 Hz, 12.0 Hz, 14.4 Hz).

(5*S*,6*R*,7*R*)-6,7-di-*t*-butyldimethylsilyloxy-2-aza-3-oxa-8-phthalimidobicyclo[3.3.0]oct-1-ene (**224**)

To a solution of compound **223** (5g, 9.48 mmol) in THF (30 ml) was added tetrabutylammonium fluoride (1M solution in THF,19 ml). The mixture was stirred at room temperature for 20 min, poured into saturated ammonium sulfate solution and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vauco*. The residue was dissolved in DMF (25 ml). To this solution were added *t* -butyldimethylchlorosilane (8.52g, 56.6 mmol) and imidazole (7.7g, 113.2 mmol) and the mixture was stirred at 40°C for 4 days. The reaction mixture was poured into aqueous saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was successively washed with water and brine, and concentrated *in vacuo*. The residue was chromatographed on silica gel (150g) and elution with hexane-ethylacetate (20:1) gave **224** (4.24g, 87%) as white solid.

IR (solution of $CHCl_3$) : ν_{max} = 1720 cm^{-1}(s), 1465(s), 1380(s), 1250(s), 1140(s), 840(s) .

^{1}H-NMR (90 MHz, $CDCl_3$) : δ =7.95–7.72 (4H, pht, m), 5.01 (1H, H-8, dd, J = 2.0 Hz, 7.5 Hz), 4.89-4.58 (2H, H-7, H-4, m), 4.29-3.78 (3H, H-6, H-5, H-4, m), 1.00-0.78 (18H, m), 0.18-0.00 (12H, m) .

(2*R*, 3*R*, 5*S*)-2,3-Di-*t*-butyldimethylsilyloxy-5-hydroxy-4-phthaliomidocyclopentanemethanol (**226**)

Ozone was bubbled into a solution of **224** (4.2g, 8.139 mmol) in CH_2Cl_2-MeOH (10:1, 240 ml) at -30°C for 12h. After the excess ozone had been removed by bubbling nitrogen for 5 min, dimethyl sulfide (3.38 ml) was added to the reaction mixture before it was allowed to warm to room

temperature. The mixture was poured into brine and extracted with EtOAc. The organic layer was successively washed with aqueous saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* . The residue was dissoived in dry THF (58 ml), and to this solution was added $Zn(BH_4)_2$ (0.15 M solution in ether,58 ml) at 0°C. The mixture was stirred at 0°C for 2h before being poured into aqueous saturated ammonium sulfate and extracted with EtOAc. The organic layer was successively washed with aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was chromatographed on silica gel (120g), and elution with hexane-ethyl acetate (2:1) gave **226** (2.09g, 52%) as white amorphous solid .

IR (solution of $CHCl_3$) : ν_{max} = 3490 cm^{-1}(br), 1715(s), 1390(s), 1255(s), 1090(m), 840(s) .

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 7.86-7.69 (4H, pht, m), 5.05-4.84 (1H, H-3, m), 4.51 (1H, H-4, dd, J = 6.0 Hz, 8.0 Hz), 4.38-4.04 (1H, H-5, m), 4.02-3.61 (3H, m), 2.91 (1H, 5-OH, d, J = 10.0 Hz), 2.57-2.15 (1H, H-1, m), 0.90 (9H, s), 0.80 (9H, s), 0.12 (6H, s), 0.01 (6H, s) .

(5*S*, 7*R*, 8*R*)-7,8-di-*t* -butyldimethylsilyloxy-6-hydroxymethyl-2-aza-4-oxabicyclo-[3.3.0]octan-3-one (**227**)

To a solution of **226** (1.2g, 2.31 mmol) in EtOH (19 ml) was added hydrazine monohydrate (2.5 ml) and the mixture was stirred at 70°C for 4h. The mixture was then concentrated *in vacuo* and co-evaporated several times with EtOH. The residue was dissolved in CH_2Cl_2-water (2:1, 38 ml) and to this solution were added benzyl chloroformate (0.5 ml, 3.5 mmol) and Na_2CO_3 (0.5g, 4.7 mmol) at 0°C. The mixture was stirred at 0°C for 100 min and poured into aqueous saturated ammonium sulfate. The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo.* The residue was dissolved in THF (38 ml). To this solution was added sodium hydride (60% dispersion in mineral oil, 0.628g) at 0°C. The mixture was stirred at room temperature

for 3h, poured into aqueous saturated ammonium sulfate and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (30g) and elution with hexane-ethylacetate (1:1) gave **227** (0.856g, 89%) .

IR (solution of $CHCl_3$) : ν_{max} = 3490 cm^{-1}(br), 1755(s), 1260(s), 1100(s), 840(s).

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 5.52 (1H, br), 5.18 (1H, H-5, d, J = 2.8 Hz), 4.09-3.90 (3H, H-1, -CH_2-OH, m), 3.89-3.65 (2H, H-8, H-7, m), 2.66 (1H, H-6, dd, J = 6.0 Hz, 8.0 Hz), 2.60-2.38 (1H, m), 0.09 (18H, s), 0.14 (6H, s), 0.08 (6H, s).

(5*S*, 7*R*, 8*R*)-6-Acetoxymethyl-7,8-diacetoxy-2-aza-4-oxabicyclo[3.3.0]octan-3-one (**228**)

To a solution of **227** (0.63g, 1.51 mmol) in MeOH (11 ml) was added conc. HCl (0.44 ml) and the mixture was stirred at room temperature for 2.5h. The mixture was then neutralized with pyridine (0.44 ml) and concentrated *in vacuo* and the residue was dissolved in pyridine (14.5 ml). To this mixture was added acetic anhydride (0.73 ml, 7.74 mmol) and the solution was stirred at room temperature for 16h. The mixture was poured into aqueous saturated ammonium sulfate and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (15g) and elution with ethyl acetate gave **228** (0.465g, quantitative yield) as a thick syrup.

IR (solution of $CHCl_3$) : ν_{max} = 3470 cm^{-1}(br), 1760(s), 1740(s), 1375(s), 1235(s), 1040(s)

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 5.82 (1H, br), 5.26 (1H, H-7, dd, J = 7.5 Hz, 9.5 Hz), 4.88 (1H, H-5, dd, J = 6.0 Hz, 9.0 Hz), 4.77 (1H, H-8, dd, J = 4.5 Hz, 7.5 Hz), 4.22 (2H, -CH_2-O-, d, J = 5.5 Hz), 3.97 (1H, H-1, dd, J = 4.5 Hz, 9.0 Hz), 2.88-2.48 (1H, H-6, m), 2.11 (9H, 3 x

OAc, s).

(5*S*, 7*R*, 8*R*)-6-Acetoxymethyl-7,8-diacetoxy-3-dimethylamino-2-aza-4-oxabicyclo[3.3.0]oct-2-ene (allosamizoline triacetate, **197b**)

To a solution of **228** (0.05g, 0.159 mmol) in CH_2Cl_2 (0.8 ml) was added triethyloxonium tetrafluoroborate (0.0759g, 0.4 mmol) and the mixture was stirred at room temperature for 20h. Dimethylamine (10.9 M soln. in toluene, 0.22 ml, 2.39 mmol) was then added and the mixture was stirred at room temperature for an additional 48h. The mixture was then poured into aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* . The residue was chromatographed on silica gel (2.5g) and elution with EtOAc-acetone (1:1) gave **197b** (0.027g, 50% and 0.026g of unreacted compound **228**) as colourless oil.

IR (solution of $CHCl_3$) : ν_{max} = 1735 cm^{-1}(s), 1655(s), 1410(s), 1365(br), 1240(s), 1030(s), 975(s).

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 5.21-4.92 (2H, H-8, H-7, m), 4.75 (1H, H-5, dd, J = 5.0 Hz, 8.5 Hz), 4.37 (1H, H-1, dd, J = 3.5 Hz, 8.5 Hz), 4.18 (2H, -CH_2-O-, d, J = 6.0 Hz), 2.9 (6H,-NMe_2, s), 2.79-2.32 (1H, H-6, m), 2.11 (3H, OAc, s), 2.04 (3H, OAc, s), 2.01 (3H, OAc, s).

3-Dimethylamino-7,8-dihydroxy-6-hydroxymethyl-2-aza-4-oxabicyclo[3.3.0]oct-2-ene (allosamizoline, **197a**).

The triacetate **197b** (0.229g, 0.669 mmol) was dissolved in aq.HCl (1.0 M, 6.5 ml) and the solution was stirred at 50°C for 4.5h. The reaction mixture was concentrated *in vacuo* to give **197a** as a hygroscopic solid, which was directly used for the preparation of compound **230** without purification.

6-*t*-Butyldimethylsilyloxymethyl-3-dimethylamino-7,8-dihydroxy-2-aza-4-oxabicyclo[3.3.0]oct-2-ene (**230**)

To a solution of the compound **197a** (0.188g, 0.744 mmol) in DMF (2.5 ml) were added chloro *t*-butyldimethylsilane (0.171g, 1.13 mmol) and imidazole (0.155g, 2.27 mmol) and the mixture was stirred at room temperature for overnight. The reaction mixture was poured into aqueous saturated brine and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel (18g) and elution with chloroform-MeOH (3:1) gave compound **230** (0.137g, 63%) as a colourless oil.

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 4.66 (1H, dd), 4.15-3.81 (may be 5H, m), 2.88 (6H, -NMe_2, s), 2.03 (1H, m), 0.89 (9H, Si-^{t}Bu, s), 0.07 (6H, Si-Me, s).

3,4,6-tri-*O*-Acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl acetate (**232**)

To a solution of sodium methoxide (10.65g of Na in 465 ml MeOH) was added the grinded compound **231** (100g,463.75 mmol) and the resulting mixture was stirred at room temperature for 30 min. To this was added powdered phthalic anhydride (34.26g, 231.29 mmol) and Et_3N (64.5 ml, 462.76 mmol) and the mixture was stirred at room temperature for 10 minute. To this was added again powdered phthalic anhydride (37.5g, 253.03 mmol) and the mixture was stirred at room temperature for overnight. The white precipitates were filtered and dried with vaccuum pump. The crude compound (164g) was dissolved in pyridine (700 ml) and acetic anhydride (408 ml, 4324 mmol) was added. The resulting mixture was stirred at room temperature for 16h. The reaction mixture was then poured into ice-water and extracted with EtOAc. The organic layer was successively washed with ice-water, 3% HCl, aqueous saturated $NaHCO_3$ and water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (3Kg) and elution

with hexane-ethyl acetate (5:1) gave compound **232** (157g, 71%) as white solid.

3,4,6-tri-*O*-Acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**233**)

To a solution of the compound **232** (5g, 10.48 mmol) in DMF (5 ml) was added hydrazine acetate (1.15g, 12.48 mmol). The resulting mixture was heated at 50°C for 15 minutes. The reaction mixture was then diluted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (170g) and elution with hexane-ethyl acetate (1:1) afforded compound **233** (3.7g, 86%) as white solid.

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 7.86-7.72 (4H, Pht, m), 5.83 (1H, H-3, dd, J = 9.1 Hz, 10.6 Hz), 5.64 (1H, H-1, dd, J = 7.3 Hz, 8.2 Hz), 5.18 (1H, H-4, dd, J = 9.1 Hz, 10.0 Hz), 4,29 (1H, H-6, dd, J = 4.5 Hz, 12.8 Hz), 4.28 (1H, H-2, dd, J = 8.2 Hz, 10.6 Hz), 4.20 (1H, H-6, dd, J = 2.1 Hz, 12.2 Hz), 3.94 (1H, H-5, ddd, J = 2.5 Hz, 4.9 Hz and 10.0 Hz), 2.10, 2.03, 1.86 (9H, 3 x Ac, s).

3,4,6-tri-*O*-Acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl trichlorimidate (**234**)

To a solution of compound **233** (3.36g, 7.72 mmol) in dry CH_2Cl_2 (39 ml) at 0°C was added trichloroacetonitrile (3.53 ml, 35.2 mmol) and DBU (0.117 ml, 0.786 mmol). The resulting mixture was stirred at 0°C for 2h. Solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (90g) and elution with hexane-ethyl acetate (5:1) gave **234** (3.76g, 86%) as white solid.

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 8.65 (1H, -NH, br s), 7.80-7.75 (4H, Pht, m), 6.57 (1H, H-3, d, J = 8.9 Hz), 5.91 (1H, H-1, dd, J = 9.3 Hz, 10.2 Hz), 5.27 (1H, H-4, dd, J = 9.27 Hz, 10.2 Hz), 4.61 (1H, H-6, dd, J = 9.27 Hz, 10.6 Hz), 4.24-3.99 (3H, m), 2.12 (3H, OAc, s), 2.04 (3H,

OAc, s), 1.89 (3H, OAc, s).

Cyclohexyl *O*-3,4,6-tri-*O*-acetyl-2-deoxy2-phthalimido-β-D-glucopyranoside (**236**)

A solution of compound **234** (0.95g, 1.78 mmol) in dry CH_2Cl_2 (7 ml) was added to a stirred solution of cyclohexanol **235** (0.1g, 0.998 mmol) in dry CH_2Cl_2 (2.6 ml) containing powdered MS AW-300 (0.26g) at 0°C, followed by the addition of trimethylsilyl triflate (0.04 ml, 0.221 mmol) after 5 min. The reaction mixture was stirred for 2h at the same temperature. The reaction mixture was quenched with $NaHCO_3$ in water-THF and warmed up to room temperature. The mixture was filtered through celite and the filtrate was extracted with $CHCl_3$. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel (35.7g) and elution with $CHCl_3$-ethyl acetate (5:1) gave **236** (0.515g, quantitative yield) as white solid.

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 7.82-7.78 (4H, Pht, m), 5.80 (1H, H-3, dd, J = 9.2 Hz, 10.7 Hz), 5.38 (1H, H-1, dd, J = 8.5 Hz, 8.8 Hz), 5.19 (1H, t, H-4, J = 9.6 Hz), 4.38 (1H, H-2, dd, J = 8.5 Hz, 10.7 Hz), 4.35 (1H, H-6, dd, J = 4.7 Hz, 12.1 Hz), 4.21 (1H, H-6, dd, J = 2.4 Hz, 12.2 Hz), 3.87 (1H, H-5, ddd, J = 2.4 Hz, 4.7 Hz, 10.1 Hz), 2.13 (3H, OAc, s), 2.03 (3H, OAc, s), 1.86 (3H, OAc, s), 1.56-1.18 (10H, cyclohexane-CH_2, m).

(5*S*, 7*R*, 8*R*)-6-Benzyloxymethyl-7,8-di-t-butyldimethylsilyloxy-2-aza-4-oxabicyclo[3.3.0]octan-3-one (**239**)

To a stirred solution of the compound **227** (0.15g, 0.3597 mmol) in dry CH_2Cl_2-cyclohexane (1:2, 4 ml) at room temperature under argon atmosphere was added benzyl trichloroacetimidate (0.138 ml, 0.7426 mmol) and trifluorosulfonic acid (0.0075 ml). The resulting mixture was stirred at the same temperature for 5h. The reaction mixture was then quenched with aqueous saturated $NaHCO_3$

solution. The aqueous layer was then extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (24g), and elution with hexane-ethyl acetate (7:1) gave **239** (0.183g, quantitative yield) as a thick syrup .

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 7.33-7.26 (5H, Ph, m), 5.51(1H, N-H, br), 5.05 (1H, H-5, dd), 4.50 (2H, -CH_2Ph, br s), 3.90-4.00 (3H, H-1, -CH_2-OBn, m), 3.57-3.48 (2H, H-8, H-7, m), 2.55 (1H, H-6, br m), 0.88 (9H,*t*-Bu-Si, s), 0.86 (9H, *t*-Bu-Si, s), 0.07 (12H, Si-CH_3, s).

(5*S*, 7*R*, 8*R*)-7,8-Diacetoxy-6-benzyloxymethyl-2-aza-4-oxabicyclo[3.3.0]octan-3-one (**241**)

To a solution of the compound **239** (0.05g, 0.0986 mmol) in MeOH (1 ml) was added conc. HCl (0.035 ml) and the mixture was stirred at room temperature for 2.5h. The mixture was then neutralized with pyridine (0.035 ml) and concentrated *in vacuo* and the residue was dissolved in pyridine (1.15 ml). To this mixture was added acetic anhydride (0.05 ml, 0.53 mmol) and the solution was stirred at room temperature for 16h. The mixture was poured into aqueous saturated ammonium sulfate and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel (2.4g) and elution with hexane-EtOAc (1:1) gave **241** (0.0217g, 70%) as colourless oil.

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 7.33-7.26 (5H, Ph, m), 5.75 (1H, N-H, br), 5.42 (1H, H-7, dd), 4.89 (1H, H-5, dd, J = 6.0 Hz, 9.0 Hz), 4.75 (1H, H-8, dd, J =4.5 Hz, 7.5 Hz), 4.52 (2H, -CH_2Ph, br s), 4.25 (1H, -CH_2-O-, d, J = 5.5 Hz), 3.97 (1H, H-1 ,dd), 3.60 (1H, H-6, dd), 2.08 (3H, -OAc, s), 2.05 (3H, -OAc, s).

(5*S*,7*R*,8*R*)-7,8-Diacetoxy-6-benzyloxymethyl-3-*N*,*N*-dimethylamino-2-aza-4-oxabicyclo[3.3.0]oct-2-ene (**242**)

To a solution of compound **241** (0.2g, 0.55 mmol) in CH_2Cl_2 (3.5 ml) containing MS-4A (0.6g) was added triethyloxonium tetrafluoroborate (1M soln. in CH_2Cl_2, 1.45 ml, 1.15 mmol) under argon atmosphere. The resulting mixture was stirred at room temperature for 20h. Dimethylamine (6.52M soln. in toluene, 8.5 ml, 55.42 mmol) was then added and the mixture was stirred at room temperature for additional 48h. The reaction mixture was filtered through celite. The filtrate was poured into aqueous saturated $NaHCO_3$ solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (23g) and elution with ethyl acetate gave **242** (0.084g, 45%) together with compound **241** (~0.092g) as colourless oil.

IR (solution of $CHCl_3$) : ν_{max} = 1740 cm^{-1}(s), 1655(s), 1455(s), 1510(s), 1240(s), 1080(br), 1035(s), 910(s), 800(s), 740(s), 700(s).

^{1}H-NMR (90 MHz, $CDCl_3$) : δ = 7.33-7.26 (5H, Ph, m), 5.24-5.09 (2H, H-8, H-7, m), 4.80 (1H, H-5, dd), 4.54 (2H, -CH_2Ph, br s), 4.25 (1H, H-1, dd), 3.55 (1H, -CH_2-O-, d), 2.90 (6H, NMe_2, s), 2.36-2.27 (1H, H-6, m), 2.00 (3H, -OAc, s), 1.98 (3H, -OAc, s).

6-Benzyloxymethyl-3-*N*,*N*-dimethylamino-7,8-dihydroxy-2-aza-4-oxabicyclo[3.3.0]oct-2-ene (monobenzyl allosamizoline, **238**)

To a solution of the compound **242** (0.07g, 0.18 mmol) in dry methanol was added MeONa (28% in methanol, one drop). The resulting mixture was stirred at room temperature for overnight. Solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (2.1g) and elution with $CHCl_3$-methanol (100:1) gave **238** (0.027g, 85%) as a colourless oil.

6-Benzyloxymethyl-3-dimethylamino-8-hydroxy-2-aza-4-oxabicyclo[3.3.0]-oct-2-enyl 3,4,6-tri-*O*-acetyl-2-phthailimido-β-D-glucopyranoside (**243**)

A solution of the compound **234** (0.052g, 0.089 mmol) in CH_2Cl_2 (0.9 ml) was added to a stirred solution of the compound **238** (0.016g, 0.052 mmol) in dry CH_2Cl_2 (0.5 ml) containing MS AW 300 (0.08g) at 0°C, followed by the addition of trimethylsilyl triflate (0.0096 ml) after 5 min. After stirring for 30 min triethylamine (0.025 ml) was added and left to stand for 10 min. The reaction mixture was warmed up to room temperature and filtered through celite. Solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (2.7g), and elution with $CHCl_3$-MeOH (60:1) gave **243** (0.015g, 48%) as a thick syrup.

IR (solution of $CHCl_3$) : ν_{max} = 1725 cm^{-1}(s), 1710(s), 1650(w), 1515(s), 1460(d), 1390(s), 1240(br), 1160(s), 1080(s), 1030(s), 910(s), 800(s), 725(s), 640(s).

^{1}H-NMR (500 MHz, $CDCl_3$) : δ = 7.83-7.70 (4H, pht, m), 7.30 (3H, Ph-H, m), 7.09 (2H, Ph-H, m), 5.73 (1H, H-3', t, J = 9.5 Hz), 5.42 (1H, H-1', d, J = 7.0 Hz), 5.03 (1H, H-4', t, J = 9.5 Hz), 4.88 (1H, H-7, br m), 4.24 (3H, H-6' and H-2', m), 3.94-3.91 (3H, H-5' and -CH_2-C_6H_5, m), 3.73 (1H, H-5, br m), 3.28 (1H, H-8, br d), 2.99 (8H, 6-CH_2 and -NMe_2, br m), 2.20 (1H, H-6, br m), 2.16 (3H, OAc, s), 1.97 (3H, OAc, s), 1.81 (3H, OAc, s).

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