SYNTHETIC STUDIES TOWARDS CAMPTOTHECIN, A-FACTOR AND DEVELOPMENT OF USEFUL SYNTHETIC METHODOLOGIES

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SEPTEMBER 2004

SYNTHETIC STUDIES TOWARDS CAMPTOTHECIN, A-FACTOR AND DEVELOPMENT OF USEFUL SYNTHETIC METHODOLOGIES

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

By

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SEPTEMBER 2004

CERTIFICATE

Certified that the work incorporated in the thesis entitled ***"Synthetic Studies Towards Camptothecin, A-factor and Development of Useful Synthetic Methodologies"*** *submitted by K. Pasupathy was carried out under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.*

September, 2004

National Chemical Laboratory,
Pune-411008.

Dr. Subhash. P. Chavan.
Research Supervisor.

Declaration

I hereby declare that the thesis entitled "***Synthetic Studies Towards Camptothecin, A-factor and Development of Useful Synthetic Methodologies***" submitted for Ph. D degree to the university of Pune has been carried out at Organic Chemistry Division (Technology), NCL, Pune, under the supervision of Dr. S. P. Chavan and the work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

September, 2004 K. Pasupathy

Organic Chemistry: Technology,
National Chemical Laboratory,
Pune-411008.

Dedicated To My Parents

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Part-2: Catalytic Acetylation of Alcohols, Phenols, Thiols and Amines with H-FER Under Solvent Free Conditions

Acknowledgements

It's my great pleasure to express heartfelt gratitude to my research guide Dr. Subhash. P. Chavan for his guidance and inspiration through out my research program.

I am thankful to Dr. T. Ravindranathan for his valuable suggestion. I am also thankful to Dr. M. K. Gurjar, Dr. Paul Ratnaswamy and Dr. Sivaram for permitting me to work at NCL. Gratitude to Dr. S. Kamat for his immense help and support. Help rendered from all senior scientists (Dr. U. R. Kalkote, Mrs. Latha Sivadasan, Dr. C. V. Ramana, Dr. A. Murugan, Dr. V. H. Deshpande, Dr. R. D. Wakharkar, Dr. Bhanu Chanda, Mrs. Kamalam Balakrishnan, Dr. R. A. Joshi, Dr. Mrs. R. A. Joshi, Dr. H. B. Bhorate, Dr. Vincent, Dr. Mohapatra, Dr. Muthukrishnan, Mr. I. Shivkumar) of the division of OCT, NCL is gratefully acknowledged.

My sincere thanks for help rendered from the members of my group (Venkat, Tripura, Gopal, Anil, Kharul, Sivappa, Shiv Shankar, Ramesh Kale, Mahesh Takkhar, Shambaji, Dhusyant, Preeti, Ramakrishna, Praveen, Pallavi, Sanjay, Swapna, Shinde, Sudhir, Manoj, Ashok). Never diminishing encouragement from my friends Kichha, Mangal, Subbu, Dandu, Sankar, Easwar, Malli, Thyagu, Ramesh, kannan, Jayanthi, Balki, Santhanam uncle, Devraj, Vijay raj, Francis, Victor, Ramesh kumar, Suresh, KT, Shivanand, Nagendar, kishore, Shinde, Mahajhan, Vasu, Subbarao, Nagaprasad, Sharad, Poorva, Abhijeet members of the open air lab and from the members of NCL GJH who have been supportive to make my stay away from home is also acknowledged. Gratitude to my FRIENDS (a long list) who have assisted me in and out of the lab. Assistance from the spectroscopic group (NMR, IR, Mass and analysis), library staff and the help rendered from the office staff of OCT NCL are gratefully acknowledged.

Words fall short to thank my parents, family members and teachers, who have contributed and sacrificed a lot for me to reach this stage and will always remain a sole source of inspiration in my life. The thesis is a form to pay respect to their attributes.

Support from CSIR for financial assistance is also duly acknowledged.

K. Pasupathy

Abbreviations

Ac	Acetyl
Aq.	Aqueous
Bn	Benzyl
bp	Boiling point.
BuLi	Butyl Lithium
Bz	Benzoyl
Cbz	Benzyloxy carbonyl
CPT	Camptothecin
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl carbodiimide
DCM	Dichloro methane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	Dihydropyran
DIBAL	Diisobutylaluminium hydride
DMAP	4-(Dmethylamino)pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMS	Dimethyl sulphide
DMSO	Dimethyl sulphoxide
DNA	Deoxyribonucleic acid
EtOAc	Ethylacetate
h	Hour/s
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
Hz	Hertz
KHMDS	Potassium Hexamethyldisilazide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LiHMDS	Lithium Hexamethyldisilazide

m-CPBA	*meta*-Chloroperbenzoic acid
MOMCL	Methoxymethylchloride
mp	Melting point
MS	Mass spectrum
MsCl	Methanesulphonyl Chloride
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
PCC	Pyridinium chlorochromate
PCy_3	Tricyclohexyl phosphine
Ph	Phenyl
rt	Room temperature
SARs	Structure activity relationship
$TBAHSO_4$	Tetrabutyl ammonium hydrogensulphate
TBAF	Tetrabutyl ammonium Fluoride.
TBDMSCl	Tertiarybutyldimethylsilyl chloride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TPP	Triphenyl phosphine

GENERAL REMARKS

1) All melting points and boiling points are uncorrected and the temperature is expressed in degree Celsius.
2) The compound numbers, scheme numbers and reference numbers given in each section refers to that particular section only.
3) All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80^{o}C.
4) Organic layers were dried over anhydrous sodium sulphate (Na_2SO_4).
5) The reaction progress was monitored by the thin layer plates pre-coated with silica gel 60 F_{254} (Merck) and visualized by flourescence quenching or iodine or by charring after treatment with p-anisaldehyde.
6) In case where chromatographic purification was done unless mentioned SiO_2 (60-120 mesh size) was used as stationary phase.
7) The IR spectra were recorded on Perkin-Elmer infrared spectrophotometer model 683B or 1605 FTIR and IR absorbance is expressed in cm^{-1}.
8) The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC200, MSL 300 and DRX 500. ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million from internal standard (tetramethylsilane) on δ scale.
9) Mass spectra were recorded at an ionization energy 70eV on Finnigan MAT-1020, automated GC/MS instrument and on API Q STARPULSAR using electron spray ionization [(ESI), solvent medium-water, acetonitrile and ammonium acetate] technique and mass values are expressed as m/z. HRMS were recorded on a micromass Q-T of Micro with spray source (ESI^{+} mode).
10) Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser within the limits of accuracy (± 0.4%).
11) All the new experiments were repeated two or more times.
12) Starting materials were obtained from commercial sources or prepared using known procedures.

ABSTRACT

The thesis entitled ***"Synthetic Studies Towards Camptothecin, A-factor and Development of Useful Synthetic Methodologies"*** is divided in to two chapters.

Chapter 1: Chapter 1 deals with the synthetic approaches towards antitumor natural product camptothecin, which is divided in to two sections.

Chapter 2: Chapter 2 constitutes the synthesis of (±)-A-factor and the Catalytic transesterification of β-ketoesters and acetylation of alcohols, thiols, phenols and amines with H-FER zeolite under solvent free conditions.

CHAPTER 1

Synthetic Studies Towards Camptothecin

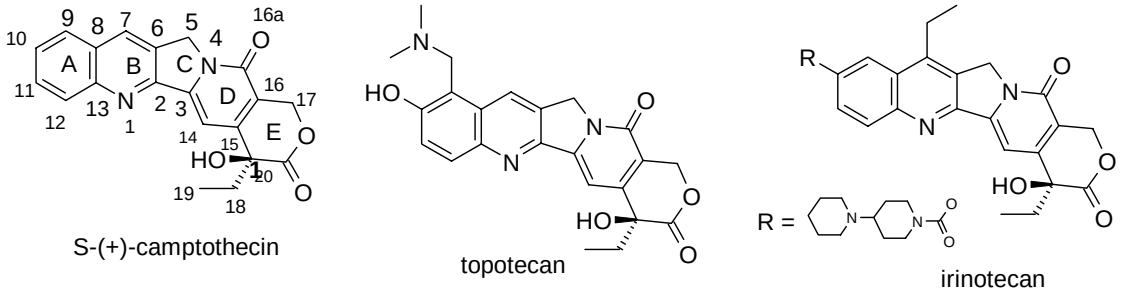


Figure 1

Camptothecin, a pentacyclic alkaloid isolated from the Chinese tree *Camptotheca acuminata* by Wall and Wani in 1966, is one of the outstanding lead compounds in anticancer drug development. Camptothecin as such was not ideal for pharmaceutical development, mostly due to its toxicity, poor solubility and the unstable nature of the lactone ring, which opens rapidly to an inactive hydroxy acid at the physiological conditions. Liu and co-workers reported in 1985 that the cytotoxicity of camptothecin was attributed to a unique mechanism of action involving selective inhibition of DNA topoisomerase I, an enzyme essential for relaxation of DNA during important cellular processes. This sparked renewed interest for intense research on camptothecins, culminated in launching two successful compounds namely irinotecan and topotecan in clinical practice and several other compounds in various stages of clinical trials. Camptothecin also demonstrates impressive antiretroviral activity against acute and chronic HIV-1 infections. Given the current continued interest, though many syntheses have been achieved still there is an evident need for the development of a new synthetic

route amenable to camptothecin and its analogues. As a part of the research program, it was decided to make necessary approaches towards the practical and efficient synthesis of camptothecins (camptothecin and related alkaloids).

SECTION I

Camptothecin: *A Brief Review*

This section presents a general introduction to camptothecin. This chapter portrays a concise account on isolation, biosynthesis, mechanism of action, structure activity and relationship studies. This section also gives a detailed account of some of the challenging approaches involved in the total synthesis of camptothecin and related alkaloids.

SECTION II

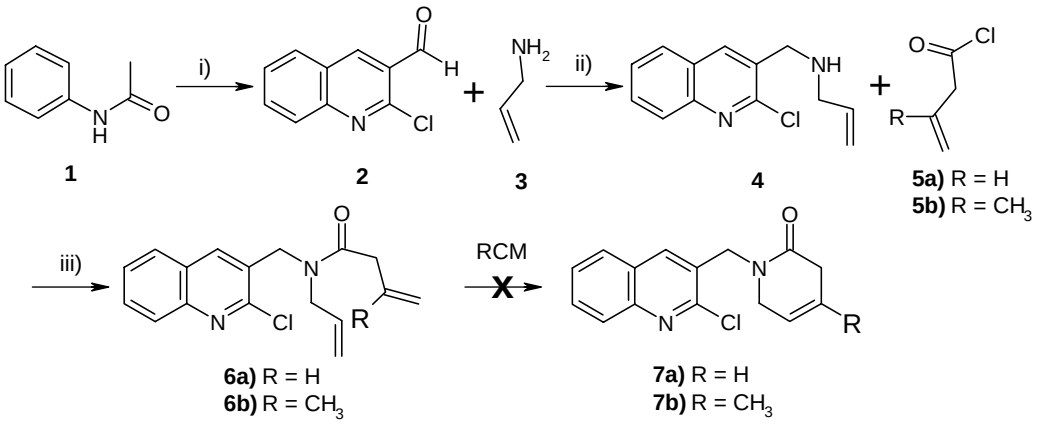
Camptothecin: *Synthetic Approaches*

Part 1:

Ring Closing Metathesis Approach towards the Synthesis of Camptothecin.

The strategy involved a new and efficient approach for the synthesis of D-ring of camptothecin utilizing intramolecular ring closing metathesis reaction. This section presents a detailed investigation of the attempts carried to transform the envisioned strategy in to reality. The following scheme delineated below shows our approach towards the synthesis of camptothecin employing RCM as the key step to construct the pyridone ring.

Scheme 1

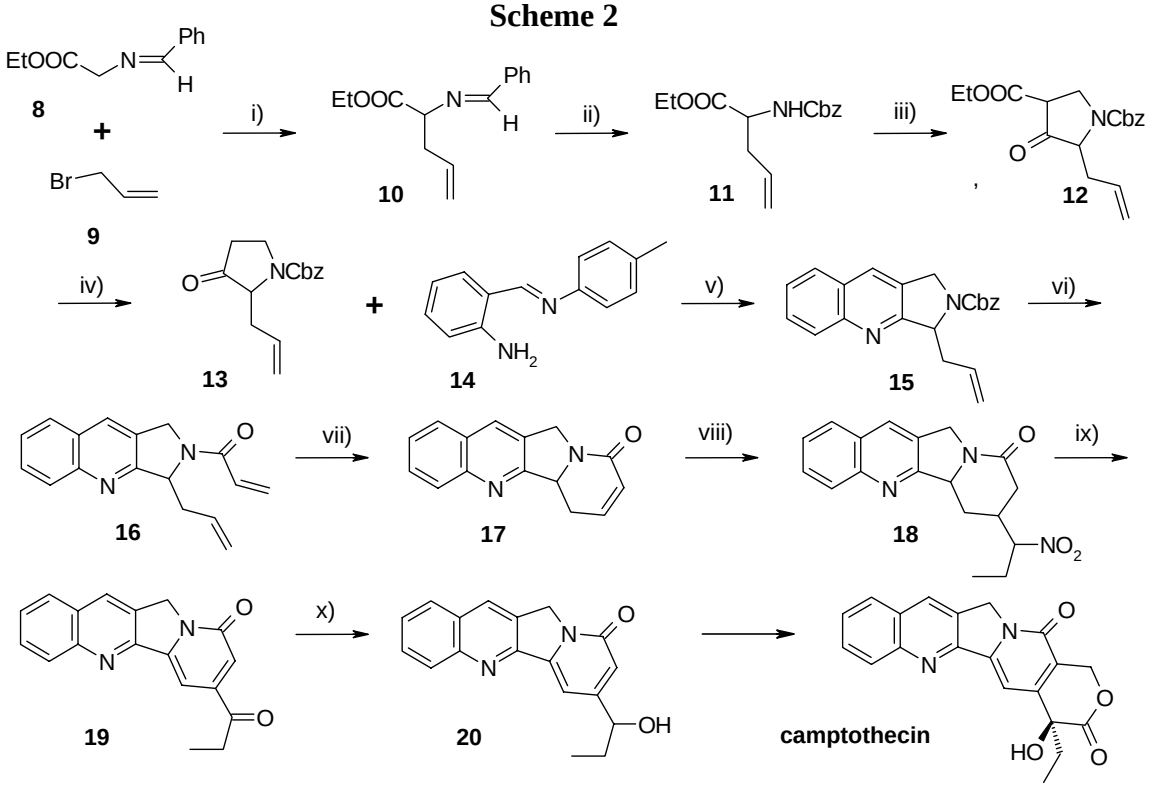


***Reagents and conditions**: i) $POCl_3$, DMF, 75 ºC, 16 h, 65%, ii) a) MeOH, rt, 0.5 h, 99% b) $NaBH_4$, MeOH, 0.5 h, 95%, iii) K_2CO_3, DCM, 0 ºC to rt, 3 h, 60%.*

Unfortunately even after several trials of experiments, the RCM reaction on the amide **6**

was met with failures (scheme 1). Failure of this strategy compelled us to shift to an alternative synthetic strategy (scheme 2).

Scheme 2



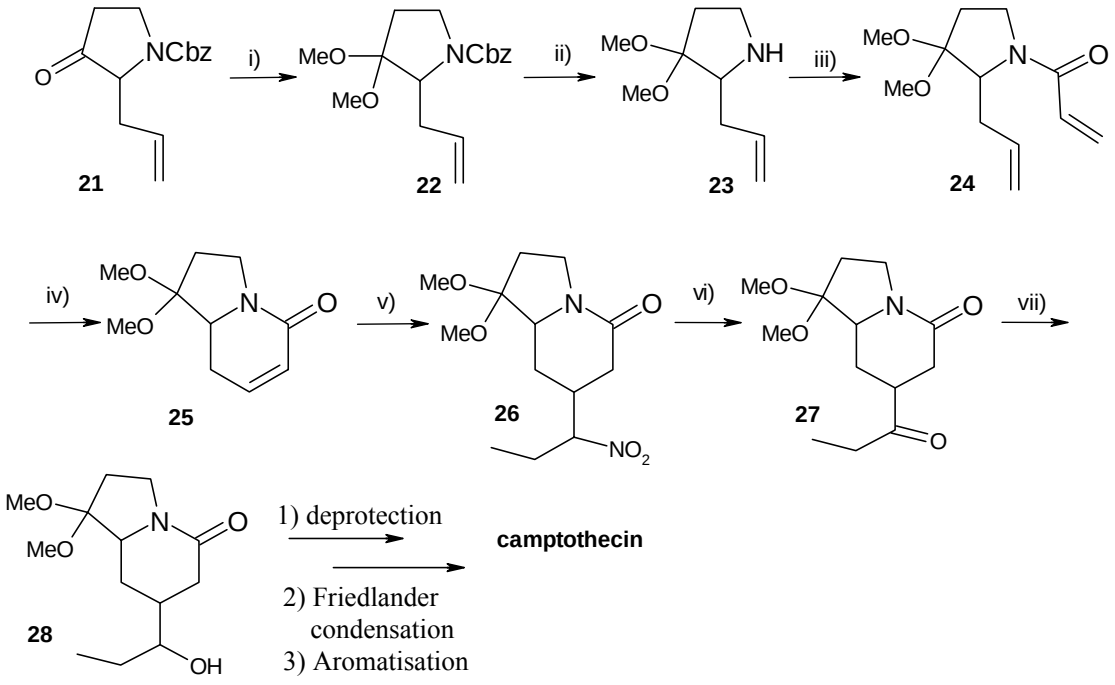
Reagents and conditions: *i) 10% NaOH, $TBAHSO_4$, DCM, rt, 0.5 h, 97%, ii) a) 10% HCl, rt, 0.5 h, 94%, b) CbzCl, K_2CO_3, DCM, rt, 3 h, 96%, iii) NaH, C_6H_6, ethyl acrylate, reflux, 3 h, 68%, iv) 10% HCl, reflux, 5 h, v) toluene, PTSA, reflux, 8 h, 70%, vi) a) KOH, EtOH, reflux, 24 h, b) acryloyl chloride, K_2CO_3, DCM, rt, 3 h, 73%, vii) Grubbs first gen catalyst (10 mmol%), Ti (OiPr)$_4$, DCM, reflux, 16-20 h, 90%, viii) nitropropane, DBU, rt, 16 h, 86%, ix) NaOH, MeOH, RT, 3 h, Conc. HCl, 0 ^oC, 1 h and rt, 12 h, 23%, x) $NaBH_4$, MeOH, 0 ºC, 1 h, 99%.*

Thus Schiff's base **8** when subjected to alkylation with allyl bromide under Phase transfer conditions furnished the alkylated Schiff's base **10** in 97% yield. Hydrolysis of Schiff's base **10** with HCl furnished the free amine, which was protected with CbzCl to provide the urethane **11** in 96% yield. Tandem-Michael-Dieckmann condensation using ethyl acrylate a as the Michael acceptor furnished keto ester **12** in 65% yield, which was subjected to hydrolysis-decarboxylation under acidic condensations followed by condensation with N-(*o*-aminobenzilidine)-*p*-toluidine **14** provided quinoline **15** in 70%

yield. Deprotection of urethane **15** and condensation of the resulting amine with acryloyl chloride furnished the amide **16** in 73% yield. The sequence involving RCM and subsequent Michael addition with nitropropane gave the nitro adduct **18**. On exposure to standard Nef conditions, not only the nitro functionality on **18** was transformed to carbonyl, but surprisingly oxidation to the corresponding pyridone **19** was also effected in 23% yield. Finally the reduction of the carbonyl group of **19** with $NaBH_4$ gave the desired hydroxy pyridone **20** in nearly quantitative yield. Hydroxy compound **20** is a key intermediate in Murata's synthesis of camptothecin. Thus, our approach constitutes a formal total synthesis of camptothecin.

It was reasoned that, the analogues of camptothecin and the related alkaloids could be achieved by delaying the construction of AB-ring. Therefore, it was decided to synthesize CD-ring with appropriate appendages for the E-ring and develop the AB-ring using standard Friedlander condensation with suitably substituted o- amino benzaldehyde (scheme 3).

Scheme 3



***Reagents and condition**: i) trimethyl orthoformate, PTSA, MeOH, reflux, 12 h, 99%, ii) KOH, EtOH, reflux, 43 h, iii) acryloyl chloride, TEA (5 eq), DCM, rt, 3 h, 40%, iv) Grubbs first generation catalyst (10 mmol%), DCM, reflux, 16-20 h, 94%, v) nitro-*

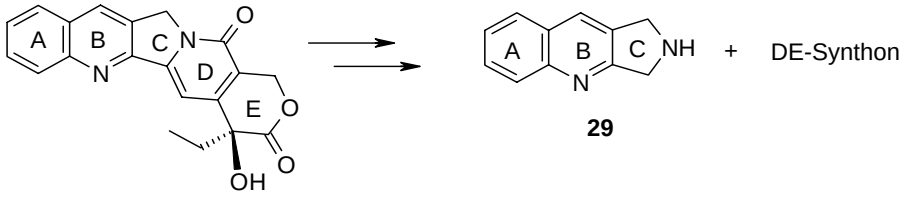
propane, DBU, rt, 16 h, 85%, vi) NaOH, Na_2HPO_4, MeOH, rt, 1 h, followed by Oxone, rt, overnight, 82%, ii) $NaBH_4$, MeOH, 0 ºC, 1 h, 85%.

Part 2:

Approaches Towards Camptothecin Skeletal Frame Work

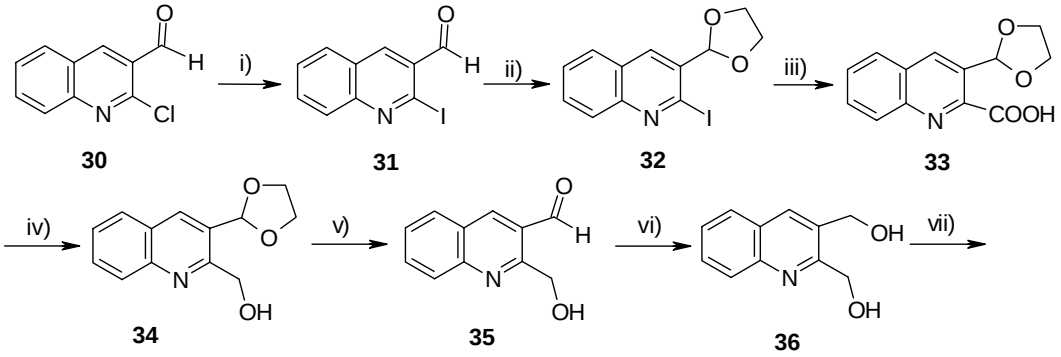
Having achieved the formal total synthesis of camptothecin it was envisaged to synthesise the same by adopting a different strategy (retrosynthesis-scheme 4).

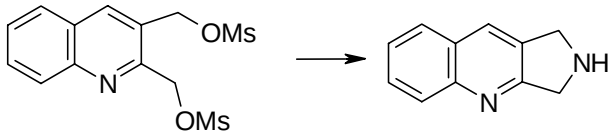
Scheme 4



Several groups involved in the convergent synthesis of camptothecin and mappicine ketone identified the tricylic amine **29** as a key synthon for the construction of ABC ring system (scheme 4). Reports involving the preparation of this key intermediate are either low yielding or have utilized chemical reagents such as acridine, 2-aminobenzaldehyde, dimethylacetylene dicarboxylate (DMAD), propargyl amine, etc, which are either expensive, unstable, or pose problems in handling. This implies that there is an evident need for new methods to synthesize this important intermediate. As a part of the research activity to explore new synthetic approaches towards camptothecin and mappicine ketone we decided to explore new synthetic sequences to provide the tricyclic amine **29** using simple and commercially available starting materials. The sequence of reactions described in scheme 5 and scheme 6 provide the rapid access to the desired tricyclic amine **29** starting from simple and inexpensive starting materials.

Scheme 5

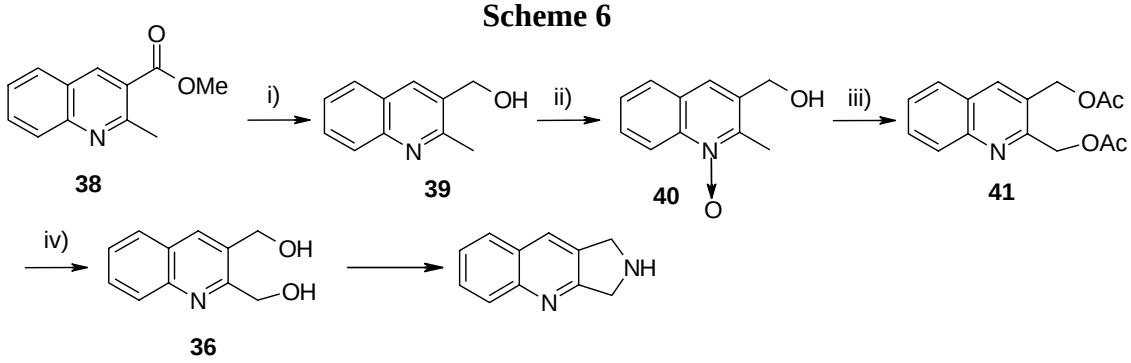




37 **29**

Reagents and conditions: *i) NaI, cat Conc. HCl, CH_3CN, 6 h, reflux, 90%, ii) Ethylene glycol, PTSA, benzene, 8 h, 110 ºC, 92 %, iii) CuCN, DMF, 135 ºC, 2 h, 96%, iv) NaOH, reflux, 2 h, 96%, iv) a) ClCOOEt, TEA, THF, 0 ºC, b) $NaBH_4$, MeOH, rt, 6 h, 58%, v) 2 N HCl, THF, rt, 1 h, vi) $NaBH_4$, MeOH, rt, 30 min, 85%, vii) MsCl, TEA, C_6H_6, 0 ºC, 1 h, 80%.*

Scheme 6

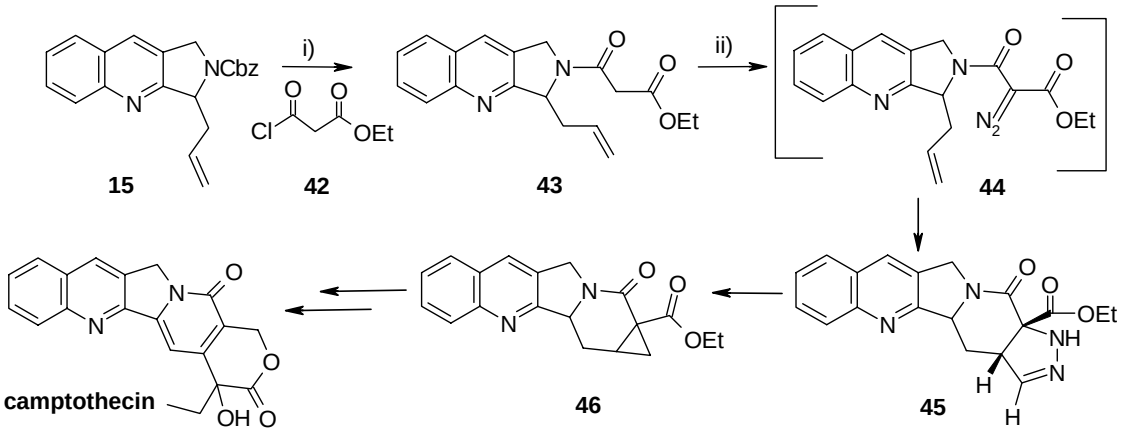


38 **39** **40** **41** **36**

Reagents and conditions*: i) LAH, THF, 0 ºC, 1 h, 55%, ii) m-CPBA, CH_3CN, rt, over night, 90%, iii) Ac_2O, 130 ºC, 2 h, 75%, iv) K_2CO_3, aq. MeOH, RT, 0.5 h, 80%.*

In pursuit of alternate strategy to synthesize camptothecin, close look at the target skeleton revealed the possibility of formation of the D ring of camptothecin in a concise manner with suitable substituents necessary for the formation of E-ring through intramolecular cyclopropanation (scheme 7).

Scheme 7



15 **42** **43** **44** **45** **46**

Reagents and conditions: *i) a) KOH, EtOH, reflux, 24 h, b)* ***42****, K_2CO_3, DCM, 0 ºC to rt, 3 h, 68%, ii) MsN_3, TEA, CH_3CN, rt, 48 h, 81%.*

As shown in the scheme 7, carbamate group on the tricyclic amine 1**5** was deprotected and the free amine thus liberated was condensed with ethoxy acetyl chloride **42** to give the amide **43**. Thus amide **43** when subjected to diazo transfer under standard conditions, instead of forming the diazo compound **44** as the product, it gave rise to pyrrazoline **45** via a intramolecular 1,3–dipolar cycloaddition. Efforts are on for the conversion of 2-pyrazoline **45** to cyclopropane **46** and the subsequent ring opening to complete the synthesis of camptothecin.

CHAPTER II

Synthesis of (±)-A-factor and Development of Useful Synthetic Methodologies

SECTION I

Synthesis of (±)-A-factor

In the mid-1960' s Khokhlov and his co-workers discovered A-factor **47** in *S. griseus*, a streptomycin producer. This factor produced in the culture broth of *S. griseus* induces streptomycin production, aerial mycelium and spore formation at very low concentration. They proposed the structure of A-factor as (*2S*)-(*6'*-methylheptanoyl)-(*3S*)-hydroxymethylbutyrolactone. Later in 1983 Mori *et al.* revised the stereochemistry of A-factor as (*2R*)-(*6'*-methylheptanoyl)-(*3R*)-hydroxymethyl-butyrolactone. The chiral centre at C-2 was shown to rapidly epimerise by enolisation.

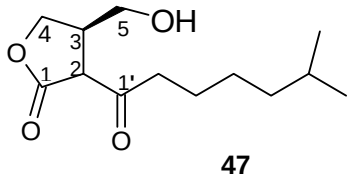


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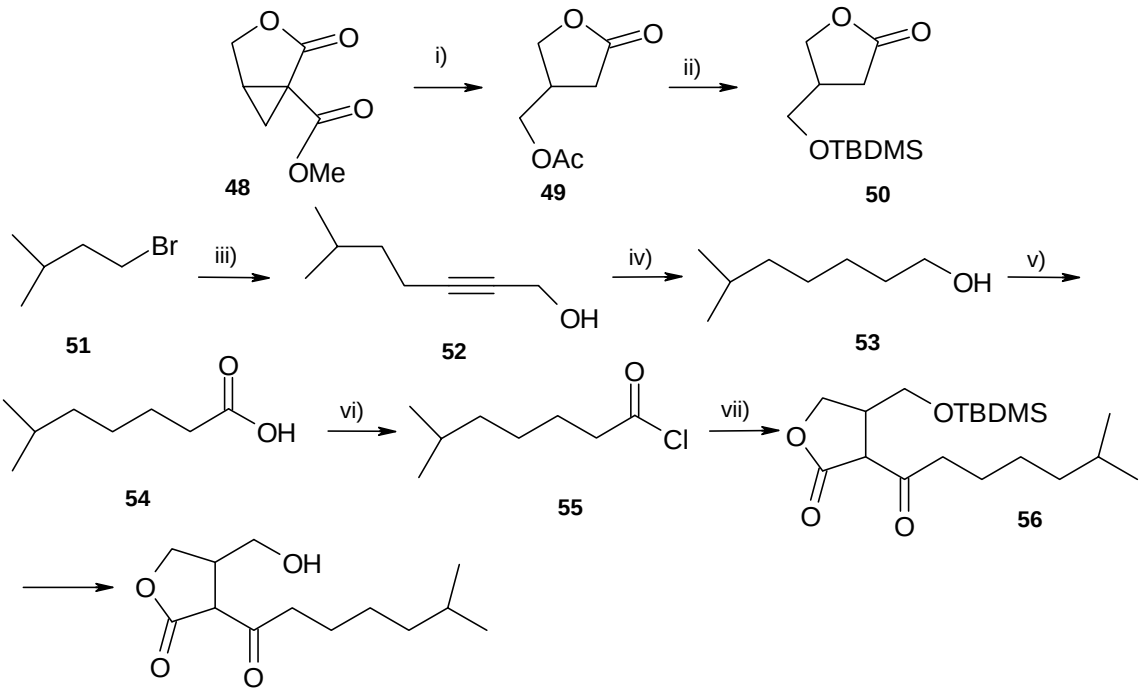
Figure 2

This section describes the studies towards the synthesis of (±)-A-factor starting from electrophilic cyclopropane **48**. A new synthetic route to (±)-A-factor has been demonstrated by use of a homoconjugate addition of KOAc/AcOH to doubly activated cyclopropane **48** (scheme 8). The notable feature of this synthetic route is that (±)-A-factor is synthesized from simple and readily available starting materials**.** The same

strategy can be very easily extended to the synthesis of biologically active (*S*)-(−)-A-factor.

Scheme 8



Reagents and conditions: *i) KOAc/AcOH, DMSO, 6 h, 110 ºC, 66%, ii) a) NaOMe (cat)/MeOH, 1 h, rt, b) TBDMSCl, imidazole, CH_2Cl_2, 3 h, rt, 77%, iii) propargyl alcohol, $LiNH_2$/liq NH_3, overnight, -33 ºC, 61% iv) Raney nickel, H_2, MeOH, overnight, rt, 81%, v) Jones reagent, 8h, 0 ºC to rt, 96%, vi) $SOCl_2$, DMF (cat), 24 h, rt, 85%, vii)* ***8****, LHMDS, THF, 1 h, -78 ºC, 85%*

SECTION II

Catalytic Organic Transformation Utilizing H-Fer Zeolite Under Solvent Free Conditions

The application of inorganic solid acids especially zeolites, as effective heterogeneous catalysts for organic synthesis have received considerable attention in the recent decades due to their interesting properties such as shape selectivity, acidic and basic nature, ease of handling, non-corrosiveness, recyclability and a very high thermal stability. Thus as a part of the research program towards development of protocols for the green synthesis, it was decided to study two fundamental synthetic transformations. This section presents the detailed study of the transesterification of β-ketoesters and

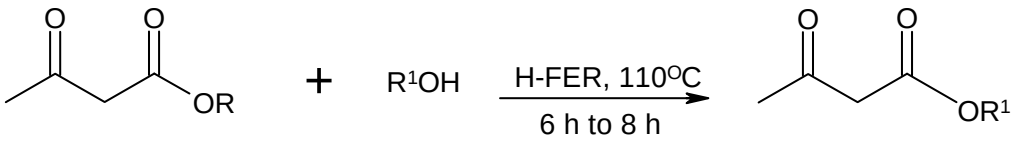
acetylation of alcohols, phenols, thiols and amines catalyzed by zeolite H-FER under solvent free conditions.

Part 1:

Catalytic Transesterification of β-ketoesters with H-FER Under Solvent Free Conditions.

Zeolite H-FER catalyzed the transesterification of structurally diverse β-ketoesters with variety of alcohols under solvent-less conditions in excellent yields. The catalyst was reused without any loss of activity (scheme 9).

Scheme 9

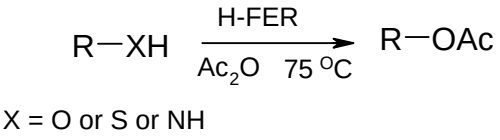


Part 2:

Catalytic Acetylation of Alcohols, Phenols, Thiols and Amines with Zeolite H-FER Under Solvent Free Conditions.

Zeolite H-FER catalyzed the acetylation of alcohols, phenols, thiols and amines under solvent-less conditions in excellent yields. The catalyst was reused several times without any loss of activity (scheme 10).

Scheme 10



X = O or S or NH

Signature of the Candidate

K. Pasupathy

Signature of the research guide

(Dr. Subhash P. Chavan)

CHAPTER I

SECTION 1: **Camptothecin:** ***A Brief Review***

SECTION 2: **Camptothecin:** ***Synthetic Approaches***

PART 1: **Ring Closing Metathesis Approach Towards The Synthesis of Camptothecin**

PART 2: **Approaches Towards Camptothecin Skeletal Frame Work**

CHAPTER I

SECTION 1: Camptothecin: *A Brief Review*

1.1.1 Introduction:

The research team led by Wall and Wani of Research Triangle Institute was responsible for the discovery of two life saving molecules for the treatment of cancer namely camptothecin a pentacyclic alkaloid from Chinese tree *Camptotheca acuminata* in 1966[1a] and Taxol from pacific yew tree from *Taxus brevifolia* in 1971[1b] are adjudged as path breaking accomplishments in the annals of natural product research.

Camptothecin and several analogues of camptothecin, collectively called, as camptothecins have been isolated from various botanical sources. Camptothecin as such was not ideal for pharmaceutical development, mostly due to its toxicity (myelosupression, severe and unpredictable hemorrhagic cystitis and diarrhoea), poor solubility and the unstable nature of the lactone ring, which opens rapidly to an inactive hydroxy acid at the physiological conditions. Nearly two decades, later the unique mode of action for this potently cytotoxic compound was found to be the selective inhibition of DNA topoisomerase 1, an enzyme essential for relaxation of DNA during important

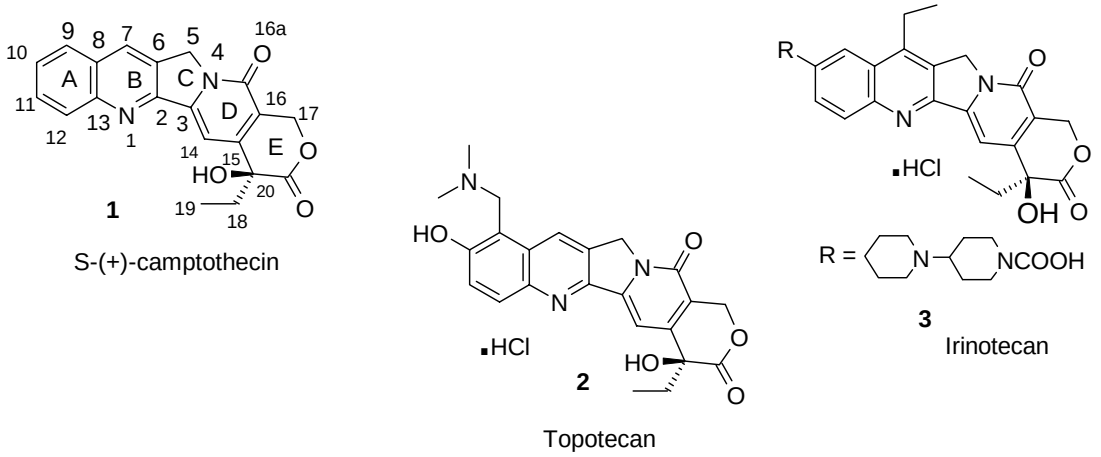
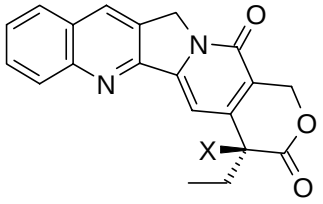


Figure 1

cellular process and trigger a cascade of events leading to apoptosis and programmed cell death. These insights provided novel rationales for the design of improved analogues. This sparked renewed interest for intense research on camptothecins, culminated in launching two successful compounds namely topotecan (**2**) and irinotecan (**3**) in clinical practice and several other compounds in various stages of clinical trials for the treatment of cancer by chemotherapy.

1.1.2 Characterization and Structural Elucidation:

The structure was elucidated by a combination of spectral methods, chemical properties and finally confirmed by the X-ray analysis of the iodoacetate **1d**. Camptothecin was found to be a very high melting solid. It was also optically active ($[\alpha]^{25}_{D}$, +31.3 ºC) and gave an intense fluorescence under UV. The molecular weight of the camptothecin obtained was 348.11 corresponding to the formulae $C_{20}H_{16}N_2O_4$. Formation of monoacetate **1a** with acetic anhydride, chloroacetate **1b** with chloroactic anhydride and chloro camptothecin **1c** using $SOCl_2$/pyridine suggested the presence of a hydroxy functional group. Rapid saponification to a sodium salt that regenerated **1** on acidification and lactol formation upon reduction with $NaBH_4$ suggested the presence of lactone moiety in the molecule. The X-ray analysis of the iodoacetate **1d** prepared by treating chloro acetate derivative with NaI in acetone decisively confirmed the structure to be 4(*S*)-4-Ethyl-4-hydroxy-1*H*-pyrano-[3',4':6,7]indolizino[1,2*b*] quinoline- 3, 14 (4*H*, 12*H*)-dione. The rings ABCD and the substituents on C-17, C-20 as well as the pyridone ring oxygen fall in same plane. The lactone ring oxygen deviates from the plane imparting a boat conformation to the E-ring.



1a) X = $OCOCH_3$
1b) X = $OCOCH_2Cl$
1c) X = Cl
1d) X = $OCOCH_2I$

Figure 2

The very fact that camptothecin does not form a stable salt with mineral acids, negative tests with Dradgendroff and Meyer reagents unlike other alkaloids suggest the neutral nature of the molecule. The unusual rapid reduction with $NaBH_4$ to the lactol, failure of the methylation of OH functionality with CH_2N_2 or dimethyl sulphate under different variety of conditions can be ascribed to the possibility of intramolecular hydrogen bonding. This is to some extent ascertained by the fact that the acetate derivative **1a** fails to form sodium salt under the same conditions as **1**.

Le Men-Taylor numbering system had been employed for camptothecin based on the close biogenetic relationship with the indole alkaloids, here represented by ajmalcine **4**. The pyridone carbonyl carbon in camptothecin has been designated 16a, even though this atom was not assigned a number in the Le Men-Taylor system.

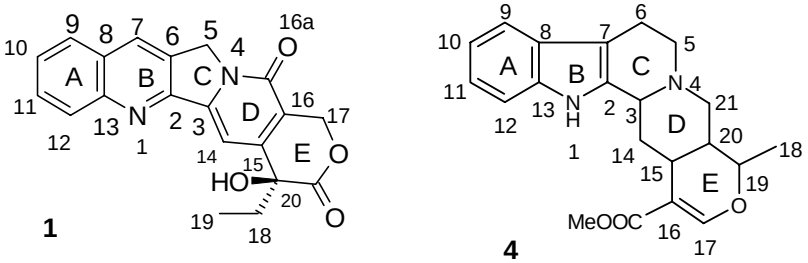


Figure 3

1.1.3 Naturally Occurring Camptothecin Analogues and Sources:

The search for new anticancer drugs from nature continues to be fruitful activity, as evidenced by the successes of natural products as pharmaceutical agents. In view of the on going active analogue development programmes of CPT it is apt to mention about some of them. Camptothecin (**1**) first isolated from *Camptotheca acuminata,* is one of the most important alkaloids having inhibitory activity against tumor cells and activity against HIV-I. Several analogues of camptothecin, collectively called as camptothecins or camptothecinoids have been isolated from various botanical species. In light of the on going active development on the efforts to find new analogs of camptothecin, this section covers few of the naturally occurring camptothecinoids.

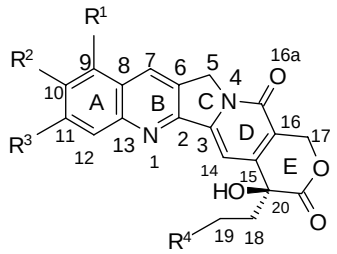


Figure 4

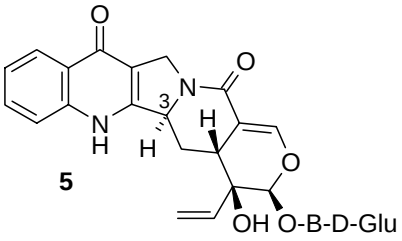
$R^1=R^2=R^3=R^4=H$	Camptothecin **1**	*Camptotheca acuminata,*[5a] *Nothapodytes foetida,*[5b] *Ophiorrhiza mungos,*[5c] *Ervatamia heyneana,*[5d] *Ophiorrhiza pumila,*[5e,5f] *Pyrenacantha klaineana*[5g]
$R^1=R^3=R^4==H$, $R^2=OH$	10-Hydroxycamptothecin **1e**	*Camptotheca acuminata,*[5h] *Nothapodytes foetida,*
$R^1=R^3=R^4=R^5=H$, $R^2=OMe$	10-Methoxycamptothecin **1f**	*Camptotheca acuminata,*[5h] *Ophiorrhiza mungos,*[5c] *Pyrenacantha klaineana,*[5g]
$R^1=OMe$, $R^2=R^3=R^4=H$,	9-Methoxycamptothecin **1g**	*Camptotheca acuminata,*[5h] *Nothapodytes foetida, Ervatamia heyneana,*[5h]
$R^1=R^2=R^4=H$, $R^3=OH$	11-Hydroxylcamptothecin **1h**	*Camptotheca acuminata,*[5i]
$R^1=R^3=H$, $R^2=OMe$, $R^4=(COCH_2)_4Me$	20-Hexanoyl-10-methoxy Camptothecin **1i**	*Camptotheca acuminata,*[5e]
$R^1=R^2=R^3=H$, $R^4=OH$,	18-Hydroxycamptothecin **1j**	*Camptotheca acuminata,*[5k]
$R^1=OMe$, $R^2=\beta$-D -Glu, $R^3=R^4=H$,	Chaboside **1k**	*Ophiorrhiza pumila champ,*[5e]
$R^1=R^2=R^3=R^4=H$	20-O-β-Glucopyranosyl camptothecin **1l**	*Mostuea brunonis*[5j]

Pumiloside[5h] **5 and Deoxypumiloside**[5f] **8**: Pumiloside was postulated as the poststrictosamide intermediate of Camptothecin biosynthesis.

22-Hydroxycuminatine[5i] **6**: It is a biogenetically novel alkaloid as A-D rings are similar to those of Camptothecin while the E-ring is of Yohimbine type. It showed cytotoxic activity during *in vitro* studies.

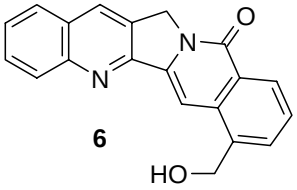
Deoxy Camptothecin[5k] **7**: Showed insignificant activity, presumably due to the lack of hydroxy group.

Foetidin I[5k] (**9**): It has A, B, C, D rings in common with Camptothecin and differs in its E-ring having a side chain through a phenolic ester bond. It showed anti tumor activity against ovarian cells and anti viral activity against HIV viruses.



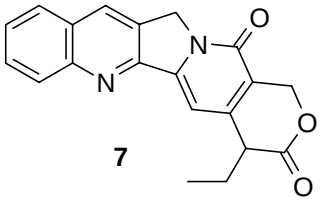
5

(3 *S*)-pumiloside



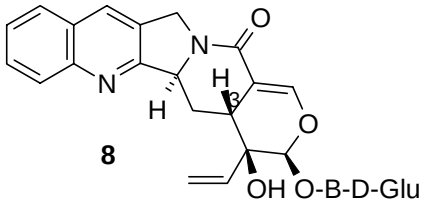
6

22-hydroxycuminatine



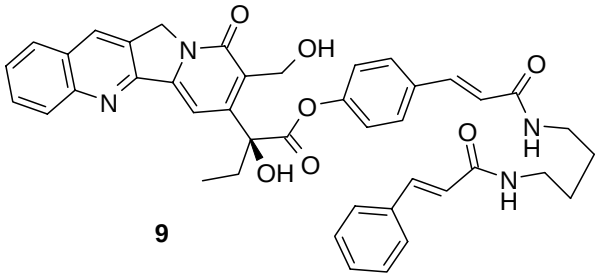
7

deoxy camptothecin

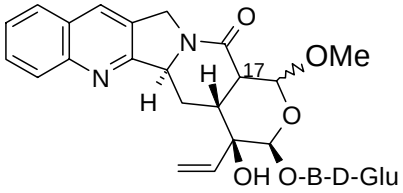


8

(3 *S*)-deoxypumiloside



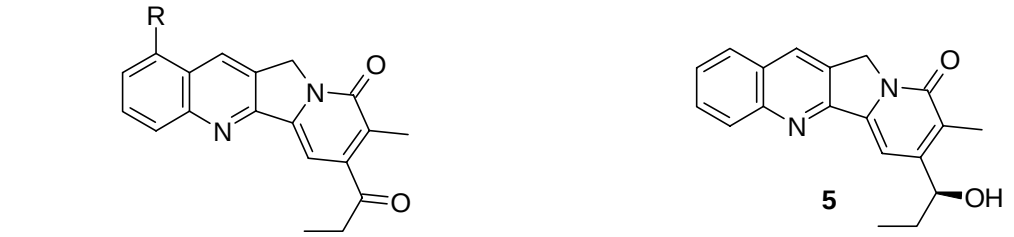
9



10a 17*S* : OPHR-23[5f]
10b 17*R* : OPHR-17

Figure 5

Mappicine ketone[6a] (nothapodytine B) **12a** an oxidized form of the natural alkaloid mappicine[6b] **11** which was isolated from Indian plant *Nothapodytes foetida* (formerly known as *Mapia foetida Miers*).



R = H, Nothapodytine B **12a** (Mappicine Ketone)

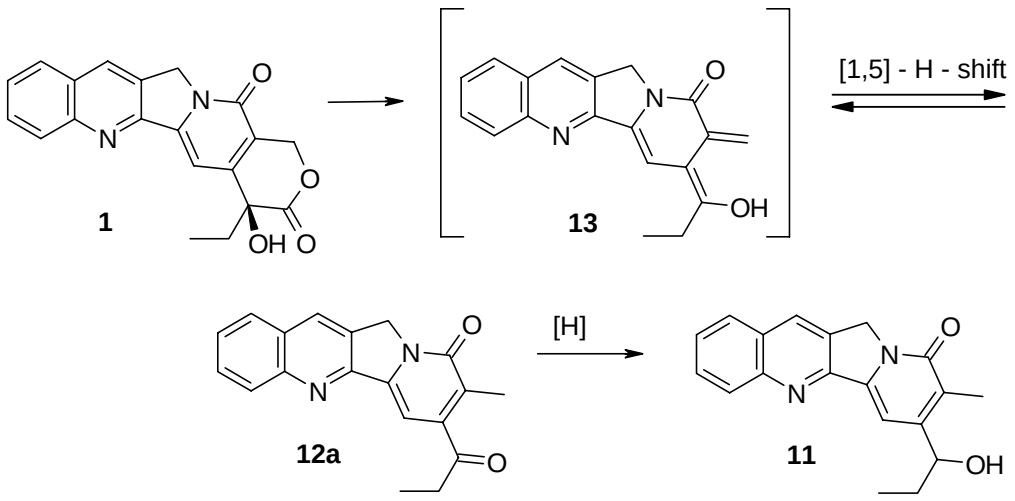
R = OMe, Nothapodytine A **12b** (Methoxymappicine Ketone)

Mappicine

Figure 6

Co-occurance of camptothecin, mappicine, Nothapodytine B (mappicine ketone) and, Nothapodytine A in *Nothapodytis foetida* suggests that these alkaloids have a common biosynthetic precursor or it is quite possible that **1** is the precursor of **11** and **12a** as shown in the following mechanism, which is observed in the fragmentation of the molecular ions produced from **1** in the electron impact mass spectrometer. Nothapodytine B **12a** has been identified as a potential antiviral lead compound with selective activity against herpes viruses HSV-1, HSV-2, acyclovir resistant virus and human cytomegalovirus (HCMV).[6c,6d]

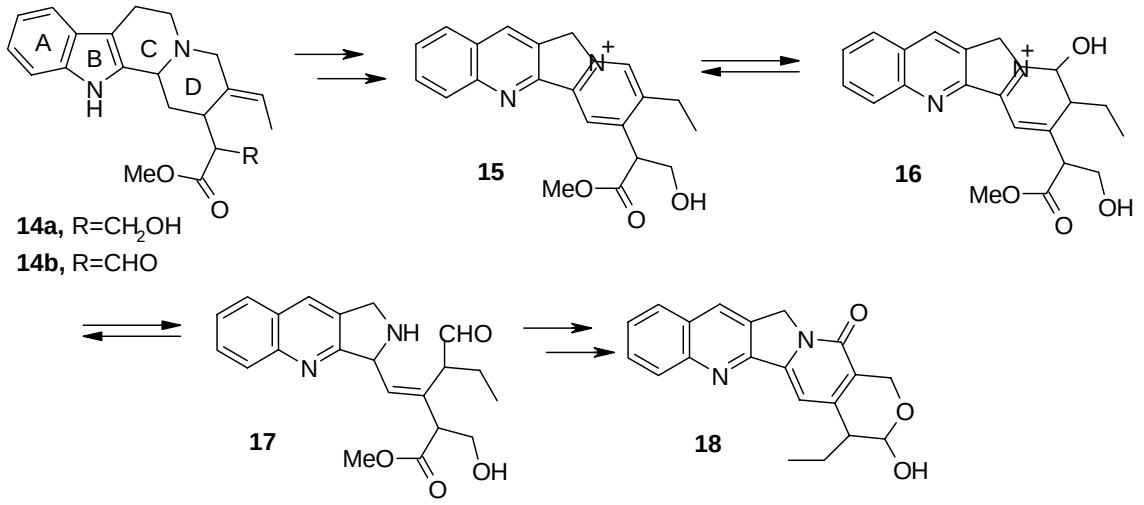
Scheme 1



1.1.4 Biogenetic Pathway :

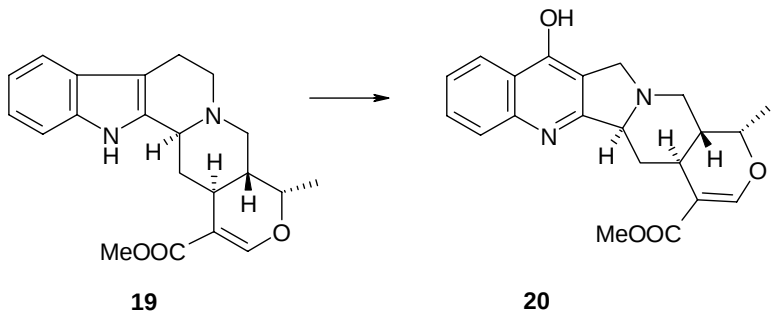
Wenkert *et al* in 1967[7] laid the foundation to explain and provide a logical biosynthesis of camptothecin and related alkaloids. He speculated camptothecin to be masked indole alkaloid of the corynantheidine type because its pentacyclic nucleus appeared to be capable of being synthesized easily by the utilization of intermediates involved in the synthesis of corynantheidine. The biogenetic scheme was charted out as shown in scheme 2 using plausible chemical transformation starting from isositsirikine **14a** or related alkaloids, similar to the biosynthetic relationship of vallesiachotamine to geissoschizine.

Scheme 2

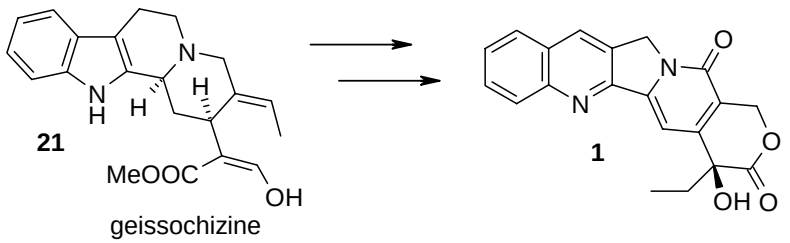


Based on Wenkert's observation and his own findings on the oxidation of indole alkaloid **19** to quinoline **20** (scheme 3), Winterfeldt's speculated and proposed gessiochizine as plausible biogenetic precursor (scheme 4).[8]

Scheme 3

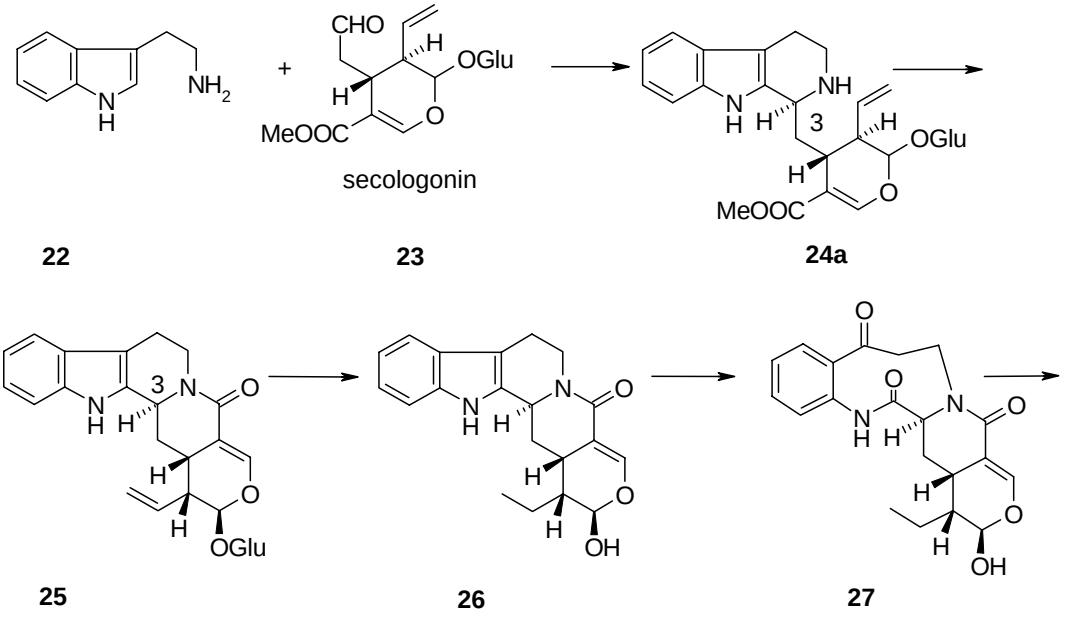


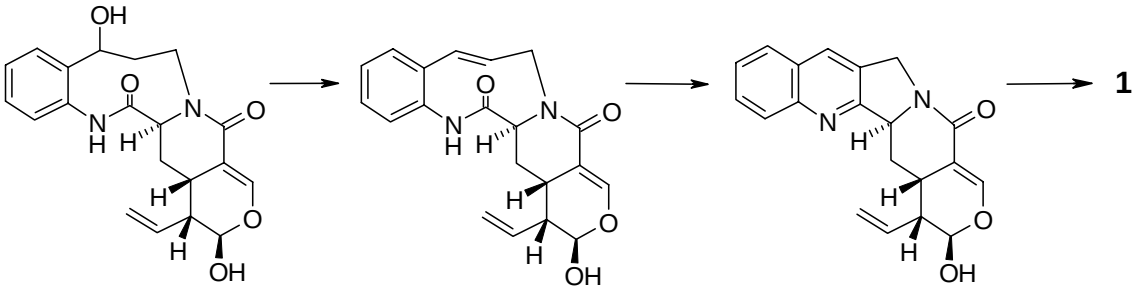
Scheme 4



The preliminary *in vivo* results based on the incorporation of radioactive tryptophan,[9a] tryptamine **22**,[9b] mevalonic acid,[9a] geraniol/nerol isomeric mixture,[9b] secologanin[9a] **23** and strictosidine[9c] **24a** gave radioactive camptothecin in apical cuttings of young seedlings of *Camptotheca. acuminata* established camptothecin was a monoterpene indole alkaloid. Experimental results of the feeding of labeled precursors carried out by Heckendrof *et al* proved strictosidine **24a** as the specific precursor and ruled out epimeric (H-3-beta) vincoside.[9d] Radio chemically labeled strictosomide **25** was also tested and found its efficient incorporation in camptothecin, facile conversion of strictosidine to strictosamide **25** under basic conditions and its structural similarity to camptothecin strongly supported the role of strictosoamide as the key biosynthetic precursor of camptothecin.[10] The probable biosynthetic sequence is depicted below.

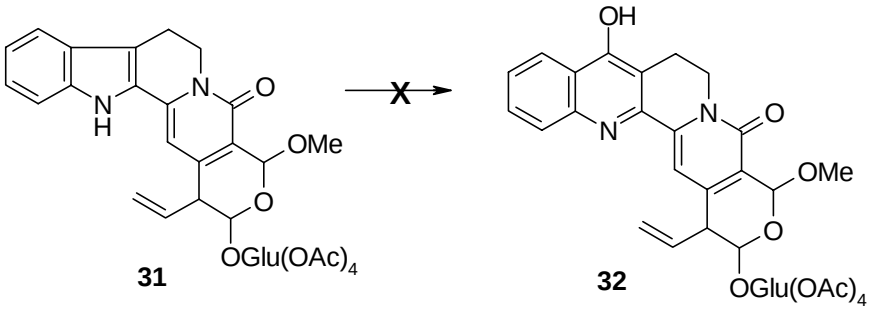
Scheme 5





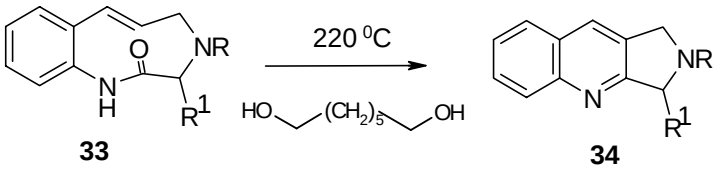
Thus mevalonate is converted by the way of geraniol and loganin in to secologanin **23**, which combines with the tryptamine **22** to form strictosidine **24a** which inturn gets transformed to strictosamide **25**. The transformation of **25** in to camptothecin could possibly involve removal of the glucose moiety, ring BC oxidation-recyclisation, ring D-oxidation and E-ring oxidation. This biogenetic hypothesis is well supported by the independent observations of Cordell and coworkers.[11] The removal of the glucose unit followed after the formation of strictosamide **25**. This presumption, hinges on the biosynthetic fate of strictosidine **24a** in other plants.[12] The very fact that conversion of pyridone **31** to quinoline **32** under standard laboratory conditions (scheme 6) met with failure asserts that prior to D-ring oxidation ABC rearrangement takes place.[13]

Scheme 6



The exact sequence of steps involved during rearrangement is still unclear. It is believed that indole moiety opens oxidatively to the ketolactam **27**. Reduction of the keto group in **27** to alcohol **28**, followed by elimination and subsequent ring closure via stepwise ionic or concerted electrocyclic process leads to **1**. This biogenetic belief is supported by the cyclisation of **33** to the corresponding quinoline **34** under thermal conditions (scheme 7).[13]

Scheme 7



33 **34**

1.1.5 Mode and Mechanism of Action:

In early 1970s, camptothecin was known to inhibit RNA and DNA synthesis, but a specific enzyme could not be identified as its site of activity.[14] While inhibition of DNA synthesis appears highly irreversible or partially reversible, inhibition of RNA synthesis is highly reversible. Another striking effect of camptothecin is its rapid fragmentation of chromosomal DNA. All the cellular effects of camptothecin remained unexplained until the identification of topoisomerase 1 as the molecular target of camptothecin. In 1979 it was recognized that several antitumor drugs promote covalent linkage of protein to DNA in tumor cells.[15] During this time, Dr Leroy F. Liu of Johns Hopkins University, had been studying the action of enzymes called DNA topoisomerases, which modulate DNA superhelicity during transcription and replication by relieving the torsional strain introduced by separation of DNA strands as the transcriptional or replication apparatus proceeds. Topoisomerase 1 (Topo 1) enzyme catalyze the topoisomerisation reactions of DNA namely relaxation/supercoiling, knotting/unknotting and catenation/decatenation via transient enzyme linked single strand breaks.

Cancer cells are more sensitive to Topo I inhibition than normal cells because they contain a higher concentration of the enzyme. This is a consequence of their faster rate of growth and reproduction. Therefore, the affinity of CPT for Topo I translates in selective toxicity for tumor cells. Topo I unwinds supercoiled DNA ahead of active transcription/translation sites (“replicating forks”). The noncovalent complex of double-stranded DNA and Topo-I, described as the "noncleavable complex," is in rapid kinetic equilibrium with the so-called "cleavable complex," which forms when Topo I creates a transient break in one DNA strand and concomitantly becomes covalently bound to the 3'-phosphoryl end of the mutilated nucleic acid. The intact DNA strand is allowed to unwind once and to pass through the break site, before Topo I religates the cleaved DNA and re-establishes the double stranded configuration. These events constitute an

obligatory stage of DNA replication/transcription, as the DNA must be unwound for the cell to express genetic information or to divide. Camptothecin interferes with the religation by binding to the DNA-enzyme binary complex resulting in a reversible enzyme-camptothecin-DNA ternary complex. Consequently, the advancing DNA polymerases operating in the replicating fork soon "collide" with the stabilized cleavable complex and create an irreparable double-strand break. This event is fatal to the cell. The structure of the cleavable ternary complex is of great interest for elucidation of the mechanism of action and development of new topoisomerase inhibitors.[16]

1. 1. 6 Structure-Activity Relationship Studies:

Full pentacyclic structure of camptothecin is essential for the antitumor activity of camptothecin and analogs. The analogs of camptothecin in which there was sequential truncating were devoid of activity (tetracyclic B-E ring, tricyclic CDE- ring, bicyclic DE- rings and monocyclic E-rings)[17] suggesting the importance of all the rings for the anti tumor activity. Alteration of the core sequence has shown to be ineffective towards antitumor activity. The failure of C-nor- 4, 6-seco camptothecin **35**,[18] tetrahydro camptothecin **36**,[19] hetero aromatic analog **37**,[20] as impressive antitumor agents when compared to parent camptothecin certainly provides ample evidence for the presence of pentacyclic core, as an essential component for biological activity.

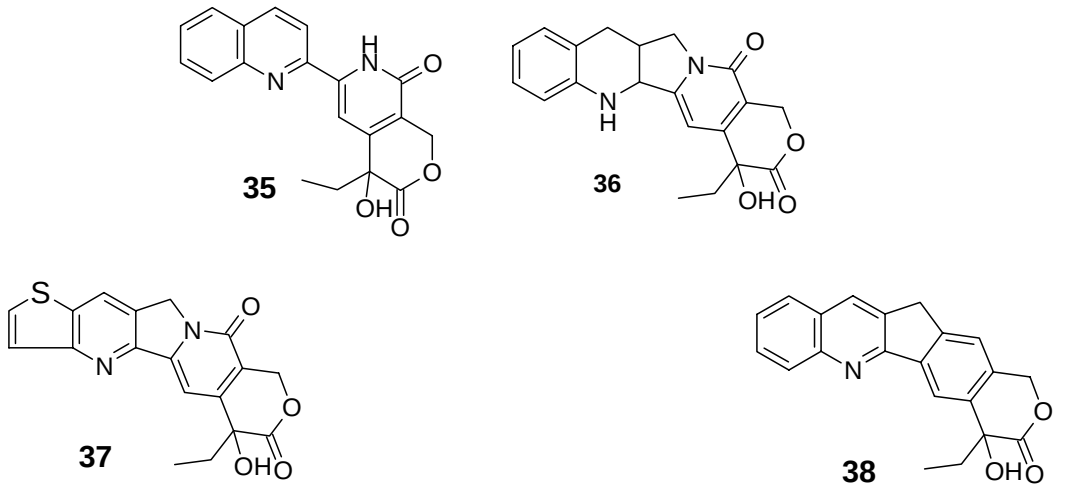
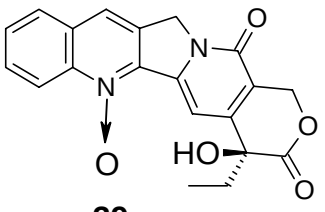


Figure 8

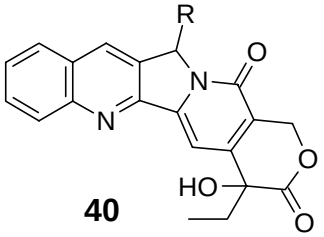
The importance of pyridone ring for the activity is evident as the compound **38** having same spatial identity was 40 to 60 fold less active when compared to

camptothecin.[21] All these observations suggest that mutilating the pentacyclic core results in the loss of planarity an essential requirement for camptothecin's antitumor activity.

In general functionalization of rings A and B modulates antitumor activity. Substituents at C-7, C-9 or C-10 often enhance potency, while substitution at positions 11 and 12 generally diminish it.[20,22] The rationale behind these results stems from the probable fact that camptothecin may bind to an enzyme or enzyme-DNA complex on the face proximal to the C-11 and C-12 region. Therefore substitution at these two carbons may pose undesirable steric and stereo-electronic interactions. Substitutients at C-9 and C-10 are more distant from this region. As a result, substitution at this location is not detrimental for biological activity. However, a 10, 11-methylene dioxy or ethylene dioxy unit greatly increases activity, while similar substitutions with two methoxy groups at 10 and 11 inactivate completely confirming the requirement of the planarity as the inevitable component for the antitumor activity of camptothecin. From a series of A-ring modified analogues of camptothecin, 9-NH_2 and 9- NO_2 camptothecin (Rubitecan) were identified as potent analogues.[23] 7-chloro camptothecin displayed improved activity when compared to (±)-camptothecin.[24] Whereas 7-methoxy or 7-acetoxy substituents decreased the activity. The camptothecin N-oxide **39** showed decreased activity indicating the importance of quinoline nitrogen for biological activity.[25] The substitution at position 5 of camptothecin showed reduced activity (figure 9).[26a, 26b]



39



40

R = OH, OAc, Et, Cl

Figure 9

The C-20 α-hydroxyl moiety with '*S*' configuration is a prerequisite for the *in vivo* and *in vitro* acitivity of camptothecin. Wall *et al* showed the (±)-camptothecin is half as active as (*S*)-camptothecin.[26c] Replacement of C-20 'OH' group in camptothecin by Cl, H, allyl, ethyl, hydroxymethyl, NH_2, N_3, exomethylene moiety showed no activity (**42**).[20,27] Isocamptothecin[20] **41a** and isohomocamptothecin[28] **41b** showed slight and no activity respectively. Replacement of C-20 ethyl group of camptothecin by allyl,

propargyl, benzyl, methoxy ethyl, show no marked change in activity. While replacement with ben zoyl group showed reduced activity suggests that ethyl group in **1** can be replaced by a suitable functionality (figure 10).[27a]

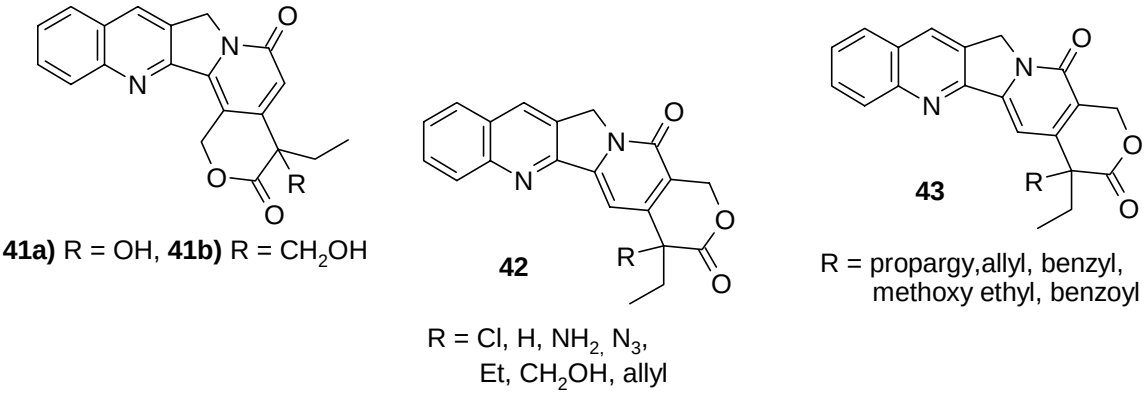
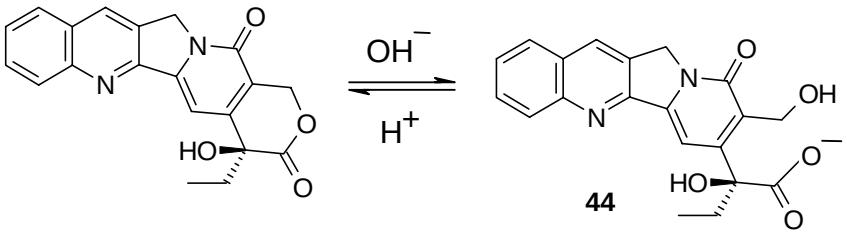


Figure10

Structure-activity relationship studies (SARs) pointed out that the ring opened carboxylate form of several camptothecin derivatives has been shown to be significantly less active.[29] The camptothecin lactone ring undergoes facile hydrolysis and equilibrates with its ring-opened form even at the physiological conditions (scheme 8).[30] The sodium salt of the carboxylate form of camptothecin was only one tenth active than that of **1** when administered intravenously.

Scheme 8



The lactol[25] **45** and lactam[21] **46** showed no antitumor activity. These observations suggested to draw conclusion that intact lactone ring might be essential for camptothecin's activity. However Sugasawa observed, ester **47** showed activity comparable to racemic camptothecin.[27a]

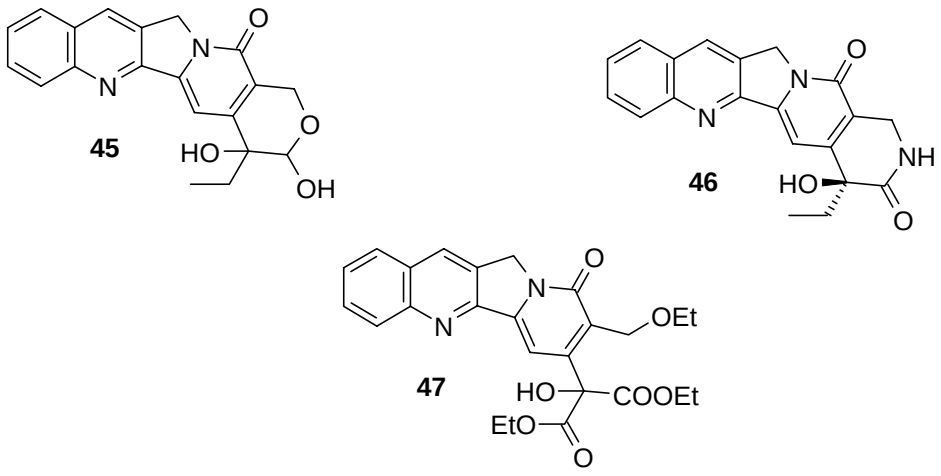


Figure 11

Although earlier SARs of the camptothecin suggested the importance of the lactone E-ring for activity, Lavergne *et al* in 1997 [31] came up with new analogs with an expanded β-hydroxy lactone ring called homocamptothecins. Homocamptothecin **48** contains a methylene spacer between the tertiary alcohol and the lactone carbonyl. In sharp contrast to the lactone ring of camptothecin, which opens rapidly and reversibly, lactone ring of homocamptothecin **48** opens very slowly and irreversibly. Therefore they exhibit high plasma stability in the biological system. Most importantly they are much more cytotoxic than camptothecin.

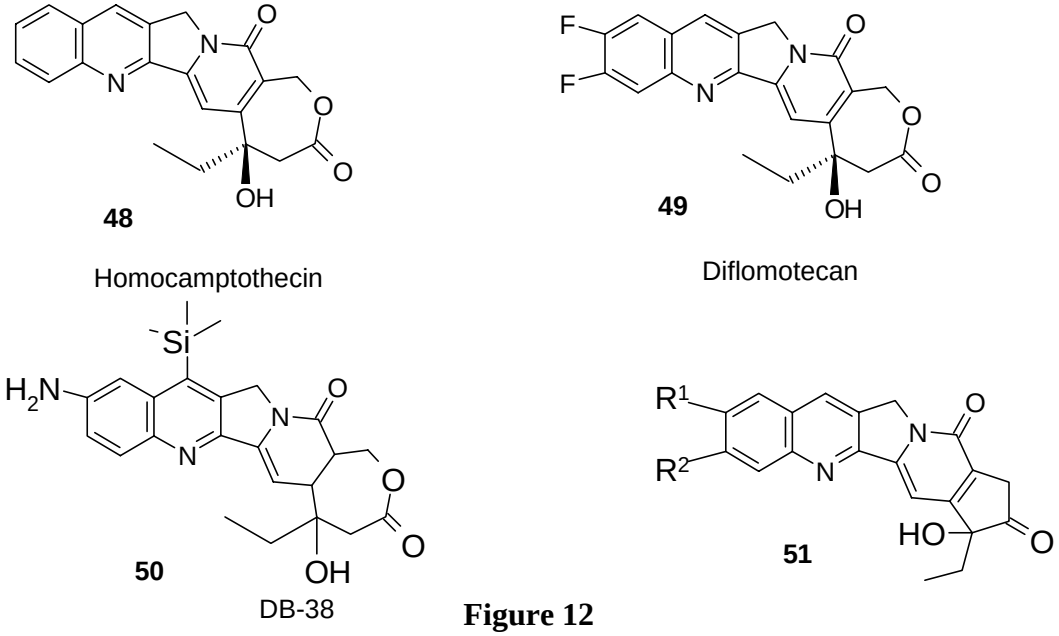
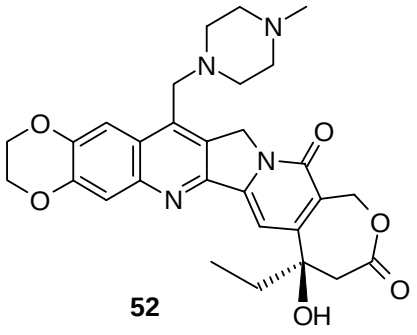


Figure 12

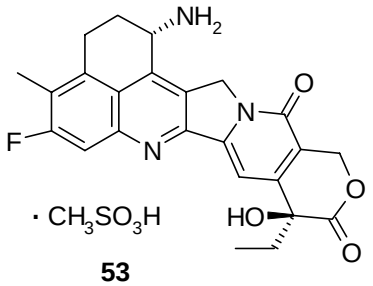
Novel analogues of homocamptothecin such as fluorinated homocamptothecin **49** and silylated homocamptothecin **50** are much more potent than parent homocamptothecin.[32] Apart from lactone and lactam E-ring, series of cyclopentyl E-ring analogues **51** have been synthesized and evaluated (figure 12).[33]

In order to improve the antitumor efficacy of camptothecins, several approaches have been undertaken. This includes the development of prodrugs, new formulations, synthesis of lipophilic and water soluble camptothecins. Particularly great deal of attention is being paid to water-soluble analogues to facilitate intravenous drug administration. Research in this direction has culminated in achieving a major milestone by successful commercial launching of two water soluble analogs namely irinotecan (prodrug) and topotecan as approved drug for the treatment of lung, cervical and metastatic ovarian cancer and several other analogues (e.g. lurtotecan **52**, exatecan mesylate **53**) in various stages of clinical trials.[2]



52

Lurtotecan



53

Exatecan Mesylate

Figure 13

Very recently in an effort to improve the water solubility of camptothecin, 20-O-phosphate and phosphonate analogues have been prepared. Among the derivatives phosphate monoester compound **54** (R-OH, figure 14) was the most toxic, although its potency was much lower than that of camptothecin itself.[34] The development of prodrugs especially conjugates and polymer bound camptothecins (e.g. DE-310 **55**) are drawing a great deal of attention. They improve the solubility and stability of lactone moiety. The therapeutic efficacy of prodrugs might be because of reduced systemic toxicity, longer retention time within the body and altered bio-distribution.

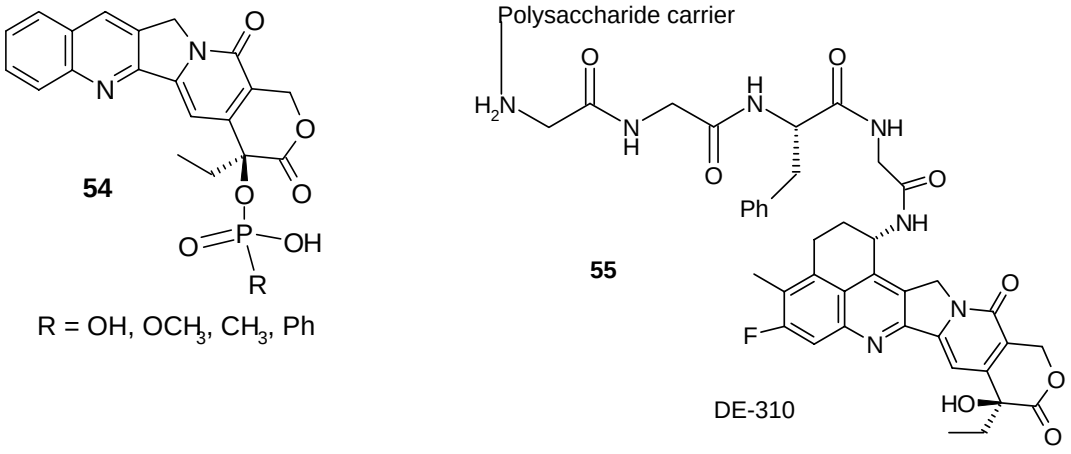


Figure 14

These approaches have proven to be promising in preclinical investigation and a plethora of camptothecin-prodrugs is under clinical scrutiny.[2]

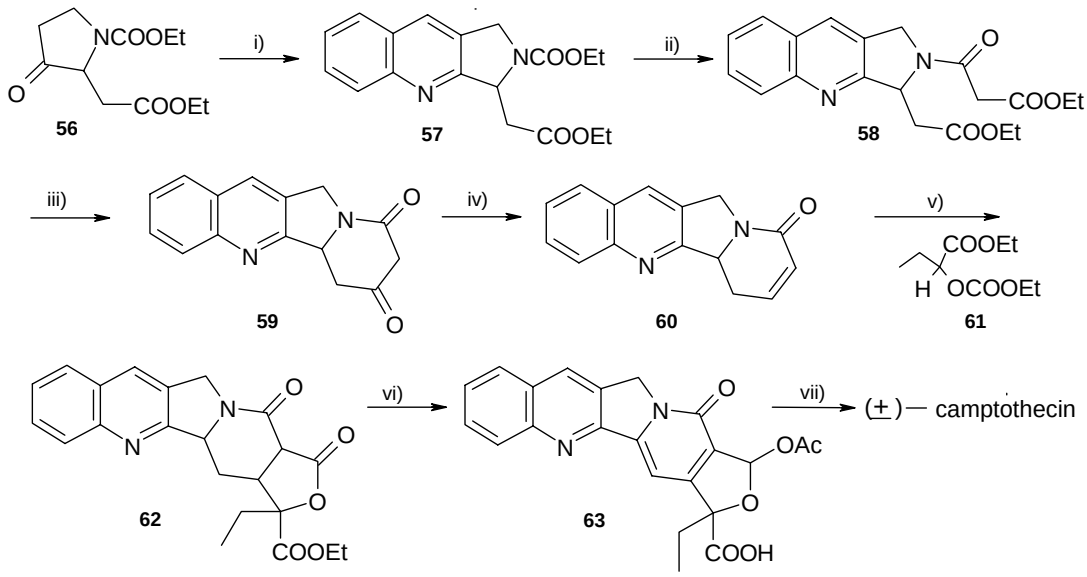
1.1.7 Literature Background:

The elucidation of the biomolecular target of the camptothecin renewed interest in camptothecin and stimulated much research on its pharmacology, medicinal chemistry and total synthesis. Camptothecin is an article of commerce, but an expensive one. The potential instability of the supplies of native camptothecin, difficulties encountered in the preparation of certain derivatives with improved pharmacological properties directly from the natural product and its prohibitively exorbitant cost are the reasons behind to pursue research towards the development of practically simple and economically viable routes for the preparation of camptothecin and its analogues by synthetic organic chemists. The first synthesis of camptothecin dates back to 1971. Though it is a deceptively simple target to synthesize, it poses a lot of difficult challenges. This is evident from the volume of literature, spanning three decades on the total synthesis of camptothecin and its analogues. The classical approach rested on a Friedlander reaction as an avenue to the quinoline (AB- ring system) unit through the condensation of 2-aminobenzaldehyde and suitable CDE synthon. The synthesis originating from 1990 involved highly efficient modern synthetic techniques or involved development of new synthetic methodology especially suitable for the production of large quantities of material. The section described below is just a tip of the iceberg of the challenging approaches involved in the total synthesis of camptothecin and related alkaloids.

Stork's approach: (*J. Am. Chem. Soc*. **1971**, *93*, 4074.)

Stork and co-workers reported the first total synthesis of (±)-camptothecin in a divergent fashion.[36] The salient features of the synthesis involved: 1) Friedlander condensation for the AB-ring construction, 2) intramolecular Dieckmann condensation for the D-ring, 3) intermolecular Michael addition approach towards E-ring skeleton. The synthesis was achieved in 15 steps in an overall yield of 1-2%. The main highlight of the synthesis is the conversion of **60** to **61,** placing five carbon atoms along with the tertiary hydroxyl group present in the camptothecin. Thus the base catalyzed Friedlander condensation of pyrrolidine **56** with 2-amino benzaldehyde gave the tricyclic quinoline-ester **57**. The amino-ester resulting from the hydrolysis of **57** followed by esterification was condensed with carbethoxy acetyl chloride to give the diester amide **58**. The tetracyclic β-keto ester obtained by the intramolecular Dieckmann condensation of **58** was subjected to decarboxylation, reduction and elimination gave the desired dihydropyridone **60**. The latter reacted efficiently at low temperature to give the crucial pentacyclic lactone **62**. Finally hydrolysis of the ethyl ester of **61** followed by reduction and protection gave the lactol, which upon oxidation with DDQ gave pyridone **63**. Subsequent three-step sequence starting from **63**, involving hydrolysis, reduction and lactonization gave the (±)-camptothecin.

Scheme 8

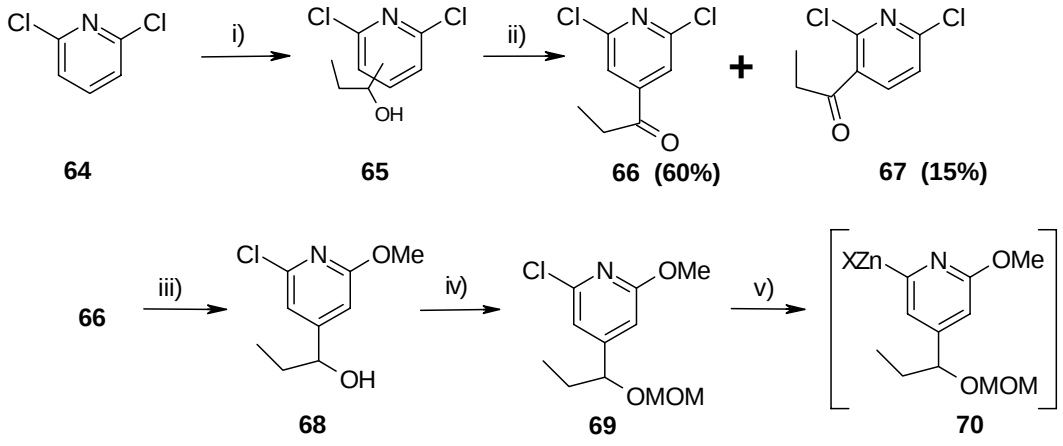


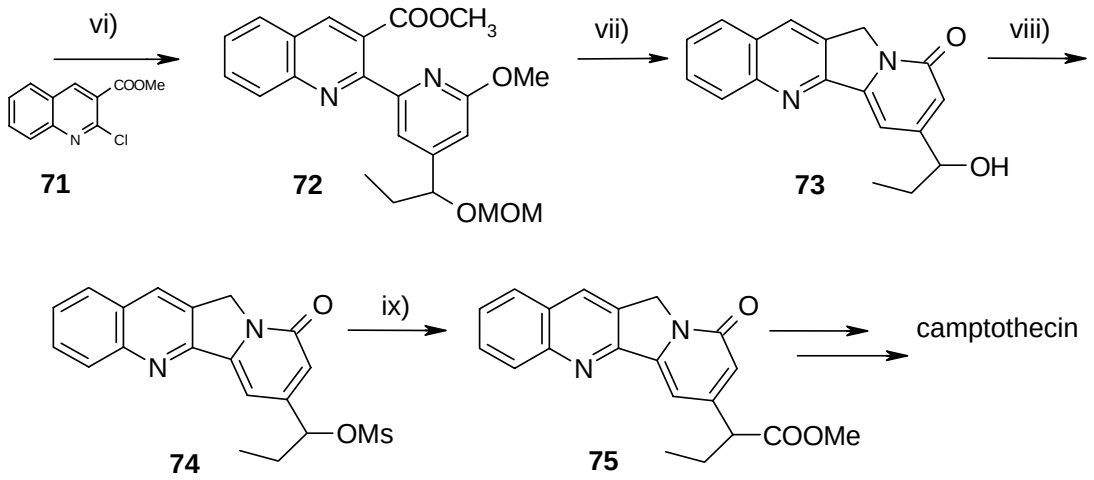
Reagents and conditions: *i) o-amino benzaldehyde, EtOH, H^+, ii) a) 50% HI, EtOH, HCl, b) $ClCOCH_2COOEt$, iii) a) NaH, EtOH/$PhCH_3$, b) 10% acetic acid, iv) $NaBH_4$, b) Ac_2O, NaOAc, v)* ***61****, LDA, -78 ºC, vi) a) $NaBH_4$, rt, 20 h, b) Ac_2O, pyridine, c) DDQ, 1,4-dioxane, vii) a) 0.1N NaOH, b) $NaBH_4$, c) dil HCl*

Murata's Approach: (*Synlett* **1997**, 298)

The formal total synthesis of camptothecin was achieved by Murata[37] (scheme 9) utilizing the powerful metallation reaction for the functionalisation of pyridine derivatives, Pd mediated Negishi coupling with chloroquinoline **71** and Pd-catalyzed carbonylation of methylsulphonate derivative **74**. Lithiation of **64** followed by quenching with propanal afforded alcohol **65** as a mixture of regioisomers. After PCC oxidation to ketones **66** and **67**, the regioisomers were separated without any problems by normal column chromatography. The ketone **66** was transformed to MOM ether **69** involving three steps. Initially the chloro functionality in **66** was replaced by methoxy group followed by subsequent reduction of the ketone functionality and protection of the resulting alcohol as its MOM ether. Compound **69** upon lithiation with Li-napthalinide was subjected to transmetallation to the zinc derivative **70** and subsequent Pd-catalyzed Negishi coupling with chloroquinoline **71** yielded intermediate **72** in 81% overall yield. Pd-mediated carbonylation of the mesyl derivative **74** yielded the methyl ester **75** whose conversion to camptothecin is known in the literature. The regioisomers formed in the first step and their seperation through oxidation followed by column chromatography (addition of two steps) reduces the synthetic utility.

Scheme 9



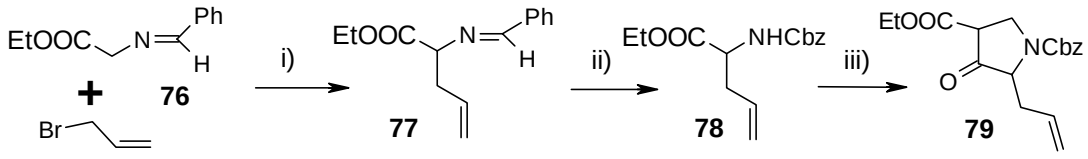


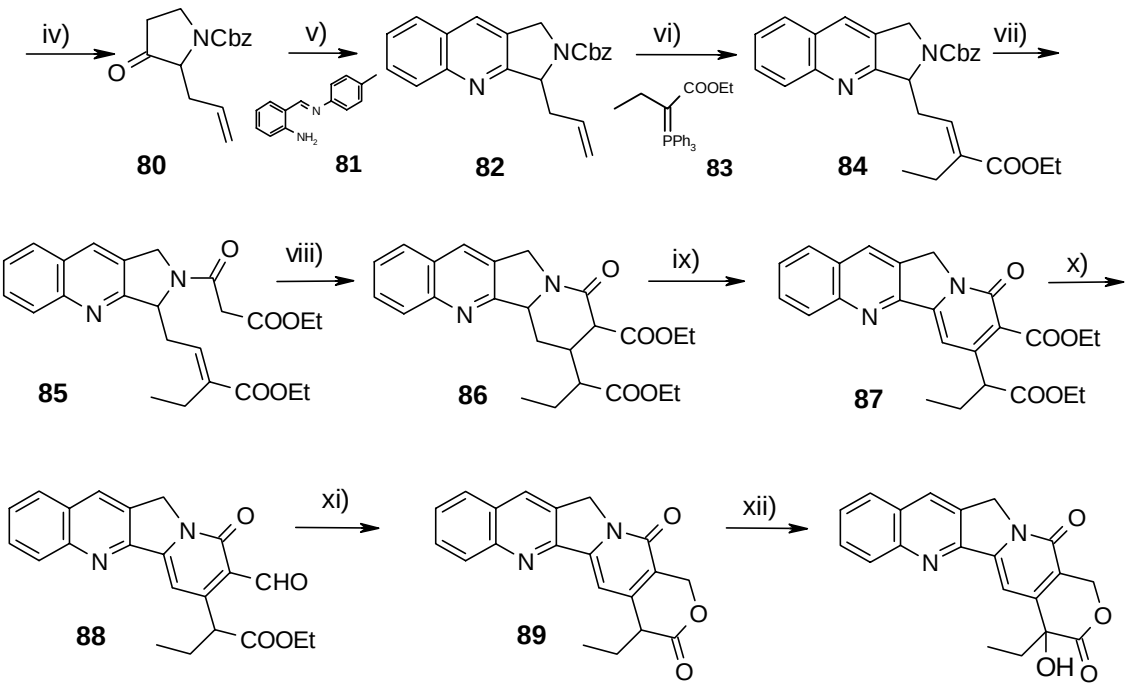
Reagents and conditions **:** *i) t-BuLi, THF, -85 ºC, EtCHO, -85 ºC to 25 ºC , 69%, ii) PCC, DCM, 25 ºC, iii) a) NaOMe, MeOH, reflux, b) $NaBH_4$, MeOH, 25 ºC, iv) NaH, MOMCl, THF, 25 ºC, v) lithium naphthalinide, THF, -90 ºC, $ZnCl_2$, -78 ºC to 25 ºC, vi)* ***71****, $Pd(PPh_3)_4$ -5 mol%, THF, reflux, vii) a) $LiALH_4$, ether, 0 ºC, b) CBr_4, PPh_3, DCM, 25 ºC, c) aq. HCl, MeOH, reflux, viii) MeSCl, TEA, DCM, 0 ºC to 25 ºC, ix) CO (10 atm), $Pd(PPh_3)_2Cl_2$ (5 mol%), TEA, MeOH, 60 ºC.*

Chavan's I Approach: (*Tetrahedron Lett*. **1998**, *39*, 6745.)

Chavan's[38] synthesis of (±)-camptothecin involved a divergent approach. AB ring was achieved by modified Friedlander condensation of pyrrolidinone **80** with Schiff base **81**. A new pyridone formation based on intramolecular Michael addition reaction was utilized as a key step. Another highlight of the synthesis was the regio-selective DIBAL-H reduction of aromatic ester in the presence of aliphatic ester in compound **87**. The keto ester **79** was prepared starting form glycine Schiff base **76**. Compound **76** was alkylated with, allylbromide under PTC conditions. Hydrolysis and protection with CbzCl yielded the urethane **78** in very high yields. A tandem Michael-Dieckmann condensation followed by decarboxylation gave the pyrrolidinone **80**.

Scheme 10





Reagents and conditions: *i) allyl bromide, NaOH, $TBAHSO_4$, DCM, RT, ½ h, 97%, ii) a) HCl, RT, ½ h, 94%, b) CbzCl, K_2CO_3, DCM, RT, 3 h, 96%, iii) NaH, C_6H_6, ethyl acrylate, reflux, 3 h, 65%, iv) a) 10% HCl, reflux, 4 h, v)* ***81****, PTSA, toluene, reflux, 6 h, 72%, vi) a) OsO_4, $NaIO_4$, dioxane, H_2O, 4 h b)* ***83****, DCM, rt, 5 h, 83%, vii) a) TMSCl/NaI, CH_3CN, 1 h, b) carbethoxy acetyl chloride, K_2CO_3, DCM, 0 ºC to rt, 3 h, 66%, viii) NaH, THF, rt, 0.5 h, 92%, ix) DDQ, dioxane, reflux, 1 h, 78%, x) DIBAL-H, THF, -60 ºC, 83%, xi) $NaBH_4$, THF, H_2O, 0 ºC, 1 h, 55%, xii) $CuCl_2$, dimethyl amine, O_2, 20 h*

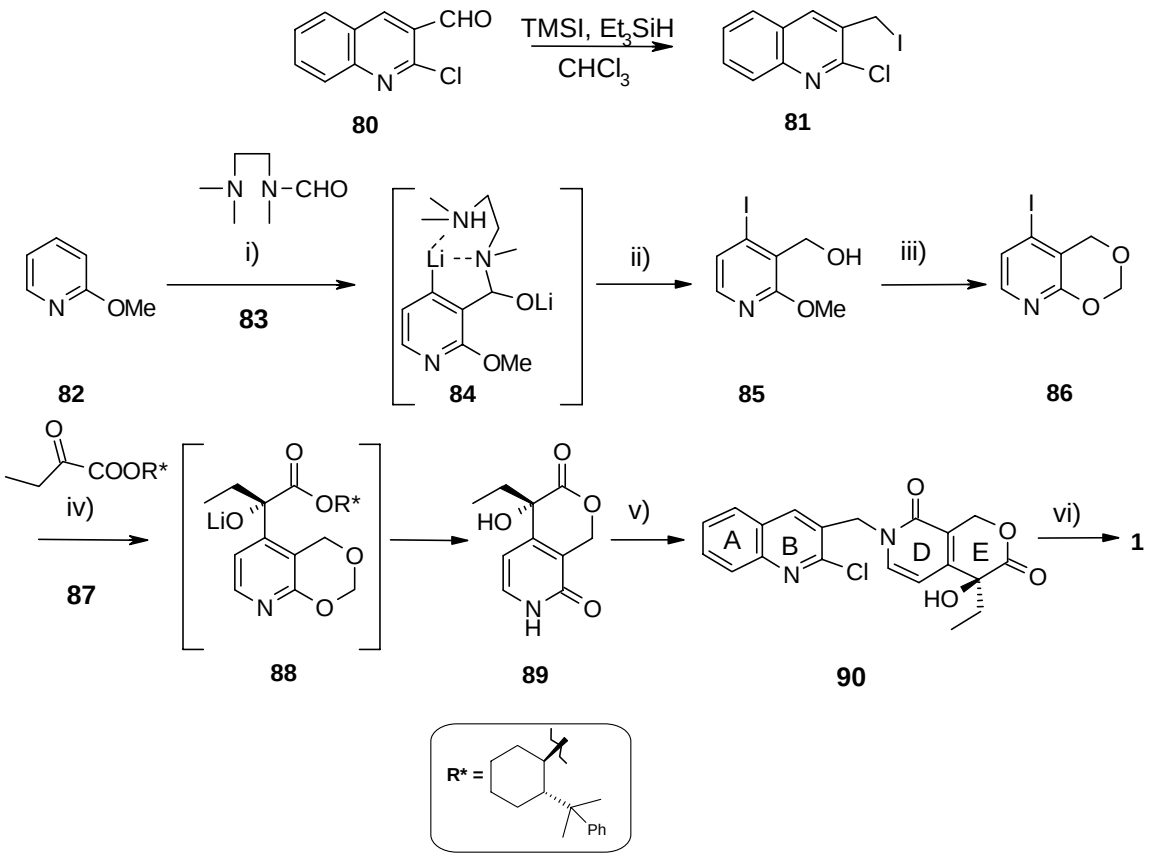
The latter was subjected to modified Friedlander condensation with Schiff base **81** to furnish the tricyclic intermediate **82**. Oxidative cleavage of the double bond in **82** resulted in aldehyde that was subsequently subjected to Wittig olefination with phosphonium salt **83** to provide the α, β-unsaturated ester **84**. Cbz group in **84** was removed employing Olah's protocol. The liberated free amine was condensed with carbethoxy acetyl chloride to obtain the key amide **85**. The intramolecular Michael addition on amide was effected with NaH. The tetrahydropyridone **86** with suitable appendages for E-ring construction was further oxidized with DDQ to complete the D-ring of camptothecin. The selective reduction of the benzoyl ester in **87** using DIBAL-H gave the aldehyde **88**, which was further reduced and lactonized to give 20-

deoxycamptothecin **89**. The oxidation of **89** was effected employing procedure of Danishefsky's protocol, utilizing oxygen as oxidant to give (±) **1**.

Comins Approach: (*Org. Lett*. **2001**, *3*, 4255.)

The Comins group has taken several initiatives in developing a short and efficient syntheses of camptothecin that are amenable to scale up for drug preparation. Several related total syntheses of camptothecin were accomplished in a convergent manner through joining of the AB-ring and the DE-ring through construction of the C-ring. Recently, Comins group[39a] reported an elegant and the shortest asymmetric synthesis of camptothecin through a six-step sequence. Some of the reactions reported in his previous syntheses were conducted in one pot. The same approach was also used to synthesize mappicine **11** and mappicine ketone **12a**.[39b] To achieve this goal AB-ring precursor was prepared in single step and DE-ring fragment was synthesized in three steps. AB-ring synthon **81** was prepared from commercially available 2-chloro-3-formyl quinoline **80** by treatment of TMSI/triethylsilane.

Scheme 11



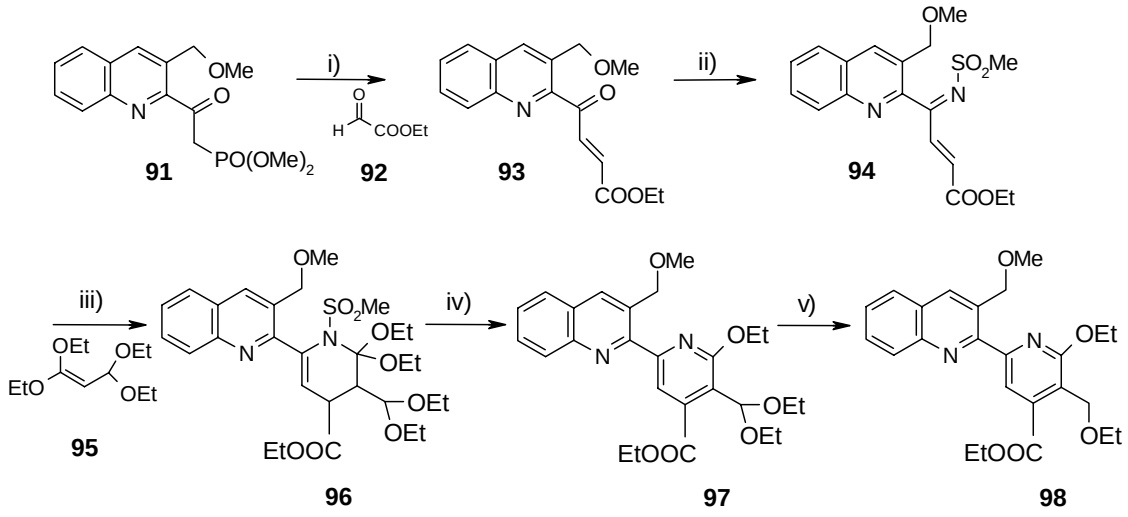
Reagents and conditions**:** *i) MesLi,* ***83****, BuLi, ii)* I_2*,* $NaBH_4/CeCl_3$*,* H_2O *(steps i) and ii) are performed in one pot), iii) TMSCl/NaI, paraformaldehyde, 87%, iv)* ***87****, BuLi, HCl/i-PrOH, v)* ***81****, t-BuOK, DME, reflux, vi)* $Pd(PPh_3)_2(OAc)_2$*, KOAc,* CH_3CN*.*

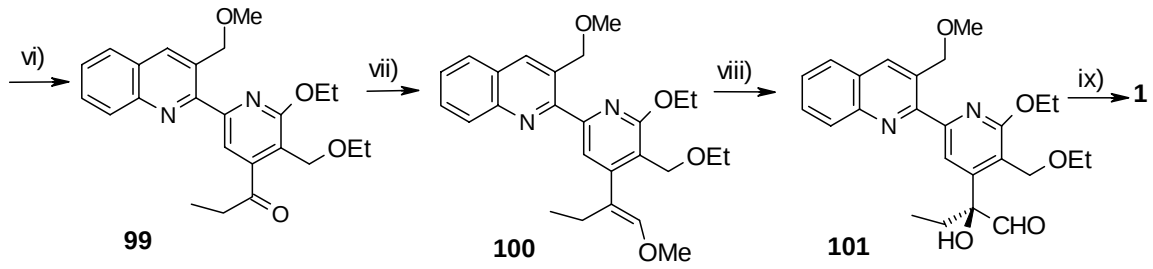
Following protocols were utilized for the synthesis of DE-ring fragment. Thus commercially available 2-methoxy pyridine **82** was lithiated at C-3 with mesityllithium and treated with formamide **83** to give the α-amino alkoxide *in situ*. Addition of n-BuLi effected α-amino alkoxide directed lithiation to give the dianion **84** followed by addition of iodine and work up with aq $NaBH_4/CeCl_3$ provided a 46% yield of alcohol 8**5** *via* a one pot process. Deprotection of the methyl ether in **85** and dual protection of the two hydroxy groups were accomplished in one pot to give directly the 1, 3-dioxane **86**. Lithiation of **86**, addition to keto ester **87**, subsequent deprotection and simultaneous lactonization were accomplished in one pot to give the DE-ring intermediate **89** in 60% yield and 93% ee. The two fragments **81** and **89**, were joined on treatment with *t*-BuOK to provide **90** in 81% yield with greater than 99% ee, which was then subjected to Heck conditions to give camptothecin **1** in 64% yield.

Boger's Approach: (*Tetrahedron* **2002**, *58*, 6343.)

The approach is based on the implementation of a room temperature inverse electron demand Diels-Alder reaction of the *N*-sulfonylimine **94** with the electron rich dienophile **95** for the introduction of the D-ring pyridone.[40a]

Scheme 12





Reagents and conditions: *i) $CH_3PO(OMe)_2$, BuLi, 80%, ii) $TiCl_4$, TEA, NH_2SO_2Me, DCM, -42 ºC-25 ºC, 60 min, iii)* ***95****, C_6H_6, 25 ºC, 4 h, 68%, iv) NaOEt, THF, 0 ºC, 75 min, v) ZnI_2, Et_3SiH, 92%, DCM, vi) EtMgBr, TEA, ether, -5 ºC, 5 h, 65%, vii) $MeOCH_2PPh_3Cl$, KHMDS, THF, 0 ºC to 25 ºC, 10 h, 74%, viii) $(DHQ)_2$-Pyr$(OMe)_3$, OsO_4, K_3FeCN_6, 84%, 86% ee, ix) a) $NaClO_2$, Na_2HPO_4, resorcinol, DMSO, 0 ºC, 1 h, 93%, b) HBr (g), 2,2,2-trifluoroethanol, 25 ºC, 14 h, c) K_2CO_3, 1 h, 72%*

The asymmetric synthesis of camptothecin based on this methodology allows for suitable modification of the E-ring permitting access to new analogues. The same strategy was also adopted towards the synthesis of mappicine ketone.[40b] Thus, the Phosphonate **91** prepared over 5 steps from 2-formyl aniline were subjected to Wardsworth-Horner-Emmons reaction condition to give the enone **93**, which was then condensed with methanesulfonamide in the presence of Lewis acid to give the aza-butadiene **94**. Diels-Alder reaction of **94** with olefin **95** proceeded at room temperature and gave the desired cycloadduct **96**, which was further treated with NaOEt to give pyridine **97** in 70% yield. The diethyl acetal in **97** was reduced under ZnI_2/Et_3SiH conditions to give an ethyl ether **98** in high yield. Reaction of **98** with EtMgBr gave the ethyl ketone **99**. Ketone **99** was subjected to Wittig reaction to give the vinyl methyl ether **100** in 74% yield. Sharpless asymmetric dihydroxylation on the vinyl ether **100** provided the α-hroxy aldehyde **101** in 84% yield and 86% ee. The aldehyde obtained was oxidized to acid, and subsequent treatment with HBr followed by K_2CO_3 resulted in C, E rings closure to complete the synthesis of (*S*)-camptothecin.

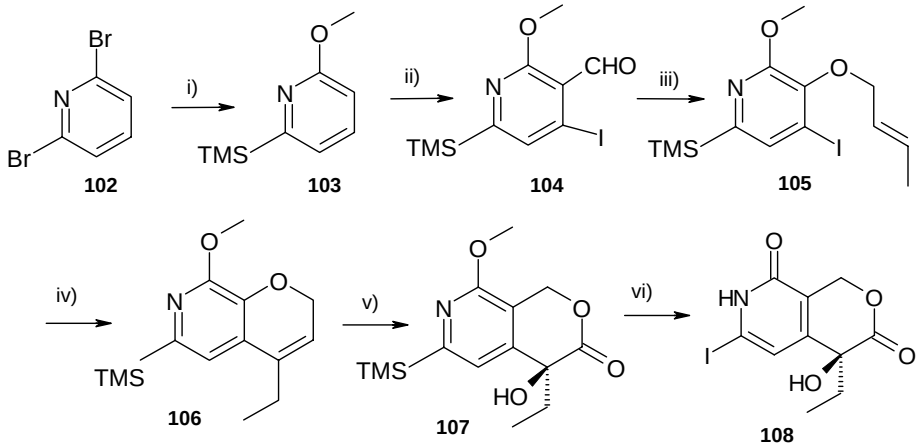
Curran's I Approach: (*Chem. Eur. J*. **1998**, *4*, 67.)

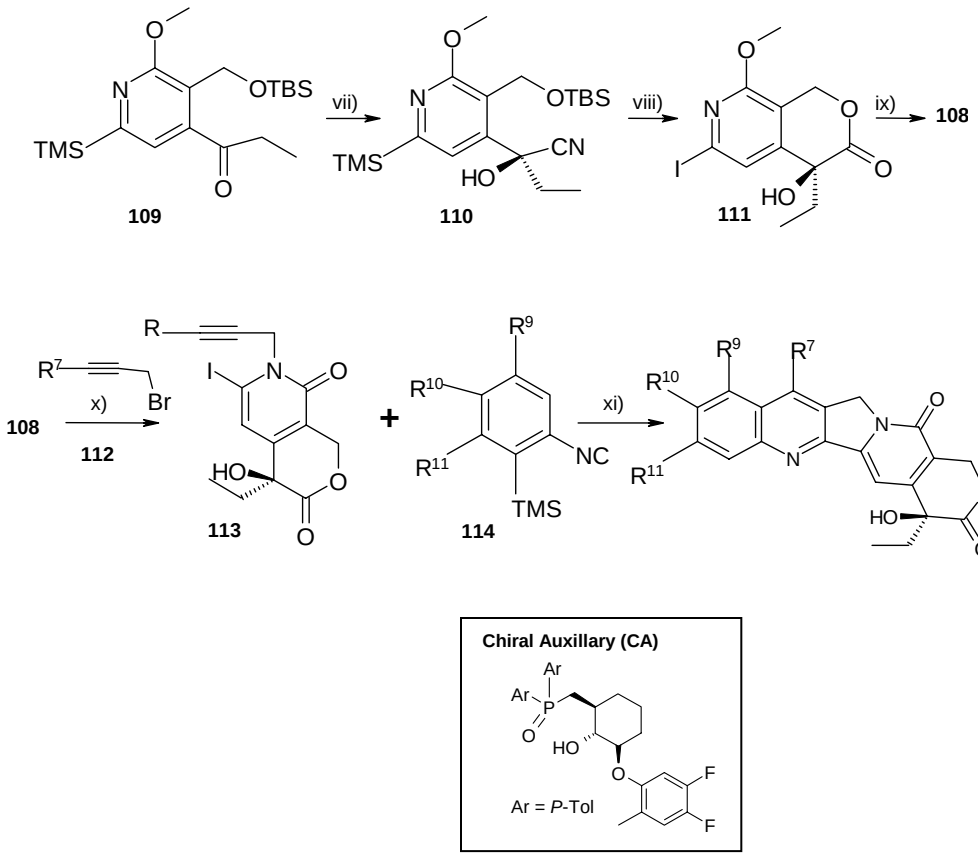
The Curran synthesis rests on a unique radical cascade process that constructs rings B and C of camptothecin through the merger of pyridone **113** with phenyl isocyanide **114**.[41a] The overall synthesis is short and reasonably efficient (10 steps, 3%

overall yield). The radical cyclisation step involves milder reaction condition. The absolute configuration of C-20 'OH' was established by Sharpless asymmetric dihydroxylation of an enol ether **106**. Various substituents at position C-7 in the B-ring can be introduced at the *N*-propargylation step. Substituents at positions C-9 to C-12 in A-ring can be introduced by using substituted phenyl isonitriles. This strategy has been exploited to synthesize a wide variety of camptothecin analogues,[41b,41c,41d] mappicine ketone and its analogues in a combinatorial fashion.[41e] The versatile nature of this strategy is very evident also from its application towards the synthesis of homocamptothecin and its analogues.

Treatment of 2,6-dibromopyridine **102** with MeONa and BuLi/TMSCl yielded silylated pyridine **103**. Compound **103** upon sequential treatment with *t*-BuLi, formamide **83**, BuLi and I_2 gave pyridine **104** in 49% yield. Reductive etherification followed by Heck reaction gave the vinyl ether **106**. Sharpless asymmetric dihydroxylation on vinyl ether **106** gave a α-hydroxy lactol, which was then oxidized under $CaCO_3/I_2$ conditions to give lactone **107** in 85% yield (94% ee). Upon treatment with ICl compound **107** was desilylated to give the iodo-lactone, which was further subjected to demethylation to provide the iodopyridine **108**. As an alternative to the asymmetric dihydroxylation towards the preparation of **108**, Shibashaki, Curran and co-workers very recently developed catalytic asymmetric cyanosilylation reaction.[41f,41g] Subsequent propargylation on **108** and the radical annulation with phenyl isonitrile **114** (R^7=R^9=R^{10}=R^{11} = H) gave (+)-camptothecin in 63% yield.

Scheme 13





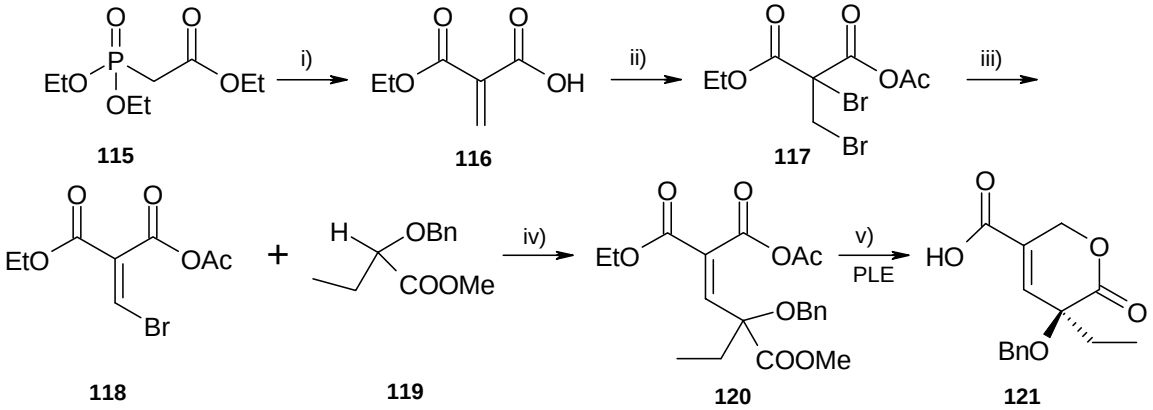
Reagents and conditions: *i) a) NaOMe, b) BuLi/TMSiCl, ii) a) t-BuLi,* ***83****, b) BuLi,* I_2*, 49%, iii) crotyl alcohol,* Et_3SiH*, TFA, 63%, iv) palladium acetate,* K_2CO_3*,* Bu_4NBr*, 69%, v) a)* OsO_4*,* $(DHQD)_2PYR$*, b)* I_2*,* $CaCO_3$*, 85%, 94% ee, vi) a) ICl, 47%, b) TMSI or HI, 72%, vii) TMSCN,* $Sm(OiPr)_3$*,* ***CA,*** *91%, 90% ee, viii) ICl, ix) HCl, x) NaH, LiBr,* ***112*** *(R = H), 88%, xi)* $Me_3SnSnMe_3$*,* ***114****,* $h\nu$*, 63%.*

Greene's Approach (E-ring Synthesis): (*J. Chem. Soc., Perkin Trans.1* **2001**, 2903)[42]

The carboxylic acid **121**, protected E-ring fragment of (*S*)-camptothecin has been prepared in 98% ee via enolate conjugate addition to a β-bromo methacrylate derivative **118**, followed by enzymatic resolution with PLE enzyme. The coupling of this E-ring synthon **121** to a suitable AB-ring moiety through the formation of CD-ring is under investigation. Treatment of triethylphosphonoacetate **115** and formaldehyde in the presence of K_2CO_3 gave the methacrylate **116**. Compound **116** was converted to its acetate and then treated with Br_2 to get the desired dibromide **117** in 53% overall yield starting from **115**. Upon treating **117** with TBAF in HMPA pure (*E*)-β-bromo acrylate **118** was obtained in 68% yield. Compound **118** when treated with lithium salt of methyl

2-benzyloxybutyrate (**119**) underwent desired conjugate addition-elimination reaction to give the desired triester **120** (*E*-derivative). Ester **120** was subjected to enzymatic hydrolysis with PLE followed by saponification and recrystallisation to provide the required lactone acid **121** in 98% ee.

Scheme 14

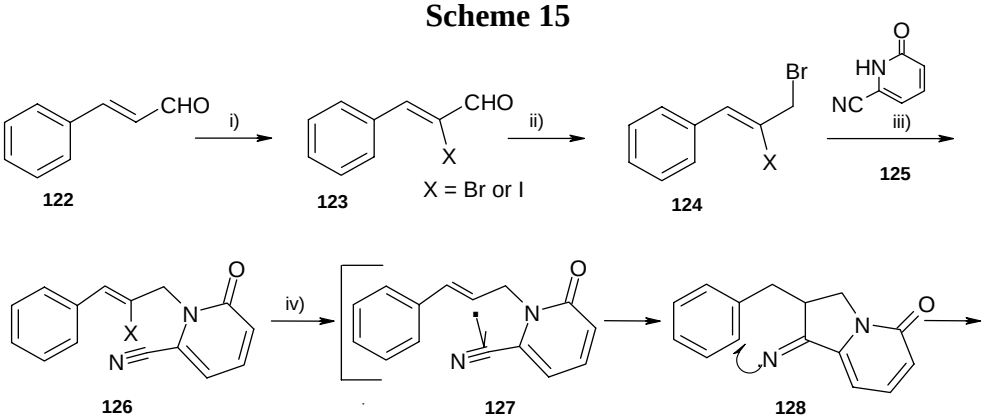


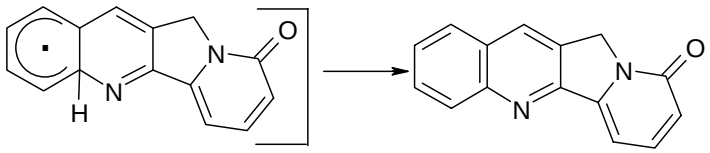
Reagents and conditions*: i) CH_2O, K_2CO_3, H_2O, 20 ºC, 2 h, ii) a) Ac_2O, H_2SO_4 (cat), Et_2O, 20 ºC, 3 h, b) Br_2, CH_2Cl_2, reflux, 53% from **115**, iii) TBAF, HMPA, 20 ºC, 24 h, 55–68%, iv) LDA, **119**, THF, -78 ºC, 15 min, then **118**, -78 ºC, 12 h, 69%; v) a) PLE, pH 7 phosphate buffer, MeCN, 25 ºC, 48 h, b), LiOH, THF–H_2O, 20 ºC, 12 h, recrystallisation, 98% ee.*

Bowman's Approach: (*J. Chem. Soc., Perkin Trans.1* **2002**, 58.)

The Bowman group developed a new radical protocol for the synthesis of the tetracyclic heteroarenes, which includes ABCD rings of camptothecin and mappicine, using 4+2 radical annulation *via* cyclisation of intermediate iminyl radicals, generated by vinyl radical cyclisation onto nitriles, onto arenes.[43a, 43b]

Scheme 15





129 **130**

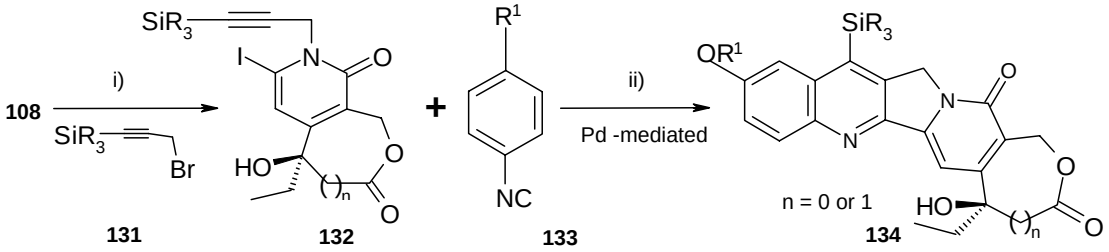
Reagents and conditions: *i) Br_2, Et_3N, CH_2Cl_2, 90% or ICl, Et_3N, CH_2Cl_2, 80%, ii) a) $NaBH_4$, $CeCl_3$, MeOH, 100%, b) CBr_4, Ph_3P, MeCN, 100%, iii)* ***125****, NaH, LiCl, DME, DMF, 71%, iv) $(Me_3Sn)_2$, t-BuPh, 150 ºC, 73%*

In addition to the model compound of camptothecin, a number of policyclic quinolines were prepared by this method. As shown in scheme 15, cinnamaldehyde was treated with Br_2 or ICl and triethylamine to produce aldehyde **123**. Compound **123** was then reduced using Luche's protocol. The resulting allyl alcohol was converted to corresponding allylic bromide **124** when treated with CBr_4/PPh_3. Under NaH, LiCl conditions, cyano-pyridone **125** was alkylated with **124** to give **126**, the precursor for radical cyclization. Heating **126** with hexamethylditin, generated vinyl radical intermediate **127**, which underwent 5-*exo* radical cyclisation to the cyano group to give iminyl radical **128**. Intramlecular radical addition of **128** produced the delocalized radical **129**, which was then oxidized to give the quinoline **130**.

Curran's II Approach: (*Org*. *Lett*. **2002**, *4*, 3215.)[44]

The simplicity of the cascade radical annulation approach described in the scheme 13 are not really ideal for discovery chemistry as it involves the usage of tin reagents which are inherently toxic. Apart from this, tin by-products pose significant isolation problems during the separation process, quite detrimental during drug discovery stage. To circumvent the application of tin reagents in constructing the B, C rings of camptothecenoids, a cascade annulation reaction between an electron rich aryl isonitrile and a propargylated iodopyridone promoted by a Pd catalyst was developed (scheme 16). This strategy was applied to prepare several silylated derivatives of camptothecin, homocamptothecin, mappicine and mappicine ketone. The only disadvantage associated with this Pd promoted cascade reaction of electron rich isonitiriles when compared to cascade radical annulation is that the later strategy tolerates high degree of freedom with respect to isonitrile substituents.

Scheme 16

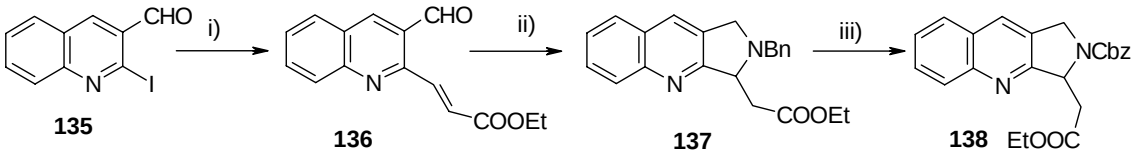


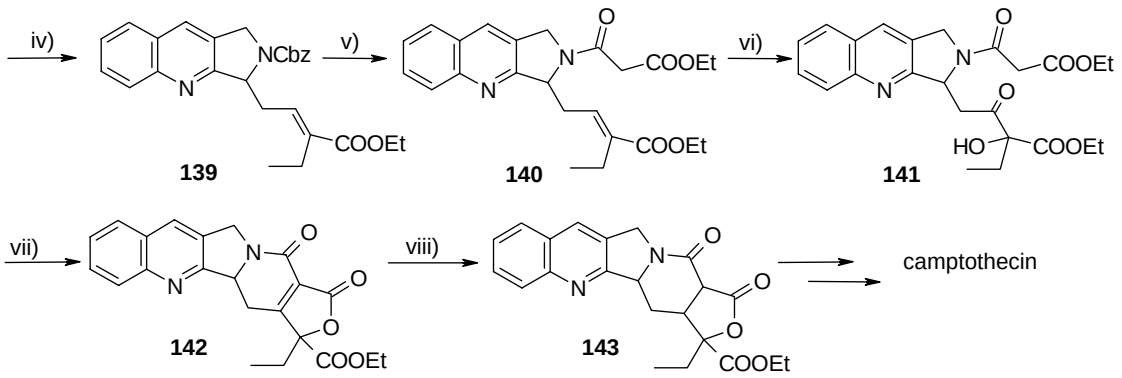
Reagents and conditions: *i)* ***131****, NaH, ii) 20% Pd(OAc)$_2$, Ag$_2$CO$_3$, toluene, 25 ºC, 1d.*

Chavan's II Approach: (*Tetrahedron Lett*. **2004**, *45*, 3113.)[45]

The Earlier synthesis from Chavan and co-workers exploited an intramolecular Michael addition approach towards camptothecin (scheme 10). Central to this formal total synthesis is the implementation of an intramolecular aldol reaction of ketol **142** to construct the pyridone D-ring with suitable functionality for manipulation to the lactone E-ring. The Pd-catalysed Heck olefination of iodoaldehyde **135** with ethyl acrylate gave the olefin-tethered aldehyde **136** in very good yield. Aldehyde **136** when subjected to reductive amination gave the tricyclic amine **137** following intramolecular Michael addition pathway. Amine was deprotected and converted to its carbamate **138** using CbzCl. Careful reduction of the ester group in **138** with DIBAL-H resulted in the formation of aldehyde. The later underwent smooth Wittig olefination with phosphorane **83** to furnish the unsaturated ester **139**. Deprotection of the carbamate followed by the condensation with carbethoxy acetyl chloride resulted in the formation of the amide **140**. Upon selective oxidation with $KMNO_4$, ketol **142** was obtained from the amide **141**. Ketol **142** was subjected to intramolecular aldol reaction to furnish the desired dihydropyridone **143** and was later reduced to tetrahydropyridone **144**, whose conversion to camptothecin was achieved by Stork and coworkers.

Scheme 17





Reagents and conditions: *i) ethyl acrylate, NaOAc, 5 mol% Pd(PPh$_3$)$_4$, DMF, 74%, ii) a) BnNH$_2$, MeOH, rt, 1 h, b) NaBH$_4$, MeOH, 0 ºC to rt, 2 h, 91%, (iii) (a) Pd/C–H$_2$, EtOH, (b) CbzCl, DCM, K$_2$CO$_3$, 90%, (iv) (a) DIBAL-H, DCM, (b)* ***83****, DCM, 80%; (v) (a) TMSCl, NaI, CH$_3$CN, rt, 1 h, (b) carbethoxy acetyl chloride 68%, (vi) KMnO$_4$, acetone–water, AcOH, 95%, (vii) NaH, THF, 90%, (viii) 10% Pd/C–H$_2$ (100 psi), EtOH, 88%.*

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CHAPTER I

SECTION 2

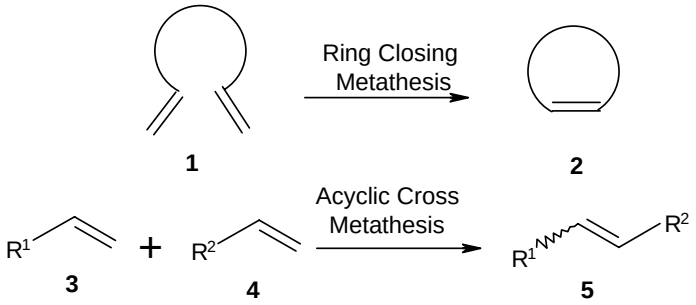
PART 1: Ring Closing Metathesis Approach Towards The Synthesis of Camptothecin.

1.2.1.1 Introduction:

The New York academy of science organized two international meetings devoted exclusively to camptothecin in the year 1996 and 2000. As of 2003 August, of the 2255 cancer clinical trials recorded, 5.3% comprises of camptothecin-derived drugs, including irinotecan and topotecan either as single agents or in combination with other anticancer agents.[1] Stimulated by the excellent biological activity, unique mode of action and challenging structure it has been the compound of choice spanning four decades for both medicinal as well as synthetic chemists. Several total syntheses have been developed over the years to find a direct and practical route amenable to preparation of analogues and scale up. Given the current continued interest, though many syntheses have been achieved, still there is an evident need for the development of a new synthetic route amenable to camptothecin and its analogues. Having understood the significant role played by camptothecin and its analogues as promising chemotherapeutic agents for the treatment of cancer, our group has been involved in developing a practical and efficient synthesis of camptothecin and mappicine ketone. Thus as a part of my research programme it was decided to explore a new and efficient approach for the synthesis of D-ring of camptothecin utilizing intramolecular ring closing metathesis (RCM) reaction.

Olefin metathesis catalyzed reactions are gaining increasing importance due to introduction of new and efficient catalysts that are more efficient, air stable and active and are becoming potentially synthetically useful.[2] Olefin metathesis (scheme 1) is a disproportionation process involving bond formation, bond breakage and reorganization. Olefins by which alkylidene groups are exchanged was first reported by Anderson and Merckling in 1955 which involved the use of Ti (IV) metal for polymerization of norbornene.[3] In the recent years, the area of RCM reactions has been considered as the most recognized field of olefin metathesis. It is the most straightforward and reliable methods for the formation of small, medium and large ring systems when compared to several existing synthetic alternatives.

Scheme 1



The pioneering development by Schrock[4] and Grubbs[2,5] in the area of RCM by introduction of Mo and Ru based catalyst which are air stable and are tolerant to diverse functional group has opened up new vistas in the area of synthetic chemistry, especially the biologically active compounds. This has resulted in a fresh and entirely different way of approaching the synthesis of desired molecules. Following are some of the commonly used catalysts for olefin metathesis and RCM (figure 1).

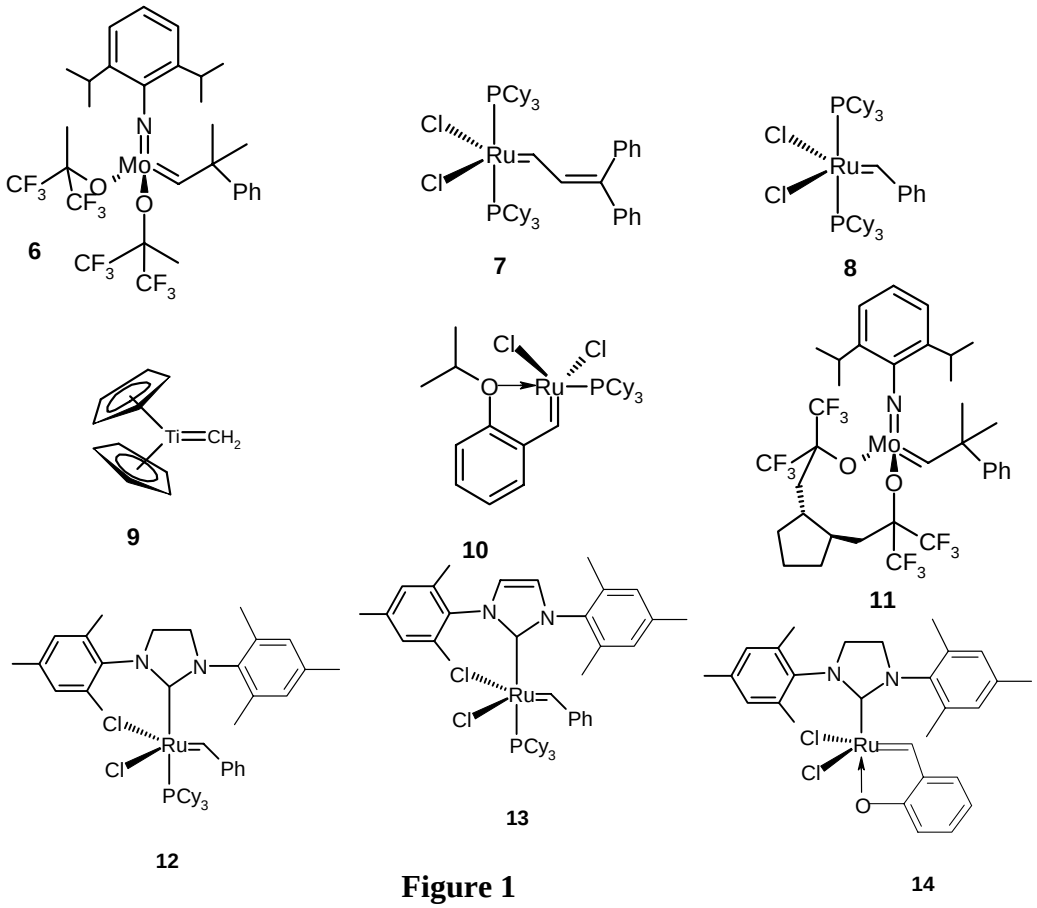
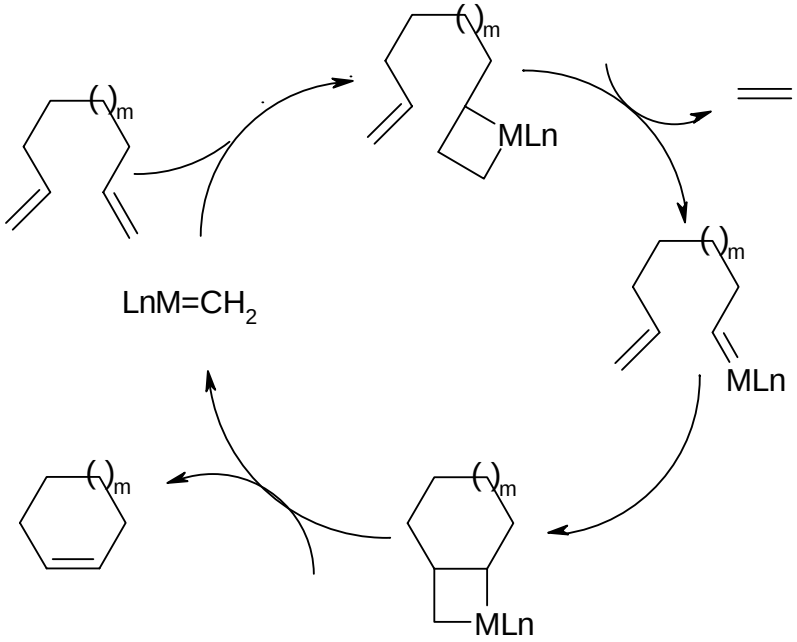


Figure 1

These metathesis reactions are believed to go by the mechanism depicted below.

Scheme 2

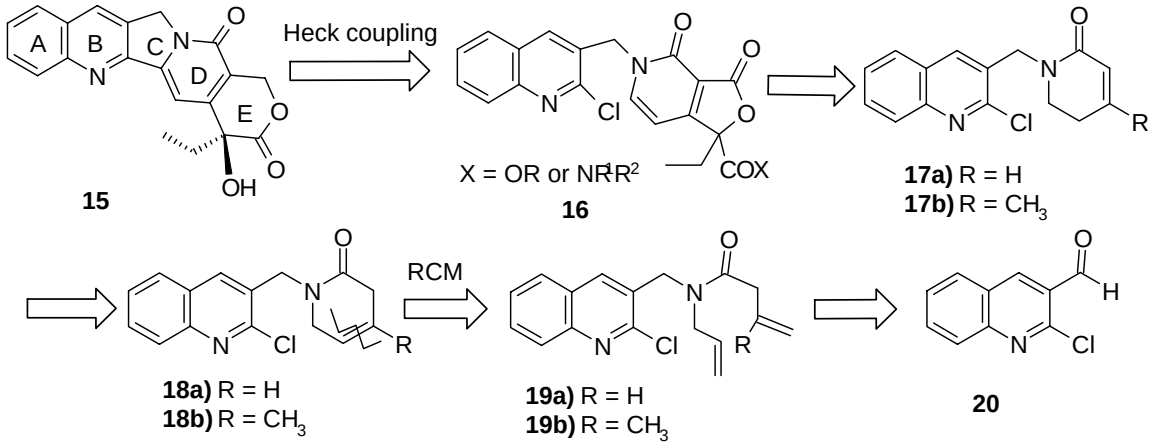


RCM reactions of molecules possessing heteroatoms like nitrogen as linkers between two olefins leads to the formation of useful nitrogen hetrocycles like mono or bicyclic pyrrolidine, pyrrolidinone, piperidine and piperidinone ring systems. By proper positioning of the nitrogen and double bond in the molecule several azasugars and alkaloids have been synthesized.[5,6] Although the RCM methodology works exceedingly well with dienes with non-complexing functional groups, its utility in the synthesis of aza-heterocycles or compounds bearing complexing groups is rather limited and unpredictable due to the propensity of amides and amines or other functional groups like olefin to form stable complex irreversibly. This often results in termination of the metathesis cycle and poor yields. Changing the steric hindrance or catalyst has circumvented this problem. Fürstner has shown that addition of complexing Lewis acids [Ti(*i*-PrO)$_4$] along with the metathesis catalyst can alleviate these problems.[7a] It is pertinent to mention that this behaviour cannot be generalized and each case has to be looked upon separately.[7b]

1.2.1.2 Present Work: *Results and Discussion*

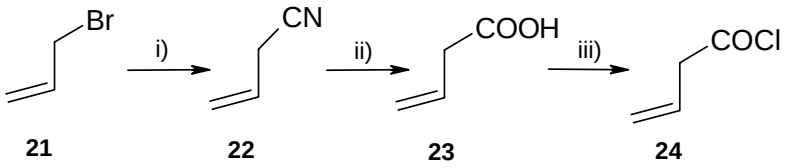
The following scheme 3 delineates our synthetic strategy of camptothecin employing RCM as the key step to construct the pyridone ring.

Scheme 3



In accordance with the synthesis planned in scheme 3, it was decided to carry out the crucial RCM and the subsequent isomerisation of double on a simple substrate as a model study. The acid chloride butene-3-oyl chloride **24** was prepared as per the literature protocol (scheme 4).[8] The first generation Grubbs ruthenium catalyst **8** required for the RCM was prepared following the procedure reported by Grubbs and coworkers.[9]

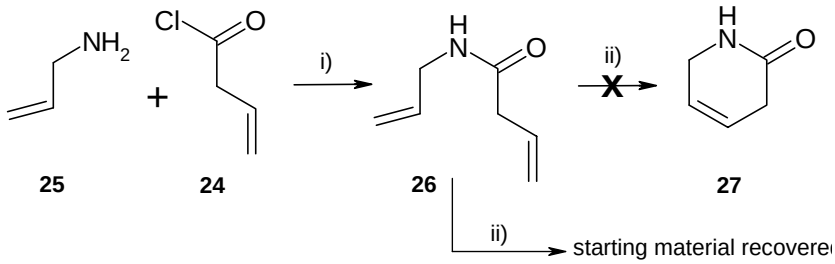
Scheme 4



Reagents and conditions*: i) CuCN, reflux, 1.5 h, 75%, ii) Con. HCl, 90 ºC, 1.5 h, 50%, iii) $SOCl_2$, 60 ºC, 4 h, 87%.*

Thus allyl amine **25** was condensed with acid chloride **24** to give the amide **26**. When amide **26** was subjected to RCM reaction as per the reported protocol, the desired pyridone **27** was not obtained (scheme 5).[10] Instead, starting material was recovered. It was reasoned that N-H group in the amide **26** could form inhibiting chelating complex with ruthenium catalyst.

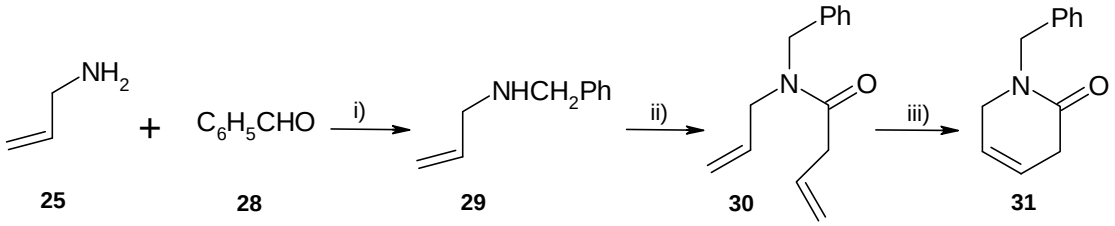
Scheme 5



Reagents and conditions*: i) K_2CO_3, DCM, 0 ºC, 3 h, 65%, ii)* ***8*** *(10 mol%), DCM, reflux, 48 h.*

Therefore it was decided to perform the RCM reaction on the tertiary amide **30** to get the pyridone **31**. Accordingly the amide **30** was prepared by the reductive amination of benzaldehyde (**28**) and allyl amine (**25**), followed by the condensation of the resulting amine **29** with acid chloride **24** in the presence of K_2CO_3. When the amide **30** was subjected to RCM reaction using catalyst **8** and benzene as a solvent, the desired pyridone **31** was obtained in 91% yield at room temperature (scheme 6).[11a]

Scheme 6



Reagents and conditions: *i) a) MeOH, rt, 0.5 h, 99%, b) $NaBH_4$, MeOH, 0.5 h, 95%, ii)* ***24****, K_2CO_3, DCM, 0 ºC-rt, 3 h, 75%, iii)* ***8*** *(5 mol%), benzene, rt, 10 h, 91%.*

Having obtained the desired pyridone the attention was focused on the isomerisation of β, γ-unsaturated double bond in **31** to α, β-unsaturated lactam **32**, a seemingly very simple reaction (scheme 7). It is very evident from the table 1 that surprisingly all our attempts towards this transformation were met with failure.

Scheme 7

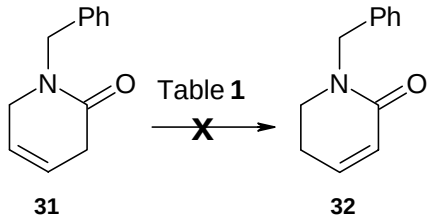
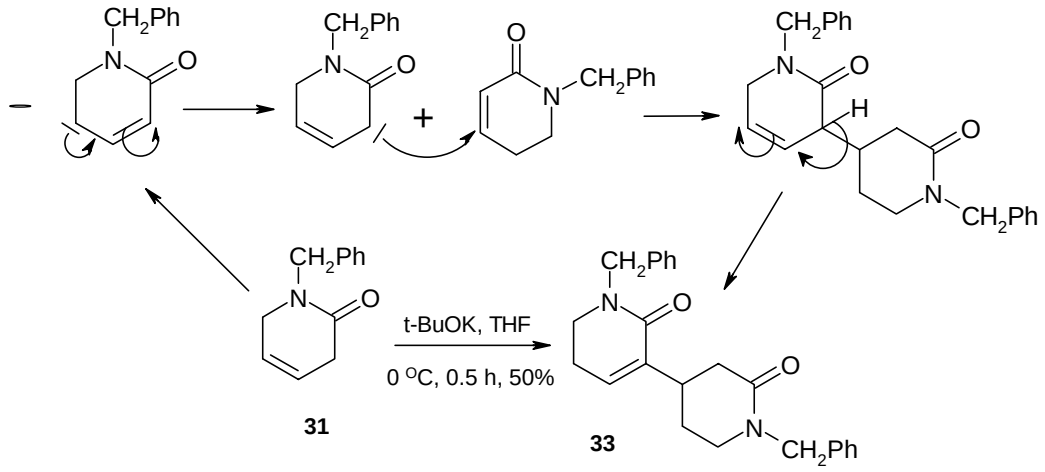


Table 1

S. No	Reagent	Solvent	Tempera-ture	Time	Observation
1	DBU	THF	0 ºC to rt	24 h	Starting material (SM) recovered
2	DBU	toluene	reflux	20 h	SM recovered
3	*t*-BuOK	THF	0 ºC to rt	3 h	Complex reaction mixture
4	cat *t*-BuOK	*t*-BuOH	rt	7 h	SM recovered
5	cat *t*-BuOK	*t*-BuOH	reflux	7 h	dimer **33**
6	*t*-BuOK	THF	0 ºC	0.5 h	dimer **33**

When the isomerisation was carried out either with cat *t*-BuOK using *t*-BuOH as a solvent under reflux condition or with stoichiometric amount of *t*-BuOK using THF at 0 ºC, instead of getting the desired pyridone **32**, dimer **33** was obtained in 50% yield. The formation of **33** can be rationalized as follows (scheme 8).

Scheme 8

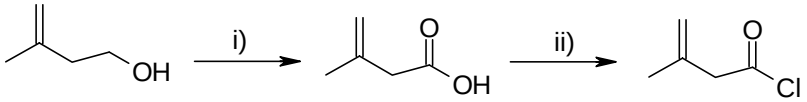


This observation is consistent with the observation made by Verkede and co-workers on the dimerization of the β, γ-unsaturated nitriles.[11b] The structure of **33** was

confirmed by the spectral analysis. Absorption at 1680 and 1630 cm^{-1} in the IR spectrum of **33** indicated the presence of two different types of amide carbonyls. In the ^1H NMR spectrum of **33,** doublets at δ 4.43 and 4.77 (*J*=14.65 Hz) each integrating for one proton and AB quartet at 4.60 (*J*=16.12 Hz) for two protons were assigned to the four benzylic protons. The multiplet at δ 6.20 for one proton was assigned to the olefinic hydrogen. In carbon 13 NMR of **33**, peaks at δ 169.9 and 164.38 was assigned to two lactam carbonyls. CH at δ 132.54 confirmed the presence of olefinic carbon. Above all mass spectrum showed m/z peak at 374 corresponding to the formulae $C_{24}H_{26}N_2O_2$ also confirmed the assigned structure.

Inspite of failing to isomerise the double bonds on the model pyridone **31** it was decided to go ahead with the original plan (scheme 3) to check the efficacy of the RCM reaction on the amide **19a** and **19b**. Thus 2-chlro quinoline-3-carbaxaldehyde (**38**) prepared from acetanilide (**37**) following Meth-Cohn's protocol[12] was subjected to reductive amination with allyl amine to give the secondary amine **39**. Subsequently amine **39** was condensed with acid chlorides **24** and **36** (preparation of **36** is depicted in scheme **9**) to give the amides **19a** and **19b** respectively. Unfortunately all our attempted RCM reactions on amides **19a** and **19b** under various conditions failed to deliver the desired pyridones **18a** and **18b** (scheme 10 and table 2).

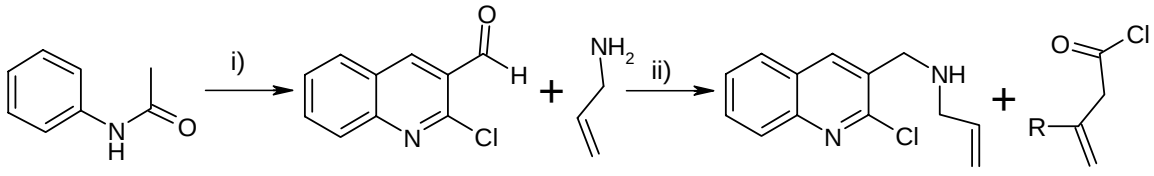
Scheme 9



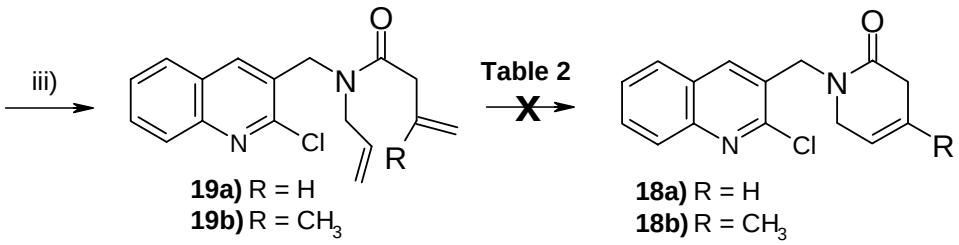
34 **35** **36**

Reagents and conditions: *i) Jones reagent, acetone, 0 ºC-rt, 8 h, 62%, ii) $SOCl_2$, 40 ºC, 6 h, 75%*

Scheme 10



37 **38** **25** **39** **24)** R = H **36)** R = CH_3



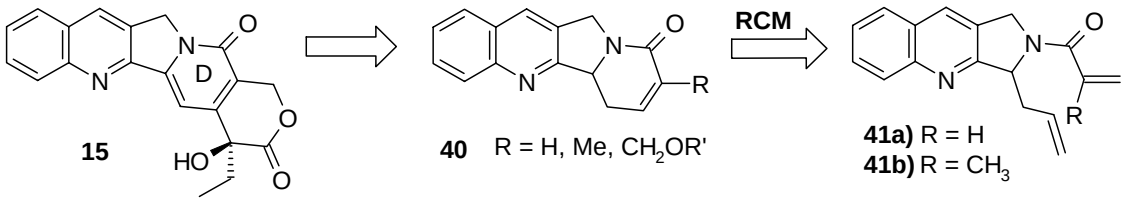
Reagents and conditions*: i) $POCl_3$, DMF, 75 ºC, 16 h, 65%, ii) a) MeOH, rt, 0.5 h, 99% b) $NaBH_4$, MeOH, 0.5 h, 95%, iii) K_2CO_3, DCM, 0 ºC to rt, 3 h, 60%,*

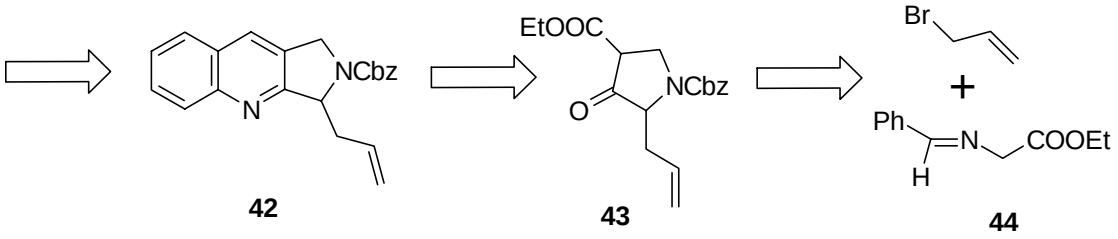
Table 2

S.No	Reagent	Solvent	Temp-erature	Time	Observation
1	Cat **8** (5 mol%)	C_6H_6	rt	48 h	Starting material (SM) recovered
2	Cat **8** (5 mol%)	C_6H_6	reflux	48 h	SM recovered
3	Cat **8** (5 mol%), 1eq TFA	C_6H_6	rt	32 h	SM recovered
4	Cat **8** (10mol%), 2 eq $Ti(OiPr)_4$	DCM	reflux	36 h	SM recovered

Failure of this strategy compelled us to shift to an alternative synthetic strategy (scheme 11). It was thought worthwhile to attempt the RCM on amide **41a** and **41b** to complete the D-ring construction of camptothecin and related alkaloid namely mappicine ketone. The amide **41** can in turn be synthesized in a facile manner from the tricyclic amine **42**. With the proper substitution of the choice, the resulting α, β-unsaturated double bond from RCM can be functionalized suitably to complete the E-ring portion of camptothecin.

Scheme 11

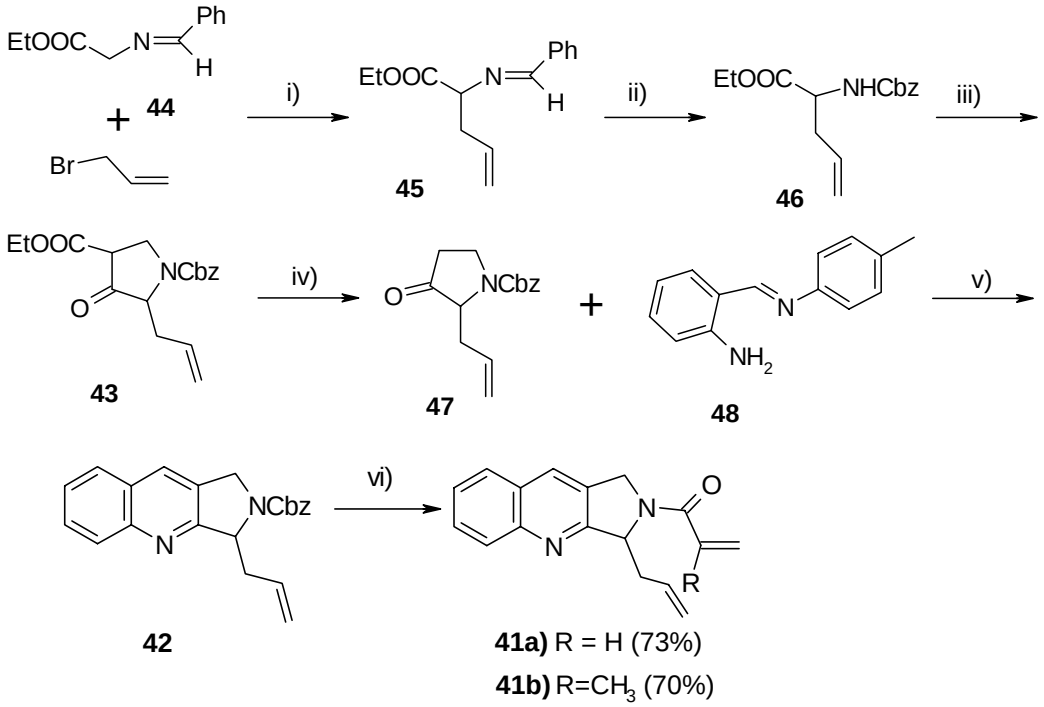




42 **43** **44**

In this direction, versatile tricyclic amine **42** was synthesized by starting from a very simple Schiff' s base **44**. Alkylation on **44** with allyl bromide under phase transfer condition ($TBAHSO_4$ as phase transfer catalyst) using 10% aq NaOH furnished the allylated Schiff's base **45** in excellent yield. Acidic hydrolysis of the **45** liberated the free amine, which in turn was protected as a carbamate **46** using CbzCl in 96% yield.

Scheme 12



Reagents and conditions*: i) 10% NaOH, $TBAHSO_4$, DCM, rt, 0.5 h, 97%, ii) a) 10% HCl, rt, 0.5 h, 91%, b) CbzCl, K_2CO_3, DCM, rt, 3 h, 96%, iii) NaH, C_6H_6, ethyl acrylate, reflux, 3 h, 68%, iv) 10% HCl, reflux, 5 h, v) Toluene, PTSA, reflux, 8 h, 70%, vi) a) KOH, EtOH, reflux, 24 h, b) acryloyl or methacryloyl chloride, K_2CO_3, DCM, rt, 3 h, 73%.*

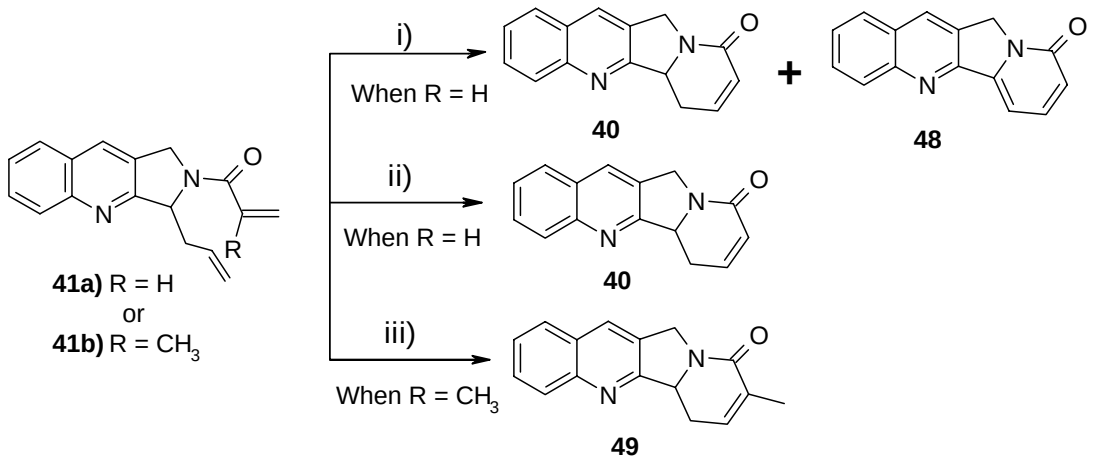
Urethane **46** underwent one pot Michael addition followed by Dieckmann cyclisation with ethyl acrylate using NaH as a base to afford the keto ester **43** in 68%

yield. Keto ester **43** when subjected to hydrolysis and decarboxylation involving 10% HCl at reflux temperature for 5 h provided the keto compound **47**. Alternatively the keto ester without purification was subjected to decarboxylation under Krapcho's condition[13] (DMSO, NaCl, 135 ºC) to furnish the keto compound **47** in 73% yield. Deprotection of the Cbz group of **42** was performed under Olah' s condition [14] employing 10 eq of TMSCl/NaI at 0 ºC to rt for 2 h using CH_3CN as the solvent, followed by direct condensation with acryloyl chloride using K_2CO_3 as the base furnished the acrylamide **41a** in very poor yields. Improved yields were achieved when the deprotection of the Cbz group was carried out under alkaline condition.[15] Thus urethane **42** strictly under degassed condition was treated with 16 eq of KOH in rectified spirit at reflux for 24 h. This was followed by acylation with acryloyl chloride to furnish the acrylamide **41a** in 73 % yield starting from urethane **42**. Under similar conditions amide **41b** was prepared using methacryloyl chloride in 70% yield. ^{13}C NMR shows that compound **41b** exists as mixture of rotamers.

Having synthesized the required amides **41a** and **41b**, the stage was now set for evaluating the construction of D-ring of camptothecin *via* ring closing metathesis protocol. It was very gratifying to employ the RCM on the amide **41a** using Grubbs first generation catalyst **8**. Thus when the amide **41a** was refluxed in benzene employing **8** for 26-32 h under nitrogen atmosphere, along with the desired dihydropyridone **40**, the completely aromatised tetracyclic pyridone **48** was also obtained. The products **40** and **48** formed were in the ratio 3:2 (^1H NMR analysis) respectively. In order to circumvent the formation of undesired pyridone **48**, the RCM reaction was effected employing Ti(*i*-PrO)$_4$ as complexing agent and DCM as solvent, under reflux condition (Marco's protocol).[16] Under these conditions the desired dihydropyridone **40** was obtained in 90% yield. dihydropyridone **40** is the key intermediate in Gilbert Stork's synthesis of camptothecin.[17] The ^1H NMR spectrum of **40,** displayed absence of olefinic protons at δ 5.69 and 5.30. Appearance of multiplets at δ 6.09 and 6.71, each integrating for one proton was assigned to two olefinic protons. ^{13}C NMR spectrum of **40** displayed the absence of olefinic $\underline{C}H_2$ at δ 119.10, 120.06, and 128.66, thus indicating the formation of dihydropyridone unit. The m/z peak at 235 $(M-1)^+$ in the mass spectrum of **40** further

confirmed the structure. Following this result amide **41b** was also subjected to RCM but employing second-generation Grubbs catalyst **12**.[18] Gratifyingly, the RCM reaction proceeded to provide the desired pyridone **49** in 92% yield (scheme 13). Pyridone **49** can serve as an advance intermediate towards the synthesis of mappicine ketone.[19]

Scheme 13



Reagents and conditions*: i)* ***8*** *(10 mol%), benzene, reflux, 26 h, 72%, ii) Ti (OiPr)$_4$, DCM,* ***8*** *(10 mol%), reflux, 16-20 h, 90%, iii)* ***12*** *(5 mol%), toluene, 80 ºC, 3 h, 92%.*

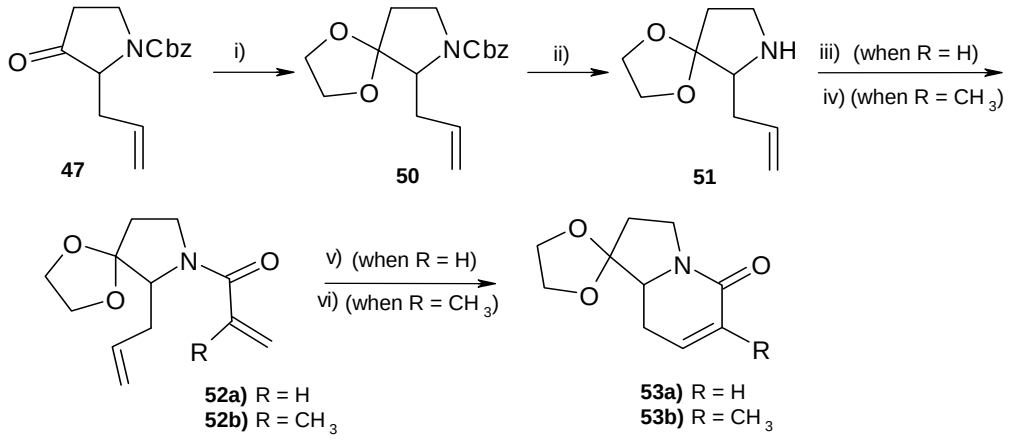
Camptothecin though synthesized more than 3 decades ago, faces considerable limitation in the clinical use. The reason being its poor solubility and toxicity associated within the biosystem. Several analogues of camptothecin can be accessed from camptothecin in a semisynthetic manner. Alternative synthetic approaches for these analogues typically involve the synthesis of suitably functionalised CDE synthons or DE-ring synthons or relevant synthons followed by coupling with suitable AB-ring counter parts either predominantly through FriedLander coupling or by radical or Heck cyclisation. Thinking on these lines, it was envisioned to synthesize first the CD-ring with suitable tethers for the E-ring and condense the same by FriedLander condensation with suitably substituted *o*-amino benzaldehyde to complete the ABCD-ring system of camptothecin.

To achieve this aim the keto compound **47** was protected with ethylene glycol under standard conditions to furnish the cyclic acetal **50** in 85% yield (scheme 14). Later the Cbz functional group in acetal **50** was deprotected employing 14 eq of KOH in

aq.ethanol under reflux condition (nitrogen atmosphere) to provide the amine **51** in 80% yield (crude). The condensation of crude amine **51** with acryloyl chloride and methacryloyl chloride gave amides **52a** and **52b** in 70% and 73% yield respectively.

It is very evident from the ^{13}C NMR of **52b** it exists as mixture of rotamers. Intramolecular RCM was accomplished on the amides **52a** and **52b** and the corresponding dihydropyridones **53a** and **53b** were obtained in very good yields.

Scheme 14

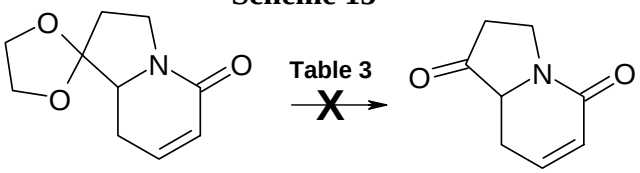


Reagents and conditions**: i) PTSA, ethylene glycol, C_6H_6, reflux, 10 h, 85%, ii) KOH, EtOH, reflux, 43 h, iii) acryloyl chloride, K_2CO_3, DCM, rt, 3 h, 70%, iv) methacryloyl chloride, K_2CO_3, DCM, rt, 3 h, 73%, v)* ***8 *(10 mol%), DCM, reflux, 16-20 h, 94%, iii)* ***12*** *(2.5 mol%), toluene, 80 ºC, overnight, 86%.*

The ^1H NMR spectrum of **53a** displayed absence of multiplet ranging from δ 5.01-5.15. Appearance of a dd ranging from δ 5.89 to 5.95 and a multiplet ranging from δ 6.5 to 6.55, each integrating only for one proton showed the formation of dihydropyridone moiety. ^{13}C NMR spectrum of **53a** displayed the absence of olefinic $\underline{C}H_2$ at δ 116.93, 118.07, 127.26 and 127.41 and presence of only two olefinic $\underline{C}H$ at δ 123.92 and 138.07. The carbonyl carbon appeared at δ 163.03. This confirmed the formation of dihydropyridone unit. The m/z peak at 196 $(M+1)^+$ in the mass spectrum of **53a** further ascertained the assigned structure. The pyridones **40, 49, 53a** and **53b** offer potential scope to complete the synthesis of camptothecin and mappicine ketone. It warranted only suitable functionaliosation of the double bond in these pyridones. Prior to this, as a first option we believed that deprotection of the acetal functionality in pyridone

53a and subsequent condensation of the resulting keto compound with *o*-amino benzaldehyde will result in the formation of tetracyclic pyridone **40**. But our efforts in this direction were abortive. As shown in scheme 15 and table 3 several conditions attempted to deprotect the acetal functionality ended in fruitless result. When the deprotection was attempted in the presence of 10%HCl under reflux condition, only undesired pyridone **55** was obtained in 38% yield (scheme 16). Absorption at 1744 cm^{-1} and 1655 cm^{-1} in the IR spectrum of **55** showed the presence of ketone and pyridone functionality. Triplet at δ 2.93 and 4.33 was assigned to methylene protons $C\underline{H_2}$-CH_2-N and $C\underline{H_2}$-N respectively. Further the m/z peak at 196 $(M+1)^+$ in the mass spectrum of **55** further confirmed the structure.

Scheme 15

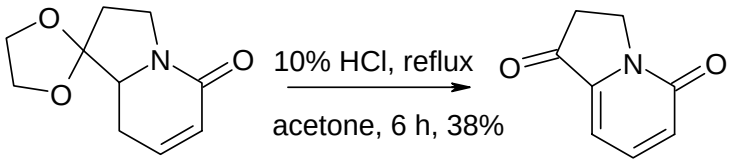


53a **54**

Table 3

S.NO	Reagent	Tempe-rature	Time	Observation
1	TFA:H_2O (1: 1)	rt	24 h	Starting material (SM) recovered
2	50% HCl THF, H_2O	rt	24 h	SM recovered
3	16 eq Oxalic acid [15] EtOH, H_2O	reflux	26 h	SM recovered
4	2.5 eq CAN [20b] CH_3CN, H_2O	reflux	1 h	SM recovered
5	0.5 eq DDQ [20c] CH_3CN, H_2O (9:1)	rt	3 h	SM recovered

Scheme 16

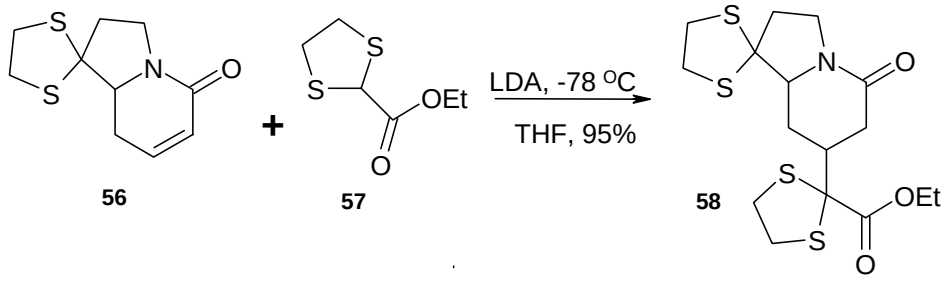


53a **55**

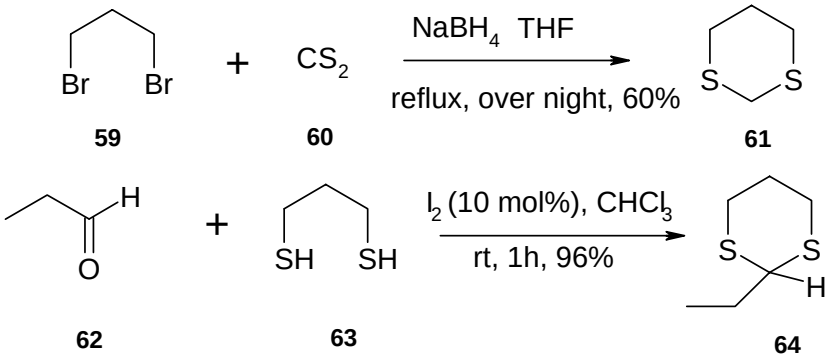
Having successfully synthesized the core skeleton of camptothecin and related alkaloids employing RCM, all that has to be done is to suitably functionalize the double bond in dihydropyridones to complete the E-ring of the target molecule. In this context, it was proposed to perform Michael addition (addition of 1,3-dithianes, diethylmalonate, nitro alkane and α-nitro ester) and 2+2 cycloaddition of ynamine across the double bond.

Literature precedent revealed that 1,2-dithiane **57** can be added successfully across the double bond on the dihydropyridone **56** to furnish the Michael adduct **58** in very good yield (scheme 17).[21] Drawing inspiration from this observation, it was planned to carry out similar reaction on pyridones **53a** and **53b** using dithianes **61** and **64**. The requisite dithianes were prepared following the procedures documented in the literature (scheme 18).[22,23]

Scheme 17

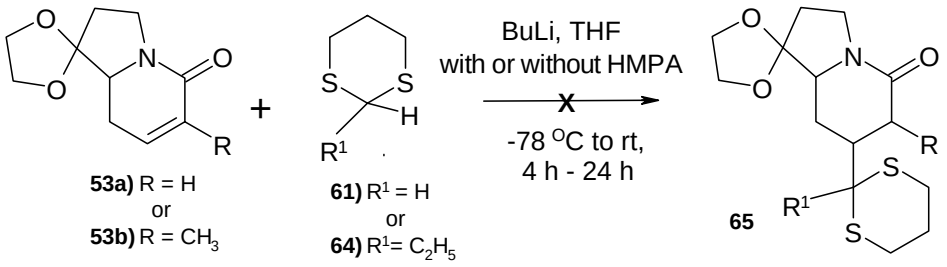


Scheme 18



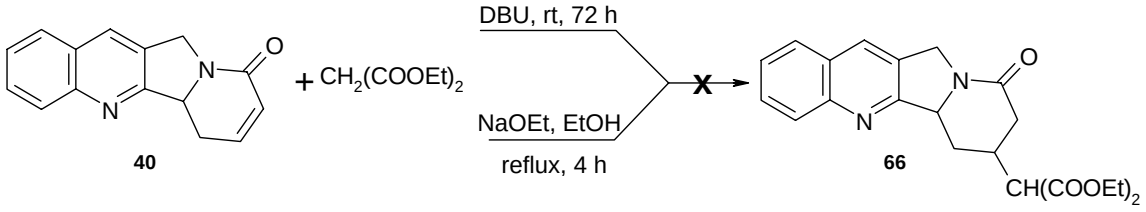
A series of attempted 1, 4-addition of dithianes **61** and **64** on the dihydropyridones **53a** and **53b** under varieties of condition did not fetch any positive results (scheme 19). Even the addition of HMPA did not have impact on the course of reaction in the desired direction. In all the cases starting material was recovered.

Scheme 19



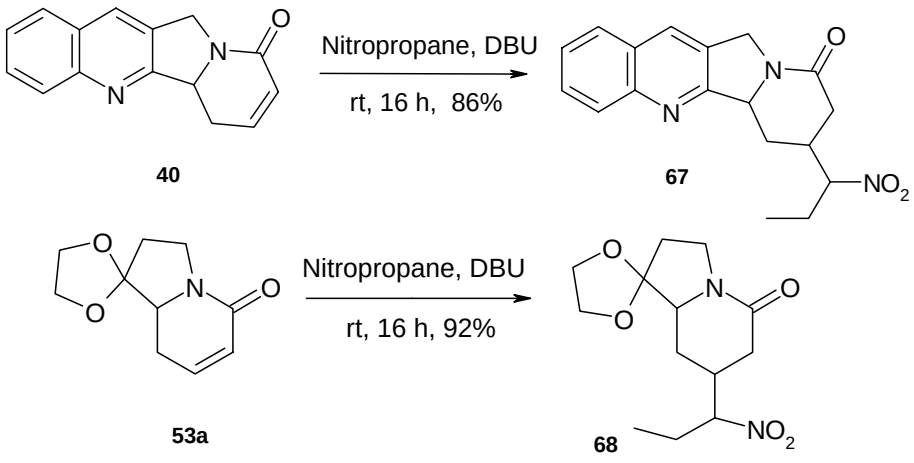
The next Michael donor that was attempted was diethyl malonate. Addition of diethyl malonate either using DBU as a base under room temperature or using NaOEt under reflux condition on dihydropyridone **40** did not provide the desired diester **66**. In both the cases only intractable mixture was obtained (scheme 20).

Scheme 20



Having had discouraging results, it was thought to use nitro propane as a Michael donor, so that classical Nef reaction can be performed to convert the nitro functionality in to carbonyl moiety. It was gratifying to observe that a mixture of DBU, nitropropane and **3** at room temperature afforded the nitro compound **67** in very high yields. Dihydropyridone **53a** was also functionalised in a similar fashion.

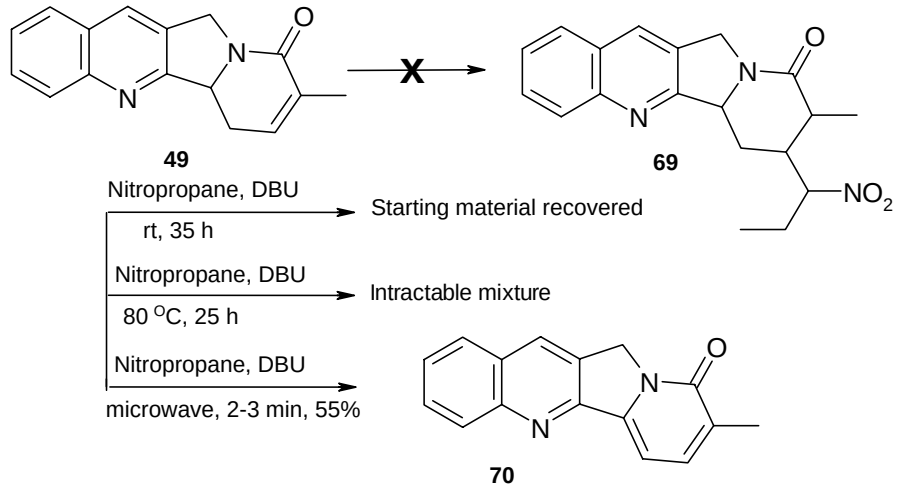
Scheme 21

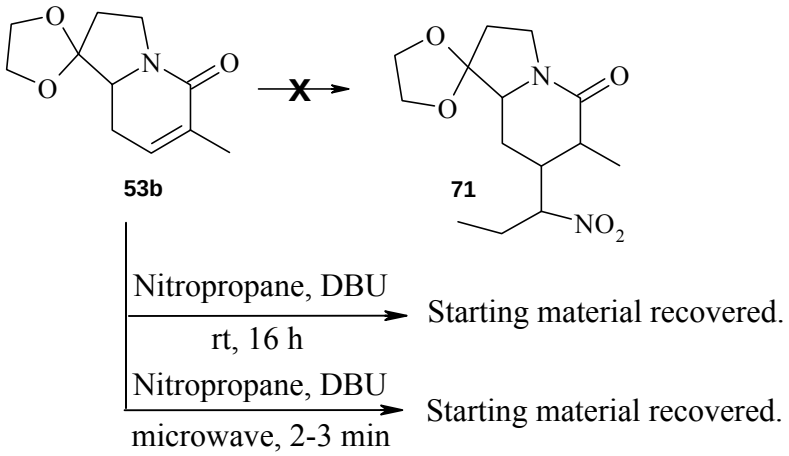


The ^{1}H NMR spectrum of **67** showed the presence of a triplet (3H) at δ 1.03. Absence of dd from δ 5.89 to 5.95 and a multiplet from δ 6.5 to 6.55, and the appearance of multiplet at δ 4.32 integrating for 1H (assigned to C<u>H</u>-NO_2) confirmed the incorporation of nitro propane tether. ^{13}C NMR spectrum showed that **67** exists as mixture of diastereomers. As expected, with respect to carbonyl carbon of dihydro-pyridone **40,** there was a down field shift of the carbonyl carbon (δ 166.85 and 167.00) in the ^{13}C NMR spectrum of **67.** The peak at δ 93.96 and 93.81 was assigned to <u>C</u>H-NO_2. Further HRMS analysis observed for $(M+H)^{+}$-326.1520 confirmed the assigned structure. It is pertinent to mention that similar Michael addition of nitroalkanes promoted by DBU have been documented on α, β-unsaturated lactams where the activation of the double bond is a prerequisite which is achieved by placing electron withdrawing groups on the nitrogen or converting the lactam in to thiolactams.[24]

Having tasted the initial success it was envisaged to carry out nitropropane additon across the double bonds of the methyl substituted dihydropyridones **49** and **53b** to complete the synthesis of mappicine ketone. However, it was observed that the presence of methyl substitution was detrimental to the success of the reaction. As shown in scheme 22, despite several attempts this reaction appeared to be a daunting task. When the same reaction was performed on **49** under microwave conditions, only undesired pyridone **70** was obtained.

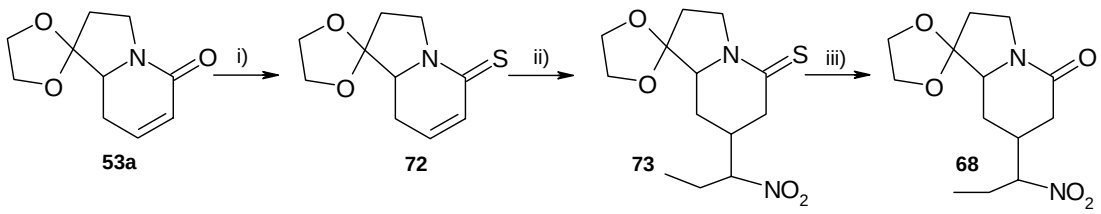
Scheme 22

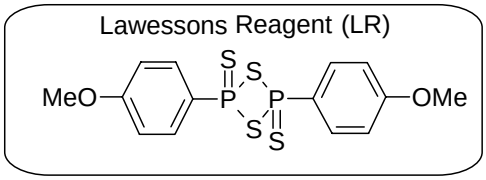




It has been demonstrated in the literature that α, β -unsaturated thioamides undergo facile Michael addition with a plethora of nucleophiles.[24c,25] Considering this fact, it was decided to convert the dihydro pyridone **49** to corresponding thio derivative so that subsequent Michael addition of nitro propane can be attempted. Since pyridones **49** and **53b** were prepared using exorbitantly priced second-generation Grubb's catalyst, it was necessary to try and set the conditions on a model substrate. Therefore dihydropyridone **53a** was choosen as a model substrate. As shown in scheme **23**, dihydropyridone **53a** under went smooth conversion to corresponding thioamide derivative with Lawesson' s reagent (LR).[25] Several attempts were made to improve and optimize the yields of this transformation [i) LR, toluene, 80 ºC, 1 h, ii) LR, THF, reflux, 1 h, iii) LR, THF, rt, 0.5 h]. Best yield of 37% was obtained, when the reaction was performed in THF at 0 ºC for 10 min. The IR spectrum of compound **72** displayed absence of absorption at 1658 cm^{-1} and the formation of new peak at 1619 cm^{-1} indicating the incorporation of thicarbonyl functionality. Observation of large down shield shift of the carbonyl carbon (δ 187.51) in the ^{13}C NMR spectrum of **72** when compared to **53a**, where the carbonyl carbon appeared at δ 161.96 certainly confirms the assigned structure. An m/z peak at 210 $(M-1)^+$ ably supports the conclusion.

Scheme 23

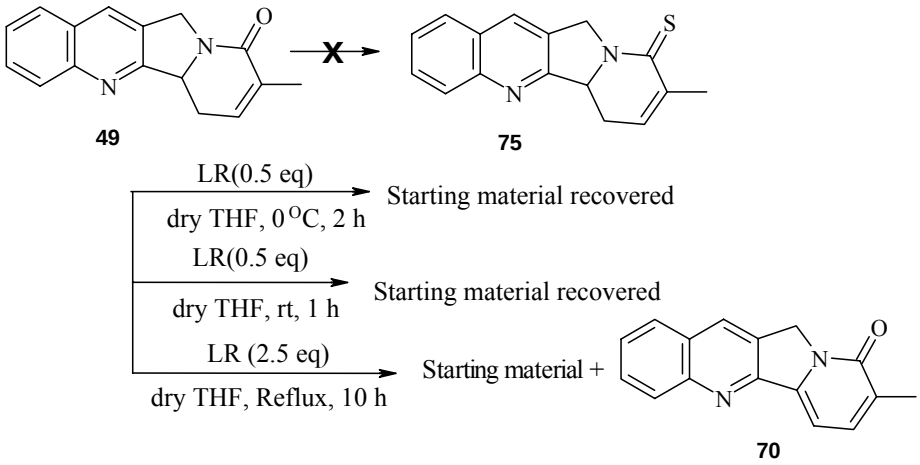




Reagents and conditions: *i) LR (0.5 eq), dry THF, 0 ºC, 10 min, 37%, ii) nitropropane, DBU(0.9 eq), rt, 35 h, 75%, iii) 55% m-CPBA, DCM, rt, overnight, 75%.*

Michael addition of nitropropane on the thioamide **72** promoted by DBU gave the nitro adduct **73** in 75%. Further thiolactam **73** was oxidized to corresponding lactam **68** using *m*-CPBA at room temperature in 75% yield [26] leading to the completion of the model study. Based on the aforementioned model study, pyridone **49** was subjected to the formation of thioamide **75** under wide variety of conditions (scheme 24). Discouragingly, only starting material was recovered in all the attempts. Increase in the amount of LR and reaction temperature did have any influence in the course of reaction.

Scheme 24

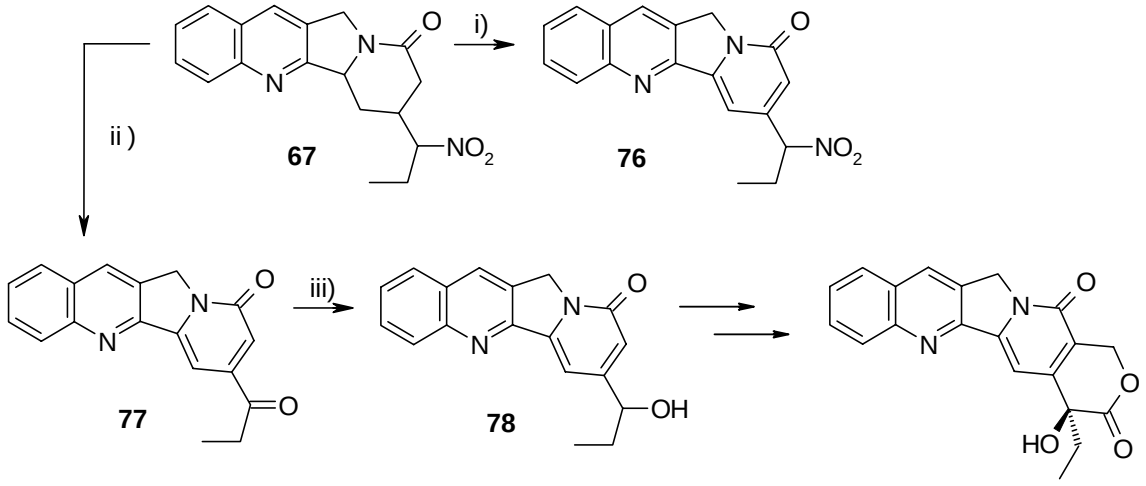


[TLC analysis with authentic samples]

Leaving the scheme **24** at that stage we decided to functionalize and transform the nitro compounds **67** and **68** to complete the synthesis of camptothecin. Therefore it was decided to first oxidize the nitro compound **67** using DDQ to pyridone **76** and perform the Nef reaction on **76** to convert the nitro functional group to provide the corresponding carbonyl compound **77**. Even though the DDQ oxidation on the nitrolactam **67** afforded the desired pyridone **76**, the poor yield of this transformation was a cause for concern. However our attempts to improve the yields by increasing the stoichiometry of the

reagent and the reaction time were abortive. Therefore we decided to perform the Nef reaction on **67** prior to the dehydrogenation procedure. In the IR spectrum of pyridone **76** two strong peaks at 1666 and 1556 cm^{-1} were assigned to the pyridone carbonyl and nitro functional group respectively. In the ^{1}H NMR spectrum of **76** a singlet at δ 6.76 and 7.39 integrating for 1H each was assigned to pyridone protons. Triplet at δ 5.35 was assigned to methine proton adjacent to nitro functional group. The assigned structure was conclusively confirmed by ^{13}C NMR, which showed the presence of pyridone at δ161 in addition to the required number of CH, CH_2 CH_3 and by the HRMS analysis [$(M+H)^+$ - 322.116].

Scheme 25



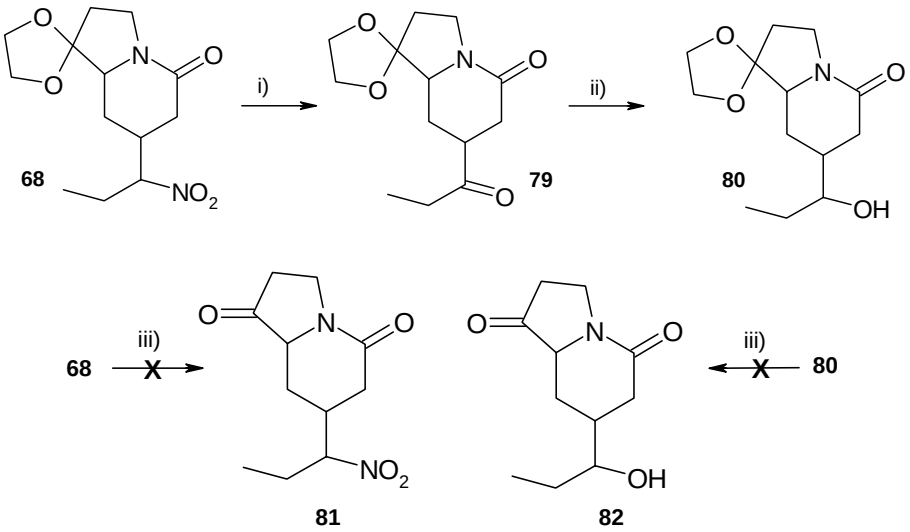
Reagents and conditions*: i) DDQ, dioxane, reflux, 5 h, 25%, ii) NaOH, MeOH, rt, 3 h, con.HCl, 0 ºC, 1 h and rt, 12 h, 23%, iii) $NaBH_4$, MeOH, 0 ºC, 1 h, 99%.*

On exposure to standard Nef conditions,[27b] not only was the nitro functionality transformed to carbonyl, surprisingly oxidation to the corresponding pyridone **67** was also effected to give the carbonyl **77** in 23% yield. However, optimum conditions for this transformation have not been extensively studied (conditions attempted are a) NaOH, MeOH, -44 ºC, 3 h, followed by H_2SO_4, MeOH, -20 ºC to 0 ºC, 4 h, b) K_2CO_3, 30% H_2O_2, MeOH, rt, 8 h,[28a] c) NaOH, Na_2HPO_4, MeOH, rt, 1 h, followed by Oxone, rt, overnight[28b]). The two strong absorption peaks at 1702 and 1666 cm^{-1} in the IR spectrum of pyridone **77** was assigned to the ketone and pyridone carbonyl respectively. In the ^{1}H

NMR spectrum of **77** the singlet at δ 5.28 integrating for two protons was assigned to the benzylic C$\underline{H}_2$. Quartet at 3.03 for two protons was assigned to C$\underline{H}_2$ adjacent to ketone carbonyl functional group. The assigned structure was conclusively confirmed by ^{13}C NMR, which showed the presence of ketone at δ 199.86 and pyridone at δ 161.93 in addition to the required number of CH, CH_2 CH_3, and by the HRMS analysis [$(M+H)^+$ - 291.1137.].

Finally the reduction of the carbonyl group of **77** with $NaBH_4$ gave the desired hydroxy pyridone **78** in nearly quantitative yields. Hydroxy compound **78** is a key intermediate in Murata's synthesis of camptothecin published in 1997.[29] Thus our approach constitutes a formal total synthesis of camptothecin. Continuing on these lines nitro compound **68** was subjected to oxidative Nef reaction using Oxone as an oxidizing agent to provide the carbonyl compound **79** in excellent yields. Later the carbonyl compound was reduced to corresponding alcohol **80** in 85% yield using $NaBH_4$. It was envisioned that at this stage deprotection of acetal moiety followed by Friedlander condensation and subsequent aromatisation would yield the tetracyclic hydroxy compound **78**. As mentioned earlier the deprotection of acetal on dihydro pyridone **53a,** a seemingly simple transformation, finally turned out to be an arduous task resulting only in the unwanted pyridone **55**. Similar deprotection of acetal on either nitro compound **68** or on hydroxy compound **80** did not give rise to desired carbonyl compounds.

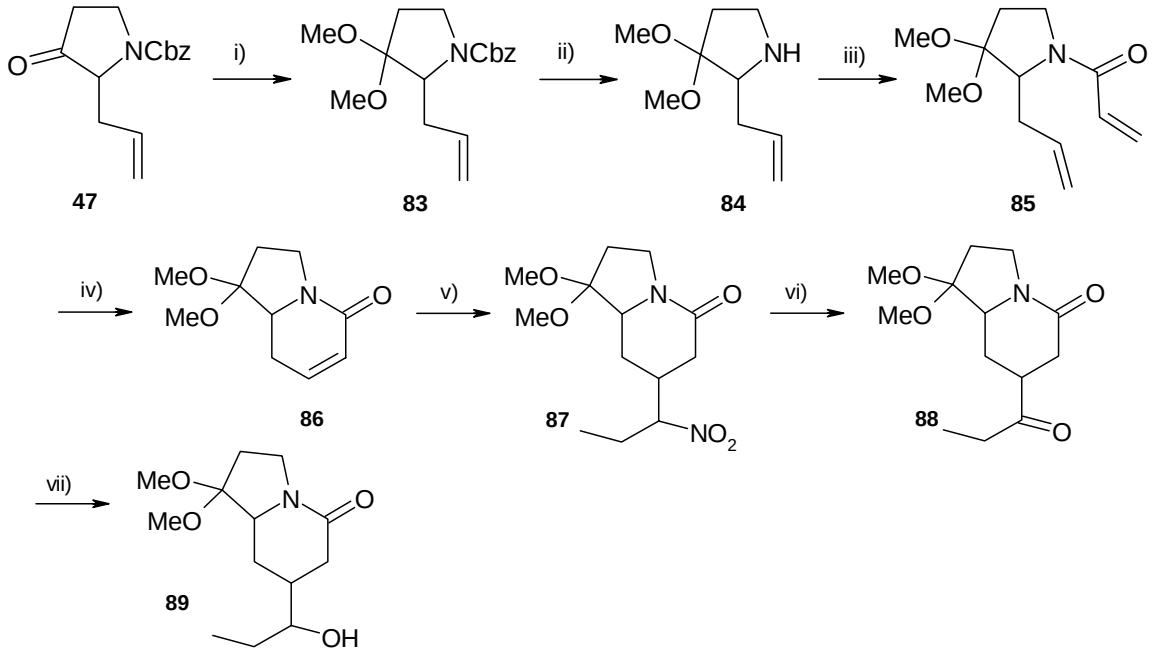
Scheme 26



***Reagents and conditions**: i) NaOH, Na_2HPO_4, MeOH, rt, 1 h, followed by Oxone, rt, overnight, 79%, ii) $NaBH_4$, MeOH, 0 ºC, 1 h, 85%, iii) 10% HCl, acetone, 8 h, reflux*

We resorted to sort out this problem by changing the ethylene glycol acetal protection in **50** to relatively labile dimethyl acetal protecting group so that at a later stage the acetal protection can be deprotected in a facile manner and further elaborated to target molecule. As a first step ketone **47** was protected as its dimethyl acetal derivative **83** using trimethyl orthoformate and PTSA in methanol under reflux condition in very good yields (scheme 27). Later the Cbz functional group in acetal **83** was deprotected employing 14 eq of KOH in aq.ethanol under reflux condition (nitrogen atmosphere) to provide the crude amine **84**. The condensation of crude amine **84** with acryloyl chloride gave amide **85** in 40% yield starting from the acetal **83**. Intramolecular RCM was performed on the amide **85** to furnish the corresponding dihydropyridone **86** in excellent yield. Subsequently Michael addition of nitropropane was carried out on **86** to furnish the adduct **87** in good yields. Later nitro compound **87** was subjected to oxidative Nef reaction using Oxone as oxidizing agent to provide the carbonyl compound **88** in excellent yield. Later the carbonyl compound was reduced to corresponding alcohol **89** in 85% yield using $NaBH_4$. Further manipulation of the hydroxy compound **89** to hydroxy pyridone **78**, an advanced intermediate for the camptothecin is in progress.

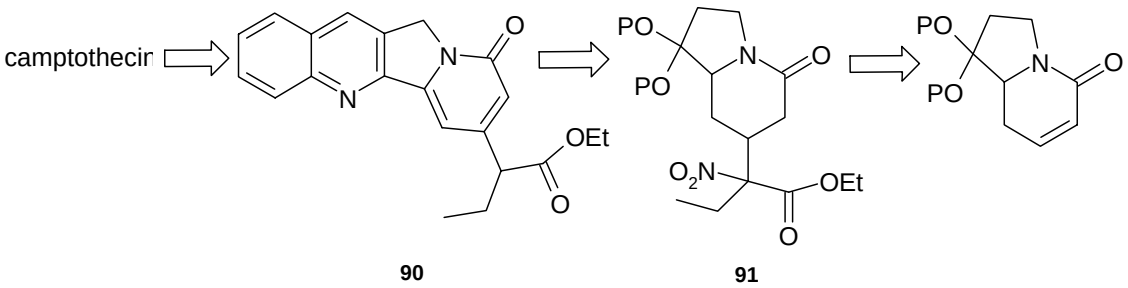
Scheme 27



***Reagents and conditions**: i) trimethyl orthoformate, PTSA, MeOH, reflux, 12 h, 99%, ii) KOH, EtOH, reflux, 43 h, iii) acryloyl chloride, TEA (5 eq), DCM, rt, 3 h, 40%, iv) **8** (10 mol%), DCM, reflux, 16-20 h, 94%, v) nitropropane, DBU, rt, 16 h, 85%, vi) NaOH, Na_2HPO_4, MeOH, rt, 1 h, followed by Oxone, rt, overnight, 82%, vii) $NaBH_4$, MeOH, 0 ^oC, 1 h, 85%.*

It was conceived that 1,4–addition of α-nitro esters on the dihydropyridones could be an excellent approach to install the appropriate appendages for the E-ring construction of camptothecin (scheme 28). Later the nitro group can be denitrated in a facile manner to get a versatile intermediate **90**.

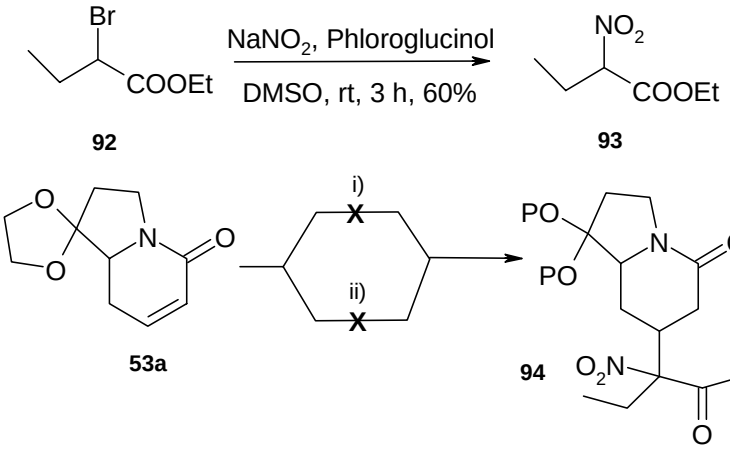
Scheme 28



90 **91**

The requisite nitro ester **93** was prepared very easily from bromo ester **92** as per reported procedure (Scheme 29).[30] When the Michael addition of the nitroester **93** was attempted on the dihydropyridone **53a**, instead of getting the desired product **94**, even under microwave conditions only starting material was recovered (scheme 29).

Scheme 29



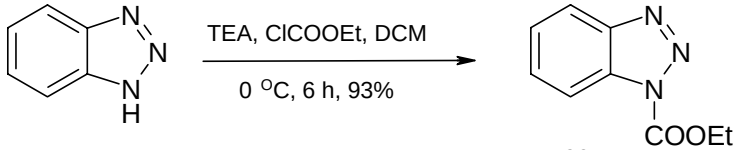
92 **93**

53a **94**

***Reagents and conditions**: i) **93**, DBU, rt, 24 h, ii) **93**, DBU, microwave, 8 min*

In order to overcome this failure it was decided to directly acylate the nitro compound. After carefully going through the literature, we found triazole **95** to be an excellent acylating agent to prepare α-nitro esters.[31] It is very tricky to acylate the α-carbon in a nitro compound because of the competing *O*-acylation. As per the literature report, preparation of the **96** involved the usage of toxic phosgene.[32] We decided to avoid this protocol and resorted to prepare the same in a much simpler manner. Gratifyingly, when benzotriazol **95** was treated with ethylchloroformate and triethylamine at 0 ºC, **96** was obtained in 93% yield as white solid (scheme 30).

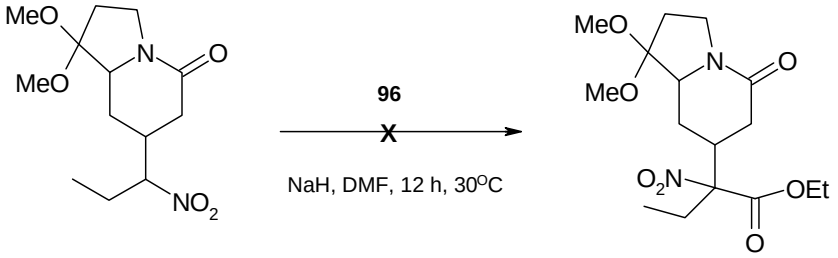
Scheme 30



95 **96**

The acylation attempt on nitro compound **87** with **96** in the presence of NaH as a base did not provide the desired ester **97**. Instead only starting material was recovered (scheme 31).

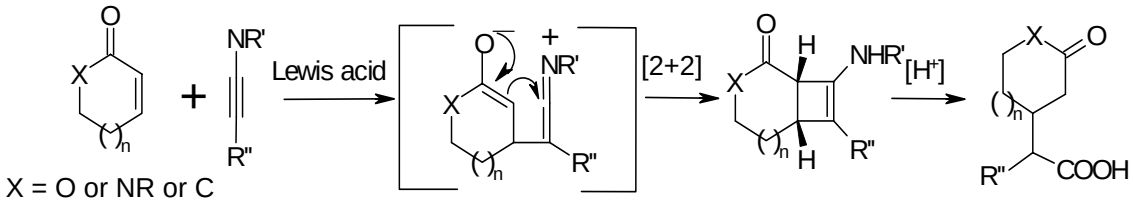
Scheme 31



87 **97**

One of the most interesting and synthetically useful cycloaddition is Ficini's thermal stepwise [2+2] cycloaddition reaction of ynamines with electron deficient alkenes such as **98**, leading to cyclobutenamines **101**.[33] Later these cyclobutenamines can be hydrolysed to corresponding carboxylic acid **102** as shown in scheme 32.

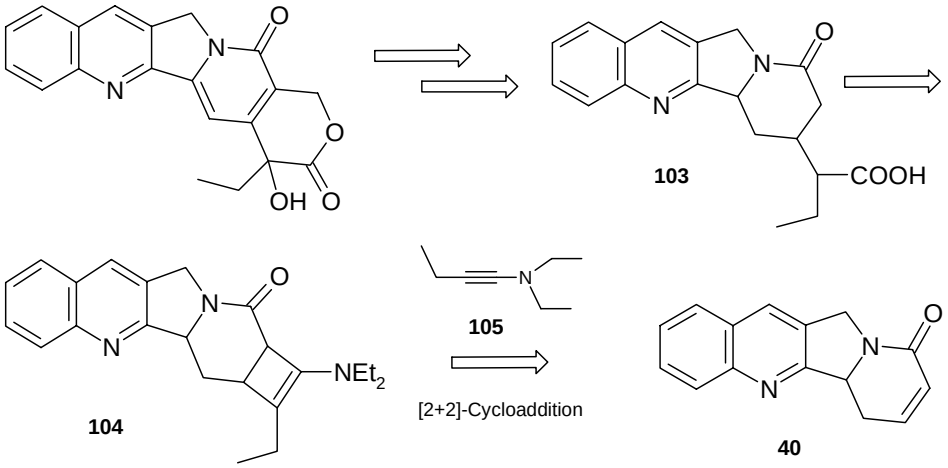
Scheme 32



98 **99** **100** **101** **102**

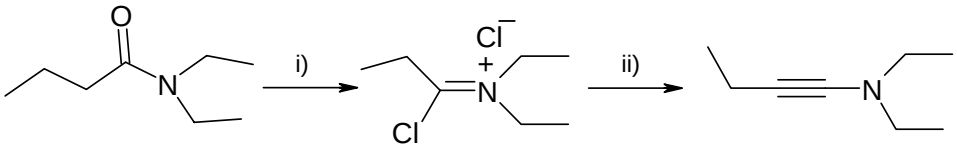
Ficini successfully utilized the same strategy in 1979 to synthesize (±)-dihydroantirhine (indole alkaloid).[34] It was reasoned that [2+2] cycloaddition reaction of ynamine **105** with dihydropyridone **40** would be an interesting and novel way to introduce the ethyl substituent and carboxylic moiety required to construct the E-ring of camptothecin in a single operation (scheme 33).

Scheme 33



As depicted in the scheme **34** below, the ynamine **105** used for the cycloaddition reaction was prepared according to reported procedures, but with a slight modification.[35] The toxic phosgene required to prepare the chloroimminium salt **107** was successfully replaced by environmentally benign triphosgene.

Scheme 34



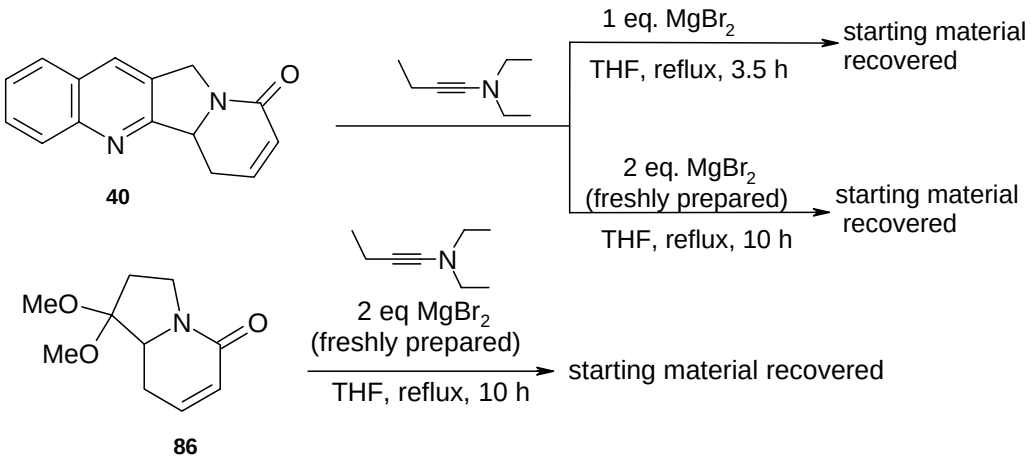
106 **107** **105**

Reagents and conditions*: i) triphosgene, toluene, 0 ºC to rt, 14 h, 64%, ii) dicyclohexyl amine, BuLi, dry ether, 0 ºC to rt, 16 h, 12%*

As shown in scheme 34, butanamide **106** was treated with triphosgene in toluene at 0 ºC to get the precursor chloroimminum salt **107** as colourless viscous oil. Later the salt **107** when treated with dicyclohexyllithium amide suffers dehalogenation and rearrangement to provide the required ynamine **105** in 12.5 % yield. The pyridones **40**

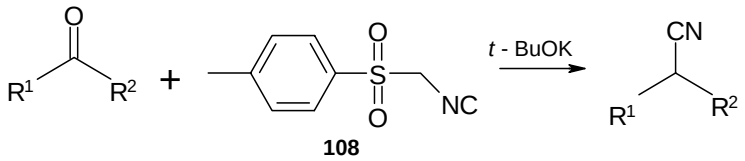
and **86** when subjected to [2+2] cycloaddition with ynamine **105** in the presence of Lewis acid $MgBr_2$ (Aldrich made as well as freshly prepared $MgBr_2$ was employed) using THF as solvent under reflux conditions failed to furnish the required cycloadducts. Instead, only starting material (pyridone) was recovered in both the cases (scheme 35).

Scheme 35



It was envisaged that nitrile **113** (scheme 38) could serve as an important intermediate towards the synthesis of camptothein. Tosylmethyl isocyanide (TosMIC) **108** a diverse and versatile synthon have been effectively employed to prepare nitriles from ketones (scheme 36).[36] Analogous to classical cyanohydrin reaction TosMIC performs one carbon homologation on the ketone in the presence of a suitable base, but without the simultaneous formation of a α-hydroxy group. In this sense this reaction is termed as reductive cyanation. The synthesis of nitriles is applicable to wide variety of ketones ranging from simple aliphatic and aromatic ketones to sterically hindered one.

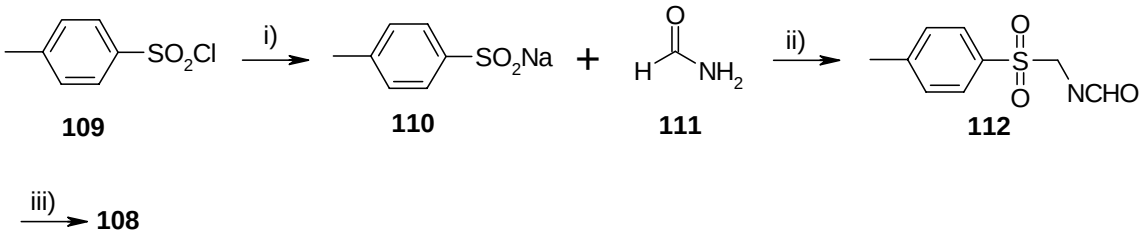
Scheme 36



The scheme **37** depicted below gives the preparation of TosMIC starting from para-toluenesulfonyl chloride (**109**).[37] Zinc mediated reduction of **109** gave the corresponding sodium para-toluenesulfinate (**110**) in excellent yields. Further Mannich condensation of **110**, formamide (**111**) and paraformaldehyde, in the presence of formic

acid furnished the formamide **112** in 79% yield. Dehydration of **112** with $POCl_3$ furnished TosMIC in 68% yield.

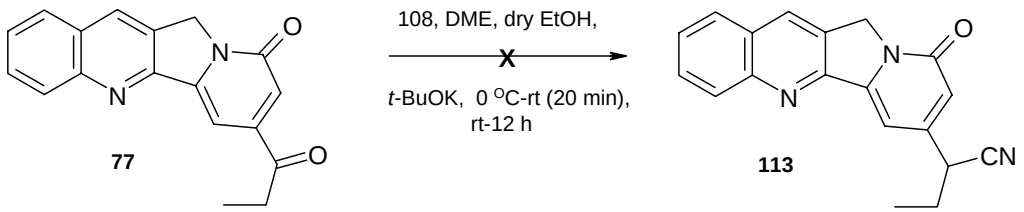
Scheme 37



Reagents and conditions*: i) a) Zn, H_2O, 90 ºC, 20 min, b) NaOH, Na_2CO_3, H_2O, 60%, ii) $(CH_2O)_n$, HCOOH, 90-95 ºC, 3 h, 79%, iii) diisopropylamine, $POCl_3$, dry THF, -20 ºC to 0 ºC-20 min, 0 ºC-1 h, 68%.*

The attempted reductive cyanation strategy on ketone using TosMIC did not provide the desired nitrile **113**. Instead intractable mixture was obtained (scheme 38). However it warrants further experimental trials ahead of taking a decision to abandon this particular transformation.

Scheme 38

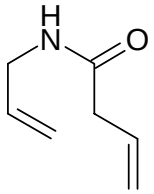


1.2.1.3 Conclusions:

1. We have established the efficacy of RCM in the construction of pyridone moiety of camptothecin.
2. Formal total synthesis of camptothecin has been achieved.
3. Model studies have led to the synthesis of C-D skeleton of camptothecin. This would lead to synthesis of analogs and a common intermediate.
4. Advanced intermediate of mappicine ketone has been achieved by RCM as a key step.
5. A facile method for the conjugate addition of nitroalkanes to unactivated α, β-unsaturated lactams promoted by DBU has been established.

1.2.1.4 Experimental:

N-Allyl- butenamide (26):



3-Butenoic acid (4.52 g, 52.6 mmol) and thionyl chloride (9.3 g, 78.94 mmol) was heated at 60 ºC for 4 h, after which excess thionyl chloride was removed to get the crude 3-butenoyl chloride (**26**). To the allyl amine (**25)** (2 g, 35 mmol) and K_2CO_3 (19.69 g, 140 mmol) in dry DCM at 0 ºC was added 3-butenoyl chloride dissolved in 5 mL of dry DCM dropwise and stirred at rt for 3 h, after which water was added and the organic layer was separated. The aq layer was extracted with DCM (3x100 mL) and the combined organic layer were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuuo.* The residue obtained was purified by column chromatography using pet-ether:ethyl acetate 3:2 to furnish the pure amide **26** in 65% (2.18 g) yield.

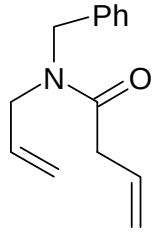
Mol. Formula: $C_7H_{11}NO$, colourless oil.

Yield: 65%.

IR ($CHCl_3$) cm^{-1}: 1634, 1544, 1427.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.89-2.93 (s, 2H), 3.69-3.74 (s, 2H), 4.95-5.11 (m, 4H), 5.61-5.93 (m, 2H), 6.95 (bs, 1H).

But-3-enoic acid allyl-benzyl-amide (30):



To the allyl amine **25** (4 g, 70.6 mmol) dissolved in dry methanol (50 mL) maintained at rt was added benzaldehyde (5 g, 47 mmol) and stirred at same temperature for 1 h. Methanol was removed under reduced pressure and quenched with water. The organic layer was extracted with DCM. Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude imine obtained was treated with

$NaBH_4$ (2 g, 56.6 mmol) at 0 ºC in dry methanol and stirred at rt for 1 h. Methanol was removed under reduced pressure. After quenching with water, the residue was extracted with DCM (3x50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give the crude amine. The condensation of crude amine with **24** was carried as per the procedure reported for the preparation of the amide **26**.

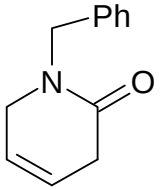
Mol. Formula: $C_{14}H_{17}NO$, thick oil.

Yield: 75%.

IR ($CHCl_3$) cm^{-1}: 1624, 1574.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 3.13-3.17 (m, 2H), 3.78-3.98 (m, 2H), 4.48, 4.55 (s, 2H), 5.02-5.21 (m, 4H), 5.73 (m, 1H), 6.01 (m, 1H), 7.22 (m, 5H).

1-Benzyl-3, 6-dihydro-1*H*-pyridin-2-one (31):



The cat **8** (19 mg, 5 mol%) was added to a homogeneous solution of diene **30** (100 mg, 0.47 mmol) in 5 mL of dry C_6H_6 under argon. The resulting mixture was stirred at 20ºC for 10 h, at which time TLC showed the reaction to be complete. The reaction mixture was concentrated, and purified by column chromatography using pet-ether:ethyl acetate (7:3) to provide 79 mg (91%) of the lactam **31**.

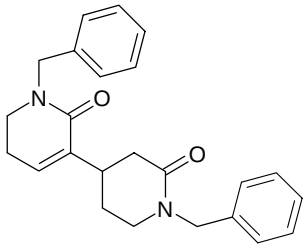
Mol. Formula: $C_{12}H_{13}NO$, thick oil.

Yield: 91%.

IR ($CHCl_3$) cm^{-1}: 1654, 1574.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 3.00 (m, 2H), 3.75 (m, 2H), 4.62 (s, 2H), 5.75 (m, 1H), 7.23 (m, 5H).

1,1'-Dibenzyl-5,6,3',4',5',6'-hexahydro-1'*H*-[3,4']bipyridinyl-2,2'-dione (33):



To the *t*-BuOK (0.119 g, 1.07mmol) in dry THF (4 mL) at 0 ºC was added lactam **31** (0.200 g, 1.07 mmol) dissolved in dry THF (3 mL) dropwise and stirred at same temperature for 0.5 h. Later the reaction mixture was quenched with 10% HCl, extracted with ethylacetate (2x20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was column chromatographed on silica gel (pet-ether:ethyl acetate, 3:7) as a thick oil in 50% yield
(0.100 g).

Mol. Formula: $C_{24}H_{26}N_2O_2$, thick liquid.

Yield: 50%.

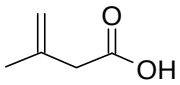
IR ($CHCl_3$) cm^{-1}: 2962, 2400, 1680, 1630, 1520, 1400.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.72 (m, 1H), 2.02 (m, 1H), 2.31-2.44 (m, 3H), 2.66-2.73 (m, 1H), 3.24 (m, 5H), 4.43 (d, *J*=14.65 Hz, 1H), 4.60 (ABq, *J*=16.12 Hz, 2H), 4.77 (d, *J*=14.65 Hz, 1H), 6.20 (m, 1H), 7.22-7.29 (m, 10H)

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4) δ: 169.4 (s), 164.3 (s), 137.6 (s), 137.3 (s), 137.3 (s), 132.5 (d), 128.8 (d, 2C), 128.7 (d, 2C), 128.3 (d, 2C), 128.1 (d, 2C), 127.6 (d), 127.5 (d), 50.3 (t), 50.2 (t), 46.2 (t), 44.6 (t), 37.4 (t), 33.0 (d), 28.7 (t), 24.0 (t)

Mass (ESI) (m/z): 374 $(M)^+$

3-Methyl-3-butenoic acid (35):



To the alcohol **34** (10 g, 0.116 mmol) dissolved in acetone (100 mL) maintained at 0 ºC was added Jones reagent [The Jones reagent was prepared by dissolving 70 g (0.70 mole) of chromium trioxide in 100 ml. of water. After it was immersed in an ice bath, 112 g. (61 mL, 1.10 moles) of concentrated (18 M) sulfuric acid followed by 200 mL of water was added cautiously with manual stirring] at rt dropwise at a rate such that the temperature did not rise above 0 ºC. Reagent was added till the solution retains the brown color. The stirring was allowed to continue overnight. After removing the acetone *in vacuo* the solution was subjected to continuous extraction with dichloromethane (3x100mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and distillation afforded the pure acid **35** in 62% (7.2 g) yield.

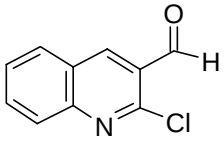
Mol. Formula: $C_5H_8O_2$, colourless oil.

Yield: 62%.

bp: 75 ºC/10 mmHg,

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.77 (s, 3H), 3.00 (s, 2H), 4.85 (d, *J*=10.2 Hz, 2H), 10.29 (bs, 1H).

2-Chloro-quinoline-3-carbaldehyde (38):[12]



To DMF (56 mL) at 0 ºC was added $POCl_3$ (96 mL) dropwise with stirring. To this solution was added the acetanilide (40 g) and after 5 min the mixture was heated at 75 ºC for 16.5 h. The reaction mixture was poured in to crushed ice (1 l) and stirred for 30 min. After 1 h, the brown-yellow solid was filtered off and washed with water (500 mL). The crude solid obtained was recrystallized in ethyl acetate to give yellow crystals of title compound in 65 % yield (37 g)

Mol. Formula: $C_{10}H_6ClNO$, yellow solid.

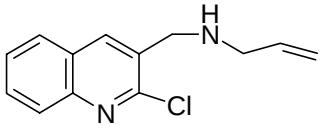
Yield: 65%.

mp: 148-149 ºC,

IR (nujol) cm^{-1}: 1690.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.65 (m, 1H), 7.83-8.15 (m, 3H), 8.74 (s, 1H), 10.56 (s, 1H).

Allyl-(2-chloro-quinolin-3-ylmethyl)-amine (39):



To the allyl amine **25** (1.07 g, 18.75 mmol) dissolved in dry methanol (15 mL) maintained at rt was added aldehyde **38** (3 g, 15.6 mmol) and stirred at same temperature for 1 h. Methanol was removed under reduced pressure and quenched with water. Excess allyl amine was removed under reduced pressure to afford the imine without purification as thick oil (2.46 g, 99% yield).

Mol. Formula: $C_{13}H_{11}ClN_2$, thick oil.

Yield: 99%.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.35 (m, 2H), 5.24 (m, 2H), 6.01- 6.08 (m, 1H), 7.24 (m, 1H), 7.48 (m, 1H), 7.52 (m, 1H), 7.64 (m, 1H), 8.58 (s, 1H), 8.79 (s, 1H).

To the imine (2.46g, 10.6 mmol) dissolved in dry methanol (15 mL) maintained at 0 ºC was added $NaBH_4$ (0.472 g, 12.7 mmol) and stirred at same temperature for 1 h. Methanol was removed under reduced pressure and quenched with water. The aqueous layer was saturated with NaCl and extracted with DCM (2x50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound **39** without purification as a yellow solid (2.35 g, 95% yield).

Mol. Formula: $C_{13}H_{13}ClN_2$, yellow solid.

Yield: 95%.

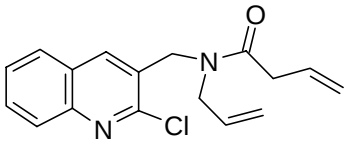
mp: 101-103 ºC

IR ($CHCl_3$) cm^{-1}: 3389, 1654, 1574,

^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.33 (d, *J*=5.9 Hz, 2H), 3.84 (s, 2H), 5.16 (m, 2H), 5.95 (m, 1H), 7.13 (m, 1H), 7.43-7.53 (m, 3H), 7.76 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 164.4 (s), 137.9 (s), 137.7 (d), 136.7 (d), 131.0 (q), 130.0 (d), 127.5 (d), 122.7 (d), 120.1 (q), 116.3 (t), 115.9 (d), 51.7 (d), 60.9 (t), 48.8 (t).

But-3-enoic acid allyl-(2-chloro-quinolin-3-ylmethyl)-amide (19a):



Title compound **19a** (1.56 g) was prepared starting from the amine **39** (2 g) as per the procedure outlined for the preparation of amide **26**.

Mol. Formula: $C_{17}H_{17}ClN_2O$, white solid.

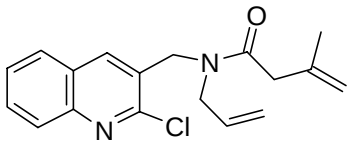
Yield: 60%.

mp: 176-178 ºC

IR (nujol) cm^{-1}: 1659, 1634, 1618, 1574

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 3.24 (m 2H), 4.18 (m, 2H), 4.60 (m, 2H), 5.21(m, 4H), 5.92 (m, 2H), 7.20 (m, 1H), 7.39-7.59 (m, 3H), 7.87 (m, 1H).

3-Methyl-but-3-enoic acid allyl-(2-chloro-quinolin-3-ylmethyl)-amide (19b):



The preparation of the title compound **19b** (1.64 g) was carried out starting from the amine **39** (2 g) as per the procedure outlined for the preparation of the **26**.

Mol. Formula: $C_{18}H_{19}ClN_2O$, white solid.

Yield: 60%.

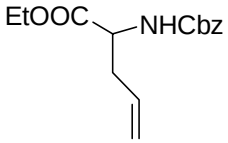
mp: 140-142 ºC

IR ($CHCl_3$) cm^{-1}: 1654, 1574.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.81 (s, 3H), 3.14-3.17 (m, 2H), 4.09-4.18 (m, 2H), 4.54-4.58 (m, 2H), 4.79-4.92 (m, 2H), 5.14-5.31 (m, 2H), 5.90 (m, 1H), 7.20-7.23 (m, 1H), 7.30-7.60 (m, 3H), 7.93 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 171.5 (s), 164.5 (s), 163.6 (s), 139.9 (d), 139.7 (d), 138.0 (s), 135.9 (d), 133.4 (d), 133.0 (d), 130.6 (d), 130.3 (d), 128.8 (s), 128.3 (d), 128.0 (d), 127.8 (d), 123.1 (d), 122.8 (d), 120.2 (s), 119.8 (s), 118.1 (d), 117.0 (d), 116.2 (d), 115.9 (d), 114.0 (t), 51.4 (t), 48.5 (t), 46.7 (t), 44.7 (t), 43.2 (t), 43.0 (t), 22.9 (q). (mixture of rotamers)

Ethyl-2-(benzoyloxycarbonyl amino)-4-pentenoate (**46**):



To 10 g (52 mmol) of Schiff's base **44** and 7.8 g (65 mmol) of allyl bromide in 30 mL of dichloromethane was added 30 mL of 10% NaOH solution and 1.78 g (5.23 mmol) of tetrabutyl ammonium hydrogen sulphate. The mixture was stirred for 0.5 h after which the organic phase was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude syrup thus obtained was redissolved in CCl_4 (30 mL) and washed with water. The organic phase was dried over anhydrous sodium sulphate and concentrated to get crude allylated Schiff's base **45** (11.9g). The crude Schiff's base **45** was stirred with 50 mL of 10% HCl for 0.5 h and 20 mL ethyl acetate was added to the reaction mixture. The aqueous layer separated was extracted further with 2 x 25 mL portions of ethyl acetate. The aqueous layer was cooled and

neutralized with ammonia solution (40% solution) and the aqueous layer (saturated with NaCl) was extracted with 3 x 20 mL portions of ethyl acetate. The organic phase was combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide crude amino ester (6 g, 94% yield). To a cold (0°C) solution of crude amino ester 6.0 g (42 mmol) in dry dichloromethane (30 mL) was added 12 gm (84 mmol) of K_2CO_3 followed by 4.78 g (27 mmol) of benzyl chloroformate dropwise. The mixture was allowed to stir at 0°C for 2 h and the reaction mixture was filtered and the residue was washed thoroughly with dichloromethane. The organic layer was washed with 25 mL of water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel to furnish pure urethane **46** (11 g, 96% yield) as colorless oil.

Mol. Formula: $C_{15}H_{19}NO_4$, thick oil.

Yield: 96%.

IR (neat) cm^{-1}: 3300, 1730, 1500, 1340, 1030.

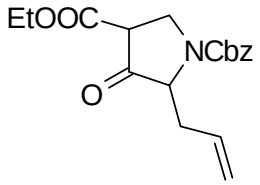
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.26 (t, *J*=7.05 Hz, 3H), 2.58 (m, 2H), 4.20 (q, *J*=7.05 Hz, 2H), 4.44 (m, 1H), 5.09-5.46 (m, 4H), 5.63 (bs, 1H), 5.72 (m, 1H), 7.34 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 171.4 (s), 155.6 (s), 136.2 (s), 132.2 (d), 128.0 (d, 3C), 127.6 (d, 2C), 118.4 (t), 66.3 (t), 60.9 (t), 53.2 (d), 36.1 (t), 13.7 (q).

Mass (ESI) (m/z): 278 $(M+1)^+$

Analysis:	**C**	**H**	**N**
Expected:	64.97	6.91	5.05
Observed:	64.55	6.60	5.15

Ethyl(1-benzyloxycarbonyl)-4-oxo-5-(2-propenyl)-3-pyrrolidinecarboxylate (43):



To a stirred suspension of 1.03 g (43 mmol) of sodium hydride (50% suspension in oil prewashed with 3 x 10 mL of dry pet-ether) in 50 mL of dry benzene was added urethane **46** (5 g, 18 mmol) in 25 mL of dry benzene. The reaction mixture was stirred

till evolution of hydrogen ceased. To the generated sodium salt was added ethyl acrylate 2.16 g (21.6 mmol) in 25 mL benzene, dropwise over 10 min. The mixture was allowed to stir at rt for 0.5 h and then refluxed for 3 h. The reaction mixture was quenched with 10% HCl and the organic phase was separated. The aqueous phase was further extracted with 2 x 25 mL of ethyl acetate and the combined organic phase was dried over anhydrous Na_2SO_4 and filtered. Concentration of the organic layer under reduced pressure furnished crude β-keto ester **43**, which on purification by column chromatography using 25% ethyl acetate pet-ether as eluent furnished pure β-keto ester **43**, 4.06 g (68% yield).

Mol. Formula: $C_{18}H_{21}NO_5$, thick oil.

Yield: 68%.

IR (neat) cm^{-1}: 1730, 1700, 1410.

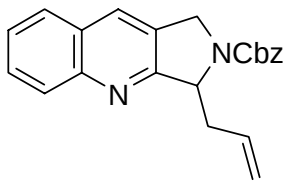
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.3 (m, 3H), 2.45-3.00 (m, 2H), 3.5-4.70 (m, 5H), 4.95-5.35 (m, 4H), 5.65 (m, 2H), 7.35 (s, 5H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 169.2 (s), 167.5 (s), 166.2 (s), 154.8 (s), 154.5 (s), 154.3 (s), 136.8 (s), 136.5 (s), 136.3 (s), 132.2 (d), 131.8 (d), 131.6 (d), 128.6 (d), 128.3 (d), 128.2 (d), 128.0 (d), 120.1 (t), 119.7 (t), 119.2 (t), 67.3 (d), 67.0 (t), 62.2 (d), 62.1 (d), 60.6 (t), 53.3 (d), 49.1 (t), 48.9 (t), 45.9 (t), 45.3 (t), 35.5 (t), 34.3 (t), 14.3 (q), 14.2 (q), 14.13 (q) (mixture of diastereomers).

Mass (m/z): 228 (5), 174 (50), 142 (90), 102 (100), 91 (50), 70 (20).

Analysis:	**C**	**H**	**N**
Expected:	65.24	6.39	4.23
Observed:	65.13	6.22	4.28

2-(Benzyloxycarbonyl)-3-(2-propenyl)-1,3-dihydro-2*H*-pyrrolo[3,4*b*]quinoline (42):



To 3.5 g (10 mmol) of β-keto ester **43** was added 25 mL of 10% HCl and the mixture was stirred under reflux for 4 h. The reaction mixture was cooled and extracted twice with 25 mL portions of DCM. The combined organic phases were dried over

anhydrous sodium sulphate, filterd and concentrated under reduced pressure to furnish crude pyrrolidinone **47** (2.7 g). To the crude pyrrolidinone **47** in dry toluene (20 mL) was added 2.22 g (10.57 mmol) of *N*-(o-aminobenzilidine)-*p*-toluidine **48** and the mixture refluxed for 0.5 h with azeotropic removal of water. At the end of half an hour, 0.201 g of *p*TSA was added and the mixture refluxed further for 3 h. The reaction was quenched with 10% sodium bicarbonate and the organic phase was separated and the aqueous phase was further extracted with 2 x 25 mL portions of ethyl acetate. The combined organic phase was dried over anhydrous sodium sulphate, filterd and concentrated on rotary evaporator to furnish crude quinoline **42**. Purification by column chromatography over silica gel using ethyl acetate-pet-ether (1:3) as eluent furnished quinoline **42**, 3.27 g (70% yield) as a white solid.

Mol. Formula: $C_{22}H_{20}N_2O_2$, white solid.

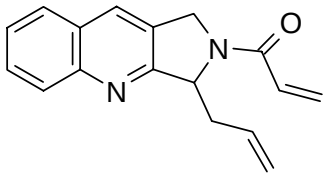
Yield: 70 %.

mp: 105-107 ºC

IR (KBr) cm^{-1}: 1690, 1420, 1220, 1130.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.8-3.3 (m, 2H), 4.7-5.1 (m, 4H), 5.3 (s, 2H), 5.3-5.6 (m, 1H), 7.3 -7.6 (m, 6H), 7.6 (m, 1H), 7.71 (t, *J*=7.04 Hz, 1H), 7.81 (d, *J*=7.82 Hz, 1H), 7.96 (d, *J*=11.35 Hz, 1H), 8.13 (m, 1H).

1-(3-Allyl-1, 3-dihydro-pyrrolo[3, 4-*b*]quinolin-2-yl)-propenone (41a):



A solution of the urethane **42** (5 g, 14.53 mmol) in 50 mL ethanol was added rapidly under a stream of nitrogen to a solution of 13 g (46.8 mmol) of KOH in 20 mL ethanol and 4 mL water. The resultant yellow solution was refluxed under nitrogen for 24 h. The dark brown solution was concentrated under reduced pressure, diluted with water and extracted with DCM (3x70 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum provided the crude amine. To the crude amine obtained (3 g, 14.28 mmol) and K_2CO_3 (5 g, 42.8 mmol) in dry DCM (50 mL) under nitrogen atmosphere at 0 ºC was added 1.95 g (5.04 mmol) of acryloyl chloride

(dissolved in 5 mL dry DCM) over a period of 10 min. The reaction mixture was further allowed to stir for 3 h. After quenching the reaction by addition of 20 mL of water dropwise the organic layer was separated. The aq layer was extracted with 3x50 mL of DCM. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was subjected to column chromatography on silica gel (eluting with pet. Ether/EtOAc = 1/1) afforded the title compound **41a** as a white solid (2.79 g, 73% yield).

Mol. Formula: $C_{17}H_{16}N_2O$, white solid.

Yield: 73%.

mp: 77-79 ºC

IR ($CHCl_3$) cm^{-1}: 3014, 1649, 1613.

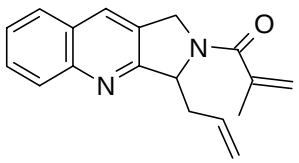
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.74-3.18 (m, 2H), 4.53-4.91(m, 4H), 5.19-5.40 (m, 2H), 5.65-5.74 (m, 1H), 6.40-6.60 (m, 2H), 7.40 (m, 1H), 7.62-7.78 (m, 2H), 7.91-7.95 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 164.6 (s), 164.4 (s), 161.6 (s), 161.5 (s), 148.4 (s), 148.0 (s), 132.4(d), 130.9 (d), 129.8 (d), 129.5 (d), 129.1 (d), 128.9 (d), 128.6 (t) 128.2 (s), 128.0 (s), 127.9 (d), 127.8 (d), 127.7 (d), 127.5 (s), 127.2 (s), 126.8 (s), 126.6 (d), 126.4 (d), 120.0 (t), 119.0 (t), 62.9 (d), 62.3 (d), 50.7 (t), 50.1 (t), 40.4 (t), 36.6 (t), (Mixture of rotamers).

Mass (ESI) (m/z): 265 $(M+1)^+$.

Analysis:	**C**	**H**	**N**
Expected:	77.25	6.10	10.60
Observed:	76.95	6.04	11.00

1-(3-Allyl-1,3-dihydro-pyrrolo[3,4-*b*]quinolin-2-yl)-propenone (41b):



The title compound **41b** (1.7 g) was prepared from **42** (3 g) as per the procedure outlined for the preparation of compound **41a**.

Mol. Formula: $C_{18}H_{18}N_2O$, white solid.

Yield: 70%.

mp: 110-112 ºC

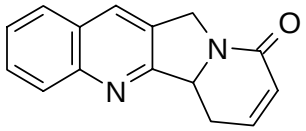
IR ($CHCl_3$) cm^{-1}: 1649, 1619, 1453, 1435, 1410

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.06 (s, 3H), 2.88-3.16 (m, 2H), 4.73-5.01 (m, 4H), 5.30-5.62 (m, 4H), 7.55 (m, 1H), 7.69-7.33 (m, 1H), 7.82 (m, 1H), 7.95-8.14 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4) δ: 170.9 (s), 161.7 (s), 148.3 (s), 141.1 (s), 132.7 (d), 131.2 (d), 129.6 (d), 129.3 (d), 129.2 (d), 129.0 (d), 128.5 (s), 127.7 (d), 127.3 (s), 126.4 (d), 119.7 (t), 118.8 (t), 116.7 (t), 116.3 (t), 63.7 (d), 62.0 (d), 52.5 (t), 50.1 (t), 39.8 (t), 37.1 (t), 20.4 (q), 19.8 (q). (mixture of rotamers)

Mass (ESI) (m/z): 277 $(M-1)^+$

5b,11-Dihydro-6*H*-indolizino[1,2-*b*]-9-one (40):



The appropriate unsaturated amide **41a** (0.400 g, 1.5 mmol) and $Ti(OiPr)_4$ (0.86 g, 3 mmol) were dissolved in dry DCM (20 mL) and heated at reflux for 1 h. Grubbs catalyst **8** (10 mol%, 0.125 g) was added and the mixture was stirred at reflux for 24-36 h (monitored by TLC). After removal of all the volatiles under reduced pressure the residue was chromatographed on silica gel (pet-ether:ethyl acetate, 1:6) to furnish the desired α, β – unsaturated lactam **40** in 89% yield (0.32 g) as a white solid.

Mol. Formula: $C_{15}H_{12}N_2O$, white solid.

Yield: 90%.

mp: 189-191 ºC.

IR ($CHCl_3$) cm^{-1}: 3014, 1659, 1598, 1452.

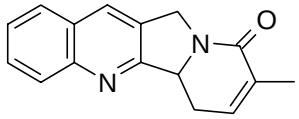
^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.45-2.59 (m, 1H), 3.09-3.24 (m, 1H), 4.78 (m, 1H), 5.09-5.21 (m, 2H), 6.07-6.12 (m, 1H), 6.69-6.77 (m, 1H), 7.67 (m, 1H), 7.72 (m, 1H), 7.82 (m, 1H), 8.06 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 163.0 (s), 161.6 (s), 148.2 (s), 138.8 (d), 130.6 (d), 129.7 (d), 129.0 (d), 128.7 (s), 128.0 (d), 127.7 (s), 126.9 (d), 126.1 (d), 60.3 (d), 47.9 (t), 28.7 (t).

Mass (ESI) (m/z): 235 $(M-1)^+$.

HRMS (m/z): calculated $(M+H)^+$- 237.1028; found - 237.1023.

8-Methyl-5*b*,11-dihydro-6*H*-indolizino[1,2-*b*]quinolin-9-one (49):



0.100 g (0.36 mmol) of **41b** was dissolved in toluene and degassed thoroughly. To the reaction mixture at 80 ºC was added 15 mg (5 mol%) of the catalyst **12** under nitrogen atmosphere. The reaction mixture was further stirred at the same temperature for 3 h. Toluene was removed under reduced pressure. The residue obtained was subjected to column chromatography on silica gel (200-300 mesh size) eluting with (ethylacetate:pet-ether = 8:2) to afford the title compound **49** as white solid in 0.082g (92%)

Mol. Formula: $C_{16}H_{14}N_2O$, white solid.

Yield: 92%.

mp: 165-167 ºC.

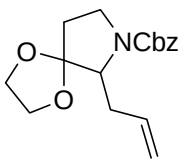
IR ($CHCl_3$) cm^{-1}: 1662, 1620, 1410.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4) δ: 2.02 (s, 3H), 2.48-2.55 (m, 1H), 3.07-3.11 (td, *J*= 5.96 Hz and 17.09 Hz, 1H), 4.81(d, *J*=17.09 Hz, 1H), 5.15-5.19 (m, 2H), 6.47 (m, 1H), 7.57 (m, 1H), 7.73 (m, 1H), 7.84 (d, *J*=7.95 Hz, 1H), 8.09 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 164.4 (s), 162.2 (s), 148.6 (s), 133.4 (s), 132.6 (d), 130.5 (d), 129.7 (d), 129.5 (s), 129.4 (d), 128.1 (s), 128.0 (d), 126.9 (d), 60.9 (d), 48.3 (t), 29. (t), 17.0 (q).

Mass (ESI) (m/z): 249.50 $(M-0.5)^+$

6-Allyl-1, 4-dioxa-7-aza-spiro[4.4]nonane-7-carboxylic acid benyl ester (50):



Pyrolidinone **47** (3 g, 11.58 mmol), ethylene glycol (1.08 g, 17.37 mmol) and catalytic amount of PTSA (100 mg) in benzene was refluxed azeotropically for 8 h. The reaction mixture was cooled to rt and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution. The aquoues layer was further extracted with ethyl acetate solution (2x30 mL). The combined organic layer was dried over anhydrous sodium sulpahte, filtered and concentrated under reduced pressure. The residue obtained was column chromatographed using pet-ether:ethyl acetate (9:1) to provide 2.98 g (85%) of the title compound as thick oil.

Mol. Formula: $C_{17}H_{21}NO_4$, thick oil.

Yield: 85%.

IR ($CHCl_3$) cm^{-1}: 2894, 1692, 1416.

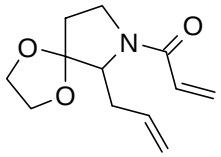
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.94-2.25 (m, 4H), 3.44-3.52 (m, 2H), 3.72 (m, 1H), 3.94 (m, 4H), 5.13 (m, 4H), 5.83 (m, 1H), 7.35 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 155.0 (s), 134.9 (d), 128.2 (d), 127.7 (d), 127.0 (d), 126.7 (d), 117.0 (t), 114.4 (s), 66.6 (t), 65.2 (t), 64.6 (t), 63.8 (t), 62.3 (d), 43.2 (t), 35.9 (t), 35.3 (t), 33.8 (t). (mixture of rotamers).

Mass (ESI) (m/z): 304 $(M+1)^+$

Analysis:	**C**	**H**	**N**
Expected:	63.88	8.93	8.28
Observed:	63.49	8.60	8.21

1-(6-Allyl-1, 4-dioxa-7-aza-spiro[4.4]non-7-yl)-propenone (52a):



A solution of the urethane **50** (2 g, 6.6 mmol) in 50 mL ethanol was added rapidly under a stream of nitrogen to a solution of 5.2 g (92 mmol) of KOH in 20 mL ethanol and 4 mL water. The resultant yellow solution was refluxed under nitrogen for 43 h. The dark brown solution was concentrated under reduced pressure, diluted with water and

extracted with DCM (3x70 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum provided the crude amine.

To the crude amine obtained (0.947 g, 5.6mmol) and K_2CO_3 (2.31 g, 16.8 mmol) in dry DCM (50 mL) under nitrogen atmosphere at 0 ºC was added 0.76 g (8.4 mmol) of acryloyl chloride (dissolved in 5 mL dry DCM) over a period of 10 min. The reaction mixture was further allowed to stir for 3 h. After quenching the reaction by addition of 5 mL of water dropwise, the organic layer was separated. The aq layer was extracted with 3x50 mL of DCM. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was subjected to column chromatography on silica gel (eluting with pet. Ether/EtOAc = 1/1) afforded the title compound **52a** as a thick oil (1.03 g, 70% yield).

Mol. Formula: $C_{12}H_{17}NO_3$, thick oil.

Yield: 70%.

IR ($CHCl_3$) cm^{-1}: 2890, 1649, 1611, 1429.

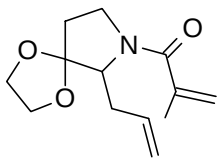
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.50-2.53 (m, 4H), 3.58-4.06 (m, 7H), 5.01-5.15 (m, 2H), 5.85-5.86 (m, 2H), 6.37-6.44 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 164.4 (s), 134.4 (d), 133.4 (d), 128.2 (d), 127.5 (d), 127.4 (t), 127.2 (t), 118.0 (t), 116.9 (t), 114.5 (s), 113.1 (s), 65.1 (t), 65.0 (t), 63.8 (t), 63.5 (t), 62.2 (d), 61.2 (d), 43.4 (t), 42.1 (t), 36.8 (t), 34.0 (t), 32.9 (t), 31.1 (t). (mixture of rotamers).

Mass (ESI) (m/z): 223 $(M)^+$

Analysis:	**C**	**H**	**N**
Expected:	64.55	7.67	6.27
Observed:	64.59	7.79	6.10

1-(6-Allyl-1,4-dioxa-7-aza-spiro[4.4]non-7-yl)-2-methyl-propenone (52b):



The title compound **52b** (1.71 g) was prepared from carbamate **50** (3 g) as per the procedure outlined for the preparation of compound **41b**.

Mol. Formula: $C_{13}H_{19}NO_3$, thick oil.

Yield: 73%.

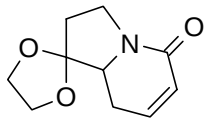
IR ($CHCl_3$) cm^{-1}: 2979, 2893, 1647, 1620, 1428.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.85, 1.90 (s, 3H), 2.03-2.47 (m, 4H), 3.58-4.06 (m, 7H), 5.00-5.26 (m, 4H), 5.69 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 171.0 (s), 141.1 (s), 140.2 (s), 134.5 (d), 131.9 (d), 119.4 (t), 116.9 (t), 115.7 (t), 114.0 (s), 65.2 (t), 63.9 (t), 60.9 (d), 60.8 (d), 45.5 (t), 36.7 (t), 33.8 (t), 19.7 (q). (mixture of rotamers)

Mass (ESI) (m/z): 236 $(M-1)^+$

1,1-Ethylenedioxy-2,3,8,8a-tetrahydro-1*H*-indolizin-5-one (53a):



The Grubbs Ist generation catalyst **8** (36 mg, 10 mol%) was added to a degassed homogeneous solution of diene **52a** (0.100 g, 0.448 mmol) in 10 mL of dry DCM under argon. The resulting mixture was stirred at reflux for 20 h. The reaction mixture was concentrated, and purified by column chromatography using pet-ether:ethyl acetate (3:7) to provide 94% (80 mg) of the lactam **53a**.

Mol. Formula: $C_{10}H_{13}NO_3$, thick oil.

Yield: 94%.

IR ($CHCl_3$) cm^{-1}: 2997, 1658, 1599

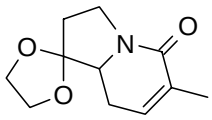
^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.07-2.44 (m, 4H), 3.46-3.68 (m, 2H), 3.76-3.86 (dd, *J*=5.47 and 13.88 Hz, 1H), 3.98 (m, 4H), 5.89-5.95 (dd, *J*=2.93 and 9.77 Hz), 6.5-6.55 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 161.9 (s), 137.9 (d), 123.9 (d), 112.6 (s), 64.4 (t, 2C), 59.0 (d), 40.5 (t), 32.2 (t), 22.4 (t),

Mass (ESI) (m/z): 196 $(M+1)^+$

Analysis:	**C**	**H**	**N**
Expected:	61.53	6.71	7.17
Observed:	61.22	6.98	7.35

1,1-Ethylenedioxy-6-methyl-2,3,8,8a-tetrahydro-1*H*-indolizin-5-one (53b):



The Grubbs IInd generation cat **12** (10 mg, 2.5 mol%) was added to a degassed homogeneous solution of diene **52b** (100 mg, 0.422 mmol) in 5 mL of dry toluene under argon. The resulting mixture was stirred at 80 ºC for 12 h. The reaction mixture was concentrated, and purified by column chromatography using pet-ether:ethyl acetate (3:7) to provide 86% (82 mg) of the lactam **53b**.

Mol. Formula: $C_{11}H_{15}NO_3$, thick oil.

Yield: 86%.

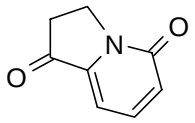
IR ($CHCl_3$) cm^{-1}: 2993, 1664, 1619, 1457, 1442.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.85 (s, 3H), 2.01-2.40 (m, 4H), 3.44-3.65 (m, 3H), 3.80-3.94 (m, 4H), 6.24 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 164.3 (s), 132.2 (d), 114.1 (s), 66.4 (t, 2C), 60.7 (d), 41.9 (t), 33.9 (t), 23.5 (t), 16.7 (q).

Mass (ESI) (m/z): 208 $(M-1)^+$

2,3-Dihydro-indolizine-1,5-dione (55):



To the lactam **53a** (0.07 g, 0.36 mmol) dissolved in 3 mL acetone was added 10% HCl solution 2 mL and refluxed for 6 h. After removing the acetone under reduced pressure, the residue was diluted with DCM. The organic layer was washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulpahte, filtered and concentrated under reduced pressure. The residue obtained was column chromatographed using pet-ether:ethyl acetate (1:4) to provide 0.02 g (38%) of the title compound as thick oil.

Mol. Formula: $C_8H_7NO_2$, thick oil.

Yield: 38%.

IR ($CHCl_3$) cm^{-1}: 3019, 1744,1655, 1599

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.93 (t, *J*=6.00 Hz, 2H), 4.33 (t, *J*=6.00 Hz, 2H), 6.84-6.89 (m, 2H), 7.58 (m, 1H).

Mass (ESI) (m/z): 148.53 $(M-0.5)^+$

[1,3]Dithiane (61):

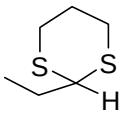
A 20mL solution of 24.76 mmol of dibromopropane (5 g) and 37 mmol of CS_2 (2.82 g) in dry THF (10 mL) was added at room temperature to slurry of 20 mmol of sodium borohydride (1.03 g) in 10 mL of THF, and the resulting solution was refluxed overnight. The reaction mixture was then worked-up with aqueous ammonium chloride (30 mL), extracted with ether, and dried over anhydrous anhydrous sodium sulfate. The solvent was removed and the product **61** was obtained after recrystallization from methanol (1.78 g, 60% yield).

Mol. Formula: $C_4H_8S_2$, white solid.

Yield: 60%.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.08 (m, 2H), 2.82 (m, 4H), 3.77 (s, 2H).

2-Ethyl-[1,3]dithiane (64):



To a solution of propianaldehyde (1 g, 17.2 mmol) and 1,3-propanedithiol (2.04 g, 18.9 mmol) at 0 ºC in $CHCl_3$ (10 mL) was added iodine (0.437 g, 1.72 mmol) and the resulting mixture was stirred at room temperature for 1 h. After completion of the reaction the reaction was quenched with aqueous solutions of NaS_2O_3 (0.1 M, 10 mL) and NaOH (10%, 10 mL), respectively. Then $CHCl_3$ (15 mL) was added to the resulting reaction mixture. The organic layer was separated and washed with H_2O and decanted. The organic layer was dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent under reduced pressure followed by SiO_2 column chromatography (pet-ether/EtOAc, 33/1) gave the product **64** as colorless oil (2.446 g, 96% yield).

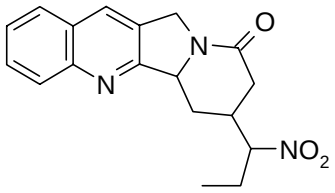
Mol. Formula: $C_6H_{12}S_2$, colorless oil.

Yield: 96%.

bp: 89 ºC/10 mmHg,

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.06 (t, *J*=7.00 Hz, 3H), 1.77-2.14 (m, 4H), 2.81 (m, 4H), 3.96 (t, *J*=8.00 Hz, 1H).

7-(1-Nitro-propyl)-5*b*,7,8,11-tetrahydro-6*H*-indolizino[1,2-*b*]quinolin-9-one (67):



To 0.400 g (1.6 mmol) of dihydropyridone **40** in 5 mL nitropropane was added DBU (0.23 g, 1.5 mmol) under nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 12 h. Excess nitropropane was removed under reduced pressure. The residue obtained was taken up in DCM (50 mL) and washed with 5% HCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was suspended in diethyl ether and filtered in order to produce after drying a pale brown solid (0.49 g). Recrystalization using DCM and pet ether (1:2 respectively) afforded 0.473 g (86%) of the title compound **67** as a white solid.

Mol. Formula: $C_{18}H_{19}N_3O_3$, white solid.

Yield: 86%.

mp: 149-151 ºC

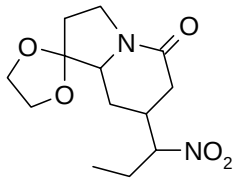
IR ($CHCl_3$) cm^{-1}: 1660, 1659, 1598, 1260.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.01 (t, *J*=7.5 Hz, 3H), 1.52-2.48 (m, 5H), 2.73 (m, 2H), 4.33 (m, 1H), 4.67 (m, 1H), 4.86-4.99 (m, 1H), 5.25-5.33 (m, 1H), 7.73-7.84 (m, 2H), 8.08 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 167.0 (s), 166.8 (s), 160.7 (s), 147.7 (s), 147.4 (s), 130.7 (d), 130.4 (d), 129.9 (d), 129.8 (d), 128.7 (d), 128.4 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.7 (s), 127.0 (d), 126.9 (d), 93.8 (d), 93.9 (d), 61.4 (d), 48.4 (t), 36.5 (d), 36.5 (d), 33.9 (t), 33.7 (t), 30.2 (t), 30.0 (t), 24.3 (t), 24.1 (t), 10.2 (q). (mixture of diastereomers).

HRMS (m/z): Calcd for $(M+H)^+$- 326.1505; found - 326.1520.

1,1-Ethylenedioxy-7-(1-nitro-propyl)-hexahydro-indolizin-5-one (68):



The title compound **68** (2.00 g) was prepared from **53a** (1.5 g) as per the procedure outlined for the preparation of compound **67**.

Mol. Formula: $C_{13}H_{20}N_2O_5$, grey solid.

mp: 93-95 ºC

Yield: 92%.

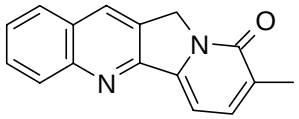
IR ($CHCl_3$) cm^{-1}: 2941, 1670, 1632, 1553, 1216.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.90 (t, *J*=7.33 Hz 3H), 1.59-2.04 (m, 6H), 2.13-2.25 (m, 1H), 2.38-2.62 (m, 2H), 3.36-3.80 (m, 3H), 3.94-4.04 (m, 4H), 4.37 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 167.4 (s), 113.2 (s), 92.6 (d), 92.3 (d), 65.1 (t), 64.9 (t), 57.9 (d), 41.6 (t), 34.3 (t), 34.0 (t), 33.5 (q), 32.7 (q), 24.6 (d), 24.1 (s), 23.5 (d), 23.0 (d), 9.7 (s). (mixture of diastereomers)

Mass (ESI) (m/z): 285 $(M+1)^+$

8-Methyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (70):



A mixture of dihydropyridone **40** (75 mg, 0.3 mmol), DBU (41mg, 0.27 mmol) and nitropropane (2 mL) was was exposed to microwave settings (BPL-SANYO, kitchen microwave) for 3 min. After the completion of the reaction, excess nitropropane was removed under reduced pressure. The residue obtained was taken up in DCM (50 mL) and washed with 5% HCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was suspended in diethyl ether and filtered in order to produce after drying a pale brown solid. Recrystalization using DCM and pet ether (1:2 respectively) afforded 40 mg (55% yield) of the title compound **70** as a white solid.

Mol. Formula: $C_{16}H_{12}N_2O$, white solid.

Yield: 55%.

mp: 235-237 ºC,

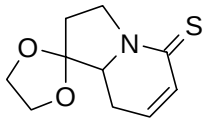
IR ($CHCl_3$) cm^{-1}: 1666, 1597.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 5.29 (s, 2H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.63 (m, 2H), 7.83 (m, 2H), 8.20 (d, *J* = 8.3 Hz, 1H), 8.34 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.0 (s), 153.6 (s), 149.0 (s), 143.8 (s), 137.8 (d), 131.0 (d), 130.6 (s), 130.4 (d), 129.7 (d), 128.3 (d), 128.1 (s), 127.6 (d), 101.0 (d), 50.1 (t), 17.2 (q).

Mass (ESI) (m/z): 249 $(M+1)^+$.

1,1-Ethylenedioxy-2,3,8,8a-tetrahydro-1*H*-indolizine-5-thione (72):



A solution of pyridone **53a** (0.100 g, 51.28 mmol) in dry THF (5 mL) was added to a solution of Lawesson's reagent (0.103 g, 25.6 mmol) at 0 ºC in dry THF (3 mL). The mixture was stirred for 10 min. After evaporation of the solvent under reduced pressure the crude reaction mixture with out routine work up was purified by column chromatography on silica gel (pet-ether:ethyl acetate, 4:1) to give **72** as a yellow solid in 37% yield (40 mg).

Mol. Formula: $C_{10}H_{13}NO_2S$, yellow solid.

mp: 125-127 ºC

Yield: 37%.

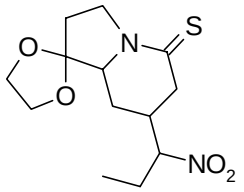
IR ($CHCl_3$) cm^{-1}: 3019, 2964, 1619, 1484, 1461, 1385, 1215

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.09-2.43 (m, 4H), 3.68-3.77 (m, 2H), 3.99 (m, 5H), 6.22-6.36 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 187.5 (s), 132.2 (d), 129.6 (d), 113.7 (s), 65.6 (t, 2C), 61.6 (d), 48.4 (t), 33.2 (t), 22.7(t)

Mass (ESI) (m/z): 210 $(M-1)^+$

1,1-Ethylenedioxy-7-(1-nitro-propyl)-hexahydro-indolizine-5-thione (73):



The title compound **73** (100 mg) was prepared from **72** (100 mg) as per the procedure outlined for the preparation of compound **67**.

Mol. Formula: $C_{13}H_{20}N_2O_4S$, yellow solid.

Yield: 75%.

mp: 105-108 ºC

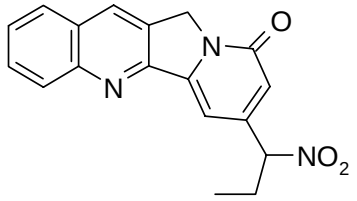
IR ($CHCl_3$) cm^{-1}: 2962, 1633, 1550, 1494, 1548.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.98 (t, *J*=7.3 Hz, 3H), 1.63-1.73 (m, 1H), 1.8-1.95 (m, 3H), 2.02-2.10 (m, 2H), 2.49-2.61 (m, 2H), 3.04-3.15 (dd, *J*=4.9 and 16.1 Hz, 1H), 3.64-3.69 (m, 1H), 3.79-4.00 (m, 6H), 4.27-4.34 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 196.1 (s), 195.4 (s), 113.6 (s), 113.4 (s), 92.7 (d), 92.8 (d), 65.7 (t, 2C), 61.6 (d), 61.5 (d), 49.3 (t), 49.2 (t), 43.5 (t), 43.4 (t), 34.3 (d), 33.1 (t), 25.2 (t), 23.9 (t), 10.5 (q), 10.4 (q). (mixture of diastereomers).

Mass (ESI) (m/z): 300 $(M)^+$.

7-(1-Nitro-propyl)-11*H*-indolizino[1,2-*b*]quinolin-9-one (76):



To 0.205 g (0.63 mmol) of tetrahydropyridone **67** in 5 mL of dry 1, 4, dioxan was added (0.315 g, 1.3 mmol) of DDQ and the resulting mixture was refluxed under nitrogen for 5 h. The reaction mixture was concentrated under reduced pressure and diluted with DCM (50 mL). The organic layer was washed with 10% $NaHCO_3$ (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was subjected to column chromatography on silica gel (230-400 mesh size), eluting with EtOAc/MeOH = 49:1 afforded the title compound **76** as a white solid (50 mg, 25% yield).

Mol. Formula: $C_{18}H_{15}N_3O_3$, white solid.

Yield: 25%.

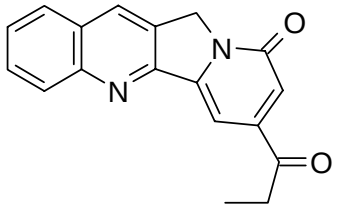
mp: decomposed at 263-265 ºC

IR ($CHCl_3$) cm^{-1}: 2928, 1666, 1618, 1556.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (t, *J*=7.4 Hz, 3H), 2.18-2.24 (m, 1H), 2.53-2.59 (m, 1H), 5.25 (s, 2H), 5.35 (t, *J*=7.4 Hz, 1H), 6.76 (s, 1H), 7.39 (s, 1H), 7.67 (t, *J*=7.3 Hz, 1H), 7.83 (t, *J*=7.3 Hz, 1H), 7.92 (d, *J*=7.7 Hz, 1H), 8.21 (d, *J*=8.7 Hz, 1H), 8.38 (s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.0 (s), 152.5 (s), 147.5 (s), 147.3 (s), 131.3 (d), 130.8 (d), 129.9 (d), 128.8 (s), 128.4 (s), 128.39 (d), 128.30 (d), 120.0 (d), 99.0 (d), 91.9 (d), 50.2 (t), 27.0 (t), 10.7 (q).

HRMS (m/z): Calcd for $(M+H)^+$- 322.1192; found - 322.1176.

7-Propionyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (77):



To 0.400 g (1.2 mmol) of tetrahydropyridone **67** in 5 mL of MeOH was added methanolic NaOH (98 mg, 2.4 mmol of NaOH dissolved in 10 mL MeOH) at 0 ºC and stirred at room temperature for 3 h. The resulting mixture was cooled to 0 ºC and rendered acidic with con.HCl and stirred at the same temperature for 1 h and continued to stir at rt overnight. Methanol was removed under reduced pressure. The resulting suspension was made basic with saturated solution of $NaHCO_3$ and extracted with DCM (3x25 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was subjected to column chromatography on silica gel (230-400 mesh size), eluting with DCM:MeOH=9:1 afforded the title compound **77** as a white solid (82 mg, 23% yield).

Mol. Formula: $C_{18}H_{14}N_2O_2$, white solid.

Yield: 23%.

mp: decomposed at 231-233 ºC

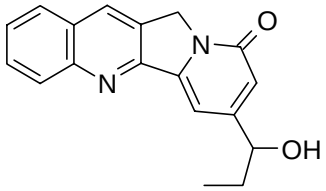
IR ($CHCl_3$) cm^{-1}: 3002, 1702, 1666, 1618, 1556.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.26 (t, *J*=7.04 Hz, 3H), 3.03 (q, *J*=7.04, 2H), 5.30 (s, 2H), 7.21 (s, 1H), 7.65 (m, 1H), 7.74-7.95 (m, 3H), 8.24 (d, *J*=8.22 Hz, 1H), 8.41 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) δ: 199.8 (s), 161.9 (s), 152.8 (s), 149.1 (s), 147.5 (s), 147.0 (s), 131.3 (d), 130.8 (d), 130.0 (d), 128.8 (s), 128.3 (d), 128.2 (d), 120.3 (d), 98.4 (d), 50.3 (t), 32.7 (t), 8.1 (q).

HRMS (m/z): Calcd for $(M+H)^+$- 291.1134; found – 291.1137.

7-(1-Hydroxy-propyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (78):



To the ketone **77** (0.100, 0.3 mmol) dissolved in methanol (5 mL) maintained at 0 ºC was added $NaBH_4$ (13 mg, 0.3 mmol) and stirred at same temperature for 1 h. Methanol was removed under reduced pressure. The resulting suspension was quenched with saturated ammonium chloride solution (5 mL). The aqueous layer was saturated with NaCl and extracted with 3x25 mL of DCM. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was subjected to column chromatography on silica gel (230-400 mesh size), eluting with DCM:MeOH =19:1 afforded the title compound **78** without purification as a white solid (99 mg, 99% yield).

Mol. Formula: $C_{18}H_{16}N_2O_2$, white solid.

Yield: 99%.

mp: 243-245 ºC

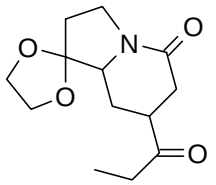
IR ($CHCl_3$) cm^{-1}: 3002, 1702, 1666, 1618, 1556.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86 (t, *J*=7.33 Hz, 3H), 1.69 (m, 1H), 1.77 (m, 1H), 4.97 (ABq, *J*=18.79 Hz, 2H), 4.46 (t, *J*=6.42 Hz, 1H), 6.41 (s, 1H), 7.21 (s, 1H), 7.17 (m, 1H), 7.25 (t, *J*=7.79 Hz, 1H), 7.40 (d, *J*=8.24 Hz, 1H), 7.48 (t, *J*=7.79 Hz, 1H), 7.26 (d, *J*=8.25 Hz, 1H), 7.89 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.8 (s), 159.8 (s), 152.2 (s), 148.4 (s), 145.8 (s), 130.7 (d), 130.2 (d), 129.3 (d), 128.5 (s), 128.0 (d), 127.7 (d), 117.3 (d), 100.0 (d), 74.8 (d), 50.0 (t), 30.5 (t), 10.1 (q).

HRMS (m/z): Calcd for $(M+H)^+$- 293.1290; found – 293.1302.

1,1-Methylenedioxy-7-propionyl-hexahydro-indoilzin-5-one (79):



To 0.100 g (0.352 mmol) of nitro compound in 5 mL of MeOH was added 5 mL of a 0.5 M solution of Na_2HPO_4 in a 1 N solution of NaOH were added. After 1 h, 0.432 g (0.704 mmol) of Oxone® in 3 mL of water was added to stirred suspension. The resulting mixture was stirred at room temperature overnight. Methanol was removed under reduced pressure. The resulting suspension was acidified with a 10% solution of HCl and extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was subjected to column chromatography on silica gel (eluting with pet. Ether:EtOAc=1:9) afforded the title compound as colorless oil (70 mg, 79% yield).

Mol. Formula: $C_{13}H_{19}NO_4$, thick oil.

Yield: 79%.

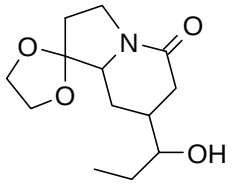
IR ($CHCl_3$) cm^{-1}: 2994, 1714, 1633, 1632, 1461.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4) δ: 1.04 (t, *J*=7.15 Hz 3H), 1.81-2.03 (m, 4H), 2.29-2.57 (m, 4 H), 2.82, 3.03 (m, 1H), 3.37-3.62 (m, 3H), 3.93 (m, 4H)

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4) δ: 211.0 (s), 210.0 (s), 167.7 (s), 167.3 (s), 114.0 (s), 113.5 (s), 65.6 (t), 65.4 (t), 65.33 (t), 62.1 (d), 58.9 (d), 45.08 (d), 43.1 (d), 42.4 (t), 42.2 (t), 34.1 (t), 33.9 (t), 33.3 (t), 33.2 (t), 33.0 (t), 32.4 (t), 24.7 (t), 23.8 (t), 8.02 (q), 7.8 (q). (mixture of diastereomers)

Mass (ESI) (m/z): 254 $(M+1)^+$

7-(1-Hydroxy-propyl)-1,1-ethylenedioxy-hexahydro-indolizin-5-one (80):



The title compound **80** (0.686 g) was prepared from compound **79** (0.800 g) as per the procedure outlined for the preparation of compound **78**.

Mol. Formula: $C_{13}H_{21}NO_4$, thick oil.

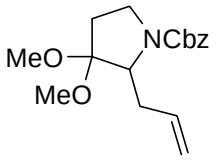
Yield: 85%.

IR ($CHCl_3$) cm^{-1}: 3392, 2997, 1628, 1466.

^1H NMR (500 MHz, $CDCl_3$ + CCl_4) δ: 0.92 (t, *J*=7.15 Hz 3H), 1.2-1.32 (m, 1H), 1.2-1.52 (m, 2H), 1.59-1.99 (m, 4H), 2.06-2.20 (m, 1H), 2.28-2.40 (m, 1H), 3.3-3.7 (m, 4H), 3.93 (m, 4H).

Mass (ESI) (m/z): 256 $(M+1)^+$

2-Allyl-3,3-dimethoxy-pyrrolidine-1-carboxylic acid benzyl ester (83):



Pyrolidinone **47** (1.3 g, 5.02 mmol), trimethylorthoformate (2.66g, 25 mmol) and cat amount of PTSA (100 mg) in methanol were refluxed for 6h. After the completion of reaction (as monitored by TLC) methanol and excess trimethyl orthoformate was removed under reduced pressure. The residue was rendered basic with saturated sodium bicarbonate and extracted with DCM (3x50 mL). The organic layer was thoroughly washed with water, dried over anhydrous sodium sulpahte, filtered and concentrated under reduced pressure. The residue obtained as yellow oil (1.50 g, 99% yield) was sufficiently pure enough for subsequent reaction.

Mol. Formula: $C_{17}H_{23}NO_4$, thick oil.

Yield: 99%.

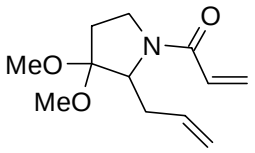
IR ($CHCl_3$) cm^{-1}: 2897, 1690, 1423.

^1H NMR (300 MHz, $CDCl_3$ + CCl_4) δ: 1.84-2.49 (m, 4H), 3.11, 3.15, 3.20, 3.22 (s, 6H), 3.72 (m, 1H), 3.91, 4.02 (t, *J*=5.54 Hz, 1H), 4.86-5.16 (m, 5H), 5.65-5.88 (m, 1H), 7.22-7.29 (m, 5H)

^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ: 154.8 (s), 137.0 (s), 135.0 (d), 128.2 (d), 127.9 (d), 127.8 (d), 127.6 (d), 127.5 (d), 116.9 (t), 108.3 (s), 107.7 (s), 66.6 (t), 66.4 (t), 59.6 (d), 59.5 (d), 50.3 (q), 48.3 (q), 43.1 (t), 35.89 (t), 35.3 (t), 31.4 (t), 30.3 (t). (mixture of rotamers).

Mass (ESI) (m/z): 306 $(M+1)^+$

1-(2-Allyl-3,3-dimethoxy-pyrrolidin-1-yl)-propenone (85):



The title compound **85** (0.590 g) was prepared from compound **83** (2 g) as per the procedure outlined for the preparation of compound **52a** using triethylamine as base.

Mol. Formula: $C_{12}H_{19}NO_3$, colorless thick oil.

Yield: 40%.

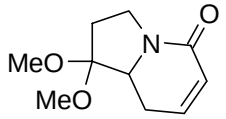
IR ($CHCl_3$) cm^{-1}: 2997, 1646, 1608, 1439.

^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) δ: 1.99-2.62 (m, 4H), 3.19 (s, 3H), 3.29 (s, 3H), 3.48-3.67 (m, 2H), 4.00, 4.43 (t, *J*=5.84 Hz, 1H), 5.00-5.14 (m, 2H), 5.8-5.88 (m, 2H), 6.35-6.49 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.9 (s), 164.7 (s), 134.9 (d), 133.8 (d), 128.4 (d), 127.7 (d), 127.4 (t), 127.2 (t), 118.2 (t), 116.8 (t), 108.4 (s), 107.0 (s), 59.9 (d), 58.7 (d), 50.3 (q), 48.3 (q), 43.7 (t), 42.3 (t), 36.5 (t), 34.5 (t), 31.4 (t), 29.1 (t). (mixture of rotamers)

Mass (ESI) (m/z): 226 $(M+1)^+$

1,1-Dimethoxy-2,3,8,8a-tetrahydro-1*H*-indolizin-5-one (86):



The title compound **86** (2.47 g) was prepared from **85** (3 g) as per the procedure outlined for the preparation of compound **53a**.

Mol. Formula: $C_{10}H_{15}NO_3$, colorless thick oil.

Yield: 94%.

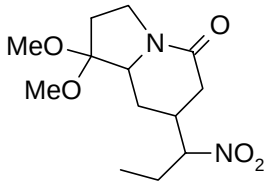
IR ($CHCl_3$) cm^{-1}: 2941, 1658, 1598.

^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) δ: 1.89-1.99 (m, 1H), 2.20-2.37 (m, 2H), 2.57-2.68 (m, 1H), 3.28 (s, 3H), 3.31 (s, 3H), 3.50-3.61 (m, 2H), 3.81-3.88 (dd, *J*=5.13 and 14.17 Hz, 1H), 5.92-5.96 (dd, *J*=2.94 and 9.53 Hz, 1H), 6.52-6.58 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 161.7 (s), 138.1 (d), 124.1 (d), 106.5 (s), 60.8 (d), 49.3 (q), 48.6 (q), 40.5 (t), 30.5 (t), 25.2 (t)

Mass (ESI) (m/z): 198 $(M+1)^+$

1,1-Dimethoxy-7-(1-nitro-propyl)-hexahydro-indolizin-5-one (87):



The title compound **87** (3.7 g) was prepared from **86** as per the procedure outlined for the preparation of compound **67**.

Mol. Formula: $C_{13}H_{22}N_2O_5$, thick oil.

Yield: 85%.

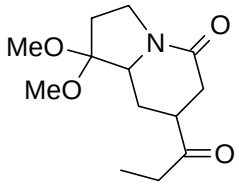
IR ($CHCl_3$) cm^{-1}: 3019, 1678, 1630, 1551, 1216.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4) δ: 0.90 (t, *J*=7.15 Hz 3H), 1.67-1.93 (m, 5H), 2.04-2.27 (m, 2H), 2.40-2.47 (m, 2H), 3.15, 3.18, 3.19 (s, 6H), 3.25 (m, 1H), 3.45-3.65 (m, 2H), 4.36 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$ + CCl_4) δ: 167.4 (s), 166.6 (s), 107.1 (s), 92.6 (d), 92.0 (d), 65.6 (t), 59.5 (d), 59.4 (d), 49.9 (q), 49.1 (q), 41.7 (t), 41.5 (t), 34.9 (d), 34.0 (d), 33.5 (t), 33.2 (t), 30.7 (t), 25.8 (t), 25.7 (t), 24.8 (t), 24.3 (t), 10.0 (q). (mixture of diastereomers)

Mass (ESI) (m/z): 287 $(M+1)^+$

1,1-Dimethoxy-7-propionyl-hexahydro-indoilzin-5-one (88):



The title compound **88** (1.46 g) was prepared from **86** (2.00 g) as per the procedure outlined for the preparation of compound **79**.

Mol. Formula: $C_{13}H_{21}NO_4$, colorless thick oil.

Yield: 82%.

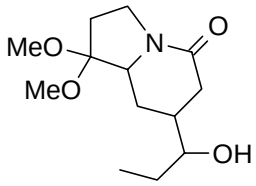
IR ($CHCl_3$) cm^{-1}: 2998, 1723, 1632, 1463.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.00, 1.01 (t, *J*=7.28 Hz, 3H), 1.66-1.83 (m, 2H), 2.04-2.16 (m, 2H), 2.25-2.47 (m, 4H), 2.72-2.99 (m, 1H), 3.19, 3.21, 3.25 (s, 6H), 3.30-3.67 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 211.0 (s), 209.7 (s), 167.8 (s), 167.3 (s), 107.3 (s), 106.7 (s), 63.4 (d), 60.0 (d), 50.0 (q), 49.8 (q), 49.0 (q), 44.5 (d), 42.4 (d), 41.7 (t), 33.5 (d), 32.4 (t), 31.7 (t), 30.4 (t), 26.5 (t), 25.5 (t), 7.5 (q), 7.2 (q). (mixture of diastereomers)

Mass (ESI) (m/z): 256 $(M+1)^+$

7-(1-Hydroxy-propyl)-1,1-dimethoxy-hexahydro-indolizin-5-one (89):



The title compound **89** (0.857 g) was prepared from **88** (1 g) as per the procedure outlined for the preparation of compound **78**.

Mol. Formula: $C_{13}H_{23}NO_4$, colorless thick oil.

Yield: 85%.

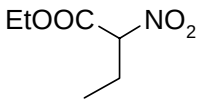
IR ($CHCl_3$) cm^{-1}: 3429, 1622, 1465.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.81 (t, *J*=7.10 Hz, 3H), 1.33-1.5 (m, 2H), 1.55-2.23 (m, 7H), 3.11, 3.16, 3.17, 3.20 (s, 6H), 3.44-3.61 (m, 4H), 4.35 (bs, 1H).

^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ: 170.2 (s), 169.5 (s), 169.1 (s), 107.5 (s), 106.8 (s), 75.1 (d), 74.1 (d), 73.9 (d), 64.2 (d), 60.5 (d), 60.4 (d), 50.1 (q), 49.8 (q), 49.2 (q), 49.1 (q), 41.78 (t), 41.54 (t), 38.1 (d), 38.0 (d), 35.4 (d), 34.7 (t), 34.1 (t), 32.0 (t), 30.6 (t), 30.4 (t), 27.6 (t), 27.5 (t), 26.8 (t), 25.7 (t), 10.1 (q), 10.0 (q), 9.74 (q). (mixture of diastereomers)

Mass (ESI) (m/z): 258 $(M+1)^+$

2-Nitro-butyric acid ethyl ester (93):[30]



Ethyl α-bromobutyrate (7.37 g,37.8 mmol) was poured into a stirred mixture of 25 ml of dry DMSO, 4.4 g of NaNO2 (64.2 mmol) and 5 g of anhydrousphloroglucinol (39 mmol) and stirred at rt for 3 h. Then the reaction mixture was placed in 40 mL of ice water layered over with 300 mL of ether. After seperation of the upper layer, the aqueous phase was extracted with 3x100 mL portions of ether. The combined organic layers dried

over anhydrous sodium sulphate. After filtration, the ether was removed completely. Fractional distillation under reduced pressure (83 ºC/8 mmHg) yielded the title nitro-ester as colorless oil in 60% yield (3.62 g).

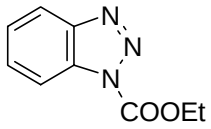
Mol. Formula: $C_6H_{11}NO_4$, colourless oil.

Yield: 60%.

bp: 83 ºC/8 mmHg

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.02 (t, *J*= 8.00 Hz, 3H), 1.28 (t, *J*= 8.00 Hz, 4H), 2.23 (m, 2H), 4.25 (q, *J*= 8.00 Hz, 2H), 4.97 (dd, *J*= 6.00 and 8.00 Hz, 1H).

1-Ethoxy carbonylbenzotriazol (96):



To 1 g (8.4 mmol) of benzotriazole and triethyl amine (1.7 g, 16 mmol) in DCM (10 mL) was added ethyl chloroformate (1.36 g, 12.5 mmol) slowly at 0 ºC. After stirring for 6 h, organic layer was washed with water (3x10 mL). The organic layer was dried over anhydrous sodium sulpahte, filtered and concentrated under reduced pressure to give **96** as a white solid in 93% yield (1.5 g).

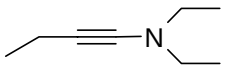
Mol. Formula: $C_9H_9N_3O_2$, white solid.

Yield: 93%.

mp: 71-73 ºC**,** lit[31]-71-73 ºC

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.57 (t, *J*= 7.04 Hz, 3H), 4.67 (q, *J*= 7.05 Hz, 2H), 7.46 (m, 1H), 7.63 (m, 1H), 8.10 (m, 2H).

Diethylaminoethylacetylene (105):



To 10 g of *N*, *N*-diethyl-*n*-butylamide (10 g, 69.9 mmol) in 50 ml of dry toluene at 0 ºC was added 13.7 g (46.16 mmol) of triphosgene dissolved in 200 ml of dry toluene drop wise. After stirring overnight, the reaction mixture was transferred to dropping funnel via cannula under nitrogen atmosphere and allowed to settle. The oil obtained after separating from toluene layer was washed repeatedly with dry toluene and the upper toluene layer was removed carefully under nitrogen atmosphere via cannula. The oil thus

obtained was dried under high vacuum for several hours at 70 ºC to give 8.9 g (64% yield) of **107**.

The compound **107** 8.9 g (44.9 mmol) was added drop wise to a solution of 49 mmol of *N*, *N*-dicyclohexyllithium amide (*N*, *N*-dicyclohexyllithium amide was prepared as follows: dicyclohexyl amine (8.97 g, 49 mmol) was added dropwise to butyl lithium (33.8 mL of 1.6 M) at 0 ºC. After stirring for 30 min hexane was removed under high vacuum to give white powder of N, N-dicyclohexyllithium amide) in 70 ml of ether at 0 ºC and left at room temperature over night. The salts were filtered under nitrogen atmosphere and the ether was removed under reduced pressure. The residue was distilled under reduced pressure to furnish the diethylaminoethylacetylene in 12% yield (0.700 g).

Mol. Formula: $C_8H_{15}N$, colourless oil.

Yield: 12%.

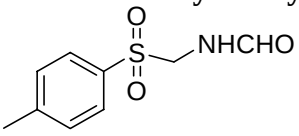
bp: 68-70 ºC/50 mmHg

IR (neat) cm^{-1}: 2232.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.12 (t, *J*= 7.5 Hz, 3H), 1.16 (t, *J*= 7.12 Hz, 6H), 2.24 (q, *J*= 7.4 Hz, 2H), 2.83 (q, *J*= 7.20 Hz, 4H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 84.5 (s), 64.0 (s), 48.9 (t, 2C), 15.7 (q), 13.0 (q, 2C), 12.7 (t).

***N*-(Toluene-4-sulfonylmethyl)-formamide (112):**[37]



A mixture of anhydrous sodium-4-toluene sulfinate **38** (9 g, 50 mmol), formamide (15 mL, 375 mmol), paraformaldehyde (6.0 g, 200 mmol), and formic acid (10 mL, 350 mmol) was heated at 90 ºC for 3 h. The clear solution was stored in refrigerator overnight. The solid was collected, washed with five 10 mL portions of ice-water, then dried under reduced pressure at 60 ºC to give 7 g (79%) of title compound as a white solid.

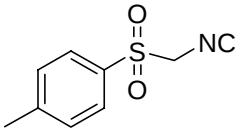
Mol. Formula: $C_9H_{11}NO_3S$, white solid.

Yield: 79%.

mp: 110-120 ºC

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 4.71 (d, *J*= 8.00 Hz, 2H), 7.04 (bs, 1H), 7.36 (d, *J*= 8.00 Hz, 2H), 7.79 (d, *J*= 8.00 Hz, 2H), 8.07 (s, 1H).

Toluene-4-sulfonylmethyl isocyanide (108):[37]



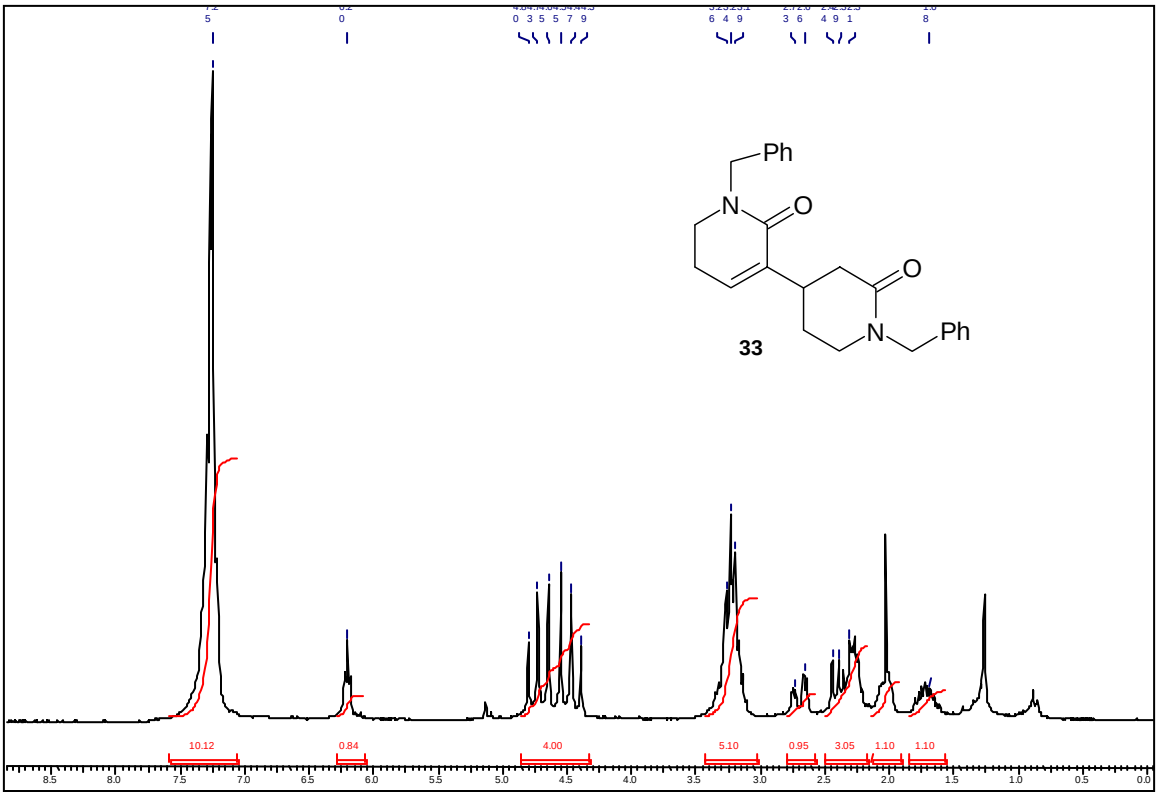
A solution of **112** (8.00 g, 37 mmol) in 10 ml of dry THF was cooled to – 20 ºC under nitrogen. Diisopropylamine (17 mL, 121 mmol) was added all at once, followed by $POCl_3$ (4.3 mL, 45 mmol) over 20 min, keeping the temperature between –10 and –20 ºC. After stirring for 1 h at 0 ºC, the mixture was poured in to a cold solution of K_2CO_3 (10 g, 75 mmol) in 300 mL of H_2O. After 10 min the solid was collected, washed with water (6 x 50 mL) and dried in vacuum. The solid obtained was dissolved in DCM and filtered through a short column of silica. The organic layer was concentrated under reduced pressure to give pure title compound as light brown solid (4.9 g, 68%).

Mol. Formula: $C_9H_9NO_2S$, white solid.

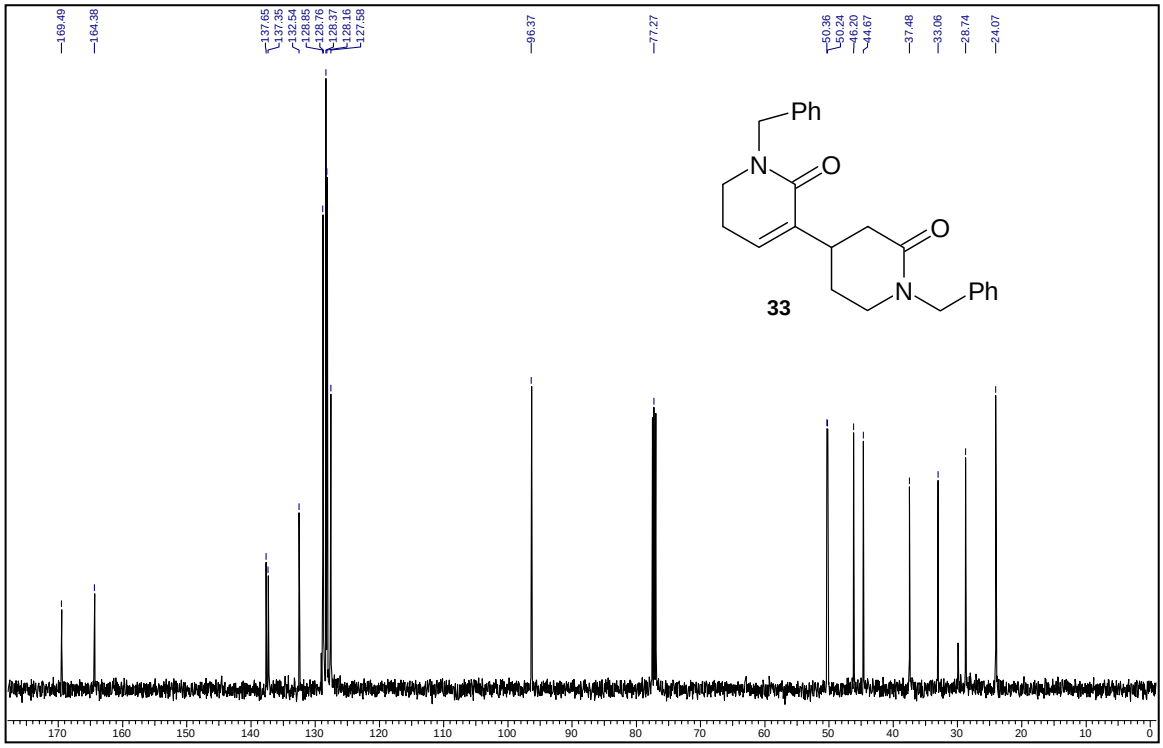
Yield: 68%.

mp: 116-117 ºC

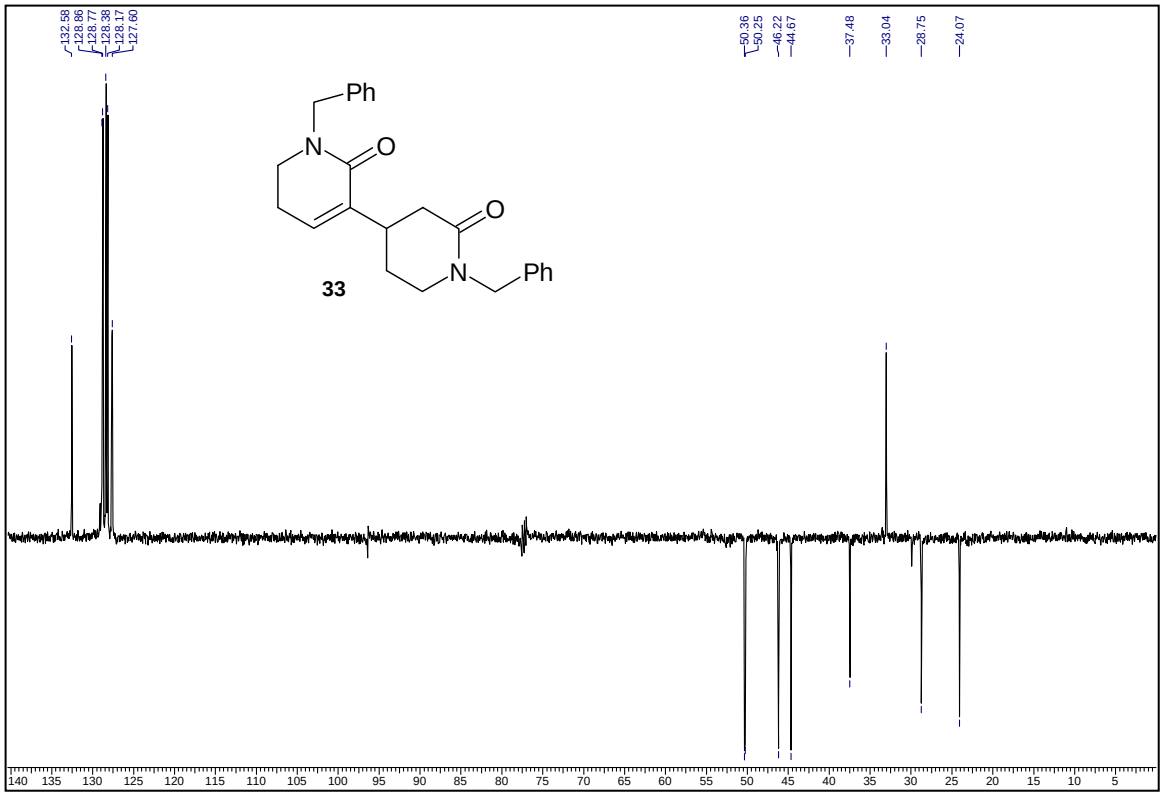
^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.50 (s, 3H), 4.58 (s, 2H), 7.44 (d, *J*= 8.00 Hz, 2H), 7.89 (d, *J*= 8.00 Hz, 2H).



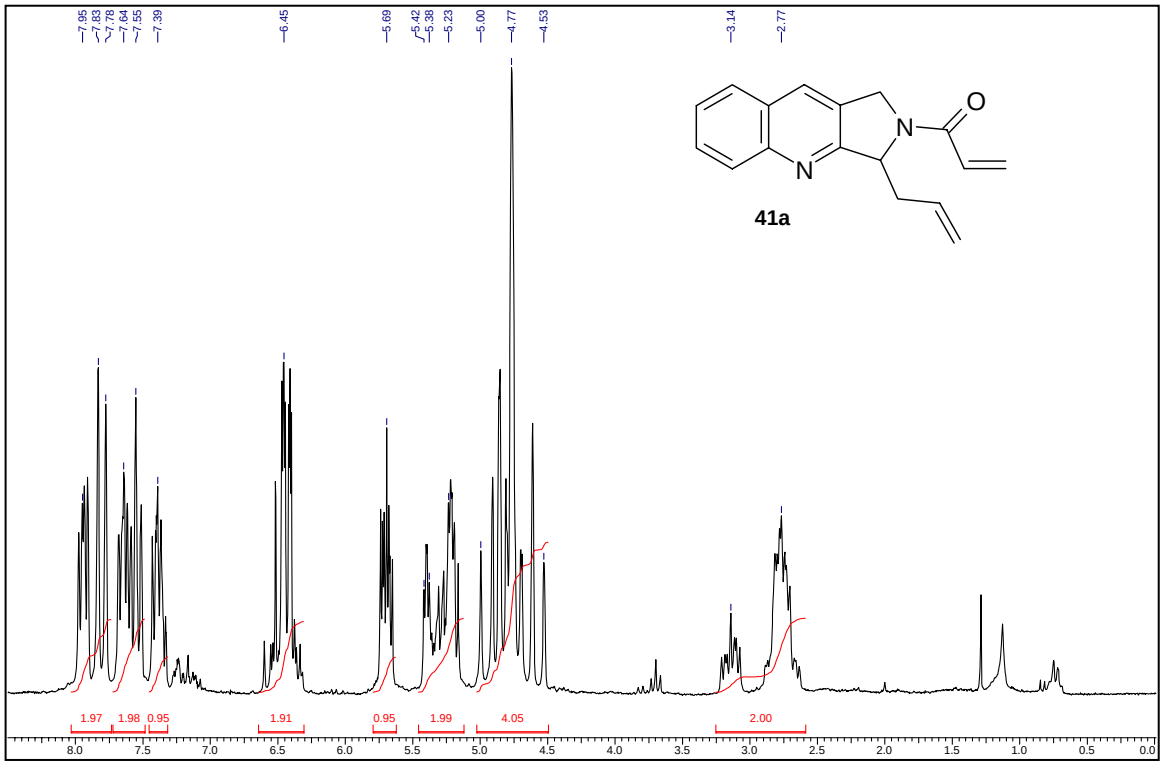
^{1}H-NMR ($CDCl_3$ + CCl_4, 200 MHz)



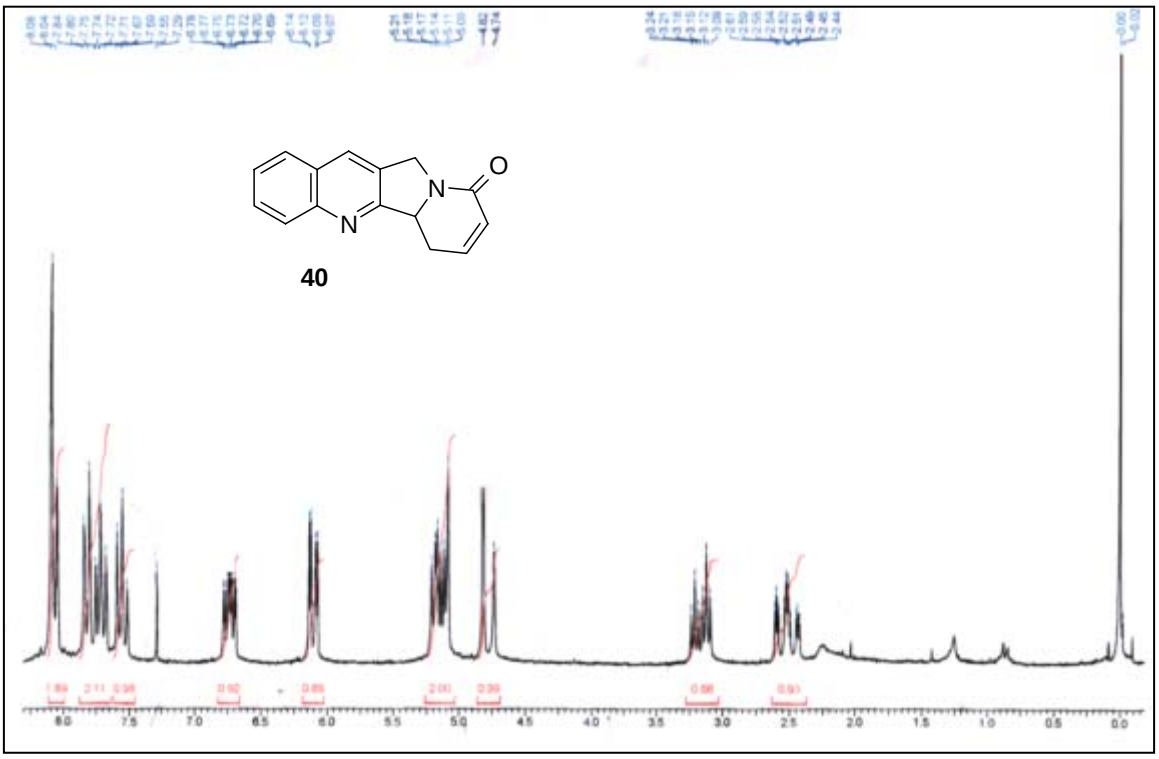
^{13}C-NMR ($CDCl_3$ + CCl_4, 125 MHz)



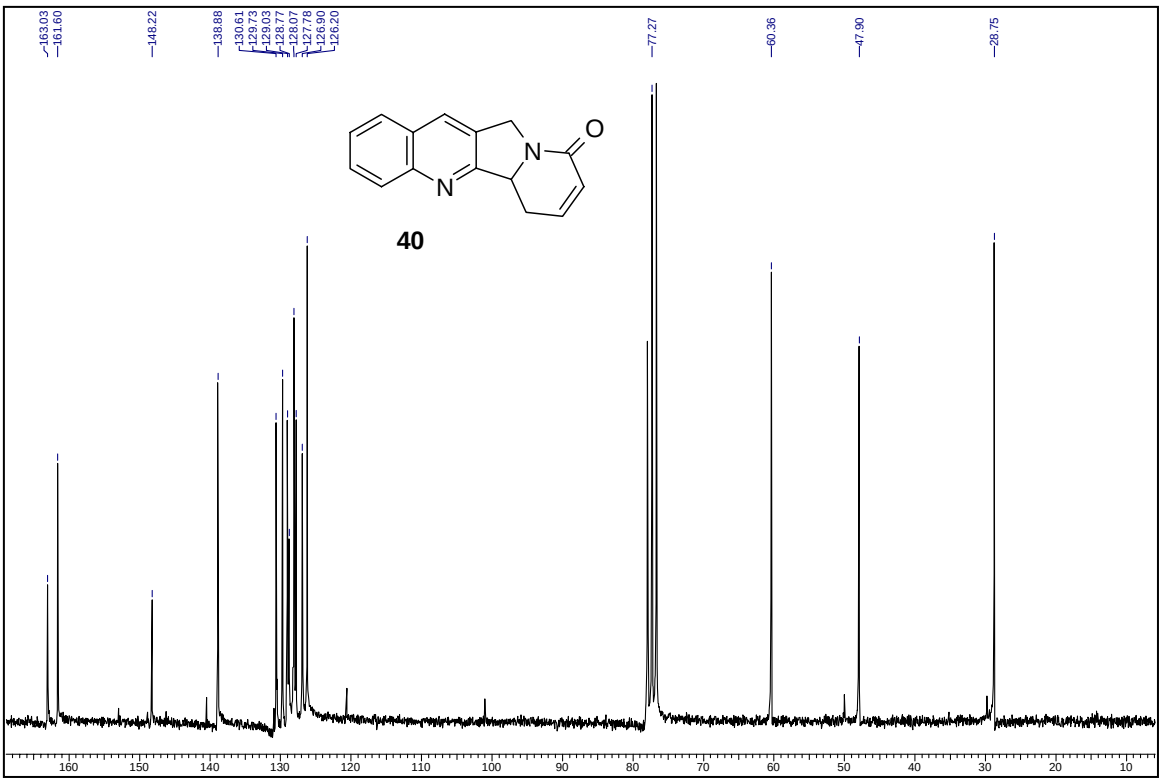
DEPT ($CDCl_3$ + CCl_4, 125 MHz)



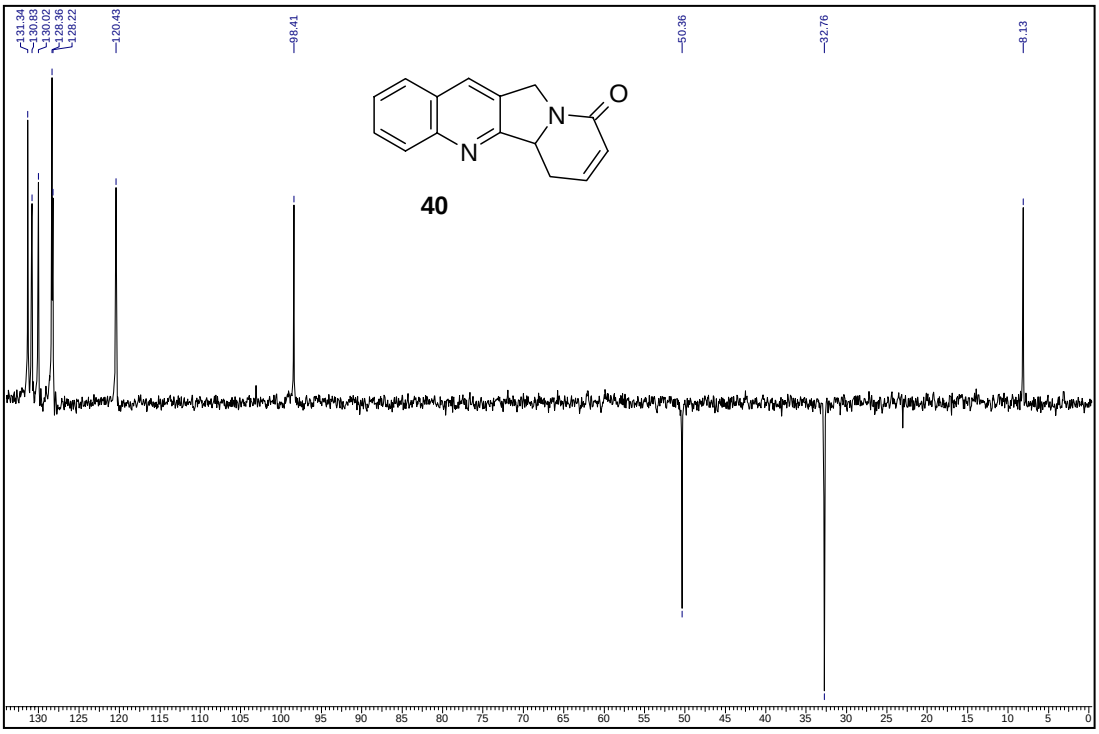
^{1}H-NMR ($CDCl_3$ + CCl_4, 200 MHz)



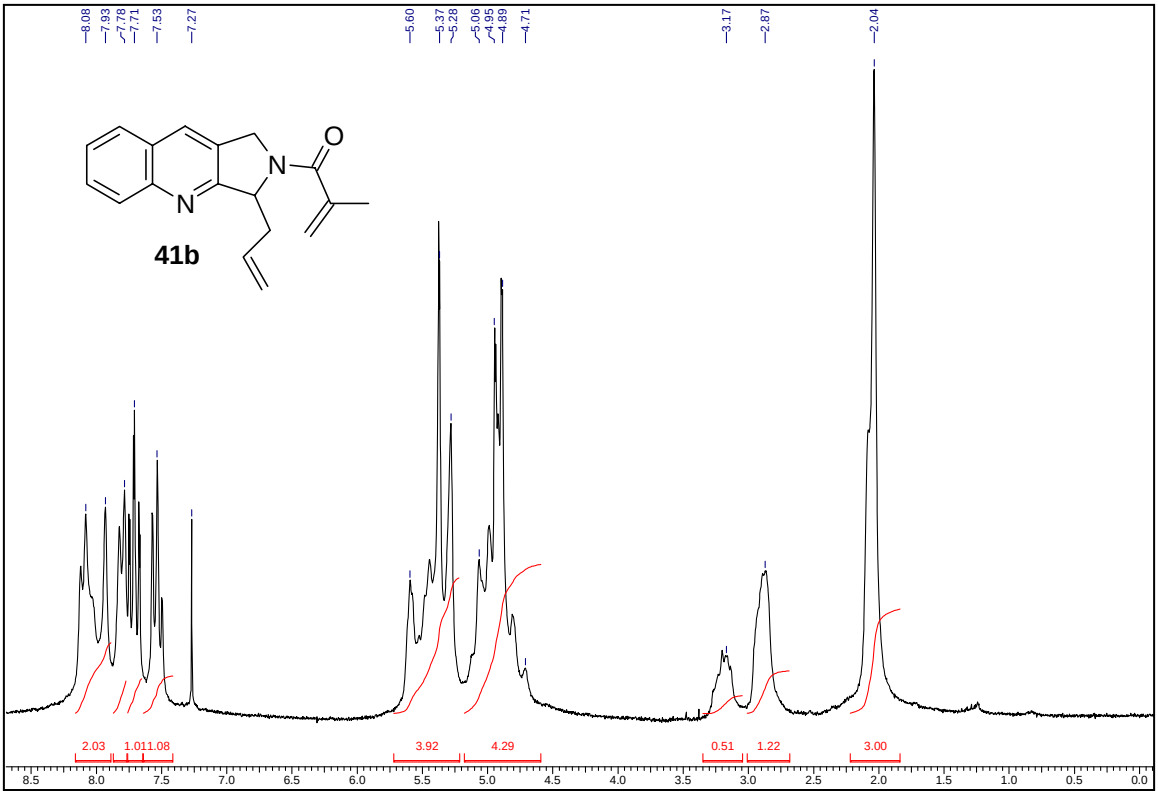
^{13}C-NMR spectrum ($CDCl_3$, 200 MHz)



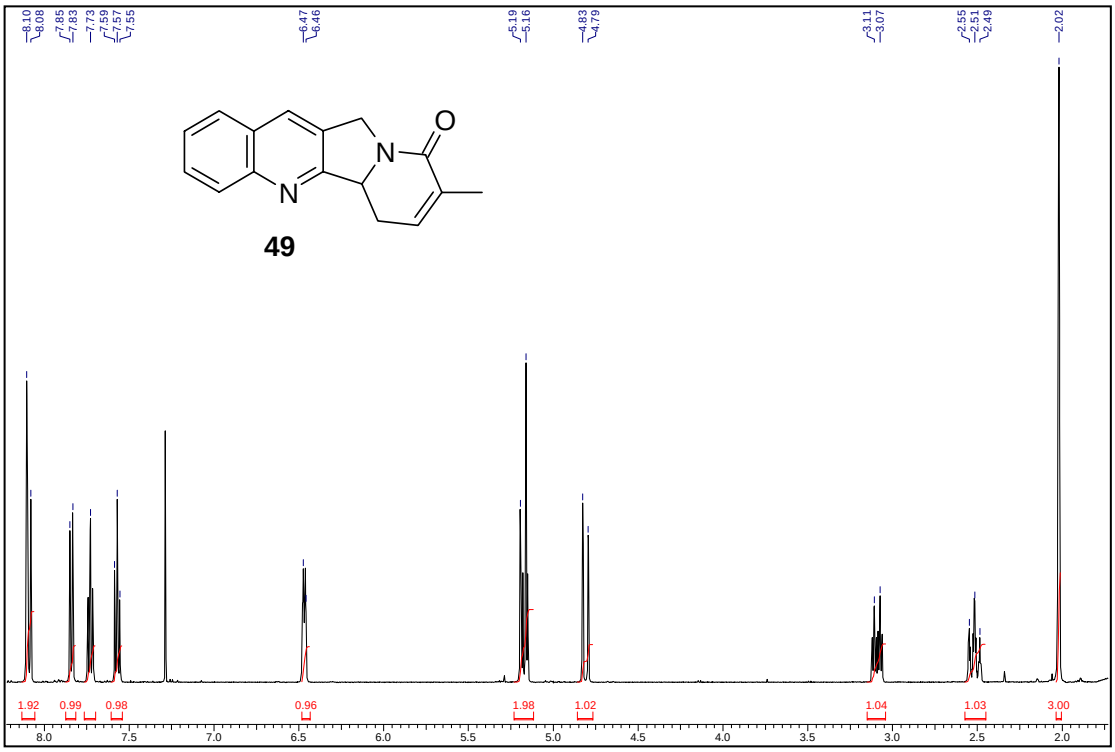
^{13}C-NMR spectrum ($CDCl_3$, 50 MHz)



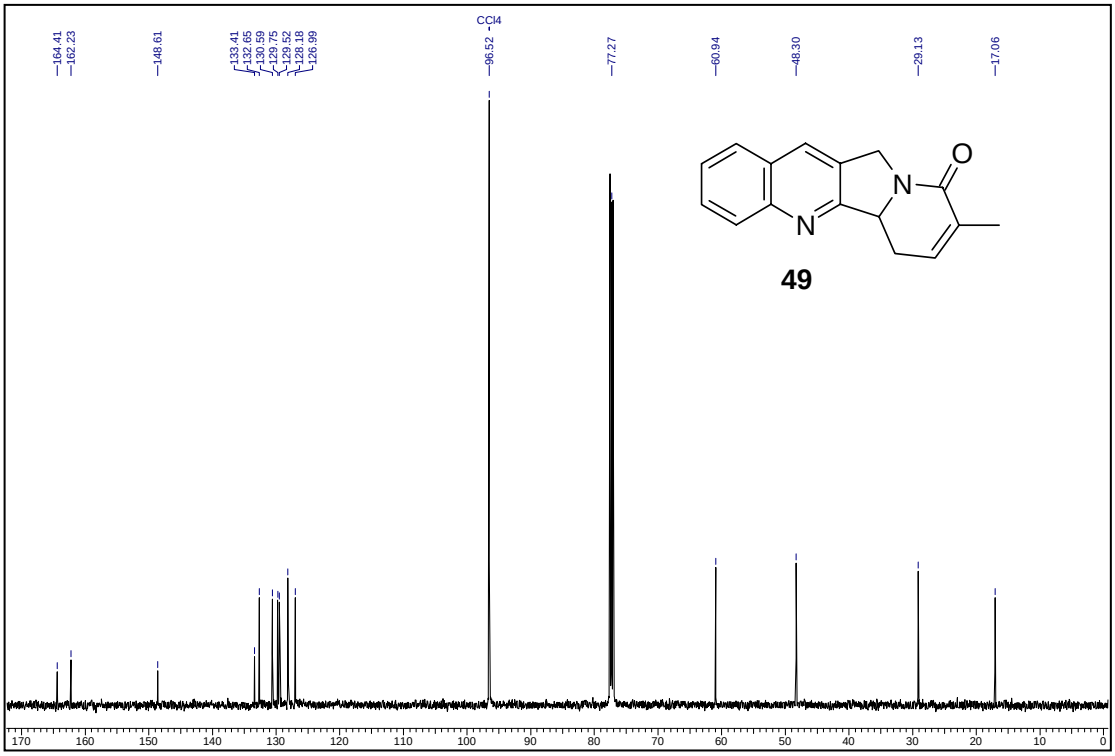
DEPT spectrum ($CDCl_3$, 50 MHz)



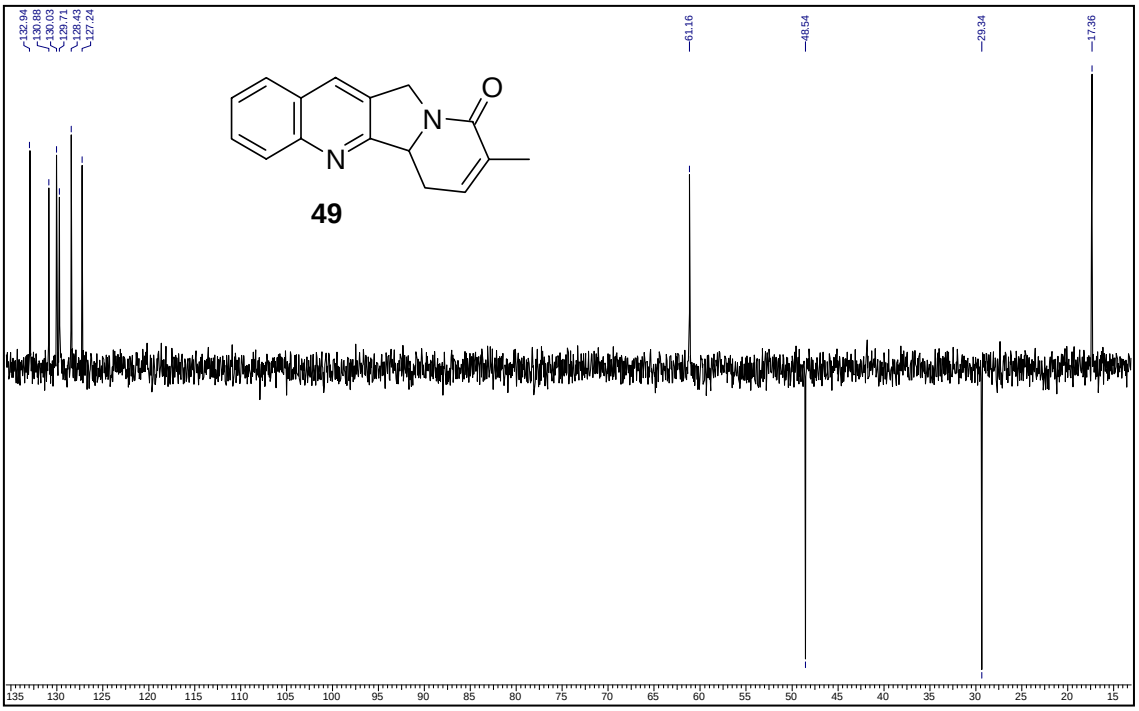
^{1}H-NMR ($CDCl_3$, + CCl_4, 200 MHz)



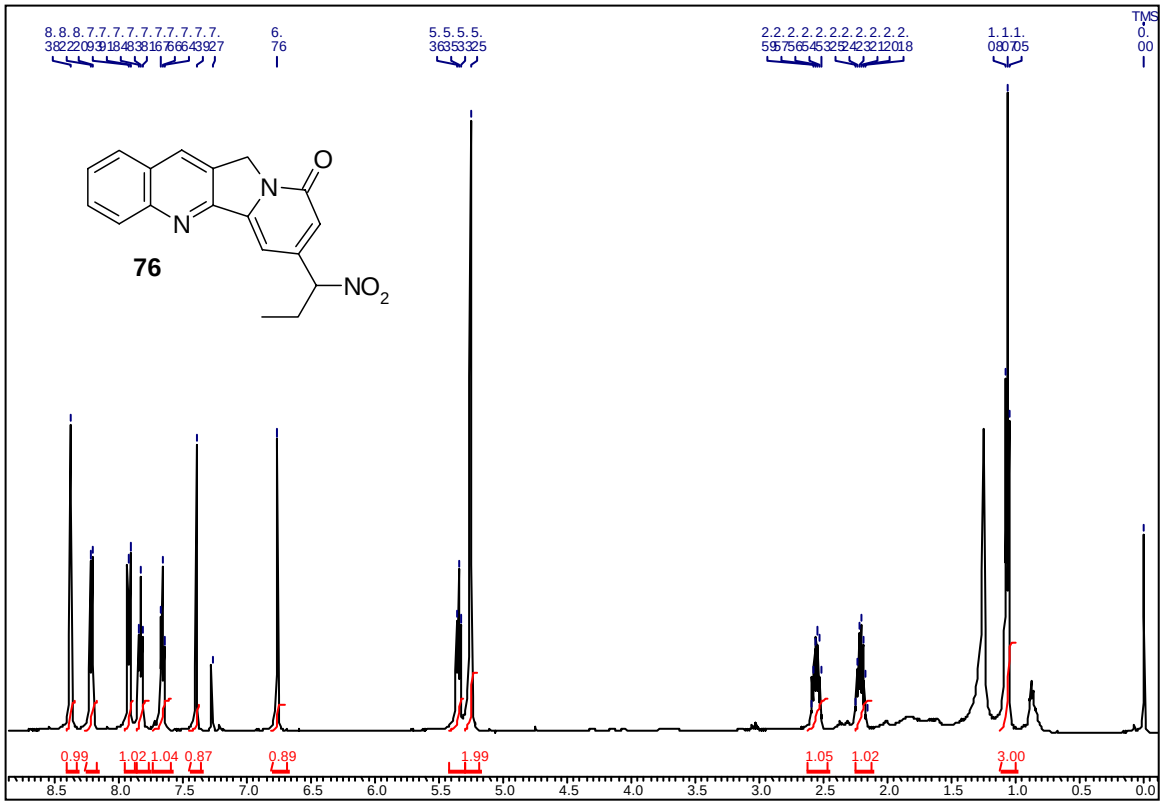
^{1}H-NMR ($CDCl_3$, + CCl_4, 500 MHz)



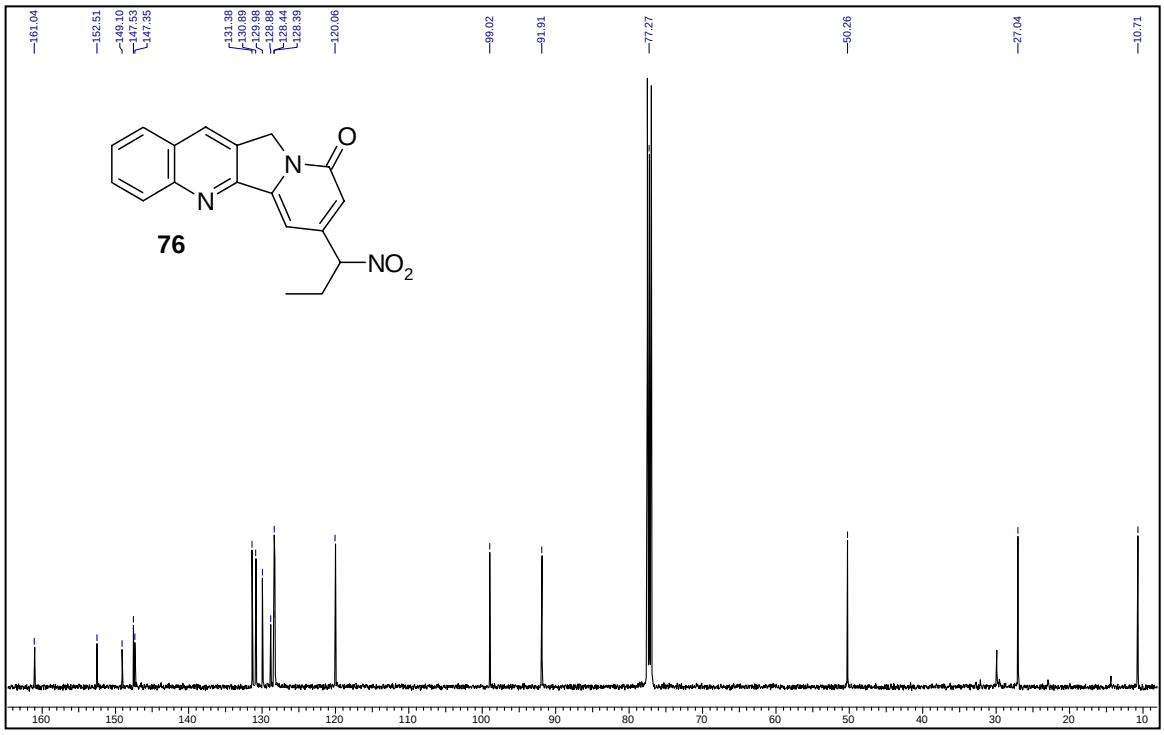
^{13}C-NMR ($CDCl_3$, + CCl_4, 125 MHz)



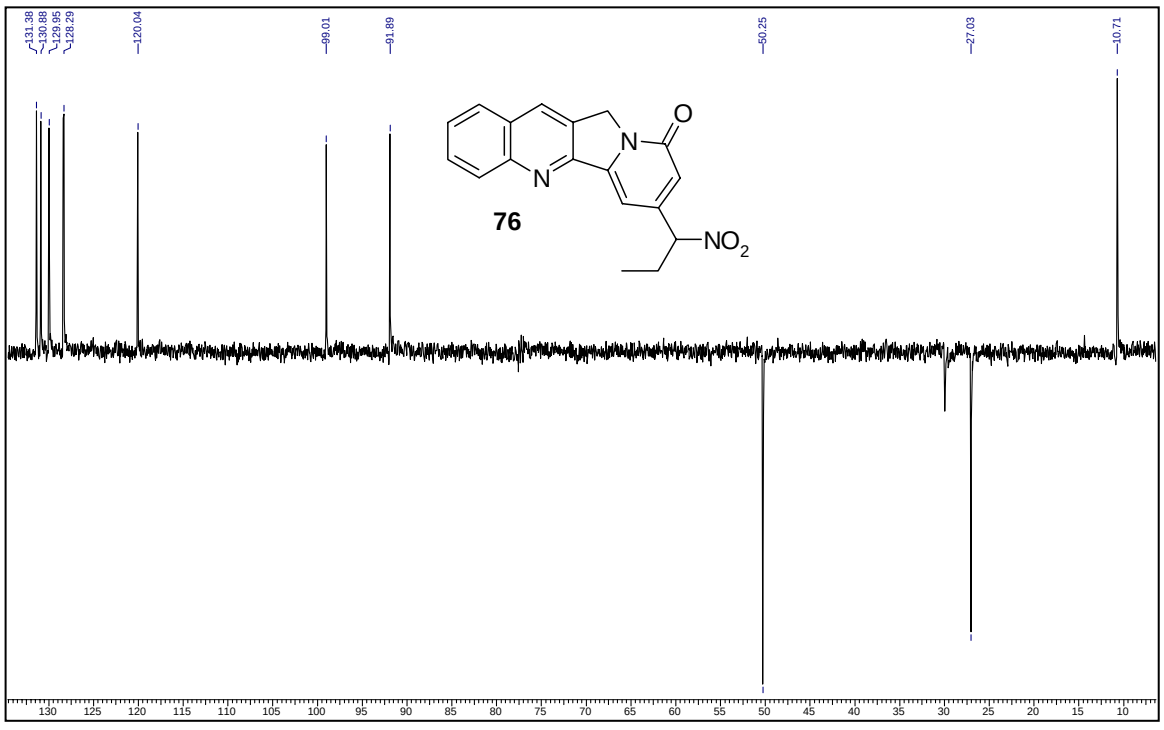
DEPT ($CDCl_3$, + CCl_4, 125 MHz)



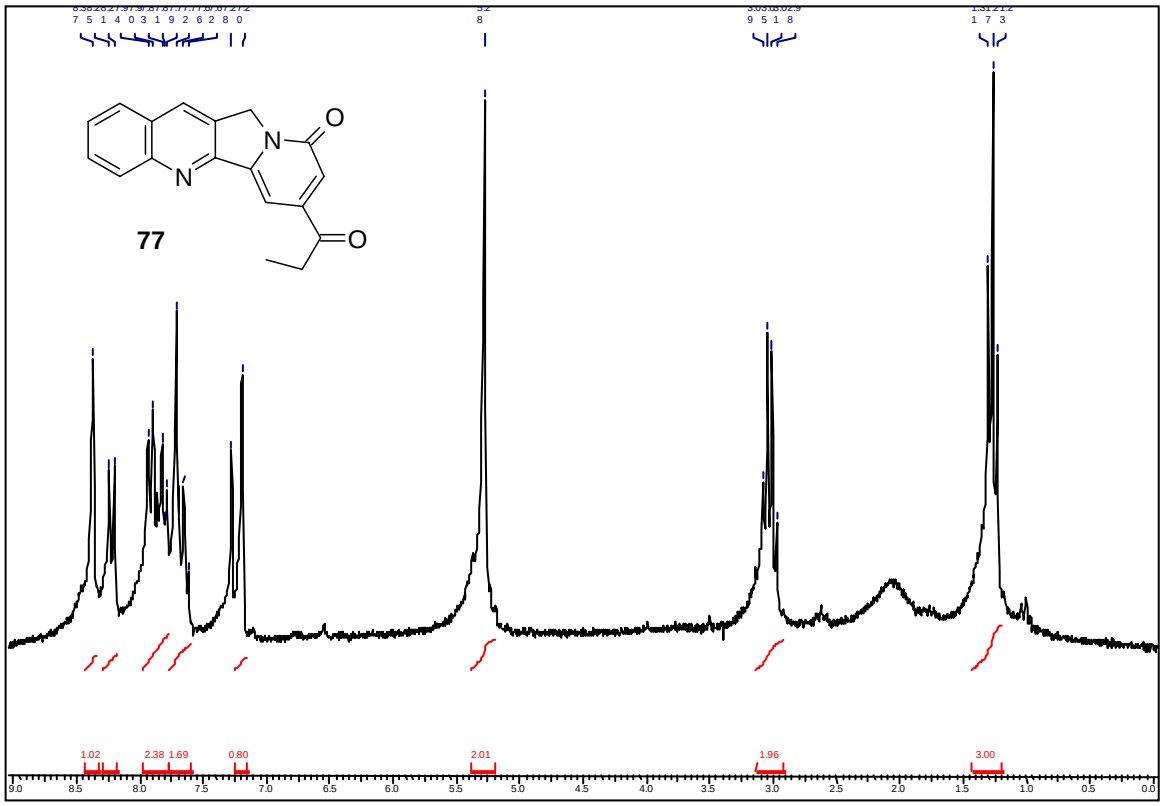
^{1}H-NMR spectrum ($CDCl_3$, 500 MHz)



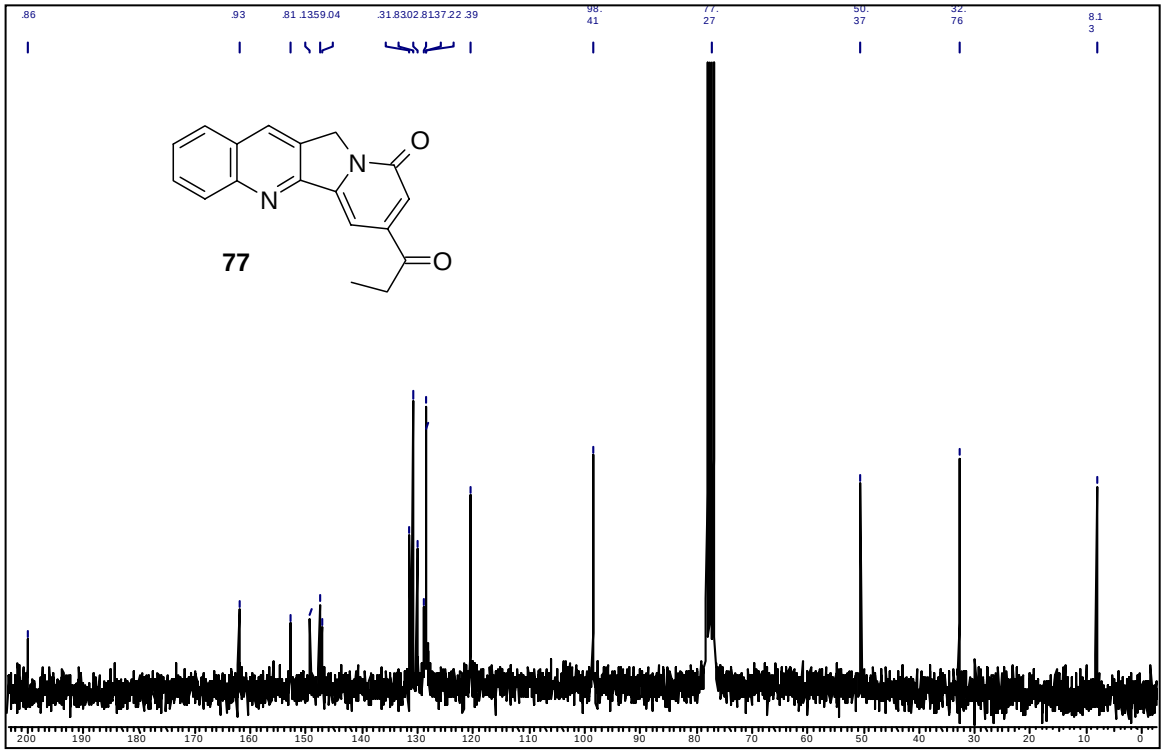
^{13}C-NMR spectrum ($CDCl_3$, 125 MHz)



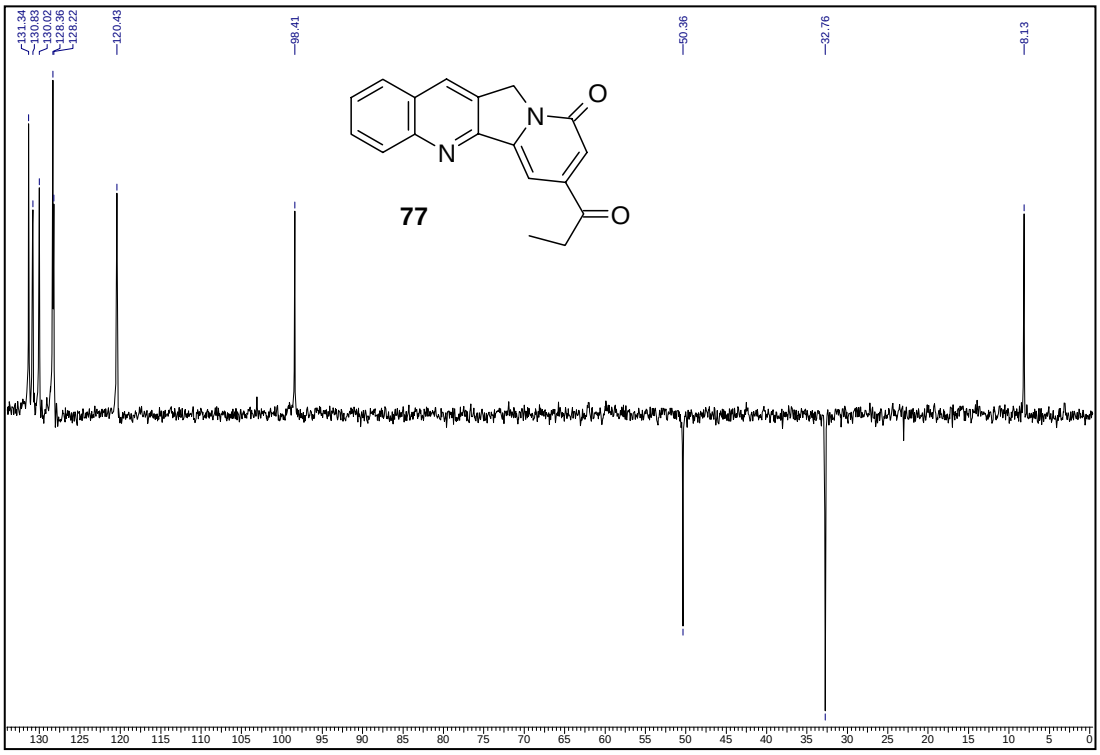
DEPT spectrum ($CDCl_3$, 125 MHz)



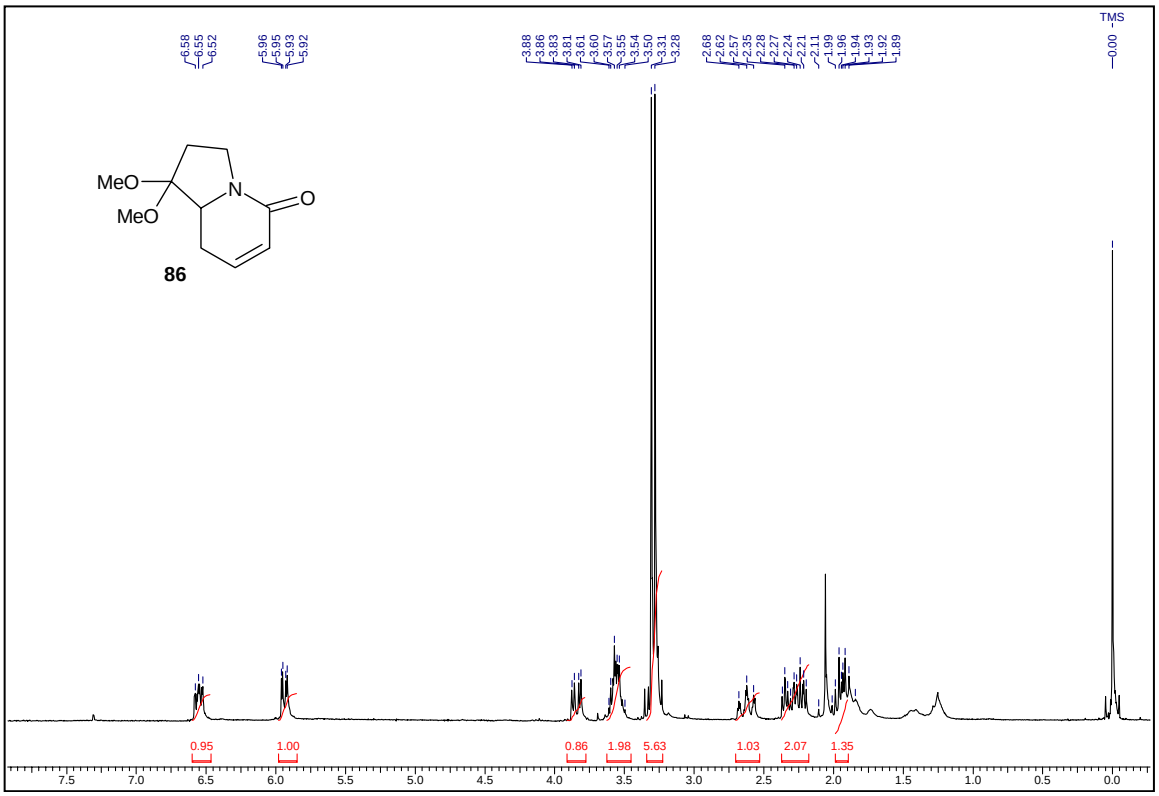
^{1}H-NMR ($CDCl_3$, 200 MHz)



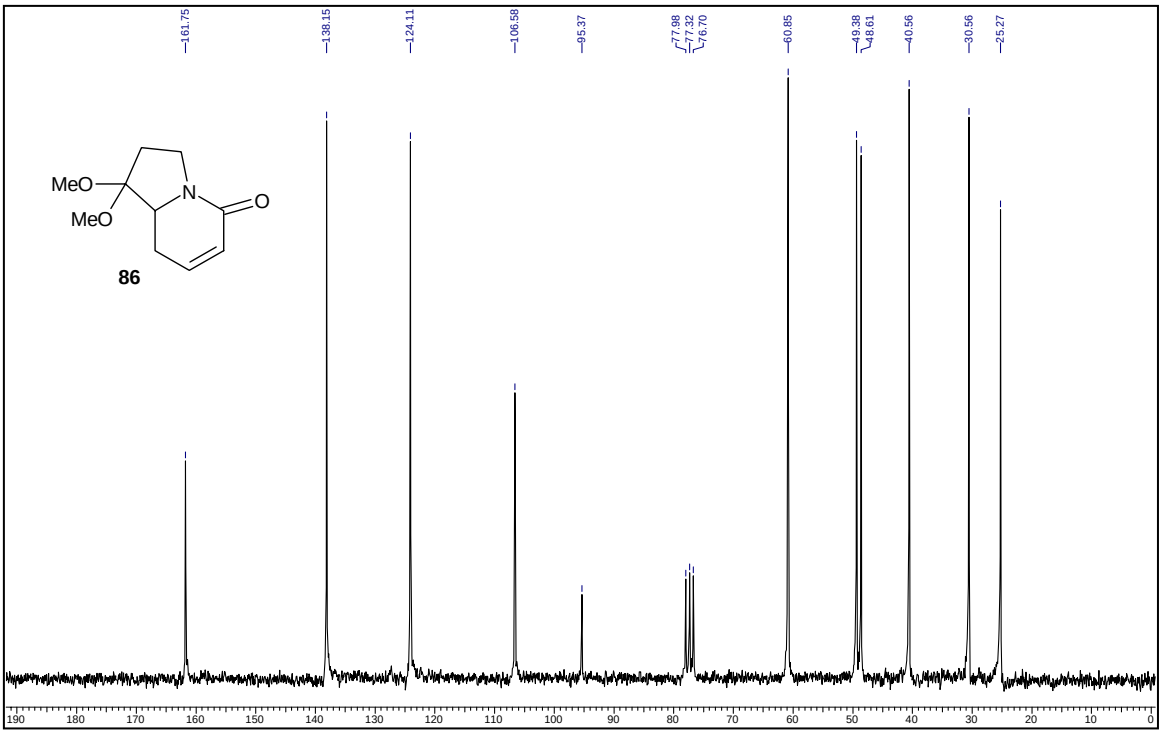
^{13}C-NMR ($CDCl_3$, 50 MHz)



DEPT ($CDCl_3$, 50 MHz)

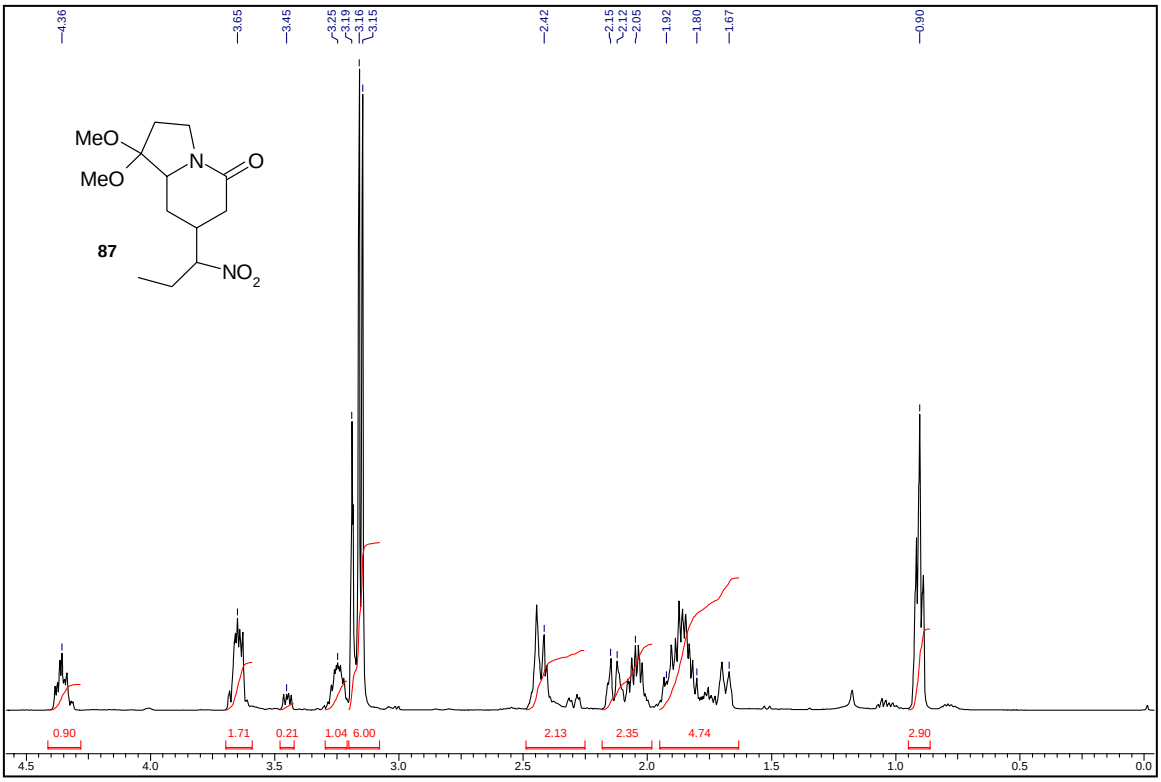


^{1}H-NMR ($CDCl_3$ + CCl_4, 300 MHz)

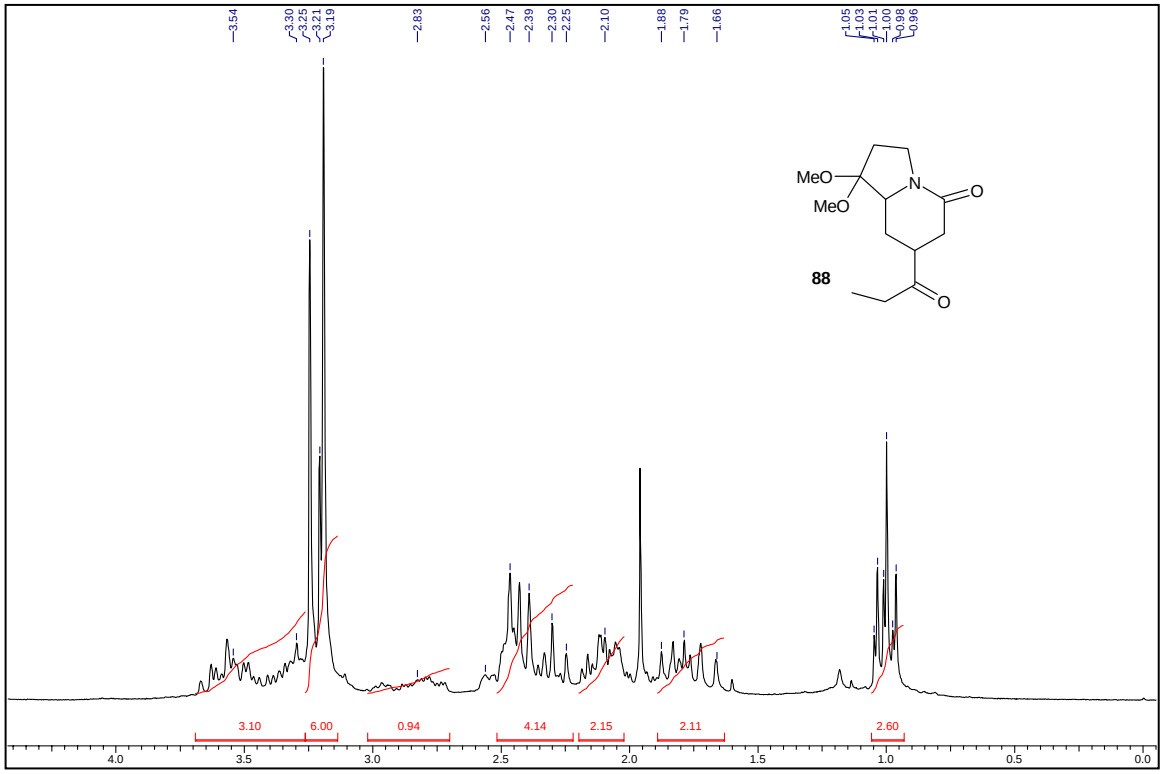


^{13}C-NMR ($CDCl_3$ + CCl_4, 75 MHz)

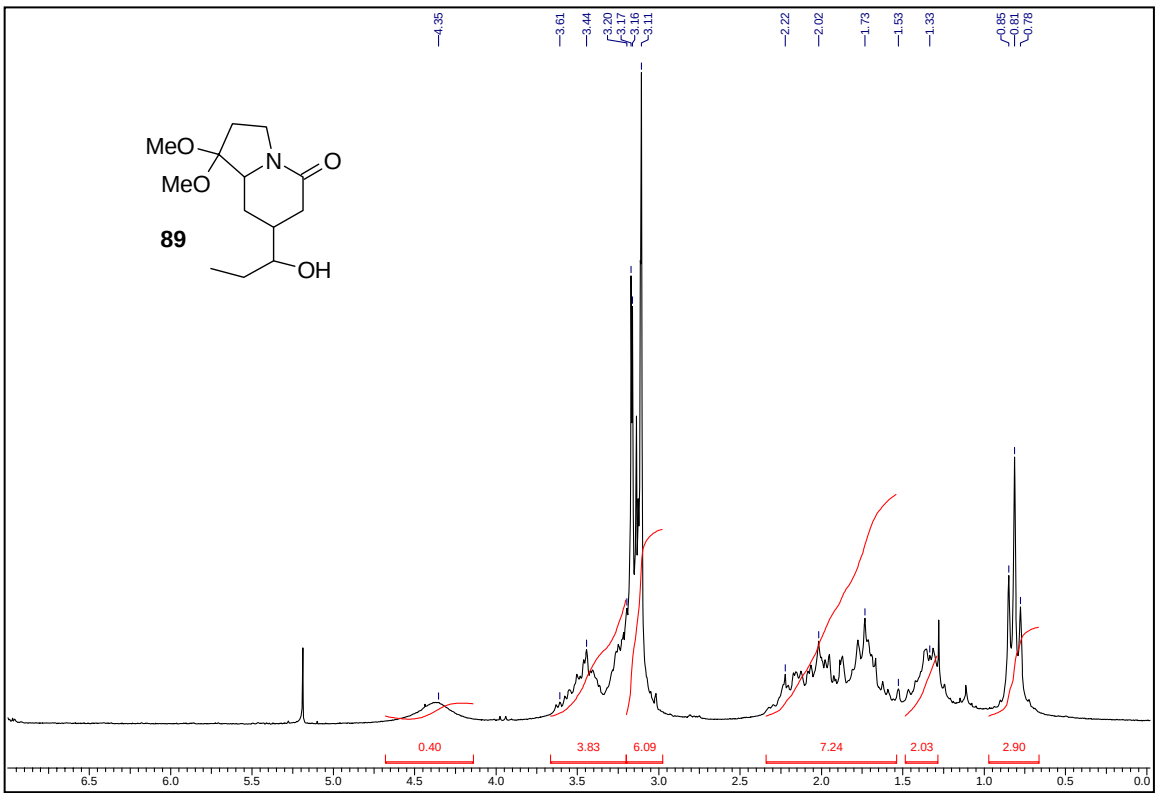
DEPT ($CDCl_3$ + CCl_4, 75 MHz)



^{1}H-NMR ($CDCl_3$+CCl_4, 200 MHz)



^{1}H-NMR ($CDCl_3$+CCl_4, 200 MHz)



^{1}H-NMR ($CDCl_3$+CCl_4, 200 MHz)

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CHAPTER I

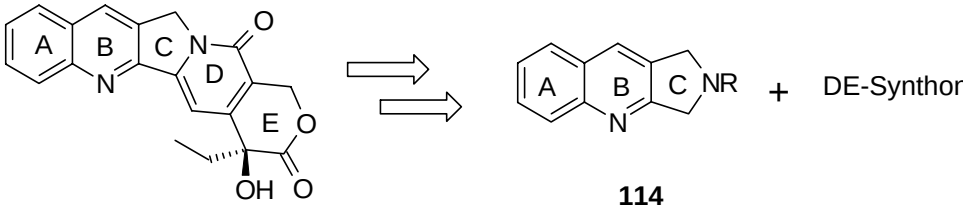
SECTION 2

PART 2: Approaches Towards Camptothecin Skeletal Frame Work

1.2.2.1 Introduction:

Several groups involved in the convergent synthesis of camptothecin and mappicine ketone identified the tricylic amine **114** as a key synthon for the construction of ABC ring system (scheme 39).[1] This strategy was first executed by Corey and co-workers for the asymmetric synthesis of camptothecin.[1c]

Scheme 39



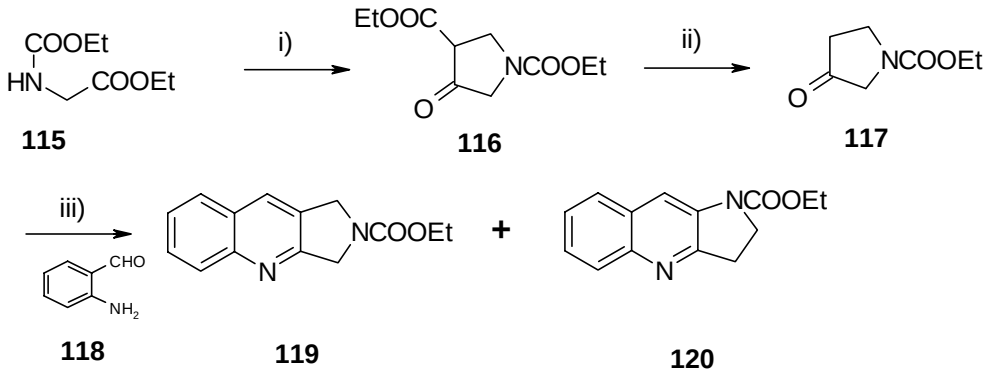
114

Reports involving the preparation of this key intermediate have utilized chemical reagents (acridine, 2-aminobenzaldehyde, dimethylacetylene dicarboxylate (DMAD), propargyl amine, etc.), which are either expensive, unstable, low yielding or pose handling problems. These limitations are certainly a drawback during large-scale preparation of this tricyclic amine **114**. This implies that there is an evident need for new methods to synthesize this important intermediate. As a part of our research activity to explore new synthetic approaches towards camptothecin and mappicine ketone, it was decided to explore new synthetic sequences to provide the tricyclic amine **114** and suitable DE-synthon using simple and commercially available starting materials. A brief literature survey on the synthetic approaches towards camptothecin involving the convergent strategy as depicted in the scheme 39 is presented below.

1.2.2.2 Literature Background:

Zalkow's Approach: (*J. Chem. Soc. (C)* **1971**, 3551.)[1a]

Scheme 40



115 **116** **117**

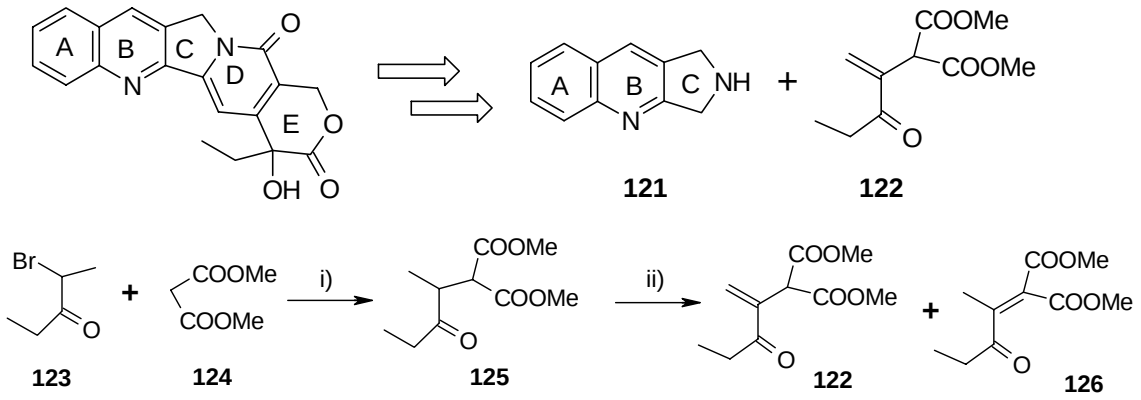
118 **119** **120**

Reagents and conditions: *i) NaH, benzene, rt, 12 h and then CH_2=CH-CO_2Et, reflux, 2 h (85%); ii) 6 N HCl : H_2O (1 : 15), reflux, 4 h (92%); iii) a) PTSA, 195 ºC, 5 min, b) NaOH, EtOH, rt, 18 h, 88%.*

Glycine carbamate **115** upon Michael addition induced ring closure with ethylacrylate in the presence of NaH provided β-keto ester **116**, which was decarboxylated to give pyrrolidone **117**. Friedlander condensation of **117** with aminobenzaldehyde **118** resulted in the formation of tricyclic amine ethylcarbamate **119**. Use of unstable aminobenzaldehyde, and the formation of unwanted regioisomer **120** in the final condensation are the drawbacks of this method.

Wall's Approach:(*J. Am. Chem. Soc.* **1972**, *94*, 3631.).[1b]

Scheme 41

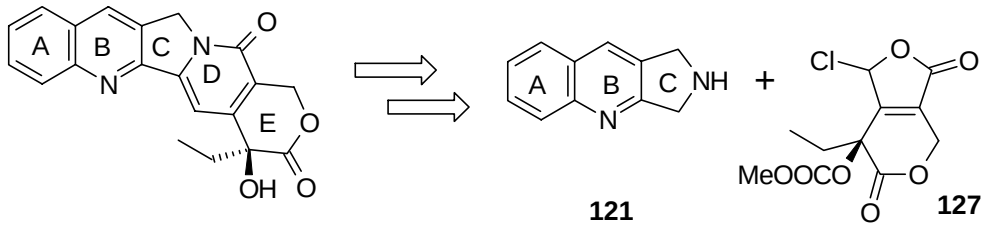


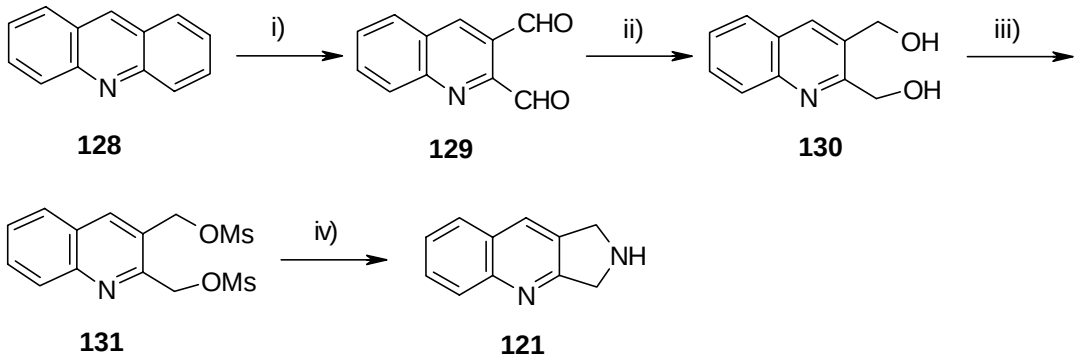
Reagents and conditions: *i) KH, DMF, 85%, ii) a) NaH, DME, b) Br_2, DME, c) pyridine, reflux, 50%.*

The Michael acceptor enone **122** was prepared from 2-bromo-3-pentanone **123** by a 3 step sequence consisting of condensation with dimethyl malonate **124** followed by bromination using sodium hydride and finally eliminating the bromo moiety employing pyridine as the base.

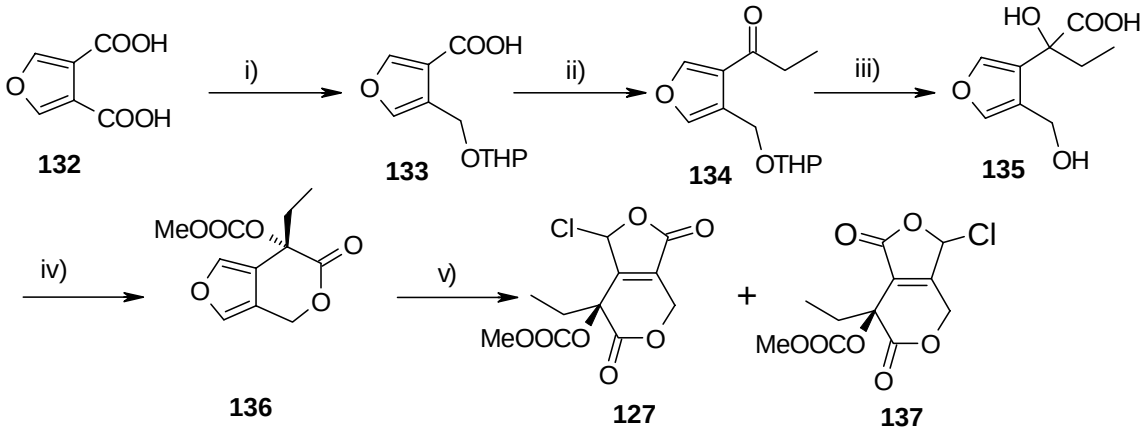
Corey's Approach: (*J. Org. Chem.* **1975**, *40*, 2140.)[1c]

Scheme 42





Reagents and conditions: *i) ozonolysis, -40 ºC, ii) $NaBH_4$, -40 ºC, 43%, iii) MsCl, benzene, 0 ºC, 1 h, 85%, iv) methanol, NH_3, 2 h, rt, 47%.*



Reagents and conditions: *i) a) ClCOOMe, TEA, 3 days, rt, 75%, b) BH_3.THF, THF, 0 ºC, 3 h, 65%, c) DHP, PTSA, d) KOH, MeOH, 40%, ii) BH_3.THF, THF, 0 ºC, 30 h, 40%, b) Jones oxidation, c) EtMgBr, d) Collin's reagent, iii) a) TBDMSCN, HMPA, 18-crown-6, 6 days, 85%, b) 30% H_2O_2, aq. K_2CO_3, c) KOH, H_2O, MeOH, 73%, d) 30% AcOH, 4 h, 65%, iv) a) quinine resolution, 76%, b) ClCOOMe, v) a) O_2, hv, eosin, b) $SOCl_2$, DMF, 50 ºC.*

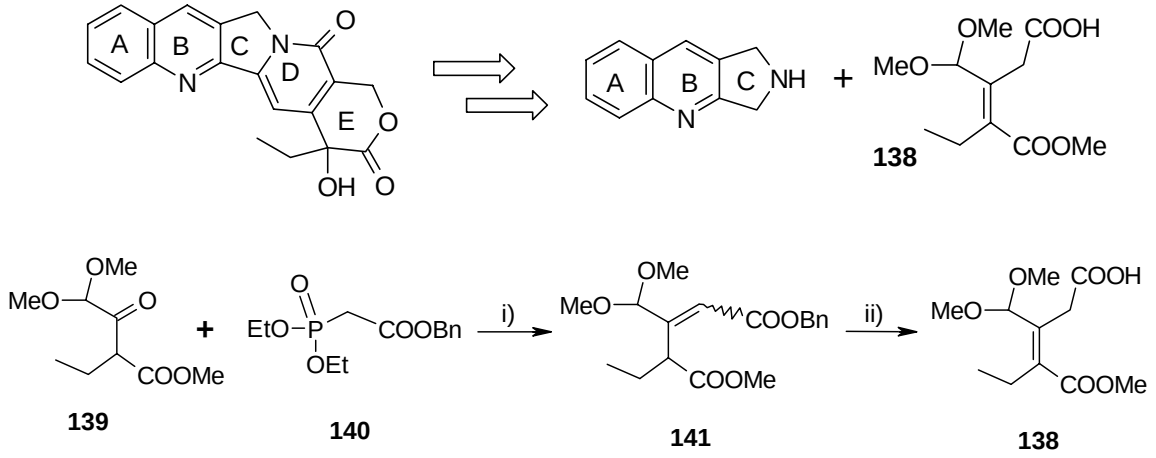
This approach was the first to furnish camptothecin in optically pure form. Quinoline-dialdehyde **129** obtained by ozonolysis of acridine **128** was reduced to diol **130** and protected as dimesylate **131**. The cyclization of dimesylate with methanolic ammonia gave the tricyclic amine **121** in 47% yield. Use of acridine limits the synthetic utility of the approach.

The pseudo-acid chloride **127** was prepared as per described below. Borane reduction of the acid **132** resulted in mono alcohol, which was protected as THP ether **133**. The acid **133** was converted to aldehyde involving reduction-oxidation sequence.

Ethylation with EtMgBr followed by Collin's oxidation furnished ketone **134** in 85% yield. The sequence involving cyanohydrin formation and hydrolysis provided hydroxy acid **135** in 47% yield. Resolution of the acid **135** using quinine followed by lactonisation and protection of the tertiary alcohol gave lactone **136** in 76% yield. Photo oxidation of **136** followed by thionyl chloride gave pseudo-acid chlorides **127** and **137**. Formation of the unwanted regioisomer **137** makes the synthesis impractical.

Buchi's Approach: (*J. Org. Chem.* **1976**, 699)**.**[1d]

Scheme 43

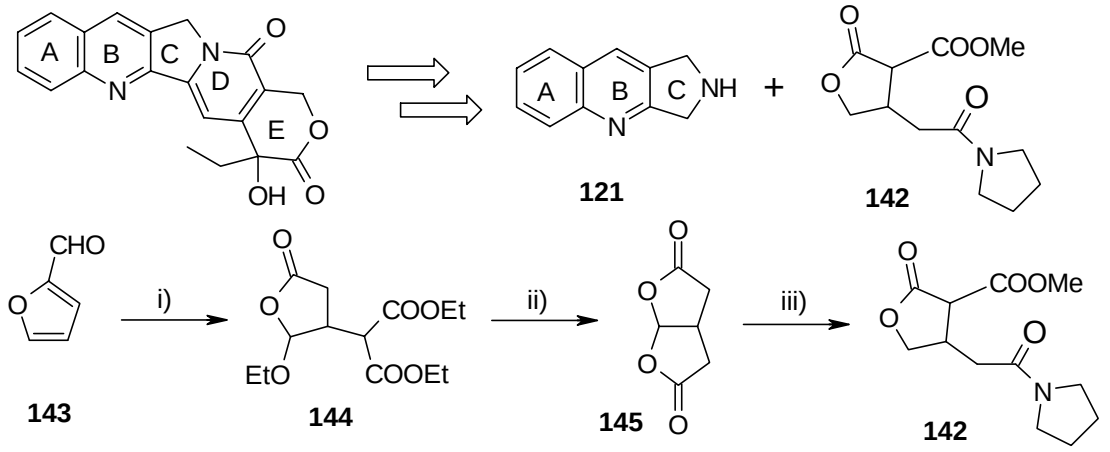


Reagents and conditions: *i) NaH, DME, ii) a) KOt-Bu, b) 10% Pd/C, H_2, MeO*H.

Wittig-Horner-Emmons reaction of benzyl diethyl phosphonoacetate **140** with keto ester **139** gave an E, Z mixture of benzyl ester **141**. Isomerization and debenzylation of **141** to acid **138** was effected using potassium *tert*-butoxide followed by hydrogenation.

Pandit's Approach: (*Tetrahedron* **1981**, 371.)[1e]

Scheme 44

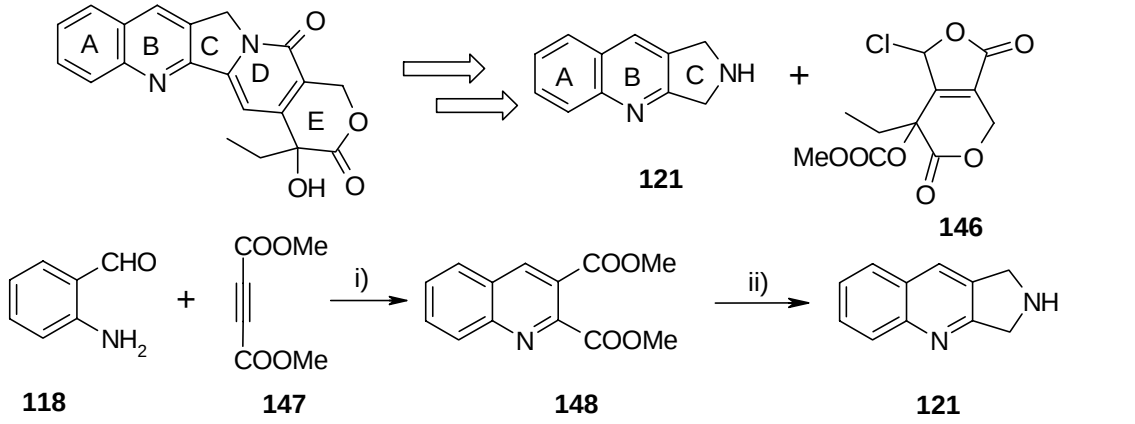


Reagents and conditions: *i) a) Photo oxidation, ethanol, 33 h, eosin, 53%, b) diethyl malonate, NaH, 5 ºC, 64%, iii) 30% HBr, AcOH, reflux, 72 h, 68%, iii) a) KOH, EtOH, reflux, b) $NaBH_4$, H_2O, reflux, 4 h; con. HCl, 96%, c) $SOCl_2$, rt, 2 h, d) Pyrrolidine, C_6H_6, 2 h, 62 %, e) NaH, dimethylcarbonate, MeOH, reflux, 5 h, 73%.*

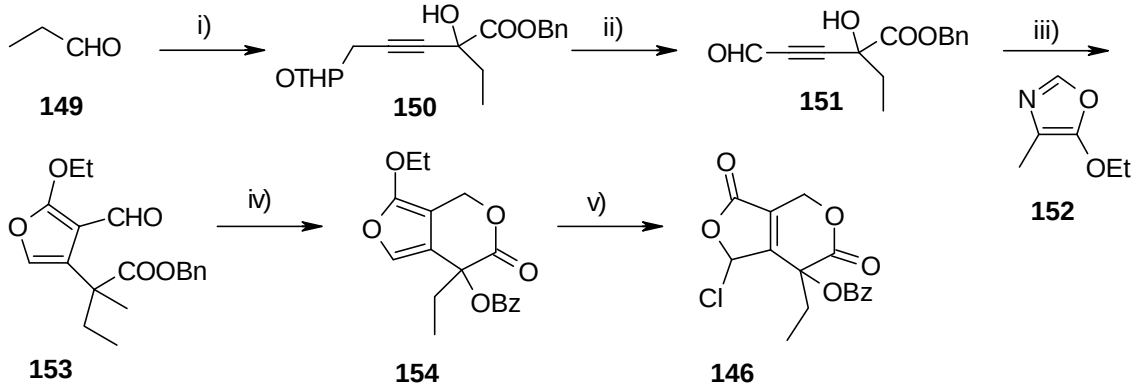
Photooxidation of furfuraldehyde **143** furnished 4-ethoxy butenolide in 53% yield. Michael addition on to the 4-ethoxy butenolide with sodium salt of diethyl malonate furnished ester **144** in 64% yield. Acidic hydrolysis of **144** gave dilactone **145** in 68% yield. Base treatment followed by sodium borohydride reduction gave acid, which in two steps was converted to amide **142**.

Rama Rao's Approach: (*Tetrahedron Lett.* **1994,** *35***,** 3613).[1f]

Scheme 45



Reagents and conditions: *i), a) MeOH, reflux, b) MeOH-$CHCl_3$ (1:1), H_2SO_4, reflux, 95%, ii) a) LAH, THF, rt, b) MsCl, TEA, DCM, c) methanolic NH_3, 80%*



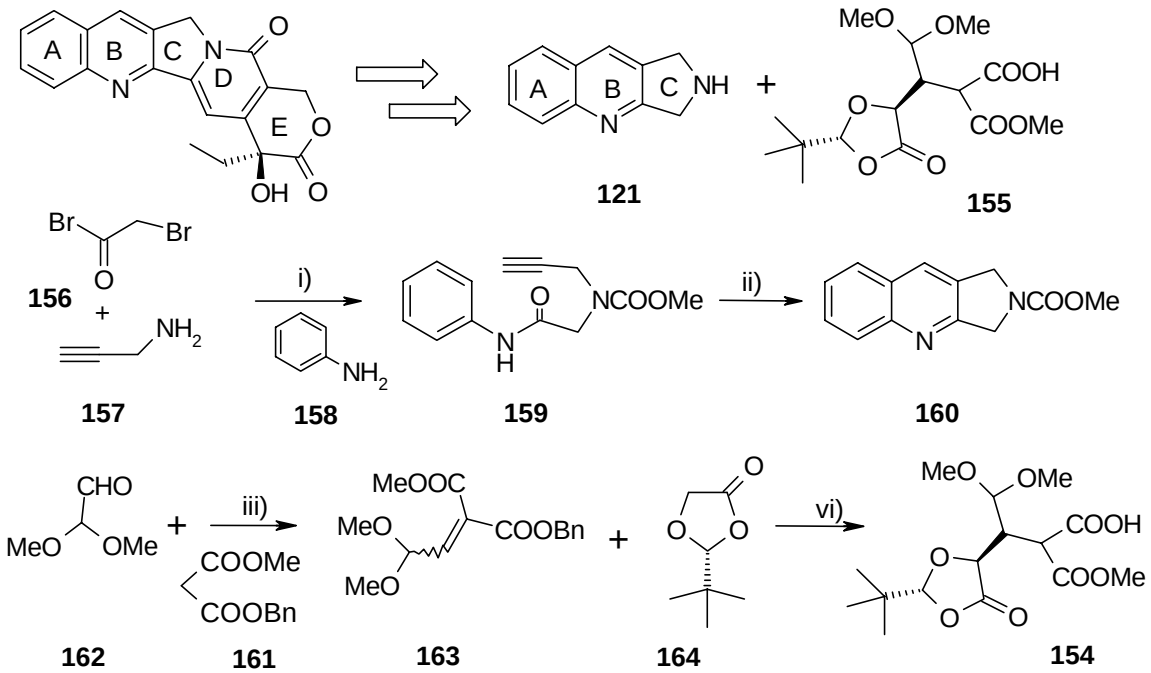
Reagents and conditions: *i) a) $HS(CH_2)_2SH$, $BF_3.Et_2O$, DCM, 0 ºC, b) BuLi, -78 ºC ClCOOBn, THF, c) $AgNO_3$, NBS, $CH_3CN:H_2O$ (4:1), rt, d) $LiC{\equiv}C\text{-}CH_2\text{-}OTHP$, THF, -78*

ºC, 85%, ii) a) BzCl, TEA, DMAP 0 ºC, b) PTSA, MeOH, c) PCC, DCM, 70%, iii) toluene, 110 ºC, iv) a) $NaBH_4$, MeOH, b) H_2/Pd-C, MeOH, c) ClCOOEt, TEA, v) a) MnO_2:HCl (4:10), -15 ºC, 75%, b) $SOCl_2$, DMF (cat), $CHCl_3$, rt.

Michael addition of aminobenzaldehyde **118** with DMAD **147** followed by sulfuric acid mediated cyclization afforded the diester **148**, which was reduced to diol and protected as dimesylate. Treatment with methanolic ammonia resulted in the formation of tricyclic amine **121**. This synthesis was aimed at obtaining pseudoacid chloride **146** in a regiospecific manner employing a clever tandem Diels-Alder, retro Diels-Alder cycloaddition methodology to overcome the problem of mixture of pseudoacid chlorides obtained by Corey in his synthesis (scheme **42**). Propionaldehyde **149** converted to alcohol **150** folllowing a protection, alkylation, deprotection and condensation sequence in 85% yield. The alcohol was protected as benzoate ester. Deprotection of THP ether and oxidation of primary alcohol provided aldehyde **151**. Tandem Diels-Alder, retro Diels-Alder reaction using 4-methyl-5-ethoxy oxazole **152** furnished aldehyde **153** in 90% yield. Reduction of aldehyde to alcohol followed by hydrogenation and cyclization gave lactone **154**. Regioselective oxidation using MnO_2-HCl and treatment with thionyl chloride furnished pseudo acid chloride **146**.

Fortunak's Approach: (*Tetrahedron Lett.* **1996**, *37*, 5683.)[1g]

Scheme 46



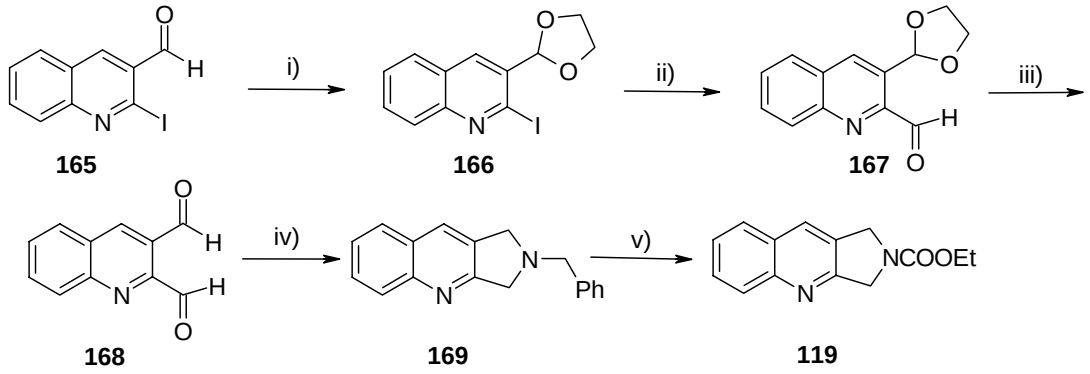
Reagents and conditions: *i) a) reflux, 84%, b) ClCOOMe, TEA, 95%, ii) a) Me_3OBF_4, -40 to 50 ºC, 72%, ii i) piperidine, toluene, reflux, 82%, iv) a) LDA, THF, -78 to –20 ºC, b) 5% Pd/C, H_2, MeOH, 100%.*

The tricyclic amine **160** was prepared from α-bromoacetyl bromide **156**. Condensation of **156** with aniline **158** followed by alkylation with propargyl amine **157** and subsequent protection furnished the urethane **159**. Treatment of **159** with Meerwin's salt furnished quinoline **160**.

Glyoxal **162** on condensation with diester **161** furnished the vinyl ester **163** in 82% yield. Michael addition on **163** with chiral dioxolane-4-one **164** using LDA and subsequent hydrogenation furnished the desired mono acid **154**.

Chavan's Approach: (*Synth. Commun.* ***2004****, in press.*)[1h]

Scheme 47



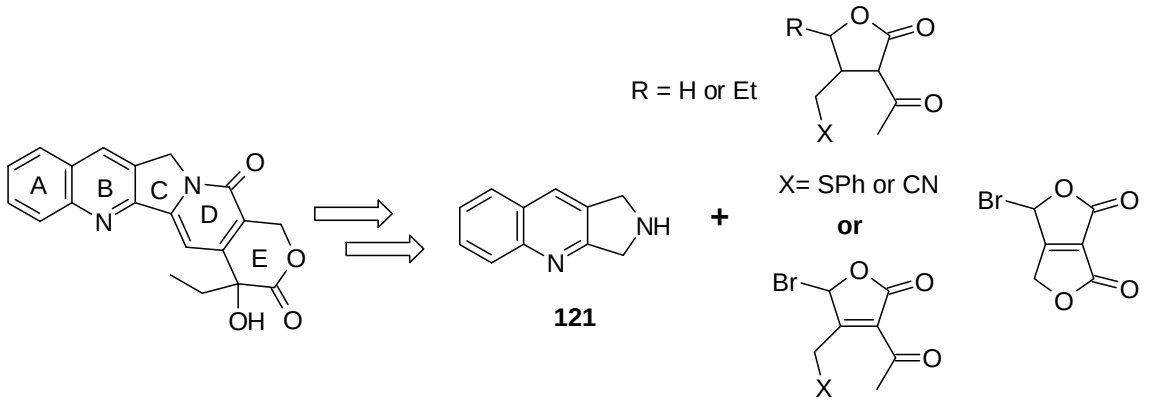
Reagents and conditions: *i) ethylene glycol, PTSA, C_6H_6, azeotrope, 6 h, 90%, ii) BuLi, DMF, ether, -78 ºC, 1 h, 57%, iii) 10% HCl, rt, 1h, 92%, iv) a) $BnNH_2$, MeOH, rt, 1 h, b) $NaBH_4$, MeOH, 0 ºC, 1 h, 80%, v) ClCOOEt, C_6H_6, reflux, 2 h, 74%.*

Formyl group of the iodoaldehyde **165** was protected as cyclic acetal **166**. Quenching the lithio derivative with DMF provided 2- formyl quinoline **167**. The acetal **167** was deprotected with 20% HCl in ether to get the dialdehyde **168.** The formation of tricyclic synthon **169** was achieved upon treatment of the dialdehyde **168** with benzyl amine in methanol followed by reduction with sodiumborohydride whose conversion to **119** was achieved in 74% yield.

1.2.2.3 Present Work: *Results and Discussion*

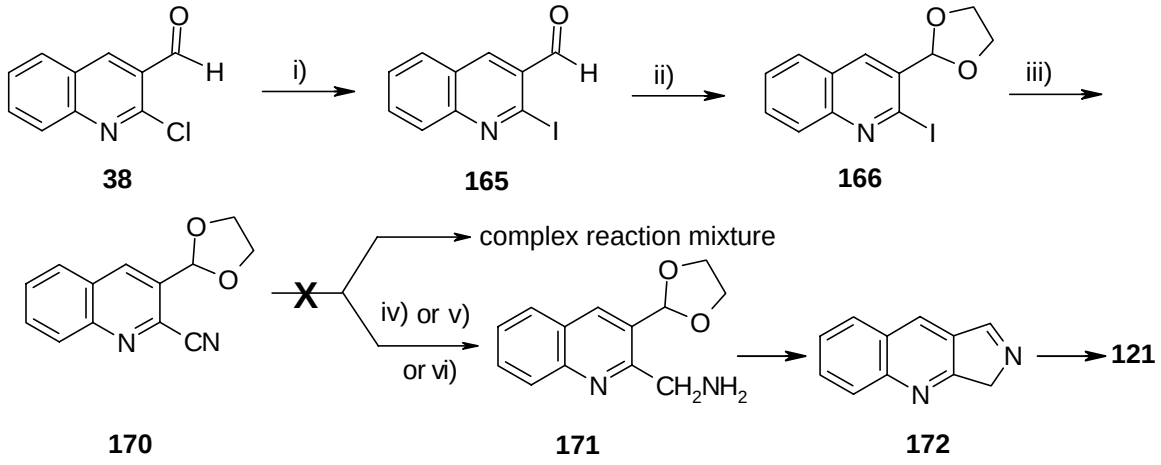
The convergent strategy adopted to build the skeletal framework of the camptothecin and related alkaloids is depicted below (scheme 48). The scheme shown below involves the synthesis of ABC synthon and DE synthon separately. These synthons can be condensed together to form the core framework of campthothecin and related alkaloids.

Scheme 48



Our journey began with the synthesis of ABC synthon **121**. Meth-Cohn's[2] quinoline aldheyde **38** with a formyl group at 3-position and the handle at 2-position for the functionalization *i.e.* C-C bond formation, given the flexibility and simplicity for the analogues preparation, appeals to be ideal starting material to do away with the shortcomings of the earlier approaches such as usage of 2-aminobenzaldehyde, regiochemistry problems encountered in Friedlander condensation and the usage of expensive starting materials like acridine, propargyl amine and DMAD.

Scheme 49

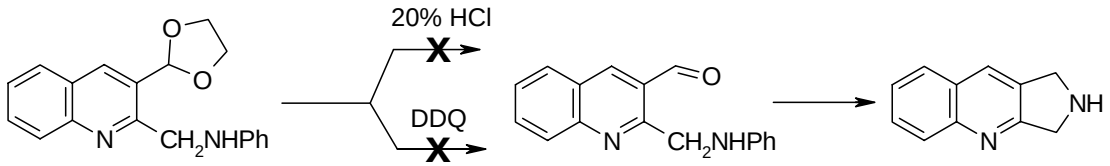


Reagents and conditions: *i) NaI, cat Conc. HCl, CH_3CN, 6 h, reflux, 90%, ii) Ethylene glycol, PTSA, benzene, 8 h, 110 ºC, 90 %, iii) CuCN, DMF, 135 ºC, 96%, iv) LAH, THF, 0 ºC, 15 min, v) DIBAL, 0 ºC, 3 h, vi) $NaBH_4/I_2$, THF, reflux, 3 h.*

It was opined that deprotection of acetal moiety in **171** followed by the reduction of the resulting imine **172** will be a straightforward method to access the tricyclic amine. Thus, the Cl group in the aldehyde **38** was replaced by "I" moiety as per reported procedure in literature. Aldehyde **165** was protected as cyclic acetal **166** under standard conditions. Subsequently the replacement of the iodo group in **166** by CN moiety was accomplished using CuCN at 135 ºC in 96% yield.[3] The absorbance peak at 2236 cm^{-1} in the IR spectrum of **170** showed the incorporation of nitrile moiety. The peak at δ 116.1 in the ^{13}C NMR of **170** confirmed the presence of "CN" group. Further confirmation of the structure was obtained by mass spectrum, which showed the M^+ peak at 226.

To our dismay attempted reduction of the cyano functionality in **170** with either DIBAL or LAH failed to give the required amine **171**. The same transformation when performed following with $NaBH_4/I_2$ in THF at reflux temperature also met with failure.[4]

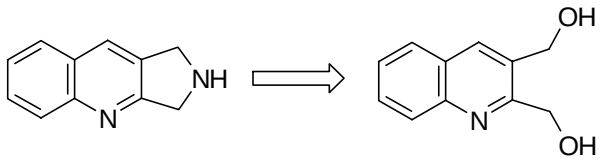
Scheme 50



173 **174** **121**

At this point of time, results from our group showed, deprotection of **173** with either 20% HCl or DDQ failed to give the aminal **174** whose reduction was expected to give the tricyclic amine.[5] Therefore we decided to abandon the present approach and directed our attempts towards the construction of diol whose conversion to tricyclic amine is documented.[1c]

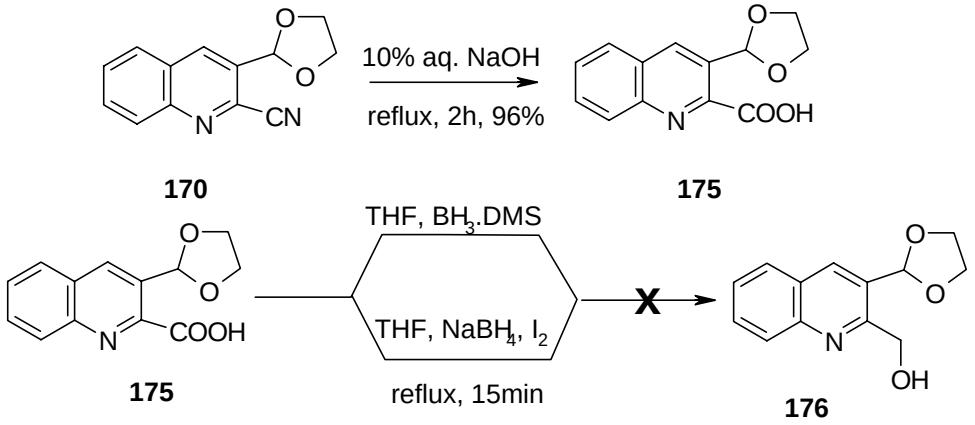
Scheme 51



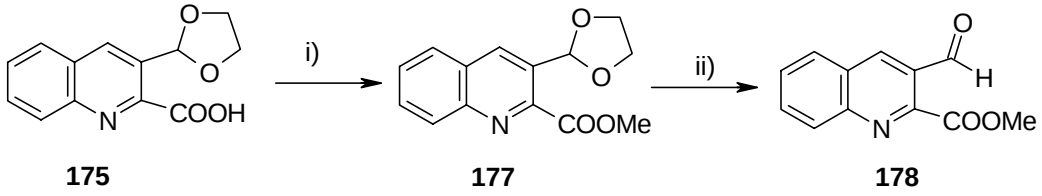
121 **130**

Accordingly, the cyano-quinoline **170** was hydrolyzed to corresponding acid **175** under alkaline conditions. The peak at 7.09 δ in the ^{1}H NMR spectrum of **175** integrating for 1 proton was assigned to hydrogen attached to acetal carbon. Absence of peak at 116.1 δ and the appearance of new peak at 163.8 δ in the ^{13}C NMR spectrum of **175** confirmed the structure of acid **175**. The acid **175** when subjected to reduction with BH_3.DMS as well as with $NaBH_4/I_2$[4] did not provide the corresponding alcohol **176**. Therefore the acid **175** was converted to corresponding methyl ester **177**. The deprotection of acetal in **175** employing 2 N HCl furnished the aldehyde-ester **178** in very high yields. IR spectrum of **178** showed the absorptions at 1775 cm^{-1} and 1714 cm^{-1}. ^{1}H NMR of **178** revealed the characteristic peak of aldehyde proton as a singlet at 10.64 δ. Apart from the ester carbonyl peak at 165.9 δ in the ^{13}C NMR of **178**, presence of peak at 189.9 δ (assigned to aldehyde carbonyl) confirmed the structure of **178**. Mass spectrum showed the molecular ion peak at 215.

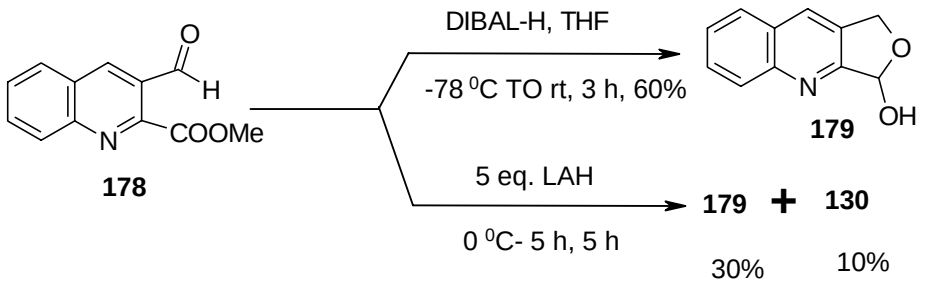
Scheme 52



Scheme 53

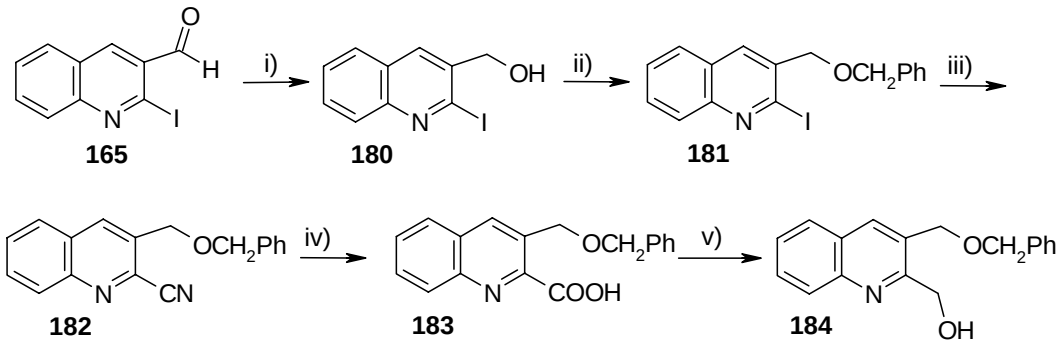


Reagents and conditions: *i) MeI, K_2CO_3, 0 ºC, 5 h, 90%, ii) 2 N HCl, THF, rt, 2 h, 79%.*



As shown in scheme 53, all our attempts towards the transformation of the aldehyde-ester **178** to the corresponding diol **130** in high yields were fruitless. By increasing the relative amount of LAH and prolonged reaction time led to intractable mixture. As a result, it was decided to change the strategy of obtaining the diol by a slightly different approach.

Scheme 54

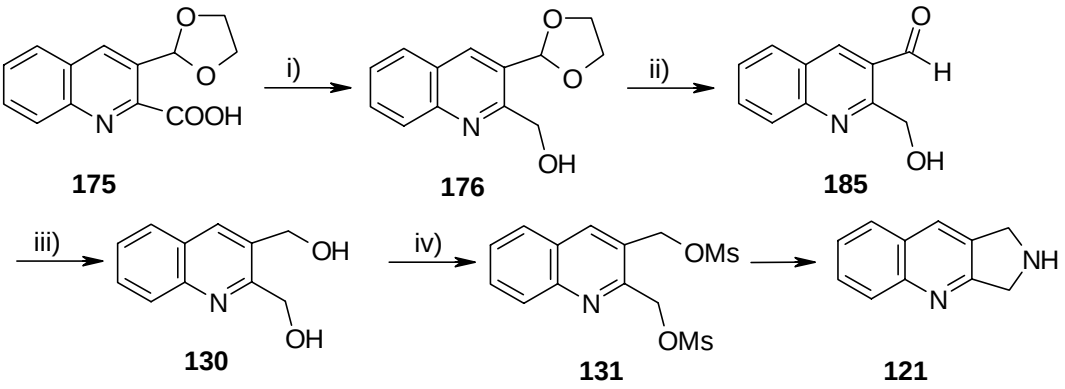


Reagents and conditions: *i) $NaBH_4$, MeOH, rt, 30 min, 90%, ii) $PhCH_2Br$, NaH, THF, rt, overnight, 81%, iii) CuCN, DMF, 145 ºC, 2 h, 83%, iv) 10% aq. KOH, reflux, 16 h, 90%, v) a) ClCOOEt, TEA, THF, 0 ºC, 1 h, b) $NaBH_4$, MeOH, rt, 6 h, 60%.*

The alcohol **180** formed by the reduction of **165** using $NaBH_4$ was protected as its benzylether. This was followed by displacement of iodo group in **181** by cyano moiety employing CuCN. The cyano-quinoline **182** thus obtained was hydrolyzed to corresponding acid **183** under alkaline conditions in excellent yields. Reduction of carboxylic acid to corresponding alcohol via their mixed anhydride using $NaBH_4$ is well documented in literature.[6] As shown in scheme 54, the acid **183** when treated with ethyl chloroformate formed the corresponding mixed anhydride whose reduction with $NaBH_4$ gave the alcohol **184** in 60% yield. IR spectrums showed absorption at 3393 cm^{-1}, confirming the presence of hydroxy moiety. The singlets at 4.62 δ and 4.89 δ totally

integrating for six protons in the ^{1}H NMR spectrum of **184** were assigned to benzylic protons and it showed up field shift in the quinoline C<u>H</u> (8.12 δ) proton para to nitrogen atom. Having successfully achieved the reduction of acid **183**, it was decided to reduce the acid **175** in a similar fashion.

Scheme 55



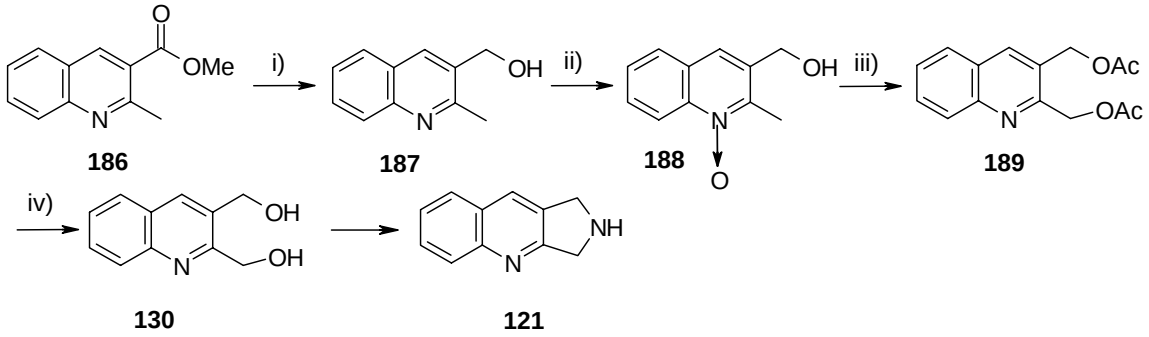
<u>Reagents and conditions:</u> *i) a) ClCOOEt, TEA, THF, 0 ºC, b) $NaBH_4$, MeOH, rt, 6 h, 58%, ii) 2 N HCl, THF, rt, 90%, 1 h, iii) $NaBH_4$, MeOH, rt, 30 min, 85%, iv) MsCl, TEA, C_6H_6, 0 ºC, 1 h, 80%.*

Gratifyingly the reduction of the acid **175** to alcohol **176** was achieved in 58% yield employing mixed anhydride protocol. The singlet peak integrating for 2 protons in the ^{1}H NMR spectrum at 5.01 δ was assigned to benzylic protons. The absence of carbonyl peak at 163.8 δ and the appearance of <u>C</u>H_2 at 62.0 δ in the ^{13}C NMR spectrum of **176** confirmed the structure. Mass spectrum of **176** revealed the molecular ion peak at 231. Deprotection of the acetal **176** using 2 N HCl followed by $NaBH_4$ reduction of the resulting aldehyde **185** furnished the desired diol **130** in 85% yield. IR spectrum of **185** confirmed the presence of aldehyde moiety by showing absorbance at 1713 cm^{-1}. The ^{1}H NMR spectrum of **185** showed the characteristic aldehyde proton at 10.24 δ as a singlet. The diol **130** obtained by reduction of **185** using $NaBH_4$ (85% yield) was converted to its dimesylate **131** whose conversion to tricyclic amine **121** can be obtained as per Corey's protocol.[1c]

Even though a new synthetic route for the construction of diol **130** was achieved, the number of steps involved was a major cause for concern. Consequently it was decided to change the strategy to synthesize the diol in minimum number of steps. A fresh look at

the problem revealed, the same diol can be accessed starting from the cheaper and readily available quinoline ester **186**.

Scheme 56

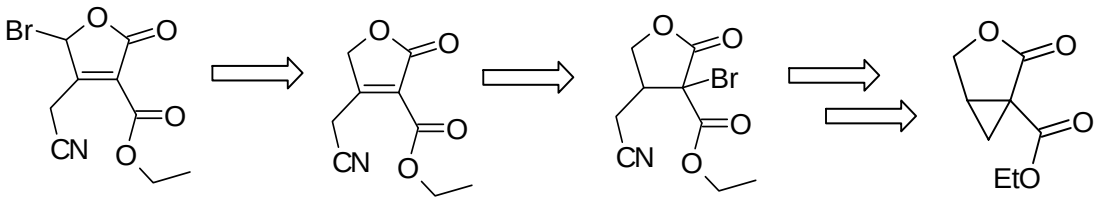


Reagents and conditions*: i) LAH, THF, 0 ºC, 1 h, 55%, ii) m-CPBA, CH_3CN, rt, 12 h, 90%, iii) Ac_2O, 130 ºC, 2 h, 75%, iv) K_2CO_3, aq. MeOH, rt, 0.5 h, 80%,*

Reduction of the ester group in quinoline **186** with lithium aluminiumhydride furnished the corresponding hydroxyquinoline **187** in 55% yield.[7] The oxidation of **187** with *m*-CPBA at room temperature resulted in the formation of corresponding quinoline *N*-oxide **188** in very high yields.[8] The same transformation was also achieved with peracetic acid as an oxidizing agent in just 35% yield. In the ^{1}H NMR spectrum of **188**, the peaks in the aromatic region were assigned to five quinoline protons. The peaks at 2.61 δ integrating for three protons and at 4.68 δ integrating for two protons were assigned to benzylic C$\underline{H}_3$ and C$\underline{H}_2$OH respectively. The structure was further confirmed by mass spectrum of **188,** which showed the molecular ion peak at 189. Quinoline *N*-oxide **188** when treated with acetic anhydride underwent acyl transfer and concomitant [3, 3]-sigmatropic rearrangement,[8] resulting in the formation of diacetate **189** in 75% yield. The absorbance at 1744 cm^{-1} in the IR spectrum of **189** showed the presence of acetate group. ^{1}H NMR spectrum of **189** showed a singlet at 1.98 δ and 2.02 δ, each integrating for 3 protons confirmed the presence of diacetate moiety. Subsequent acetate hydrolysis furnished the diol **130** in good yields. Further the structure of **189** was ascertained by mass spectrum, which showed the molecular ion peak at 273.

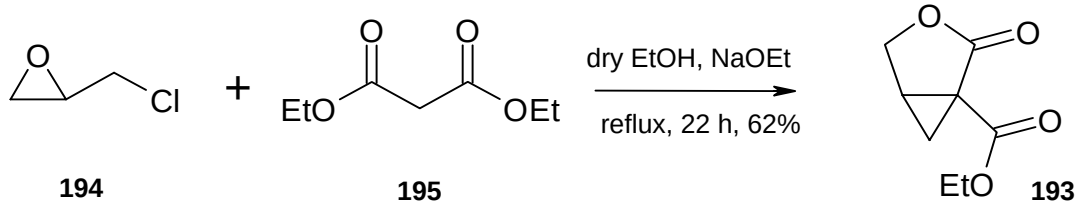
Having been successful in the synthesis of ABC synthon, we turned our attention to the preparation of DE-precursors. It was believed that pseudo acid chloride **190** could be very easily accessed from the electrophilic cyclopropane **193**, which inturn can be synthesized from known literature procedures.[9]

Scheme 57

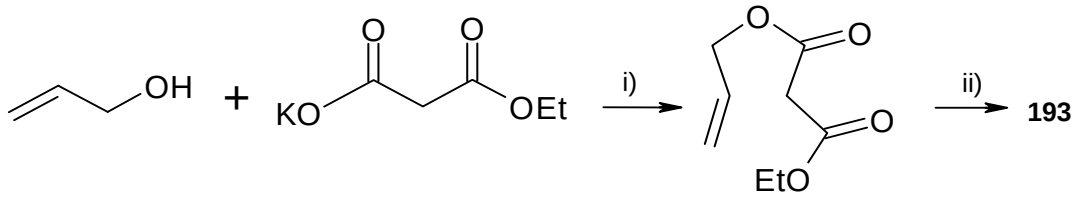


190 **191** **192** **193**

Scheme 58



194 **195** **193**



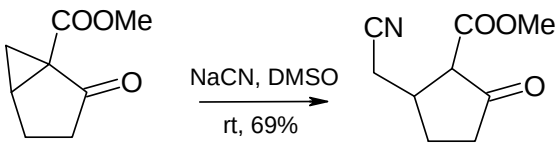
196 **197** **198** **193**

Reagents and Conditions: *i) $SOCl_2$, dry DCM, 8 h, rt, 82%, ii) I_2, K_2CO_3, aliquot 336, toluene, reflux, 3 h, 60%.*

As shown in scheme **58** the requisite cyclopropane **193** was prepared in satisfactory yield either by the nucleophilic attack of diethyl malonate anion on the epichlorohydrin[9a] as well as by the intramolecular single electron transfer radical elemental steps in the transformation of malonic ester **198** under solid–liquid PTC condition.[9b] However, it was observed that when the preparation of **193** was attempted on higher scale (> 5 g), method involving nucleophilic attack of diethyl malonate anion on the epichlorohydrin gave consistent yields of **193** as compared to the latter protocol.

Kondo and coworkers in 1978 observed the nucleophilic ring opening of doubly activated bicyclo[3.1.0]hexane **199** with NaCN in DMSO at rt to give the ring opened adduct **200** in good yield (scheme 59).[10]

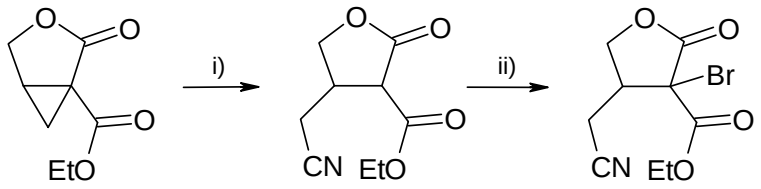
Scheme 59



199 **200**

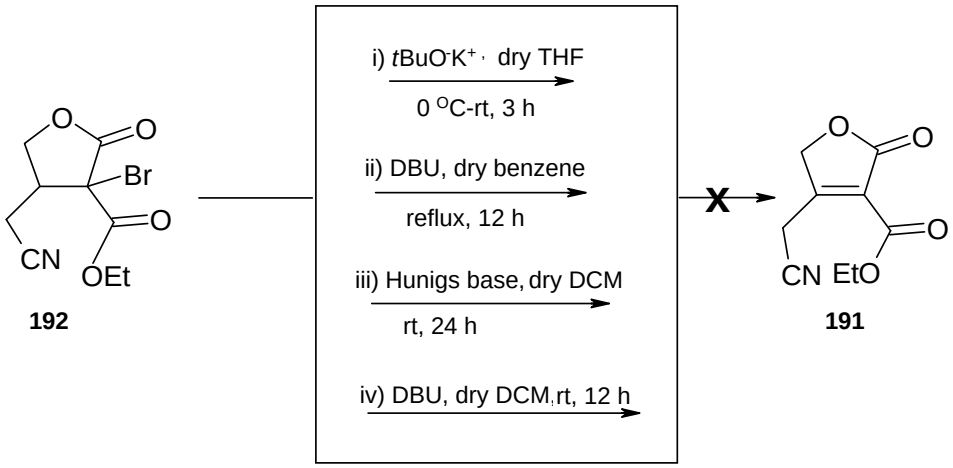
When similar reaction was performed on cyclopropane **193** was treated with NaCN at rt in DMSO, cyano-lactone **201** was formed in 86% yield. This was followed by successful preparation of bromo compound **192** in 83% by treating **201** with Br_2 and K_2CO_3 at rt in 83%. Unfortunately bromo-lactone **192** did not undergo elimination of HBr under a wide variety of conditions. Instead, along with the starting material **192,** debrominated lactone **201** was isolated.

Scheme 60



193 **201** **192**

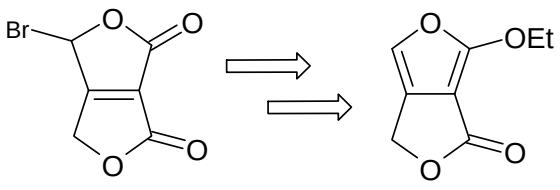
Reagents and conditions*: i) NaCN, DMSO, 24 h, rt, 86%, ii) K_2CO_3, Br_2, DCM, 0.5 h, 83%*



192 **191**

In one another approach towards the synthesis of DE-precursor, we speculated pseudo acid halide **202** to be an interesting synthon, which can be very easily obtained from the acid hydrolysis of alkoxy furan **203** followed by bromonation (scheme 61).

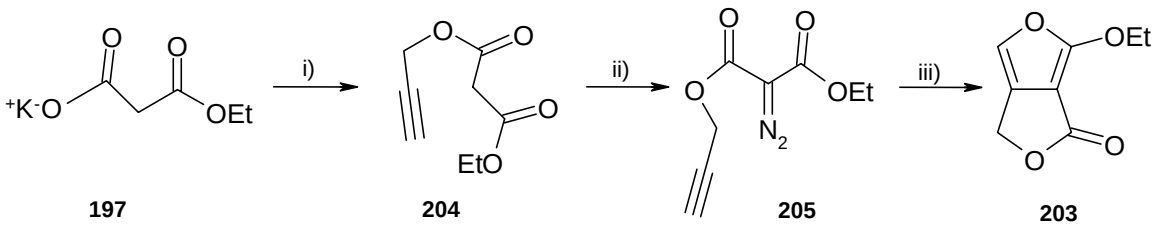
Scheme 61



202 **203**

In accordance with the planned synthesis, mixed ester **204** when subjected to standard diazotransfer protocol using MsN_3 provided the diazo compound **205** in 81% yield. Treatment of **205** with catalytic amount of rhodium acetate in dry benzene at reflux temperature for 3 h furnished the desired alkoxy furan **203** in 65% yield.[11a,11b] The reaction proceeds by addition of a rhodium-stabilized carbenoid on to acetylenic π-bond to give a vinyl carbenoid, which subsequently cyclizes onto the neighboring carbonyl group to produce the furan ring.

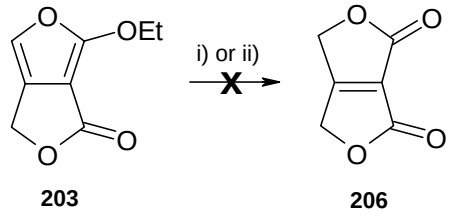
Scheme 62



Reagents and conditions*: i) propargyl alcohol, $SOCl_2$, dry DCM, 8 h, rt, 85%, ii) MsN_3, TEA, CH_3CN, 24 h, rt, 81%, iii) $Rh(OAc)_2$, dry benzene, reflux, 65%*

After having synthesized the required alkoxy furan **203**, it was subjected to hydrolysis under variety of conditions (scheme 62). Unfortunately our attempts to convert the alkoxy furan **203** to butenolide **206** met with failures (scheme 63).

Scheme 63

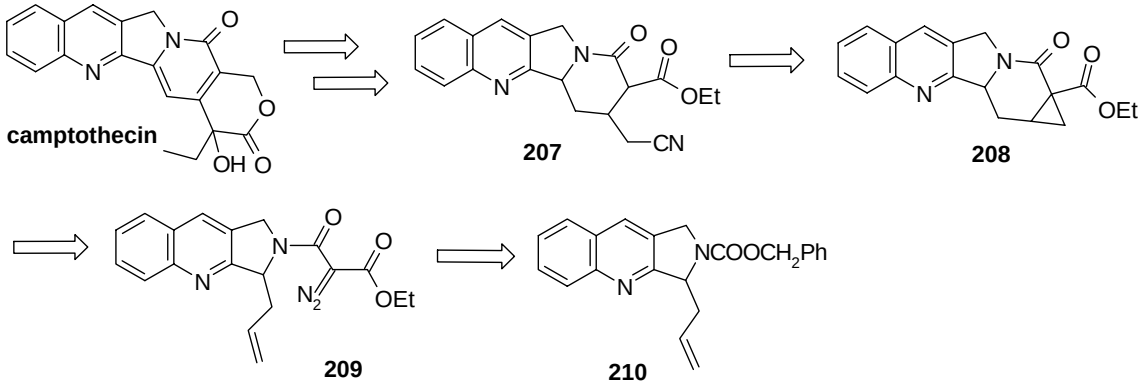


Reagents and conditions: *i) 5N HCl, 50 ºC, MeOH, 6 h, ii) PTSA, MeOH, rt, 17 h.*

In pursuit of alternate strategy to synthesize camptothecin, close look at the target skeleton revealed the possibility of formation of the D ring of camptothecin in a concise manner with suitable substituents necessary for the formation of E-ring through intramolecular cyclopropanation. The electrophilic cyclopropane **208** can suitably be opened as shown in scheme 64 to complete the synthesis of camptothecin. In this context diazo compound stabilized by possessing one or more electron-withdrawing groups such as ketones, esters and amides are of great utility.[12] Therefore it appeared diazo compound

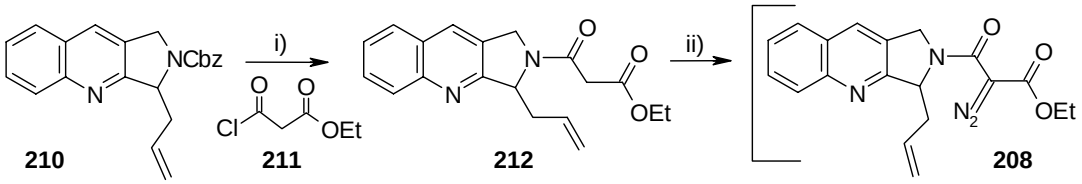
209 will be the appropriate starting material to achieve the proposed strategy, which in turn could be very easily derived from the versatile tricyclic amine **210**. The details of the synthesis of tricyclic amine **210** are available in the Part 1 of this section.

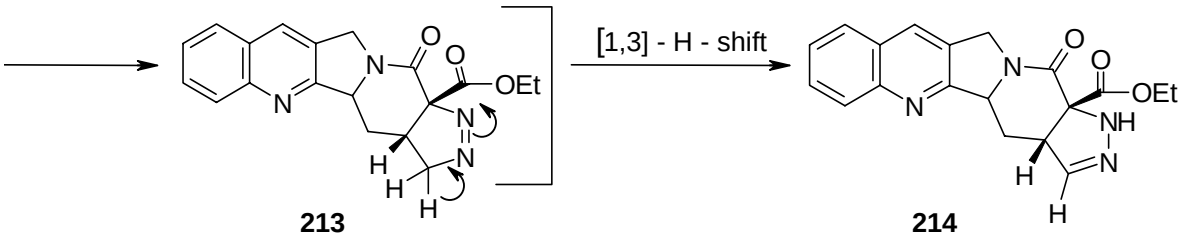
Scheme 64



Thus urethane **210** strictly under degassed condition was treated with 16 eq of KOH in rectified spirit at reflux for 24 h. This was followed by acylation with ethylmalonoyl chloride **211** to furnish the desired ester **212** in 68 % yield starting from urethane **210**. Treatment of **212** with diazotransfer reagent mesyl azide and triethyl amine as base in CH_3CN at room temperature did not provide the desired diazo compound **208**. Interestingly only 2-pyrazoline **214** was isolated in high yields. ^1H spectrum of **214** showed the quinoline pattern comprising of 5 protons in aromatic region. Singlet at δ 6.89 (D_2O exchangeable) and δ 6.53 each integrating for one proton was assigned to N<u>H</u> and vinylic proton respectively. Doublets at δ 4.65 (1 H) and δ 5.15 (1 H), and dd at δ 5.02 (1 H) were assigned to three benzylic protons. The dd at δ 3.84 (1 H) was assigned to allylic proton. The dd at 1.53 (1H) and ddd at 2.94 (1H) was assigned to the C<u>H</u>$_2$ protons present in the terahydropyridone ring. The m/z peak at 351 $(M+1)^+$ in the Mass spectrum of **214** confirmed the structure.

Scheme 65

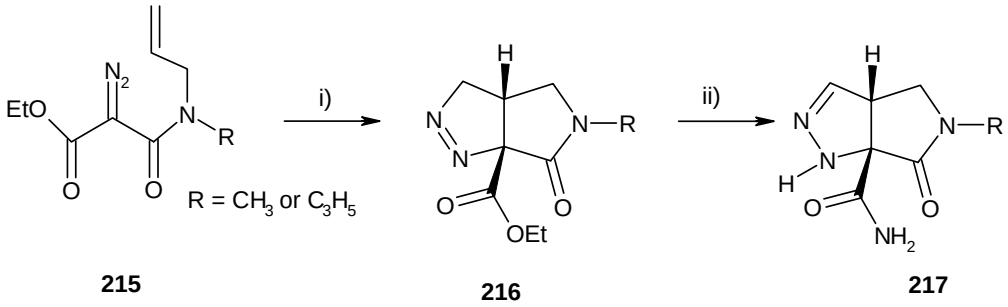




***Reagents and conditions**: i) a) KOH, EtOH, reflux, 24 h, b) K_2CO_3, DCM, 0 ºC to rt, 3 h, 68%, ii) MsN_3, TEA, CH_3CN, rt, 48 h, 81%.*

At this point of time we became aware that *N*-allyldiazomalonamidester **215** are unstable at room temperature and yield pyrazoline **216** in the course of an intramolecular 1,3-dipolar cycloaddition without any catalyst (scheme 66).[11b,13]

Scheme 66



***Reagents and conditions:** i) DCM, rt, 100%, ii) NH_4OH, 20 ºC, 24 h, 72%*

The formation of 2-pyrazoline **214** can be rationalized as follows. Initially formed transient diazo comopound **208**, undergoes facile 1,3-dipolar cycloaddition on to the homoallylic double bond to give the fused 1-pyrazoline **213**, which inturn suffers 1,3-hydrogen shift resulting in the formation of thermodynamically stable 2-pyrazoline **214**. Literature precedents show formation of cyclopropane can be achieved even from 2-pyrazolines by spontaneous extrusion of nitrogen using thermal[14] or photochemical means.[15] Efforts are on for the conversion of 2-pyrazoline **214** to cyclopropane **208** and the subsequent ring opening to complete the synthesis of camptothecin.

1.2.2.4 Conclusions:

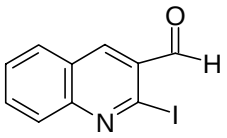
Novel and efficient syntheses of the ABC ring skeleton of camptothecin and related alkaloids is achieved.

Following are the main features of the protocol:

1. We report simple and efficient syntheses of the ABC skeleton of camptothecin, which allows the use of commercially available inexpensive chemical reagents.
2. Our strategy certainly circumvents the short comings of the earlier approaches such as usage of 2-aminobenzaldehyde, regiochemistry problems encountered in Friedlander condensation and the usage of expensive starting materials like acridine, propargyl amine and DMAD.
3. The synthetic sequences presented open the door for efficient preparation of analogues of camptothecin and related alkaloids.

1.2.2.5 Experimental:

2-Iodo-quinoline-3-carbaldehyde (165):[2]



To NaI (23 g, 157 mmol), concentrated HCl (2 mL), and acetonitrile (200 mL) was added 2-chloro-3-formylquinoline (10 g, 52.3 mmol) and the mixture was stirred under reflux for 5.5 h. Solvent was removed under reduced pressure. To the resulting was added water and saturated sodium bicarbonate solution to render the mixture alkaline. The crude product (13 g, 90% yield) was filtered off, washed well with water, and dried in air, and was pure enough for further use.

Mol. Formula: $C_{10}H_6INO$, brown solid.

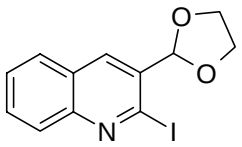
mp: 303-305 ºC

Yield: 90%.

IR ($CHCl_3$) cm^{-1}: 1714, 1692, 1461.

^1H NMR (200 MHz, $CDCl_3$) δ: 7.67 (m, 1H), 7.88 (m, 1H), 7.94 (m, 1H), 8.12 (d, *J*=8.33 Hz, 1H), 8.56 (s, 1H), 10.30 (s, 1H).

3-[1,3] Dioxaolan-2-yl-2-iodo-quinoline (166):



A solution of 2-iodo-3-formyl quinoline (**165**) (28.3g, 0.1 mol) in benzene (300 mL) containing ethylene glycol (18.62 g, 0.3 mol) and catalytic amount of PTSA was heated under reflux for 7 h with azeotropic removal of water. The solution was cooled and treated with saturated $NaHCO_3$ solution (100 mL). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to give **166** as a white solid (34.1g, 90%), which was pure enough for further use.

Mol. Formula: $C_{12}H_{10}INO_2$, white solid.

mp: 110 ºC.

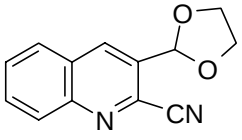
Yield: 90%.

IR (Nujol) cm^{-1}: 1625, 1555, 1310, 1175.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 4.14 (m, 4H), 5.99 (s, 1H), 7.54 (m, 1H), 7.7-7.82 (m, 2H), 8.02 (m, 1H,), 8.15 (s, 1H).

Mass m/z (%): 327 (M^+, 5), 235 (80), 204 (10), 200 (30), 190 (50), 163 (100), 148 (75), 127 (50), 101 (30).

3-[1,3]Dioxolan-2-yl-quinoline-2-carbonitrile (170):



The mixture containing aryl iodide **166** (1 g, 3 mmol), CuCN (0.328 g, 3.66 mmol), and dry DMF (5 mL) under nitrogen atmosphere was heated at 135 ºC for 3h. DMF was removed from the reaction mixture under reduced pressure. After cooling the resulting solid residue, aqueous ammonia (50 mL) followed by ethyl acetate (50 mL) was added and stirred vigorously till the solid disintegrated. Organic layer was separated and washed with water (3x10 mL). The ethyl acetate layer was dried using anhydrous sodium sulphate, filtered and concentrated under vacuum. The residue obtained was column chromatographed using silica gel and pet-ether/EtOAc (7/3) to afford the nitrile **170** as white solid in 96% yield (0.663 g).

Mol. Formula: $C_{13}H_{10}N_2O_2$, pale yellow solid.

mp: 121-123 ºC

Yield: 96%.

IR ($CHCl_3$) cm^{-1}: 2236

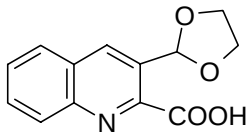
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 4.15-4.33 (m, 4H), 6.13 (s, 1H), 7.70 (m, 1H), 7.81-7.92 (m, 2H), 8.16 (d, *J*=8.8 Hz, 1H), 8.37 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 148.4 (s), 136.9 (d), 133.1 (s), 132.9 (s), 131.7 (d), 130.2 (d), 129.9 (d), 128.8 (d), 116.1 (s), 101.6 (d), 66.3 (t).

Mass (m/z): 226 (M^+ 24), 181 (14), 154 (26), 127 (10), 101 (19), 73 (100), 63 (8).

Analysis:	**C**	**H**	**N**
Expected:	69.02	4.46	12.38
Observed:	69.14	4.30	12.30

3-[1,3]Dioxolan-2-yl-quinoline-2-carboxylic acid (175):



The nitrile **170** (10 g, 44 mmol), and 10% sodium hydroxide (200 mL) solution were heated under reflux for 6 h. The solution was cooled and extracted with DCM (2x100 mL). The aqueous solution was rendered acidic with 10% HCl solution and extracted with DCM (3x100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuuo* to afford the acid **175** as white solid in 96% yield (10.4 g).

Mol. Formula: $C_{13}H_{11}NO_4$, white solid.

mp: decomposed above 160 ºC

Yield: 96%.

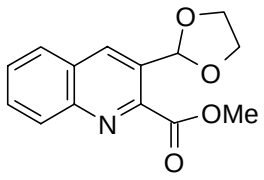
IR (nujol) cm^{-1}: 3200, 1740

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 4.16 (s, 4H), 7.01 (s, 1H), 7.71 (t, *J*=7.33 Hz, 1H), 7.85 (t, *J*=7.81 Hz, 1H), 7.96 (d, *J*=7.81 Hz, 1H), 8.14 (d, *J*=8.30 Hz, 1H), 8.72 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 163.8 (s), 145.0 (s), 144.4 (s), 137.0 (d), 131.9 (s), 131.5 (d), 129.4 (d), 128.8 (d), 128.2 (d), 99.4 (d), 65.5 (t, 2C).

Analysis:	**C**	**H**	**N**
Expected:	63.67	4.52	5.71
Observed:	63.74	4.60	5.47

3-[1,3]Dioxolan-2-yl-quinoline-2-carboxylic acid methyl ester (177):



To the mixture of acid **175** (0.500 g, 2 mmol) and K_2CO_3 in dry DCM maintained at rt was added 0.842 g (6 mmol) of MeI and stirred at room temperature for 5 h. The reaction mixture was filtered. The precipitate was repeatedly washed with DCM. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated

under reduced pressure to give the pure title compound as white solid in 90% yield (0.477 g).

Mol. Formula: $C_{14}H_{13}NO_4$, white solid

mp: 163-165 ºC

Yield: 90%.

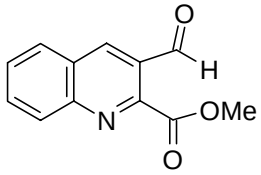
IR ($CHCl_3$) cm^{-1}: 2952, 1732, 1566, 1458.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 3.95-4.00 (m, 4H), 4.01 (s, 3H), 6.56 (s, 1H), 7.55 (m, 1H), 7.71 (m, 1H), 7.81 (m, 1H), 8.15 (m, 1H), 8.42 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 166.6 (s), 148.5 (s), 148.6 (s), 134.7 (d), 130.6 (s), 130.4 (d), 129.7 (d), 128.2 (d), 127.8 (d), 100.1 (d), 65.1 (t, 2C), 52.8 (q).

Mass (m/z): 258 ($[M-1]^+$, 2), 228 (5), 200 (45), 156 (10), 129 (100), 101 (10), 73 (10), 63 (3).

3-Formyl-quinoline-2-carboxylic acid methyl ester (178):



To the acetal **177** (0.700 g, 2.7 mmol) in THF (5 mL) was added 10% HCl (5 mL) and stirred at room temperature for 2 h. After THF was removed under reduced pressure, the mixture was rendered basic by saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3x10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was column chromatographed using silica gel and pet-ether/EtOAc (9/11) to afford the ester-aldehyde **178** as a white solid in 79% yield (0.46 g).

Mol. Formula: $C_{12}H_9NO_3$, white solid.

mp: 103-105 ºC

Yield: 79%.

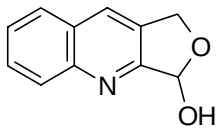
IR ($CHCl_3$) cm^{-1}: 1775, 1714, 1692, 1461.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.15 (m, 3H), 7.75 (m, 1H), 7.94 (m, 1H), 8.04 (m, 1H), 8.31 (d, *J*=8.33 Hz, 1H), 8.81 (s, 1H), 10.64 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 189.9 (d), 165.9 (s), 148.6 (s), 148.4 (s), 139.3 (d), 132.9 (d), 130.0 (d), 129.2 (d), 128.8 (d), 127.7 (s), 53.4 (q).

Mass (m/z): 215 (M^+, 2), 201 (5), 173 (65), 157 (10), 129 (100), 101 (30), 75 (30), 63 (5).

1, 3-dihydrofuro[4, 3-*b*]-quinolin-3-ol (179):[16]



To the ester-aldehyde **178** (0.5 g, 2.3 mmol) dissolved in dry THF maintained at –78 ºC was added 4 mL of DIBAL solution (1.7 molar) dropwise. Reaction temperature was raised slowly and stirred at room temperature for 3 h. The reaction mixture was quenched with saturated ammonium chloride solution, dilluted with ethyl acetate and filtered over a bed of celite. After washing the celite bed repeatedly with ethyl acetate, the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue upon column chromatography using pet-ether and ethyl acetate (11:9) gave the title compound as thick oil in 60 % (0.260 g).

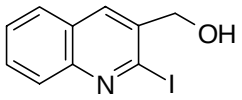
Mol. Formula: $C_{11}H_9NO_2$, thick oil.

Yield: 60%.

IR ($CHCl_3$) cm^{-1}: 3500, 1600.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 5.18 (d, *J*=12.5 Hz, 1H), 5.46 (d, *J*=12.5 Hz, 1H), 6.70 (s, 1H), 7.54-7.60 (m, 1H), 7.68-7.71 (m, 1H), 7.79-7.83 (m, 1H), 8.02 (s, 1H), 8.19 (m, 1H).

(2-Iodo-quinolin-3-yl)-methanol (180):



To the aldehyde **165** (3 g, 10.6 mmol) dissolved in methanol maintained at 0 ºC was added $NaBH_4$ (0.483 g, 12.7 mmol). Reaction temperature was raised slowly and stirred at room temperature for 1 h. Methanol was removed under reduced pressure. The residue was quenched with saturated ammonium chloride solution, dilluted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the pure title compound in 90% yield (2.71 g).

Mol. Formula: $C_{10}H_{18}INO$, brown solid.

mp: 187-189 ºC

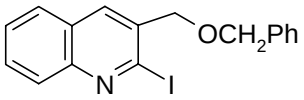
Yield: 90%.

IR ($CHCl_3$) cm^{-1}: 3390, 3017, 1414.

^1H NMR (200 MHz, $CDCl_3$) δ: 4.78 (s, 2H), 7.50-7.54 (m, 1H), 7.58-7.75 (m, 2H), 8.04-8.08 (m, 2H).

Mass (m/z): 285 (M^+, 2), 158 (4), 130 (3), 158 (10), 62 (100).

3-Benzyloxymethyl-2-Iodo-quinoline (181):



To the 50% NaH (0.100 g, 4.6 mmol) in dry DMF at 0 ºC was added hydroxy compound **180** (0.555 g, 1.9 mmol) dropwise. The reaction mixture was allowed to stir at the same temperature for 10 min. To the reaction mixture, benzyl bromide (0.274 g, 2.3 mmol) dissolved in DMF was added dropwise and allowed to stir at rt overnight. The reaction mixture was rendered acidic and extracted in ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using silica gel with pet-ether and ethyl acetate (8:2) as eluent to furnish the title compound as a white solid in 81 % yield (0.588 g)

Mol. Formula: $C_{17}H_{14}INO$, white solid.

mp: 96-98 ºC

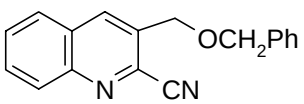
Yield: 70%.

IR ($CHCl_3$) cm^{-1}: 3017, 1588, 1560.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 4.64 (s, 2H), 4.76 (s, 2H), 7.36-7.47 (m, 5H), 7.56 (m, 1H), 7.60 (m, 1H), 7.69 (m, 1H), 8.03-8.10 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ: 148.8 (s), 137.8 (s), 134.59 (s), 134.50 (d), 129.8 (d), 128.7 (d), 128.6 (d, 2C), 128.0 (d), 127.9 (d, 2C), 127.7 (d), 127.4 (s), 127.2 (d), 122.3 (s), 74.16 (t), 73.21 (t).

3-Benzyloxymethyl-quinoline-2-carbonitrile (182):



The title compound **182** (0.910 g) was prepared from **181** (1.5 g) as per the procedure outlined for the preparation of compound **170**

Mol. Formula: $C_{18}H_{14}N_2O$, white solid.

mp: 70-71 ºC

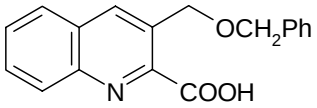
Yield: 83%.

IR ($CHCl_3$) cm^{-1}: 3019, 2864, 2233, 1561, 1493.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 4.73 (s, 2H), 4.86 (s, 2H), 7.30-7.40 (m, 5H), 7.61-7.69 (m, 1H), 7.74-7.86 (m, 2H), 8.11 (d, *J*=8.33 Hz, 1H), 8.32 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 147.5 (s), 137.4 (s), 135.9 (s), 133.3 (s), 131.0 (d), 129.9 (d), 129.6 (d), 128.7 (d, 2C), 128.2 (d), 128.1 (d, 2C), 127.9 (d), 116.05 (s), 73.7 (t), 68.4 (t).

3-Benzyloxymethyl-quinoline-2-carboxylic acid (183):



The title compound **183** (0.962 g) was prepared from **182** (1.00 g) as per the procedure outlined for the preparation of compound **175**

Mol. Formula: $C_{18}H_{15}NO_3$, white solid.

mp: decomposed above 160 ºC

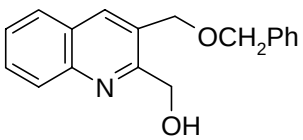
Yield: 90%.

IR ($CHCl_3$) cm^{-1}: 3218, 1743

^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.73 (s, 2H), 5.17 (s, 2H), 7.29-7.37 (m, 5H), 7.04-8.04 (m, 4H), 8.59 (s, 1H), 10.13 (bs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.1 (d), 143.7 (s), 142.5 (s), 138.0 (s), 136.8 (d), 133.4 (s), 130.8 (d), 129.9 (s), 129.3 (d), 128.5 (d, 2C), 128.4 (d), 127.9 (d), 127.8 (d, 2C), 127.7 (d), 73.3 (t), 68.6 (t)

(3-Benzyloxymethyl-quinolin-2-yl)-methanol (184):



A solution of ethylchloroformate (0.414 g, 3.75 mmol) in dry THF (10 mL) was added drop-wise at –5 ºC to a solution of carboxylic acid **175** (1 g, 3.4 mmol) and triethyl amine (0.39 g, 3.9 mmol) in THF (10 mL) in the course of 30 min at the same temperature. The white precipitate was filtered off, washed with 3x5 mL of THF, and the washings were added during 30 min to a solution of $NaBH_4$ (0.301 g, 8.5 mmol) in water (5 mL) at 10 -15 ºC by external cooling. After the addition was complete, the reaction mixture was stirred at room temperature for additional 3 h. THF was removed under reduced pressure and the residue was extracted with 3x15 ml of DCM. The aqueous layer was acidified with dil HCl, neutralized by saturated sodium bicarbonate solution and extracted with 3x20 ml of DCM. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was column chromatographed using silica gel and pet-ether/EtOAc (3/2) to afford the hydroxy compound in 60% yield (0.571 g).

Mol. Formula: $C_{18}H_{17}NO_2$, white solid.

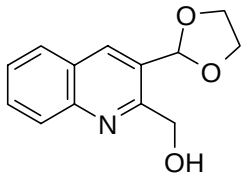
mp: 96-98 ºC

Yield: 60%.

IR ($CHCl_3$) cm^{-1}: 3393, 1622, 1452.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 4.62 (s, 4H), 4.89 (s, 2H), 7.37 (s, 5H), 7.54 (m, 1H), 7.71 (m, 1H), 7.82 (m, 1H), 8.06-8.12 (m, 2H).

(3-[1,3]Dioxolan-2-yl-quinolin-2-yl)-methanol (176):



The title compound **176** (2.73 g) was prepared from compound **175** (5.00 g) as per the procedure outlined for the preparation of compound **184**.

Mol. Formula: $C_{13}H_{13}NO_3$, orange solid.

mp: 72-73 ºC.

Yield: 58%.

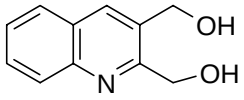
IR ($CHCl_3$) cm^{-1}: 3393, 1625, 1414

^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) δ: 4.07- 4.16 (m, 4H), 5.01 (s, 2H), 5.99 (s, 1H), 7.55 (m, 1H), 7.74 (m, 1H), 7.85 (m, 1H), 8.09 (d, *J*=8.80 HZ, 1H), 8.29 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 157.5 (s), 146.3 (s), 134.6 (d), 130.2 (d), 128.4 (d), 128.0 (d), 127.7 (s), 126.9 (s), 126.6 (d), 101.1 (d), 65.3 (t, 2C), 62.0 (t)

Mass (m/z): 231 (M^+ 5), 213 (80), 186 (74), 158 (97), 130 (76), 101 (23), 73 (78), 63 (12).

2-Hydroxymethyl-quinolin-3-yl-methanol (130):



To the diacetate **189 (**1g, 5.29 mmol) dissolved in aq. MeOH (10 mL) was added K_2CO_3 (1.46 g, 10.58 mmol) at room temperature for 30 min. After the methanol was removed under reduced pressure, the residue was extracted with dichloromethane (3x20 mL). The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Column chromatography on silica gel (eluting with pet. ether-EtOAc=32:1) furnished the dihydroxy compound **130** as a pale yellow solid in 80% yield (0.550 g).

Or

To the hydroxy compound **176** (1.5 g, 6.5 mmol) in THF (5 mL) was added 10% HCl (5 mL) and stirred at room temperature for 6 h. After THF was removed under reduced pressure, the mixture was rendered basic by saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3x10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was column chromatographed using silica gel and pet-ether/EtOAc (1.45/1) to afford the hydroxy aldehyde **185** as a white solid in 90% yield (1.09 g).

Mol. Formula: $C_{11}H_9NO_2$,

mp: 102-103 ºC

Yield: 90%.

IR ($CHCl_3$) cm^{-1}: 3380, 1713, 1561

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 5.21 (s, 2H), 7.68-7.75 (m, 1H), 7.88-7.99 (m, 2H), 8.07-8.20 (m, 1H), 8.64 (s, 1H), 10.24 (s, 1H).

To the hydroxy aldehyde **185** (1 g, 5.4 mmol) in methanol (10 mL) at 0 ºC was added sodium borohydride (0.197 g, 5.35mmol). The reaction mixture was stirred at same temperature for 1 h. The reaction mixture was quenched with 10 mL of water. Methanol was removed under reduced pressure and the residue was extracted with 3x 20 mL of DCM. The aqueous layer was acidified with dil HCl, neutralized by saturated sodium bicarbonate solution and extracted with 3x50 mL of DCM. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was column chromatographed using silica gel and pet-ether/EtOAc (3/7) to afford the diol **130** in 85% yield (0.85 g).

Mol. Formula: $C_{11}H_{11}NO_2$, pale yellow solid.

mp: 118 ºC-120 ºC, lit[6b]115 ºC-118 ºC

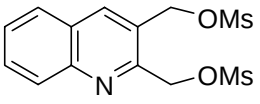
Yield: 80%.

IR ($CHCl_3$) cm^{-1}: 3202.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.77 (b, 1H), 4.83 (s, 2H), 4.93 (s, 2H), 7.56 (m, 1H), 7.73 (m, 1H), 7.84 (d, *J*=8.22 Hz, 1H,), 8.08 (d, *J*=8.22 Hz, 2H), 8.18 (s, 1H).

Mass (m/z): 189 (M^+, 7), 171 (53), 160 (27), 143 (100), 130 (33), 115 (30), 103 (20).

Methanesulfonic acid 2-methanesulfonyloxymethyl-quinolin-3-ylmethyl ester (131):



To a mixture of **130** (0.500 g, 2.7 mmol) and triethylamine (1.0 6 g, 10.5mmol) in dry benzene at –5 ºC was added MsCl (0.909 g, 7.9 mmol) drop wise. The reaction mixture was stirred at the same temperature for 2 h. The resulting mixture was washed with water (10 mL), saturated sodium bicarbonate solution (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was subjected to column chromatography on silica gel (eluting with 40% pet. ether-EtOAc) afforded the title compound **131** as colorless oil (0.73g, 80% yield).

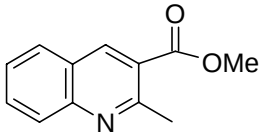
Mol. Formula: $C_{13}H_{15}NO_6S_2$, thick oil.

Yield: 80%.

IR ($CHCl_3$) cm^{-1}: 3020, 1604, 1497, 1360, 1215, 1175.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 3.07 (s, 3H), 3.10 (s, 3H), 5.47 (s, 2H), 5.54 (s, 2H), 7.57 (s, 1H), 7.7-7.84 (m, 2H), 8.04 (d, *J*=8.30 Hz, 1H), 8.24 (s, 1H).

2-Methyl-quinoline-3-carboxylic acid methyl ester (186):[17]



To a mixture containing redistilled aniline 23 g (0.25 mol), 33 g of ethylaceto acetate (0.25 mol) and 1 mL of glacial acetic acid, was added 100 mL of benzene. The mixture was refluxed azeotropically until no more water separates (6 h). The benzene was then removed under reduced pressure. The residue was diluted with DCM and washed with saturated bicarbonate solution. The organic layer was separated dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 37 g of pure enamine.

To the DMF (6.31 g) at 0-5 ºC was added $POCl_3$ (39.4 g). The resultant reagent was stirred for a further 30 min at rt and cooled to 5 ºC. To the reaction mixture was added enamine (15 g) dissolved in chloroform. After refluxing for 6 h, the cooled reaction mixture was poured in to saturated sodium bicarbonate solution and extracted chloroform. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 13.10 g (83%) of title compound as a white solid.

Mol. Formula: $C_{12}H_{11}NO_2$,

mp: 64-66 ºC

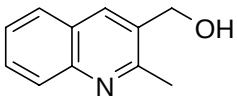
Yield: 83%.

IR ($CHCl_3$) cm^{-1}: 2957, 1725, 1440.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.91 (s, 3H), 3.88 (s, 3H), 7.42 (m, 1H), 7.68 (m, 2H), 7.95 (s, 1H), 8.61 (s, 1H).

Mass (m/z): 201 (M^+, 33), 169 (45), 142 (70), 115 (65), 101 (53), 89 (49), 75 (100), 63 (78).

2-Methyl-3-hydroxymethylquinoline (187):



The ester **186** (5 g, 24.8 mmol) in dry THF (50 mL) was added slowly at 0 ºC to the suspension of LAH (0.945 g, 24.8 mmol) in dry THF (20 mL). The reaction mixture

was stirred for 1 h at 0 ºC, quenched with methanol and the precipitate was filtered. The precipitate was washed with ethyl acetate (3x20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuuo*. Chromatography on silica gel (eluting with pet. ether-EtOAc=9:11) afforded the title compound **187** as a pale yellow solid (2.37g, 55%).

Mol. Formula: $C_{11}H_{11}NO$, pale yellow solid.

Yield: 55%.

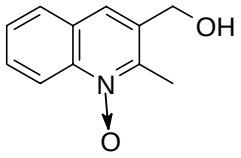
mp: above 240 ºC

IR (Nujol) cm^{-1}: 3150, 2943, 2922, 1455.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.72 (s, 3H), 4.89 (s, 2H), 7.50 (m, 1H), 7.69 (m, 1H), 7.79 (d, *J*=8.00 Hz, 1H), 8.03 (d, *J*=8.00 Hz, 1H), 8.12 (s, 1H).

Mass m/z (%): 173 (M^+, 100), 155 (84), 144 (100), 131 (30), 115 (40), 103 (19), 89 (17), 77 (38), 63 (30).

2-Methyl-3-hydroxymethylquinoline 1- oxide (188):



To the hydroxyquinoline **187** (2.5 g, 14.4 mmol) in acetonitrile (40 mL) was added 55 % *m*-CPBA (5 g, 16 mmol) dissolved in acetonitrile (15 mL) dropwise. The reaction mixture was stirred overnight at room temperature. The solid obtained was filtered, washed with saturated Na_2SO_3 solution (10 mL), $NaHCO_3$ solution (10 mL) and acetonitrile (10 mL), dried under reduced pressure as a white solid. The crude quinoline *N*-oxide **188** thus obtained (2.45 g, 90% yield) was sufficiently pure for the subsequent reaction.

Mol. Formula: $C_{11}H_{11}NO_2$, white solid.

Yield: 90%.

mp: 191 ^{O}C-193 ^{O}C

IR (Nujol) cm^{-1}: 2924, 2855,1601, 1564, 1461, 1377.

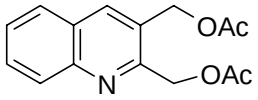
^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.61 (s, 3H), 4.68 (s, 2H), 7.39 (m, 3H), 7.68 (m, 1H), 8.56 (d, *J* = 10.00 Hz, 1H).

^{13}C NMR (CD_3OD, 75 MHz) δ: 148.5 (s), 140.9 (s), 136.2 (s), 131.9 (d), 129.5 (d, 2C), 127.8 (d), 11.9 (d), 62.4 (t), 14.3 (q).

Mass (m/z): 189 (M^+, 27), 172 (60), 155 (13), 144 (100), 128 (37), 115 (53), 102 (23), 89 (27), 77 (54).

Analysis:	**C**	**H**	**N**
Expected	69.84	5.82	7.40
Observed:	69.54	5.97	7.15

Acetic acid 2-acetoxymethyl-quinolin-3-ylmethyl ester (189):



To Ac_2O (15 mL) preheated at 110 ºC, quinoline *N*-oxide **188** (2 g, 10.6 mmol) was added. After stirring at the same temperature for 5 min, the reaction mixture was heated at 130 ºC for 90 min. Excess Ac_2O was removed under reduced pressure. The residue obtained was subjected to column chromatography on silica gel (eluting with 30% pet. ether-EtOAc) afforded the title compound **189** as colorless oil (2.17g, 75%).

Mol. Formula: $C_{15}H_{15}NO_4$, thick oil.

Yield: 75%.

IR ($CHCl_3$) cm^{-1}: 1744, 1374.

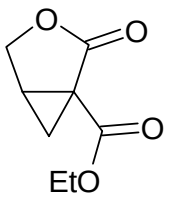
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.98 (s, 3H), 2.02 (s, 3H), 5.17 (s, 2H), 5.29 (s, 2H), 7.38 (m, 1H), 7.55 (m, 2H), 7.94 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 169.6 (s, 2C), 153.9 (s), 147.0 (s), 136.8 (d), 129.6 (d), 129.1 (d), 127.5 (s), 127.2 (d), 126.8 (d), 65.5 (t), 62.6 (t), 20.4 (q, 2C).

Mass (m/z): 273 (M^+, 25), 230 (45), 170 (83), 143 (100), 130 (13), 115 (27).

Analysis:	**C**	**H**	**N**
Expected	65.93	5.53	5.13
Observed:	65.45	5.44	5.10

2-Oxa-3-oxa-bicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (193):[9]



Sodium (2.4, 105 mmol) was dissolced in absolute EtOH (200 mL), and diethyl malonate (17 mL, 110 mmol) was added at 0 ºC over 5 min to the solution. Epichlorohydrin (8 mL, 100 mmol) in EtOH (10 mL) was added dropwise to the solution at rt over 1 h, and the mixture was stirred at 75 ºC for 20 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in DCM and washed with water. The organic layer was concentrated under reduced pressure, and the residue was chromatographed on silica gel eluting with pet-ether:ethyl acetate (4:1) to yield the title compound as a colourless oil (11 g, 65%)

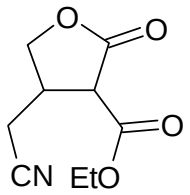
Mol. Formula: $C_8H_{10}O_4$, thick liquid.

Yield: 65%.

IR ($CHCl_3$) cm^{-1}: 1782, 1717.

^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4) δ: 1.26 (t, *J*=6.54 Hz, 3 H), 1.32 (dd, *J*=3.37 and 6.20 Hz, 1H), 2.01 (dd, *J* =3.37 and 6.35 Hz, 1H), 2.65 (m, 1H), 4.14 (d, *J*=9.58 Hz, 1H), 4.19 (q, *J*=6.54 Hz, 2H), 4.31 (dd, *J*=3.77 and 9.35 Hz, 1H).

4-Cyanomethyl-2-oxo-tetrahydro-furan-3-carboxylic acid ethyl ester (201):



To the mixture containing cyclopropane **193** (0.400 g, 2.35 mmol) in DMSO (3 mL) was added NaCN (0.130 g, 2.58 mmol) dropwise. The reaction mixture was further stirred for 24 h at room temperature. After the completion of the reaction as monitored by TLC, the reaction mixture was subjected to column chromatography on silica gel (eluting with pet. ether:EtOAc=6:4) to afford the title compound **201** as thick oil (0.398 g, 86 % yield).

Mol. Formula: $C_9H_{11}NO_4$, thick liquid.

Yield: 86%.

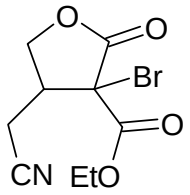
IR ($CHCl_3$) cm^{-1}: 2260, 1779, 1732.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.31 (t, *J*=8.2 Hz, 3H), 2.72 (m, 2H), 3.36 (m, 1H), 3.98 (m, 1H), 4.06 (dd, *J*=8.1 and 8.8 Hz, 1H), 4.26 (q, *J*=7.3 Hz, 2H), 4.56 (dd, *J*=8.45 and 8.10 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.2 (s), 166.3 (s), 116.5 (s), 70.0 (t), 62.6 (t), 50.9 (d), 36.2 (d), 19.2 (t), 14.0 (q).

Analysis:	**C**	**H**	**N**
Expected:	54.82	5.62	7.10
Observed:	54.79	5.97	6.84

3-Bromo-4-cyanomethyl-2-oxo-tetrahydro-furan-3-carboxylic acid ethyl ester (192):



To the mixture containing lactone **201** (0.300 g, 1.522 mmol mmol) and K_2CO_3 (0.420 g, 3.04 mmol) in dry DCM at 0 ºC was added Br_2 (0.288 g, 1.8 mmol) dissolved in dry DCM (2 mL) dropwise. The reaction mixture was further stirred for 0.5 h at room temperature. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure. The residue obtained was subjected to column chromatography on silica gel (eluting with pet. ether:EtOAc=7:3) to afford the title compound **192** as thick oil (0.347 g, 83 % yield).

Mol. Formula: $C_9H_{10}BrNO_4$, thick liquid.

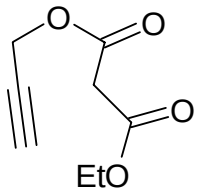
Yield: 83%.

IR ($CHCl_3$) cm^{-1}: 2257, 1779, 1726.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.34 (t, *J*=8.4 Hz, 3H), 2.70 (m, 2H), 3.34 (m, 1H), 3.98 (m, 1H), 4.33 (q, *J*=8.4 Hz, 2H), 4.56 (m, 1H).

Mass m/z (%): 230 (2), 203 (5), 170 (55), 163 (10), 143 (60), 125 (75), 108 (100), 97 (30), 85 (75), 80 (35), 69 (10).

Malonic acid ethyl ester prop-2-ynyl ester (204):



To the mixture of acid-salt **197** (5 g, 29.4 mmol) and propargyl alcohol (2 g, 35.3 mmol) in dry benzene at 0 ºC was added thionyl chloride (5.25 g, 44.1 mmol) dropwise

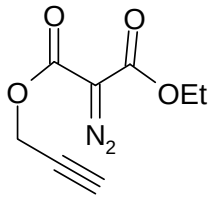
and stirred for 4 h. Water was added dropwise to the reaction mixture. The organic layer was separated, dried over anhydrous sodium sulpahte, filtered and concentrated under reduced pressure. The residue obtained was subjected to column chromatography on silica gel (eluting with pet. ether:EtOAc=9:1) to afford the title compound **204** as thick oil (4.25 g, 85 % yield).

Mol. Formula: $C_8H_{10}O_4$, thick liquid.

Yield: 85%.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.26 (t, *J*=7.05 Hz, 3H), 2.51 (t, *J*=2.35 Hz, 1H), 3.25 (s, 2H), 4.25 (q, *J*=7.05 Hz, 2H), 4.78 (d, *J*=2.35 Hz, 2H).

2-Diazo-malonic acid ethyl ester prop-2-ynyl ester (205):



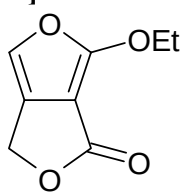
To the mixture containing keto-ester **204** (1.00 g, 5.8 mmol) and triethyl amine (1.2 g, 11.6 mmol) in acetonitrile (7 mL) at 0 ºC was added mesyl azide (1.035 g, 8.7 mmol) dropwise. The reaction mixture was further stirred for 48 h at room temperature. After the completion of the reaction as monitored by TLC acetonitrile was removed under reduced pressure. The residue was extracted with ethyl acetate and was washed with 10% NaOH solution. The organic layer was thoroughly washed with water, dried over anhydrous sodium sulpahte, filtered and concentrated under reduced pressure. The residue obtained was subjected to column chromatography on silica gel (eluting with pet. ether:EtOAc=3:7) to afford the title compound **214** as white solid (0. 933 g, 81% yield).

Mol. Formula: $C_8H_8N_2O_4$, thick liquid.

Yield: 81%.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.31 (t, *J*=7.05 Hz, 3H), 2.48 (t, *J*=2.35 Hz, 1H), 4.29 (q, *J*=7.05 Hz, 2H), 4.80 (d, *J*=2.35 Hz, 2H).

6-Ethoxy-3*H*-furo[3,4-*c*]furan-1-one (203):



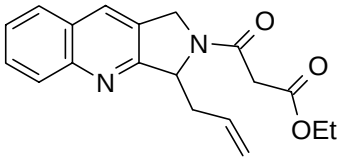
To a stirred solution containing 0.200 mg (1.02 mmol) of the diazocompound **205** in 5 mL of dry benzene was added 7 mg of rhodium (II) acetate. The mixture was heated at reflux for 5 h. At the end of this time the solution was concentrated under reduced pressure and the dark yellow residue was purified by column chromatography on silica gel (eluting with pet. ether:EtOAc=7:3) to afford the title compound **203** as thick oil (0.111 g, 65 % yield).

Mol. Formula: $C_8H_8O_4$, thick liquid.

Yield: 65%.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.44 (t, *J*=6.84 Hz, 3H), 4.65 (q, *J*=6.84 Hz, 2H), 5.11 (s, 2H), 6.65 (s, 1H).

3-(3-Allyl-1,3-dihydro-pyrrolo[3,4-*b*]quinolin-2-yl)-3-oxo-propionic acid ethyl ester (212):



A solution of the urethane **210** (1.15 g, 3.34 mmol) in 50 mL ethanol was added rapidly under a stream of nitrogen to a solution of 3 g (46.8 mmol) of KOH in 10 mL ethanol and 2 mL water. The resultant yellow solution was refluxed under nitrogen for 24 h. The dark brown solution was concentrated under reduced pressure, diluted with water and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum provided the crude amine in quantitative yield.

To the crude amine (0.702 g, 3.34 mmol) and K_2CO_3 (1.4 g, 10 mmol) in dry DCM (50 mL) under nitrogen atmosphere at 0 ºC was added 0.757 g (5.04 mmol) ethyl malonyl chloride (dissolved in 5 mL dry DCM) over a period of 10 min. The reaction mixture was further allowed to stir for 3 h. After quenching the reaction by addition of water dropwise the organic layer was separated. The aqueous layer was extracted with 3x25 ml of DCM. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue obtained was subjected to column chromatography on silica gel (eluting with pet. Ether/EtOAc = 3/2) afforded the title compound **212** as white solid (0.734g, 68% yield).

Mol. Formula: $C_{19}H_{20}N_2O_3$, white solid.

Yield: 68%.

mp: 77-79 ºC

IR ($CHCl_3$) cm^{-1}: 1710, 1635.

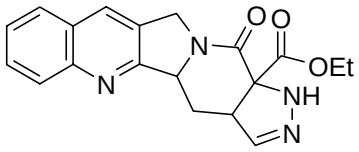
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.30,1.31 (t, *J*=7.05 Hz, 3H), 2.82-2.93 (m, 1H), 3.53, 3.60 (m, 2H), 3.67 (m, 1H), 4.61-5.21 (m, 4H), 4.23 (q, *J*=7.04 Hz, 2H), 5.28-5.59 (m, 2H), 7.54 (m, 1H), 7.68-7.81 (m, 2H), 7.95-8.12 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4) δ: 167.3 (s), 165.4 (s), 164.8 (s), 161.7(s), 148.4 (s), 132.4 (d), 131.2 (d), 130.1 (d), 129.8 (d), 129.6 (d), 129.5 (d), 129.2 (d), 128.5 (s), 128.1 (d), 127.9 (d), 127.5 (d), 126.9 (d), 126.8 (d), 120.5 (t), 119.4 (t), 63.5 (d), 61.8 (t), 51.5 (t), 50.5 (t), 42.7 (t), 41.7 (t), 40.1 (t), 36.7 (t), 14.4 (q). (mixture of rotamers.)

Mass ESI (m/z): 325 $(M+1)^+$

Analysis:	**C**	**H**	**N**
Expected:	70.35	6.21	8.64
Observed:	69.98	6.37	8.79

Pyrrazoline (214):



To the mixture containing keto-ester **212** (0.500 g, 1.54 mmol) and triethyl amine (0.55g, 5.39 mmol) in acetonitrile (7 mL) at 0 ºC was added mesyl azide (0.55 g, 4.62 mmol) dropwise. The reaction mixture was further stirred for 48 h at room temperature. After the completion of the reaction as monitored by TLC acetonitrile was removed under reduced pressure. The residue was extracted with ethyl acetate and was washed with 10% NaOH solution. The organic layer was thoroughly washed with water, dried over anhydrous sodium sulpahte, filtered and concentrated under reduced pressure. The residue obtained was subjected to column chromatography on silica gel (eluting with pet. ether:EtOAc=3:7) to afford the title compound **214** as white solid (0. 437 g, 81% yield).

Mol. Formula: $C_{19}H_{18}N_4O_3$, white solid.

Yield: 81%.

mp: 203-205 ºC

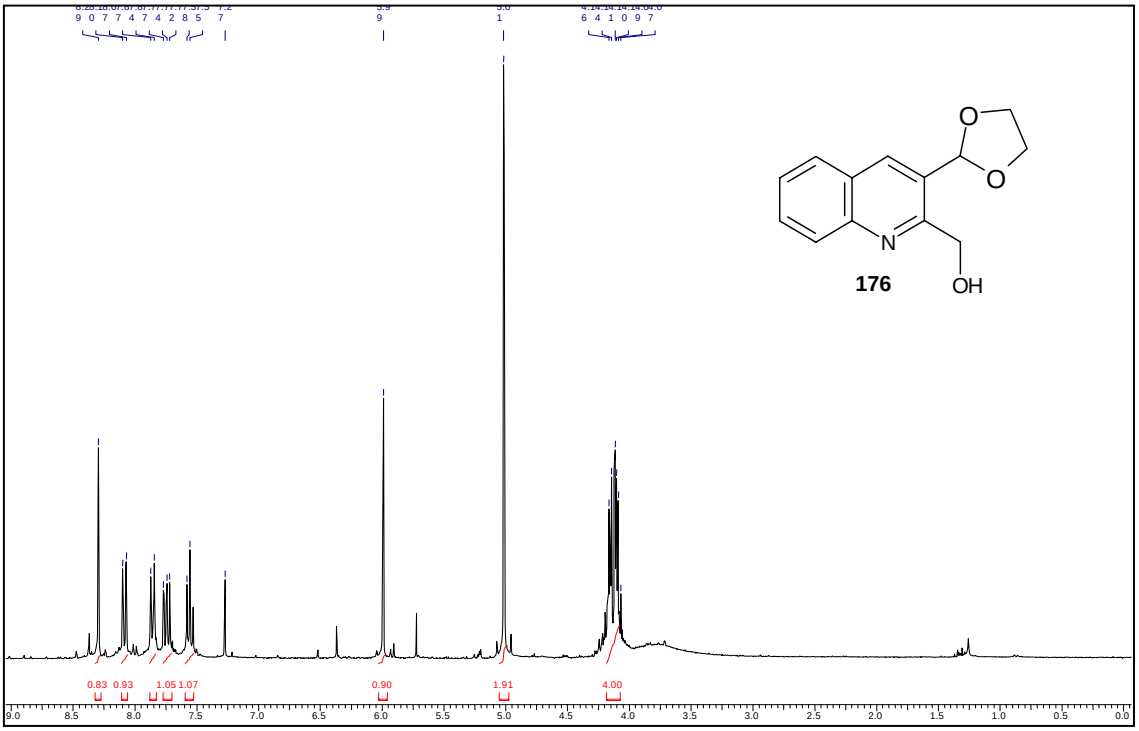
IR ($CHCl_3$) cm^{-1}: 1740, 1650.

^{1}H NMR (500 MHz, $CDCl_3$ + CCl_4) δ: 1.21 (t, *J*=7.20 Hz, 3H), 1.53 (dd, *J*=12.4 HZ, 1H), 2.94 (ddd, *J*=2.8, 6.5 and 12.4 Hz, 1H), 3.84 (dd, *J*=12.3 and 6.8 Hz, 1H), 4.19 (q, *J*=7.3 Hz, 2H), 4.65 (d, *J*=16.4 Hz, 1H), 5.02 (dd, *J*=2.3 and 11.9 Hz, 1H), 5.15 (d, *J*=16 Hz, 1H), 6.63 (s, 1H), 6.89 (s, 1H, D_2O, exchangeable), 7.46 (t, *J*=7.5 Hz, 1H), 7.62 (t, *J*=7.7 Hz, 1H), 7.72 (d, *J*=8.2 Hz, 1H), 7.96 (m, 2H).

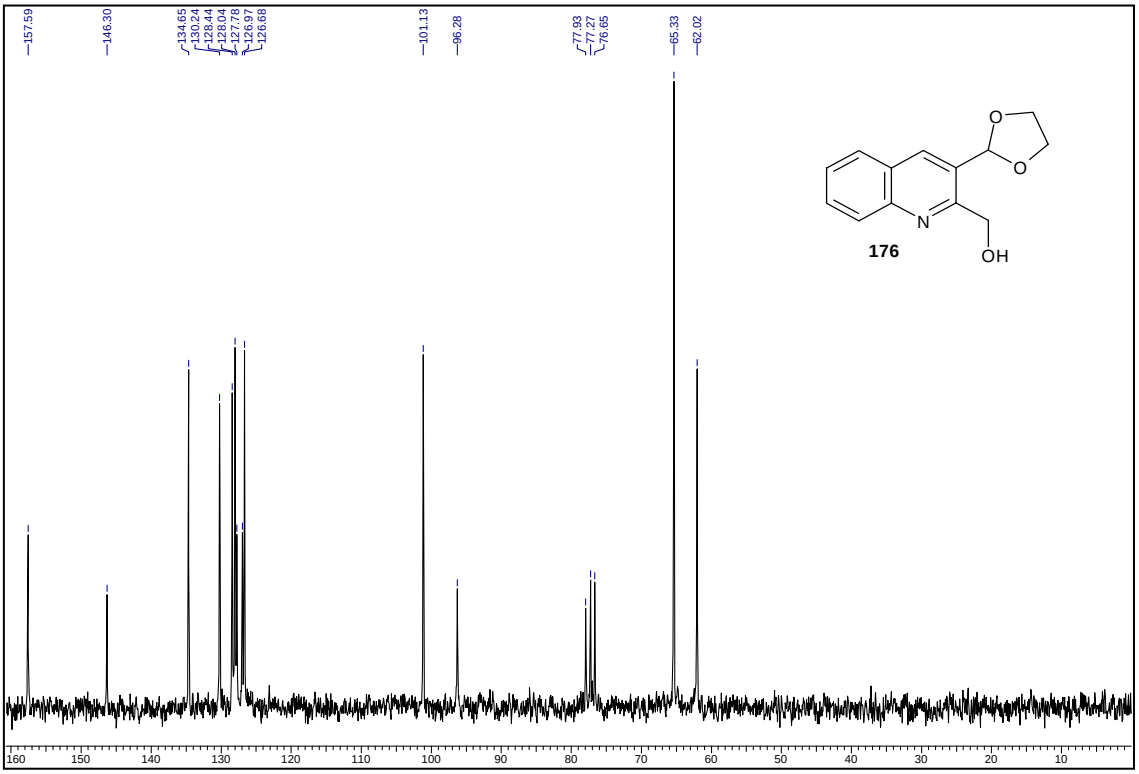
^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4) δ: 170.6 (s), 165.0 (s), 160.6 (s), 148.5 (s), 144.0 (d), 130.6 (d), 130.0 (d), 129.3 (d), 128.1 (d), 128.0 (s), 127.6 (s), 127.2 (d), 72.7 (s), 63.0 (t), 61.22 (d), 49.5 (d), 49.2 (t), 30.7 (t), 14.3 (q).

Mass ESI (m/z): 351 $(M+1)^+$

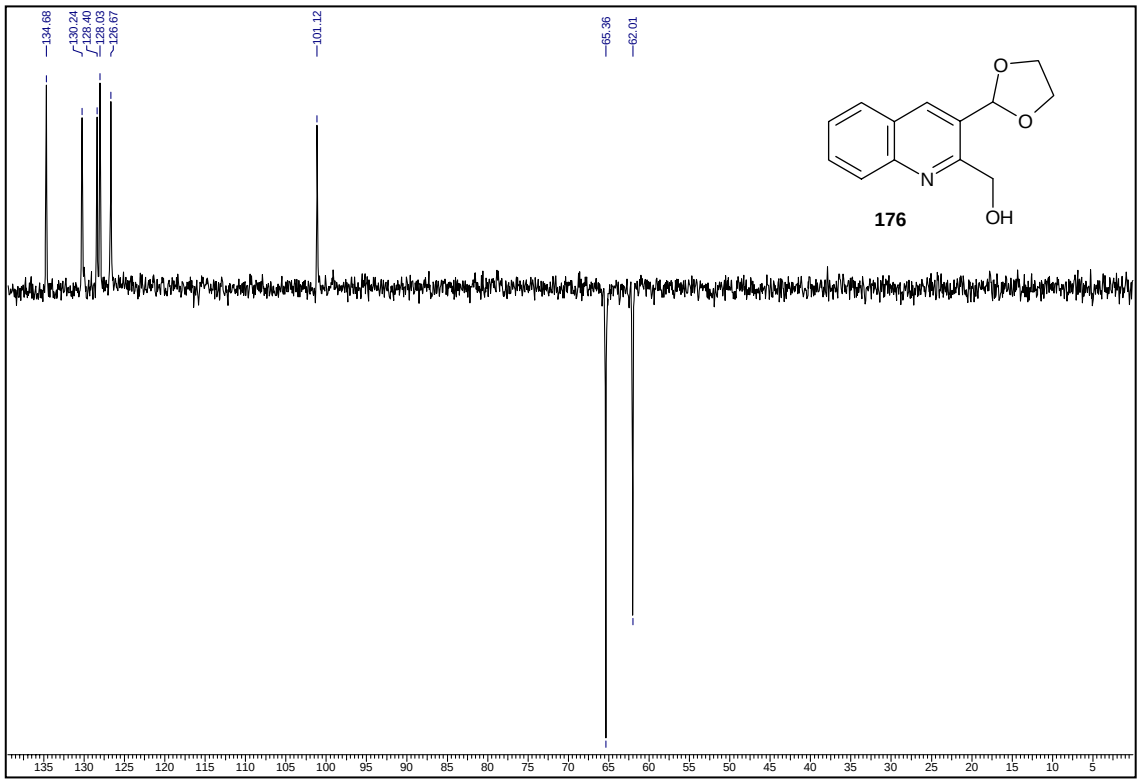
Analysis:	**C**	**H**	**N**
Expected:	65.14	5.14	16.00
Observed:	64.85	5.37	16.00



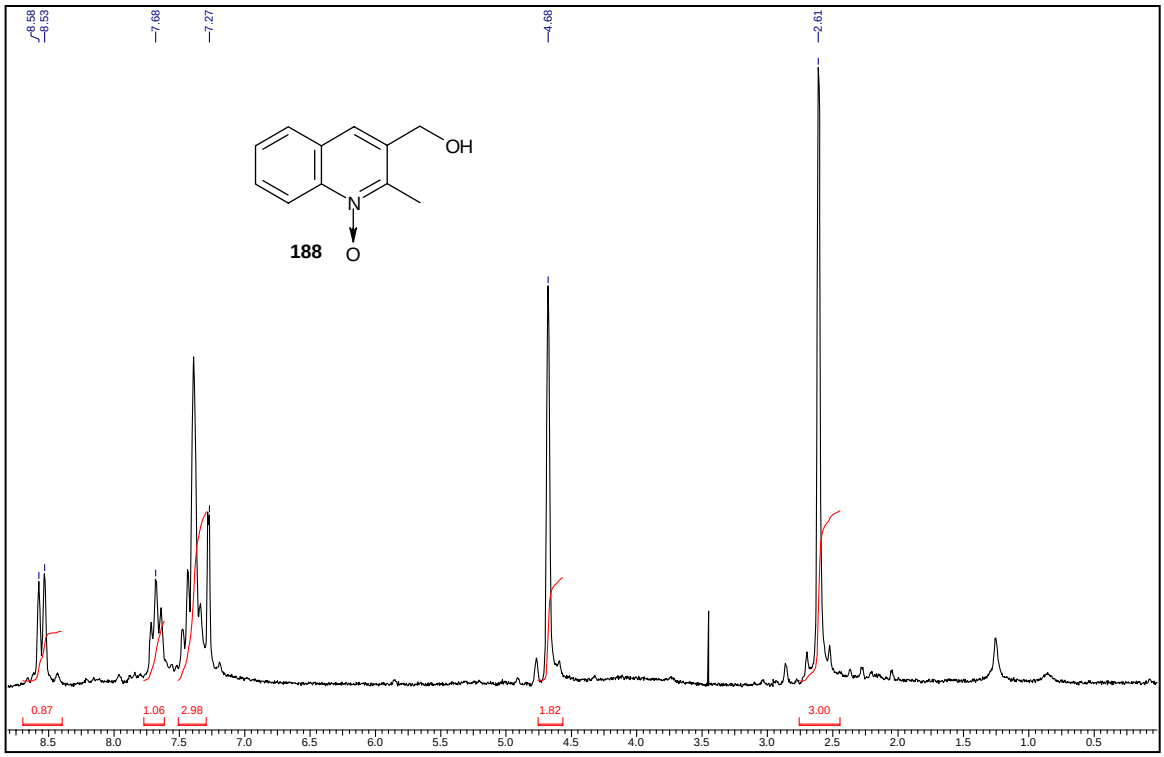
^{1}H-NMR ($CDCl_3$ + CCl_4, 300 MHz)



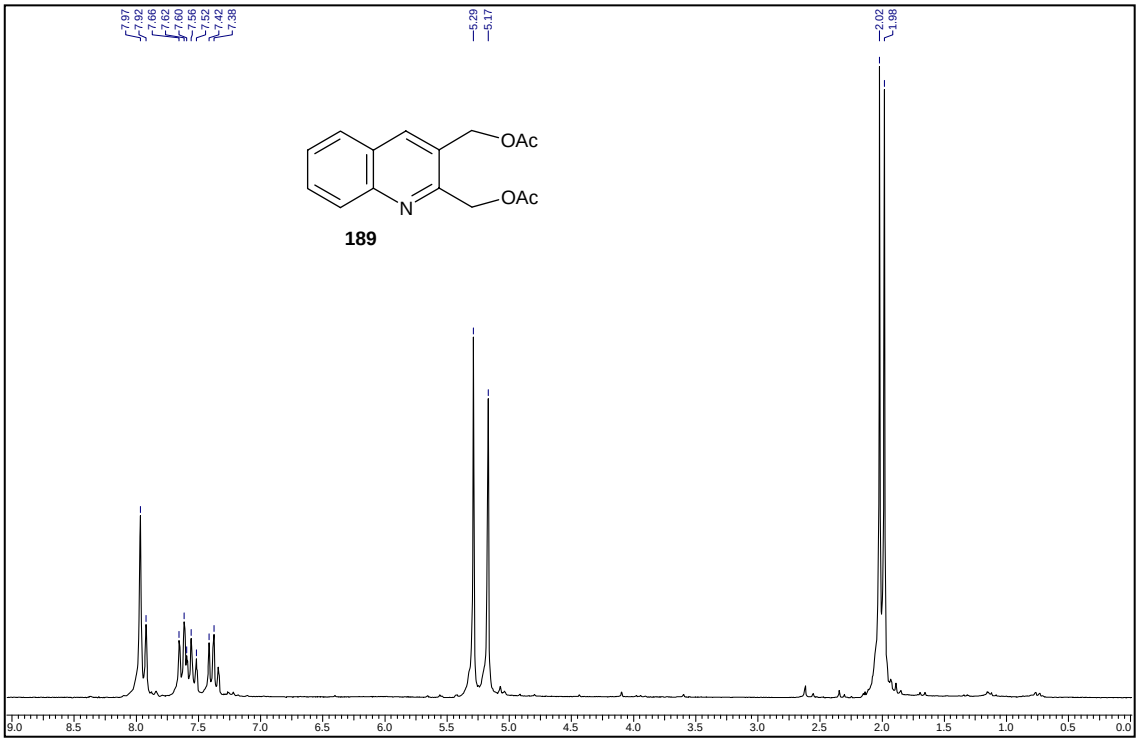
^{13}C-NMR ($CDCl_3$ + CCl_4, 50 MHz)



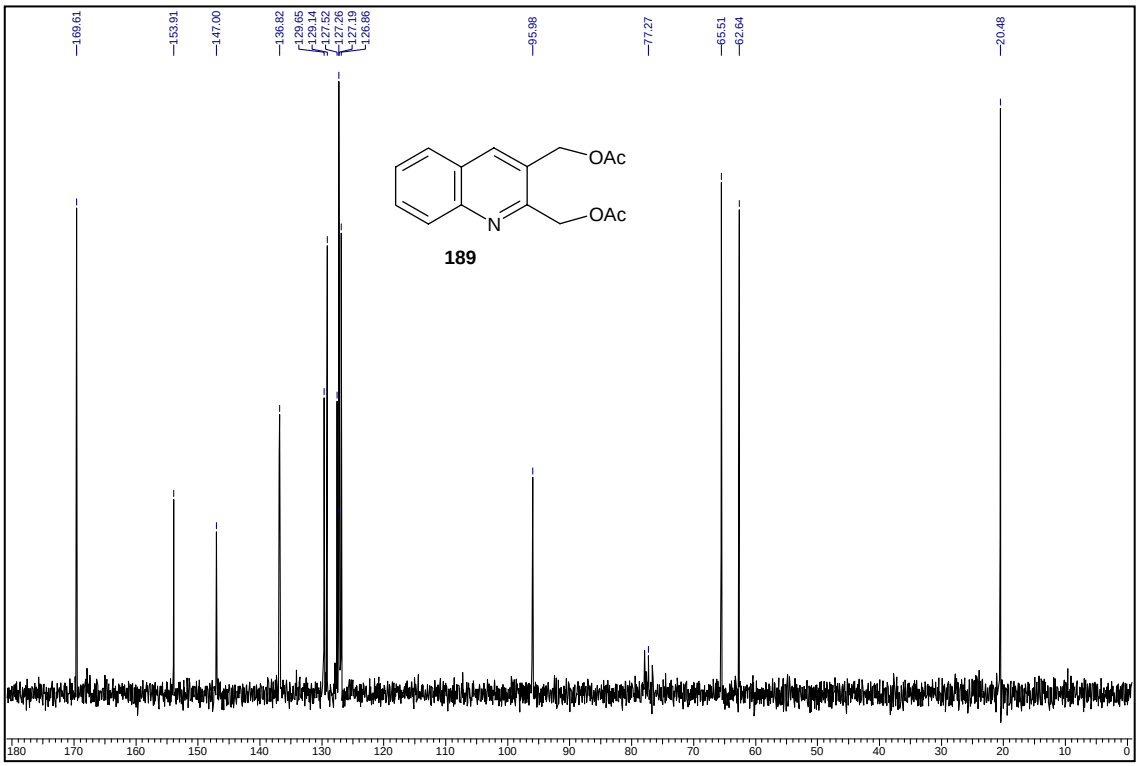
DEPT ($CDCl_3$ + CCl_4, 50 MHz)



^{1}H-NMR ($CDCl_3$, 200 MHz)



^{1}H-NMR ($CDCl_3$ + CCl_4, 200 MHz)



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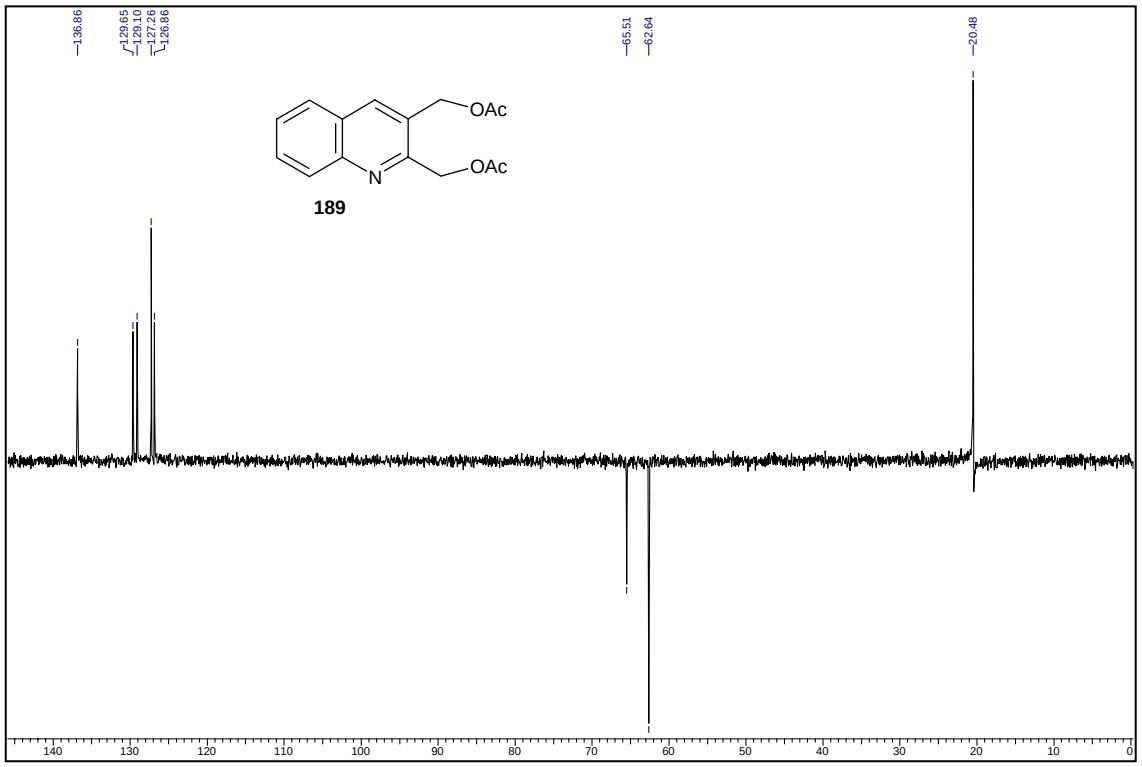
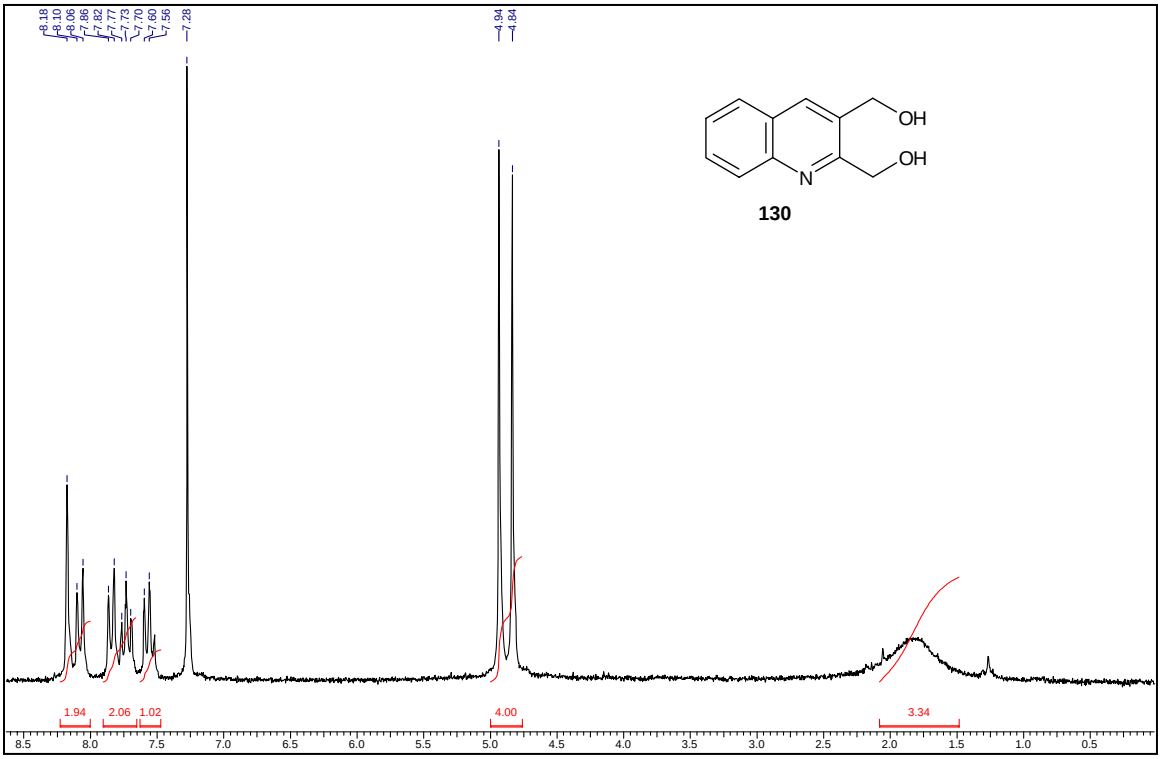
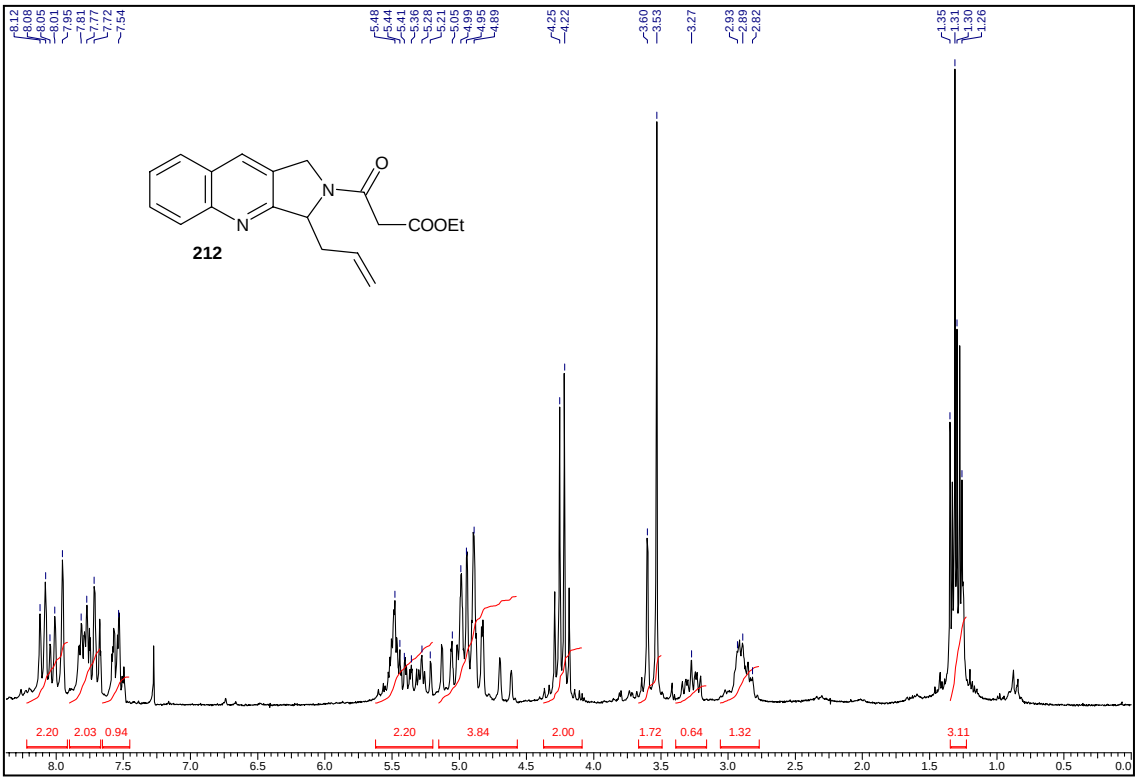


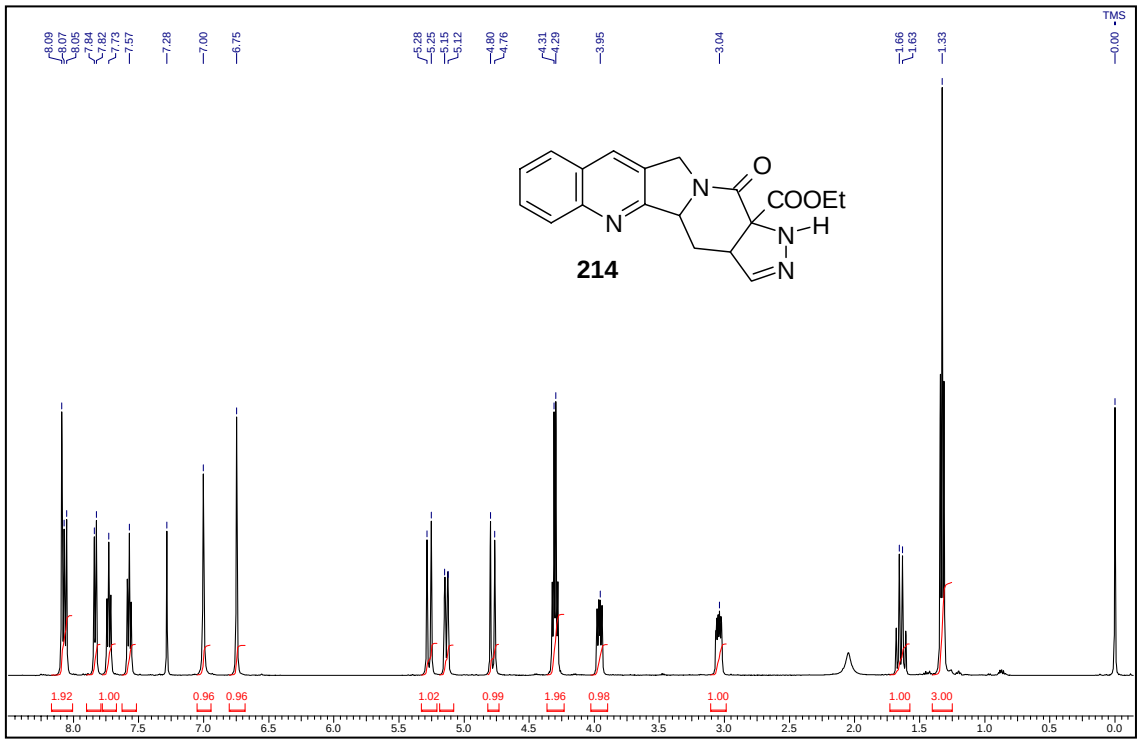
DEPT ($CDCl_3$ + CCl_4, 50 MHz)



^{1}H-NMR ($CDCl_3$ + CCl_4, 200 MHz)



^{1}H-NMR ($CDCl_3$ + CCl_4, 200 MHz)



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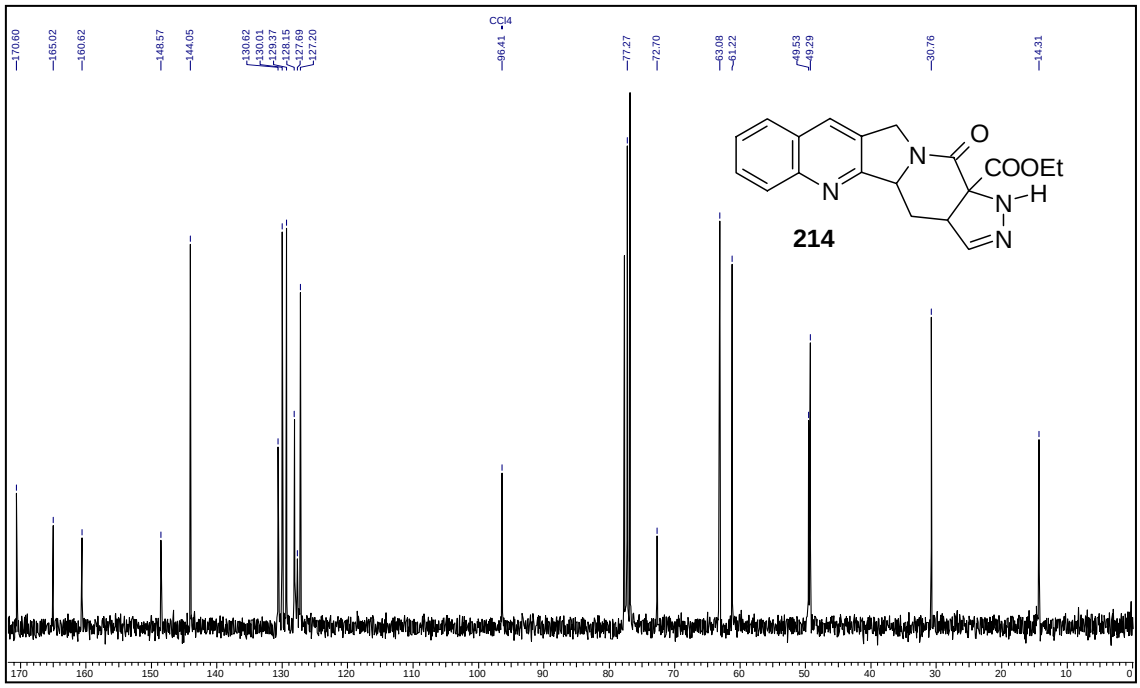
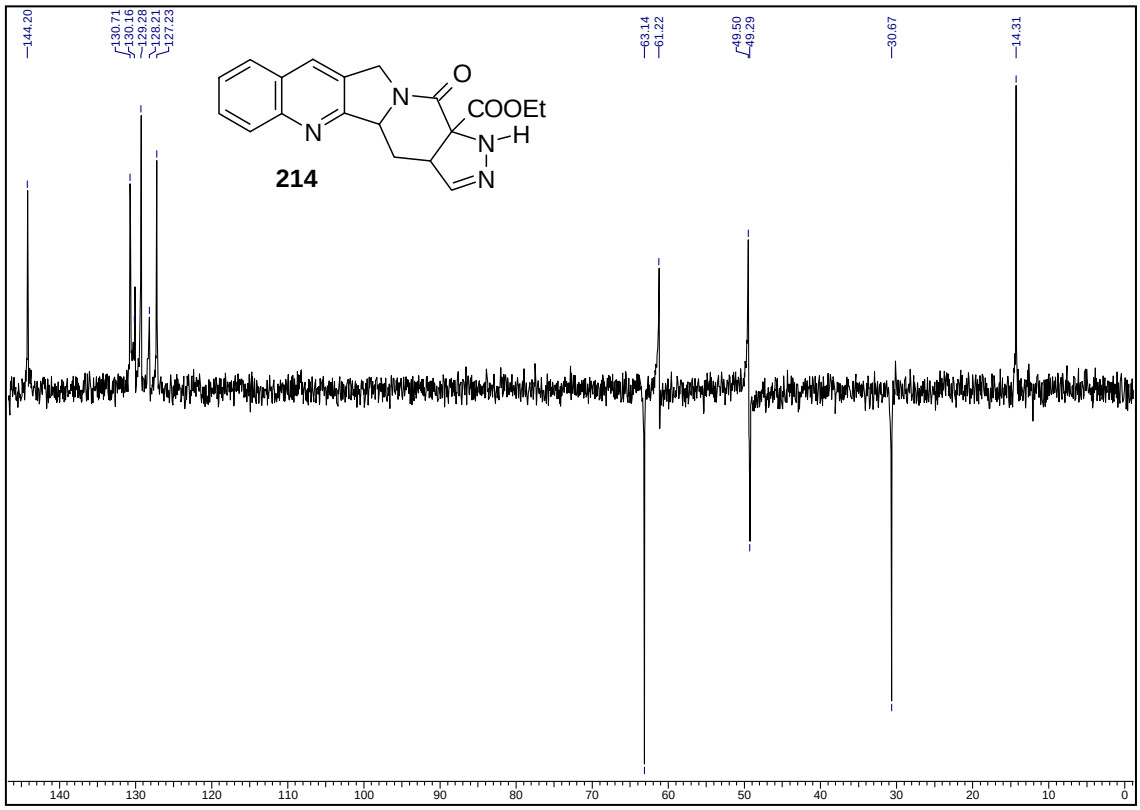


^{13}C-NMR ($CDCl_3$ + CCl_4, 75 MHz)



DEPT ($CDCl_3$ + CCl_4, 75 MHz)

1.2.2.6 References:

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CHAPTER II

SECTION 1: **Synthesis of (±) –A-Factor**

SECTION 2: **Catalytic Organic Transformation Utilizing H-Fer Zeolite Under Solvent Free Conditions**

PART 1: **Catalytic Transesterification of β-Ketoesters with H-FER Under Solvent Free Conditions**

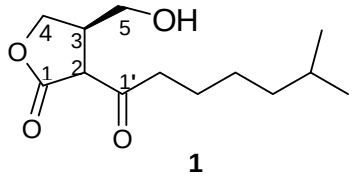
PART 2: **Catalytic Acetylation of Alcohols, Phenols, Thiols and Amines with H-FER Under Solvent Free Conditions**

CHAPTER II

SECTION 1: Synthesis of (±) – A-factor

2.1.0 Introduction:

Streptomyces is the major genus in Actinomycete, which is known to produce a variety of secondary metabolites including antibiotics, pigments, enzyme inhibitors and other versatile physiologically active compounds. The remarkable feature of microorganisms belonging to this family is their diversity in species and also in products. For example one such species *S. griseus* has produced 187 physiologically active compounds. In the mid-1960' s, Khokhlov and his co-workers discovered A-factor **1** in *S. griseus*, a streptomycin producer.[1] This factor produced in the culture broth of *S. griseus* induces streptomycin production, aerial mycelium and spore formation at very low concentration. As Khokhlov, the first discoverer of this factor coined the general name "autoregulator" for this unique signal substance, although autoregulator is also used to imply an intracellular proteinic regulator in molecular biology.[2]



1

Figure 1

The gross structure of A-factor was determined on the basis of the structural studies and a synthesis of (±)-A-factor. The absolute configuration at C-2 and C-3 were deduced from the circular dichroism spectrum of A-factor. Based on their observations Khokhlov *et al.* proposed the structure of A-factor as (2*S*)-isocapryloyl-(4*S*)-hydroxymethyl butyrolactone.[3] They studied the structure and activity using synthesized A-factor analogues and showed that hydroxy methyl group at C-3 is essential for its activity and also the length of the alkyl side chain at C-2 is critical for induction of streptomycin biosynthesis.[4] The stereochemistry of this natural product was revised by Mori *et al*.[5] as being 3*R*, position C-2 readily epimerising by enolisation by synthesis of the A-factor from *S*- (–)-paraconic acid **5**. Also it was demonstrated by Mori that the unnatural enantiomer possesses 40% biological activity of the natural product.

2. 1. 1 Mode of Action:

Beppu and co-workers at the Tokyo University initiated molecular biological studies of A-factor and proposed the A-factor regulatory networks (Figure 2). The mode

of signal transduction with A-factor is initiated by its binding to the A-factor receptor protein, ArpA. This A-factor receptor protein was isolated from cells of *S. griseus* using tritium labeled A-factor.[6] ArpA is a cytoplasmic protein with 272 amino acid residues and each cell contains 30 to 40 molecules of ArpA.[7] The signal transduction initiated by the A-factor-ArpA complex triggers the expression of A-factor-dependent-binding protein (Adp),[8] which induces a regulator, StrR.[9] StrR is the main pleiotropic up-regulator of streptomycin production and it releases the production of AphD which causes streptomycin resistance.

A-factor regulatory network in *Streptomyces griseus*

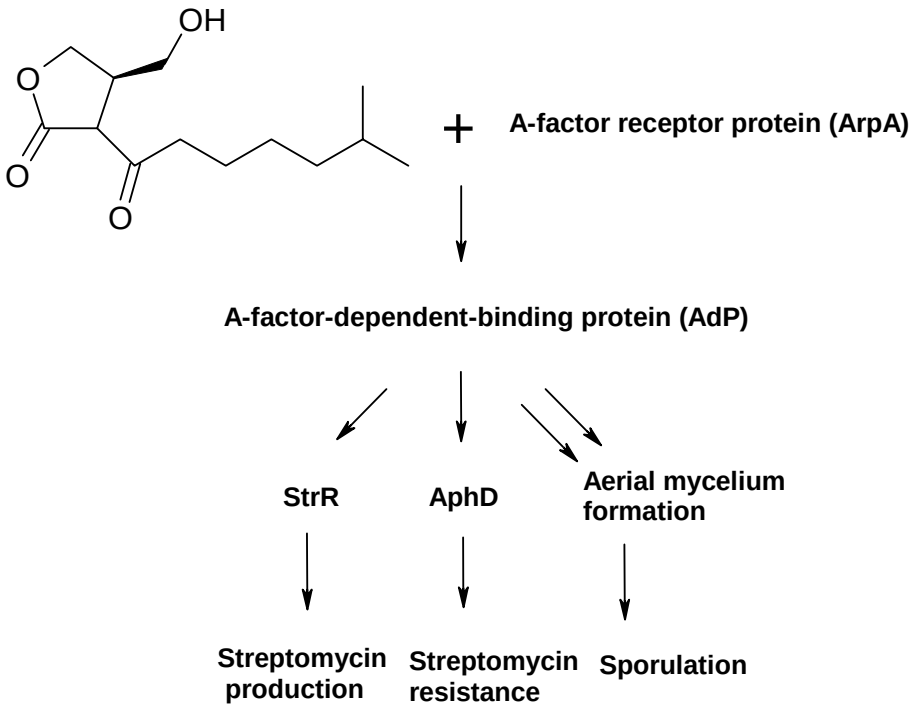


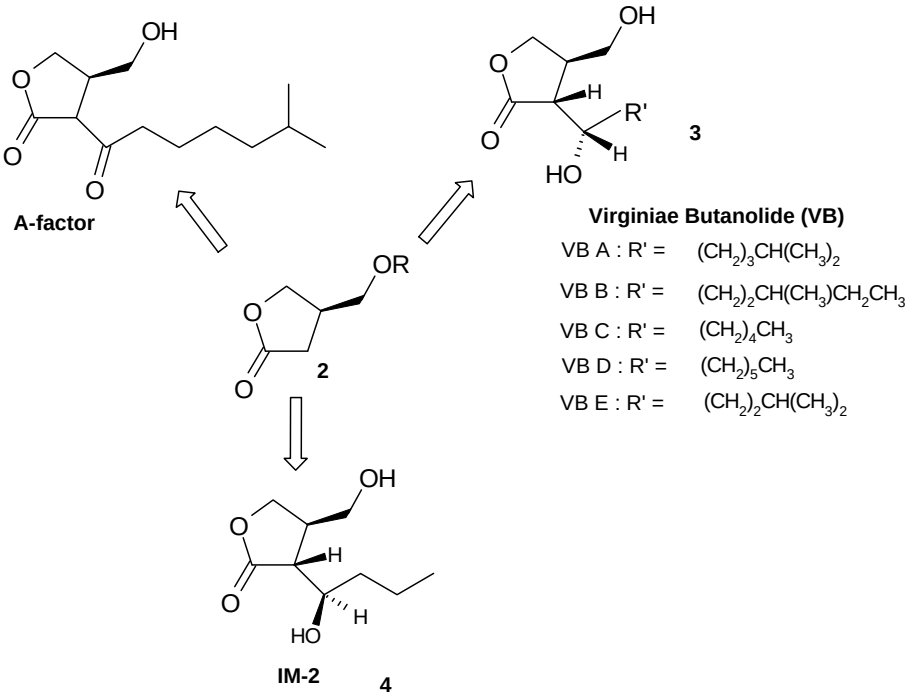
Figure 2

2.1.2 Synthesis of A-factor: A Literature Background

This section describes the total synthesis of racemic and optically pure A-factor documented in the literature. The key step of most syntheses revolves around the construction of 3-alkoxymethyl butanolide **2**. Literature precedents shows that chiral 3-alkoxymethyl butanolides **2** are the most useful precursors for the synthesis of three known type of butyrolactone autoregulators of *Streptomyces* species namely A-factor isolated from *Streptomyces griseus*, Virginiae butanolides (**VB**) **3** isolated from

Streptomyces virginiae and IM-2 **4** isolated from *Streptomyces FRI-5*.[10] Based on the butanolide skeleton all of these autoregulators are structurally homologous compounds. They possess a hydroxy methyl group at the 3-position, but differ in the C-2 side chain containing functional groups such as 6-hydroxy or 6-keto groups, and in the length or branching of the alkyl chain.

Scheme 1



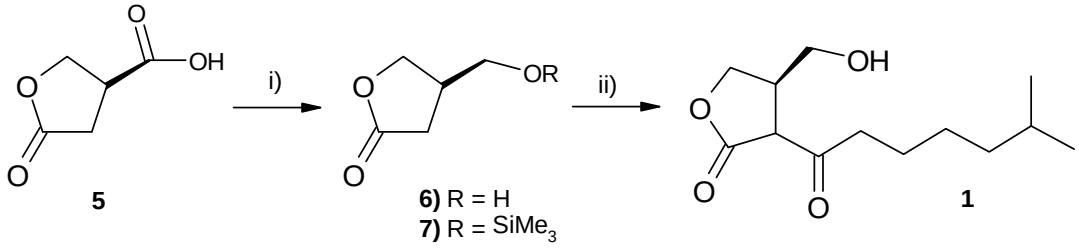
2.1.2a Synthesis of (–) – A - factor:

Mori' s Approach: (*Tetrahedron* **1982**, *38*, 2919.)

Mori reported the synthesis of enantiopure A-factor starting from (–)-paraconic acid (**5**), which was obtained from racemic paraconic acid by repeated recrystallisation as its salt with enantiopure (*R*)-(1-phenylethyl)amine.[10b] He also synthesized optically active paraconic acid based upon the monohydrolysis of 2-(acetoxy-methyl)-3-phenylpropanoyl acetate using porcine pancreatic lipase in 62 % ee. Mori' s synthesis of (-)-A-factor from (–)-paraconic acid confirmed the identity of (–)-A-factor with the natural A-factor. This means that the absolute configuration at C-3 of A-factor is same as that of (–)-paraconic acid. In 1965 Tocanne *et al*. established the absolute configuration of (-)-paraconic acid to be *R*. Therefore based on their result Mori assigned (3*S*) configuration to (–)-A-factor.

Later Tocanne and co-workers correlated (+)-paraconic acid to (*S*)-(+)-3-methyl nonadecane by a nine-step process to conclude that (+)-paraconic acid posses (*R*)-configuration contrary to their earlier result. In view of the key role of paraconic acid in establishing the absolute configuration of various natural products including A-factor Mori came up with an unambiguous correlation of (+)-paraconic acid. This proved beyond doubt that (+)-paraconic acid belongs to the (*R*)-series. Since the natural A-factor was synthesized from (−)-paraconic acid with (*S*)-configuration, the absolute configuration at C-3 of (−)-A-factor should be *R*, which contradicts the Khokhlov' s proposal based on the lactone sector rule.

Scheme 2



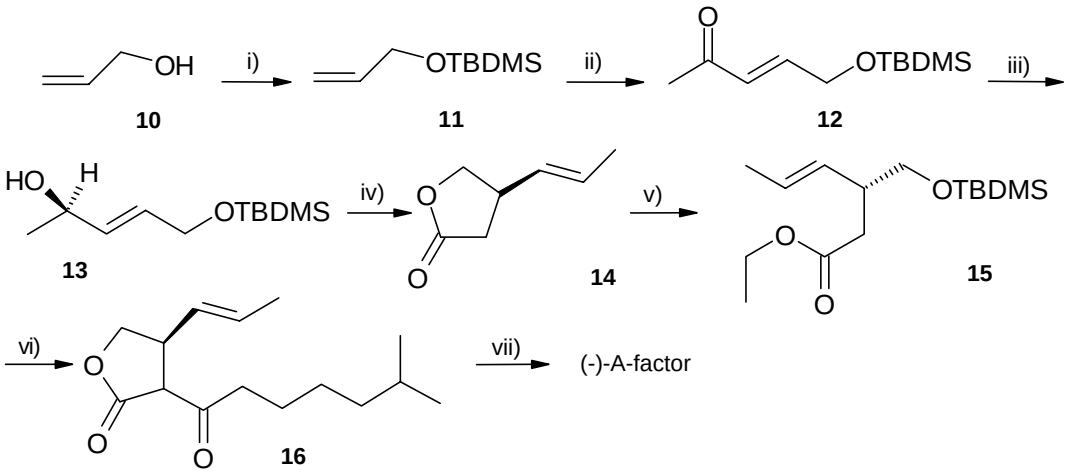
Reagents and conditions: *i) a) $BH_3.SMe_2$, THF, 0-5 ºC, 3 h, 89%, b) $(Me_3Si)_2NH$, Me_3SiCl, TEA, $CHCl_3$, 0-5 ºC, 2 h, 52%, ii) a) LDA,* ***8****, THF, –78 ºC, 1h, b) EtOH-H_2O (4:1), reflux, 10 min, 30%.*

As shown in the scheme 2, reduction of (−)-paraconic acid with $BH_3.SMe_2$ afforded the (*S*)-(−)-3-hydroxymethyl-4-butanolide **6**. The hydroxy group in **6** was protected as its trimethylsilyl ether **7**. The lactone enolate generated by treating **7** with LDA in THF at –78 ºC was acylated with 6-methylheptanoyl chloride (**8**) to furnish the silyl ether protected (−)-A-factor **9**. Deprotection of silyl group in ethanol-water under reflux condition furnished A-factor in 15% overall yield starting from enantiopure (*S*)-(−)- paraconic acid.

Parsons Approach: (*J. Chem. Soc., Chem. Commun*. **1995**, 437.)

Johnson-Claisen rearrangement of the chiral ketene acetal derived from the corresponding chiral allylic alcohol **13** was used by Parsons to prepare optically active (3*R*)-(−)-A-factor and 3(*S*)-(+)-A-factor. Both the isomers were obtained in a three-step process from the allylic alcohol **13** (scheme 3 and scheme 6).[10f]

Scheme 3

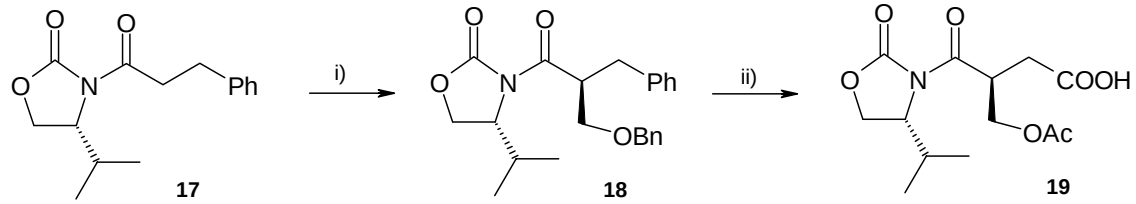


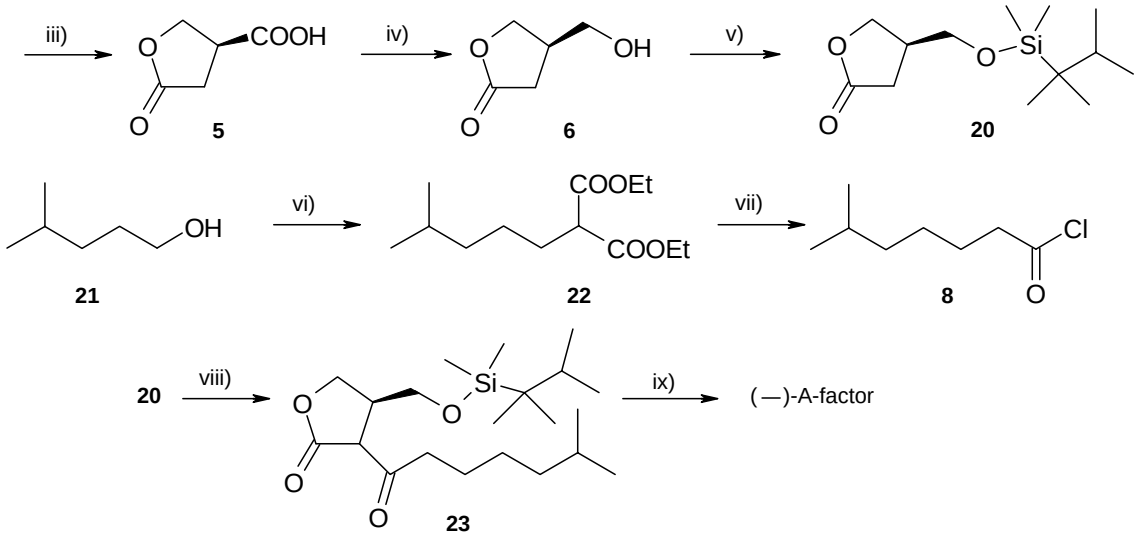
Reagents and Conditions: *i) TBDMSCl, TEA, DMAP, DCM, ii) a) O_3, DCM, PPh_3, 90%, b) K_2CO_3, diethyl(2-oxopropyl)phosphonate, H_2O, 80%, iii) BH_3.THF, oxazaborolidine, THF, 80%, 84% ee. iv) triethyl orthoacetate, hexanoic acid, 138 ºC, 75%, v) Conc. HCl (trace), THF/water (20:1), vi) LiHMDS, 6-methylheptanoyl chloride, THF, –70 ºC, vii) a) OsO_4, $NaIO_4$, dioxane/H_2O 1:1, b) $Zn(BH_4)_2$, Et_2O/THF (1:1).*

A stabilized Horner-Emmons reaction using diethyl (2-oxo-propyl)phosphonate afforded the trans α, β-unsaturated ketone **12** in 80% yield (scheme 3). Enantioselective reduction of **12** using CBS conditions afforded the allylic alcohol **13** in 80% yield with 84% ee. Jonson-Claisen rearrangement of **13** followed by acid catalysed lactonisation of **14** and subsequent acylation of the resulting lactone **15** with 6-methylheptanoyl chloride furnished the unsaturated lactone **16**. Treatment of **16** with osmium tetroxide and sodium metaperiodate afforded the corresponding aldehyde, which was reduced to the alcohol with zinc borohydride to yield (3*R*)-(−)-A-factor in 50% ee. The main drawback of the strategy is the unavailability of enantiopure allylic alcohol **13** coupled with partial racemization via enolisation of the aldehyde between **16** and (−)-A-factor, resulting in the product (3*R*)-(−)-A-factor possessing only 50% ee.

Rawlings Approach: (*J. Chem. Soc., Perkin Trans. 1* **1998**, 1721).

Scheme 4





Reagents and Conditions: *i) $TiCl_4$, DIPEA, $BnOCH_2Cl$, 0 ºC, 1 h, DCM, 94%, ii) a) H_2/Pd-C, cat HCl, ethyl acetate, rt, 4 h, 99%, b) Ac_2O, pyridine, rt, 24 h, 99%, c) $H_5IO_6/RuCl_3$, 6 h, water-CH_3CN-CCl_4 (5:3:3), 65%, iii) a) LiOH, H_2O_2, b) HCl (6 M), 40%, iv) $BH_3.SMe_2$, 0-5 ºC, THF, 2 h, 60%, v) $(CMe_2CHMe_2)Me_2SiCl$, imidazole, rt, 24 h, DMF, 87%, vi) a) CBr_4, PPh_3, 0 ºC, 10 min, DCM, 77%, b) diethyl malonate, NaH, rt, 2 h, DMF, 70%, vii) a) NaOH, rt, 48 h, water, THF, b) HCl, reflux, 36 h, 71%, c) $SOCl_2$, DMF(cat), rt, 85%, viii) LiHMDS, –78 ºC,* ***8****, 1 h, THF, 45%, ix) TBAF, THF, rt, 24 h, 43%.*

Rawlings reported the asymmetric synthesis from pure (*S*)-(-)-paraconic acid based upon the diastereoselective benzyloxymethylation of (*4R*)-3-(3-phenylpropanoyl)-4-isopropyloxazolidin-2-one (**17**) (scheme 4).[10g] Titanium enolate of **17** was diastereoselectively hydroxymethylated with 3, 5-trioxane in moderate yield. Phenyl functionality was readily converted to free carboxylic acid with ruthenium tetroxide to afford **19** in 65 % yield. (*S*)-(−)-Paraconic acid obtained after the removal of chiral auxillary was reduced carefully with $BH_3.SMe_2$ to afford the (*S*)-(−)-3-hydroxymethyl-4-butanolide **6**. The hydroxy group in **6** was protected as its silyl ether **20**. Unlike in Mori' s approach, protection was carried out with stable silyl group. Also the protection proceeded in much higher yield (87%) than that reported for trimethylsilyl protection (52%). The acyl group **8** was prepared from 4-methylpentanol (**21**). Malonate extension of the bromo compound prepared from **21** followed by hydrolysis and decarboxylation

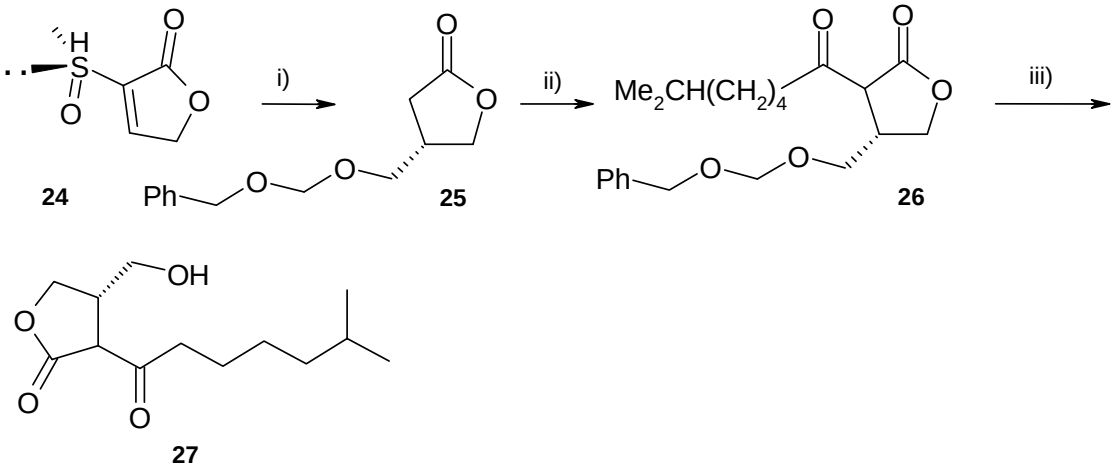
resulted in 6-methylheptanoic acid (**23**), which was converted to 6-methylheptanoyl chloride in 32% overall yield. The lactone enolate generated by treating **20** with LiHMDS in THF at –78 ºC was acylated with 6-methylheptanoyl chloride, gave silyl ether **23**. Deprotection of silyl group in **23** with TBAF furnished (–)-A-factor. The overall synthesis is reasonably efficient and unlike other approaches the (–)-A-factor produced was in optically pure form.

2.1.2b Synthesis of (+)-A-factor:

Posner' s Approach: (*Synth*. *Commun*. **1987**, *17*, 611.)

Posner' s strategy involved the 1, 4-addition of $PhCH_2OCH_2OCH_2Li$ to the enantiomerically pure sulfinyl alkenolide (*S*)-(+)-(**24**) in 87% ee (scheme 5).[10c] Lactone enolate formation with freshly prepared LiHMDS and *C*-acylation with **8** led to *O*-protected (+)-A-factor **26** in 79% yield. The final deprotection of hydroxyl group was performed *via* hydrogenolysis under neutral conditions to produce **27** in mere 50 % ee. The loss of enantiomeric purity from 87% to 50% in going from *O*- protected (+)-A-factor to (+)-A-factor is due to the great ease with which the interchange of the free hydroxyl group with the lactone alkyl oxygen atom occurs under essentially neutral conditions. An effective procedure for generation of hydroxymethyl anion ($^-CH_2OH$) *via* tin-lithium exchange and for conjugate addition of this equivalent to butenolide sulfoxide was developed .

Scheme 5

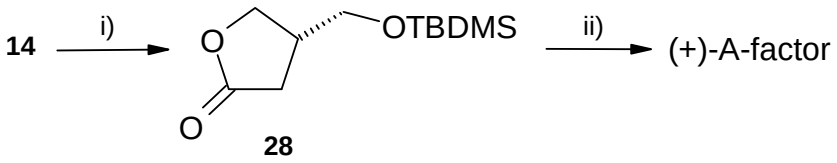


24 **25** **26** **27**

Reagents and conditions: *i) $PhCH_2OCH_2OCH_2Li$, 2,5-dimethyltetrahydrofuran, –78 ºC, 10 min, 48%, 87.3% ee. ii)* ***8****, LiHMDS, THF, –78 ºC, 2 h, 79%, iii) 55 psi H_2, Pd/charcoal, ether, overnight, 91%, 50% ee.*

Parsons Approach: (*J. Chem. Soc., Chem. Commun*. **1995,** 437.)

Scheme 6

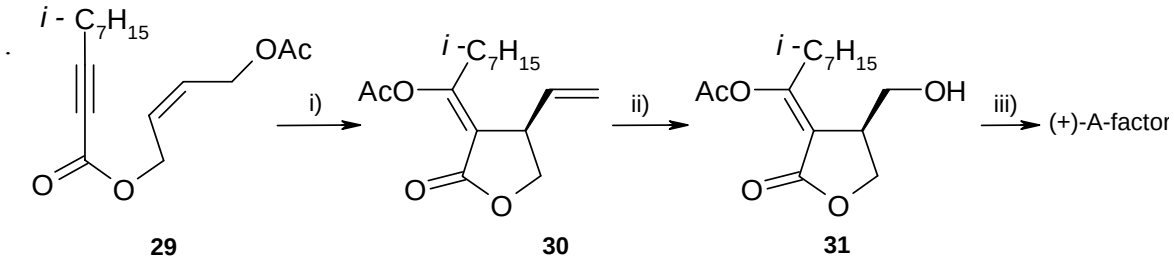


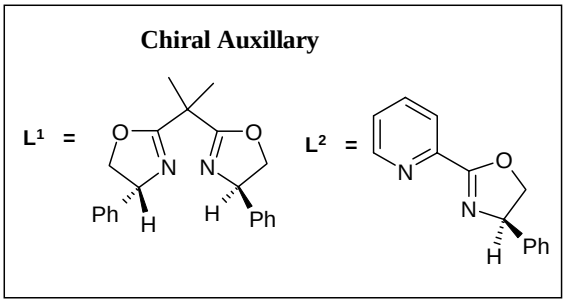
Reagents and conditions: *i) O_3, DCM, $NaBH_4$, EtOH, ii) a) LiHMDS, 6-methylheptanoyl chloride, THF –70 ºC, b) TBAF, wet THF.*

Ozonolysis of **14** and subsequent reduction of the resulting ozonide afforded the five membered lactone **28** in 6% yield. The side chain was introduced by acylating the lactone **28** with 6-methylheptanoyl chloride. Silyl deprotection with TBAF completed the synthesis of 3(*S*)-(+)-A-factor.[10f] The highlight of the synthesis is that both (-)-A-factor and (+)-A-factor are synthesized via the same chiral intermediate.

Lu' s Approach: (*J. Org. Chem.* **2001**, *66*, 7676.)

Scheme 7





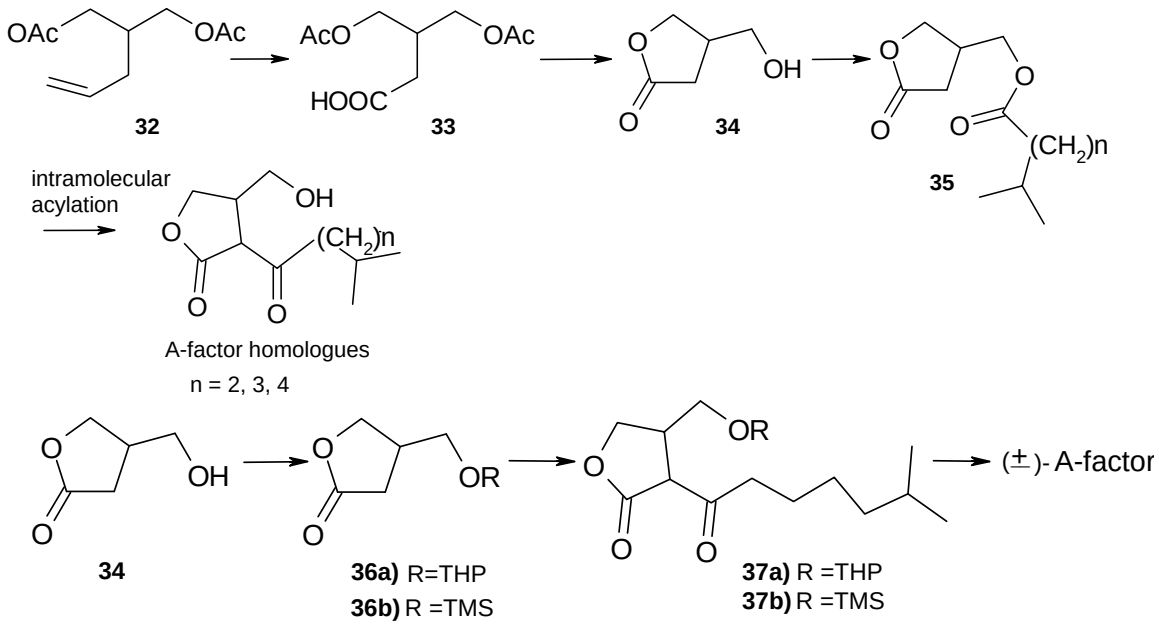
Reagents and Conditions: *i) $Pd(OAc)_2$, (R)-L^1, AcOH, 60 ºC, 86%, 84% ee or $Pd(OAc)_2$, (R, R)-L^1, AcOH, 60 ºC, 48 h, 77%, 85% ee, ii) a) cat. K_2OsO_4, NMO, acetone-H_2O, rt, b) $NaIO_4/SiO_2$, CH_2Cl_2, rt, 70%, c) $NaBH_4$, MeOH, -2 ºC, iii) cat. DMAP, MeOH, 9 ºC, 3 days, 70%, 86% ee.*

Lu' s approach[11] (scheme 7) involved the carbocyclisation of enyne ester **30** for the synthesis of γ-butyrolactone 3**1** initiated by acetoxypalladation under Pd (II) catalysis combined with nitrogen containing ligands L^1 or L^2 with high efficiency and stereoselectivity. Thus oxidative cleavage of the terminal olefin in lactone **30** followed by the reduction of the resulting aldehyde furnished the hydroxy compound **31** in 82% overall yield starting from **29**. Final transformation of vinylacetate **31** to ketone under the catalysis of DMAP, furnished the 3(*S*)-(+)-A-factor (86% ee) in 70% yield. This work is the first example of realizing the efficient asymmetric synthesis of the optically active γ-butyrolactones from the cyclization of enyne esters catalyzed by Pd (II) species.

2.1.2c Synthesis of (±)-A-factor:

Khokhlov' s approach: (*Frontiers of Bioorganic and Molecular Biology,* Pergamon Press, Oxford, 1980, pp-201.**)**

Scheme 8

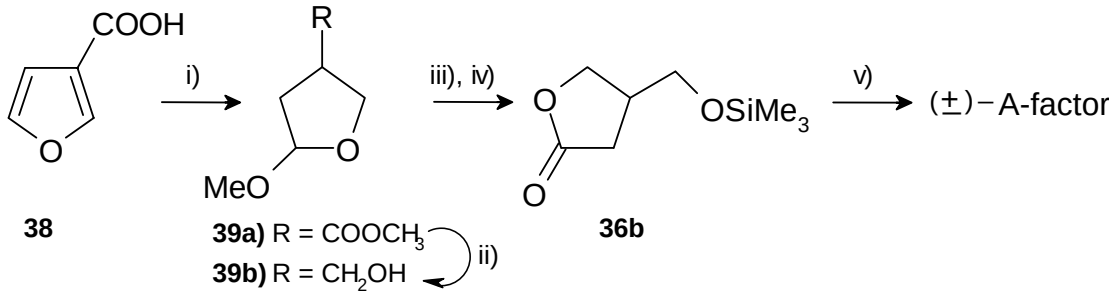


Khokhlov and co-workers synthesized A-factor as shown in scheme 6.[2] They studied the structure and activity relationship using synthesized A-factor analogues. Accordingly the synthesis of (±)-A-factor was carried out either by protecting the 3-hydroxymethylbutyrolactone **34** followed by condensation with methyl caprylate in the presence of dimsylsodium or without the protection of the hydroxyl followed by

intramolecular *O* to *C* acyl migration. However better yields were achieved by method involving the intramolecular acylation. Also this approach does not involve unnecessary protection and deprotection steps.

Kinoshita' s Approach: (*J. Heterocyclic Chem.* **1992**, *29*, 1025.)

Scheme 9



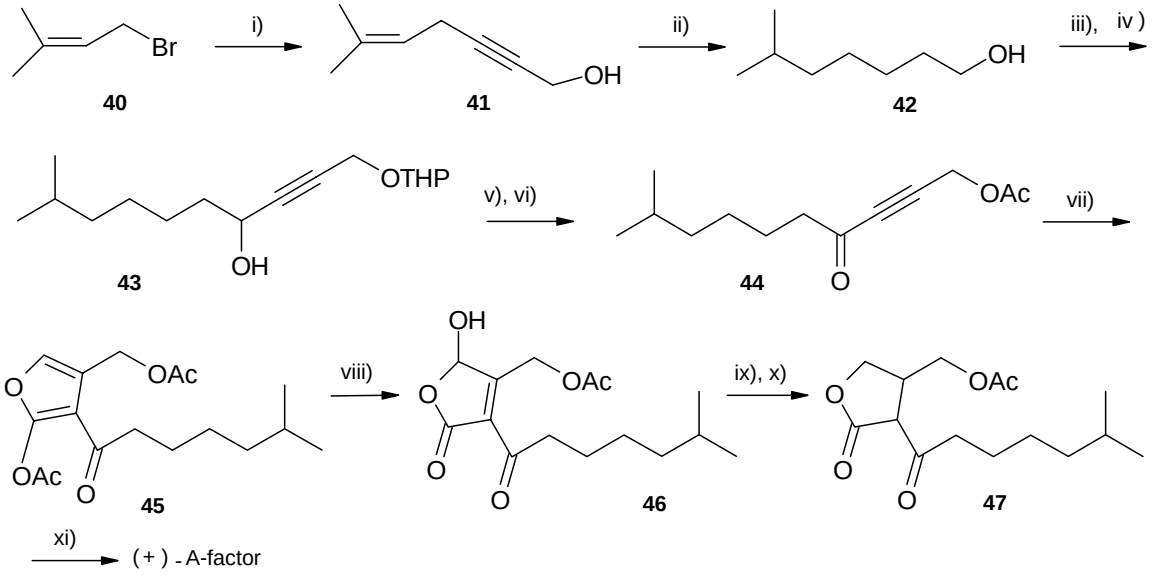
Reagents and Conditions: *i) a) Na, liq. NH_3, MeOH, b) CH_2N_2, c) CH_3COCl, 98%, ii) LAH, Dry ether, reflux 3 h, 92%, iii) cat. $BF_3.OEt_2$, MCPBA, DCM, rt, 3 h, 71%, iv) dry pyridine, HMDS, TMSCl, 0 ºC, 3 h, 87%, v) a) LDA, HMPA, THF, –78 ºC, 30 min, b) EtOH-H_2O (4:1), reflux, 15 min, 53%.*

(±)-A-factor was conveniently synthesized from 3-furoic acid (**38**) *via* the Birch reduction.[10e] The methoxy acetal methyl ester **39a** required for the synthesis of (±)-A-factor was prepared in quantitative yield by the Birch reduction of **38** followed by esterification and treatment with acetyl chloride in methanol. The acetal ester **39a** was a mixture of *anti* and *syn* (2:1) isomers, which were separable by column chromatography. LAH reduction of **39a** followed by Grieco' s oxidation and silyl protection afforded the lactone **36b** in 71% yield. The lactone enolate generated by treating **36b** with LDA in THF at –78 ºC was acylated with 6-methylheptanoyl chloride gave silyl ether protected (±)-A-factor **37b** 54% yield. Deprotection of silyl group in ethanol-water under reflux condition furnished the (±)-A-factor.

Yadav' s Approach: (*Tetrahedron Lett*. **1994**, 35, 3609.)

In 1994 Yadav *et al.*[12] accomplished the total synthesis of (±)-A-factor *via* regioselective oxidation of an acetoxy furan derivative **45** using MnO_2-HCl as a key step (scheme 10). Alkylation of propargyl alcohol with prenyl bromide (**40**) and subsequent hydrogenation gave the saturated alcohol **42**. Swern oxidation of **42** followed by carbon extension yielded the acetylenic alcohol **43** in 78% overall yield.

Scheme 10

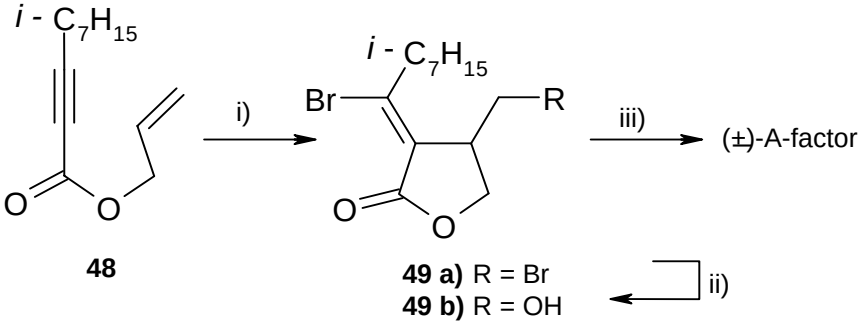


Reagents and Conditions: *i) propargyl alcohol, EtMgBr, THF, 0 ºC, 75%, ii) H_2/Pd-C, MeOH, 99%, iii) $(COCl)_2$, DMSO, TEA, DCM, –78 ºC, iv) Li-C≡C-CH_2OTHP, –78 ºC, 78%, v) PCC, DCM, vi) a) AcOH-HCl (4:1), rt, 82%, b) Ac_2O, TEA, DMAP, DCM, vii) 4-Methyl-5-ethoxy oxazole, toluene, 110 ºC, 80%, viii) MnO_2-HCl (4:10), 85%, ix) $SOCl_2$, DMF(cat), $CHCl_3$, x) H_2/Pd-C, MeOH, 92%, xi) NaOMe (cat), MeOH, rt.*

Collins oxidation of **43,** deprotection of THP group and acetylation gave the corresponding acetate **44**, which on subsequent refluxing with 4-methyl-5-ethoxy oxazole gave **45** in overall 80% yield. Chlorination, hydrogenation and deacetylation sequence afforded the target molecule. The regioselective construction of hydroxy butenolide via selective oxidation of alkoxy furan in the above synthesis is noteworthy.

Lu' s Approach: (*J. Org. Chem.* **1995**, *60*, 1160.)

Scheme 11



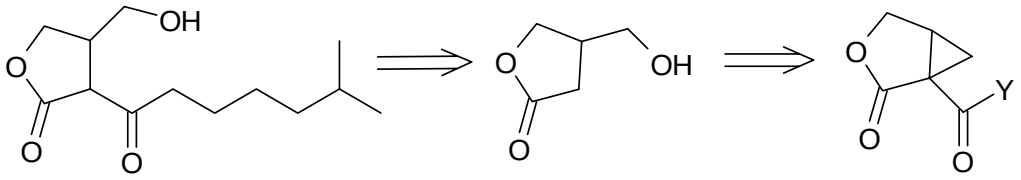
Reagents and Conditions *: i) $Pd_2(dba)_3.CHCl_3$, $CuBr_2$, LiBr, AcOH, rt, 97%, ii) LiOH, dioxane/water, reflux, 10 h, 60%, iii) a) Et_2NH, CH_3CN, rt, 3 days, b) 3 N HCl, 10 h, 50%.*

2'-Alkenyl 2-alkynoate **48** (scheme 11) underwent facile stereoselective cyclization to α-(bromoalkylidene)-γ-butyro-lactone **49** upon treatment with $Pd_2(dba)_3.CHCl_3$, $CuBr_2$ and LiBr in 97% yield. Alkaline hydrolysis of the bromomethyl unit gave the hydroxymethyl lactone **49b** and then treatment with diethylamine transformed the vinylbromide in **49b** to ketone function to afford the (±)-A-factor.[13] A novel and effecient Pd-mediated catalytic system to prepare bromo-functionalized α-alkylidene-γ-butyrolactone derivatives from 2'-alkenyl 2-alkynoates was achieved. (±)-A-factor was synthesized in 3 steps starting from **48** in 29 % yield.

2.1.3 Present Work: *Results and Discussion*

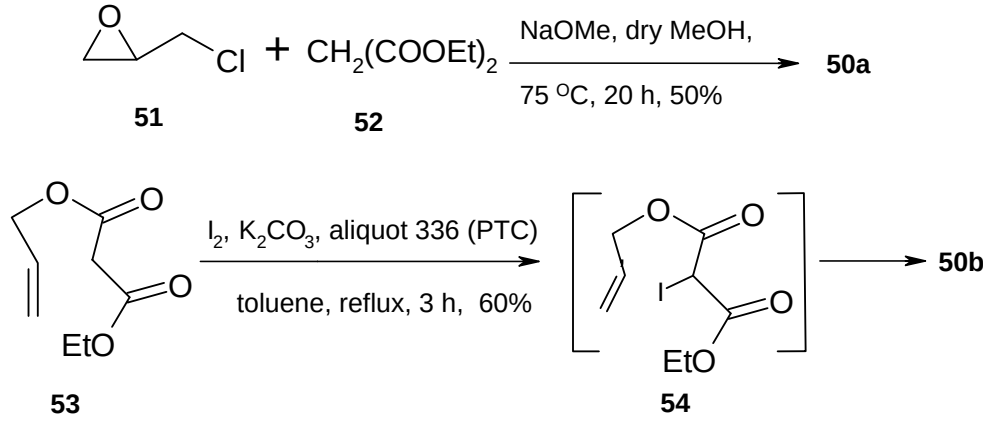
A-factor is an interesting molecule that has received a great deal of interest among synthetic organic chemists. It was our desire to synthesize (±)-A-factor in a minimum number of steps, which allows the use of commercially available and inexpensive chemical reagents such that the same strategy can be utilized for the synthesis of optically active A-factor. The retrosynthesis delineated in scheme **12** revealed that the target molecule could be achieved from ring opening of electrophilic cyclopropane, which can be very easily prepared from reported literature procedures.

Scheme 12



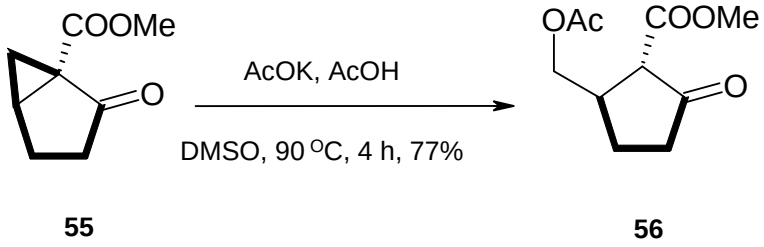
As shown in scheme 12 the requisite cyclopropane **50a** or **50b** was prepared in satisfactory yield either by the nucleophilic attack of diethyl malonate anion on the epichlorohydrin[14] or by the intramolecular singlet electron transfer radical elemental steps in the transformation of iodomalonic ester **54** under solid –liquid PTC condition.[15]

Scheme 13



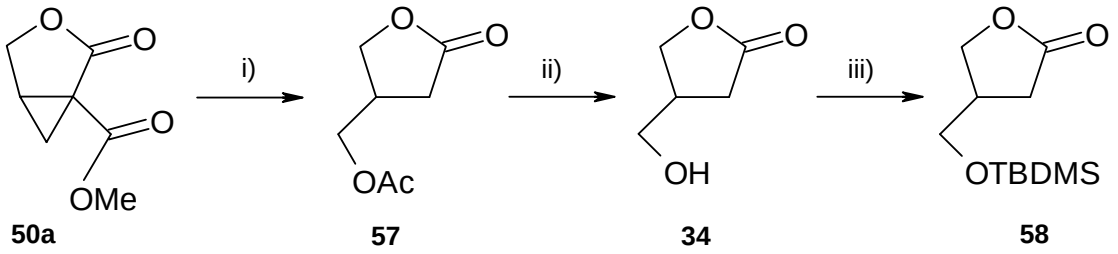
As per the literature protocol, [16a] activated cyclopropane **50a** when treated with acetic acid and H_2SO_4 failed to furnish the desired ring opened product (starting material remained intact.). Tanimori and coworkers in 1995 observerd the nucleophilic ring opening of doubly activated bicyclo[3.1.0]hexane **55** with CH_3COOH and KOAc in DMSO at 90 ºC for 4 h to give the ring opened adduct **56** in good yield (scheme 14).[17]

Scheme 14



In accordance with the planned synthesis, when the cyclopropane **50a** was subjected to crucial ring opening adopting Tanimori' s protocol, but at a slightly elevated temperature [KOAc/AcOH in dry DMSO at 110 ºC (scheme 15)], it gave rise to ring opened as well as decarboxylated acetoxy lactone **57** in 66% yield. ^{1}H NMR spectrum of the compound **57** revealed the absence of methyl ester group. The presence of singlet at 2.10 ppm integrating for 3 protons indicated the presence of acetate moiety. The sharp peak at 1780 cm^{-1} and 1730 cm^{-1} confirmed the presence of lactone and acetate functionality. The structure of the compound **57** was further confirmed by the presence of molecular ion peak at 156 in its mass spectral analysis.

Scheme 15



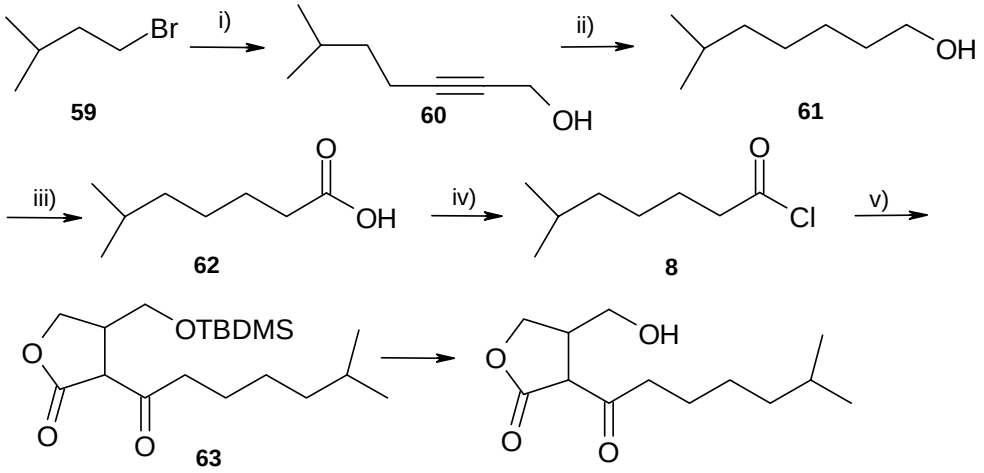
50a **57** **34** **58**

Reagents and conditions*: i), a) KOAc/AcOH, DMSO, 6 h, 110 ºC, 66%, ii) NaOMe (cat)/MeOH, 1 h, rt, iii) TBDMSCl, imidazole, CH_2Cl_2, 3 h, rt, 77%.*

Deacetylation of lactone **57** with K_2CO_3/aq. MeOH furnished the hydroxy-lactone **34** in poor yield (27%). In order to improve the yields of deacetylation, acetoxy-lactone **57** was subjected to deacetylation with catalytic NaOMe as shown in scheme 15. Improved yields during deacetylation was obtained using NaOMe (cat)/MeOH. Disappearance of peak at 1730 cm^{-1} and appearance of broad peak at 3220 cm^{-1} in the IR spectrum of compound **34** confirmed the absence of acetate moiety and the presence of hydroxy functional group. Later the hydroxylactone **34** was efficiently converted to the *tert*-butyldimethylsilyl ether **58** in 77% overall yield starting from acetoxy lactone **57**.

The 4 steps preparation of the acid chloride **8** reported in the literature produces an overall yield of 32% only (scheme 4).[10g] The synthesis of 6-methylheptanoyl chloride (**8**) reported in the literature procedure utilizes expensive 4-methylpentanol (**21**) as starting material. Therefore it was decided to synthesize the acid chloride **8** in higher yields starting from simple and commercially available inexpensive reagents.

Scheme 16



59 **60** **61** **62** **8** **63**

Reagents and conditions**: i) propargyl alcohol, $LiNH_2$/liq NH_3, overnight, -33 ºC, 61%, ii) Raney nickel, H_2, MeOH, overnight, rt, 81%, iii) Jones reagent, 8h, 0 ºC to rt, 96%, iv) $SOCl_2$, DMF (cat), 24 h, rt, 85%, v)* ***8*, LiHMDS, THF, 1h, -78 ºC, 85%*

As shown in the scheme 16, 1-bromo-3-methylbutane (**59**) was condensed with propargyl alcohol using $LiNH_2$/liqNH_3 to furnish 6-methyl-2-heptyne-1-ol (**60**) in 61% yield. The acetylenic alcohol **60** was subjected to hydrogenation using 10% Pd/C (40 *psi*) as well as with Raney nickel under normal pressure.

It was observed that hydrogenation under Raney nickel gave consistent and higher yields (81%) of completely saturated alcohol as compared to Pd/C catalyzed hydrogenation (61% yield). The saturated alcohol **61** was subjected to Jones oxidation to give 6-methylheptanoic acid (**62**) in 96% yield. The acid thus obtained was converted to 6-methylheptanoyl chloride (**8**) using $SOCl_2$ in 85% yield. The overall yield of the preparation of **8** staring from propargyl alcohol is 40%. The spectral data obtained for the acid chloride **8** was in total agreement with the reported value in the literature. Having the desired acid chloride **8** and the silylether **58** in hand, the stage was set for the crucial acylation.

Gratifyingly, condensation of silylether **58** and 6-methylheptanoyl chloride (**8**) with lithium hexamethyldisilazane (LiHMDS) provided the silyl protected A-factor **63** in 85% yield (scheme 16), whose conversion to (±)-A-factor can be obtained from the established protocol.[10f] It is pertinent to mention that similar acylation reaction reported in literature[10b,10g,18] either using LDA or LiHMDS furnished the corresponding acylated products in poor yields. It is believed that freshly prepared LiHMDS is the reason for observing unusually very high yields of C-acylated product. This observation is supported by Posner and co-workers attempts towards the synthesis of (+)-A-factor (scheme 5).[10c] When they performed the acylation on the lactone **25** with 6-methylheptanoyl chloride (**8**) using freshly prepared LiHMDS, they obtained 79% of the corresponding C-acylated product **26**. Lactone **63** was thoroughly characterised by the IR, NMR (^{1}H and ^{13}C) and mass spectroscopy. The sharp peak at 1717 cm^{-1} in the IR spectrum of the compound **63** confirmed the presence of ketone functionality. Appearnce of multiplet at 3.15 ppm (1H), dt at 2.91 ppm (1H) and 2.53 ppm (1H) with J = 8 Hz and 18 Hz and multiplet from 1.21 to 1.55 ppm (7H) confirmed the incorporation of acyl side

chain. Further the presence of a peak at 202.33 ppm (ketone carbonyl) apart from the 172.16 ppm (assigned to lactone carbonyl) in the ^{13}C spectrum of lactone **63** unambiguously confirmed the structure.

2.1.4 Conclusions:

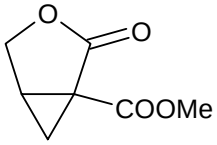
(±)-A-factor was synthesized by a novel and efficient manner via homoconjugate addition of KOAc/AcOH to doubly activated cyclopropane **50a**.

Following are the main features of the protocol:

1. Simple and efficient synthesis of (±)-A-factor in a minimum number of steps, which allows the use of commercially available inexpensive chemical reagents.
2. This scheme provides an advantage of both ring opening of cyclopropane **50a** and the concomitant decarboxylation to take place in one pot.
3. Facile and high yielding synthesis of 6-methylheptanoyl chloride is reported starting from readily available propargyl alcohol and isoamyl bromide
4. This synthetic sequence opens the door for efficient preparation of biologically active (*S*)-(−)-A-factor.

2.1.5 Experimental :

2-Oxo-3-oxa-bicyclo[3.1.0]hexane-1-carboxylic acid methyl ester (50a):



Sodium (1.8 g, 75mmol), was dissolved in dry MeOH (80 mL), and to it was added diethyl malonate (14.5 g, 90 mmol). To this solution epichlorohydrin (7.8 g, 84 mmol) in MeOH (10 mL) was added dropwise at room temperature over 1 h, and the mixture was stirred at 75 ºC for 20 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*, and chromatography on silica gel (eluting with Pet. ether-EtOAc=6:4) afforded **50a** as colorless oil in 50% (5.5 g) yield.

Mol. Formula: $C_7H_8O_4$, viscous oil

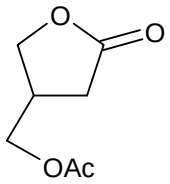
Yield: 50%.

IR ($CHCl_3$) cm^{-1}: 1778 s, 1730 s.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.39 (m, 1H), 2.07(m, 1H), 2.75 (m, 1H), 3.79 (s, 3H), 4.2(m, 1H), 4.36 (dd, J=9.37 Hz and 4.9 Hz, 1H)

Mass m/z (%): 156 (M^+, 17), 126 (100), 100 (45), 97 (45), 83 (76), 69 (79), 59 (41), 53 (69).

Acetic acid 5-oxo-tetrahydro-furan-3-ylmethyl ester (57):



A mixture of **50a** (2 g, 15.625 mmol), potassium acetate (6.3 g, 64 mmol), and acetic acid (4.62 g, 76 mmol) in dry DMSO (20 mL) was heated at 110 ºC for 6 h. After cooling, the reaction mixture was diluted with EtOAc, and the organic phase was washed with water brine and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Chromatography on silica gel (eluting with Pet. ether-EtOAc=6:4) afforded **57** (1.33 g, 66%) as colorless oil.

Mol. Formula: $C_6H_{10}O_2$, viscous oil.

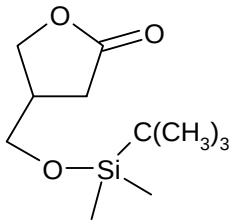
Yield: 66%.

IR (neat) cm^{-1}: 1780, 1737.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.1 (s, 3H), 2.33 (dd, J=6.34 Hz and 17.58 Hz, 1H), 2.62 (dd, J=9.04 Hz and 17.58 Hz, 1H), 2.87 (m, 1H), 4.07 (m, 3H), 4.38 (dd, J=7.32 Hz and 9.32 Hz, 1H).

Mass m/z (%): 159 ($M+1^+$, 2), 128(10), 98 (100), 85 (60), 70 (20).

4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-dihydro-furan-2-one (58):



To a solution of acetoxy lactone **57** (1 g, 6.32 mmol) in dry MeOH under argon atmosphere at 0 ºC was added catalytic amount of NaOMe. After stirring for 1 h at 0 ºC, the solution was quenched with 2N HCl. After concentration *in vacuo* the residue was dissolved in CH_2Cl_2 and washed with water. The water layer was saturated with NaCl and extracetd with CH_2Cl_2 (3x25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, dried and concentrated *in vacuo* to afford the hydroxy lactone 3**4**.

Mol. Formula: $C_5H_8O_3$, viscous oil

IR (neat) cm^{-1}: 3 220, 1781

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.35 (dd, J=5.61 Hz and 17.09 Hz, 1H), 2.58 (dd, J=8.79 Hz and 17.09 Hz, 1H), 2.73 (m, 1H), 3.63 (m, 2H), 4.19 (dd, J=4.88 Hz and 9.2 Hz, 1H), 4.38 (dd, J=7.33Hz and 9.28 Hz, 1H).

Mass m/z (%): 117 ($M+1^+$, 20), 98 (20), 85 (30), 74 (45), 69 (20), 57 (100).

To a solution of alcohol **34** (0.595 g, 5.12 mmol) in dry dichloromethane (5 mL) under argon atmosphere was added imidazole (0.768g, 11mmol) followed, after a 10 min delay, was added TBDMSCl (0.92 g, 6.15 mmol) and the reaction was stirred at room temperature overnight. The reaction mixture was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Chromatography on silica gel

(eluting with Pet. ether-EtOAc=9:1) afforded the title compound (1.12g) as a colorless oil in 77% starting from compound .

Mol. Formula: $C_{11}H_{22}O_3Si$, viscous oil

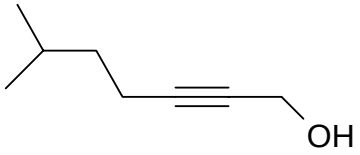
Yield: 77%.

IR (neat) cm^{-1}: 1781 s

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.00 (s, 6H), 0.83 (s, 9H), 2.29 (dd, J=4 Hz and 12 Hz, 1H), 2.49 (dd, J=6 Hz and 12 Hz, 1H), 3.57 (m, 2H), 2.66 (m, 1H), 4.11 (dd, J=4Hz and 6Hz, 1H), 4.3 (dd, J=4 Hz and 6 Hz, 1H).

Mass m/z (%): 215 (2), 174 (47), 173 (45) 155 (47), 145 (30), 115 (13), 99 (13), 75 (100), 73 (37).

6-Methyl-hept-2-yn-1-ol (60):



To a stirred flask charged with 700 mL of liquid ammonia, was added 400 mg of Fe $(NO_3)_2$ with stirring. After few seconds, a small portion of the lithium (from 3.9 g, 0.561mol) was added. As soon as the blue color of the dissolved metal has disappeared and a white grayish suspension has formed, the remaining lithium was introduced in similar manner. The entire amount of lithium was consumed in 30 min. Freshly distilled propargyl alcohol (15 g, 0.267 mol) was then added dropwise over 30 min. Ten minutes after the addition of propargyl alcohol, isoamyl bromide (**59**) (48.5 g, 0.32 mol), was added dropwise over 30 min. Stirring was continued for additional 6 h. The ammonia was then allowed to evaporate. The solid thus obtained was hydrolyzed by stirring with a saturated ammonium hydrochloride solution (200 mL). The solution was subjected to continuous extraction with ethyl acetate (3x100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*, and chromatography on silica gel (eluting with Pet. ether-EtOAc=8.5:1.5) afforded the title compound as colorless oil (20.56 g, 61%).

Mol. Formula: $C_8H_{14}O$, viscous oil

Yield: 61%.

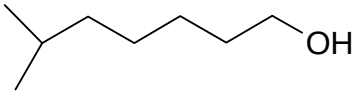
IR (neat) cm^{-1}: 3344, 2289, 2223

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.87(d, J=6.35 Hz, 2H), 1.38 (dd, J=6 Hz and 14Hz, 2H), 1.65 (m, 1H), 2.18 (m, 2H), 2.59 (s br, 1H), 4.19 (s, 2H),

^{13}C NMR (50MHz, $CDCl_3$ + CCl_4) δ: 85.9 (s), 78.34 (s), 50.7 (t), 37.5 (t), 27.1 (d), 22 (2C, q), 16.6(t).

Mass m/z (%): 111 (32), 107 (7), 95 (56), 93 (100), 83 (30), 77 (20), 70 (40), 55 (43).

6-Methyl-heptan-1-ol (61):



To a solution of alcohol **6** (10 g, 79.3 mmol) in 100 mL of methanol was added 6 g of Raney nickel (washed with 3x10 mL methanol). Hydrogen was then admitted to the system under normal pressure and the reaction mixture was stirred at room temperature overnight. After hydrogenation was complete, the catalyst was removed by filtration of the reaction mixture through a celite pad. The filtrate was concentrated *in vacuo*. Chromatography on silica gel (eluting with Pet. ether-EtOAc=8:2) afforded 2 (8.25 g, 81%) as an oil.

Mol. Formula: $C_8H_{18}O$, viscous oil

Yield: 81%.

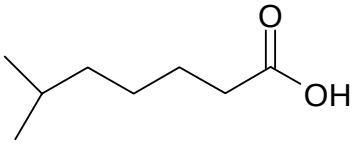
IR ($CHCl_3$) cm^{-1}: 3350.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.84 (d, J=6.34 Hz, 6H), 1.17 (m, 2H), 1.32 (m, 4H), 1.52 (m, 3H), 2.72 (s br, 1H), 3.58 (t, J=6.35 Hz, 2H).

^{13}C NMR (50MHz, $CDCl_3$ + CCl_4) δ: 85.9 (s), 78.34 (s), 50.7 (t), 37.5 (t), 27.1 (d), 22.0 (2C, q), 16.6 (t).

Mass m/z (%): 97 (34), 84 (24), 83 (12), 70 (31), 69(80), 56 (100), 55 (73).

6-Methyl-heptanoic acid (62):



The Jones reagent was prepared by dissolving 70 g (0.70 mole) of chromium trioxide in 100 ml. of water. After it was immersed in an ice bath, 112 g. (61 mL, 1.10 moles) of concentrated (18 M) sulfuric acid followed by 200 mL of water was added cautiously with manual stirring. The solution was cooled to 0 ºC–5 ºC. A solution of 10g

(1.00 mole) of alcohol **61** in 200 ml. of acetone was cooled to 0 ºC–5 ºC. The cooled Jones reagent prepared above was added dropwise with vigorous stirring, at a rate to maintain the temperature of the reaction mixture at about 20 ºC till the solution retains the brown color. The stirring was continued for 3h after the addition was complete. After removing the acetone *in vacuo* the solution was subjected to continuous extraction with dichloromethane (3x100 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the pure acid **62** in 96% (10.63 g) yield.

Mol. Formula: $C_8H_{16}O_2$, viscous oil

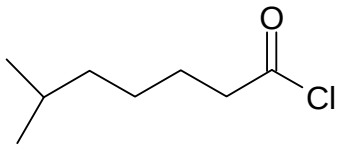
Yield: 96%.

IR ($CHCl_3$) cm^{-1}: 3425, 1707

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.88 (d, J=6.34Hz, 6H), 1.25-1.33 (m, 4H), 1.63 (m, 3H), 2.35 (t, J=8 Hz, 2H).

Mass m/z (%): 145 ($M+1^+$, 2), 129 (3), 101 (48), 85 (70), 82 (100), 72 (50), 59 (20)

6-Methylheptanoyl chloride (**8**):



Thionyl chloride (18.17 g, 0.15 mol), acid **62** (10 g, 0.069 mol) and a catalytic amount of dry DMF were combined and stirred at room temperature for 24 h, and the excess thionyl chloride was removed by distillation. Kughelrohr distillation furnished the title acid chloride **8** as a colorless liquid (9.54 g, 85%).

Mol. Formula: $C_8H_{15}ClO$,

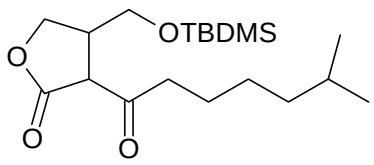
BP: 110 ºC (5mmHg)

Yield: 85%.

IR (neat) cm^{-1}: 1806

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.88 (d, J=6.35 Hz, 6H), 1.2 (m, 2H), 1.36 (m, 2H), 1.7 (m, 2H), 1.55 (m, 1H), 2.88 (t, J=6.83 Hz, 2H),

4-tert-Butylsilanyloxymethyl-3-(6-methyl-heptanoyl)-dihydro-furan-2-one. (63)



To a solution of protected alcohol **5** (0.5 g, 2.17 mmol) in dry THF (20 mL) under argon atmosphere at –78 ºC was added freshly prepared lithium bis(trimethylsilyl)amide (5.43mmol) in THF (5 mL) dropwise. After a 20 min delay, acid chloride **8** (0.493 g, 3.03 mmol) in THF (5 mL) was added drop wise during 10 min at –78 ºC. After stirring for 1 h at –78 ºC, the reaction mixture was allowed to warm to room temperature. The mixture was poured into ice-AcOH-H_2O and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ solution (20 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo.* Chromatography on silica gel (eluting with pet. Ether:EtOAc = 32:1) afforded the title compound as colorless oil (0.66 g, 85%).

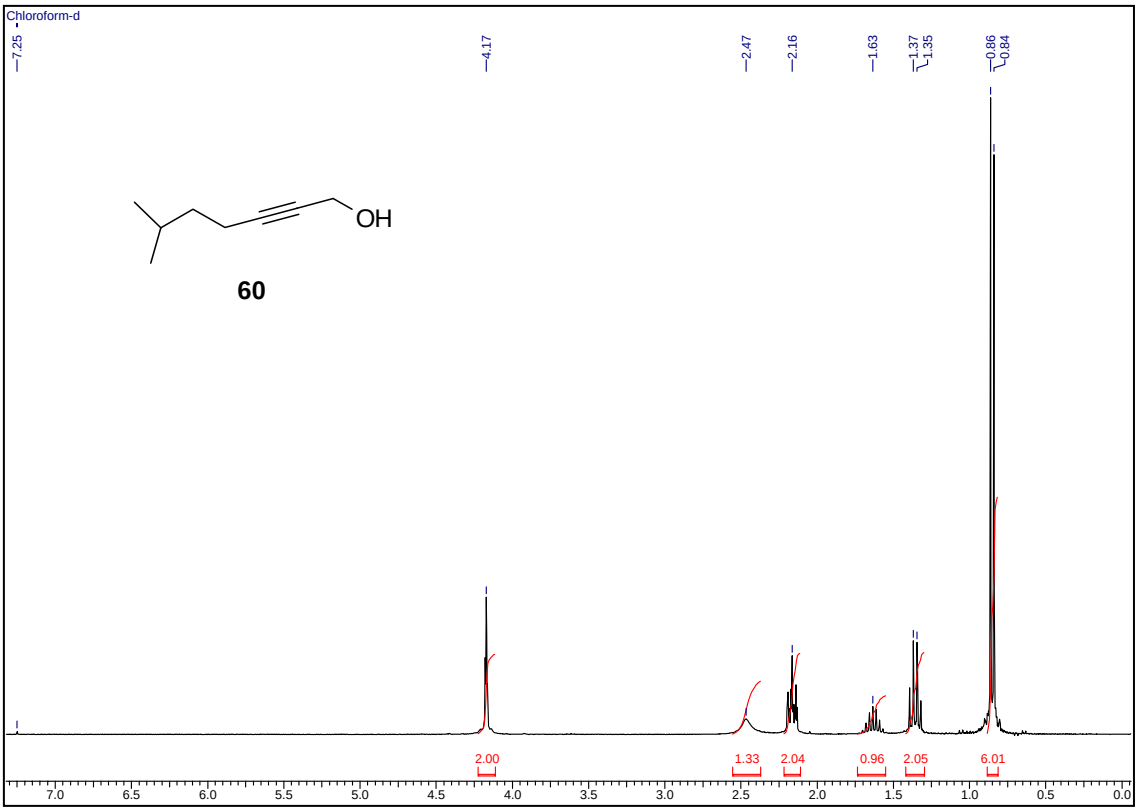
Mol. Formula: $C_{19}H_{36}O_4Si$, viscous oil

IR ($CHCl_3$) cm^{-1} : 1774 , 1717.

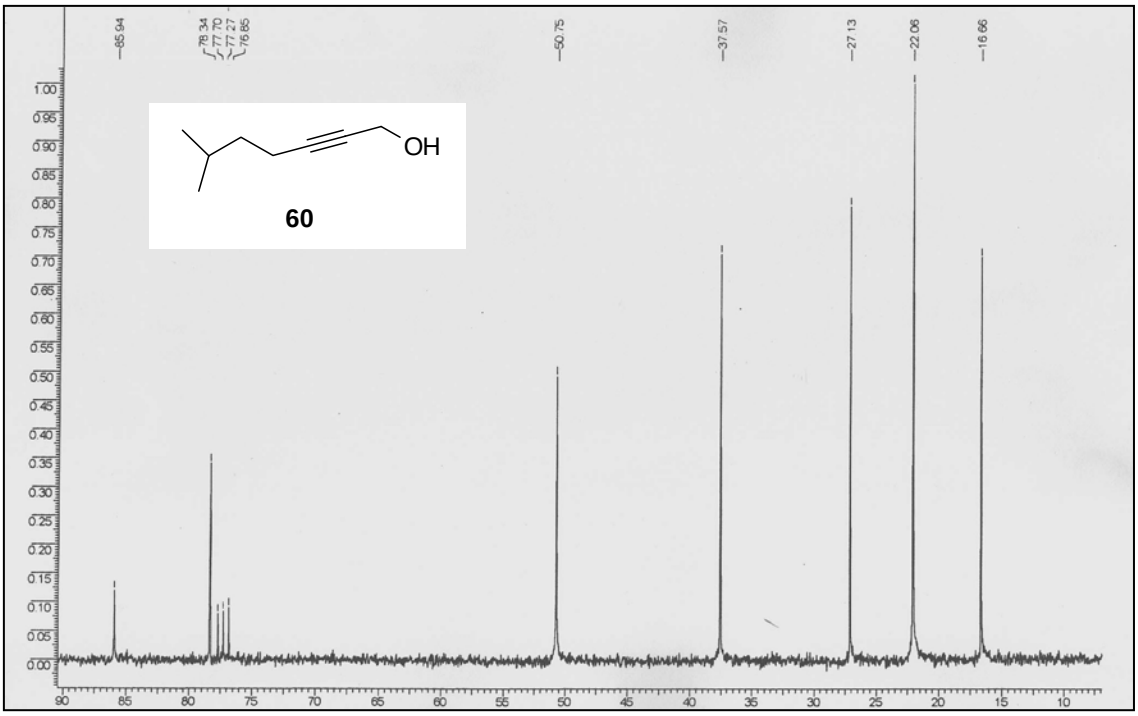
^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.0 (s, 6H), 1.21-1.55 (m, 8H), 0.81 (m, 15H), 2.53 (dt, J=8 Hz and 18 Hz, 1H), 2.91 (dt, J=8 Hz and 18 Hz, 1H), 3.15 (m, 1H), 3.59 (m, 3H), 4.15 (dd, J=5.49 Hz and 9.16 Hz, 1H), 4.36 (dd, J=7.9 Hz and 9.16 Hz, 1H).

^{13}C NMR (50MHz, $CDCl_3$ + CCl_4) δ: 202.3 (s), 172.1 (s), 69.2 (t), 62.4 (t), 42.6 (d), 39.5 (d), 38.9 (t), 27.0 (t), 26.0 (3C, q), 23.8 (t), 22.9 (2C, q), 18.1 (s), -5.2 (2C, q)

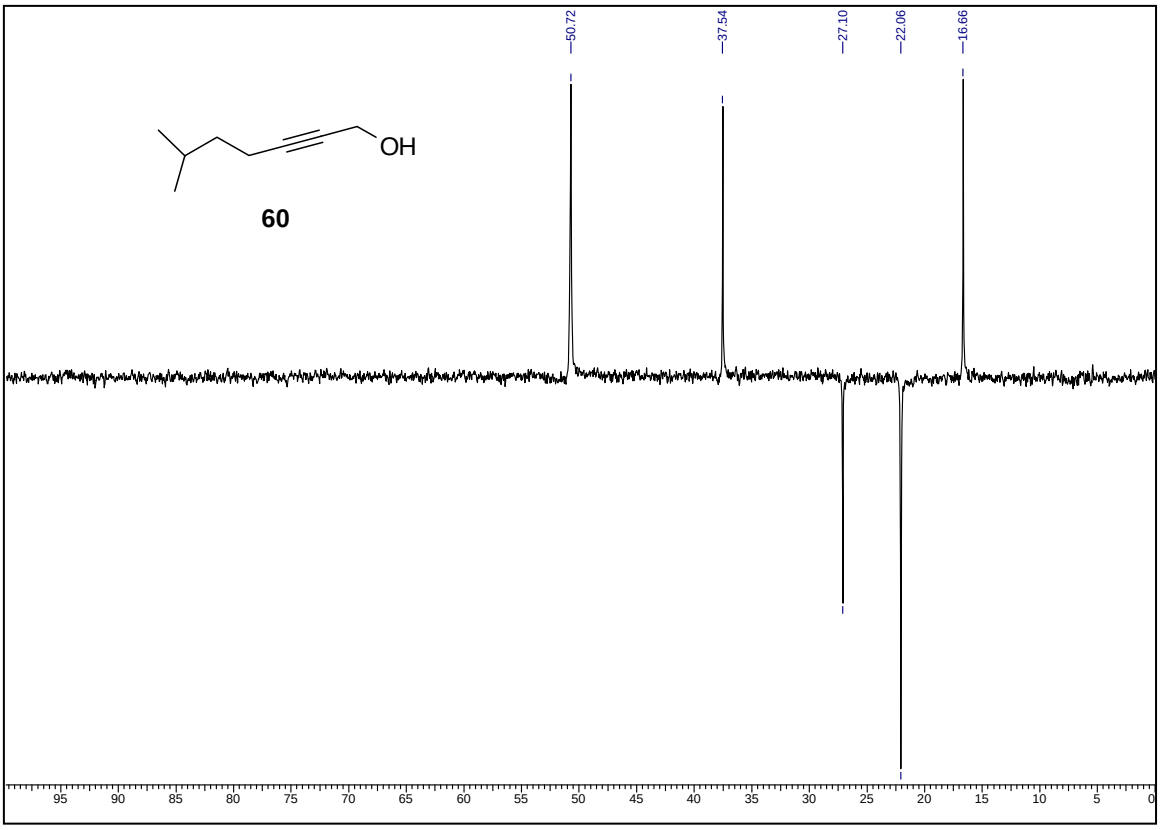
Mass m/z (%): 299 (11), 145 (21), 131 (25), 109 (42), 83 (28), 69 (21), 57 (79), 56 (100).



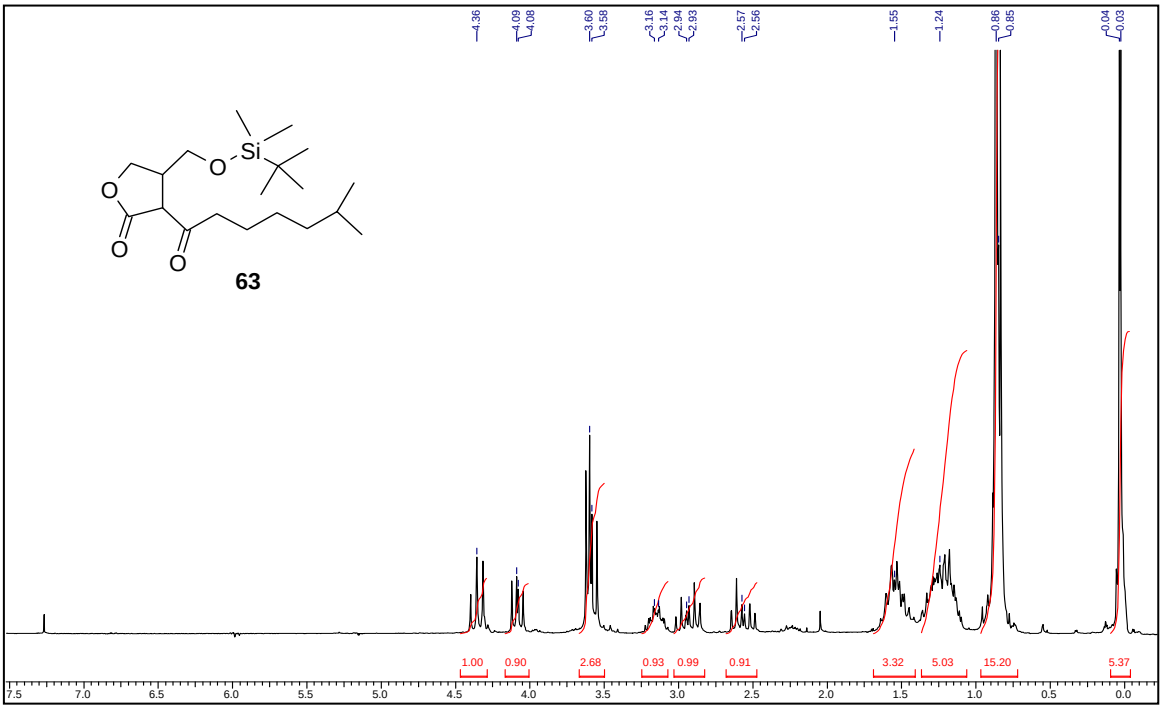
^{1}H-NMR ($CDCl_3$ + CCl_4, 200 MHz)



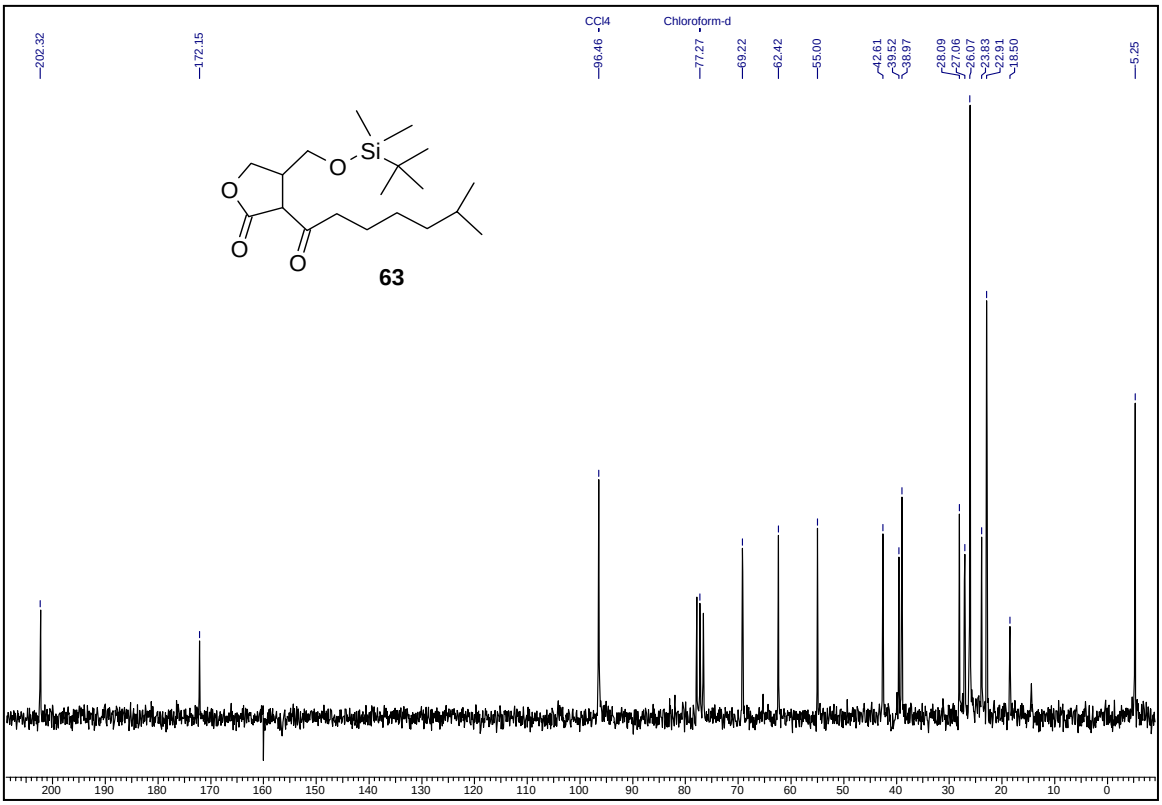
^{13}C-NMR ($CDCl_3$ + CCl_4, 200 MHz)



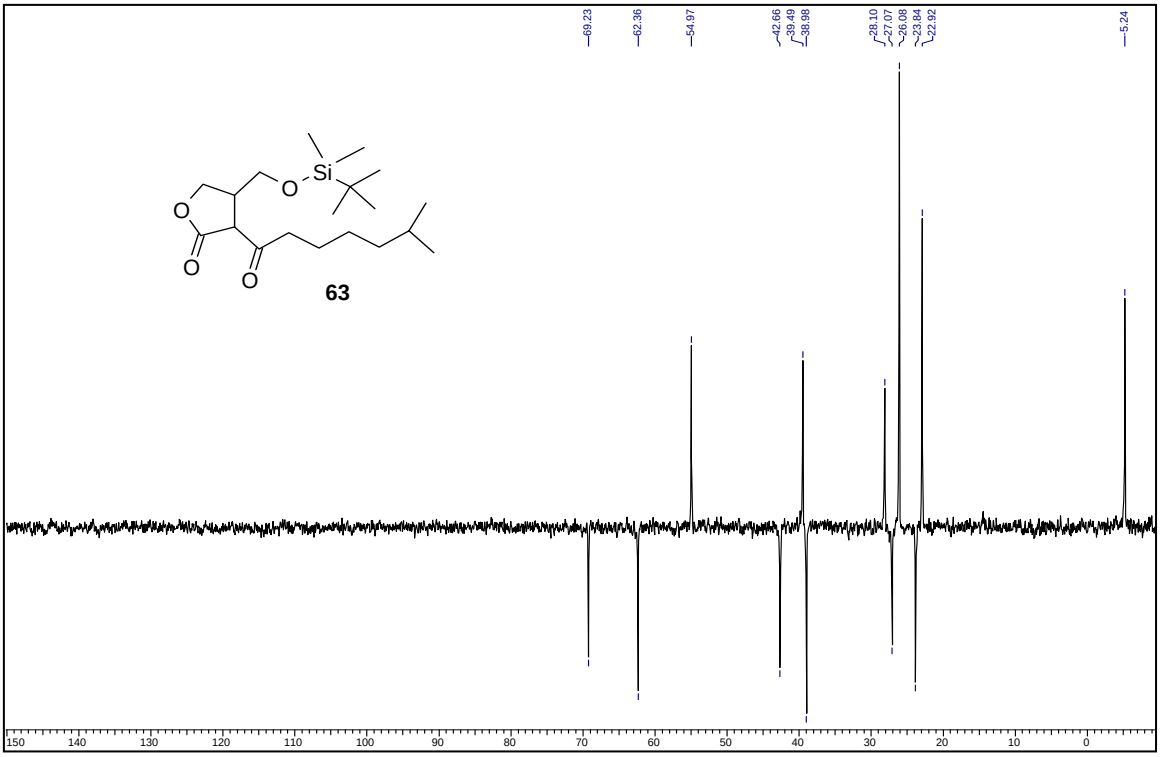
DEPT ($CDCl_3$ + CCl_4, 200 MHz)



^{1}H-NMR ($CDCl_3$, + CCl_4, 200 MHz)



^{13}C-NMR ($CDCl_3$, + CCl_4, 50 MHz)



DEPT ($CDCl_3$, + CCl_4, 50 MHz)

2.1.6 References:

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CHAPTER II

SECTION 2

PART 1: Catalytic Transesterification of β-Ketoesters with H-FER Under Solvent Free Conditions

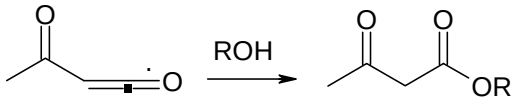
2.2.1.1 Introduction:

Transesterification is one of the fundamental organic reactions that have commanded wide industrial and academic applications. [1] It is the process where an ester is transformed in to another through interchange of the alkoxy moiety. The reaction is equilibrium driven and mandates the use of either acid or alcohol in excess to obtain the products in reasonable yield. However several acid and base catalysts accelerate the reaction. Transesterification is the method of choice employed to prepare esters either when the parent carboxylic acid are labile and difficult to isolate or they have poor solubility in organic solvent whereas the esters are mostly soluble. β-Ketoesters are multicoupling reagents having an electrophilic carbonyl and nucleophilic carbon, which make them a valuable tool for the synthesis of several complex natural products. They occupy a special position in the organic synthesis because all the four carbon atoms can form facile bond, selectively under suitable reaction conditions.

2.2.1.2 Literature Background:

There are numerous methods documented in the literature to synthesize β-ketoesters. They are classically prepared by Claisen condensation:[2a] the cyclic congener by its intramolecular Dieckmann condensation.[2b] The alternative process of getting β-ketoesters is by the alcoholysis of acetyl ketene **1** (scheme 1), the use of which is avoided due to their lachrymatory and toxic properties as well as shipping problems.[2c]

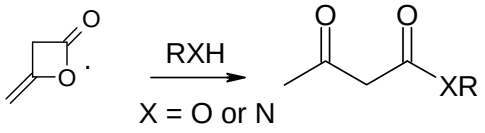
Scheme 1 (*Chem. Rev.* **1986**, *86*, 241.)



1

Although inexpensive and highly reactive 4-methyleneoxetan-2-one (diketene) **2** is commonly used for the preparation of acetoacetateesters and acetoacetamides on laboratory and industrial scale (scheme 2), use of diketene should be avoided because, it is lachrymatory, causes injury burns to the skin or respiratory tract and reactions of diketene are often highly exothermic in nature.[2c]

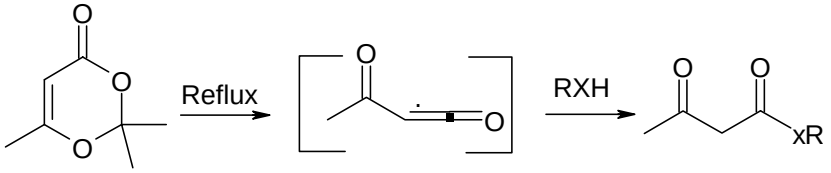
Scheme 2 (***Chem. Rev.* 1986, *86***, 241.)



2

Several diketene-free approaches to the preparation of β-ketoesters have been documented in the literature. Clemens in 1985 suggested the usage of 2,2,6-trimethyl-4*H*, 1,3-dioxin-4-one **3** as acylating agents of alcohols.[2d] Other modes of preparations are, acylation of ketones with chloroformates,[2e] acylation of Meldrum's acid[2f] and by the condensation of ethyl diazoacetate with aldehydes.[2g]

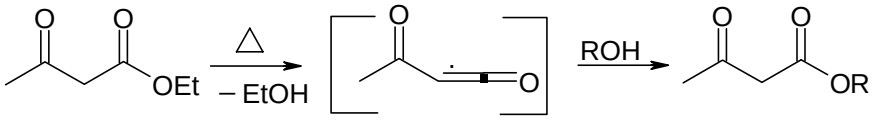
Scheme 3: (*J. Org. Chem.*, **1985**, *50*, 2431.)



3

Particularly useful is the preparation of β-ketoesters by transesterification. Though there are several methods reported for transesterification, most of them are not general as far as β-ketoesters are concerned because of their propensity to undergo facile decarboxylation. Caroll *et al*[3a] and Bader *et al*[3b] independently found that in the absence of any catalyst, β-ketoesters were transesterified by heating esters and alcohols. A large excess of β-ketoester and prolonged reaction time were necessary. The presence of active hydrogen is a prerequisite for the success of this reaction (scheme 4).

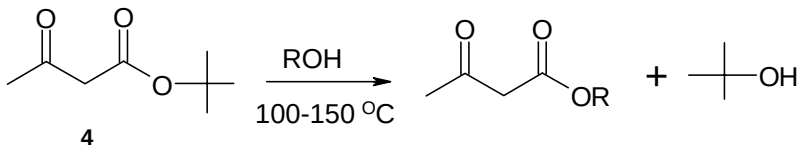
Scheme 4: (***J. Am. Chem. Soc.*, 1951, *73*,** 4195.)



Witzeman *et al*[3c] have reported a very efficient method of transesterification in the absence of any catalyst involving sterically hindered *tert*-butyl acetoacetate (**4**) and equimolar amount of alcohol using xylene or toluene as a solvent (scheme 5). The *tert*-butyl acetoacetate reacted 15-20 fold faster than other sterically less hindered esters. This

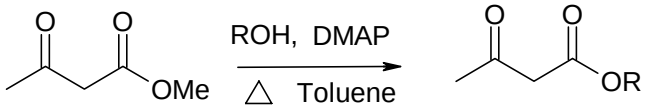
method lacks generality because it is limited to the use of only *tert*-butyl acetoacetate as staring material.

Scheme 5 (***J. Org. Chem.* 1991, *56*,** 1713.)



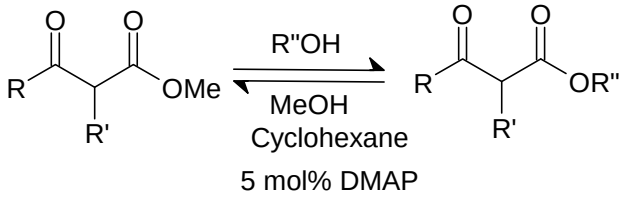
Recent modification to the transesterification of β-ketoesters in the absence of catalysts involves the usage of microwave under solvent free conditions developed by Massimo *et al*.[3d] The products are obtained in very high yields. The disadvantage of the process being the presence of active hydrogen is mandatory for the success of this reaction. Taber *et al*[4a] found that methylacetoacetates were effeciently transesterified with primary or secondary alcohols in the presence of DMAP toluene at reflux (scheme 6). Few disadvantage associated with this protocols are as follows. The reaction was inert to nonenolizable β-ketoesters, demands the usage of stoichiometric amount of DMAP and tertiary alcohols were not effective for transesterification.

Scheme 6 (***J. Org. Chem.* 1985, *50*,** 3612.)



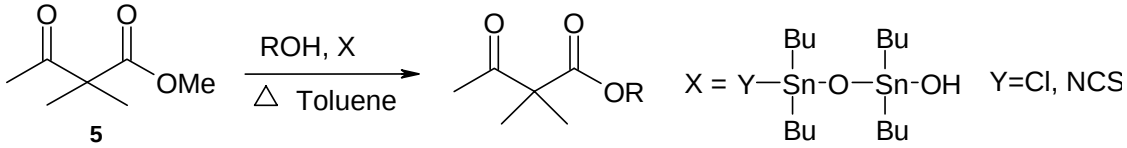
Gilbert and Kelly[4b] modified the experimental conditions of aforesaid protocol by adding 4A^{o} molecular sieves for the removal of ethanol and biased the equilibrium in order to achieve the preparation of allyl acetoacetates. However the same shortcomings previously encountered still remained. Jens and coworkers[4c] recently suggested a modification of Taber's protocol. MeOH formed was removed continuously as an azeotrope leading to quantitative conversions (scheme 7). The starting materials are converted in stoichiometric ratio, which makes the purification of the product very simple.

Scheme 7: (*Eur. J. Org. Chem*. **2000**, *8*, 1633.)



Otera *et al*[5] were able to effect the transesterification of non-enolizable β-ketoesters essentially under neutral conditions employing 1,3 disubstituted tetrabutyl stannoxanes (scheme 8)

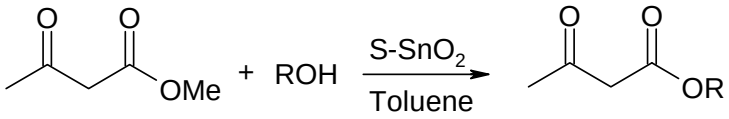
Scheme 8: (***Tetrahedron Lett***. **1986, *27*,** 2383.)



Other homogeneous catalysts employed in effecting the transesterification of β-ketoesters are, DBU,[6a] $Ti(OR)_4$,[6b] NBS,[6c] Zn/I_2,[6d] I_2 [6e] and ionic liquid regulated NH_2SO_3H.[6f]

Heterogeneous catalysts have certain advantages when compared to the traditional reagents in catalyzing the transesterification of β-ketoesters because they are stable, reusable and allow easy workup and purification. Our group was the first to describe the utility of heterogeneous catalyst S-SnO_2 a solid acid as an efficient catalyst in effecting transesterification (scheme 9).[7a] The salient features of this protocol are: the reaction proceeded with stoichiometric amounts of the keto ester and alcohol, the tertiary butyl esters could be easily obtained and the catalyst was recovered and reused. After this publication several other heterogeneous catalysts were also shown to be effective.

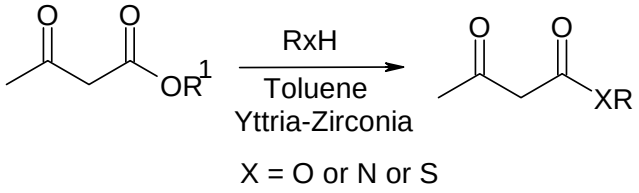
Scheme 9 (*Tetrahedron Lett*. **1996**, *37*, 233.)



Apart from S-SnO_2, other solid acid catalysts employed for the transesterification of β-ketoesters are Mo-ZrO_2 by Reddy et al in 1999[7b] and Yttria-Zirconia by Pandey *et al*

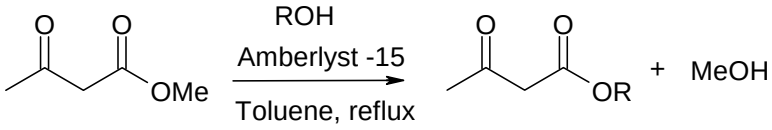
in 2000.[7c] Yttria-Zirconia has been used as an effective and selective catalyst to effect the transesterification (scheme 10). Wide variety of alcohol has been used. Noteworthy feature of this procedure is that it has been extended to other nucleophiles such as thiols and amines.

Scheme 10 (*Synlett* **2000**, 251.)



Application of Amberlyst –15 as an efficient catalyst for transesterification was also reported from our group.[7d] Short reaction times and high yields are the salient features of this protocol. The ready availability of this Amberlyst-15 commercially makes this protocol very attractive (scheme 11).

Scheme 11 (*Synth. Commun*. **2001**, *31*, 289.)



Even zeolites (Hβ)[7e] and clays (natural Kaolinitic,[7f] Envirocat EPZG[7g] and Montmorillonite K-10[7h]) have been reported as catalysts for the transesterification of β-ketoesters by employing toluene as the solvent. Having both Bronsted and Lewis acid sites they function as efficient catalysts for the transesterification.

2.2.1.3 Present work:

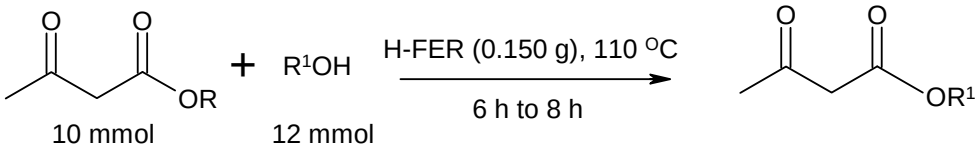
Organic reactions using conventional organic solvents especially chlorinated hydrocarbons have posed a serious threat to the environment owing to their toxicity and volatile nature. Therefore it is imperative to perform organic reactions under solvent free conditions. In this regard solvent free catalytic organic reaction has received tremendous attention in recent times.[8]

The application of inorganic solid acid especially zeolites, as effective heterogeneous catalyst for organic synthesis have received considerable attention in the

recent decades due to their properties such as shape selectivity, acidic and basic nature, ease of handling, non-corrosiveness, recyclability and a very high thermal stability.[9]

Ferrierite (FER) [10a] is a natural zeolite mineral with a ten member ring (4.2 X 5.4 Å) intersecting eight member (3.5 x 4.8 Å) with unit cell formulae as $(Na, K)_4 Mg_2(Si_{30}Al_6)O_{72}(OH)_2. 18H_2O$. Zeolite lattice contains cavities of varying diameters depending on the type of zeolite. Classification based on the pore diameter is very pertinent. Based on this parameter FER falls under medium pore zeolite with a tubular diameter of 5-6.5 A. The zeolite Ferrierite in its acidic form H-Ferrierite (H-FER)[10b] is an exceptionally selective and stable catalyst for the skeletal isomerisation of linear butanes to isobutene.[10c,10d] Thus as a part of research program towards development of protocols for the green synthesis, it was decided to study one of the fundamental synthetic organic transformation namely transesterification of β-ketoesters catalyzed by zeolite H-FER under solvent free condition (scheme 12).

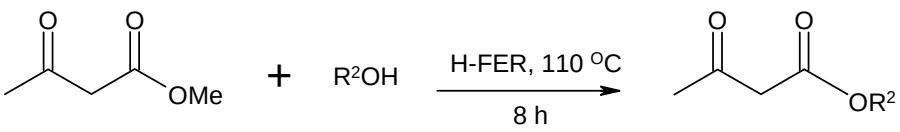
Scheme 12

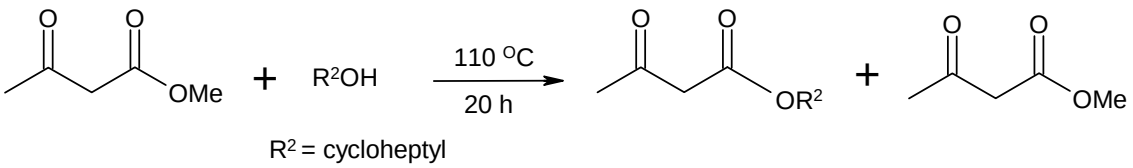


2. 2.1.4 Results and Discussion

In order to ascertain the role of H-FER as catalyst in enhancing the rate of the reaction, transesterification of cycloheptanol was conducted in the absence of H-FER. From scheme 13 it is clear that the time taken for the reaction by employing H-FER as the catalyst is considerably reduced. A variety of β-ketoesters was treated with alcohols in the presence of H-FER as the catalyst to give the corresponding transesterified esters in good to excellent yields. The low boiling alcohol (methanol or ethanol) formed in the reaction was continuously removed by distillation. The results of this protocol are summarized in table 1.

Scheme 13

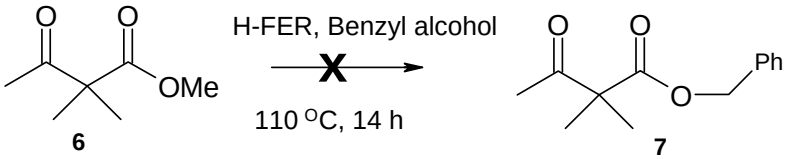




R^2 = cycloheptyl

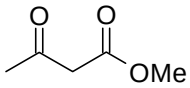
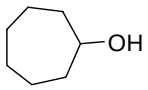
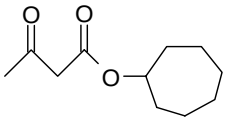
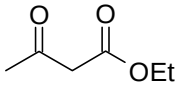
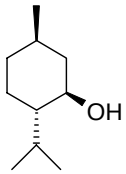
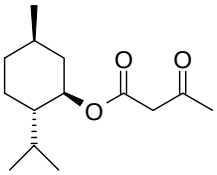
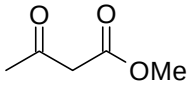
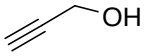
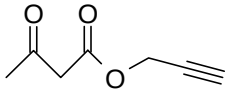
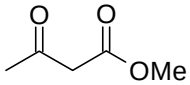
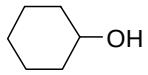
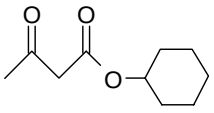
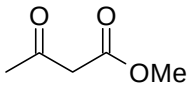
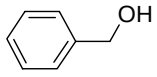
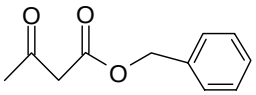
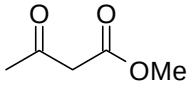
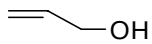
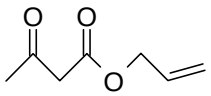
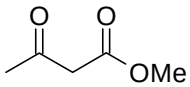
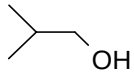
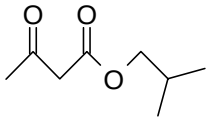
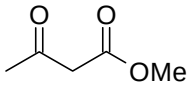
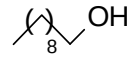
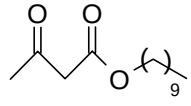
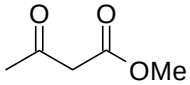
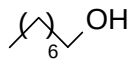
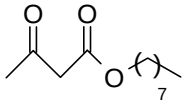
In most of the cases only 1.2 equivalents of alcohols were used. Only in case of volatile alcohols (Table-1, entries 3, 6, 7, 12 and 13) like propargyl alcohol, allyl alcohol, isobutanol, isopropanol, propanol, 2 equivalents of alcohol were used. A note worthy feature of the present protocol is that benzyl, allyl and propargyl esters (entries 3, 6 and 10) become readily accessible. The allyl and propargylesters are known to be difficult to prepare as they readily undergo the Carrol rearrangement.[11] It is evident from the table 1 that both the primary and secondary alcohols participate well in the reaction. However tertiary alcohol (*tert*- butanol) did not furnish the corresponding *tert*-butyl ester. Apart from methyl and ethyl acetoacetate, this synthetic methodology focuses on structurally varied beta-keto esters such as ethyl benzoylacetate[12] (entry 14) and cyclopentanone keto ester (entry 15), which underwent smooth transesterification to provide the corresponding transesterified esters in good yields. Keto ester **14C** exists as keto : enol tautomers in the ratio 3:1(^{1}H NMR analysis). Substitution at the α-position of β-ketoester was found to be detrimental for smooth transesterification. This was evident with the reaction of 2-methyl-3-oxo-butyric acid ethyl ester (entry 16) with benzyl alcohol even after 16 h reaction was found to be only 44% complete as per ^{1}H NMR analysis. Under similar conditions keto ester **6** (scheme 14) failed to undergo transesterification suggests that the reaction proceeds via the activation of carbonyl groups of the β-ketoester leading to the formation of acyl ketene as proposed by Campbell and co-workers.[13]

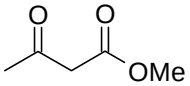
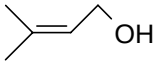
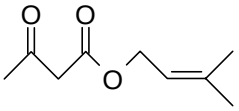
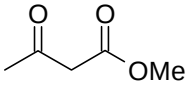
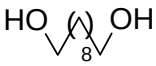
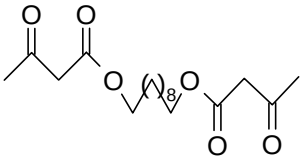
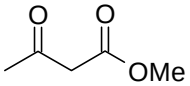
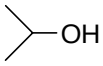
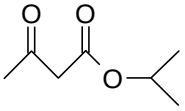
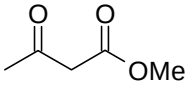
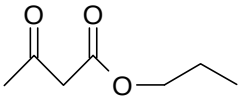
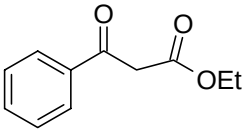
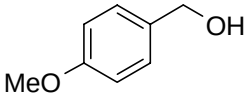
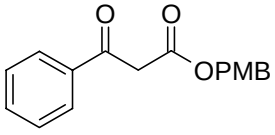
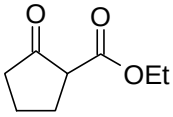
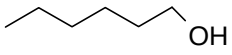
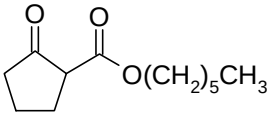
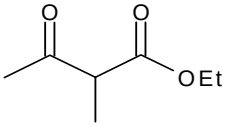
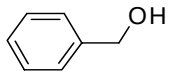
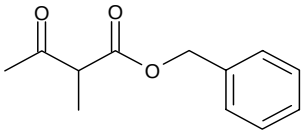
Scheme 14



It should be pointed out that phenol, p-cresol, m-chlorophenol failed to undergo transesterification. This zeolite was reused several times without any loss of activity by filtering the catalyst, washing with acetone, drying and reusing immediately.

Table 1

Sr. No.	Ester (A)	Alcohol (B)	Product (C)	% Yield (Isolated)
1.				72
2.				90
3.				61
4.				85
5.				90
6.				65
7.				84
8.				70
9.				71

Sr. No.	Ester (A)	Alcohol (B)	Product (C)	% Yield (Isolated)
10.				80
11.				55
12.				59
13.				65
14.				74
15.				72
16.				44

2.2.1.5 Conclusions:

In conclusion, the present protocol describes a simple and efficient method for the transesterification of β-ketoesters by different alcohols catalyzed by H-FER under solvent free condition. It has been demonstrated that transesterification of β-ketoesters with different alcohols proceeded with fairly high yields in a relatively short reaction time and avoids the use of aromatic solvents such as toluene and xylene that are usually employed. The obvious advantages of heterogeneous catalysis in terms of simple operation coupled with the ease of workup and recyclability of the catalyst without any loss of its activity are noteworthy. These conditions enable minimum waste and offer an environmentally benign protocol.

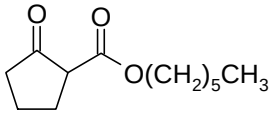
2.2.1.6 Experimental:

The zeolite H-FER catalyst was synthesized according to the reported procedure.[10b] In a typical batch, 52.5 g of sodium silicate (in 25 ml of distilled water) was stirred with 10 ml pyrrolidine. To this solution, 2.4 g of aluminum sulfate hexadeca-hydrate (in 25 ml distilled water) and 1.8 g of sulfuric acid (in 10 ml distilled water) was added. Finally, 30 ml of distilled water was added and the gel (pH 11.5 ± 0.2) was stirred vigorously for 2 h and autoclaved in a 300 ml stainless steel Parr autoclave (4842, 300 ml) and heated at 160 °C for 60 h. The initial gel composition was: 20 Na_2O+Al_2O_3+37 pyrrolidine + 66.5 SiO_2+6.3 H_2SO_4 +1460 H_2O. The autoclave was quenched and the product filtered off, washed and dried at 100 °C for 6–8 h. The resulting material was calcined in air at 550 °C for 18–20 h and then exchanged with 1 M NH_4NO_3 solution three times, followed by calcination at 550 °C for 10 h to yield H-FER zeolite. The catalyst was characterized by X-ray powder diffraction (Rigaku, D-Max III VC diffractometer with Cu-Ka radiation, l= 1.5404 Å) for its phase purity. The chemical composition of silica and alumina was established by a wavelength dispersive XRF (3070 Rigaku) spectrophotometer. Thermogravimetric analysis (TGA) and differential thermal analysis (DTA) were carried out in flowing air at a heating rate of 10 °C/21 min on an autonomic TG/DTA (SETRAM 92). An Omnisorp100 CX (COULTIER Corporation, USA) analyzer was used for the measurement of low-pressure nitrogen adsorption to determine the surface area. The Lewis and Bronsted acidity of the H-FER catalyst sample

was determined by adsorbing CD_3CN on the catalyst wafer and then characterized by FTIR spectrometry (Nicolet Magne-550 FTIR).

General Procedure: In a typical example 2-oxo-cyclopentanecarboxylic acid ethyl ester (entry **15A**, 10mmol), hexanol (**15B**, 12 mmol) and H-FER (0.15 g) was stirred at 110ºC for 8 h. After completion of the reaction (monitored by TLC), catalyst was removed by filtration and washed with ethyl acetate. The solvent was removed under reduced pressure to obtain the crude product which was further purified by column chromatography on silica gel {ethyl acetate: petroleum-ether (bp 40 ºC-60 ºC) =1:9}.

2-oxo-cyclopentanecarboxylic acid hexyl ester (15C):



Mol. Formula: $C_{12}H_{20}O_3$.

Yield: 72%.

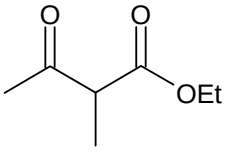
IR (neat) cm^{-1}: 1750, 1720.

^{1}H-NMR (500 MHz, $CDCl_3$ + CCl_4) δ: 0.84 (t, 3H, J = 6.75 Hz), 1.26 - 1.32 (m, 6H), 1.59 (m, 2H), 1.83 (m, 1H), 2.09 (m, 1H), 2.25 (m, 4H), 3.09 (t, J = 8.74 Hz, 1H), 4.09 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$ + CCl_4) δ: 212.20 (s), 169.51 (s), 65.50 (t), 54.83 (t), 38.07 (t), 31.50 (t), 28.64 (t), 27.51 (t), 25.56 (t), 22.61 (t), 21.09 (t), 14.08 (q).

Mass ESI (m/z): 213 $(M+1)^+$.

2-Methyl-3-oxo-butyric acid ethyl ester (16A):



To the reaction mixture containing dry acetone (50 mL), activated K_2CO_3 (15.92 g, 0.115 mol) and ethyl acetoacetate (5 g, 0.038 mol) was added methyl iodide (27.2 g, 0.192 mol) and stirred at room temperature for 16 h. Reaction mixture was filtered and washed with DCM (3x20 mL). The organic layer was concentrated under reduced pressure. The residue obtained was chromatographed on silica gel (60-120 mesh size)

with pet-ether (boiling range-60 ºC-80 ºC):ethyl acetate (97:3) to provide the title compound in 85% yield (4.70 g).

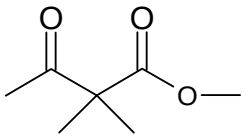
Mol. Formula: $C_7H_{12}O_3$,

Yield: 85%.

IR ($CHCl_3$) cm^{-1}: 1740, 1710.

^{1}H-NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.07-1.16 (m, 6H), 2.06 (s, 3H), 3.33 (q, J=7.04 Hz, 1H), 4.02 (q, J=7.04 Hz, 2H).

2,2-dimethyl-3-oxo-butyric acid methyl ester (6):



To the reaction mixture containing dry acetone (50 mL), activated K_2CO_3 (21.2 g, 0.15 mol) and methyl acetoacetate (5 g, 0.043 mol) was added methyl iodide (61 g, 0.43 mol) and stirred at reflux temperature for 20 h. Reaction mixture was filtered and washed with DCM (3 X 20 mL). The organic layer was concentrated under reduced pressure. The residue obtained was chromatographed on silica gel (60-120 mesh size) with pet-ether (boiling range-60 ºC-80 ºC): ethyl acetate (95:5) to provide the title compound in 80% yield (4.96 g).

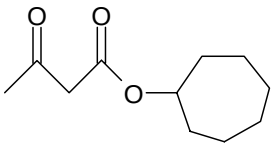
Mol. Formula: $C_7H_{12}O_3$

Yield: 80%

IR ($CHCl_3$) cm^{-1}: 1745, 1716.

^{1}H-NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.30 (s, 6H), 2.09 (s, 3H), 3.67 (s, 3H).

Cyclohexyl 3-oxo-butanoate (1C):[7d]



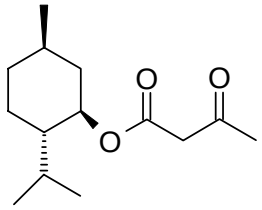
Mol. Formula: $C_{11}H_{18}O_3$.

Yield: 72%

IR ($CHCl_3$) cm^{-1}: 1740, 1720.

^{1}H-NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.42-1.73 (m, 10 H), 1.86-1.98 (m, 2H), 2.25 (s, 3H), 3.39 (s, 2H), 4.97 (m, 1H).

Menthyl-3-oxobutanoate (2C):[7d]



Mol. Formula: $C_{14}H_{24}O_3$.

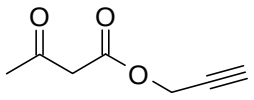
Yield: 90%

$[\alpha]_D^{25}$-72.00 (c=10.24, benzene), lit.[3d] $[\alpha]_D^{25}$-69.30 (c=10, benzene).

IR (neat) cm^{-1}: 1742, 1710.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.85 (d, J=6 Hz, 3H), 1.4-1.5 (m, 2H), 0.9-1.2 (m, 9H), 1.65-1.75 (m, 2H), 1.9-2.1 (m, 2H), 2.25 (s, 2H), 4.75 (dt, J = 4.4 Hz and 10.7 Hz, 1H).

Propargyl 3-oxobutanoate (3C):[7f]



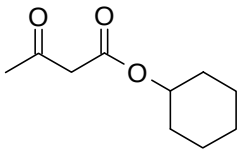
Mol. Formula: $C_7H_8O_3$.

Yield: 61%

IR (neat) cm^{-1}: 2290, 2260, 1740, 1720.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.24 (s, 3H), 2.48 (t, J = 2.4 Hz, 1H), 3.46 (s, 2H), 4.70 (d, J = 2.4 Hz, 2H).

Cyclohexyl-3-oxo Butanoate (4C):[7d]



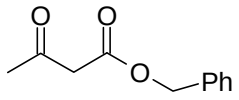
Mol. Formula: $C_{10}H_{16}O_3$.

Yield: 85%

IR (neat) cm^{-1}: 1750, 1720.

^{1}H-NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.37 (m, 6H), 1.71 (m, 2H), 1.80 (m, 2H), 2.4 (s, 3H), 3.4 (s, 2H), 4.8 (m, 1H).

Benzyl 3-oxobutanoate (5C):[7d]



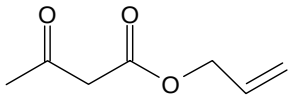
Mol. Formula: $C_{11}H_{12}O_3$.

Yield: 90%

IR (neat) cm^{-1}: 1740, 1720.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.25 (s, 3H), 3.50 (s, 2H), 5.18 (s, 2H), 7.36 (s, 5H).

3-oxo-butyric acid allyl ester (6C):[3b]



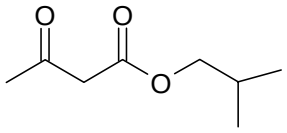
Mol. Formula: $C_7H_{10}O_3$.

Yield: 65%

IR ($CHCl_3$) cm^{-1}: 3010, 2980, 1750, 1730, 1650, 1560.

^{1}H-NMR (200 MHz, $CDCl_3$ + CCl_4) δ; 2.2 (s, 3H), 3.4 (s, 2 H), 4.6 (d, J = 5.6 Hz, 2H), 5.25 (dd, J = 8.9 Hz and 4.4 Hz, 2H), 5.8 (m, 1H).

Isobutyl 3-oxo-butanoate (7C):[7f]

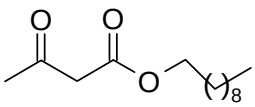


Mol. Formula: $C_8H_{14}O_3$.

Yield: 84%

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.96 (d, J = 8Hz, 6H), 1.97 (m, 1H), 2.29 (s, 2H), 3.45 (s, 3H), 3.93 (d, J = 6 Hz, 2H).

Decyl 3-oxobutanoate (8C):[7d]



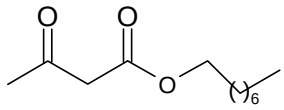
Mol. Formula: $C_{14}H_{26}O_3$.

Yield: 70%

IR (neat) cm^{-1}: 2928, 1742, 1717.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.82 (t, J = 6.4 Hz, 3H), 1.14-1.40 (m, 14H), 1.51-1.61 (m, 2H), 2.21 (m, 3H), 3.37 (s, 2H), 4.06 (t, J = 6.4 Hz, 2H).

Octyl 3-oxobutanoate (9C):[7d]



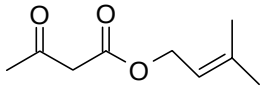
Mol. Formula: $C_{12}H_{22}O_3$.

Yield: 71%

IR ($CHCl_3$) cm^{-1}: 1742, 1720.

^{1}H-NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.9 (t, J = 6.4 Hz, 3H), 1.3 (m, 10 H), 1.6 (m, 2H), 2.6 (s, 3H), 3.42 (s, 2H), 4.1 (t, J = 6.4 Hz, 2H).

Prenyl 3-oxobutanoate (10C):[7f]



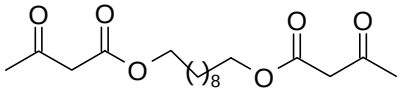
Mol. Formula: $C_9H_{14}O_3$.

Yield: 80%

IR (neat) cm^{-1}: 2975, 1739, 1718, 1676, 1648.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.67 (s, 3H), 1.72 (s, 3H), 2.21 (s, 3H), 3.38 (s, 2H), 4.57 (d, J = 7.3 Hz, 2H), 5.29 (t, J = 7.3 Hz, 1H).

Decane-1, 10-diyl Bis(3-oxobutanoate) (11C):[7d]



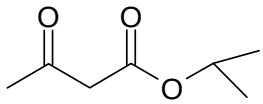
Mol. Formula: $C_{18}H_{30}O_6$,

Yield: 55%

IR (neat) cm^{-1}: 1742, 1720

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.1-1.40 (m, 12H), 1.5-1.65 (m, 4H), 2.24 (s, 6H), 3.40 (s, 4H), 4.09 (t, J = 6.4 Hz, 4H).

Isopropyl 3-oxobutanoate (12C):[7f]

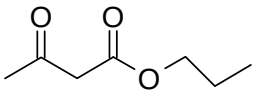


Mol. Formula: $C_7H_{12}O_3$.

Yield: 59%

^{1}H-NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.20 (d, J = 6.4 Hz, 6H), 2.19 (s, 3H), 3.33 (s, 2H), 4.99 (m, 1H),

Propyl 3-oxobutanoate (13C):[7d]



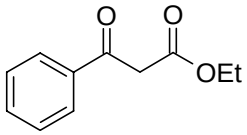
Mol. Formula: $C_7H_{12}O_3$.

Yield: 65%

IR (neat) cm^{-1}: 1740, 1716.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.93 (t, J = 6.8 Hz, 3H), 1.65 (m, 2H), 2.24 (s, 3H), 3.42 (s, 2H), 4.06 (t, J = 6.8 Hz, 2H),

Ethyl benzoyl acetate (14A):[12]



Mol. Formula: $C_{11}H_{12}O_3$.

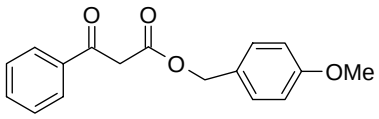
Yield: 85%

IR (neat) cm^{-1}: 1742, 1687.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: [1.25 (t, J = 7.04 Hz), 1.33 (t, J = 7.04 Hz), 3H], [3.96, 5.64, 12.55 (s, 2H)], [4.20 (q, J = 7.04 Hz), 4.25 (q, J = 7.04 Hz), 2H], 7.42-7.61 (m, 3H), 7.76-7.91 (m, 2H).

.**Mass ESI (m/z)**: 193 $(M+1)^+$

3-Oxo-3-phenyl-propionic acid 4-methyoxy-benzyl ester (14C):



Mol. Formula: $C_{17}H_{16}O_4$.

Yield: 74%.

IR ($CHCl_3$) cm^{-1}: 1740, 1687.

^{1}H-NMR (200 MHz, $CDCl_3$ + CCl_4) δ: [3.80, 3.82 (s, 3H)], [4.00, 5.70, 12.55 (s, 2H)], [5.13, 5.19 (s, 2H)], 6.87 (m, 2H), 7.33-7.55 (m, 4H), 7.59 (m, 1H), 7.77-7.52 (m, 2H).

Mass ESI (m/z): 285 $(M+1)^+$.

2.2.1.7. References:

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CHAPTER II

SECTION 2

PART 2: Catalytic Acetylation of Alcohols, Phenols, Thiols and Amines with H-FER Under Solvent Free Conditions.

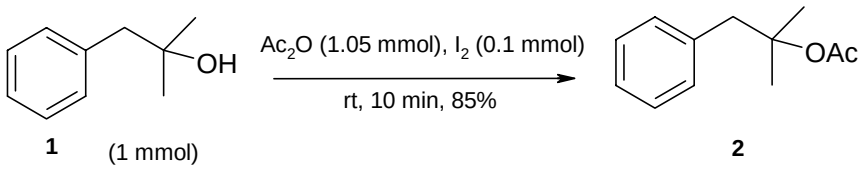
2.2.2.1 Introduction:

The acylation of alcohols is one of the important and routinely utilized transformations in organic synthesis,[1] especially in the synthesis of complicated natural products and glycosylation of sugars acyl groups play a pivotal role as protecting groups of hydroxyls. Despite a number of precedents, new efficient methodologies for acylation are still in great demand. Acid anhydrides have been the most commonly used acylating reagents in the presence of an acid or base catalyst.[2] The most commonly employed basic catalysts for this purpose are triethyl amine, pyridine or DMAP (4-dimethylamino) pyridine.[3] Nevertheless, there is still a great demand for acid catalysts to generate esters under mild conditions.

2.2.2.2 Literature Background:

This section briefs about some of the recent developments reported in literature for the acylation of alcohols, phenols, thiols and amines. Although numerous methods to achieve acylation are known, newer methods continue to attract attention for their experimental simplicity and effectivenes.

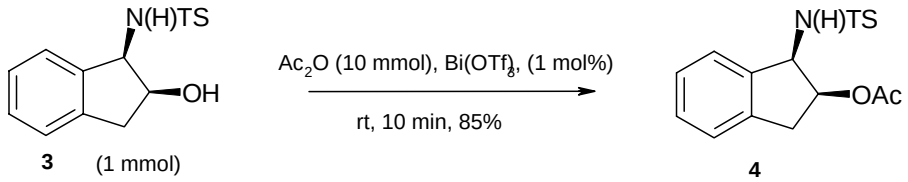
Scheme 1 (Phukan, P. *Tetrahedron Lett*. **2004**, *45*, 4785.)



1 (1 mmol) **2**

Phukhan[4a] reported molecular I_2 as an extremely powerful catalyst for the acetylation of alcohols under solvent free conditions (scheme 1). Nearly equimolar amounts of alcohol and acetic anhydride are typically used avoiding waste and providing very simple experimental and workup procedures. The general efficiency of this reaction is evident from the variety of hydroxy compounds including tertiary alcohols being acetylated within a very short time.

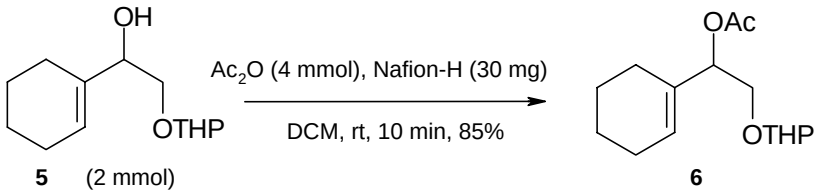
Scheme 2 (*J. Org. Chem*. **2001**, *66*, 8926)



3 (1 mmol) **4**

Otera and coworkers[4b] have reported $Bi(OTf)_3$-catalyzed acylation of alcohols with acid anhydrides at ambient temperature in comparison with other acylation methods (scheme 2). This method includes a lot of unique merits namely, a cheap and easy-to-handle catalyst, operational simplicity. $Bi(OTf)_3$ is removable at ease by washing with water. This proto-col was applicable to wide spectrum of alcohols bearing various functionalities. Even acylation of functionalised tertiary alcohols was effected at room temperature.

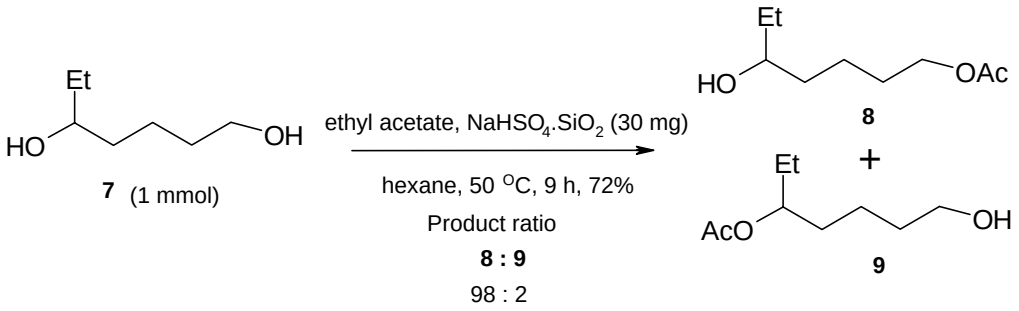
Scheme 3 (*Synlett* **2000**, 1652.)



5 (2 mmol) **6**

Nafion-H,[4c] a solid acid catalyst, catalyzed acetylation of alcohols using acetic anhydride as acylating agent at room temperature has been reported by Vankar and co-workers (scheme 3). A wide variety of alcohols, some containing acid sensitive groups also underwent smooth acetylation. The catalyst was recovered and reused. This protocol was not suitable for acetylation of tertiary alcohols, which underwent facile dehydration.

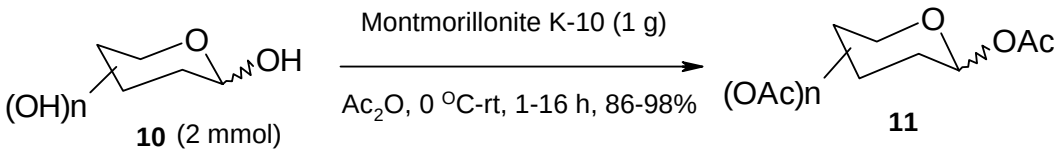
Scheme 4 (Breton, G. W. *J. Org. Chem.* **1997**, *62*, 8952.)



7 (1 mmol)

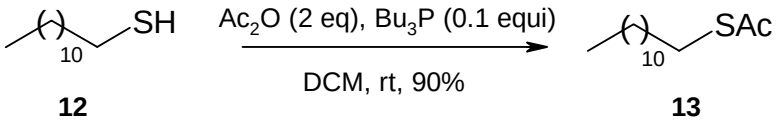
Breton[4d] reported (scheme 4) selective monoacetylation of unsymmetrical diols via transesterification using ethyl acetate catalyzed by silicagel-supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$). Small amounts of catalyst at reasonable temperatures (60 ºC) effectively catalyzed the transesterification process. This method affords greater yields of monoacetate products and higher selectivity for primary hydroxyl groups over secondary and phenolic groups. The possibility of recycling the catalyst has been not reported.

Scheme 5 (*Tetrahedron Lett*. **1998**, *39*, 2215.)



Per-*O*-acetylation is most commonly used for the protection of hydroxyl groups in sugars. The inexpensive solid acid, montmorrilonite K-10, has shown to be an efficient catalyst for the per-*O*-acetylation of several mono-, di-, and trisaccharide (scheme 5).[4e] The main disadvantages of this protocol are partial anomarisation and the usage of acetic anhydride in large excess. Also the possibility of recycling the catalyst has been not reported.

Scheme 6 (*J. Org. Chem.* **1993**, *58*, 7286.)



Vedejs and co-workers[4f,4g] have showed that tributylphosphine is a potent catalyst for the acylation of ROH/RSH/phenols by acetic anhydride or benzoic anhydride or benzoyl cyanide or diketenes (scheme 6). Although the phosphorous catalyst is very useful with regard to high catalytic activity, the procedure is tedious because all the manipulations should be performed strictly under anhydrous and degassed conditions due to the instability of the phosphorus catalyst in air. Furthermore Bu_3P is highly flammable (flash point: 37 ºC).

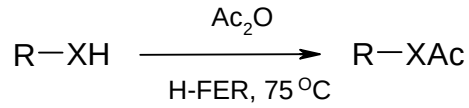
There are several other Lewis acids (bismuth oxide perchlorate,[5a] $LiClO_4$,[5b] Mn(III) salen complex,[5c] $CoCl_2$,[5d] $ZnCl_2$,[5e] $MgBr_2$,[5f] LiCl,[5g] LiBr,[5h] $Sc(OTf)_3$,[5i] etc) and heterogeneous catalysts (Yttria-Zirconia,[6a] $BF_3.SiO_2$,[6b] WO_3-ZrO_2,[6c] Zeoliotes HZSM-5,[6d] $ZnCl_2$-HY[6e] and HSZ-360,[6f] etc) known in the literature to catalyze the acylation reaction.

2.2.2.3 Present work:

In recent years there has been a tremendous upsurge of interest in various chemical transformations performed under heterogeneous catalysts, which are inexpensive, noncorrosive and perform transformation with higher efficiency. Moreover

the easy work-up and recyclability associated with heterogeneous catalysts makes the chemical transformations appear very attractive for industrial processes. Having successfully demonstrated the H-FER catalysed transesterification of β-ketoesters with different alcohols under solvent free conditions (Chapter II, Section 2, Part 1), it was decided to study the most fundamental synthetic organic transformation, acetylation of alcohols, phenols, thiols and amines using acetic anhydride catalyzed by zeolite H-FER under solvent free conditions (scheme 7). This protocol relates to the use of a simple stable solid catalyst H-FER, which can be easily recovered and reused, and gives excellent conversions in a range of reactions. This synthetic methodology focuses on developing fundamental organic processes in solvent-less condition there by offering a green chemistry.

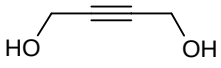
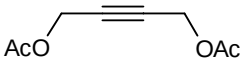
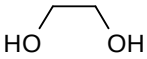
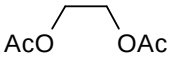
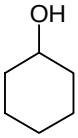
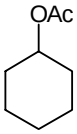
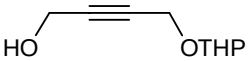
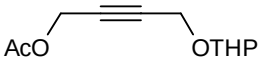
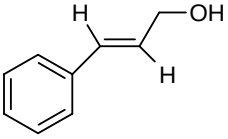
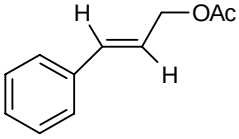
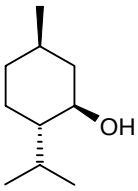
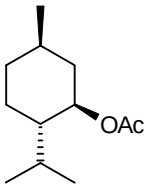
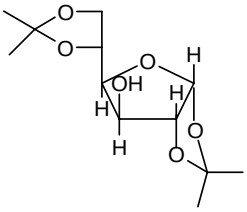
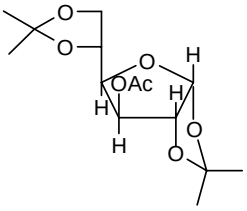
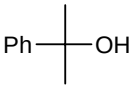
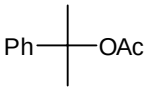
Scheme 7

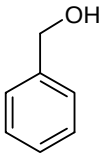
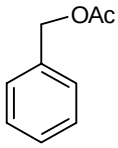
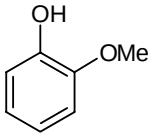
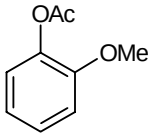
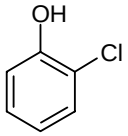
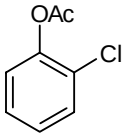
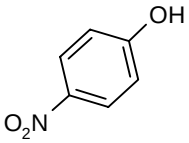
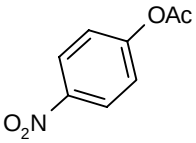
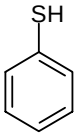
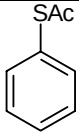
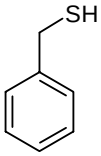
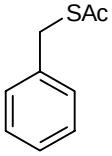
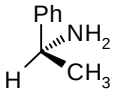
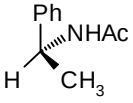
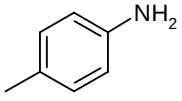
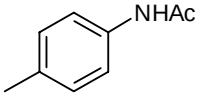


2.2.2.4 Results and Discussion

As shown in Table 1, several alcohols, phenols and thiols underwent acetylation very smoothly in excellent yields. Under our reaction conditions chiral alcohols can be easily acetylated with complete retention of optical activity (entry 7) in high yields. The mildness of the present protocol is the key feature, which is evident in acetylation of alcohols containing acid sensitive groups such as acetal (entry 8) and tetrahydropyranyl ether (entry 5), which survived under the reaction conditions. It was observed that primary allylic alcohol (entry 6) underwent smooth acetylation under the applied reaction conditions. An additional feature of the present reaction system is that it tolerates other acid sensitive functionalities such as C–C double and triple bonds (entries 1, 2 and 5, 6). Attempted acetylation of a tertiary alcohol (entry 9) however, gave the acetylated product in only 45% yield based on the recovery of the starting material. This zeolite was reused several times without any appreciable loss of activity, simply by filtering the catalyst, washing with acetone, drying and reusing immediately.

Table1

S. NO	Reactant (A)	Product (B)	Reaction time (h)	Isolated yield (%)
1			2[a]	98
2			2 [a]	98
3			2 [a]	98
4			2.5	97
5			2	91
6			2	94
7			2.5	94
8			2.5	85
9			6	45[b]

S. NO	Reactant (A)	Product (B)	Reaction time (h)	Isolated yield (%)
10			1.5	99
11			2	95
12			5	94
13			5	99
14			5	91
15			5	94
16			2[c]	99
17			2[c]	99

a: 3 equivalents of acetic anhydride was used.

b: based on recovery of the starting material.

c: Reaction was carried out at room temperature. All other reactions were carried out at 75 ºC.

2.2.2.5 Conclusions:

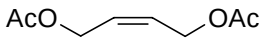
In conclusion, we have demonstrated the H-FER catalyzed acetylation of alcohols, phenols and thiols using acetic anhydride under solvent-less condition in excellent yields. This protocol offers an efficient catalyst for acetylation of alcohols, phenols, thiols and amines with acetic anhydride under solventless conditions. All acetates were obtained in excellent yields under operationally simple experimental conditions. The mildness of the protocol is evident as acid labile groups such as THP ethers and acetals, which survived under the reaction condition. The catalyst was reused without any loss of activity.

2.2.2.6 Experimental:

General Procedure:

To a mixture of acetic anhydride (15 mmol) and alcohol/thiol/amine (10 mmol), the catalyst (0.15 g) was added and the reaction mixture was stirred at 75 °C for the length of time indicated in Table 1. After the completion of the reaction (monitored by TLC and GC), the reaction mixture was extracted with Et_2O and the catalyst filtered off. The filtrate was washed with water. The organic layer was then dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure followed by chromatography over silica gel using light petroleum–ethyl acetate as eluent furnished the corresponding acetate.

Acetic acid 4-acetoxy-but-2-enyl ester (1B):



Mol. Formula: $C_8H_{12}O_4$, colorless oil.

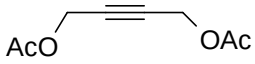
Yield: 95%.

IR ($CHCl_3$) cm^{-1}: 3023, 1738, 1441.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.05 (s, 6H), 4.66 (m, 4H), 5.72 (m, 2H).

Mass (m/z): 112 (40), 99 (5), 82 (7), 70 (100), 60 (10), 53 (3).

Acetic acid 4-acetoxy-but-2-ynyl ester (2B):



Mol. Formula: $C_8H_{10}O_4$, colorless oil.

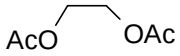
Yield: 98%.

IR ($CHCl_3$) cm^{-1}: 3025, 2945, 1748.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.03 (s, 6H), 4.63 (s, 4H).

Mass (m/z): 128 (2), 110 (5), 103 (65), 100 (10), 86 (100), 82 (30), 68 (30), 61 (5).

Acetic acid 2-acetoxy-ethyl ester (3B):



Mol. Formula: $C_6H_{10}O_4$, colorless oil.

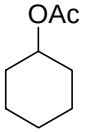
Yield: 98%.

IR ($CHCl_3$) cm^{-1}: 1732.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.03 (s, 6H), 4.20 (m, 4H).

Mass (m/z): 116 (35), 103 (25), 86 (100), 73 (47), 61 (2).

Acetic acid cyclohexyl ester (4B):



Mol. Formula: $C_8H_{14}O_2$, colorless oil.

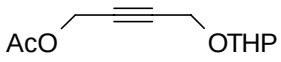
Yield: 97%.

IR ($CHCl_3$) cm^{-1}: 2937, 2859, 1733.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.23-1.45 (m, 6H), 1.7-1.87 (m, 4H), 1.99 (s, 3H), 4.69 (m, 1H).

Mass (m/z): 99 (2), 82 (100), 71 (5), 67 (65), 61 (13), 57 (14).

Acetic acid 4-(tetrahydro-pyran-2-yloxy)-but-ynyl ester (5B):



Mol. Formula: $C_{11}H_{16}O_4$, colorless oil.

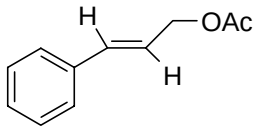
Yield: 91%.

IR ($CHCl_3$) cm^{-1}: 1742.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.4-2.0 (m, 6H), 2.03 (s, 3H), 3.40 (m, 1H), 3.80 (m, 1H), 4.19 (m, 2H), 4.59 (t, *J*=1.94 Hz, 2H), 4.72 (m, 1H).

Mass (m/z): 169 (2), 139 (2), 111 (40), 97 (7), 85 (100), 79 (30), 55 (77), 43 (55).

Acetic acid 3-phenyl-allyl ester (6B):



Mol. Formula: $C_{11}H_{12}O_2$, colorless oil.

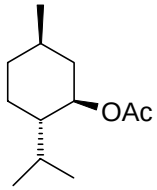
Yield: 94%.

IR ($CHCl_3$) cm^{-1}: 3025, 2943, 1737, 1444, 1371.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.1 (s, 3H), 4.72 (d, *J*=6.35 Hz, 2H), 6.28 (td, *J*=15.62 and 6.34 Hz, 1H), 6.60 (d, *J*=15.62 Hz, 1H), 7.28-7.37 (m, 5H).

Mass (m/z): 176 (M^+, 30), 170 (3), 130 (40), 128 (42), 115 (100), 105 (67), 92 (65), 77 (57), 63 (23), 57 (10).

Acetic acid 2-isopropyl-5-methyl-cyclohexyl ester (7B):



Mol. Formula: $C_{12}H_{22}O_2$, colorless oil.

Rotation: $[\alpha]_D^{25}$ = -78.12 º (c=8, C_6H_6).

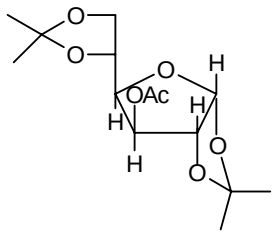
Yield: 94%.

IR ($CHCl_3$) cm^{-1}: 2934, 2855, 1721.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 0.76 (d, *J*=7.33 Hz, 3H), 0.88 (d, *J*=6.9 Hz, 3H), 0.91 (d, *J*=6.69 Hz, 3H), 1.04 (m, 3H), 1.35 (m, 1H), 1.49 (m, 1H), 1.67 (m, 2H), 1.86 (m, 1H), 2.01 (s, 3H), 1.96 (m, 1H), 4.65 (dt, *J*=4.28 and 10.82 Hz, 1H).

Mass (m/z): 139 (23), 123 (25), 109 (15), 95 (100), 81 (100), 71 (40), 67 (37), 54 (5).

3-*O*-Acetyl-1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose (8B):



Mol. Formula: $C_{14}H_{22}O_7$, white solid.

Yield: 85%.

mp: 61-62 ºC.

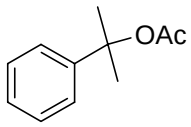
Rotation: $[\alpha]_D^{25}$ = -37.47 º (c=1, $CHCl_3$)

IR ($CHCl_3$) cm^{-1}: 1746, 1375.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.31 (s, 3H), 1.32 (s, 3H), 1.41 (s, 3H), 1.52 (s, 3H), 2.11 (s, 3H), 4.03-4.18 (m, 4H), 4.48 (m, 1H), 5.23 (m, 1H), 5.85 (m, 1H)

Mass (m/z): 287 (55), 229 (3), 169 (4), 143 (7), 127 (5), 101 (100), 85 (15), 72 (15), 59 (15).

Acetic acid 1-methyl-1-phenyl-ethyl ester (9B):



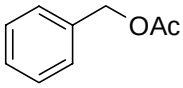
Mol. Formula: $C_{11}H_{14}O_2$, colorless oil.

Yield: 45%.

IR ($CHCl_3$) cm^{-1}: 3081, 1725.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.80 (m, 6H), 2.06 (s, 3H), 7.36 (m, 5H).

Acetic acid benzyl ester (10B):



Mol. Formula: $C_9H_{10}O_2$, colorless oil.

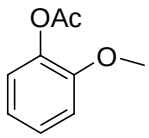
Yield: 99%.

IR (neat) cm^{-1}: 3022, 2938, 1729, 1360.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.11 (s, 3H), 5.11 (s, 2H), 7.36 (s, 5H).

Mass (m/z): 150 (M^+, 30), 108 (100), 91 (72), 79 (55), 65 (10).

Acetic acid 2-methoxy-phenyl ester (11B):



Mol. Formula: $C_9H_{10}O_3$, colorless oil.

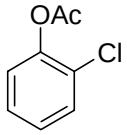
Yield: 95%.

IR (neat) cm^{-1}: 3003, 2941, 1755, 1447.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.36 (s, 3H), 3.66 (s, 3H), 7.01 (m, 3H), 7.09 (m, 1H).

Mass (m/z): 166 (M^+, 3), 124 (100), 109 (93), 95 (5), 81 (44), 77 (20), 65 (20), 52 (5).

Acetic acid 2-chloro-phenyl ester (12B):



Mol. Formula: $C_8H_7ClO_2$, colorless oil.

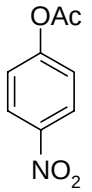
Yield: 94%.

IR ($CHCl_3$) cm^{-1}: 1770, 1584, 1475.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.36 (s, 3H), 7.13 (m, 1H), 7.20 (m, 1H), 7.30 (m, 1H), 7.45 (dd, *J*=7.33 and 1.47 Hz, 1H).

Mass (m/z): 170 (13), 143 (3), 128 (100), 99 (15), 92 (10), 73 (10), 63 (10).

Acetic acid 4-nitro-phenyl ester (13B):



Mol. Formula: $C_8H_7NO_4$, white solid.

Yield: 99%.

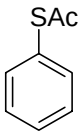
mp: 75-76 ºC.

IR ($CHCl_3$) cm^{-1}: 3024, 1763, 1591, 1525.

^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.34 (s, 3H), 7.27 (d, *J*=8.29 Hz, 2H), 8.26 (d, *J*=8.29 Hz, 2H).

Mass (m/z): 181 (M^+, 50), 139 (85), 123 (53), 109 (100), 93 (54), 81 (30), 75 (10), 62 (65).

Thioacetic acid *S*-phenyl ester (14B):



Mol. Formula: C_8H_8OS, colorless oil.

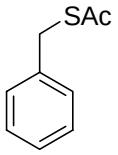
Yield: 91%.

IR ($CHCl_3$) cm^{-1}: 1703.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.43 (s, 3H), 7.43 (s, 5H).

Mass (m/z): 152 (M^+, 10), 110 (100), 82 (7), 65 (5), 57 (2).

Thioacetic acid *S*-phenyl ester (15B):



Mol. Formula: $C_9H_{10}OS$, colorless oil.

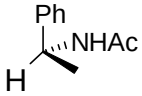
Yield: 94%.

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

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.45 (s, 3H), 4.20 (s, 2H), 7.30 (s, 5H).

Mass (m/z): 166 (M^+, 5), 123 (15), 91 (100), 77 (7), 65 (7).

***N*-(1-Methyl-1-phenyl-ethyl)-acetamide (16B):**



Mol. Formula: $C_{10}H_{13}NO$, white solid.

Yield: 99%.

mp: 103-104 ºC.

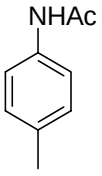
Rotation: $[\alpha]_D^{25}$ = -166º (c=2, EtOH)

IR ($CHCl_3$) cm^{-1}: 3290, 1666, 1599.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 1.49 (d, *J*=6.33 Hz, 3H), 1.97 (s, 3H), 5.10 (q, *J*=6.33 Hz, 1H), 5.81 (br s, 1H), 7.29 (m, 5H).

Mass (m/z): 164 ($M+1^+$, 27), 148 (12), 120 (15), 106 (100), 91 (10), 77 (50), 69 (3), 58 (2).

***N*-*p*-Tolyl-acetamide (17B):**



Mol. Formula: $C_9H_{11}NO$, white solid.

Yield: 99%.

mp:151-152 ºC.

IR ($CHCl_3$) cm^{-1}: 3267, 3060, 1641.

^1H NMR (200 MHz, $CDCl_3$ + CCl_4) δ: 2.15 (s, 3H), 2.32 (s, 3H), 7.19 (d, *J*=8.00 Hz, 2H), 7.36 (d, J=8.00 Hz, 2H).

Mass (m/z): 149 (M^+, 10), 106 (100), 77 (65), 65 (5), 57 (2).

2.2.2.7 References:

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