SYNTHETIC STUDIES TOWARDS CAMPTOTHECIN, ITS ANALOGUES AND OTHER BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS

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by

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic Studies Towards Camptothecin, Its Analogues And Other Biologically Active Compounds"** submitted by Mr. Ashok B. Pathak was carried out by him under my supervision at National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in this thesis

Date:

Subhash P. Chavan

(Research Supervisor)

DECLARATION

I hereby declare that the thesis entitled **"Synthetic Studies Towards Camptothecin, Its Analogues And Other Biologically Active Compounds"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, under the supervision of Dr Subhash P. Chavan. This 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.

Date: Ashok B. Pathak

Division of Organic Chemistry

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Pune-411 008, India.

Dedicated

To

My

Family and Teachers

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Acknowledgements

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Last but not least, I am thankful to CSIR, New Delhi for fellowship.

NCL, Pune *Ashok B. Pathak*

General Remarks

1. All melting points and boiling points are uncorrected and the temperatures are in the centigrade scale.
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. Solvents for anhydrous reaction were prepared according to the procedures reported in Perrin's book.
5. TLC analysis was carried out using thin layer plates pre-coated with silica gel 60 F254 (Merck) and visualized by fluorescence quenching or Iodine or by charring after treatment with *p*-anisaldehyde.
6. In cases where chromatographic purification was done, silica gel (230-400 mesh) was used as the stationary phase or otherwise as stated.
7. IR spectra were recorded on Perkin-Elmer Infrared Spectrophotometer Model 68B or on Perkin-Elmer 1615 FT Infrared spectrophotometer.
8. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AC-200** (50 MHz) or **Bruker MSL-300** (75 MHz) or **Bruker AV-400** (100 MHz) or **Bruker DRX-500** (125 MHz). Figures in parentheses refer to ^{13}C frequencies. Tetramethylsilane was used as the internal standard.
9. GCMS were recorded on Shimadzu's GCMS-QP5050-A.
10. Mass spectra were recorded at ionization energy 70eV on Finnigan MAT-1020, automated GC/MS instrument and on API Q STARPULSAR using electron spray ionization [(ESI), solvent medium, a mixture of water, acetonitrile and ammonium acetate] technique and mass values are expressed as m/z.
11. Starting materials were obtained from commercial sources or prepared using known procedures.
12. Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental analyzer within the limits of accuracy (± 0.4%)

Abbreviations

Ac	Acetyl
AIBN	2,2-Azobis(isobutyronitrile)
AIDS	Acquired Immuno deficiency syndrome
Ar	Aromatic
aq	Aqueous
BBr_3	Borane tribromide
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl
n-BuLi	normal butyllithium
sBu	secondary butyl
tBu	tertiary butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
Cat.	Catalytic
Cbz	Carbobenzyloxy
CM	Cross metathesis
COM	Cross olefin metathesis
CPT	Camptothecin
^oC	Temperature in degrees Centigrade
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DHP	Dihydropyran
$(DHQD)_2$-PYR	Dihydroquinidine diphenylpyrimidine
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMB	Dimethoxy benzyl
DME	Dimethoxy ethane
DMF	*N*,*N*-Dimethylformamide

DMS	Dimethyl sulphate
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
equiv (eq)	Equivalent
Et	Ethyl
Et_3N	Triethyl amine
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	gram/s
GCMS	Gas Chromatograph Mass Spectrometer
h	hour/s
HMPA	Hexamethylphosphoramide
HMDS	Hexamethyldisilazane
IR	Infrared
LA	Lewis acid
LAH	Lithium Aluminium Hydride
LDA	Lithium diisopropyl amide
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MF	Molecular formula
mL	millilitre/s
mmol	millimole
MOM	methoxymethyl
m.p.	melting point
MS	Mass spectroscopy or Molecular sieves
MW	Microwave or Molecular weight
NaH	Sodium hydride
$NaIO_4$	Sodium metaperiodate
NCS	*N*-Chlorosuccinamide
NMO	*N*-Methyl morpholine *N*-oxide
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl

PMB	4-methoxybenzyl
^{i}Pr	Isopropyl
PTP	Protein tyrosine phosphatase
PTSA	*para*-Toluene sulfonic acid
Py	Pyridine
QSAR	Quantitative structure activity relationship
RCM	Ring-closing metathesis
rt	root temperature
SAR	Structure activity relationship
TBABr	Tetrabutyl ammonium bromide
$TBAHSO_4$	Tetrabutyl ammonium hydrogen sulphate
TBDMSOTf	*tert*-Butyldimethylsilyl triflate
TBTH	tributyltin hydride
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMSCl	Trimethyl silyl chloride
TMSI	Trimethyl silyl iodide
TPP	Triphenyl phosphine
Ts	Tosyl
UV	Ultraviolet

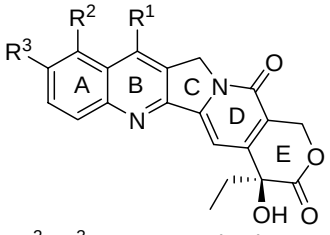
Abstract

The thesis entitled **"Synthetic studies towards camptothecin, its analogues and other biologically active compounds"** is divided into three chapters.

Chapter 1

Section I: General introduction of camptothecin

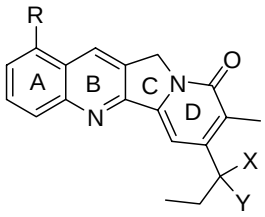
The camptothecin **1** was first time isolated by Wall and Wani in 1966 from *Camptotheca acuminata*, the structural elucidation and antitumor activity of its various derivatives by a unique mechanism involving the inhibition of DNA Topoisomerasse I triggered a great deal of interest at the chemical level. Nothapodytine B **5** (mappicine ketone) has been recently isolated from *Nothapodytine foetida* which is an oxidized form of mappicine **6** and E-ring decarboxylative analogue of CPT **1**. It exhibited potent antiviral activities against HSV-1, HSV –2 and HCMV. Although numerous imaginative syntheses of camptothecins have been reported still there is an evident need for the development of a novel and practical synthetic routes.



1 R^1 , R^2 , R^3 = H Camptothecin

2 R^1 = Et, R^2 = H, R^3 = OCON–N .HCl $3H_2O$ Irinotecan

3 R^1 = H, R^2 = CH_2NMe_2.HCl, R^3 = OH Topotecan



4 R = OMe, X = Y = O Nothapodytine A
5 R = H, X = Y = O Nothapodytine B (mappicine ketone)
6 X = H, Y = (S)-OH Mappicine

Fig. 1

A general introduction of camptothecin and its analogues along with its brief review on their synthesis emphasizing mainly the synthetic approaches is presented.

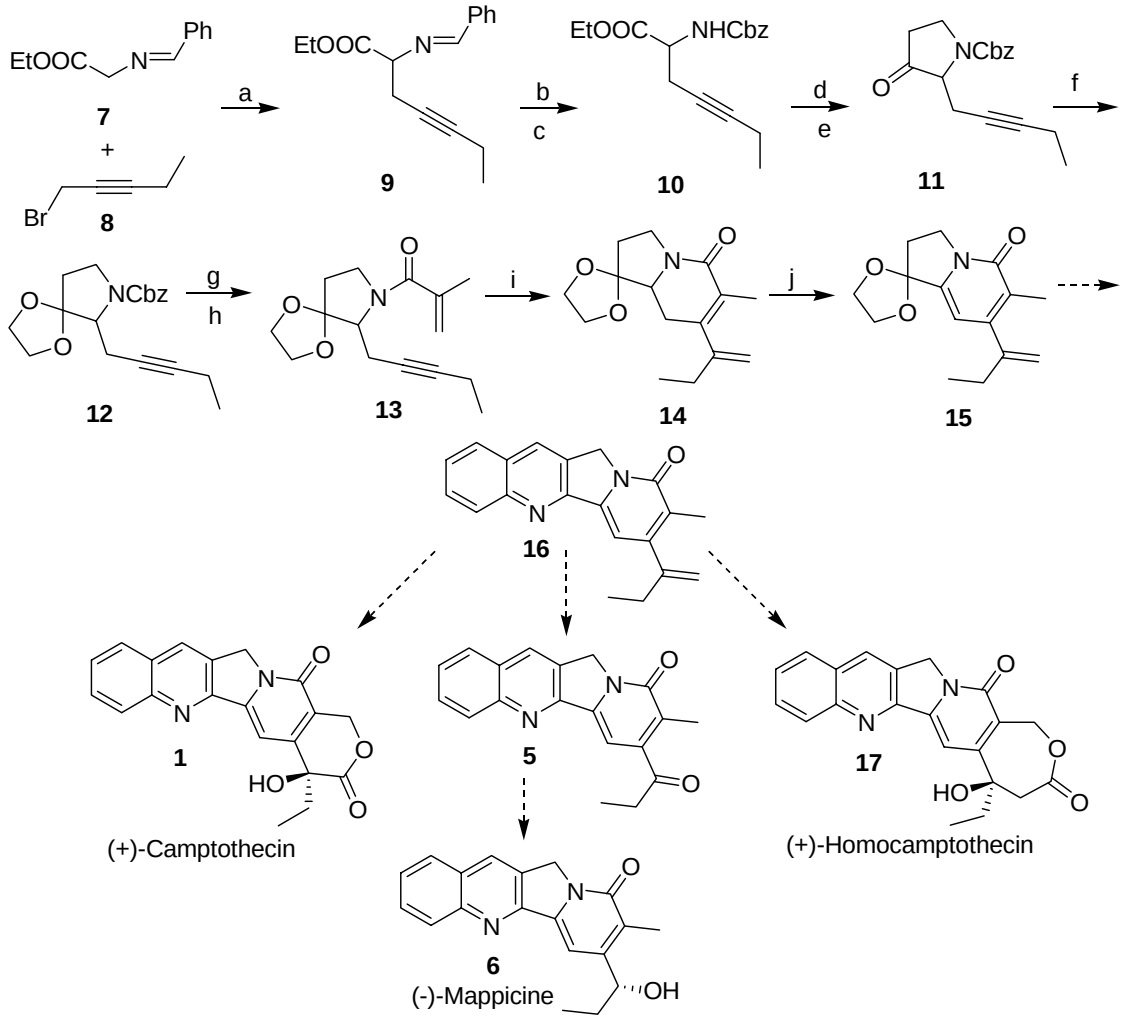
Section II: General account on metathesis

This section describes a history of metathesis, different catalysts for metathesis, types of metathesis, and proposed mechanisms.

Section III: Studies towards synthesis of camptothecin and its analogues employing tandem ethylene cross enyne metathesis and RCM.

The present section describes the synthesis of advanced intermediate of camptothecins employing tandem ethylene cross enyne metathesis and RCM. Thus alkylation of Schiff's base **7** with the bromo compound **8** under PTC conditions to give alkylated Schiff's base **9** which on hydrolysis liberated free amine and subsequently the resultant amine was protected as its benzyl carbamate **10.** The Michael addition followed by

Dieckmann condensation sequence with ethyl acrylate furnished β-ketoester, which was further decarboxlated to pyrrolidone **11.** The ketone was protected as its cyclic ketal **12.** The carbamate was deprotected with KOH in ethanol to provide amine which was further condensed with methacryloyl chloride in DCM to furnish the amide **13.** Treatment of amide **13** in the presence of Grubbs' 2 nd generation catalyst furnished α,β-unsaturated lactam **14** in good yield, the DDQ oxidation of the dihydropyridone gave pyridone **15.** The pyridone **15** can be converted into advanced intermediate **16** by deprotection followed by Friedlander condensation and it can be further manipulated into other related molecules (mappicine **6**, mappicine ketone **5**, camptothecin **1** and homocamptothecin **17**).



Scheme 1 *reagents and conditions: (a) Et_3N (1.2 equiv), PhCHO (0.9 equiv), MS, dry CH_2Cl_2, 0 ^oC, 1 h, 98%. (b) 10% NaOH (1.5 equiv), allyl bromide (1.2 equiv), $TBAHSO_4$ (0.1 equiv), CH_2Cl_2, rt 2 h, 96%. (c) 10% HCl (1.5 equiv), rt, 0.5 h, 92%. (d) K_2CO_3 (3.0 equiv), benzylchloroformate (1.1 equiv), anhydrous CH_2Cl_2, 0 ^oC, 1h, 91%. (e) NaH (1.2 equiv), ethyl acrylate (1.2 equiv), C_6H_6, rt 1h, reflux 2-3 h, 72%. (f) NaCl*

(4.0 equiv), DMSO-H_2O (3:1), 120-130 ^oC, 6 h, 78%.(g) ethylene glycol (1.2 equiv), p-TSA (cat.), C_6H_6, reflux, 6h, 96% (h) KOH (14.0 equiv), EtOH, reflux, 6h (i) K_2CO_3 (3.0 equiv), methacryloyl chloride (1.2 equiv), anhydrous CH_2Cl_2, 0 ^oC, 3 h, 73% over two steps. (j) Grubbs' catalyst 2 nd generation (10 mol%), C_2H_4, anhydrous toluene, 80 ^oC, 3 h, 98%.Grubbs catalyst 2 nd generation (10 mol%), anhydrous toluene, 80 ^oC, 24 h, 92% on the recovery basis of starting material. (k) DDQ (1.2 equiv), anhydrous 1, 4 dioxane, reflux, 8 h, 96%.

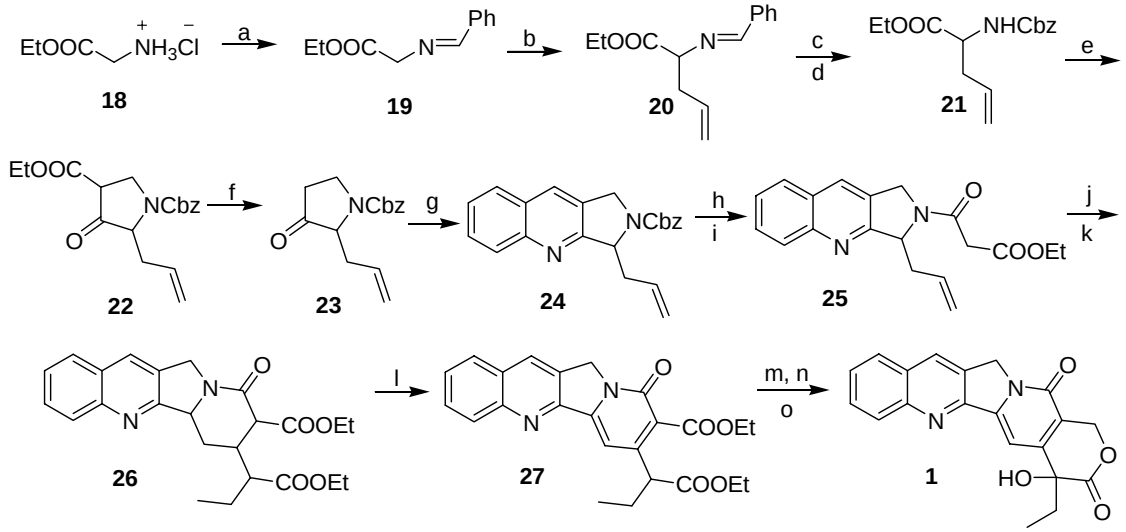
In conclusion, the advanced intermediate of camptothecins **15** has been synthesized employing tandem ethylene cross enyne metathesis followed by ring-closing metathesis protocol as the key step for the construction of pyridone D-ring.

Chapter 2

Section I: Total synthesis of (±)-camptothecin employing tandem Knoevenagel condensation and Michael addition.

Encouraged by the results achieved in the synthesis of advanced intermediate of CPT employing tandem ethylene cross enyne metathesis followed by ring-closing metathesis (Ch. 1, Sec. III). This section deals with the formal synthesis of (±)-CPT employing tandem Knoevenagel condensation and Michael addition as a key step.

Accordingly the key precursor **25** which is important for the tandem Knoevenagel condensation and Michael addition was synthesized as per literature procedure and shown in scheme 2.



Scheme 2 *Reagents and conditions (a) PhCHO (0.9 equiv), Et_3N (1.2 equiv), MS, CH_2Cl_2, 0 ^oC, 1-2 h, 98%. (b) 10% NaOH (1.5 equiv), allyl bromide (1.2 equiv), $TBAHSO_4$ (0.1 equiv), CH_2Cl_2, rt 2 h, 96%. (c) 10% HCl (1.5 equiv), rt, 0.5 h, 95%. (d) K_2CO_3 (3.0 equiv), benzylchloroformate (1.1 equiv), anhydrous CH_2Cl_2, 0 ^oC, 1h, 94%.*

(e) NaH (1.2 equiv), ethyl acrylate (1.2 equiv), C_6H_6, rt 1h, reflux 2-3 h, 72%. (f) NaCl (4.0 equiv), DMSO-H_2O (3:1), 120-130 ^oC, 6 h, 78%. (g) N-(o-aminobenzilidine)p-toluidine (1.2 equiv), PTSA (cat), anhydrous toluene, azeotropic distillation 3-4 h, 75%. (h) KOH (14.0 equiv), EtOH, reflux, 8h. (i) K_2CO_3 (1.2 equiv), ethyl malonyl chloride (1.2 equiv), anhydrous CH_2Cl_2, 0 ^oC, 1 h, 71% in two steps. (j) OsO_4 (cat.), $NaIO_4$ (2.1 equiv), acetone-water (3:1), rt, 6 h, (k) n-BuLi (2.1 equiv), ethyl butyrate, THF, -78 ^oC-rt, 3-4 h, 56%. (l) DDQ (2.1 equiv), 1,4-dioxane, reflux, 2-3 h, 97%. (m) LiOH (1.0 equiv), EtOH, rt, 7-8 h. (n) $LiBH_4$ (0.3 equiv), THF, 0 ^oC-rt, 6 h, 43% in two steps. (o) $CuCl_2.7H_2O$, Me_2NH, O_2, DMF, rt, 24 h, 87%.

Compound **25** was converted to aldehyde by oxidative cleavage using catalytic OsO_4 and $NaIO_4$ and the generated aldehyde without isolation was subjected to the treatment with enolate of ethyl butyrate in THF at -78 ^{o}C-rt resulted the desired tetracyclic compound **26** in 56% yield. The tetracyclic compound **26** was aromatized using DDQ in 1,4-dioxane, afforded compound **27** in excellent yield. Tricyclic compound **27** was converted deoxycamptothecin by hydrolysis of aliphatic acid salt using LiOH followed by lactonization using $LiBH_4$ in 43% yield. Finally deoxycamptothecin was transformed to (±)-camptothecin **1**.

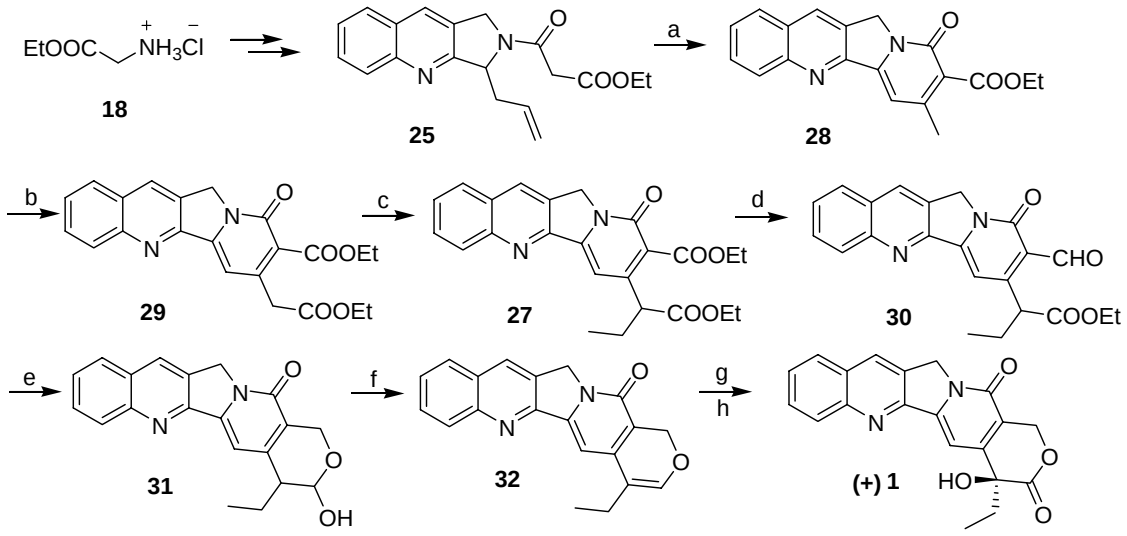
In conclusion, total synthesis of (±)-camptothecin **1** has been achieved employing tandem Knoevenagel condensation and Michael addition.

Section II: Total synthesis of (+)-camptothecin employing Pd-catalyzed cyclization strategy.

After achieving the formal synthesis of racemic CPT employing tandem Knoevenagel condensation and Michael addition as described in Chapter 1, section I, this section demonstrates the total synthesis of (+)-CPT *via*. tandem novel Pd-mediated cyclization and aromatization under Wacker condition.

Accordingly the important precursor **25** was synthesized from **18** as shown in section I. The compound **25** was treated with catalytic amounts of $PdCl_2$ and 2.1 equivalent $CuCl_2.2H_2O$ in DMF-H_2O (3:1) at 95 ^{o}C, furnished the compound **28** in 54% yield. The compound **28** was treated with diethyl carbonate using LDA in THF at -78 ^{o}C to afford the compound **29** in 70% yield, the treatment of compound **29** with ethyl iodide using NaH in THF furnished diester compound **27** in 64% yield which is the same intermediate as described in earlier section. The selective reduction of aromatic ester **27** to aldehyde **30** in 83% yield was achieved using DIBAL-H. The aldehyde **30** was further reduced to lactol **31** in 90% yield *via* the intermediacy of alcohol which

underwent lactonization and further reduction into lactol **31** using $NaBH_4$. The lactol **31** was transformed into enol ether **32** in excellent yield (92%) via *O*-mesylation followed by elimination. Sharpless asymmetric dehydroxylation on **32** followed by oxidation furnished (+)-camptothecin **1**.



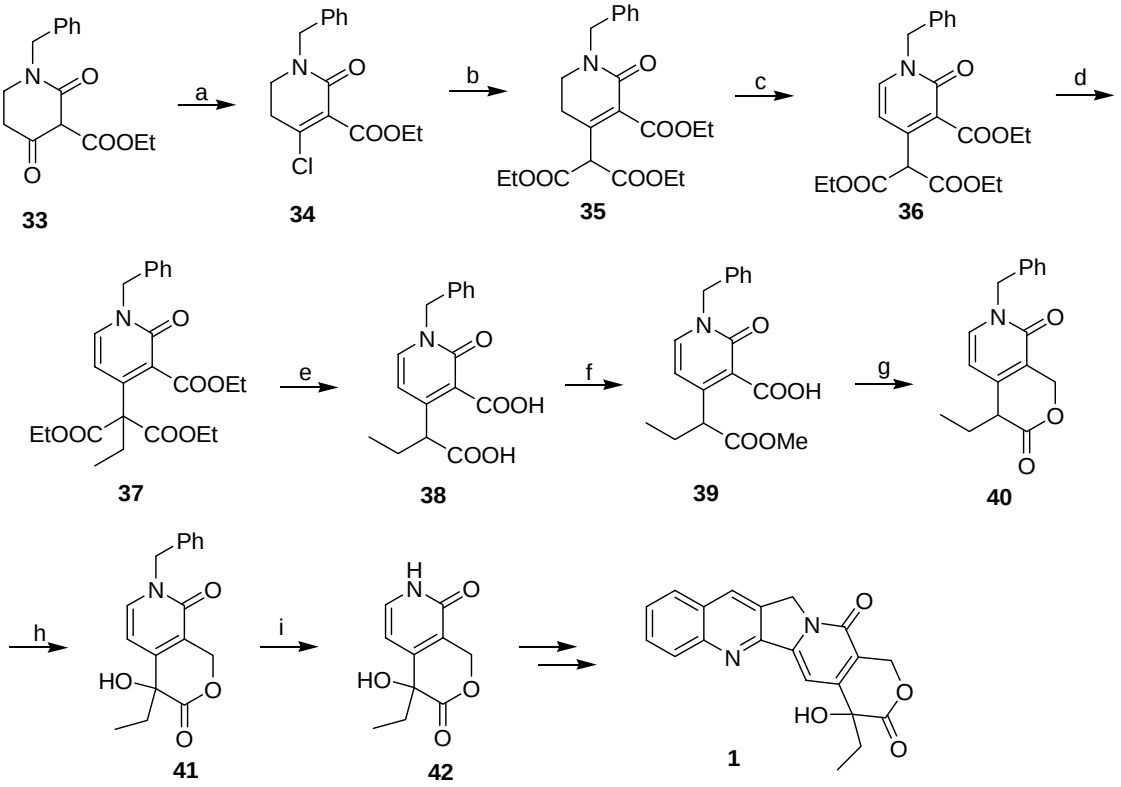
Scheme 3 *Reagents and conditions (a) $PdCl_2$ (0.1 equiv), $CuCl_2$ (2.1 equiv), DMF-H_2O (3:1), 95 ^oC, 6 h, 54%. (b) LDA (1.1 equiv), Diethyl carbonate (1.0 equiv), THF, -78 ^oC, 3-4 h, 70%. (c) NaH (1.1 equiv), EtI (1.1 equiv), anhydrous DME, 0 ^oC- rt, 3-4 h, 64%. (d) DIBAL-H (3.0 equiv), dry THF, -60 ^oC, 2 h, 83%. (e) $NaBH_4$ (2.0 equiv), THF-H_2O (5:1), 0 ^oC, 0.5 h, 90%. (f) MsCl (4.0 equiv), Et_3N (8.0 equiv), anhydrous THF, rt, 24 h, 92%. (g) $(DHQD)_2$-PYR (cat.), OsO_4 (cat.), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $CH_3SO_2NH_2$ (1.0 equiv), t-BuOH-H_2O (1:1), 0 ^oC, 7 h (h) I_2 (12.5 equiv), $CaCO_3$ (12.5 equiv), CH_3OH-H_2O (10:1), rt, 24 h, 33% in two steps.*

In conclusion, total synthesis of (+)-CPT **1** has been achieved employing cascade novel Pd-catalyzed cyclization followed by aromatization under Wacker condition.

Section III: Formal synthesis of (±)-camptothecin

The clinical use of camptothecin's has been limited owing to its insolubility and toxicity, but extensive structure activity relation studies have identified its various analogues having better solubility and with equal or better antitumor activity, which resurged the interest of the chemists as well as oncologists. Synthetic approaches for these analogues have typically involved synthesis of suitably functionalized CDE-rings or DE-rings or precursors thereof, which was then coupled with appropriate counter

parts. Keeping this concept in mind it proposed to synthesize the DE-ring which would have the flexibility to obtained the analogues of camptothecin as shown in scheme 4.



Scheme 4 *Reagents and conditions (a) $POCl_3$ (1.2 equiv), CH_2Cl_2, reflux, 3h, 97%. (b) NaH (1.2 equiv), diethylmalonate (1.2 equiv), C_6H_6, rt, overnight, 85%. (c) DDQ (1.2 equiv), anhydrous 1, 4 dioxane, reflux, 6 h, 96%. (d) K_2CO_3 (3.0 equiv), ethyl iodide (1.2 equiv), anhydrous acetone, reflux, 12 h, 91%. (e) LiOH (5.0 equiv), EtOH, rt, 24 h, 84%. (f) $NiCl_2$ (0.1 equiv), MeOH, reflux, 12 h, 76%. (g) i) Et_3N (1.0 equiv), methylchloroformate (1.0 equiv), anhydrous THF, 0 ^oC, 1 h. ii) $NaBH_4$ (4.0 equiv), -78 ^oC, 3 h, 10% HCl, rt, 12 h, 84%. (h) $CuCl_2$ (4.0 equiv), Me_2NH, O_2, DMF, rt, 24h, 92%. (i) $Pd(OH)_2$, H_2, EtOH, 50 ^oC, 5h, 62%.*

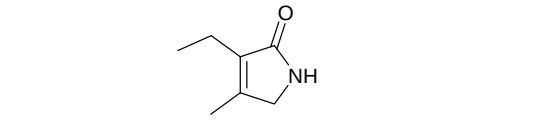
Accordingly the β-ketoester **33** was prepared as per literature procedure and treatment of **33** with $POCl_3$ in DCM furnished 4-chloro dihydropyridone **34**. Michael addition of diethyl malonate was accomplished on **34** using NaH in benzene to furnish triester dihydropyridone **35**. The aromatization of dihydropyridone **35** using DDQ in refluxing 1,4-dioxane furnished pyridone **36** in 96% yield. The triester **36** was treated with ethyl iodide in the presence of K_2CO_3 as the base to give alkylated product **37** in 91% yield. The global hydrolysis of esters followed by mono decarboxylation of aliphatic acid was achieved in one pot using excess lithium hydroxide at room temperature to furnish diacid **38** in good yield. The selective esterification of aliphatic acid in presence of

heteroaromatic acid was accomplished using nickel chloride as a catalyst to deliver compound **39** in good yield. Compound **39** was subjected to the treatment with methyl chloroformate in THF at 0 ^{o}C to furnish mixed anhydride intermediate whose subsequent reduction to alcohol resulted in lactonization using $NaBH_4$ to furnish lactone **40** in 84% yield. The hydroxylation was carried out using $CuCl_2$ and catalytic amount of dimethyl amine under oxygen atmosphere to furnish α-hydroxy lactone **41** in 98% yield. Finally the *N*-debenzylation was successfully carried out employing catalytic amount of palladium hydroxide in ethanol at 50 ^{o}C, furnished desired DE-ring synthon **42** in 62% yield. This is the common intermediate in Comins synthesis which could be converted to (±)-camptothecin **1** by a two step sequence i.e. coupling of pyridone with quinoline nucleus and intramolecular Heck reaction.

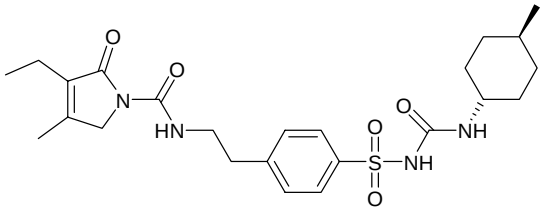
In summary, a formal total synthesis of (±)-camptothecin **1** has been achieved employing addition elimination reaction as a key step.

Chapter 3

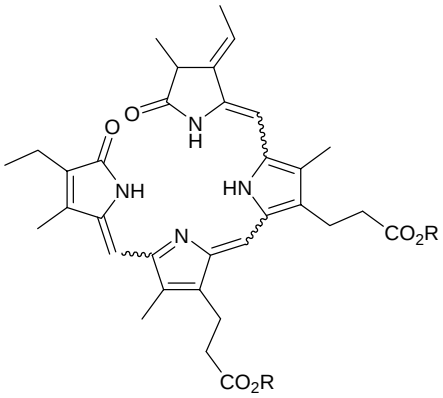
Section I: Synthesis of 3- Ethyl –4- methyl –3- pyrroline –2- one



3-ethyl-4-methyl-3-pyrrolin-2-one **43**



Glimepiride **44**



C-phycocyanin **45**

Figure 1

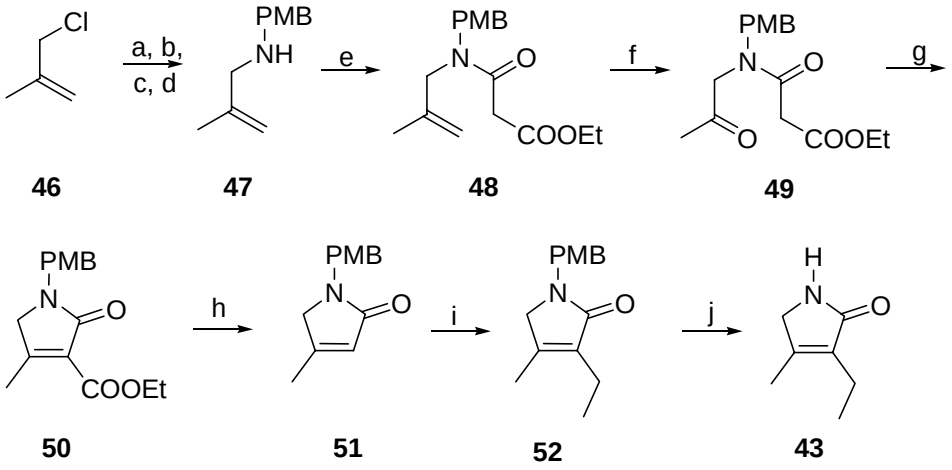
3- Ethyl –4- methyl –3- pyrroline –2- one **43** is key intermediate in anti-diabetic drug *viz*. Glimepiride **44**. It belongs to sulfonylureas kind of drug and shows potent activity against diabetic disease. The intermediate **43** is also present as main precursor in bile pigments C-phycocyanin **45** present in plants. Bile pigment takes part in the very useful photosynthesis reaction which prepares its own food and it is basic need of human being and other animals.

This seemingly simple but commercially very important molecule has been earlier synthesized in very low overall yields involving use of hazardous reagents and high pressure hydrogenation.

A programme was initiated to look into a practical synthesis of this substituted unsaturated lactam by three different approaches which are described below.

Part A: Knoevenagel condensation approach:

The amine **47** was prepared from commercially available methallyl chloride **46** using simple and straight forward transformation shown in scheme 5. Amine **47** was further treated with ethyl malonyl chloride and it was converted into its tertiary amide **48** in 86% yield. The oxidative cleavage of **48** was carried out using catalytic OsO_4 & 2.1 equivalent $NaIO_4$ to furnish its corresponding keto compound **49**. The intramolecular Knoevenagel condensation was carried out employing NaH in THF furnished cyclized product **50** in 84% yield, compound **50** was further decarboxylated under Krapcho's condition to give α,β-unsaturated lactam **51** in 87%. The selective ethylation at α-carbon on α,β- unsaturated lactam **51** was accomplished using NaH in THF at 0 ^oC to afford compound **52** in 71% yield & finally deprotection of PMB group of lactam **52** employing cerium ammonium nitrate in acetonitrile-water (5:1) at rt furnished desired intermediate **43** in 80% yield.



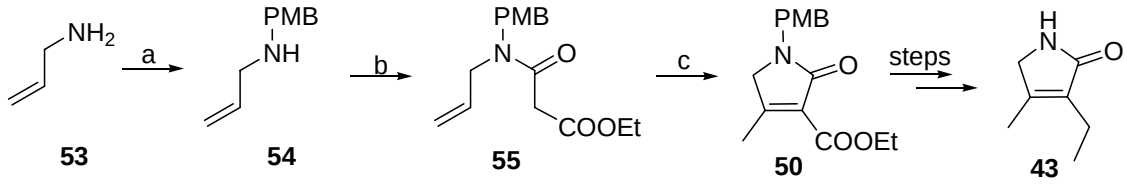
Scheme 5 *reagents & conditions* ***(****a) NaN_3 (1.5 equiv), dry DMSO, 70 ^oC, 12 h. (b) PPh_3 (1.1 equiv), Et_2O, 0 ^oC, 15 h. (c) p-anisaldehyde (1.2 equiv), dry MeOH, 0 ^oC, 1 h. (d) $NaBH_4$ (1.0 equiv), MeOH, 0 ^oC, 1 h, 61% over four steps (e) K_2CO_3 (1.2 equiv), dry DCM, ethyl malonyl chloride (1.2 equiv), 0 ^oC, 3 h, 86%. (f) OsO_4 (cat.), $NaIO_4$ (2.2 equiv), acetone-water (3:1), rt, 3 h, 89%. (g) NaH (2.0 equiv), dry THF, 0 ^oC, 3 h,*

84%. (h) NaCl (4.0 equiv), DMSO-H_2O (3:1), 120-130 ^oC, 12 h, 87%. (i) NaH (1.2 equiv), ethyl iodide (1.2 equiv), dry THF, 0 ^oC-rt, 3 h, 71%. (j) CAN (2.5 equiv), acetonitrile: water (5:1), rt, 2 h, 80%.

Part B: Pd-catalyzed cyclization approach:

Having a synthesis of **43** employing intramolecular Knoevenagel condensation strategy, it was thought to minimize the number of steps and improve the yield using cheap starting materials employing a novel Pd-mediated cyclization as a key step.

Thus, the synthesis started from readily available allyl amine **53**, which was converted into its secondary amine **54** (97%) by reductive amination using *p*-anisaldehyde, Et_3N and $NaBH_4$ in methanol. The treatment of **54** with ethyl malonyl chloride using K_2CO_3 as the base in DCM at 0 ^oC furnished tertiary amide **55** in 86% yield. When **55** was subjected to the treatment with catalytic $PdCl_2$ and 2.1 equiv $CuCl_2.2H_2O$ in DMF-H_2O (6:1) at 95 ^oC resulted the cyclized product **50** in 62% yield which is common intermediate in scheme 5 and which was converted into target compound **43**.



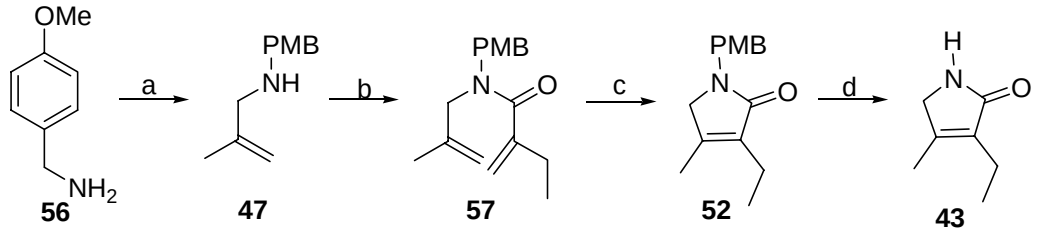
Scheme 6 *Reagents and conditions: (a) (i) p-anisaldehyde (1.0 equiv), MeOH, 0 ^oC, 1h. (ii) $NaBH_4$, MeOH, 0 ^oC, 1h, 97%. (b) K_2CO_3 (3.0 equiv), ethyl malonyl chloride (1.2 equiv), CH_2Cl_2, 0 ^oC, 1h. 86%. (c) $PdCl_2$ (10 mol %), $CuCl_2.2H_2O$ (2.1 equiv), DMF-H_2O (3:1), 95 ^oC, overnight, 62%.*

Part C: RCM approach:

After the synthesis of **43** by two routes shown above, it was believed that it can be synthesized utilizing RCM strategy in short manner.

Thus, the amine **47** was synthesized from commercially available *p*-methoxybenzylamine **56** and methallyl chloride using K_2CO_3 as the base. Acylation of the amine **47** with ethacryloyl chloride using K_2CO_3 as the base in DCM at 0 ^oC furnished acrylamide **57** in 91% yield. Ring-closing metathesis was accomplished employing Grubbs' 2nd generation catalyst in dry toluene at 80 ^oC to furnish lactam **52** in 40% yield (90% based on recovery of SM). Finally the deprotection of PMB group

of lactam **52** was effected to using CAN in acetonitrile-water (5:1) at room temperature for 2 h to furnish the desired intermediate **43** in 80% yield.

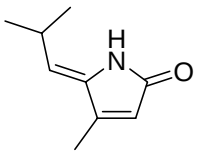


Scheme 7 *Reagents and conditions: (a) methallyl chloride (0.33 equiv), K_2CO_3 (1.2 equiv), KI (cat.), dry DCM, 0 ^oC-rt, 12 h, 84%. (b) K_2CO_3 (1.2 equiv), ethacryloyl chloride (1.2 equiv), dry DCM, 0 ^oC, 1 h, 91%. (c) Grubbs' 2nd generation catalyst (10 mol %), dry toluene, 80 ^oC, 12 h, 90%. (d) CAN (2.0 equiv), acetonitrile-water (5:1), rt, 2h, 80%.*

In conclusion, the synthesis of 3- ethyl –4- methyl –3- pyrroline –2- one **43** was achieved by employing three different strategies intramolecular Knoevenagel condensation, Pd-mediated cyclization and RCM strategies.

Section II: Total synthesis of (*Z*)-pulchellalactam

(*Z*)-Pulchellalactam (**58**) a pyrrolidinone isolated in 1997 from the marine fungus *Corollospora pulchella* by Alvi *et al*. It shows the potent inhibitory action against protein tyrosine phosphatase, (PTP) CD45, which in turn activates B and T cells. Protein tyrosine phosphatase has been a target implicated in autoimmune and anti-inflammatory diseases.



(Z)-Pulchellalactam (**58**)

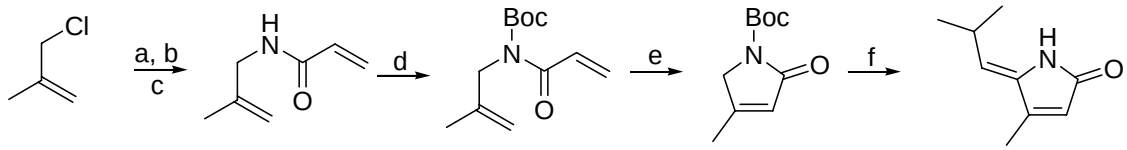
Figure 1

The scarcity of effective inhibitors of protein tyrosine phosphatase has lead to a search for other small molecule inhibitors. (*Z*) Pulchellalactam (**58**) has been shown to possess remarkable inhibitory action against CD45.

Total synthesis of (*Z*)-pulchellalactam via RCM path:

Accordingly the acrylamide **59** was prepared in 59% yield from readily available methallyl chloride **46** by the transformation shown in scheme 12. Acrylamide **59** was further treated with Boc-anhydride to furnish the carbamate **60**. The resulted carbamate **60** underwent facile ring closing metathesis employing Grubbs' 2 nd generation catalyst

furnished the α,β-unsaturated lactam **61**. The lactam **61** is the common intermediate in the syntheses reported in the literature and which was accordingly converted into the target molecule pulchellalactam **58**.



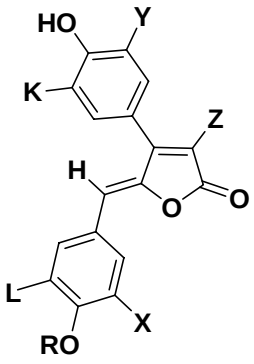
46 **59** **60** **61** **58**

Scheme 8 *Reagents and conditions: (a) NaN_3 (1.5 equiv.), DMSO, 70 ^oC , 15 h. (b) PPh_3 (1.1 equiv.), Et_2O-H_2O, 0 ^oC - rt, 14 h. (c) acryloyl chloride (1.2 equiv.), K_2CO_3 (1.2 equiv.), dry DCM, 0 °C, 3 h, 59% over three-steps. (d) Boc-anhydride (1.2 equiv.), DMAP (0.1 equiv.), dry CH_3CN, rt, 3 h, 82%. (e) Grubbs' 2 nd generation catalyst (10 mol %), dry toluene, 80 ^oC, 12 h, 85%. (f) NaH (1.5 equiv.), isobutyraldehyde (3.0 equiv.), THF, rt, 10 % HCl, 85%.*

In conclusion, the total synthesis of (*Z*)-pulchellalactam **58** was realized employing ring-closing metathesis strategy.

Section III: Total synthesis of Rubrolide E

Rubrolides (**62, A-F, I-N**) are the biologically active marine tunicate metabolites which have been isolated in1991 by Andersen from tunicate *Ritterella rubra* and later in 2000 by Salva and his coworkers from tunicate *Synoicum blochmanni*. Structurally, rubrolides contain butenolide frameworks with two *para*- hydroxyphenyl moieties with or without halogen atoms. These rubrolides show potent *in-vitro* antibiotic activity and cytotoxicity against cancer cell lines and also exhibit moderate but selective inhibition of protein phosphatases.

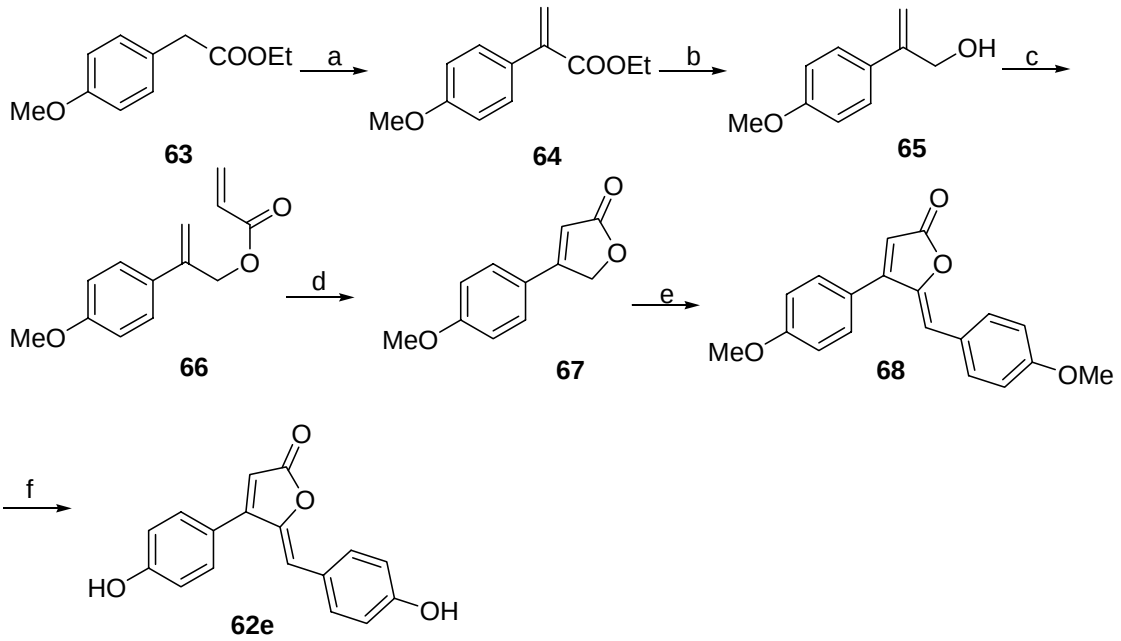


Rubrolide A (62a) R = Z = H; K = L = X = Y = Br
Rubrolide B (62b) R = H; K = L = X = Y = Br; Z = Cl
Rubrolide C (62c) R = K = Y = Z = H; L = X = Br
Rubrolide D (62d) R = L = X = Z = H; K = Y = Br
Rubrolide E (62e) R = L = K = X = Y = Z = H
Rubrolide F (62f) R = Me; L = K = X = Y = Z = H
Rubrolide I (62i) R = K = H; L = X = Y = Br; Z = Cl
Rubrolide J (62j) R = K = Z = H; L = X = y = Br
Rubrolide K (62k) R = K = L = H; X = Y = Br; Z = Cl
Rubrolide L (62l) R = K = Y = H; L = X =Br; Z = Cl
Rubrolide M (62m) R = K = L = Y = H; X = Br; Z = Cl
Rubrolide N (62n) R = K = L = H; Y = Cl; X = Z = Br

Fig. 4

Part A: RCM approach

It was decided to synthesize the butenolide moiety by employing ring-closing metathesis reaction. Accordingly the α,β-unsaturated ester **64** was prepared in very good yield by the treatment of the ester **63** with para formaldehyde using K_2CO_3 as the base and $TBAHSO_4$ as a phase transfer catalyst. The reduction of the ester **64** to alcohol **65** was accomplished using DIBAL-H at –78 ^oC, the alcohol **65** was subjected to react with acryloyl chloride using Et_3N as a base to furnish corresponding ester **66** in 92% yield. Compound **66** was underwent facile RCM reaction employing Grubbs' 2 nd generation catalyst in presence of titanium isopropoxide as a Lewis acid in DCM resulted the butenolide **67** which was converted to rubrolide E **62e** by literature method.

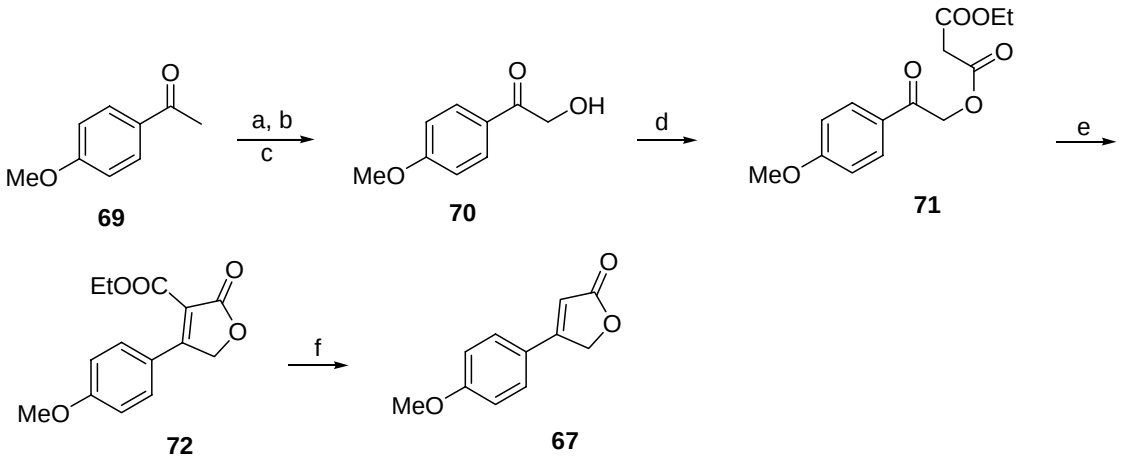


Scheme 9 *Reagents and conditions: (a) $(CH_2O)_n$ (1.5 eq.), K_2CO_3 (1.5 eq.), $TBAHSO_4$ (0.1 eq.), toluene, 80 ^oC, 6 h, 89%. (b) DIBAL-H (2.1 eq.), dry DCM, -78 ^oC, 3 h, 97%. (c) Et_3N (1.5 eq.), acryloyl chloride (1.2 eq.), dry DCM, 0 ^oC, 1 h, 92%. (d) Grubbs' 2nd gen. catalyst (10 mol %), titanium isopropoxide (1.2 eq.), dry DCM, reflux, 12 h, 83%. (e) Piperidine (0.7 eq.), anisaldehyde (1.0 eq.), MeOH, rt, 15 h, 81%. (f) BBr_3 (3.0 eq.), dry DCM, -78 ^oC, 30 min, rt, 24 h, 95%.*

Part B: Knoevenagel condensation approach:

After the synthesis of rubrolide E employing RCM strategy it was thought to develop an alternative route using mild reaction conditions employing intramolecular Knoevenagel condensation.

Accordingly, the alcohol **70** was prepared from *p*-methoxyacetophenone **69** by transformations as shown in scheme 11. The treatment of **70** with ethyl malonyl chloride using Et_3N as the base in DCM furnished ester **71,** which on intramolecular Knoevenagel condensation, carried out using NaH in THF at 0 ^oC, resulted in the cyclized product **72** in excellent yield. The ester moiety present on α-carbon was decarboxylated under Krapcho's condition to furnish the desired butenolide **67** in 91% yield.

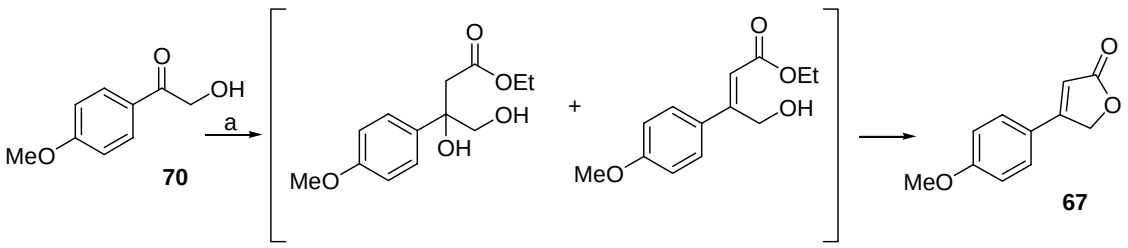


Scheme 10 Reagents and conditions: (a) Et_3N (2.0 equiv), TMSCl (1.5 equiv), dry CH_3CN, reflux, 12 h. (b) 5% $NaHCO_3$ solution (2.0 equiv), MCPBA (1.2 equiv), CH_2Cl_2, rt, 3 h. (c) 10% HCl solution (1.5 equiv), CH_2Cl_2, rt, 12 h, 87% over three-steps. (d) Et_3N (2.0 equiv), ethyl malonyl chloride (1.2 equiv), dry CH_2Cl_2, 0 ^oC, 1 h, 97%. (e) NaH (1.2 equiv), dry THF, 0 ^oC, 1 h, 95%. (f) NaCl (4.0 equiv), DMSO-H_2O (3:1), 120-130 ^oC, 6 h, 91%.

Part C: Reformatsky reaction pathway:

Having the two different synthetic routes to rubrolide in hand shown as an above, it was still felt that it can be synthesized by another approach (Reformatsky reaction) using mild reaction conditions.

Thus, the alcohol **70** was obtained from *p*-methoxyacetophenone **69** as shown in scheme 11**.** Reformatsky reaction was carried out on **70** with ethylbromoacetate and zinc in refluxing C_6H_6-Et_2O and further treatment with catalytic *p*-TSA furnished desired butenolide **67** in 78% yield.



Scheme 12 *Reagents and conditions: (a) Zinc power (3.0 equiv), ethyl bromoacetate (1.5 equiv), C_6H_6-Et_2O (1:1), reflux, 6 h, PTSA (cat), reflux, 3-4 h, 78%.*

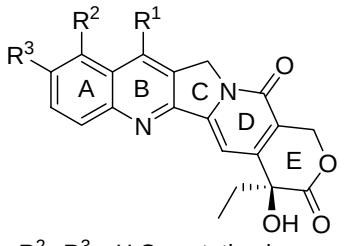
In conclusion, three synthetic routes of rubrolide E **62e** employing RCM, intramolecular Knoevenagel condensation and Reformatsky reaction protocol have been achieved**.**

Chapter 1, Section I

General introduction of camptothecin

1.1.1 Introduction:

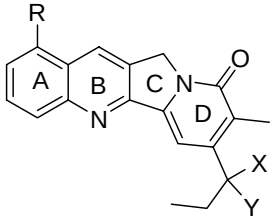
Wall and Wani discovered very important anticancer molecules *viz*. camptothecin **1** which is pentacyclic quinoline alkaloid isolated from Chinese plant *Camptotheca acuminata*[1] in 1966. This invention became milestone in the area of chemical and medicinal science, camptothecin and its analogues, collectively called, as camptothecins or camptothecinoids which have been isolated from various plants. Nothapodytine A **4**, Nothapodytine B (mappicine ketone) **5** which was isolated from *Nothapodytis foetida*[2a] is an oxidized derivative of mappicine **6**[2b] and E-ring decarboxylated analogue of camptothecin **1**. Camptothecin as such can not be used as drug, due to its toxic nature (myelosupression, severe and unpredictable hemorrhagic cystitis and diarrhoea), poor solubility and the unstable α-hydroxy 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 I, an enzyme essential for relaxation of DNA during important cellular process and trigger a cascade of events leading to apoptosis and programmed cell death. These insights provided novel rationales for the design of its improved analogues.



1 R^1 , R^2 , R^3 = H Camptothecin

2 R^1 = Et, R^2 = H, R^3 = OCON–N .HCl $3H_2O$ Irinotecan

3 R^1 = H, R^2 = CH_2NMe_2.HCl, R^3 = OH Topotecan



4 R = OMe, X = Y = O Nothapodytine A

5 R = H, X = Y = O Nothapodytine B

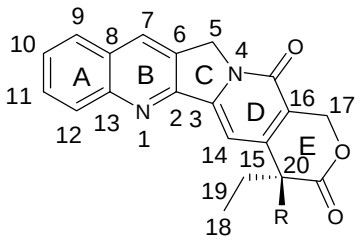
6 X = H, Y = (S)-OH Mappicine

Figure 1.

After the continuous efforts of synthetic and medicinal chemists on the study of camptothecins, their efforts became fruitful and they discovered its two analogues *viz.* irinotecan (**2**) and topotecan (**3**) which are being used in clinical practice as anticancer drugs and several other analogs are currently under clinical trials at different phases for the treatment of different kinds of cancer by chemotherapy.

1.1.2 Isolation, properties and structural elucidation of camptothecin:

The structure of the CPT was elucidated by a combination of chemical and physical (spectral) methods, and finally confirmed by the X-ray analysis of the iodoacetate **1d**. The m.p. of the Camptothecin was high; it was also optically active ($[\alpha]_D$ 25, +31.3 ºC) and displayed an intense fluorescence under UV. The molecular formula of was found to be $C_{20}H_{16}N_2O$ and molecular weight was 348.11. The formation of monoacetate **1a** with acetic anhydride, chloroacetate **1b** with chloroactic anhydride and chloro camptothecin **1c** using $SOCl_2$/pyridine indicated the presence of a hydroxy functional group. The treatment with sodium hydroxide gave sodium salt and again regenerated **1** on acidification and lactol formation after treatment with $NaBH_4$ indicated 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 pyridine ring oxygen fall in same plane. The lactone ring oxygen deviates from the plane imparting a boat conformation to the E-ring.



1a R = OAc
1b R = $OCOCH_2Cl$
1c R = Cl
1d R = $OCOCH_2I$

Figure 2.

Actually camptothecin does not form a stable salt with mineral acids, negative tests with Dradgendroff and Meyer reagents unlike other alkaloids. This clearly indicates neutral nature of the molecule. The unusual fast reduction with $NaBH_4$ into its lactol, failure of the methylation of OH with diazomethane or dimethyl sulphate under various reaction conditions may be ascribed to probably 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**.

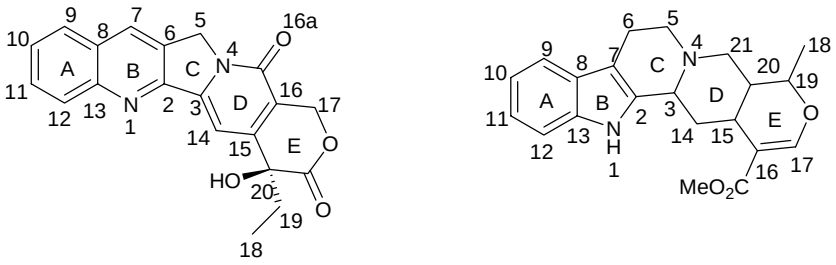


Figure 3.

Le Men-Taylor numbering system had been employed for camptothecin based on the close biogenetic relationship with the indole alkaloids, ajmalicine **7**. 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.

1.1.3 Naturally occurring camptothecins and its sources:

The investigation 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. The parent molecule camptothecin (**1**) and its other analogs collectively called as camptothecins or camptothecinoids have been isolated from various botanical species as mentioned in the table 1 which are clinically very important having inhibitory activity against various kind of cancers and recently one of its analogue shows activity against HIV-I.

This section describes some of the clinically important naturally occurring camptothecins and its natural sources.

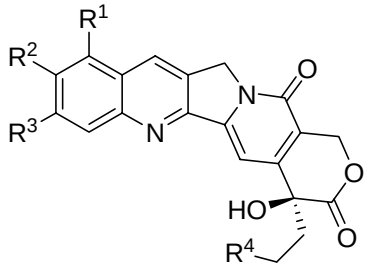
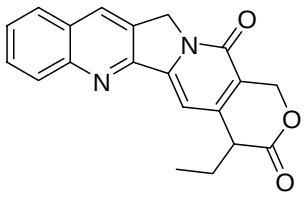
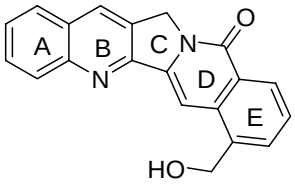


Figure 4.

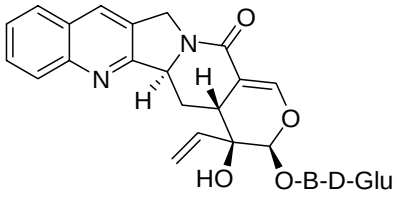
$R^1= R^2= R^3= R^4= H$	Camptothecin **1**	*Camptotheca acuminata,*[3a] *Nothapodytes foetida,*[3b] *Ophiorrhiza mungos,*[3c] *Ervatamia heyneana,*[3d] *Ophiorrhiza pumila,*[3e,3f] *Pyrenacantha klaineana*[3g]
$R^1= R^3= R^4= H$, $R^2= OH$	10-Hydroxycamptothecin **1e**	*Camptotheca acuminata,*[3h] *Nothapodytes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



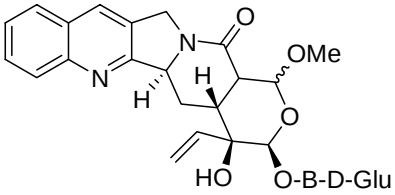
deoxy camptothecin **8**



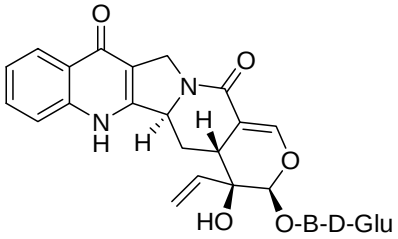
22-hydroxycuminatine **9**



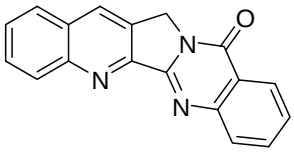
(3S)-deoxypumiloside **10**



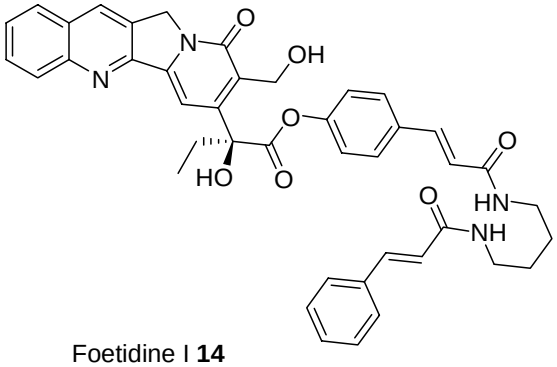
11a 17S : OPHR 23
11b 17R : OTHR 17



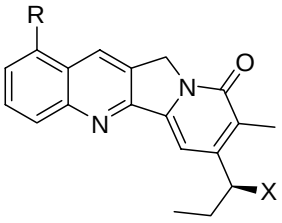
(3S)-pumiloside **12**



Luotonin A **13**



Foetidine I **14**



4 R = OMe and X = O: Nothapodytine A
5 R **=** H and X = O: Nothapodytine B
6 R = H and X = OH: mappicine

Figure 5.

Deoxy Camptothecin[3k] **8**: Displayed insignificant activity, may be due to the lack of hydroxy group.

22-Hydroxycuminatine[3i] **9**: It is a biogenetically novel alkaloid as A-D rings are similar to camptothecin while the E-ring is of Yohimbine type. It revealed cytotoxic activity during *in vitro* studies.

Deoxypumiloside[3f] **10 and Pumiloside**[3h] **12**: Pumiloside was postulated as the poststrictosamide intermediate of Camptothecin biosynthesis.

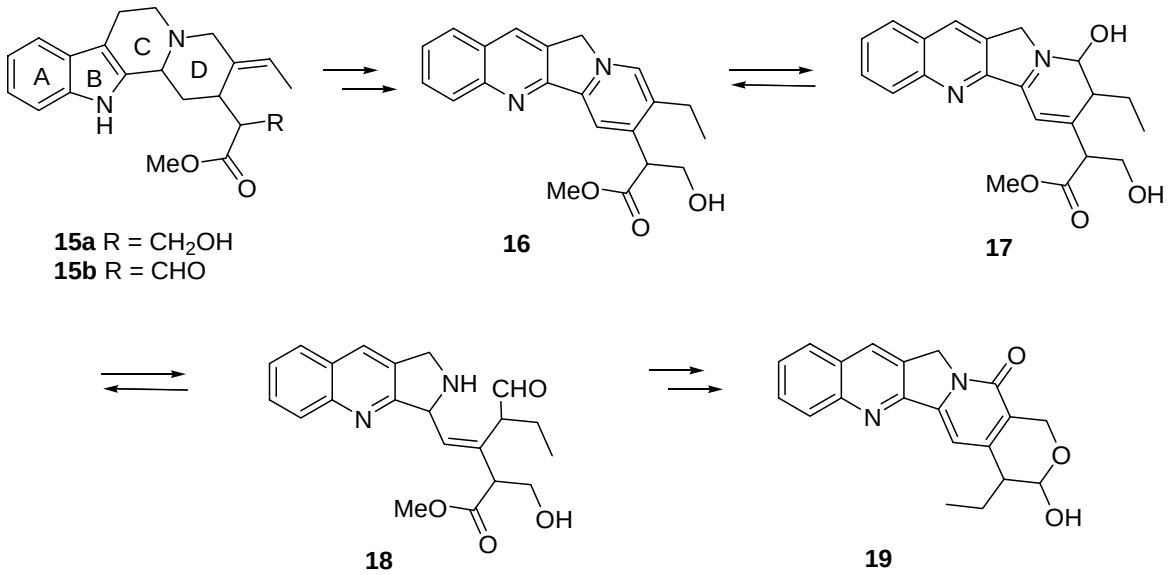
Luotonin A[3l] **13:** It is one more CPT-family alkaloid isolated from Chinese plant *Peganum nigellastrum* in 1997 it shows potent cytotoxicity against P-388 cell.

Foetidin I[3K] **14**: It has A, B, C, D rings in common with Camptothecin, but having a side chain through a phenolic ester bond instead of E-ring. It exibited potent anti tumor activity against ovarian cells and anti viral activity against HIV viruses.

Nothapodytine A[2a] **3, Nothapodytine B**[2a] **4 and Mappicine**[2b] **6 :** It has also contains A, B, C, D rings common like CPT, which was isolated by Govindachari in 1971 from Indian plant *Nothapodytes foetida* (formerly known as *Mapia foetida Miers*). Its oxidative form called Nothapodytine B (mappicine ketone) **5** has revealed a potential antiviral activity against herpes viruses HSV-1, HSV-2, acyclovir resistant virus and human cytomegalovirus (HCMV).[2c, 2d]

1.1.4 Biogenesis:

Wenkert *et al.*[4] has first time suggested a logical biosynthesis of camptothecin and related alkaloids in 1967. He imagined 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 pathway was outlined as shown in scheme 2 using plausible chemical transformation starting from isositsirikine **15a** or related alkaloids, similar to the biosynthetic relationship of vallesiachotamine to geissoschizine.

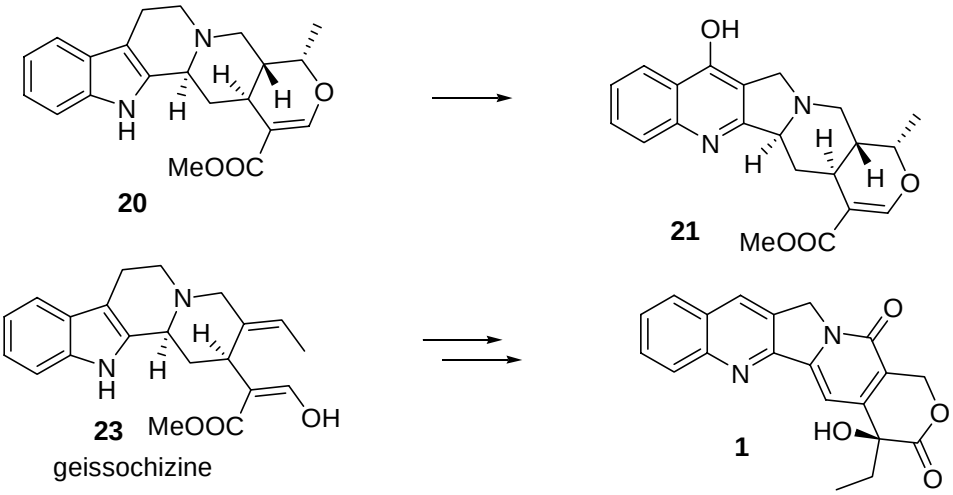


15a R = CH_2OH
15b R = CHO

16 **17** **18** **19**

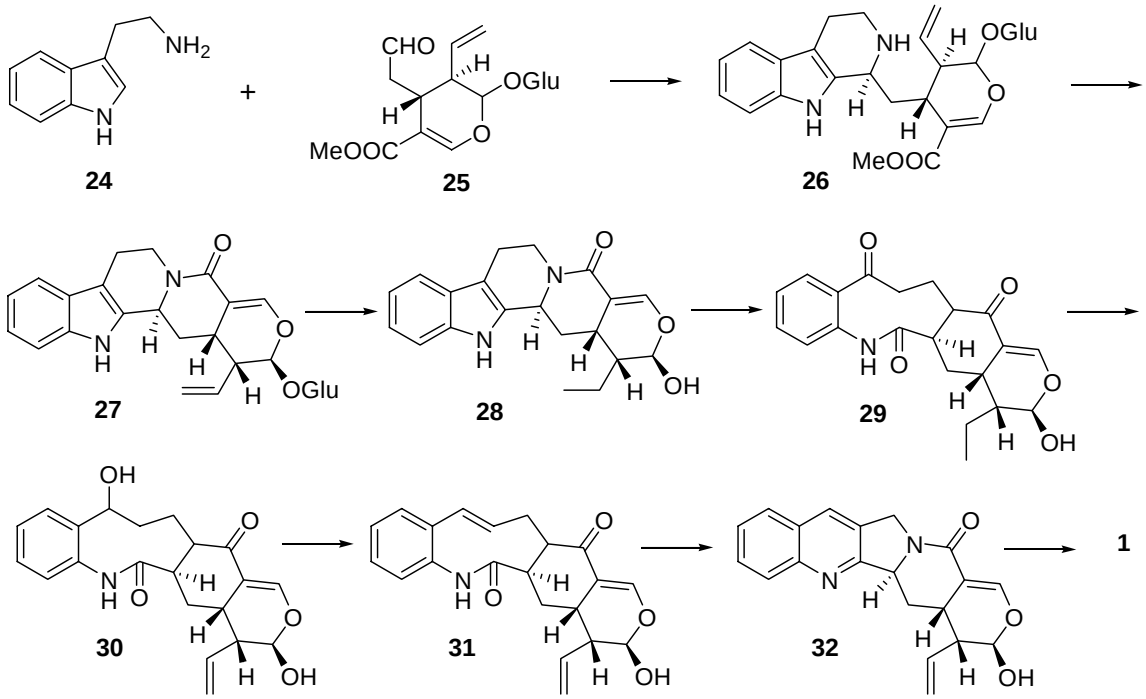
Scheme 1.

According to Wenkert results, the oxidation of indole alkaloid **20** results in the formation quinoline **21** (scheme 1). Winterfeldt thought and proposed gessiochizine as plausible biogenetic precursor (scheme 2).[5]



Scheme 2.

Initially *in vivo* results in which the incorporation of radioactive tryptophan,[6a] tryptamine **24**,[6b] mevalonic acid,[6a] geraniol/nerol isomeric mixture,[6b] secologanin[6a] **25** and strictosidine[6c] **26** delivered radioactive camptothecin in apical cuttings of young seedlings of *Camptotheca acuminata* established camptothecin was a monoterpene indole alkaloid.

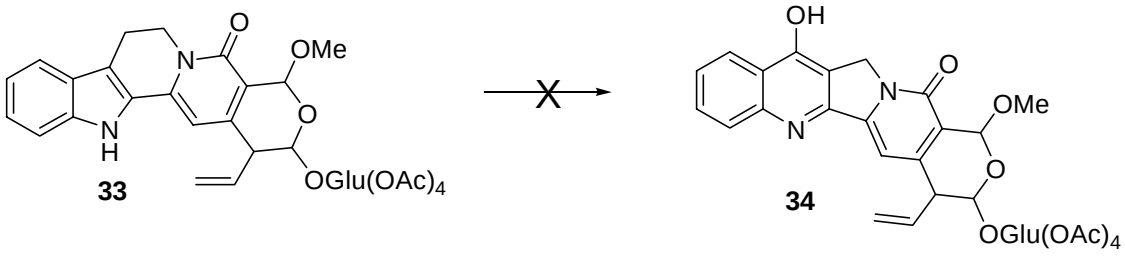


Scheme 3.

Heckendrof *et al* feeded the isotopically labeled precursors and confirmed strictosidine **26** as the specific precursor and eliminated epimeric (H-3-beta) vincoside[6d] possibility. Radiochemically labeled strictosomide **25** was also tested and efficient incorporation was observed in camptothecin. An easy conversion of strictosidine into strictosamide **25** under

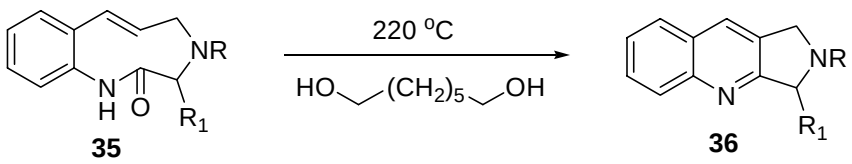
basic conditions and its structural similarity to camptothecin also indicated that strictosoamide as main biosynthetic precursor of camptothecin.[7] The probable biosynthetic path is depicted in scheme 3.

Hence, mevalonate is converted into secologanin **23** *via* geraniol and loganin, which combines with the tryptamine **22** to give strictosidine **26** which in turn was transformed into strictosamide **25**. The formation of camptothecin from **25** is possible by the removal of the glucose moiety, oxidation-recyclisation of BC-ring, and oxidation of D- and E-rings. This biogenetic hypothesis is strongly supported by the observations of Cordell and co-workers [8] the removal of the glucose unit followed after the formation of strictosamide **25**. This possibility depends on the biosynthetic fate of strictosidine **26** in other plants.[9] Actually the conversion of pyridone **33** to quinoline **34** would not realize (scheme 4) suggested that prior to D-ring oxidation BC rearrangement takes place.[10]



Scheme 4.

The mechanism of rearrangement is not still understood. It is assumed that indole moiety gets opened by oxidative cleavage into the ketolactam **29**, which in turn reduce to alcohol **30**, followed by dehydration and subsequent ring closure via stepwise ionic or concerted electrocyclic process results in formation of **1**. The proposed biogenetic route is supported by the cyclisation of **35** to the corresponding quinoline **36** at high temperature as shown in scheme 5.[10]

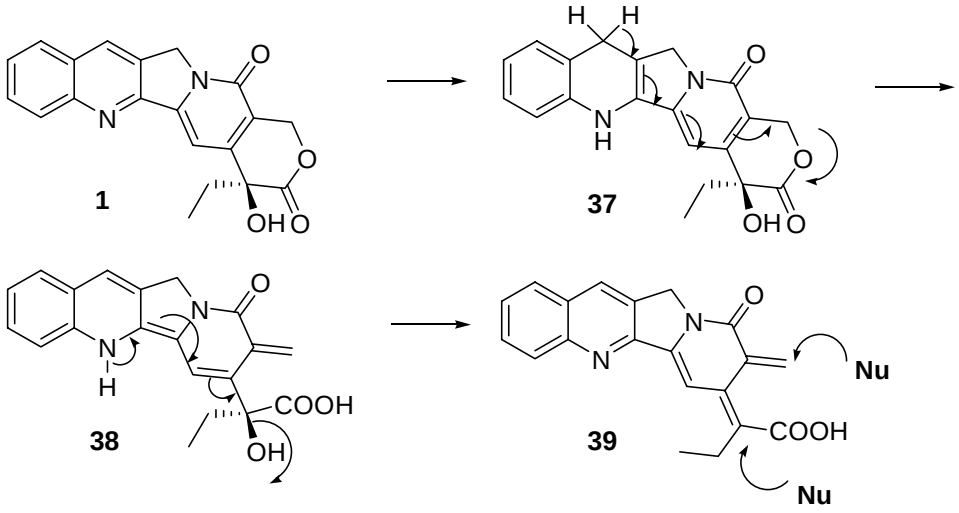


Scheme 5.

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.[11] While inhibition of DNA synthesis

appears highly irreversible or partially reversible, inhibition of RNA synthesis is highly reversible.[12] 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 discovered that most of the antitumor drugs promote covalent linkage of protein to DNA in tumor cells.[13] During this time, 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 proceeds. Topoisomerase I, which catalyze the topoisomerisation reactions of DNA *viz.* relaxation/supercoiling, knotting/unknotting and catenation/decatenation *via* transient enzyme linked single strand break.



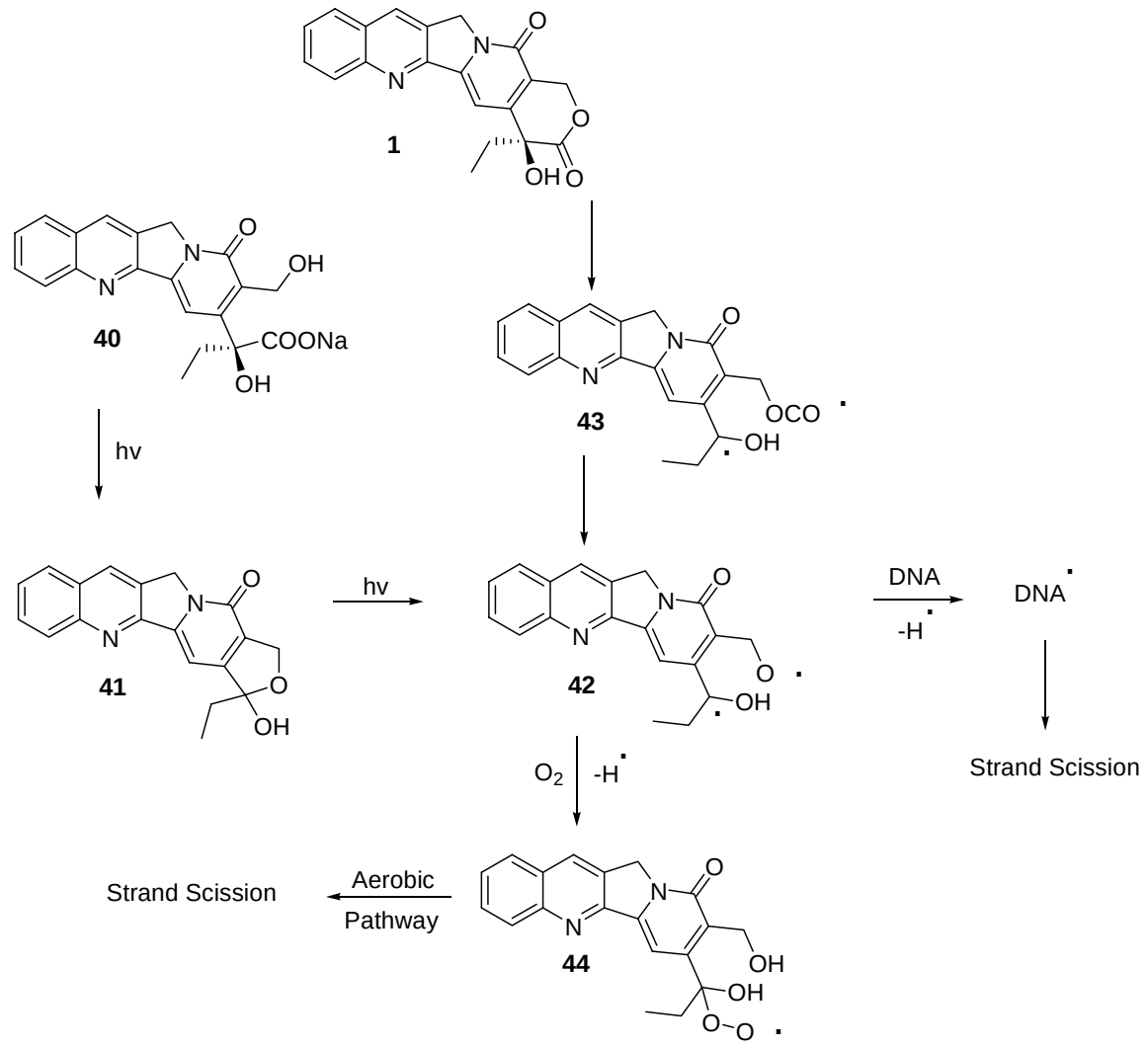
Scheme 6.

Generally the cancer cells are more effective to topoisomerase I inhibition compared to the normal cells because they contain a higher concentration of the enzyme, due to that cancer cells grows and reproduce fastly. Therefore, the affinity of CPT for Topoisomerase I translate in selective toxicity for tumor cells. Topoisomerase I relaxed supercoiled DNA ahead of active transcription/translation sites (replicating forks), the non covalent complex of double stranded.

DNA and Topoisomerase-I, described as the "non cleavable complex," is in rapid kinetic equilibrium with the so-called "cleavable complex," which forms when Topoisomerase I generates 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 Topoisomerase I religates the cleaved DNA and regenerate the double stranded configuration. These events conobligatory 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 causes to cell death. The cleavable ternary complex structure is very important for elucidation of the mechanism of action and development of new topoisomerase inhibitors.[14]

Lown *et al*[15] proposed a free radical mechanism as shown in scheme 7.



Scheme 7.

1.1.6 Structure-Activity Relationship Studies of camptothecin:

Initially it was reported that the entire planar pentacyclic ring structure (A-E rings) of camptothecins is essential for the antitumor activity, but recently according to the QSAR study investigation show that the lactone E-ring is not essential for its activity.

Modification in A and B rings:

The camptothecin *N*-oxide **45** showed decreased activity indicating the importance of quinoline nitrogen for biological activity.[16] Rubitecan **46** serves as a metabolic precursor to 9-amino CPT **47** and currently it is in phase III clinical trials for the pancreatic cancer[17,18] Lurtotecan **48** and exatecan mesylate **49** are the most successful derivative of CPT and presently it is in clinical trials for breast, colorectal and small cell lung cancers.[19, 20]

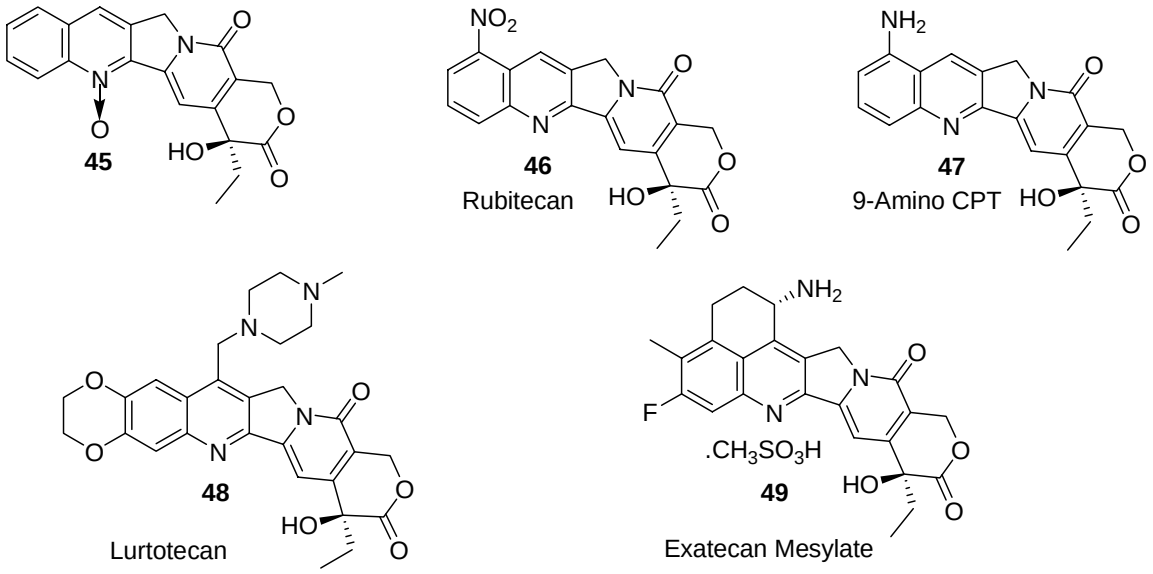


Figure 6.

The heteroatomic analog **50,**[21] and tetrahydro CPT **51**[22] shows less activity than parent CPT this suggest the quinoline moiety is essential for biological activity, The DE-310 **52** is a prodrugs which is especially conjugate and polymer bound camptothecins, they improve the solubility and stability of lactone moiety and its therapeutic efficacy might be on account of reduced toxicity, longer retention time within the body and altered bio-distribution. These approaches have proven to be promising in preclinical investigation and a plethora of camptothecin-prodrugs is under clinical survey.[1b]

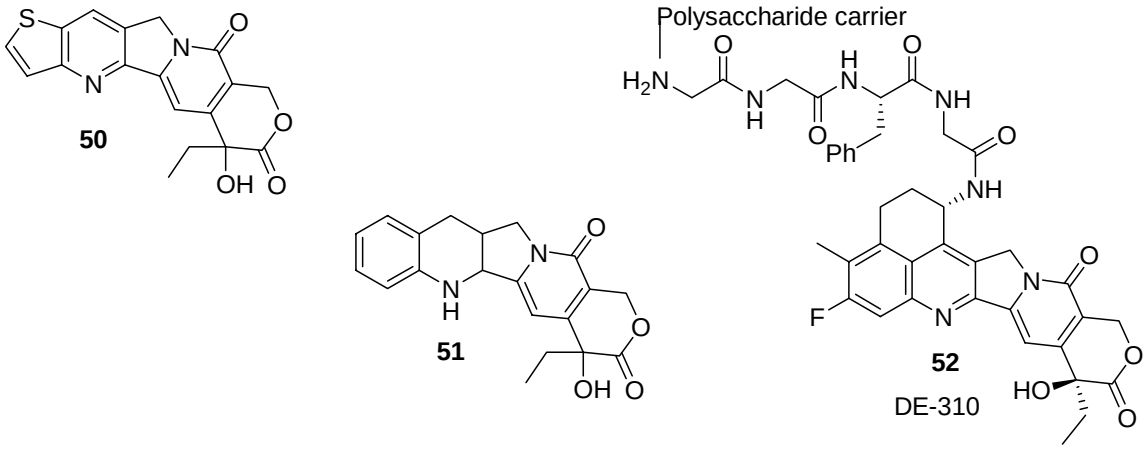


Figure 7.

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[21,23] 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.

Modification in C and D rings:

The C-nor-4, 6-seco CPT **53**,[24] compound **54** the modifications at C-5 derivative **55** have been reported to result in less or loss of activity,[25a, 25b] it might be due to loss of planarity which is essential for enzyme-DNA-CPT ternary complex stabilization. The azacamptothecin **56** is the hybrid of Luotonin A **13** and camptothecin **1** it showed promising cytotoxicity due to its shape and planarity.[26] Reduction of 17-carbonyl **57** loses its activity. This evidence indicates that the pyridine carbonyl and pyridone ring is essential for receptor binding.[27]

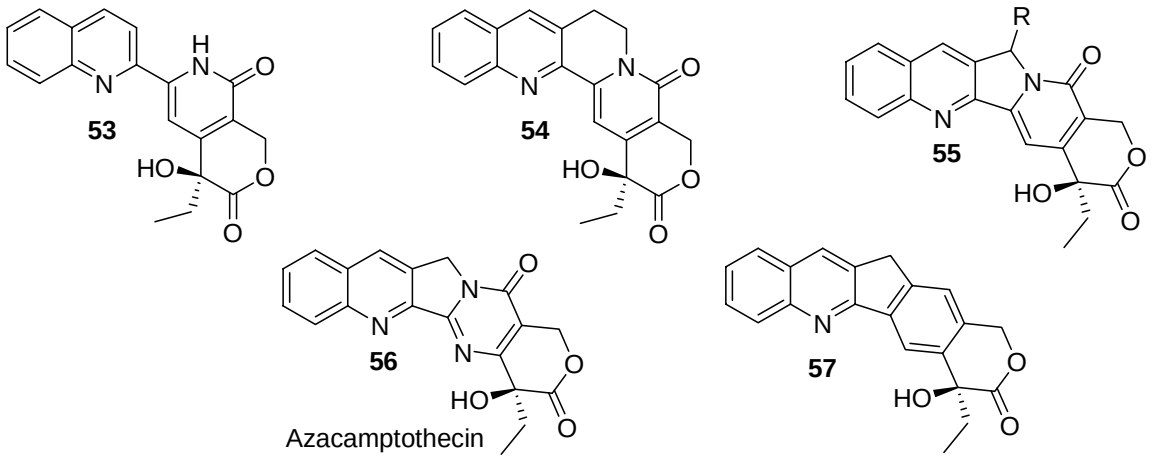


Figure 8.

Modification in E ring:

Isocamptothecin[21] **58a** showed slight activity while isohomocamptothecin[28] **58b** exhibited no activity respectively, replacement of C-20 'OH' group in camptothecin by N_3, NH_2, Cl, H, ethyl, hydroxymethyl, allyl moieties showed no activity **59**[21, 29] respectively. Replacement of C-20 ethyl group of camptothecin **60** by allyl, propargyl, benzyl, methoxy ethyl, show no marked change in activity while replacement by benzoyl group showed reduced activity suggests that ethyl group in **1** can be replaced by a appropriate functionality (figure 9).[29a]

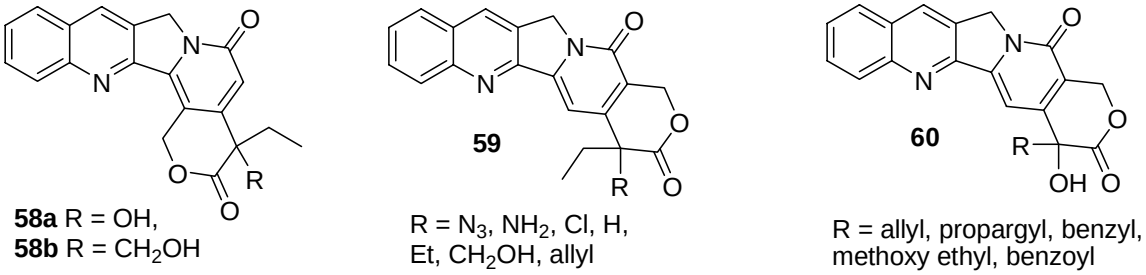


Figure 9.

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.[30] The camptothecin lactone ring undergoes facile hydrolysis and equilibrates with its ring-opened form even at the physiological conditions (figure 10).[31] The sodium salt of the carboxylate **61** form of camptothecin was only one tenth active than that of **1** when administered intravenously.

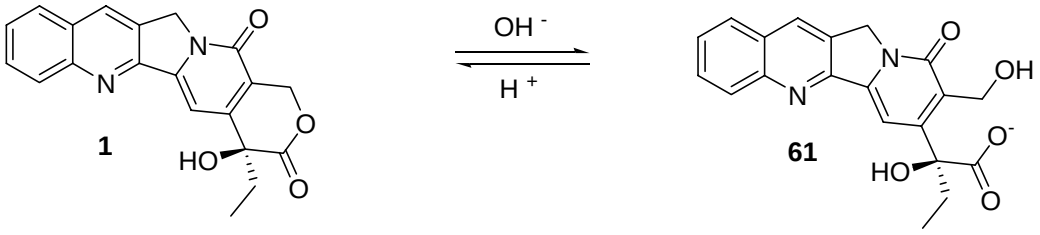


Figure 10.

The lactol **62,**[16] lactam **63**[27] and **64**[32] (figure 11) showed no antitumor activity, this indicated that intact lactone ring might be essential for camptothecin's activity. Sugasawa reported, ester **65** showed activity comparable to racemic camptothecin.[29a] The thiolactone **66** have also been reported with activity,[32] the phosphate monoester compound **67** was very toxic, though it was less powerful than CPT.[33]

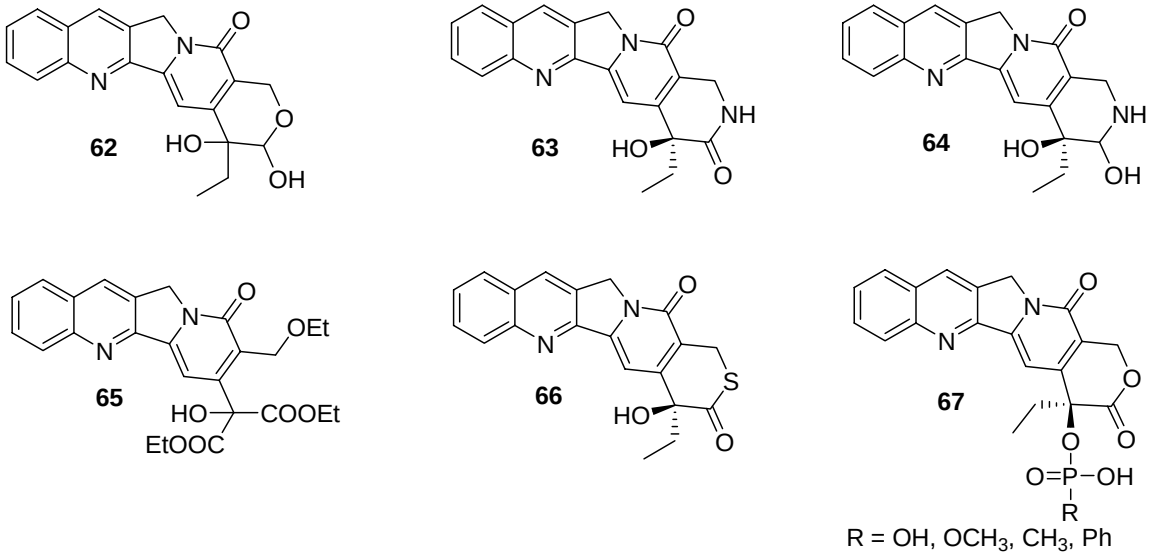


Figure 11.

Although earlier SARs of the camptothecin suggested the importance of the lactone E-ring for activity, Lavergne *et al* in 1997[34] reported new analogs with an expanded β-hydroxy lactone ring called homocamptothecin **68** (figure 12). The lactone ring of camptothecin opens rapidly and reversibly while lactone ring of homocamptothecin opens very slowly and irreversibly. Therefore they exhibit high plasma stability in the biological system; most importantly they are much more cytotoxic than camptothecin. Novel analogues of homocamptothecin such as fluorinated homocamptothecin **69** and silylated homocamptothecin **70** are much more potent than parent homocamptothecin **68.**[35]

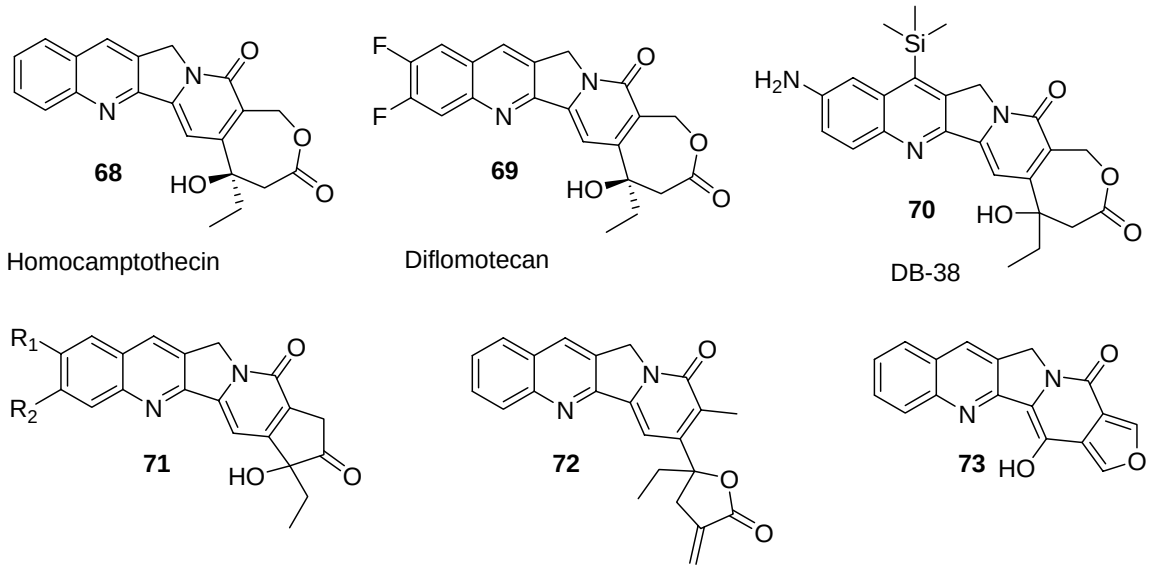


Figure 12.

Apart from lactone and lactam E-ring, series of cyclopentyl E-ring analogues like **71, 72** and **73** have been synthesized and evaluated (figure 12).[36]

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 **48**, exatecan mesylate **49**, figure 6) in various stages of clinical trials.[1a]

The stereochemistry at C-20:

The stereochemistry at C-20 is very important for its activity. As 20(*S*) hydroxyl is active while 20(*R*) hydroxyl is inactive.[37] Cushman and coworkers[38] demonstrated that the preferred conformation of CPTs has the 20-Et pseudo axial while the 20-OH is pseudo equatorial based on quantum mechanical study.

In summary, A-E rings are essential for *in vitro* and *in vivo* activity, modifications in A and B rings are well tolerated and resulted in better activity than CPT in many cases. Saturation of B ring compounds show less activity, D-ring pyridone is required for antitumor activity, α-hydroxy lactone is necessary for activity, Oxygen at C-20 is essential for activity, replacement of this oxygen by sulfur or nitrogen abolishes the activity of CPT.

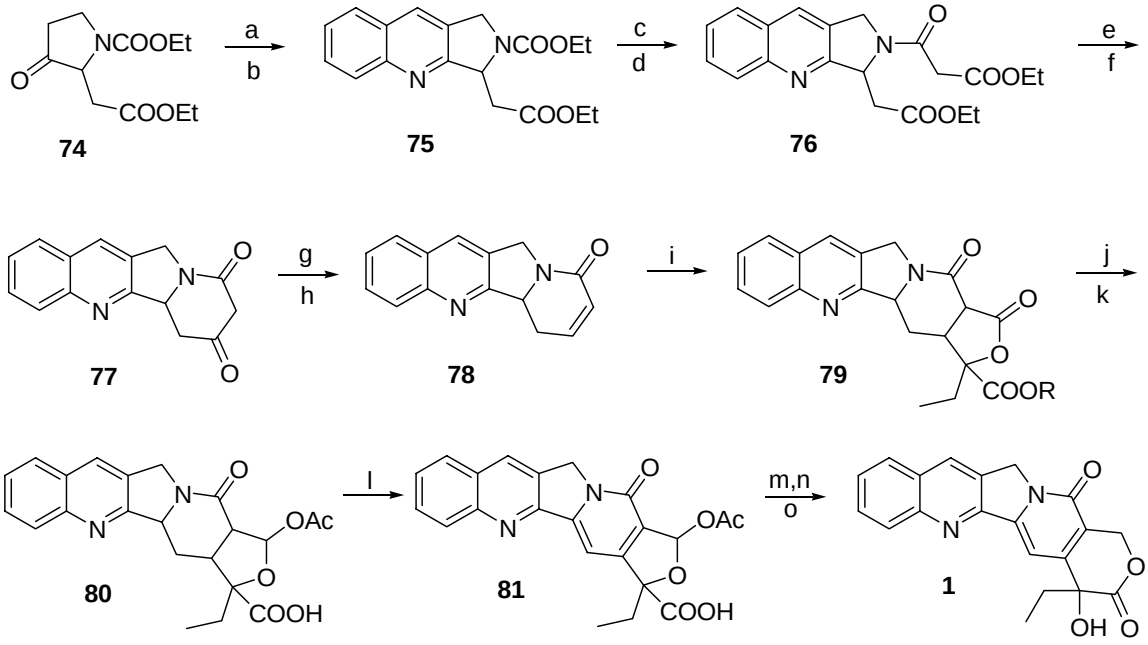
Conformation at C-20 is important for better activity as 20(*S*) isomer is 10- to 100-times more active than 20 (*R*).[37]

1.1.7 Brief literature survey:

Owing to its challenging pentacyclic ring structure including a pyrrole (3,4β)quinoline moiety and having one chiral centre within the α-hydroxy lactone ring with 20(*S*) configuration(ring-E), unique mode of action and impressive biological activity, numerous imaginative (including novel chemistry as well as practical) syntheses have been reported by several research groups.[39] Since the review on synthesis has already covered by and previously by Pasupathy,[39l] Sivappa,[39m] and Venkat[39n] from this group only few representative syntheses have been described in the present section.

Stork's approach[40]: (Stork *et al*. *J. Am. Chem. Soc*. **1971**, *93*, 4074)

Five years after the isolation of camptothecin, Stork and co-workers disclosed the first racemic synthesis of camptothecin in divergent fashion (scheme 8). The key steps of the synthesis are: Friedlander condensation for the AB-ring construction, intramolecular Dieckmann condensation for the D-ring construction and intermolecular Michael addition for the construction of E-ring. The synthesis was achieved in 15-steps in 1-2% overall yield. The main highlight of the synthesis is the conversion of **78** to **79,** placing five carbon atoms along with the tertiary hydroxyl group present in the camptothecin.



Scheme 8. *Reagents and conditions: (a) o-amino benzaldehyde, NaOH; (b) EtOH, H^+, (c) 50% HI, EtOH, HCl, (d) $ClCOCH_2COOEt$, (e) NaH, EtOH/$PhCH_3$, (f) 10% acetic acid, (g) $NaBH_4$, (h) Ac_2O, NaOAc, (i) LDA, -78 ºC, (j) $NaBH_4$, rt, 20 h, (k) Ac_2O, pyridine, (l) DDQ, 1,4- dioxane, (m) 0.1N NaOH, (n) $NaBH_4$, (o) dil HCl.*

Thus the base catalyzed Friedlander condensation of pyrrolidine **74** with 2-amino benzaldehyde gave the tricyclic quinoline ester **75**. The amino-ester resulting from the hydrolysis of **75** followed by protection with ethyl malonyl chloride furnished the diester amide **76**. The tetracyclic *β*-keto ester was obtained by the intramolecular Dieckmann condensation of **76**, was subjected to decarboxylation, reduction and elimination gave the desired dihydropyridone **78**. The unsaturated lactam underwent smooth intermolecular Michael addition efficiently at low temperature to give the crucial pentacyclic lactone **79**. Finally hydrolysis of the ethyl ester of **79** followed by reduction and protection gave the lactol, which upon oxidation with DDQ gave pyridone **81**. Subsequent three-step sequence starting from 7**9**, *viz*. hydrolysis, reduction and lactonization gave the (±)-camptothecin **1**.

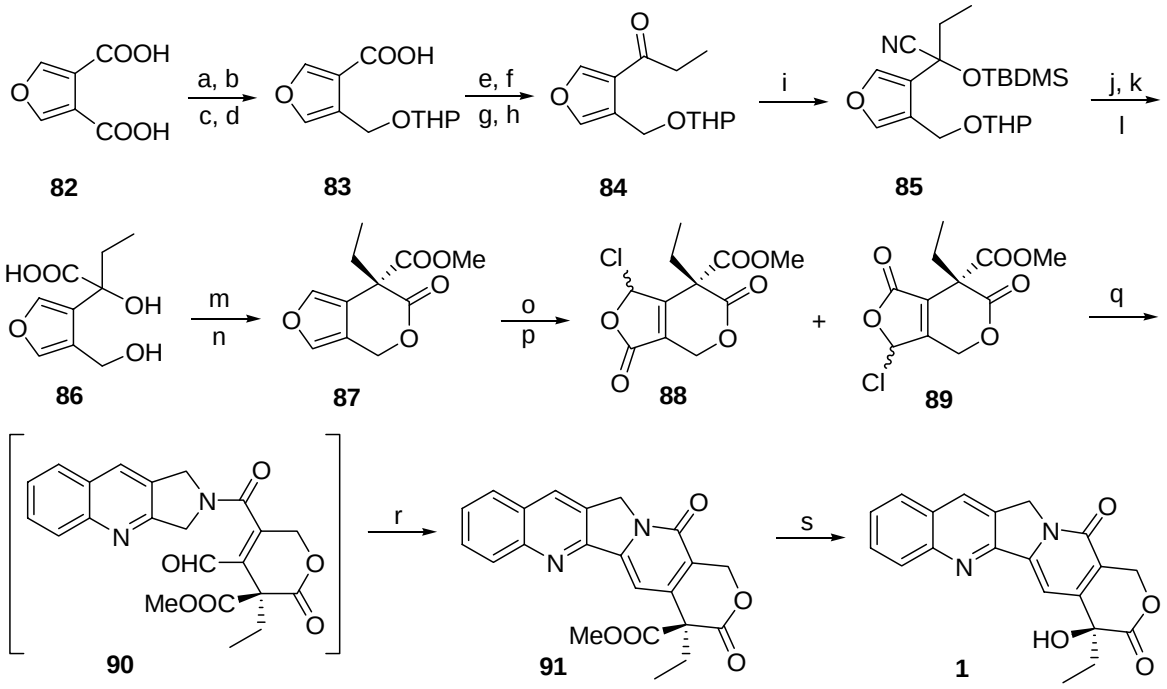
Corey's approach[41]: (Corey *et al J.Org.Chem*, **1975**, 40, 2140)

Corey *et al*. devised elegant first total synthesis of (-) camptothecin. It involved condensation of half ester **89** with tricyclic amine in a convergent manner and further condensation of the resulting aldehyde to furnish the pyridone moiety (scheme 9).

This synthesis began form furan 3, 4-dicarboxylic acid **82** as the starting material selective esterification of one acid to ester while borane reduction in THF at 0 °C for 3 hrs provided alcohol which was protected as THP ether **83**. Hydrolysis of ester furnished the corresponding acid 8**2** in 30% yields. The acid **83** was converted to aldehyde employing a reduction-oxidation sequence using treatment of **83** with borane followed by oxidation using manganese dioxide. Ethylation using ethyl magnesium bromide followed by Collin's oxidation furnished ketone **84** in 69% yields. Cyanation using TBDMSCN furnished protected cyanohydrin **85** in 85% yield, which was converted to hydroxy acid **86** in 47% yield *via* the amide. Resolution using quinine followed by lactonization and protection of the tertiary alcohol with methyl chloroformate gave lactone **87** in 76% yields. Photooxidation followed by treatment with thionyl chloride gave pseudo acid chlorides **88** and **89**. Condensation of **89** with tricyclic amine and cyclisation with generated aldehyde

furnished compound **91** and finally the deprotection of alcohol using lithium mercaptide furnished target molecule camptothecin.

The first chiral synthesis was achieved in 20-steps with 0.46% overall yield.

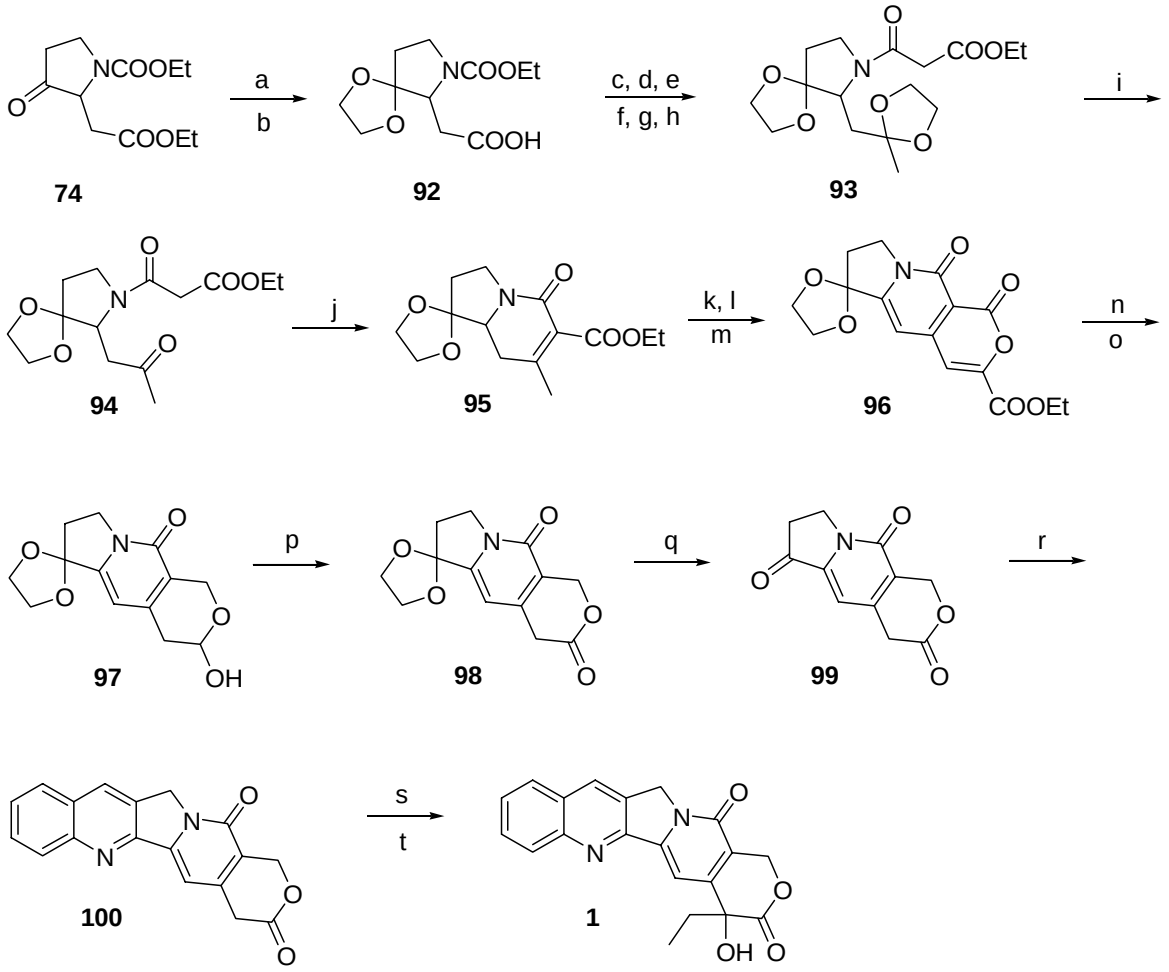


Scheme 9. *Reagents and conditions: (a) $ClCO_2Me$, Et_3N; (b) BH_3, THF, 0 ^oC; (c) DHP, PTSA; (d) KOH, MeOH; (e) BH_3, THF; (f) MnO_2; (g) EtMgBr; (h) Collin's reagents; (i)TBDMSCN; (j) 30% H_2O_2, aq. K_2CO_3; (k)H_2O/ KOH/MeOH; (l)30% AcOH; (m)Quinine resolution (n) $ClCO_2Me$ (o) O_2/hv, eosin (p) $SOCl_2$, DMF; (q)Tricyclic amine (r)Base Catalyst (s) Lithium mercaptide.*

Shamma's approach[42]: (Shamma *et al Tetrahedron,* **1973**, 1949)

An intramolecular aldol condensation has been employed for the construction of pyridone ring of molecule. The pyrrolidinone **74** was protected as its ethylene glycol acetal. Hydrolysis of ester gave the corresponding acid **92** in 91% yields (scheme 10). Acid was converted to methyl ketone by a 3-step sequence of acid chloride formation, condensation with diethyl malonate sodium salt followed by hydrolytic decarboxylation. The carbonyl group was protected as 1, 3-dioxolane using ethylene glycol. The deprotection of urethane under basic conditions furnished amine which on condensation with carbethoxy acetyl chloride furnished amide **93** in 91% yield. Deprotection to methylketone **94** was effected using acetic acid at 60°C. Aldol condensation using sodium ethoxide furnished dihydropyridone **95** in 83% yields. Oxidation to pyridone using DDQ followed by

condensation with diethylmalonate and esterification furnished pyridone **96** in 65% yields. Borohydride reduction followed by periodate oxidation provided lactol **97**. Oxidation to lactone **98** using Pt/O_2 and deprotection of acetal using oxalic acid gave ketone **99** in 57% yield. Friedlander condensation with o-amino benzaldehyde gave lactone **100** which on ethylation and oxidation furnished (±) **1**.

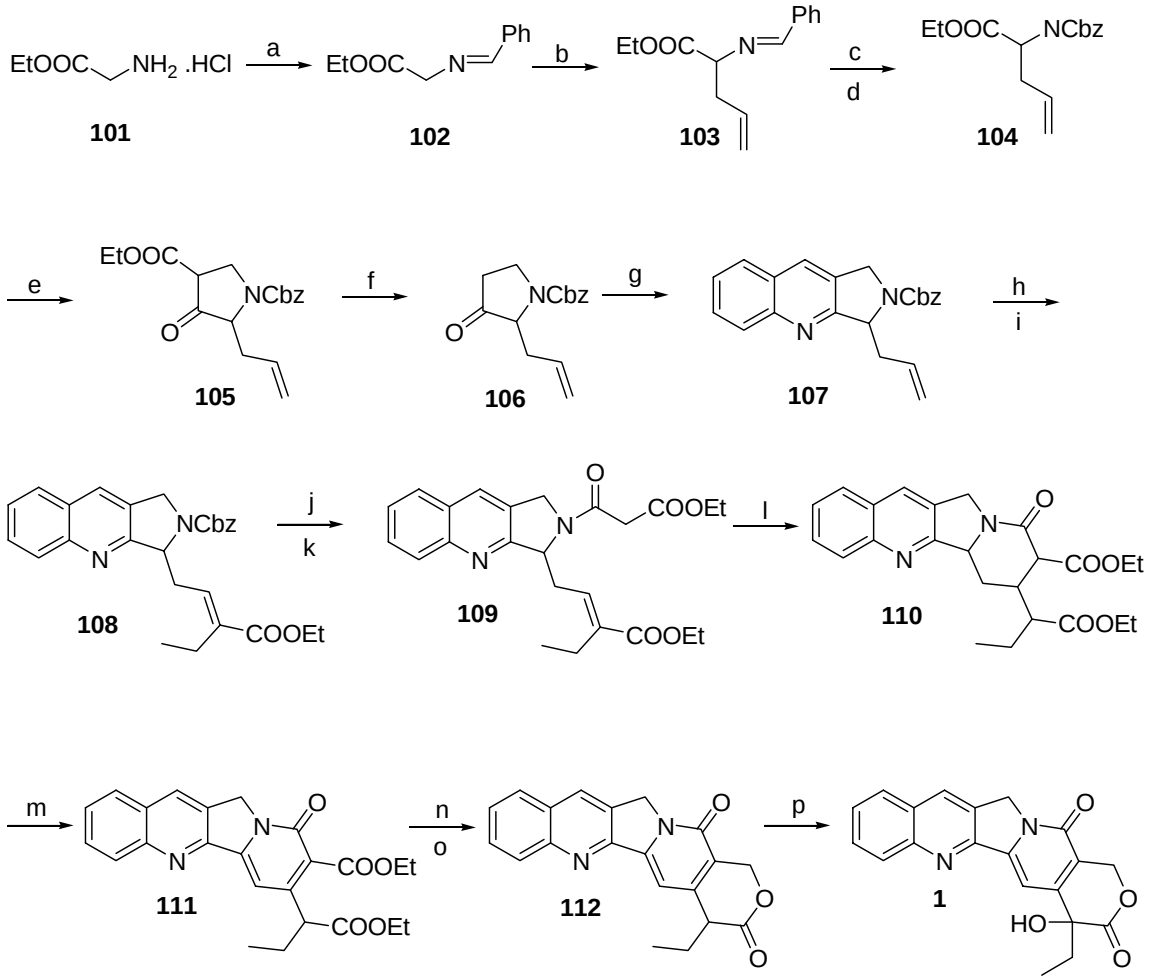


Scheme 10. *Reagents and conditions: (a) $HO(CH_2)_2OH$, H^+; (b) KOH, EtOH; (c) $SOCl_2$; (d) $NaCH(CO_2Et)_2$; (e) HCl; (f) $HO(CH_2)_2OH$, H^+; (g) KOH, MeOH; (h) $ClCOCH_2CO_2Et$; (i) AcOH, 60 ^oC; (j)NaOEt, 0 ^oC; (k) DDQ; (l) NaOEt, $(CO_2Et)_2$; (m) EtOH, H^+; (n)$NaBH_4$; (o) $NaIO_4$; (p)Pt/O_2; (q) Oxalic acid, aq EtOH; (r) o-amino benzaldehyde base; (s) EtI, Base; (t) CuCl, O_2.*

Even though the synthesis was achieved in 20 steps in an overall yield of 6.5% upto **99,** by delaying construction of the quinoline ring the authors have made synthesis of derivatives possible by this route.

Chavan's I approach[43a]: (Chavan *et al*. *Tetrahedron Lett*. **1998**, *39*, 6745)

Our group first synthesized (±)-camptothecin employing intramolecular Michael addition as a key reaction. Another highlight of the synthesis is the regio-selective DIBAL-H reduction of aromatic ester in the presence of aliphatic ester in **111**. Synthesis began from hydrochloride salt of ethyl ester of glycine **101**. This was converted its Schiffs base **102** and it was alkylated with allyl bromide under PTC condition to give **103**. The imine **103** was hydrolysed and protection of the resultant amine with CbzCl yielded the urethane **104** in very high yields. A tandem Michael-Dieckmann condensation furnished β-keto ester **105** which on subsequent decarboxylation gave the pyrrolidinone **106**.



Scheme 11. *Reagents and conditions: (a) Benzaldehyde, Et_3N, molecular seives, DCM, 1h, 98%. (b) allyl bromide, NaOH, $TBAHSO_4$, DCM, rt, 0.5 h, 97%. (c) HCl, rt, 0.5 h, 94%, (d) CbzCl, K_2CO_3, DCM, rt, 3 h, 96%. (e) NaH, C_6H_6, ethyl acrylate, reflux, 3 h, 65%. (f) 10% HCl, reflux, 4 h, (g) N-(o-amino benzilidine)p-toluidine, PTSA, toluene, reflux, 6 h, 72%. (h) OsO_4, $NaIO_4$, dioxane, H_2O, 4 h (i) $PPh_3C(Et)CO_2Et$, DCM, rt, 5 h, 83%. (j)*

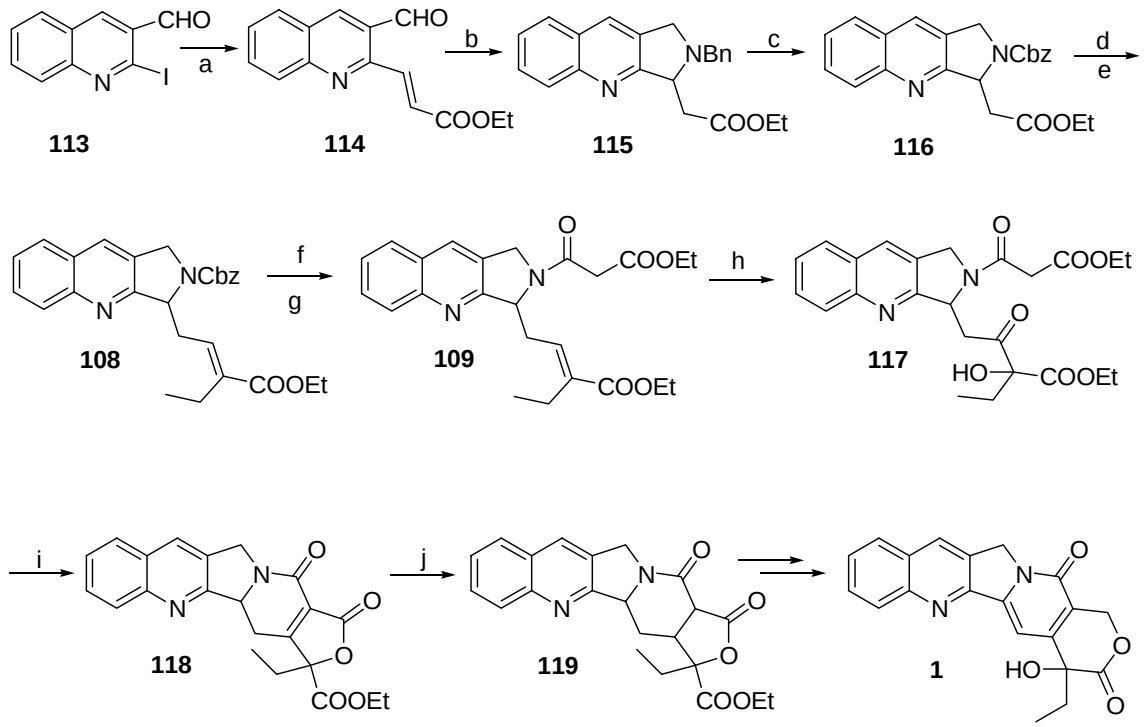
TMSCl/NaI, CH_3CN, 1 h, (k) ethyl malonyl chloride, K_2CO_3, DCM, 0 ºC to rt, 3 h, 66%. (l) NaH, THF, rt, 0.5 h, 92%. (m) DDQ, dioxane, reflux, 1 h, 78%. (n) DIBAL-H, THF, -60 ºC, 83%. (o) $NaBH_4$, THF, H_2O, 0 ºC, 1 h, 55%. (p) $CuCl_2$, dimethyl amine, O_2, 20 h, 98%.

The pyrrolidinone **106** underwent modified Friedlander condensation with Schiff base to furnish the tricyclic carbamate **107**. Oxidative cleavage of the double bond in **107** furnished aldehyde which was subjected to Wittig olefination with phosphonium salt furnished the α,β-unsaturated ester **108**. Deprotection of carbamate of **108** was carried out employing Olah's protocol. The resulted free amine was reacted with ethyl malonyl chloride to afford the key amide **109**. The intramolecular Michael addition was carried on **109** using NaH to deliver tetrahydropyridone **110.** The tetrahydropyridone **110** was oxidized using DDQ to provide pyridone **111**. The regioselective reduction of the aromatic ester in **111** using DIBAL-H furnished the aldehyde, which was followed by reduction using $NaBH_4$ underwent lactonization to give 20-deoxycamptothecin **112**. The hydroxylation of **112** was done employing Danishefsky's protocol, utilizing oxygen as oxidant to give (±) **1**.

Chavan's II approach[43b]: (Chavan *et al*. *Tetrahedron Lett*. **2004**, *45*, 3113)

In earlier synthesis our group exploited an intramolecular Michael addition approach towards (±) camptothecin (scheme 10). Central to this idea formal total synthesis is the implementation of an intramolecular "aldol"/Knoevenagel reaction of ketol **142** to construct the pyridone D-ring with suitable functionality for manipulation to the lactone E-ring (scheme 12). The Heck olefination of iodoaldehyde **113** was carried out with ethyl acrylate gave the olefin-tethered aldehyde **114** in very good yield. Aldehyde **114** was subjected to reductive amination gave the tricyclic amine **115** following intramolecular Michael addition pathway. The benzyl group of amine **115** was deprotected by hydrogenation and treated with CbzCl to convert it to the corresponding carbamate **116**. The carbamate **116** was subjected DIBAL-H to give aldehyde. The resulted aldehyde underwent Wittig olefination with phosphorane to furnish the α,β-unsaturated ester **118**. Deprotection of the carbamate followed by the condensation with ethyl malonyl chloride afforded amide **109**. The oxidation of **109** was accomplishing using $KMnO_4$ to furnish ketol **117**. Ketol **117** was subjected to intramolecular "aldol"/Knoevenagel reaction to deliver the desired dihydropyridone **118** which was then reduced to tetrahydropyridone

119. The tetrahydropyridone **119** is the common intermediate in Stork's approach and in this way formal synthesis of camptothecin was achieved.

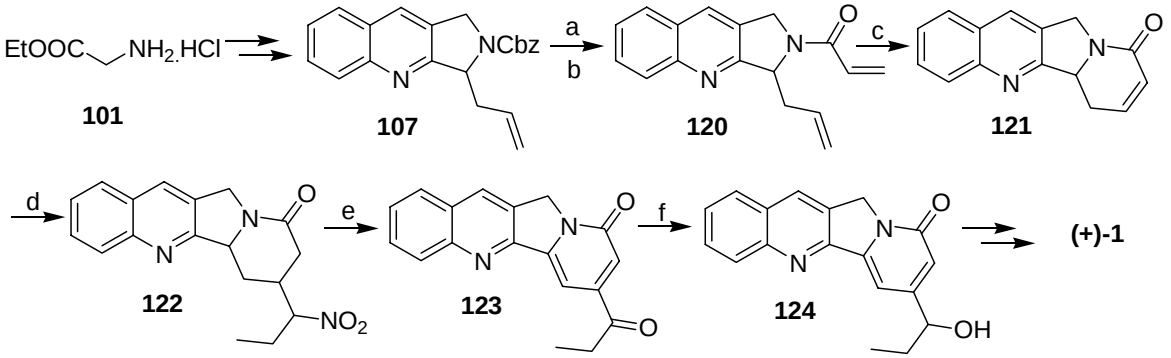


Scheme 12. *Reagents and conditions:* (a) *ethyl acrylate, NaOAc, 5 mol% Pd(PPh$_3$)$_4$, DMF, 74%, (b) BnNH$_2$, MeOH, rt, 1 h, NaBH$_4$, MeOH, 0 ºC to rt, 2 h, 91%, (c) Pd/C–H$_2$, EtOH, CbzCl, DCM, K$_2$CO$_3$, 90%, (d) DIBAL-H, DCM, (e) PPh$_3$C(Et)CO$_2$Et, DCM, 80%; (f) TMSCl, NaI, CH$_3$CN, rt, 1 h, (g) carbethoxy acetyl chloride 68%, (h) KMnO$_4$, acetone–water, AcOH, 95%, (i) NaH, THF, 90%, (j) 10% Pd/C–H$_2$ (100 psi), EtOH, 88%.*

Chavan's III Approach[43c]: (Chavan *et al*. *Tetrahedron Lett*. **2004**, *45*, 6879)

In earlier two approaches Chavan and co-workers described two syntheses employing intramolecular Michael addition and intramolecular "aldol" condensation. In this approach the formal total synthesis was achieved employing ring-closing metathesis as the key reaction to construct the pyridone moiety of camptothecin (scheme 13). The tricyclic carbamate **107** was prepared as shown in the first approach (scheme 11). The Cbz group was deprotected by ethanolic KOH and the generated amine was condensed with acryloyl chloride to give acrylamide **120** well suited for the RCM reaction. When **120** was subjected to the treatment with Grubbs' first generation catalyst and titanium isopropoxide as a Lewis acid in refluxing benzene it furnished dihydropyridone **121**. The Michael addition of nitropropane was carried out on **121** using DBU as a base to furnish

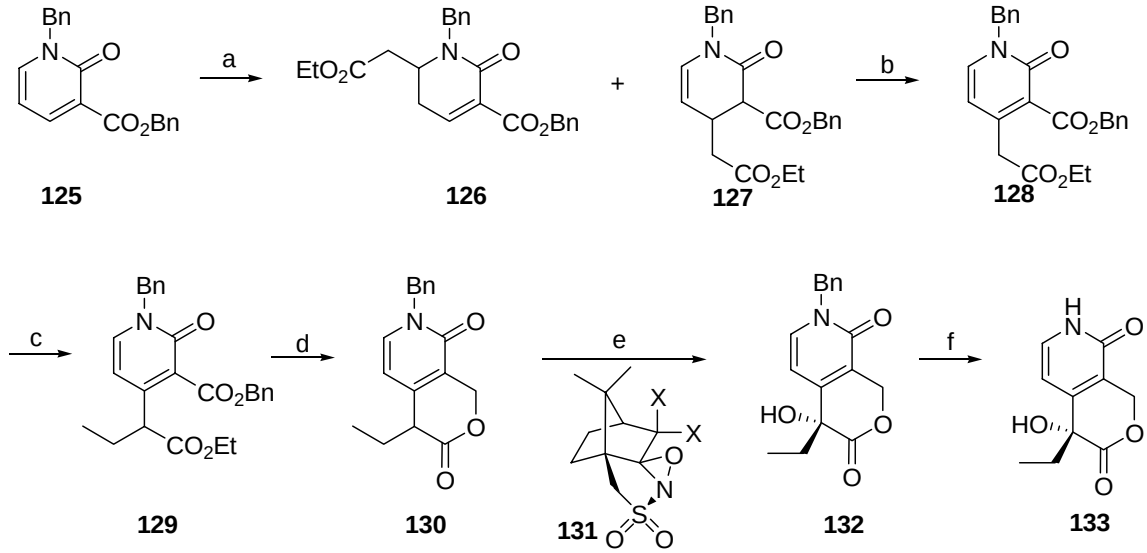
tetrahydropyridone **122** in 86% yield. When tetrahydropyridone **122** was subjected to the treatment with sodium hydroxide in methanol and further with concentrated hydrochloric acid the Nef reaction as well as the aromatization occurred in one pot to deliver keto compound **123** in very poor yield. Keto compound **123** was reduced to its hydroxyl compound **124** in 99% yield using sodium borohydride. This intermediate **124** was converted to camptothecin by Murata's group. This constituted a formal synthesis of camptothecin.



Scheme 13. *Reagents and conditions: (a) KOH, EtOH, reflux, 24 h; (b) acryloyl chloride, K_2CO_3, DCM, rt, 3h, 73%; (c) Grubbs 1st gen. cat. (10 mol%), $Ti(OiPr)_4$, C_6H_6, reflux, 16-20 h, 89%; (d) nitropropane, DBU, rt, 16h, 86%; (e) NaOH, MeOH, rt, 3h, conc. HCl, 0 ^oC, 1 h and RT, 12 h, 23%. (f) $NaBH_4$, MeOH, 0 ^oC, 1h, 99%.*

Hiroya approach[44]: (Hiroya *et al*. *Synlett*. **2006**, *16*, 2636)

Hiroya *et al*. began the synthesis from pyridone **125.** The reaction between **125** and silyl ketene acetal resulted in two products **126** and desired **127**. Treatment of **127** with NaH and $CuBr_2$ resulted in formation of pyridone **128** (scheme 14).

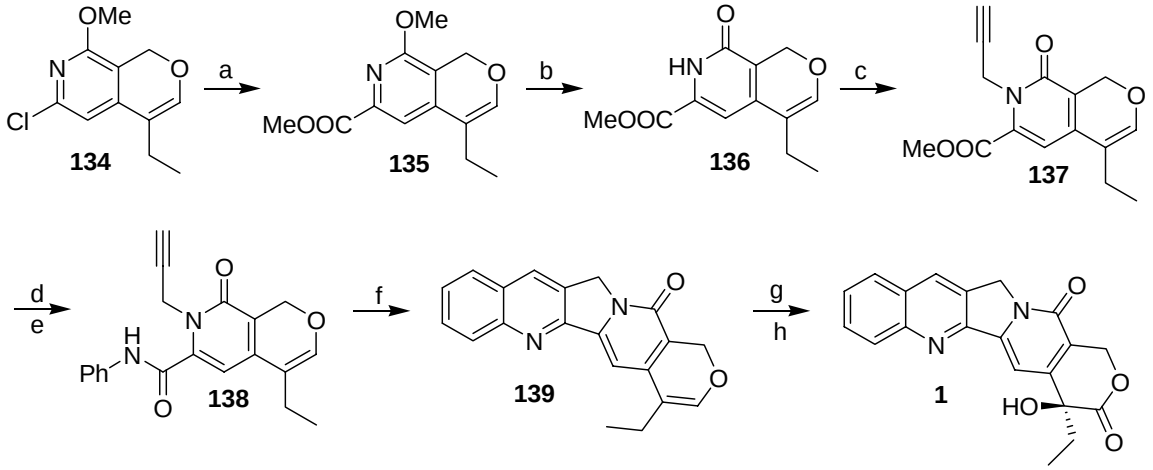


Scheme 14. *Reagents and conditions: (a) enol ether, Et_2AlCl, -40 ^oC, 5 h, (27+53) 80%. (b) NaH, $CuBr_2$, DMF-DMSO (1:1), 0-50 ^oC, 28 h, 56%. (c) LiHMDS, EtI, THF, -78 ^oC to rt, 11 h, 71%. (d) $NaBH_4$, $CeCl_3.7H_2O$, EtOH, 0 ^oC, 1.5 h, then 1N HCl, rt, 8 h, 57%. (e) Base,* **7**, *THF, -78 ^oC, 5 h, 84%. (f) H_2, $Pd(OH)_2$/C, EtOH, 50 ^oC, 3 h, 77%.*

Ethylation was carried out using LiHMDS as a base to give alkylated product **129** in 71% yield. The reduction of aromatic benzyloxy carbonyl group to alcohol and *in situ* lactonization was accomplished using $NaBH_4/CeCl_3.7H_2O$. Asymmetric hydroxylation of **130** was achieved using KHMDS as a base and **131** as the reagent to furnish hydroxyl compound **132** in 84% yield. Finally the debenzylation was successfully carried out by hydrogenation using $Pd(OAc)_2$/C to provide **133** in 77% yield and 95% ee. Thus starting from commercially available pyridone, synthesis of optically active DE synthon was accomplished in few steps though the problem of regioselective addition of the ketene silyl acetal remained unresolved.

Yao's approach[45]: (*Org. Lett*. **2007**, *9*, 2003)

Very recently, Yao and coworkers disclosed very short and an elegant synthesis of CPT utilizing domino reaction and mild reagents starting with chloro pyridine **134** (scheme 15).



Scheme 15. *Reagents and conditions: (a) $PdCl_2(CH_2Cl_2)$dppf (2 mol%), CO (120 psig), Et_3N, MeOH, 97%. (b) TMSCl, NaI, CH_3CN, H_2O (cat.), 5h, 96%. (c) propargyl bromide, K_2CO_3, LiBr, Bu_4NBr, H_2O (cat.), toluene, 70%. (d) LiOH, THF-H_2O (3:1), 94%. (e) $(COCl)_2$, aniline, CH_2Cl_2, rt, 96%. (f) Ph_3PO (3.0 equiv), Tf_2O (1.5 equiv), 0 ^oC-rt, 96%. (g) $K_2OsO_2(OH)_4$ (cat.), $(DHQD)_2$-PYR (cat.), $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, t-BuOH-H_2O (1:1), 0 ^oC. (h) I_2, $CaCO_3$, CH_3OH-H_2O (2:1), 40 ^oC, 83% (two steps), 95% ee.*

The carbonylation on **134** was smoothly accomplished employing $PdCl_2(CH_2Cl_2)$dppf and Et_3N in methanol under the CO atmosphere at 90 ^oC to furnish methyl ester **135** in excellent yield. Selective *O*-demethylation of **135** using TMSI in CH_3CN afforded pyridone **136** in 96% yield. *N*-Propargylation of **136** was accomplished with propargyl bromide and K_2CO_3 using PTC and LiBr in toluene resulted in the formation of *N*-alkylated pyridone **137** in 70% yield. The basic hydrolysis of ester **137** afforded corresponding acid and subsequently the resultant acid was converted into its amide **138** in 90% yield via acid chloride. The intramolecular hetero-Diels-Alder reaction was successfully carried out by treating with bis(triphenyl)oxodiphosponium trifluromethanesulfonate at rt resulted in the formation of quinoline enol ether **139** in excellent yield. Finally the Sharpless asymmetric dihydroxylation followed by oxidation was accomplished furnished the (+) **1** in 83% yield and 95% ee.

1.1.8 References

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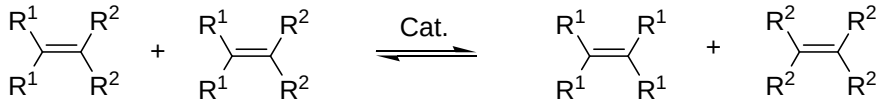
Chapter 1, Section II

General account on metathesis

1.2.1 Introduction

The carbon-carbon double bond formation is a very important protocol in synthetic organic chemistry. Till date a wide variety of methods have been reported for C=C formation involving olefin metathesis. Recently olefin metathesis has become a very powerful tool for the C=C formation within the same molecule or different molecules employing various catalysts developed by researchers.

The word metathesis is derived from the Greek words *Meta* (change) and *thesis* (position). Metathesis is the exchange of parts of two substances. In the reaction, AB + CD → AC + BD, B has changed position with C. An olefin metathesis reaction is shown in Scheme 1. Through carbene (alkylidene) exchange between the two starting olefins two new olefins have been formed.



Scheme 1.

Catalyzed metathesis was discovered in the industry following observations in the 1950's of the polymerization of ethylene by Ziegler (Nobel Prize in Chemistry 1963). In a series of patents novel processes were reported; but their mechanisms were not understood. One of the reports was filed in 1957 by Eleuterio at Du Pont. It described the formation of unsaturated polymers. Such a polymer was obtained from the highly-strained starting material norbornene when it was added to molybdenum oxide on alumina combined with lithium aluminium hydride.[1a] In the same year another patent application claimed an additional and seemingly novel transformation disproportionation of olefins as evidenced by the conversion of propene into ethene and butene upon treatment with a mixture of triisobutylaluminum and molybdenum oxide on alumina.[1b, 1c]

In 1966 Natta (Nobel Prize in Chemistry 1963) and co-workers showed that combinations of tungsten hexachloride with either triethylaluminum or diethylaluminum chloride polymerize cycloheptene, cyclooctene and cyclododecene.[2] The following year Calderon and coworkers reported their extension of these findings to other cycloolefins using a mixture of tungsten hexachloride and ethylaluminum chloride as initiator.[3a,3b] Calderon suggested that the polymerization of cyclic alkenes to polyalkenemers and the disproportionation of acyclic alkenes are the same type of reaction and named the reaction

olefin metathesis.[3d] Their results drew the attention of other researchers into organic and organometallic reactions to the potential of this novel reaction. However, the mechanism underlying metathesis remained a mystery.

1.2.2 Catalysts:

The numerous catalysts were developed by Tebbe, Schrock and Grubbs (figure 1) for different kinds of metathesis reactions, which are tolerant to different functional groups and which is wide range in chemical area and their uses are described.

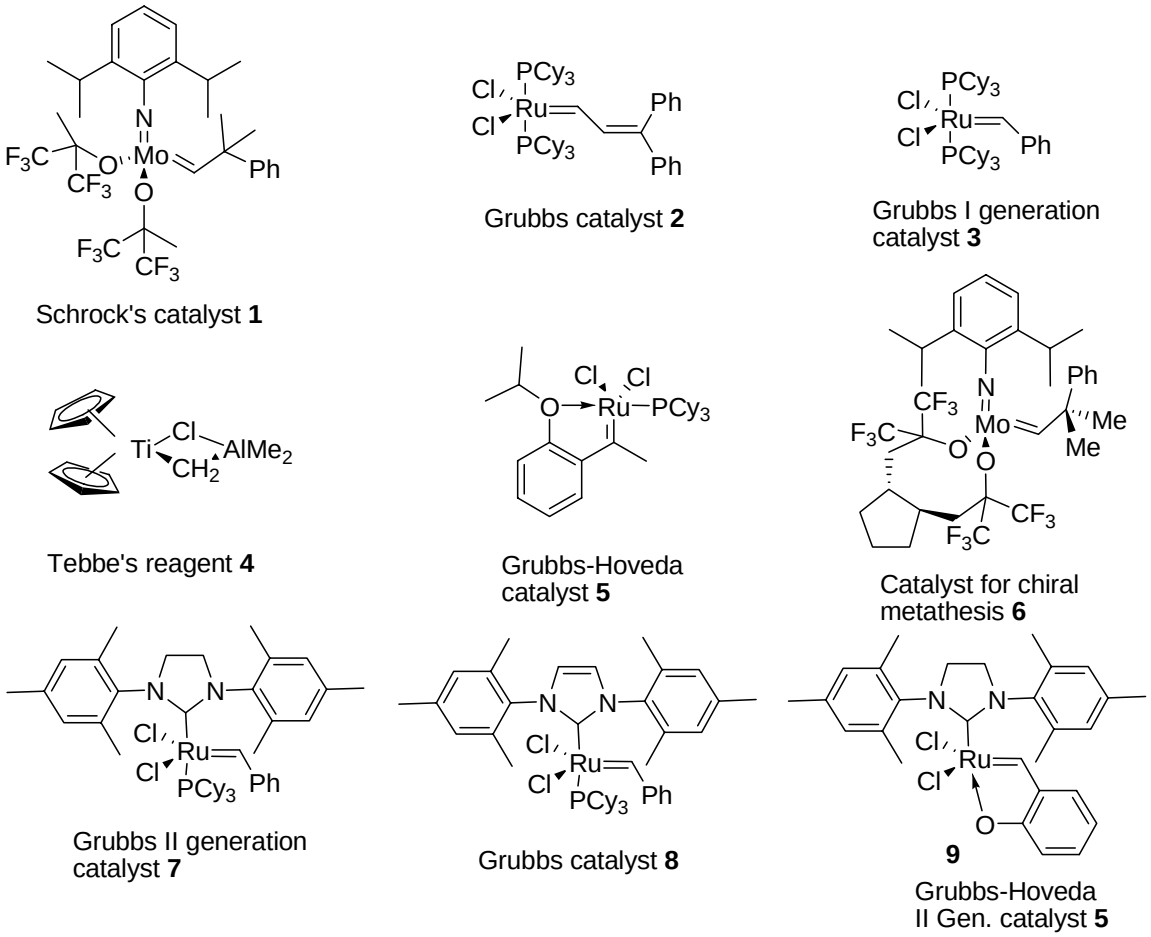
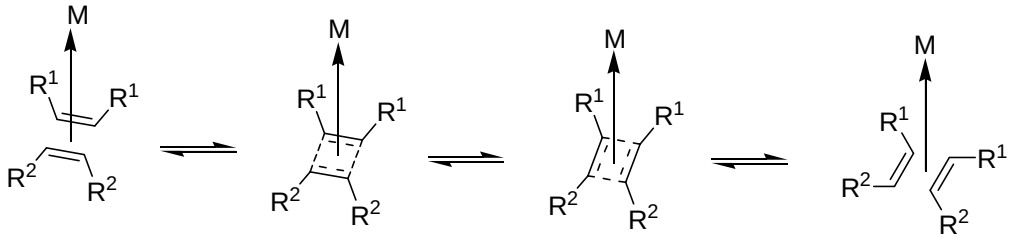


Figure 1.

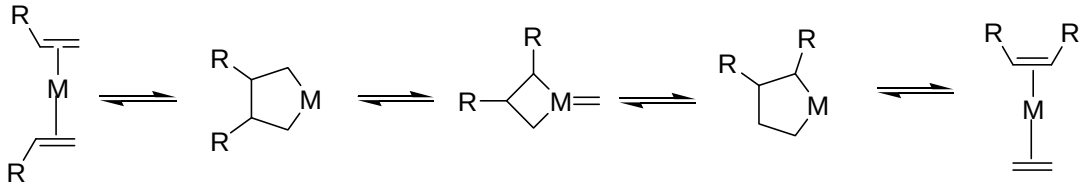
1.2.3 Mechanisms:

Several mechanistic hypotheses were in existence during this early period of olefin metathesis exploration. At first it was questioned whether olefin metathesis exchanged alkyl or alkylidene groups. Experiments by Calderon and by Mol using isotopically labelled alkenes demonstrated that the groups interchanged in olefin metathesis were alkylidenes.[3a-c] But the mechanism by which interchange occurred and the role played by the metal species remained mere guesswork.

Among several ideas about the mechanism circulating at the time to explain alkylidene exchange were the metal-coordinated cyclobutane model of Calderon[3d] and later the metal or alkyl acyclopentane model of Grubbs'.[8a] The first of these models tended to be depicted in different ways by different authors (Scheme 2 and 3).



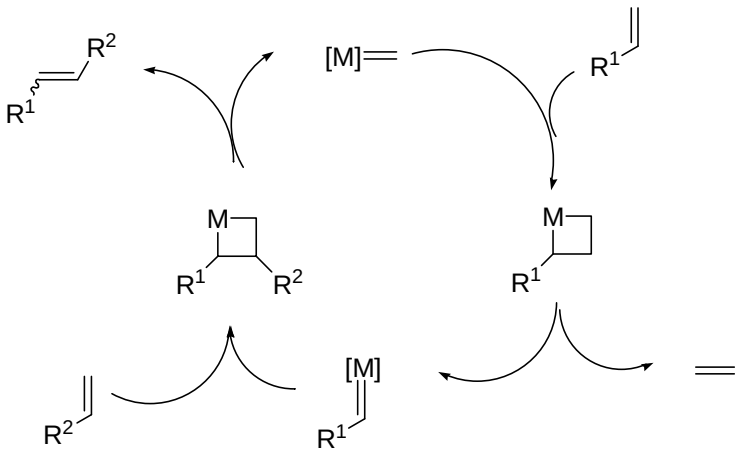
Scheme 2.



Scheme 3.

However, it was not until Chauvin at the Institut Français du Pétrole, in his efforts to understand the metathesis mechanism, combined reports by Fischer (Nobel Prize in Chemistry 1973) on the synthesis of a tungsten-carbene complex, Natta on the polymerization of cyclopentene through ring-opening catalyzed with a mixture of WCl_6 and $AlEt_3$ and Banks and Bailey on the formation of ethylene and 2-butene from propene catalyzed with $W(CO)_6$ on alumina, that a viable mechanism was presented. In 1971 Chauvin and his student Hérisson published their metathesis mechanism as illustrated in modified form in Scheme 4.

In Scheme 4 the Chauvin catalytic cycle is shown, the metal methylene (metal alkylidene) reacts with the olefin, forming a metallocyclobutane intermediate. This intermediate then cleaves into ethylene and a new metal alkylidene, although the metathesis reaction is reversible but removal of ethylene molecule is the driving force for the completion of reaction. The generated metal alkylidene reacts with a new substrate alkene molecule to give another metallocyclobutane intermediate. After decomposition in the forward direction this intermediate yields the product internal olefin (mixture of *E* & *Z* isomers) and regenerate metal methylene which can be used for next catalytic cycle. Thus each step in the catalytic cycle involves exchange of alkylidenes – metathesis.



Scheme 4.

In this way Chauvin and co-workers also presented experimental support for the mechanism which could not be explained by the other proposed mechanisms.[4] The mechanism has also experimental support by Grubbs', Katz, Schrock and others and is now generally accepted as the mechanism for metathesis.

Many researchers have contributed to the ensuing development of catalysts, and important early contributions were made by Lappert on rhodium (I) complexes as catalysts[5a], Casey on metathesis with tungsten complexes[5b] and others. Here, however, the focus is on the breakthroughs made by Schrock and by Grubbs' in the development of the metal-alkylidene complexes that have had such a dramatic influence on modern organic synthesis.

Many researchers foresaw the great synthetic potential of metathesis. But applications to organic chemistry were generally complicated by the sensitivity of the traditional catalysts to air and moisture, by side-reactions and by relatively short lifetimes. Progress required identifiable, relatively stable compounds that would behave as long-lived catalysts, whose reactivity could even be "tuned" for the desired task.

Schrock at Du Pont in early 1970s tried to synthesize [$Ta(CH_2CMe_3)_5$], which was expected to be a stable compound. However, what he isolated instead was the first stable metalalkylidene complex, [$Ta(CH_2CMe_3)_3(=CHCMe_3)$], which has the high oxidation state of V.[6a]

Schrock then synthesized other tantalum-alkylidene complexes, including the first methylene complex. These complexes were characterized using X-ray crystallography and

NMR. He also found that metallocyclobutanes were formed. But metathesis had to wait since none of these alkylidene complexes catalyzed the metathesis of olefins.[6b]

In 1980, Schrock and his group at MIT reported a tantalum-alkylidene complex $[Ta(=CHC(CH_3)_3)Cl(PMe_3)(O\text{-}C(CH_3)_3)_2]$, which catalyzed the metathesis of *cis*-2-pentene. The reason that this complex worked, whereas the other members of the family of the niobium and tantalum-alkylidene complexes failed to do so, was the presence of alkoxide ligands.[6c,d]

As indicated above, molybdenum and tungsten were the most active metals in alkene metathesis. Schrock and his group increased their efforts to find stable molecular alkylidene and alkylidyne complexes of these metals. The search eventually produced a whole family of molybdenum- and tungsten-alkylidene complexes of the general formula other chemists including Osborn in Strasbourg and Basset in Lyon has also made important contributions reporting tungsten complexes that are active as olefin metathesis catalysts.

The advantage of Schrock's catalysts, of which the most efficient were reported in 1990, was that besides being extremely active, they are molecular (without additives). One has been made commercially available. Schrock has also developed chiral catalyst for asymmetrically catalyzed metathesis together with Hoveyda.

Grubbs' had early been interested in the metathesis reaction, as indicated by his mechanistic proposal of a metallocyclopentane intermediate.[8a] After some exploration that started in the mid 1980`s of ill-defined catalysts that were prepared from late metal salts Grubbs' and his co-workers found that ruthenium trichloride polymerized olefins even in water.[8b] Actually ruthenium chloride had already been used by Natta as a catalyst for polymerisation of cyclobutene by ring opening.[7] Grubbs' assumed that this catalyst system also operated by a metal carbene mechanism. Their results initiated the development of well-defined catalysts that can be used with standard organic techniques and tolerate a broad range of functional groups.

As a result of their development work Grubbs' and co-workers 1992 reported their first molecularly well-defined ruthenium-carbene complex that was not only active towards polymerization of norbornene but was also stable in presence of protic solvents.[8c] The complex was of the vinylidene type $[RuCl_2(PR_3)(=CH\text{-}CH=CPh_2)]$ with R=Ph. To increase the reactivity of the catalyst the phenyl groups were exchanged for cyclohexyl groups (R=Cy).[8d,e] This change produced the desired reactivity and the catalyst polymerized unstrained olefins and induced reactions with acyclic olefins. It promoted many of the

same reactions as the Schrock's molybdenum-based alkylidene complexes but had greater functional group tolerance and could be handled using standard organic techniques.[8f] Noels' group also reported on Ru-catalyzed ROMP of cycloolefins in 1992.

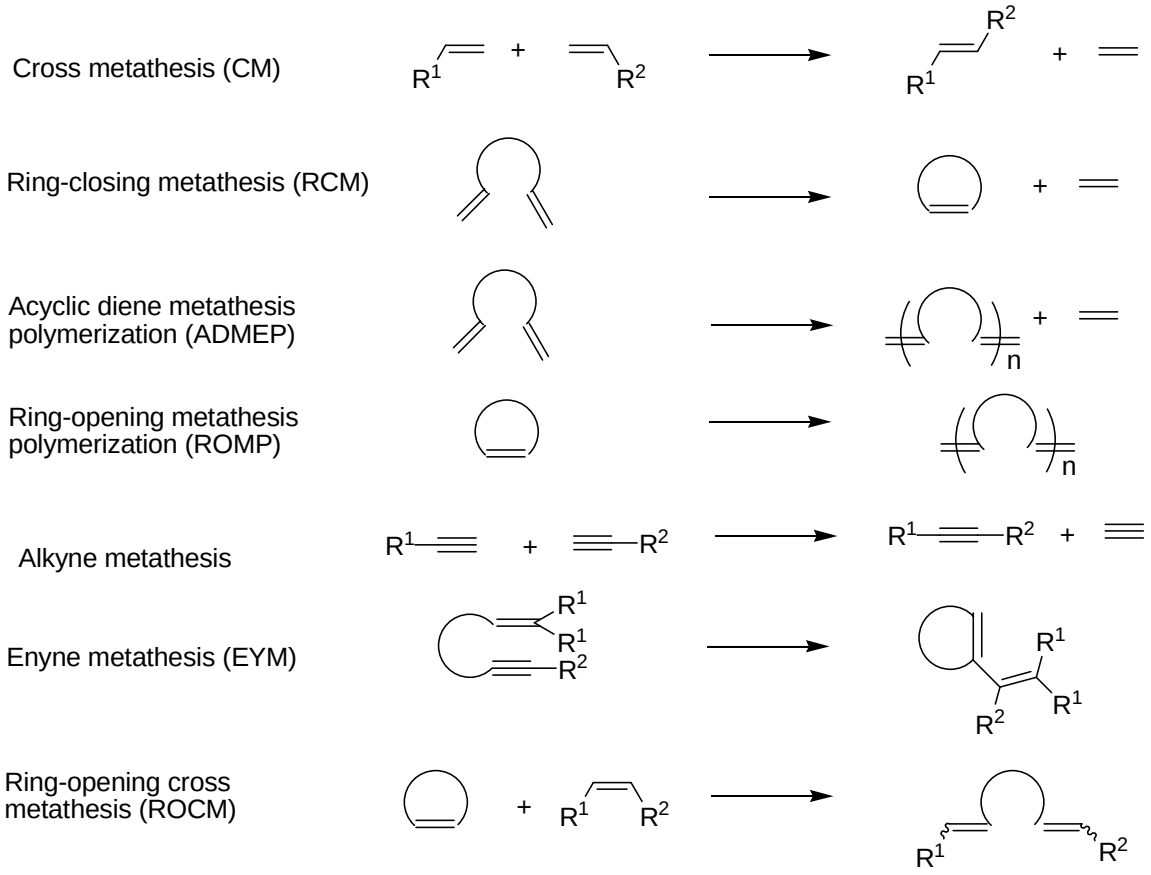
As the need for larger quantities of catalyst grew, more efficient methods for its synthesis were required. A practical route to ruthenium benzylidene complexes was developed. In 1995 Grubbs reported new molecularly-well-defined catalysts $[Ru(=CHPh)Cl_2(PR_3)_2]$, R = Ph or Cy (cyclohexyl).[8g,h] These structures are closely related to the vinylidene ones. The compound with R = Cy $[Ru(=CHPh)Cl_2(PCy_3)_2]$ has been commercialized and is known as the first-generation Grubbs' catalyst (Scheme 2). This compound is still the metathesis catalyst most used by organic chemists, because of its stability in air and compatibility with a large variety of groups.

In a number of difficult ring-closing reactions, the lifetime of the catalyst was insufficient to give high yields of products with reasonable catalyst loadings. Apparently catalysts with improved properties were needed. Detailed mechanistic studies led Grubbs' group to conclude that the reaction first involved the dissociation of one of the phosphines to generate the reactive ruthenium intermediate. To accelerate the dissociation Grubbs' replaced one of the phosphines with a cyclic bis-amino carbene ligand. Herrmann had earlier synthesized ruthenium complexes with two such carbene ligands, but the catalytic activity of such compounds was modest. In Grubbs'catalysts containing only one such ligand the dissociation rate of the remaining phosphine is increased, increasing metathesis activity. Similar results were published 1999 almost simultaneously by Nolan and by Fürstner and Herrmann in 1999. The new, more reactive, catalysts are called second generation Grubbs`catalysts. $[RuCl_2\{C(N(mesityl)CH_2)_2\}(PCy_3)(=CHPh)]$ is currently the most used catalyst for efficient cross-metathesis reactions.[8i] This new ruthenium catalyst, with its greater thermal stability is now also available commercially.

Grubbs' success has inspired also other researchers Hoveyda, Hofmann, Grela, Blechert and others to improve ruthenium-based catalysts for new tasks.

The Grubbs' and Schrock's catalysts offer synthetic chemists novel opportunities. Their widespread use in organic chemistry is due to their tolerance of a large variety of functional groups, combined with their efficiency and, for Grubbs' catalysts, their ease of handling in air.[9]

1.2.4 Types of metathesis:



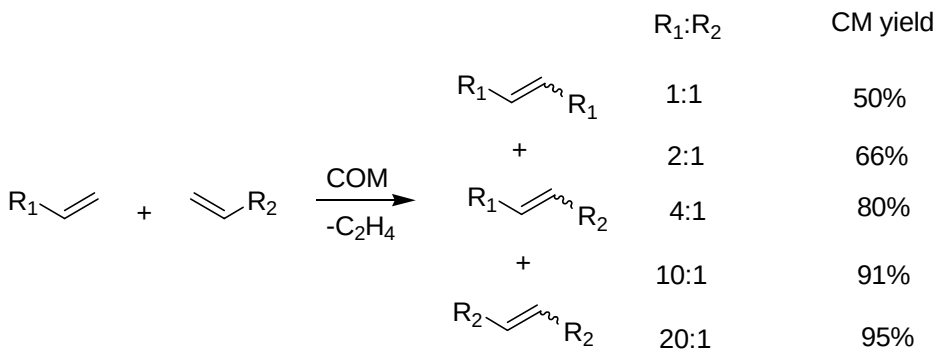
Scheme 5.

Scheme 5 shows different types of metathesis reactions.

Cross metathesis:

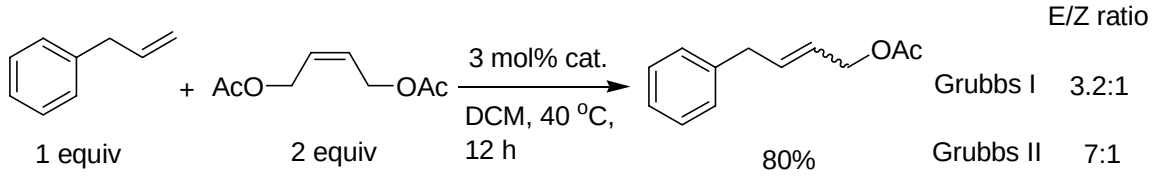
Cross olefin metathesis is best method for the C=C formation, which is best option to other C=C formation methods like palladium-catalyzed methods (Suzuki coupling, Stille coupling and Heck coupling) as well as non-metal-mediated processes like Wittig reaction, Peterson olefination and various other methods. The major limitation in CM is to control the elements of selectivity viz. cross-coupling product selectivity, olefin stereo-selectivity and olefin chemo-selectivity in complex organic molecules. The degree of selectivity depends on the nature of olefin, catalysts and effect of secondary metathesis.

The degree of selectivity depends on the nature of olefin, catalysts and effect of secondary metathesis (the homodimeric products remain metathesis active and are consumed by secondary metathesis pathway into desired CM product).



Scheme 6. *Statistical distribution of CM products.*

The CM reaction between allylbenzene and an allylic alcohol equivalent affords the CM product in 80% isolated yield (scheme 7), the observed yields are consistent with those predicted statistically, i.e. 4 equivalent of allyl acetate are used in reaction and CM product was obtained in 80% yield (scheme 6).



Scheme 7. *Olefin isomerization by secondary metathesis processes.*

A comprehensive product selectivity model developed by the Caltech group which is valuable for the prediction of both selective and non-selective CM reaction, which can also predicts the various possible alkylidene intermediates and the numerous primary and secondary metathesis pathway involved in CM (fig. 2 and table 1).

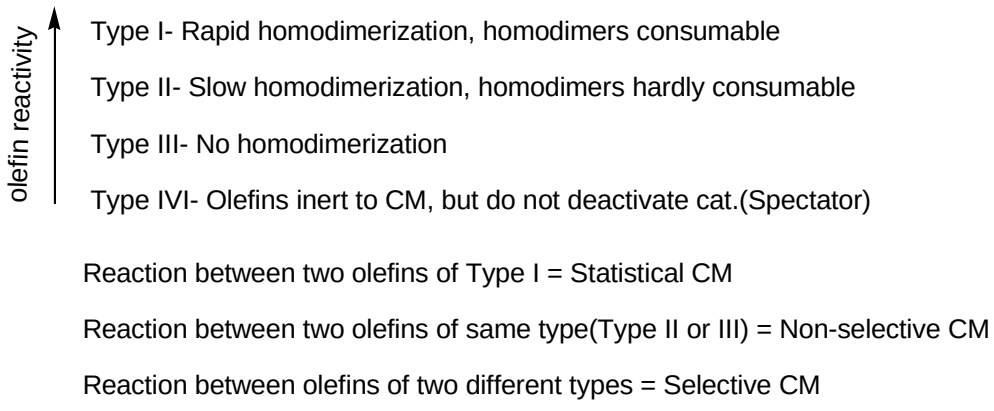


Figure 2. *Olefin categorization and rules for selective CM.*

Table 1. Olefin categories for selective CM.

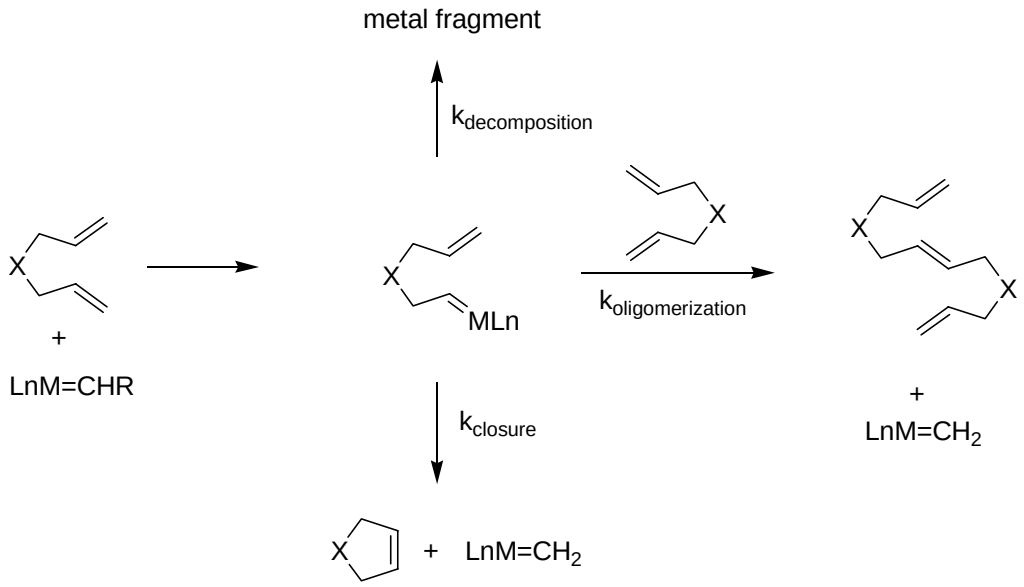
Olefin type	Schrock's cat.**1**	Grubbs I gen. cat.**3**	Grubbs II gen. cat. **7**
Type 1 (fast homodimerization)	Terminal olefins Allylsilanes	Terminal olefin Allylsilanes, 1^o alcohols, ethers, esters, Allylboronate esters	α-olefins, 1^o allylic alcohols, esters, Allylboronate esters, Allylic halides, styrenes (no large ortho substit.), Allylphosponates, allylsilanes, phosphine oxides, sulfides, protected amines.
Type 2 (slow homodimerization)	Styrene, Allylstannanes.	Styrene, 2^o allylic alcohols, vinyl dioxolanes, vinyl boronates	Styrenes (large ortho substit.), Acrylate, acrylamides, acrylic acids, acrolein, vinyl ketones, unprotected 3^o allylic alcohols, vinyl epoxides, 2^o allylic alcohols, Perfluorinated alkane olefins.
Type 3 (no homodimerization)	Tertiary allylamines, Acrylonitrile	Vinylsiloxanes	1,1-Disubstituted, non-bulky trisub.olefins, Vinylphosphonates, phenylvinyl sulfone, 4^o allylic carbons (all alkyl substituents), 3^o allylic alcohols (protected)

Type 4 (spectators to CM)	1,1-disubstituted olefins	1,1-disubstituted olefins, disubstituted α,β-unsaturated carbonyls, 4^{o} allylic carbon containing olefins, Perfluorinated alkane olefins, 3^{o} allylamines (protected)	Vinyl nitro olefins, Trisubstituted allylic alcohols (protected)

Ring-closing metathesis:

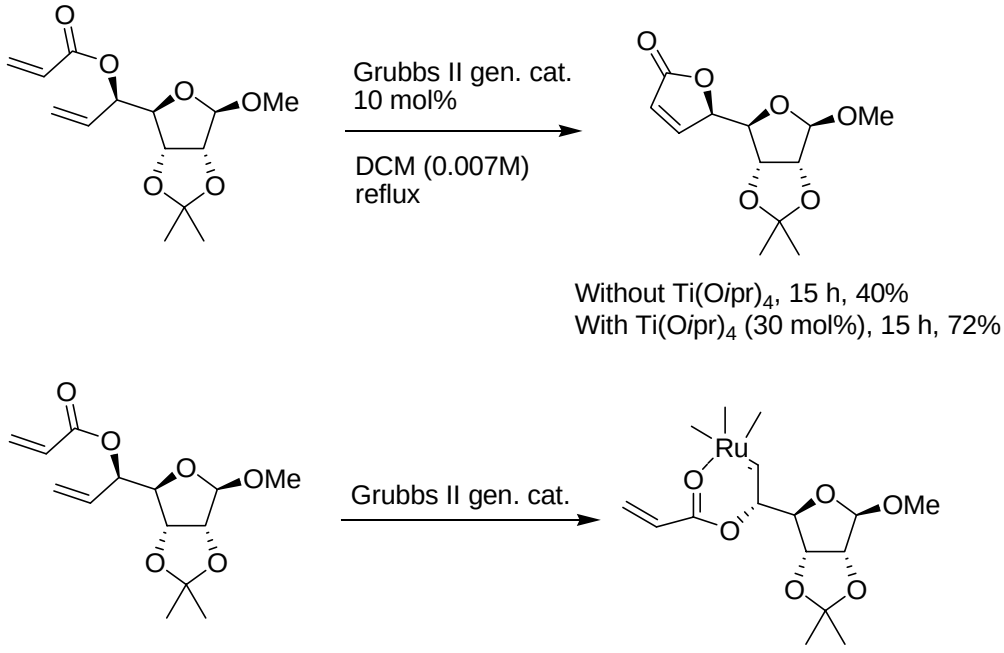
There are several key factors to the success of RCM reaction (a) The availability of efficient catalysts having sufficiently well-defined electronic and coordinative unsaturation to allow convenient use and higher turnover performance (b) the exceptional tolerance of these initiators to diverse functional groups, including the capacity of the Lewis-acidic metal-carbene centre to engage in intramolecular coordination to polar substituents in order to maximize proper orientation of the reacting centers (c) one's ability to profit from the gain in entropy that is the driving force for RCM due to the generation of ethylene as a volatile byproduct.

The key competing reaction to RCM is the oligomerization (scheme 8) the rate of RCM reaction decreases due to ring size and conformational effect. The competing reaction viz. oligomerization interfere to the desired RCM reaction, the rate of oligomerization is nearly constant for specific olefin substitution, can be decreased by lowering the concentration of the diene, using slow addition and using higher temperature but at higher temperature the rate of decomposition of catalyst is more hence closure of larger rings usually requires more catalyst.



Scheme 8. *Competing reactions between RCM and oligomerization.*

Generally the diene substrates bearing γ,δ- or β,γ-unsaturated carbonyl moiety do not undergo RCM at all.



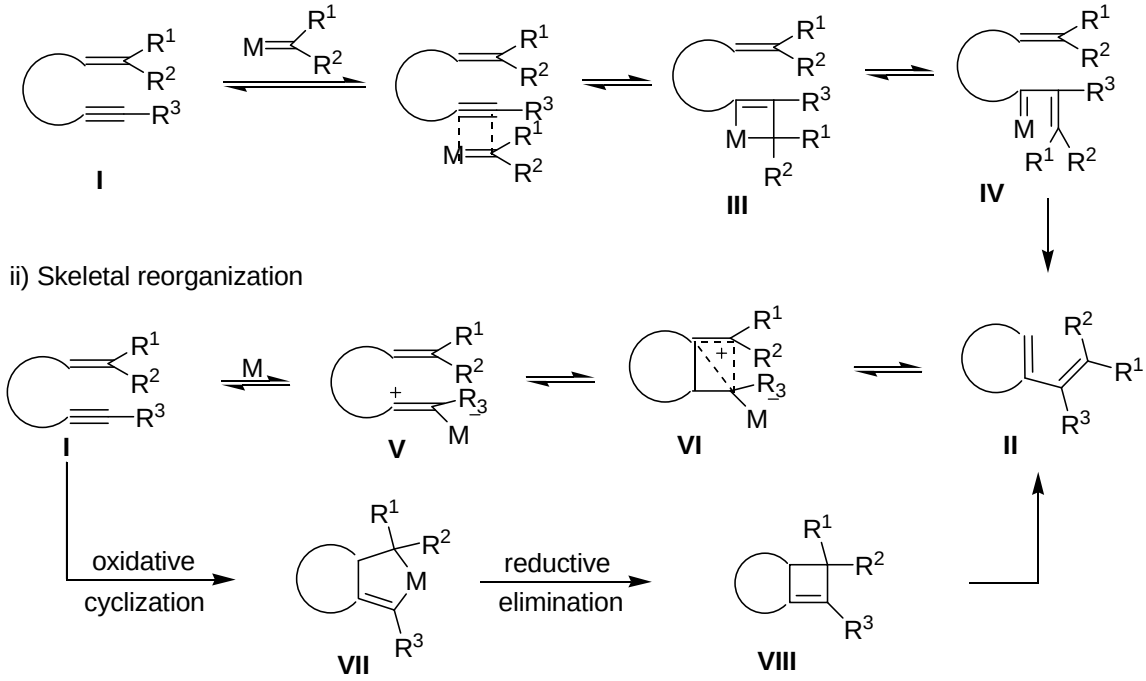
Scheme 9.

This is mainly attributed to the formation of a stable and thus inactive 6- or 7-membered metal-chelation complex that blocks the catalytic cycle. The chelation can be prevented by the addition of catalytic amount of certain Lewis acid such as Ti(O*i*Pr)$_4$ to the reaction mixture and therefore to proceed with the RCM of carbonyl substrate (scheme 9).

Enyne metathesis:

Enyne metathesis is a unique and interesting reaction between alkene and alkyne part in this reaction double and triple bonds are cleaved and double bond is simultaneously formed, as a result, the alkylidene part of the double bond are introduced onto the respective alkyne carbons to give a diene moiety and triple bond is converted into a single bond. Overall this reaction is just rearrangement or skeletal reorganization (100% atom economy). Enyne metathesis was first discovered by Katz[10] in 1985 using Fischer tungsten-carbene complex and until now there are numerous reports are available

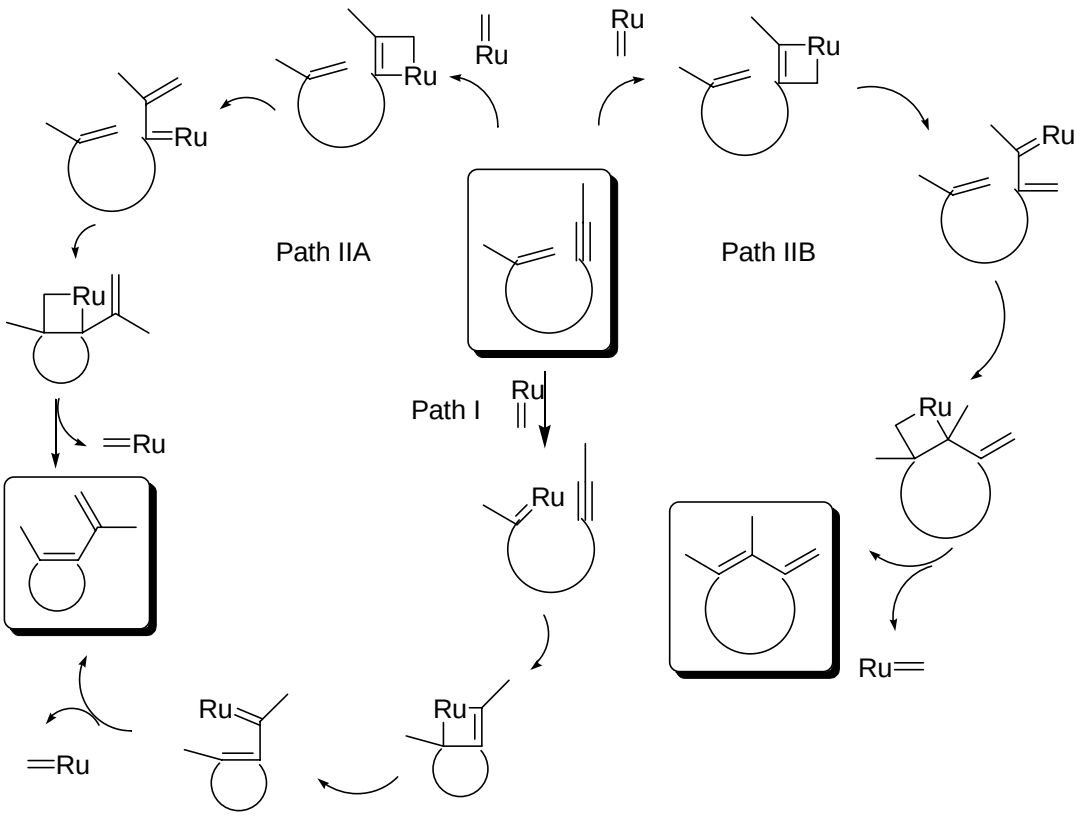
i) Transition metal-carbene complex-catalyzed reaction



Scheme 10. *Enyne metathesis.*

Two mechanisms of enyne metathesis were proposed one is transition metal-carbene complex-mediated reaction (e.g. W, Mo, Cr & Ru), it proceeds by a [2+2] cycloaddition between triple bond of substrate and carbene complex of catalyst to give metallacyclobutene III, ring opening of III to give carbene complex IV, which reacts with olefin intramolecularly to give cyclized diene II and second mechanism is skeletal reorganization catalyzed by transition metal *viz*. Pd, Pt, Ir, Ru, Ga etc. but second mechanism is not clear yet, presumably the transition metal coordinates to the triple bond to give V and then alkene carbon reacts with alkyne part to form VI then it would be converted into II. Mori[11] reported chromium-catalyzed enyne metathesis and Trost developed enyne metathesis using Pd and Pt catalyst. [12] This reaction proceeds via

oxidative cyclization of enyne to form VII and reductive elimination of VII to form cyclobutene VIII, after ring opening gives II (scheme 10).



Scheme 11.

Possible reaction course for formation of two metathesis products is outlined in scheme 11. Thus, finally their continuous efforts on the study of metathesis became fruitful, widely accepted and practiced by various scientists across the globe and they received the Nobel Prize in chemistry in 2005, Richard Schrock and Robert Grubbs for the development and application of their catalysts and Yves Chauvin for his mechanistic study.

1.2.6 Reference

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Chapter 1, Section III

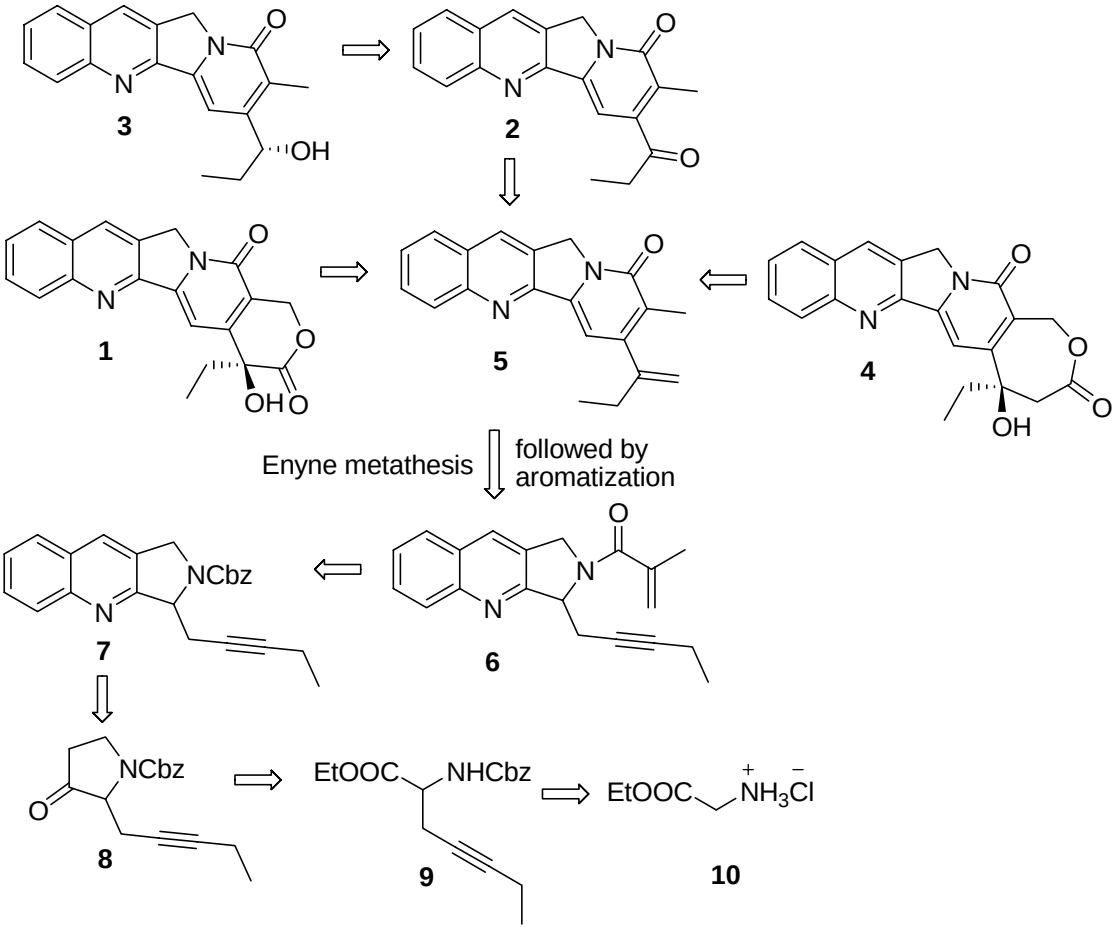
Studies towards synthesis of camptothecin and its analogues employing tandem ethylene cross enyne metathesis and RCM

1.3.1 Introduction:

As a part of an ongoing programme on synthesis of bioactive natural products specially the synthesis of camptothecin and its analogues[1-5] as well as implementation of metathesis reaction,[6] this group has already developed the synthetic routes particularly for the construction of pyridone (D-ring) of camptothecins. Considering the pharmaceutical importance and traces amount of availability from natural sources of CPT **1,** till date numerous imaginative syntheses have been disclosed by different research groups. This section describes the conceptually novel strategy *viz.* intramolecular enyne metathesis for the construction of D-ring of camptothecin and its analogues.

1.3.2 Present work:

According to retrosynthetic analysis depicted in scheme 1 (+)-camptothecin **1** and its analogues *viz*. mappicine ketone **2**, mappicine **3** and homocamptothecin **4** could be accessed from a common tetracyclic intermediate **5** by simple transformation.



Scheme 1. *Retrosynthetic analysis.*

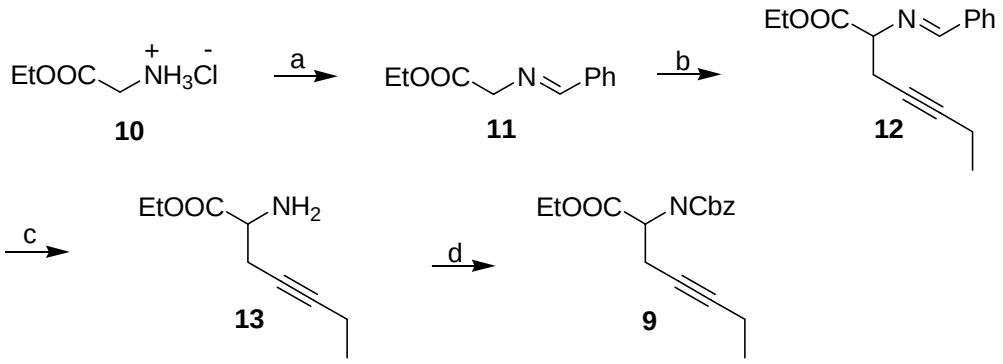
Teracyclic intermediate **5** would be realized from alkyne compound **6** by intramolecular enyne metathesis and aromatization. The alkyne compound **6** could be obtained from tricyclic carbamate **7** by Cbz deprotection followed by condensation with acryloyl chloride, the carbamate **7** in turn could be accessed from keto compound **8** by Friedlander condensation with suitable Schiff's base and the keto compound **8** could be synthesized from carbamate **9** by tandem Michael addition followed by Dieckmann condensation and decarboxylation. The carbamate **9** in turn could be synthesized from cheap and commercially available ethyl ester of glycine hydrochloride **10** by simple transformation described in scheme 2.

1.3.3 Results and discussion:

According to the retrosynthetic analysis outlined in scheme 1 the synthesis commenced from readily available ethyl ester of glycine hydrochloride **10,** which was converted into corresponding Schiff's base **11** in 98% yield using benzaldehyde and triethyl amine as the base and molecular sieves as water scavenger. Alkylation of O'Donnell's Schiff's base **11** with 1-bromo-2-pentyne[7] under phase transfer condition ($TBAHSO_4$ as a phase transfer catalyst) using 10% aqueous NaOH furnished the alkylated Schiff's base **12** in excellent yield. Compound **12** was hydrolyzed into amine **13** using 10% HCl and subsequently the liberated amine **13** was subjected to treatment with CbzCl using K_2CO_3 as the base in anhydrous methylene chloride to furnish carbamate **9** in 96% yield.

The structure of **9** was confirmed by spectral methods. IR spectrum of **9** displayed the absorption bands at 1725 cm^{-1} and 1653 cm^{-1} indicated the presence of ester and carbamate functional groups respectively. ^1H NMR spectrum of **9** revealed a triplet and quartet at δ 1.09 & δ 2.12 (J = 7.5 Hz) integrating for three and two protons respectively, doublet of doublet at δ 2.70 (J = 8.7 & 4.5 Hz) integrating for two protons, indicated the incorporation of propargyl group, triplet and quartet at δ 1.29 & δ 4.23 (J = 7.1 Hz) integrating for three and two protons respectively suggested the presence of ethyl ester functionality. A multiplet at δ 4.40-4.49 integrated for one protons, doublet at δ 5.55 (J = 8.2 Hz) integrated for one proton was assigned to (-N<u>H</u>Cbz), singlet at δ 5.12 integrating for two benzylic protons and singlet at δ 7.35 integrated for five aromatic protons indicated the presence of benzyl group. ^{13}C NMR spectrum of **9** displayed fourteen signals and DEPT spectrum of **9** showed four methylene carbons the structure of **9** was confirmed by

mass spectrum where it showed *m/z* peaks at 304 and 321 $(M + H)^+$ along with $(M + NH_4)^+$ respectively and finally the structure of **9** was ascertained by its elemental analysis also.



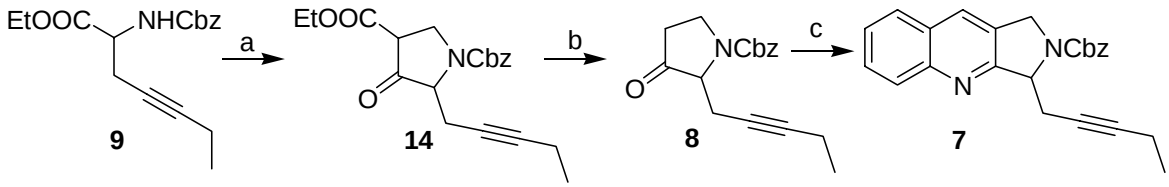
Scheme 2. *Reagents and conditions: (a) Et_3N (1.2 equiv), PhCHO (0.9 equiv), MS, dry CH_2Cl_2, 0 ^oC, 1 h, 98%. (b) 10% NaOH (1.2 equiv), 1-bromo-2-pentyne (1.2 equiv), $TBAHSO_4$ (0.1 equiv), CH_2Cl_2, rt 2 h, 96%. (c) 10% HCl (1.2 equiv), rt, 0.5 h, 92%. (d) K_2CO_3 (1.2 equiv), benzyl chloroformate (1.1 equiv), anhydrous CH_2Cl_2, 0 ^oC, 1h, 91%.*

Carbamate **9** underwent tandem Michael addition followed by Dieckmann condensation with ethyl acrylate using NaH as the base furnished the *β*-ketoester **14** in good yield.[8] The ^1H NMR, ^{13} NMR and DEPT spectra of **14** exhibited the mixture of isomers (tautomers and rotamers). Further the structure of **14** was confirmed by mass spectrum which showed the *m/z* peaks at 358 and 375 which correspond to $(M + H)^+$ and $(M + Na)^+$ respectively. The *β*-ketoester **14** was decarboxylated under Krapcho's method using NaCl in (DMSO-H_2O, 3:1) at 120-130 ^oC for 6-8 hours delivered the keto compound **8** in 78% yield.[9]

The formation of **8** was confirmed by spectral data. IR spectrum of **8** showed the disappearance of the absorption band corresponding to ester group while newly appeared absorption band at 1717 cm^{-1} indicated the presence of ketone functionality. ^1H NMR spectrum of **8** showed the disappearance of signals corresponding to ester functionality while two triplets appeared at δ 2.62 and δ 3.97 (J = 8.1 Hz) integrating for two protons each respectively indicated the conversion of **14** to **8**. ^{13}C NMR along with DEPT spectra of **8** revealed the mixture of rotamers and finally the structure of **8** was confirmed by mass spectral and elemental analysis, the *m/z* peak at 286, 303 and 318 corresponding to $(M + H)^+$ and $(M + NH_4)^+$ and $(M + Na)^+$ respectively were observed in mass spectrum and in elemental analysis the experimental values were in good agreement with the theoretical

values. The keto compound **8** underwent Friedlander condensation with Schiffs base *N*-(o-amino)*p*-toluidine and catalytic PTSA in toluene at reflux temperature for 12 hours furnished tricyclic carbamate **7** in very good yield.

The structure of compound **7** was confirmed by spectral methods. ^{1}H NMR spectrum of **7** displayed absence of triplet corresponding to α-methylene protons of ketone while the new signals appeared in aromatic region at δ 7.54-8.11 integrated for five aromatic protons. ^{13}C NMR spectrum of **7** showed the new nine signals that appeared in aromatic region. DEPT spectrum of **7** displayed the four methylene carbons and showed the mixture of rotamers, the *m/z* peaks at 371 and 393 were observed in mass spectrum of **7** corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively. Finally the structure of **7** was ascertained by its elemental analysis as well.

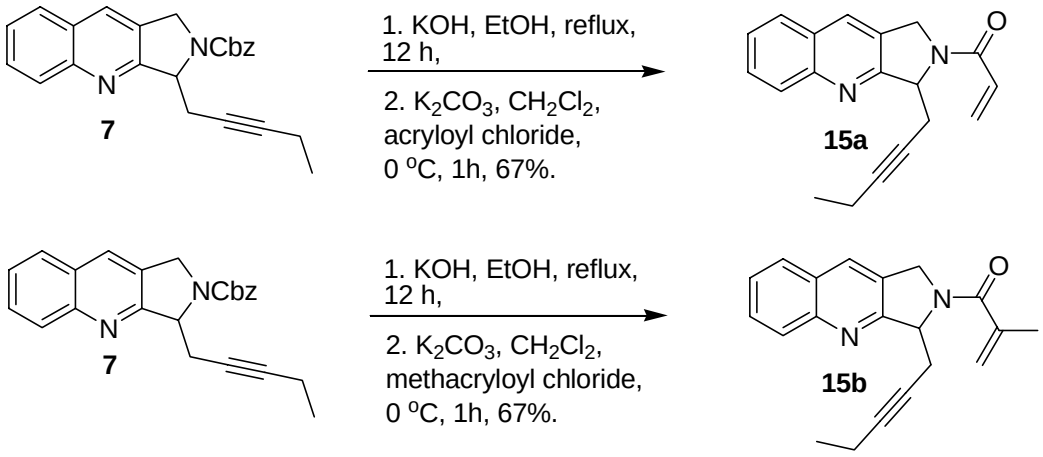


Scheme 3. *Reagents and conditions: (a) NaH (1.2 equiv), ethyl acrylate (1.2 equiv), C_6H_6, rt 1h, refluxed 2-3 h, 72%. (b) NaCl (4.0 equiv), DMSO-H_2O (3:1), 120-130 ^{o}C, 6 h, 78%. (c) Schiff,s base (1.2 equiv), PTSA (cat), anhydrous toluene, reflux, 6 h 86%.*

The Cbz deprotection of compound **7** was carried out in ethanolic KOH at reflux temperature for 6 h to afford secondary amine[10] which subsequently was further condensed with acryloyl chloride using K_2CO_3 as the base, delivered the acrylamide **15a** in 67% yields. The conversion of **7** to **15a** was confirmed by spectral data. ^{1}H NMR spectrum of **15a** revealed the disappearance of signals corresponding to Cbz group while two new signals appeared in the olefinic region at δ 5.80-5.84 integrated for one proton and at δ 6.54-6.65 integrated for two protons. ^{13}C NMR along with DEPT spectra of **15a** revealed it to be a mixture of rotamers. Mass spectrum of **15a** displayed the *m/z* peaks at 291 $(M + H)^+$ and 313 $(M + NH_4)^+$ respectively. The structure of **15a** was confirmed by its elemental analysis also, which was found to be in good agreement with the calculated values.

Similarly methacrylamide **15b** was prepared in 72% yield employing identical reaction conditions for the formation of **15a** using methacryloyl chloride. Methacrylamide **15b** was characterized by spectral methods. ^{1}H NMR spectrum of **15b** displayed absence of signals

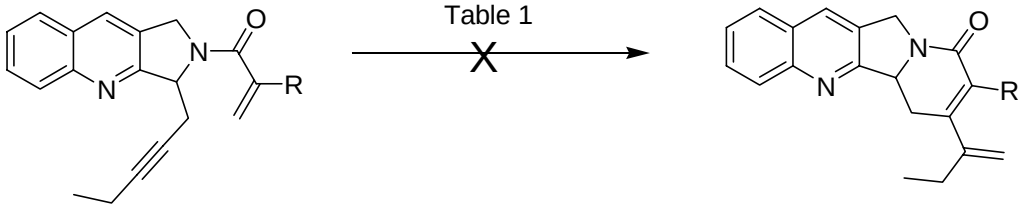
due to two benzylic protons and multiplet for five aromatic protons while a singlet appeared at δ 2.07 integrated for three protons due to vinylic methyl and two peak appeared at δ 5.36 and δ 5.46 integrated for two protons was assigned to olefinic protons. The spectral analysis of the product thus obtained indicated the conversion of **7** to **15b**. ^{13}C NMR along with DEPT spectra of **15b** exhibited it to be a mixture of rotamers. It was further confirmed by mass spectral and elemental analysis. The *m/z* peaks at 305 $(M + 1)^+$ and 327 $(M + Na)^+$ in mass spectrum confirmed the structure of **15b,** in an elemental analysis the experimental values were in good agreement with the theoretical values.



Scheme 4.

With acrylamide compounds **15a** and **15b** in hand, attention was focused towards the key step i.e. intramolecular enyne metathesis. Thus compounds **15a** and **15b** were subjected to intramolecular enyne metathesis reaction employing Grubbs' first and second generation catalysts under a variety of reaction conditions including various solvents, concentrations, mode of additions and in the presence of additives like $Ti(OiPr)_4$ as Lewis acid mentioned in table 1. Unfortunately the desired products **16a** and **16b** could not be obtained.[6] Trost *et al* have reported the enyne metathesis employing Pd and Pt catalyzed enyne cyclization.[11] Accordingly **15a** & **15b** were subjected to the intramolecular enyne metathesis under identical reaction conditions but the required intermediate could not be accessed. Mori and co-workers reported in a seminal report reported formation of 1,3-butadiene when alkyne was subjected to enyne metathesis under the ethylene atmosphere.[12] Even performing this reaction under ethylene atmosphere was not fruitful, probably this might be due to the

interference of the quinoline nitrogen, which had a detrimental effect on the success of the reaction.



15a R = H
15b R = Me

16a R = H
16b R = Me

Scheme 5.

Table 1

S. No.	Reagent	Solvent	Temperature	Time	Observation
1	Grubbs 1st Gen. cat. (10 mol %), 2 eq $Ti(OiPr)_4$	CH_2Cl_2	rt	24 h	SM recovered
2	Grubbs 1st Gen. cat. (10 mol %), 2 eq $Ti(OiPr)_4$	CH_2Cl_2	reflux	24 h	SM recovered
3	Grubbs 2nd Gen. cat. (10 mol %),	C_6H_6	reflux	24 h	SM recovered
4	Grubbs 2nd Gen. cat. (10 mol %), 2 eq $Ti(OiPr)_4$	C_6H_6	reflux	24 h	SM recovered
5	Grubbs 2nd Gen. cat. (10 mol %)	$PhCH_3$	80 ^oC	12 h	SM recovered
6	Grubbs 2nd Gen. cat. (10 mol %), 2 eq $Ti(OiPr)_4$	$PhCH_3$	80 ^oC	24 h	SM recovered
7	Grubbs 2nd Gen. cat. (10 mol %) ethylene atmosphere	$PhCH_3$	80 ^oC	12 h	SM recovered
8	$PtCl_2$ (10 mol %)	$PhCH_3$	80 ^oC	15 h	SM recovered

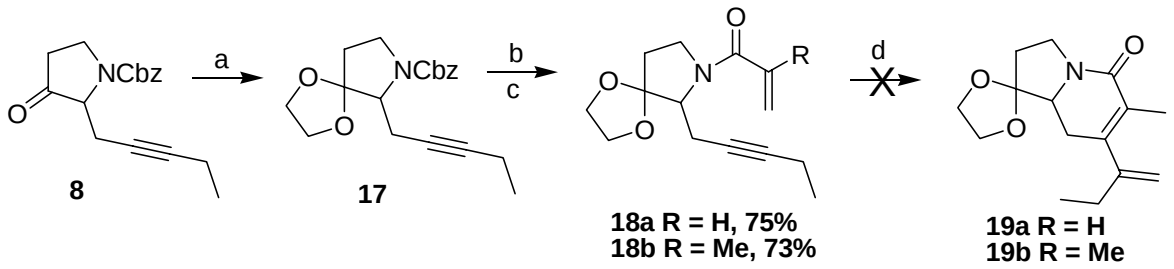
After the failure of intramolecular enyne metathesis on compound **15a** and **15b** under different reaction conditions mentioned in table 1, it was decided to carry out the same reaction on protected compound **17** to construct the CD-ring and lastly build the tetracyclic advanced intermediate **5** by Friedlander condensation with appropriate Schiff's base. Keeping this idea in mind the treatment of keto compound **8** with ethylene glycol using PTSA (cat.) in anhydrous benzene under azeotropic removal of water furnished the acetal **17** in an excellent yield (96%). The formation of **17** was confirmed by spectral study. IR spectrum of **17** revealed the disappearance of absorption band corresponded to ketone functional group. ^{1}H NMR spectrum of **17** displayed two singlets appeared at δ 3.96 & 3.97 that integrated for two protons each of which were assigned to methylene of the acetal group (-O-C$\underline{H_2}$-C$\underline{H_2}$-O-). ^{13}C NMR spectrum of **17** showed the appearance of new signals at δ 63.9, 64.6, 65.4, 66.5 due to rotamers. Lastly the structure was confirmed by mass spectral and elemental analysis. The mass spectrum of **17** showed the peaks at *m/z* 330 $(M + H)^+$ and 352 $(M + Na)^+$, and elemental analysis showed the experimental values were in good agreements with the calculated values.

The Cbz deprotection of compound **17** was carried out in refluxing ethanolic KOH and the resultant the secondary amine was subsequently condensed with acryloyl chloride and methacryloyl chloride furnished amides **18a & 18b** in 75% & 73% yield respectively.

The formation of amide **18a** was confirmed by spectral data. ^{1}H NMR spectrum of **18a** showed the absence of signals that corresponded to Cbz group while the presence of a multiplet at δ 5.63-5.70 integrated for one proton was assigned to a α-proton of acrylamide and multiplet at δ 6.32-6.54 integrating for two protons were assigned to β-protons of acrylamide. ^{13}C NMR along with DEPT spectra of **18a** also revealed that, compound **18a** exists as a mixture of rotamers and its structure was further confirmed by mass and elemental analysis. The mass spectrum of **18a** revealed the *m/z* peaks at 250 and 271 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively and the elemental analysis revealed that the experimental values were found to be in good agreement with the calculated values.

Similarly the structure of **18b** was confirmed by spectral analysis. ^{1}H NMR spectrum of **18b** revealed the disappearance of signals due to two benzylic protons and aromatic protons, while new singlet which appeared at δ 1.93 integrated for three protons was assigned to methyl of acryloyl group and two singlets that appeared at δ 5.08 & 5.17

integrating for one proton each were assigned to the olefinic protons. ^{13}C NMR spectrum along with DEPT spectrum of **18b** showed it to be a mixture of rotamers. The structure of **18b** was further supported by mass and elemental analysis, the peak at *m/z* 264 $(M + H)^+$ and 286 $(M + Na)^+$, which was further ascertained by its elemental analysis as well. Having **18a & 18b** in the hand the key step intramolecular enyne metathesis reaction was performed under various reaction conditions mentioned in table 1 but again the formation of anticipated dihydropyridone **19a & 19b** could not be accomplished.

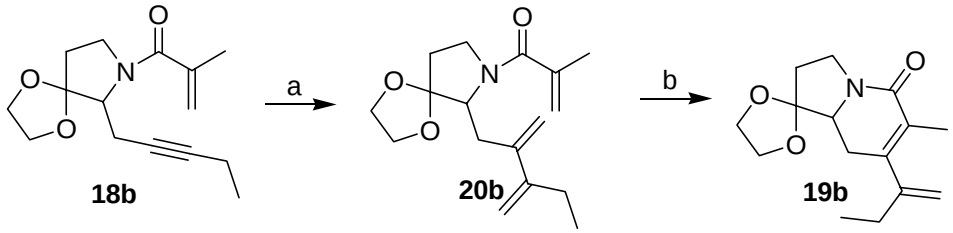


Scheme 6. *Reagents and conditions: (a) ethylene glycol (1.2 equiv), pTSA (cat), C_6H_6, reflux, 6h, 96% (b) KOH (14.0 equiv), EtOH, reflux, 6h (c) K_2CO_3 (1.2 equiv), acryloyl chloride & methacryloyl chloride (1.2 equiv), anhydrous CH_2Cl_2, 0 ^oC, 3 h, 75% & 73% respectively (in two steps).*

However when the acetal **18b** was subjected to the intramolecular enyne metathesis employing Grubbs' second generation catalyst (10 mol %) under ethylene atmosphere in anhydrous toluene at 80 ^oC within 1 h the starting material disappeared (TLC) and afforded the triene **20b** *via* ethylene cross enyne metathesis in excellent yield (98%).

The formation of trine **20b** was confirmed by spectroscopic techniques. ^1H NMR spectrum of **20b** displayed the signals at δ 4.92-5.29 integrating for six protons and which were attributed to olefinic protons which indicated the addition of ethylene to triple bond and formation of conjugated diene. ^{13}C NMR spectrum of **20b** showed the disappearance of the signals corresponding to alkyne carbons while new signals appeared at δ 111.0, 113.9, 144.8 and 148.8 corresponding to olefinic carbons. DEPT spectrum of **20b** revealed additional two methylene carbons in olefinic region, and finally the structure of **20b** was confirmed by mass spectral and elemental analysis. The mass spectrum of **20b** exhibited the $(M + H)^+$ peak at *m/z* 292 along with $(M + Na)^+$ at *m/z* 314. In elemental analysis the experimental values were found to be in good agreement with the theoretical values.

The resultant triene **20b** was further subjected to the treatment with Grubbs' second generation catalyst (10 mol %) in anhydrous toluene at 80 ^{o}C for 48 h, furnished the desired entropically and thermodynamically favored six-membered α,β-unsaturated lactam **19b** exclusively in 40% yield (90% based on recovery of starting material).

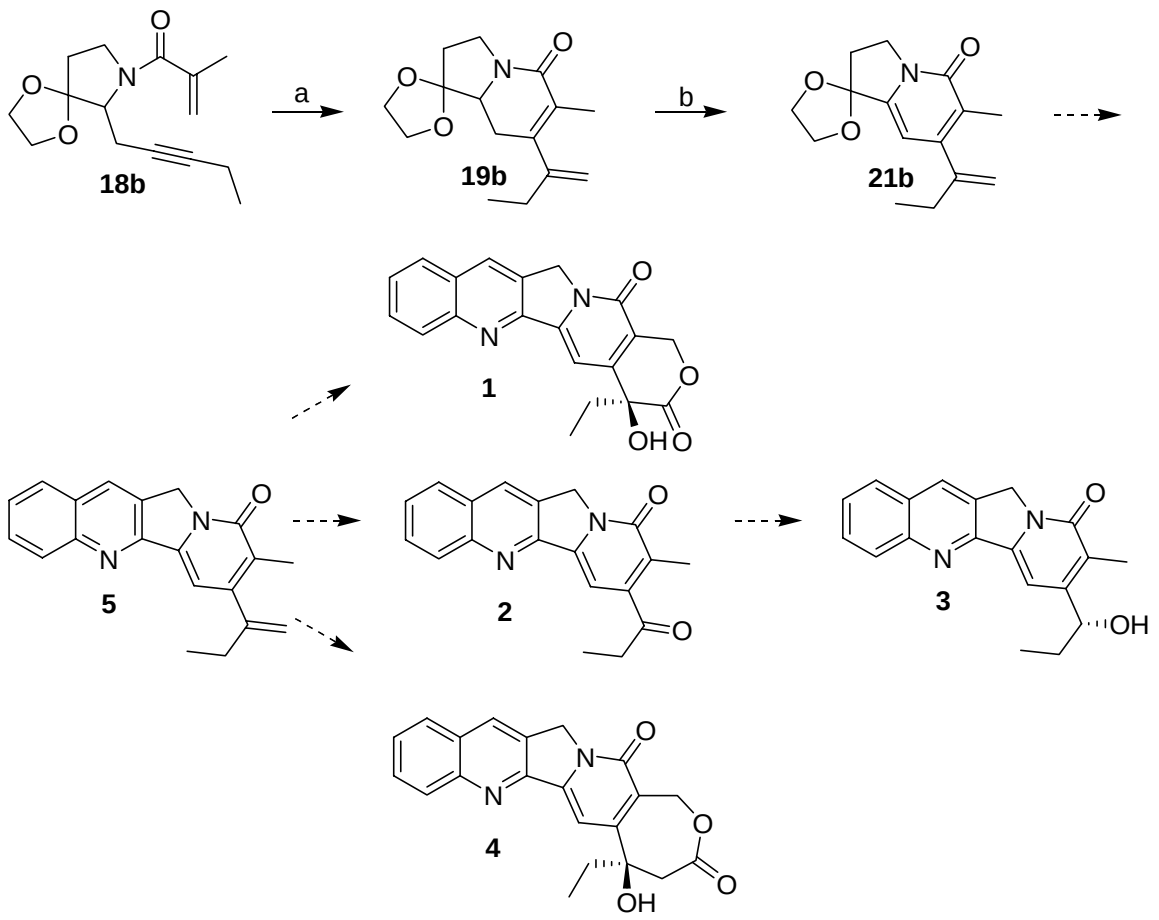


Scheme 7. *Reagents and conditions: (a) Grubbs second generation catalyst (10 mol %), C_2H_4, anhydrous toluene, 80 ^{o}C, 3 h, 98%. (b) Grubbs' second generation catalyst (10 mol %), anhydrous toluene, 24 h, 90% (based on recovery of starting material).*

After obtaining the desired pyridone **19b** *via* triene intermediate **20b**, it was thought that the two reactions *viz.* ethylene cross enyne metathesis and ring-closing metathesis can be carried out in one-pot (tandem intermolecular enyne metathesis and intramolecular ring-closing metathesis).

For the execution of this hypothesis the compound **18b** was treated with Grubbs' second generation catalyst (5 mol %) and the reaction was monitored by TLC. After the disappearance of starting material, additional (15 mol %) Grubbs' second generation catalyst was further added to the reaction mixture and heating was continued for additional 24 h. It was indeed gratifying to note that the desired anticipated dihydropyridone **19b** was obtained in 98% yield (based on recovery of starting material).

The structure of compound **19b** was ascertained by spectral study. ^{1}H NMR spectrum of **19b** displayed the absence of signals corresponding to olefinic protons while the two doublet of doublet appeared at δ 4.77 (J = 1.6, 0.9 Hz) & 5.02 (J = 3.15, 1.6 Hz) that integrated for one proton each which were attributed to exomethylene protons. This clearly indicated the loss of ethylene molecule. ^{13}C NMR spectrum of **19b** showed the disappearance the signals that corresponded to acrylamide olefin and internal olefin of diene. DEPT spectrum of **19b** displayed the six signals corresponding to methylene carbons. The *m/z* peak at 264 $(M + H)^+$ and 286 $(M + Na)^+$ in mass spectrum confirmed the structure of **19b** which was further ascertained by its elemental analysis also, which was found to be in good agreement with the theoretical values.



Scheme 8. *Reagents and conditions: (a) Grubbs catalyst 2 nd generation (5 mol %), C_2H_4, anhydrous toluene, 80 ^{o}C, 1 h, Grubbs catalyst 2 nd generation (15 mol %), 24 h, 98% (based on the recovery of **20b**). (b) DDQ (1.2 equiv), anhydrous 1, 4 dioxane, reflux, 8 h, 96%.*

After achieving the crucial step tandem ethylene cross enyne metathesis followed by ring-closing metathesis reactions, the dihydropyridone **19b** was aromatized by DDQ in refluxing 1,4-dioxane resulted pyridone **21b** in 96% yield. The structure of **21b** was confirmed by spectral methods. ^{1}H NMR spectrum of **21b** displayed the absence of the signals corresponding to methylene and methine protons of dihydropyridone ring while a presence new singlet at δ 6.90 which was attributed to methine proton of pyridone ring. ^{13}C NMR along with DEPT spectra of **21b** revealed the disappearance of signals corresponding to methylene and methine carbons of dihydropyridone ring while the signal appeared at δ 114.1 that was assigned to methine carbon of pyridone ring. Finally the

structure of **21b** was confirmed by mass spectrum which displayed the *m/z* peaks at 262 $(M + H)^+$ and 284 $(M + Na)^+$.

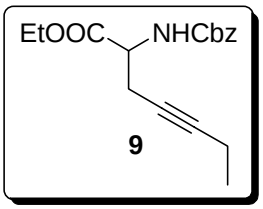
The synthesis of advanced intermediate **5** could be accessed from **21b** by acetal deprotection followed by Friedlander condensation with suitable Schiffs' base and further **5** could be manipulated to camptothecin **1** as well as its analogues. Due to paucity of time these transformations could not be realized which look straightforward.

1.3.4 Conclusion:

The synthesis of advanced intermediate **21b** was achieved employing tandem ethylene cross enyne metathesis followed by ring-closing metathesis as a key step for the construction of pyridone. The intermediate **21b** would serve as a common precursor/synthon which could be transformed to camptothecin **1**, nothapodytine B **2**, mappicine **3** or homocamptothecin **4** *via* intermediate **5**.

1.3.5 Experimental

Ethyl 1-(ethoxycarbonyl) hex-3-ynylcarbamata (9)



(a) To a stirred solution of **10** (15.79 g, 113.2 mmol) in anhydrous CH_2Cl_2 (50 mL), Et_3N (11.43 g, 15.74 mL, 113.2 mmol) was added at 0 ^oC in the presence of molecular sieves (4 A^o) PhCHO (10.0 g, 94.3 mmol) was added and reaction mixture was allowed to stir for 0.5 h. After the completion of reaction (TLC) the reaction mixture was filtered and residue was washed with CH_2Cl_2 (3 x 50 mL). The organic phase was washed with H_2O (100 mL), brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated on rotary evaporator under diminished pressure to furnish Schiff's base **11** as a pale yellow coloured liquid (17.67 g, 98% yield).

(b) To a solution of **11** (10.0 g, 52.35 mmol) in CH_2Cl_2 (50 mL), 1-bromo-2-pentyne (9.23 g, 6.4 mL, 62.28 mmol), $TBAHSO_4$ (1.77 g, 5.23 mmol), and 10% NaOH (2.51 g, 62.28 mmol) were added at 0 ^oC and was allowed to stir for 1 h. After the completion of reaction (TLC), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed on rotary evaporator under reduced pressure furnished crude alkylated Schiff's base **12** as a yellow coloured liquid (12.9 g, 96% yield).

(c) To a stirred compound of **12** (10.0 g, 38.91 mmol) 10 % HCl (17 mL, 46.69 mmol) was added at 0 ^oC and the reaction mixture was allowed to stir for 0.5 h till the completion of reaction (TLC). The organic phase was separated and aqueous phase was washed with CH_2Cl_2 (3 x 20 mL). The aqueous phase was neutralized by addition of ammonia solution (40%), and aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* afforded the crude amine **13** as a pale yellow liquid (6.04 g, 92% yield).

(d) To a stirred solution of amine **13** (5.0 g, 29.58 mmol) in anhydrous CH_2Cl_2 (50 mL), K_2CO_3 (4.93 g, 35.50 mmol) was added and the reaction mixture was stirred for 15 minutes and then benzyl chloroformate (6.05 g, 5.06 mL, 35.50 mmol) was added dropwise at 0 ^oC and allowed to stir further for 2-3 h. After the completion of reaction (TLC), the reaction mixture was filtered and K_2CO_3 was washed with CH_2Cl_2 (3 x 20 mL). The filtrate was washed with water (50 mL) and organic layer was dried over anhydrous sodium sulphate, filtered and solvent was removed on rotary evaporator under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) using

ethyl acetate-petroleum ether (1:9) as eluent furnished carbamate **9** as a viscous colourless liquid (8.6 g, 96% yield).

MF: $C_{17}H_{21}NO_4$, **MW**: 303

IR ($CHCl_3$) ν_{max}: 1725, 1702, 1653, 1511 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 300 MHz) δ: 1.09 (t, *J* = 7.5 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 2.12 (q, *J* = 7.5 Hz, 2H), 2.70 (bs, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.45 (m, 1H), 5.12 (s, 2H), 5.55 (d, *J* = 8.2 Hz, 1H), 7.35 ppm (s, 5H).

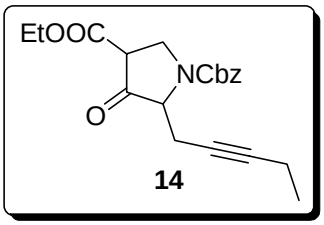
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 12.4, 14.1, 14.3, 23.2, 52.9, 61.6, 67.0, 73.3, 85.4, 128.2, 128.55, 136.4, 155.7, 170.6 ppm.

MS (ESI) *m/z*: 321 $(M + NH_4)^+$, 304 $(M + H)^+$, 260, 172.

Elemental analysis Calculated: C, 67.32; H, 6.9; N, 4.62%.

Found: C, 67.47; H, 6.67; N, 4.52%.

Diethyl 4 -oxo-5-(pent-2-ynyl) pyrrolidine-1, 3-dicarboxylata (14)



14

To a stirred suspension of 60% NaH (1.03 g, 43 mmol) was prewashed with anhydrous petroleum ether (3 x 10 mL) and anhydrous benzene (50 mL) was added and urethane **9** (5 g, 18 mmol) in anhydrous benzene (25 mL) was added gradually. The reaction mixture was stirred at room temperature till the evolution of hydrogen ceased. To the generated sodium salt was dropwise added ethyl acrylate (2.16 g, 2.33 mL, 21.6 mmol) in anhydrous benzene (25 mL) over 10 minutes. The reaction mixture was allowed to stir at room temperature for 0.5 h and then refluxed for 3 hours. The progress of reaction was monitored by TLC. After the completion of reaction the reaction mixture was quenched with the addition of 10% HCl and the organic phase was separated and the aqueous phase was further extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The residue was flash chromatographed on silica gel using ethyl acetate-petroleum ether (1:3) as eluent resultant the β-keto ester **14** as viscous oil in 4.65 g, 79% yield.

MF: $C_{20}H_{23}NO_5$, **MW**: 357

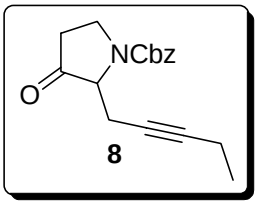
IR (Neat) ν_{max}: 3405, 1772, 1708, 1642 $cm^{-1.}$

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.08 (t, *J* = 7.5 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 2.02-2.17 (m, 2H), 2.51-3.14 (m, 2H), 3.53-3.64 (m, 0.65H), 3.97-4.64 (m, 5H), 5.19 (s, 2H), 7.35 (s, 5H), 10.02 ppm (bs, 0.35H).

^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 12.45, 13.8, 14.1, 14.2, 14.4, 21.1, 22.3, 45.8, 49.3, 49.6, 60.5, 61.1, 61.6, 61.8, 62.1, 67.0, 67.3, 73.2, 73.65, 83.95, 97.6, 97.9, 128.0, 128.1, 128.2, 128.6, 136.45, 136.7, 154.1, 168.4, 168.9 ppm.

MS (ESI) *m/z*: 375 $(M + NH_4)^+$, 358 $(M + 1)^+$, 326, 321, 296, 259, 242, 227, 200, 187, 172.

Ethyl 3-oxo-2-(pent-2-ynyl) pyrrolidine-1-carboxylate (8)



To a stirred solution of β-keto ester **14** (4.5 g, 12.6 mmol) in DMSO: H_2O (3:1) (20 mL), NaCl (2.92 g, 50.4 mmol) was added and the resultant reaction mixture was allowed to stir at 120-130 ^oC for 6 h. After the completion of reaction (TLC), the reaction mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:9) as eluent delivered pyrrolidinone **8** as a viscous pale yellow liquid (3.26 g, 91% yield).

MF: $C_{17}H_{19}NO_3$, **MW**: 285

IR ($CHCl_3$) ν_{max}: 1719, 1701, 1418, 1216, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.07 (t, *J* = 7.5 Hz, 3H), 2.09 (t, *J* = 7.3 Hz, 2H), 2.57-2.64 (m, 4H), 3.77-3.98 (m, 3H), 5.19 (s, 2H), 7.35 ppm (s, 5H).

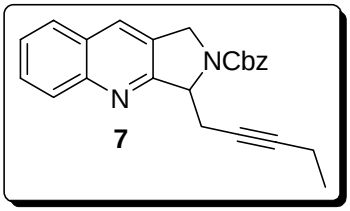
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ:12.3, 14.0, 20.6, 21.8, 36.0, 36.4, 42.8, 60.9, 61.1, 63.8, 64.0, 64.9, 67.1, 73.3, 73.8, 74.2, 84.0, 84.4, 126.85, 127.3, 127.9, 128.15, 128.35, 128.5, 136.2, 136.4, 141.3, 154.65, 211.6, 211.9 ppm (mixture of rotamers).

MS (ESI) *m/z*: 303 $(M + NH_4)^+$, 286 $(M + H)^+$, 252, 227, 224, 200, 172.

Elemental analysis Calculated: C, 71.57; H, 6.65; N, 4.91%.

Found: C, 71.55; H, 6.62; N, 4.79%.

Ethyl 3-(pent-2-ynyl) -1 H-pyrrolo [3, 4-*b*] quinoline-2(3*H*)-carboxylate (7)



To a stirred solution of pyrrolidinone **8** (3.0 g, 10.52 mmol) in anhydrous toluene (30 mL), *N*-(o-aminobenzilidine)-*p*-toluidine (2.46 g, 12.62 mmol) was added. The resultant reaction mixture was refluxed for 0.5 h with azeotropic removal of water and after 0.5 h, 0.201 g of *p*-TSA was added and the reaction mixture was further refluxed for 3 h. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction was quenched with the addition of 10% $NaHCO_3$ and the organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2) eluting with the mixture of ethyl acetate-petroleum ether (1:3) furnished quinoline **7** as a yellow solid (2.72 g, 70% yield).

MF: $C_{24}H_{22}N_2O_2$, **MW**: 370

M. P.: 109 ^oC

IR ($CHCl_3$) ν_{max}: 1703, 1630, 1516, 1407, 1216, 1113, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.79, 0.81 (t, t, *J* = 7.5 Hz, 3H), 1.84 (q, *J* = 7.5 Hz, 2H), 2.96-3.44 (m, 2H), 4.90-5.03 (m, 2H), 5.25 (bs, 1H), 5.29 (s, 2H), 7.33-7.45 (m, 5H), 7.54-7.55 (bs, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.83 (t, *J* = 8.7 Hz, 1H), 7.98, 8.04 (s, s, 1:1, 1H), 8.11 ppm (t, *J* = 8.7 Hz, 1H) (mixture of rotamers).

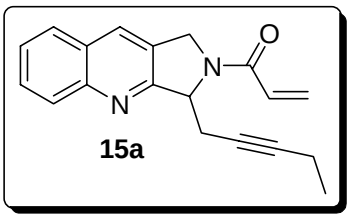
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 12.15, 13.8, 23.7, 24.9, 50.8, 51.1, 61.9, 62.4, 67.0, 67.3, 74.1, 74.5, 83.6, 84.0, 126.5, 127.6, 127.7, 127.8, 128.1, 128.55, 129.0, 129.15, 129.3, 136.5, 136.75, 148.1, 154.4, 154.8, 161.4, 161.7 ppm (mixture of rotamers).

MS (ESI) *m/z*: 371 $(M + H)^+$, 393 $(M + Na)^+$.

Elemental analysis Calculated: C, 77.81; H, 5.99; N, 7.56%.

Found: C, 77.75; H, 6.16; N, 7.59%.

1-(3-(pent-2-ynyl)-1H-pyrrolo [3, 4-*b*] quinolin-2(3*H*)-yl) prop-2-en-1-one (15a)



15a

To a stirred solution of urethane **7** (3.0 g, 8.1 mmol) in ethanol (30 mL), KOH (6.3 g, 113.5 mmol) in ethanol (30 mL) was added and the solution was degassed under N_2 atmosphere and resultant yellow solution was refluxed under nitrogen atmosphere till completion (TLC, 6 h). The resultant dark brown solution was concentrated under reduced pressure, the residue was diluted with water and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* provided the crude amine. To the stirred solution of crude amine in anhydrous CH_2Cl_2 (30 mL), K_2CO_3 (1.35 g, 9.7 mmol) was added and stirred for 5-10 minutes at 0 ^oC after that acryloyl chloride (0.88 g, 0.79 mL, 9.7 mmol) was added dropwise under nitrogen atmosphere at 0 ºC over a period of 10 minutes. The reaction mixture was allowed to stir for 3 h. After the completion of reaction (TLC), the reaction mixture was filtered and residue was washed with CH_2Cl_2 (3 x 10 mL), the filtrate was washed with H_2O (50 mL), brine (30 mL) and organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (2:3) afforded the compound **15a** as a pale yellow solid (1.66 g, 71% yield).

MF: $C_{19}H_{18}N_2O$, **MW**: 290

M.P.: 105 ^oC

IR (CHCl3) ν_{max}: 1697, 1631, 1513, 1409, 1214, 1117, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.79, 0.85 (t, t, *J* = 7.5 Hz, 3H), 1.84 (q, *J* = 7.5 Hz, 2H), 2.89-3.53 (m, 2H), 4.86-5.48 (m, 3H), 5.30, 5.50 (t, t, *J* = 3.9 Hz, 1H), 5.82 (dd, *J* = 9.3, 2.8 Hz, 1H), 6.54-6.65 (m, 2H), 7.55-7.59 (m, 1H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.80 (t, *J* = 6.8 Hz, 1H), 7.99-8.13 ppm (m, 2H) (mixture of rotamers).

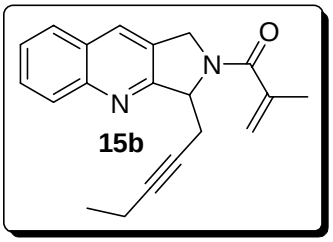
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 12.35, 13.8, 14.1, 23.55, 27.2, 29.9, 50.7, 51.5, 61.8, 62.3, 73.5, 74.9, 83.4, 85.1, 126.9, 127.8, 128.0, 128.9, 129.0, 129.1, 129.5, 129.6, 129.9, 148.1, 148.6, 161.4, 161.5, 164.6, 164.9 ppm (mixture of rotamers).

MS (ESI) *m/z*: 291$(M + H)^+$, 313 $(M + Na)^+$.

Elemental analysis Calculated: C, 78.59; H, 6.25; N, 9.65%.

Found: C, 78.63; H, 6.28; N, 9.57%.

2-methyl-1-(3-pent-2-ynyl)-1H-pyrrolo [3, 4-*b*] quinolin-2(3*H*)-yl) prop-2-en-1-one (15b)



To a stirred solution of urethane **7** (5.0 g, 14.53 mmol) in ethanol (50 mL), KOH (13.0 g, 46.8 mmol) in ethanol (40 mL) was added and the solution was degassed under N_2 atmosphere and resultant yellow solution was refluxed under nitrogen atmosphere till completion (6 h). The resultant dark brown solution was concentrated under reduced pressure, the residue was diluted with water and extracted with CH_2Cl_2 (3 x 70 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* provided the crude amine. To the stirred solution of crude amine obtained (3 g, 14.28 mmol) in anhydrous CH_2Cl_2 (50 mL), K_2CO_3 (2.3 g, 17.14 mmol) was added and stirred for 5-10 minutes at 0 ^oC. Methacryloyl chloride (1.95 g, 1.8 mL, 5.04 mmol) was added dropwise under nitrogen atmosphere at 0 ºC over a period of 10 minutes to the above reaction mixture. The reaction mixture was allowed to stir for 3 h. After completion of reaction (TLC), the reaction mixture was filtered and residue was washed with CH_2Cl_2 (3 x 10 mL), the filtrate was washed with H_2O (50 mL), brine (30 mL) and organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether afforded the compound **15b** as a pale yellow solid (2.95 g, 72% yield).

MF: $C_{20}H_{20}N_2O$, **MW**: 304

M.P.: 104-106 ^oC

IR ($CHCl_3$) ν_{max}: 1722, 1651, 1621, 1412, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.83 (t, *J* = 7.5 Hz, 3H), 1.86 (q, *J* = 7.5 Hz, 2H), 2.04 (s, 3H), 2.89, 3.44 (d, d, *J* = 16.4 Hz, 2H), 4.98 (dd, *J* = 14.0, 9.8 Hz, 2H), 5.31-5.46 (m, 3H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.92 (s, 1H), 8.06 ppm (d, *J* = 7.4 Hz, 1H) (mixture of rotamers).

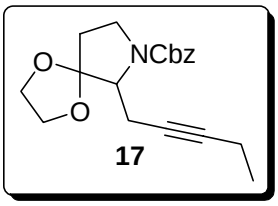
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 12.2, 13.8, 14.0, 19.8, 20.3, 23.6, 26.4, 29.7, 50.9, 53.2, 61.5, 63.0, 74.7, 83.3, 116.1, 117.0, 126.7, 127.6, 127.8, 129.0, 129.5, 129.65, 141.1, 148.1, 161.3, 171.2, 171.6 ppm (mixture of rotamers).

MS (ESI) *m/z*: 305 $(M + 1)^+$, 327 $(M + Na)^+$.

Elemental analysis Calculated: C, 78.92; H, 6.62; N, 9.20%.

Found: C, 78.95; H, 6.56; N, 9.17%.

Compound (17)



17

To a stirred solution of pyrrolidinone **8** (3.0 g, 11.58 mmol) in anhydrous benzene (20 mL), ethylene glycol (1.08 g, 0.97 mL, 17.37 mmol) and *p*-TSA (0.1 g) was added and the resultant reaction mixture was refluxed with azeotropic removal of water for 12 h. After completion (TLC), the reaction mixture was cooled to room temperature and quenched with addition of 10% sodium bicarbonate solution. The organic phase was separated and aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated on rotary evaporator under diminished pressure. The residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:9) afforded compound **17** as viscous pale yellow liquid (2.98 g, 85% yield).

MF: $C_{19}H_{23}NO_4$, **MW**: 329

IR ($CHCl_3$) ν_{max}: 1698, 1417, 1216, 1107, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.10, 1.11 (t, t, *J* = 7.5 Hz, 3H), 1.89-2.01 (m, 2H), 2.06-2.22 (m, 2H), 2.37-2.64 (m, 2H), 3.27-3.75 (m, 3H), 3.96, 3.97 (s, s, 4H), 5.14 (s, 2H), 7.34 ppm (s, 5H) (mixture of rotamers).

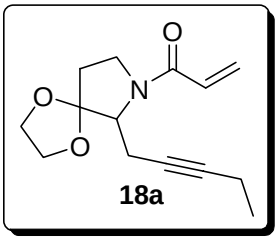
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 12.3, 14.0, 14.6, 20.1, 21.05, 32.4, 33.1, 33.3, 43.3, 43.4, 43.6, 60.8, 61.3, 61.5, 63.9, 64.6, 65.4, 66.5, 66.7, 75.6, 75.9, 82.7, 83.1, 113.7, 114.35, 125.5, 126.7, 127.0, 127.55, 128.1, 128.3, 136.6, 136.7, 141.4, 154.6, 154.7, 154.9 ppm (mixture of rotamers).

MS (ESI) *m/z*: 330 $(M + H)^+$, 352 $(M + Na)^+$.

Elemental analysis Calculated: C, 69.28; H, 7.04; N, 4.25%.

Found: C, 69.33; H, 6.98; N, 4.27%.

Compound (18a)



18a

To a stirred solution of the urethane **17** (2.0 g, 6.07 mmol) in ethanol (20 mL), KOH (13.0 g, 4.76 mmol) in ethanol (20 mL) was added and the solution was degassed under N_2 atmosphere and resultant yellow solution was refluxed under nitrogen for 6 h. The progress of reaction was monitored by TLC and the resultant dark brown solution was concentrated on rotary evaporator under reduced pressure. The residue

obtained was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* provided the crude amine. To a stirred solution of the resultant crude amine in anhydrous CH_2Cl_2 (20 mL), K_2CO_3 (1.00 g, 7.29 mmol) was added and stirred for 5 minutes and acryloyl chloride (0.66 g, 0.59 mL, 7.29 mmol) was added under nitrogen atmosphere at 0 ºC over a period of 10 minutes. The reaction mixture was allowed to stir for 3 h. After the completion of reaction (TLC) the reaction mixture was filtered and residue was washed with CH_2Cl_2 (3 x 10 mL) the filtrate was washed with H_2O (20 mL), brine (15 mL) and organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The residue obtained was purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (2:3) afforded the compound **18a** as a viscous liquid (1.13 g, 75% yield).

MF: $C_{14}H_{19}NO_3$, **MW**: 249

IR ($CHCl_3$) ν_{max}: 1695, 1614, 1432, 1215, 1119, 1044, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.06 (t, *J* = 7.5 Hz, 3H), 1.98-2.82 (m, 6H),3.53-3.79 (m, 3H), 3.97 (s, 4H), 5.63-5.70 (m, 1H), 6.32-6.54 ppm (m, 2H) (mixture of rotamers).

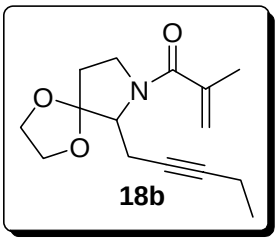
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 12.0, 13.4, 13.75, 19.1, 22.5, 30.9, 33.1, 42.35, 43.9, 60.6, 61.1, 63.7, 64.0, 65.3, 74.7, 75.5, 82.5, 84.0, 112.8, 114.1, 126.8, 127.4, 128.3, 164.5, 164.6 ppm (mixture of rotamers).

MS (ESI) *m/z*: 250 $(M + H)^+$, 272 $(M + Na)^+$.

Elemental analysis Calculated: C, 67.45; H, 7.68; N, 5.62%.

Found: C, 67.39; H, 7.73; N, 5.57%.

Compound (18b)



18b

To a stirred solution of the urethane **17** (3.0 g, 9.11 mmol) in ethanol (40 mL), KOH (13.0 g, 7.14 mmol) in ethanol (30 mL) was added and the solution was degassed under N_2 atmosphere and resultant yellow solution was refluxed under nitrogen for 6 h. The progress of reaction was monitored by TLC and the resultant dark brown solution was concentrated on rotary evaporator under reduced pressure. The residue obtained was diluted with water and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*

provided the crude amine. To a stirred solution of crude amine in anhydrous CH_2Cl_2 (30 mL), K_2CO_3 (1.51 g, 10.94 mmol) was added and stirred and methacryloyl chloride (1.14 g, 1.05 mL, 10.94 mmol) was added under nitrogen atmosphere at 0 ºC over a period of 10 minutes. The reaction mixture was allowed to stir for 3 h. After the completion of reaction (TLC) the reaction mixture was filtered and residue was washed with CH_2Cl_2 (3 x 10 mL) the filtrate was washed with H_2O (30 mL), brine (15 mL) and organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The residue obtained was purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (2:3) afforded the compound **18b** as a viscous liquid (1.75 g, 73% yield).

MF: $C_{15}H_{21}NO_3$, **MW**: 263

IR ($CHCl_3$) ν_{max}: 1695, 1614, 1432, 1215, 1119, 1044, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.07 (t, *J* = 7.5 Hz, 3H), 1.93 (s, 3H), 2.11 (q, *J* = 7.5 Hz, 2H), 2.27-2.90 (m, 4H), 3.55 (m, 2H), 3.94 (s, 4H), 5.08, 5.17 ppm (s, s, 2H) (mixture of rotamers).

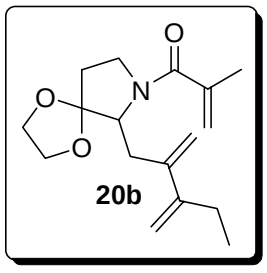
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 12.5, 14.2, 19.3, 20.0, 34.0, 46.1, 60.55, 64.3, 65.8, 113.7, 116.05, 141.2, 171.7 ppm (mixture of rotamers).

MS (ESI) *m/z*: 264 $(M+H)^+$, 286 $(M+Na)^+$.

Elemental analysis Calculated: C, 68.42; H, 8.04; N, 5.32%.

Found: C, 68.37; H, 8.09; N, 5.29%.

Compound (20b)



To the stirred solution of **18b** (0.2 g, 0.76 mmol) in anhydrous toluene (20 mL), Grubbs' second generation catalyst (0.064 g, 10 mol %) was added and degassed thoroughly. The reaction mixture was heated at 80 ºC for 1 h under ethylene atmosphere. The progress of reaction was monitored by TLC and after the completion of reaction, toluene was removed on rotary evaporator under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (230-400 mesh size) eluted with ethyl acetate-petroleum ether (8:2) afforded the compound **20b** as a colourless liquid (0.216 g, 98% yield).

MF: $C_{17}H_{25}NO_3$, **MW**: 291

IR ($CHCl_3$) ν_{max}: 1691, 1613, 1431, 1215, 1118, 1045, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.01 (t, *J* = 7.5 Hz, 3H), 1.86 (s, 3H), 1.97-2.71 (m, 6H), 3.45-4.18 (m, 7H), 4.92-5.29 ppm (m, 6H).

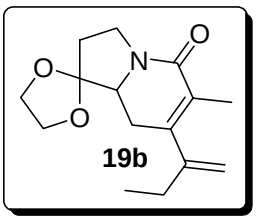
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.0, 19.8, 26.7, 34.0, 34.2, 45.7, 59.6, 64.0, 65.3, 111.0, 113.9, 116.4, 141.05, 144.8, 148.8, 171.4 ppm.

MS (ESI) *m/z*: 292 $(M + H)^+$, 314 $(M + Na)^+$.

Elemental analysis Calculated: C, 70.07; H, 8.65; N, 4.81%.

Found: C, 69.94; 8.67; N, 4.77%.

Compound (19b)



To the stirred solution of **20b** (0.1 g, 0.34 mmol) in anhydrous toluene (10 mL), Grubbs' second generation catalyst (0.029 g, 0.034 mmol, 10 mol %) was added and degassed thoroughly. The reaction mixture was heated at 80 ºC under nitrogen atmosphere till the completion of reaction (TLC, 12 h). Toluene was removed *in vacuo* and the resultant residue was purified by flash column chromatography on silica gel (230-400 mesh size) eluting with ethyl acetate-petroleum ether (6:4) provided the dihydropyridone compound **19b** as colourless syrup (0.036 g, 40% yield) and 0.055 g of starting material was recovered.

MF: $C_{15}H_{21}NO_3$, **MW**: 263

IR (CHCl3) ν_{max}: 1719, 1647, 1609, 1439, 1215, 1159, 1038, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.01 (t, *J* = 7.5 Hz, 3H), 1.85 (d, *J* = 2.6 Hz, 3H), 1.99-2.22 (m, 6H), 3.54-3.81 (m, 3H), 3.95 (s, 4H), 4.77 (dd, *J* = 1.6, 0.9 Hz, 1H), 5.02 ppm (dd, *J* = 3.2, 1.6 Hz, 1H).

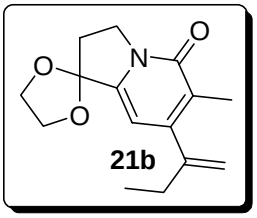
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 12.35, 13.5, 27.9, 28.2, 33.8, 42.1, 59.8, 65.4, 112.0, 114.3, 126.25, 145.7, 150.2, 165.0. ppm.

MS (ESI) *m/z*: 264 $(M + H)^+$, 286 $(M + Na)^+$.

Elemental analysis Calculated: C, 68.42; H, 8.04; N, 5.32%.

Found: C, 68.44; 8.07; N, 5.27%.

Compound (21b)



To the stirred solution of **19b** (0.1 g, 0.38 mmol) in anhydrous 1, 4-dioxane (20 mL), DDQ (0.095 g, 0.41 mmol) was added and the resultant reaction mixture was refluxed under nitrogen atmosphere till the completion of reaction (TLC, 8 h). The reaction mixture was cooled to room temperature and quenched with addition of saturated $NaHCO_3$ solution and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue obtained was purified by flash column chromatography on silica gel (230-400 mesh size) eluting with ethyl acetate-petroleum ether (7:3) furnished the pyridone compound **21b** as viscous liquid (0.082 g, 92% yield).

MF: $C_{15}H_{19}NO_3$, **MW**: 261

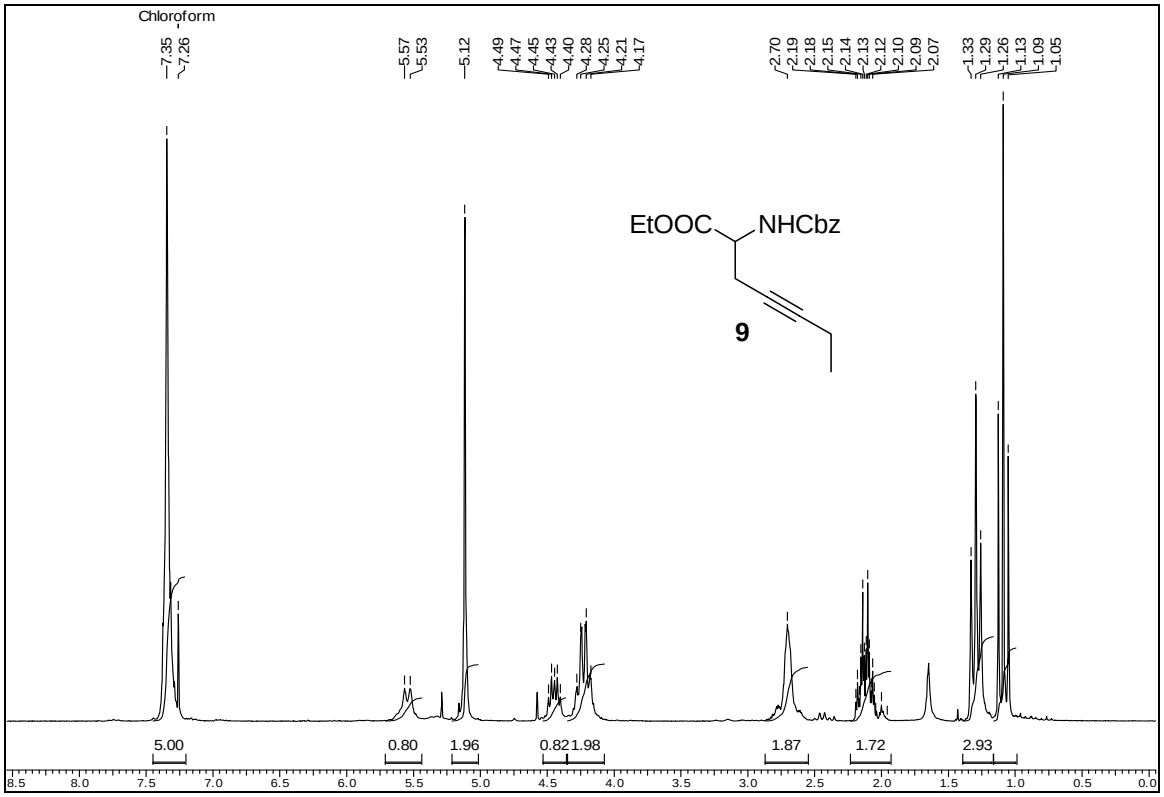
IR (CHCl3) ν_{max}: 3056, 1657, 1605 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.88 (t, *J* = 7.5 Hz, 3H), 2.04 (t, 2H), 2.17 (s, 3H), 2.32 (q, *J* = 7.5 Hz, 2H), 3.60-3.84 (m, 2H), 3.96-4.62 (m, 4H), 4.93 (s, 1H), 5.58 (s, 1H), 6.90 ppm (s, 1H).

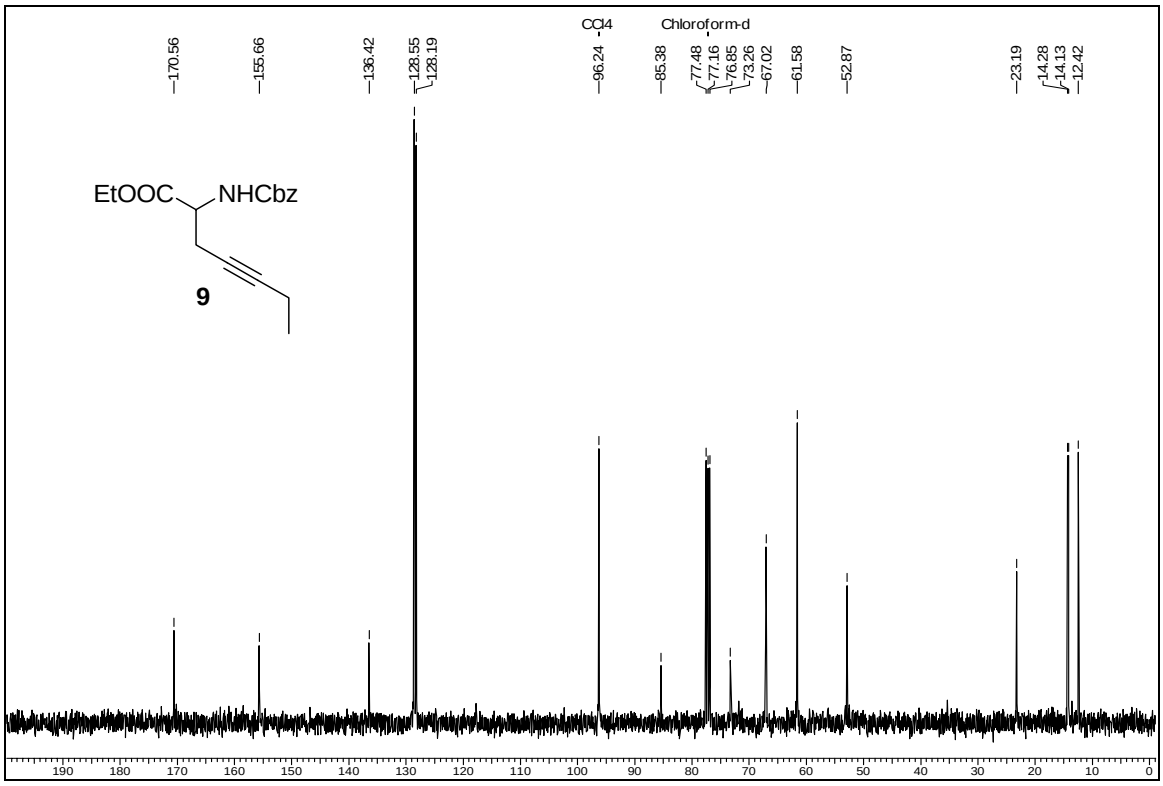
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 12.1, 14.3, 24.9, 41.1, 47.9, 66.3, 114.1, 115.4, 126.5, 129.85, 131.1, 139.4, 155.5 ppm.

MS (ESI) *m/z*: 262 $(M + H)^+$, 284 $(M + Na)^+$.

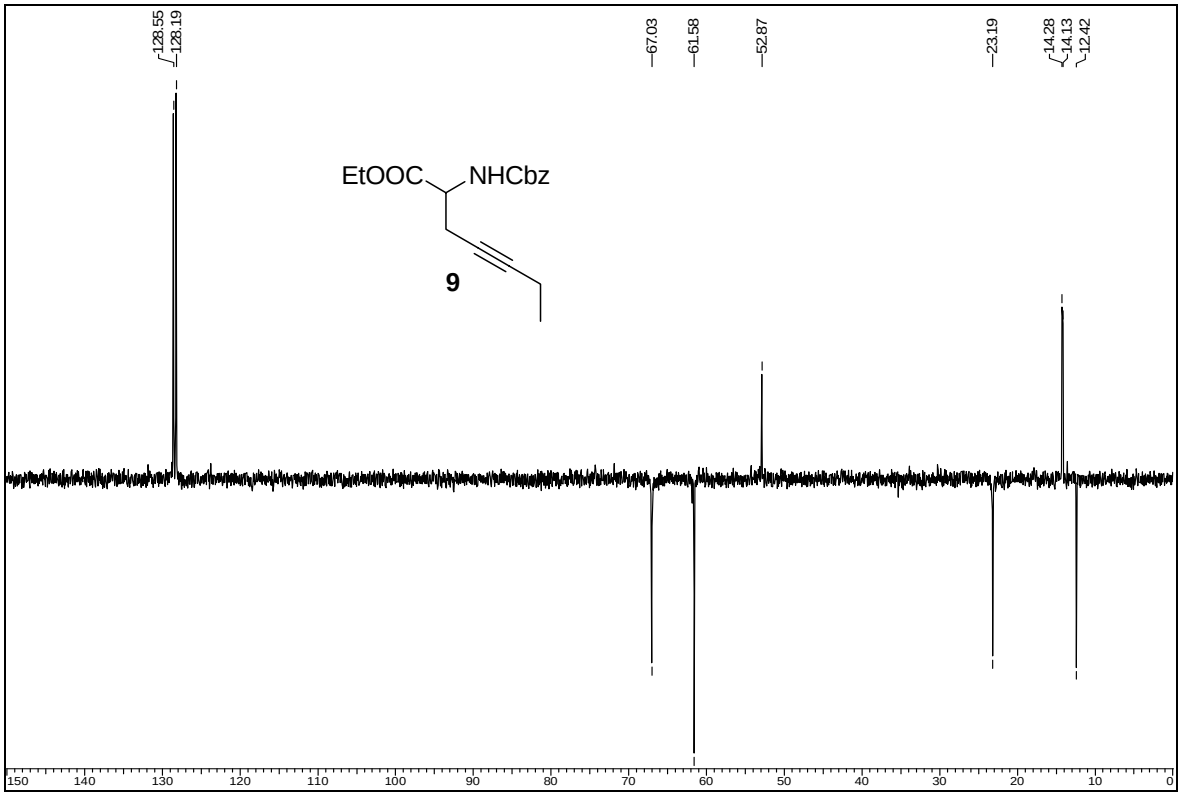
1.3.6 Spectra



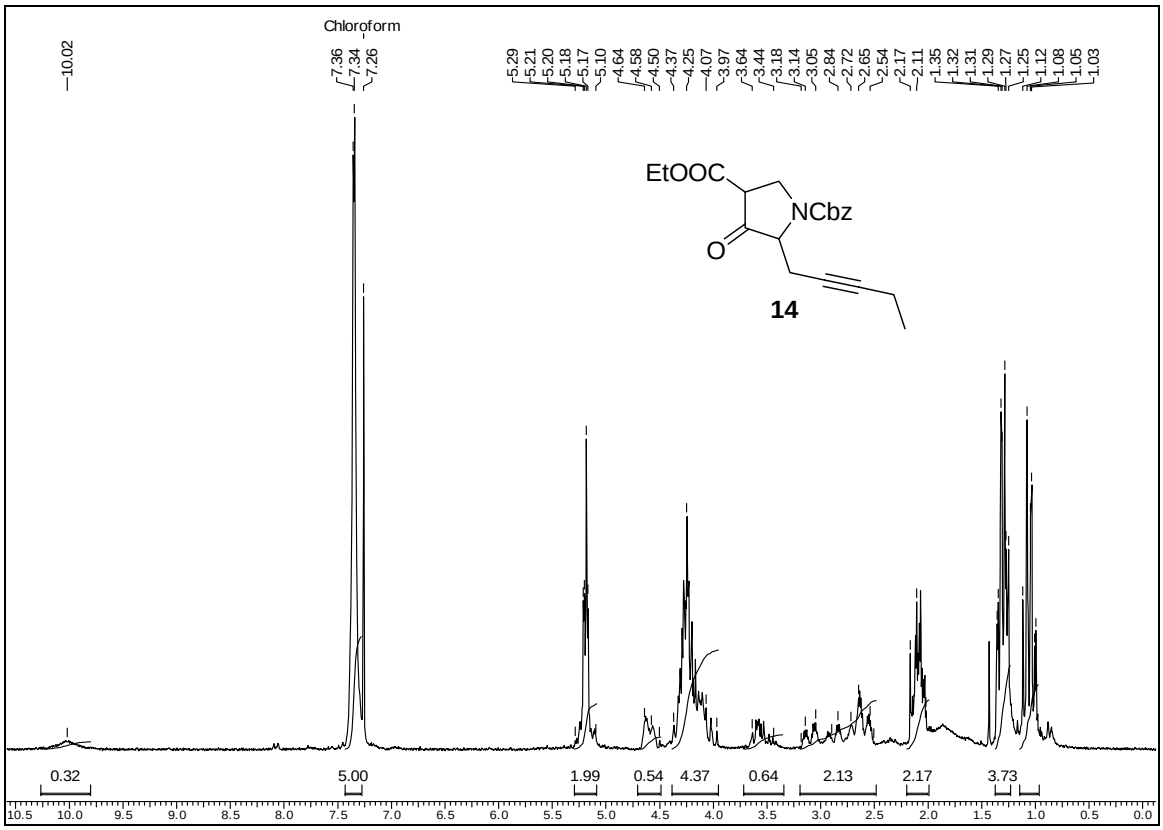
^{1}H NMR spectrum of compound 9 ($CDCl_3$ + CCl_4, 300 MHz)



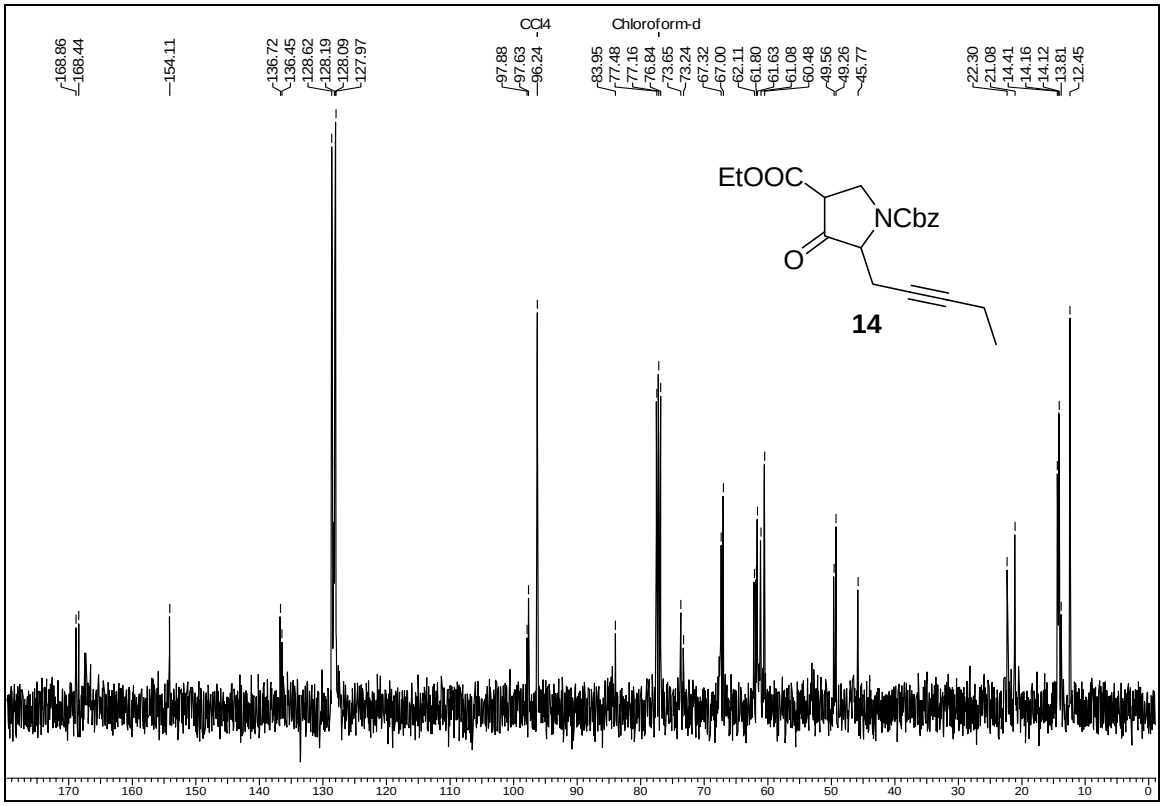
^{13}C NMR spectrum of compound 9 ($CDCl_3$ + CCl_4, 100 MHz)



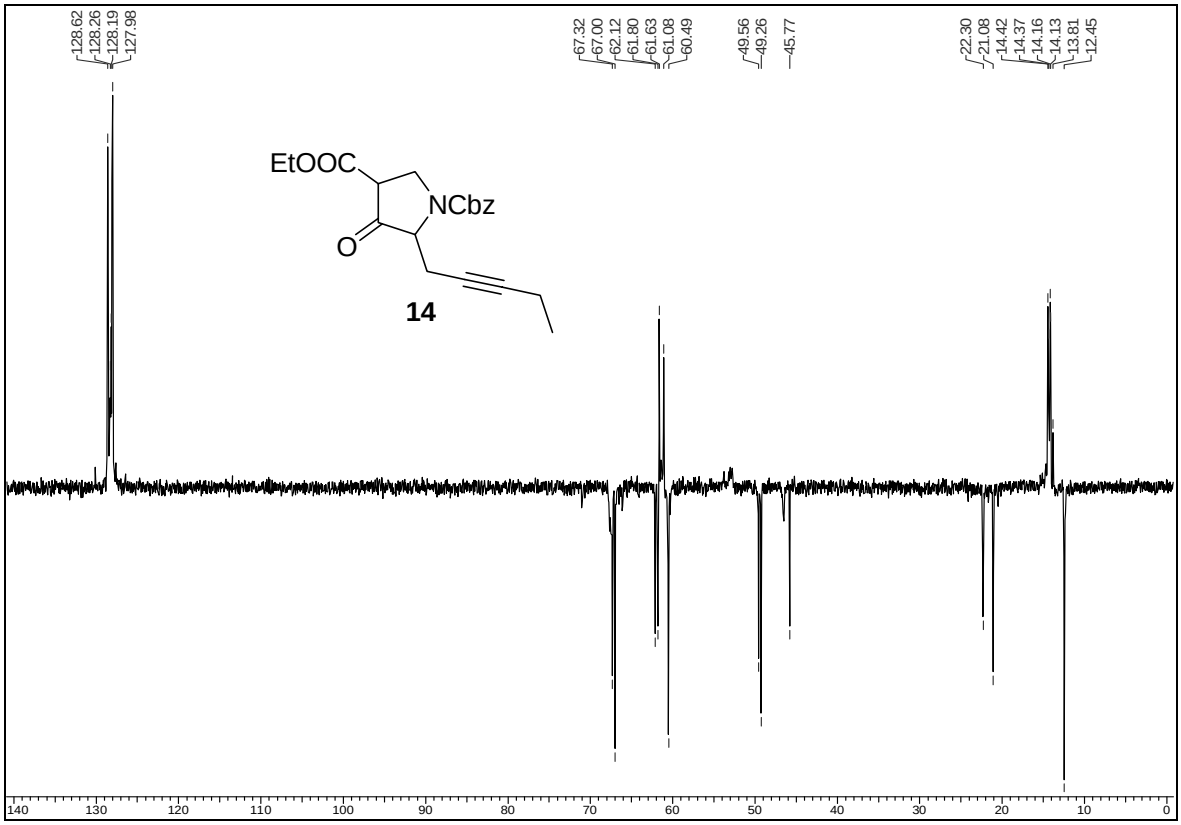
DEPT spectrum of compound 9 ($CDCl_3$ + CCl_4, 100 MHz)



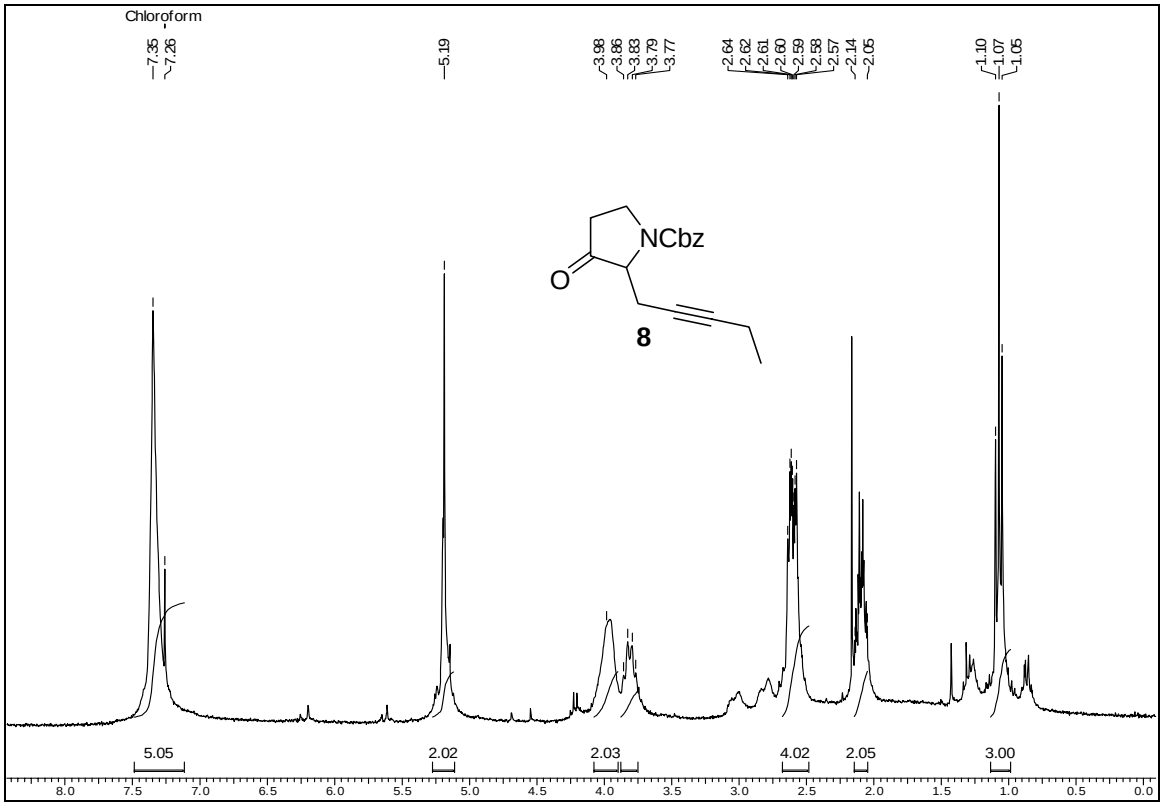
^{1}H NMR spectrum of compound 14 ($CDCl_3$ + CCl_4, 200 MHz)



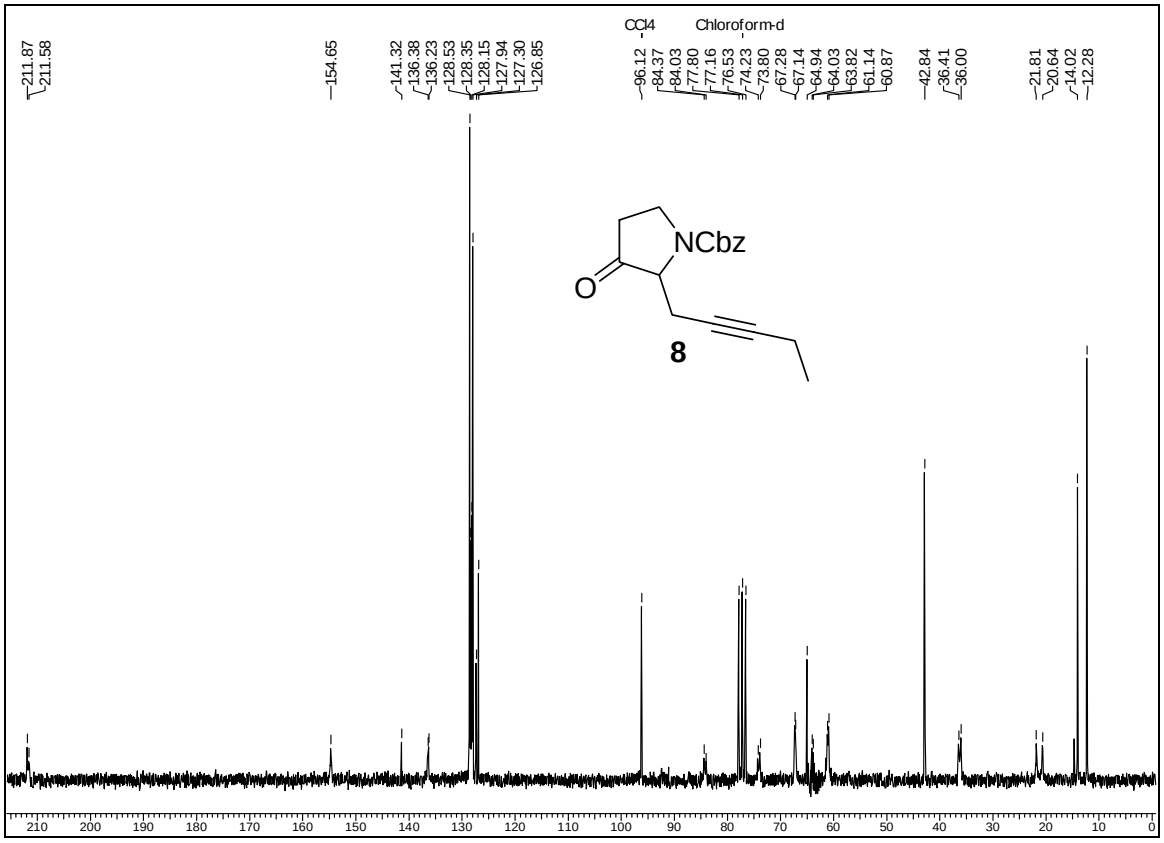
^{13}C NMR spectrum of compound 14 ($CDCl_3$ + CCl_4, 100 MHz)



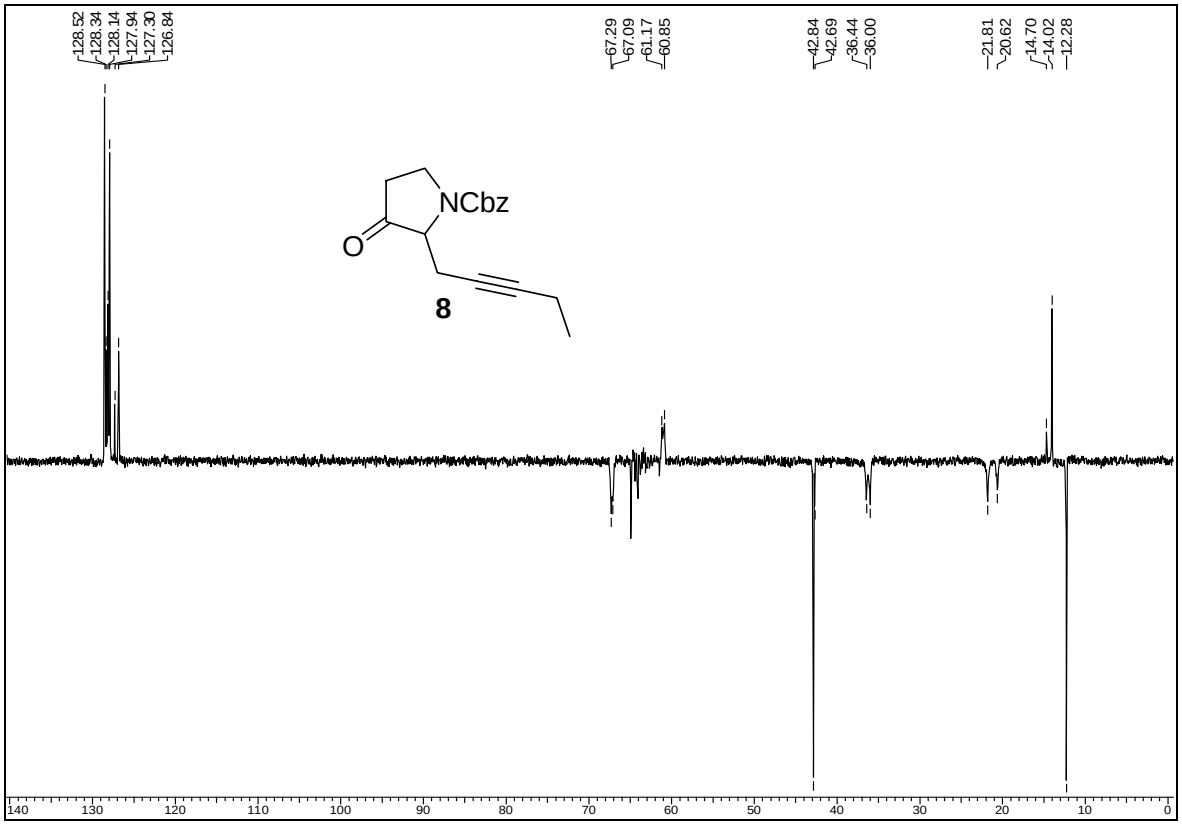
DEPT spectrum of compound 14 ($CDCl_3$ + CCl_4, 100 MHz)



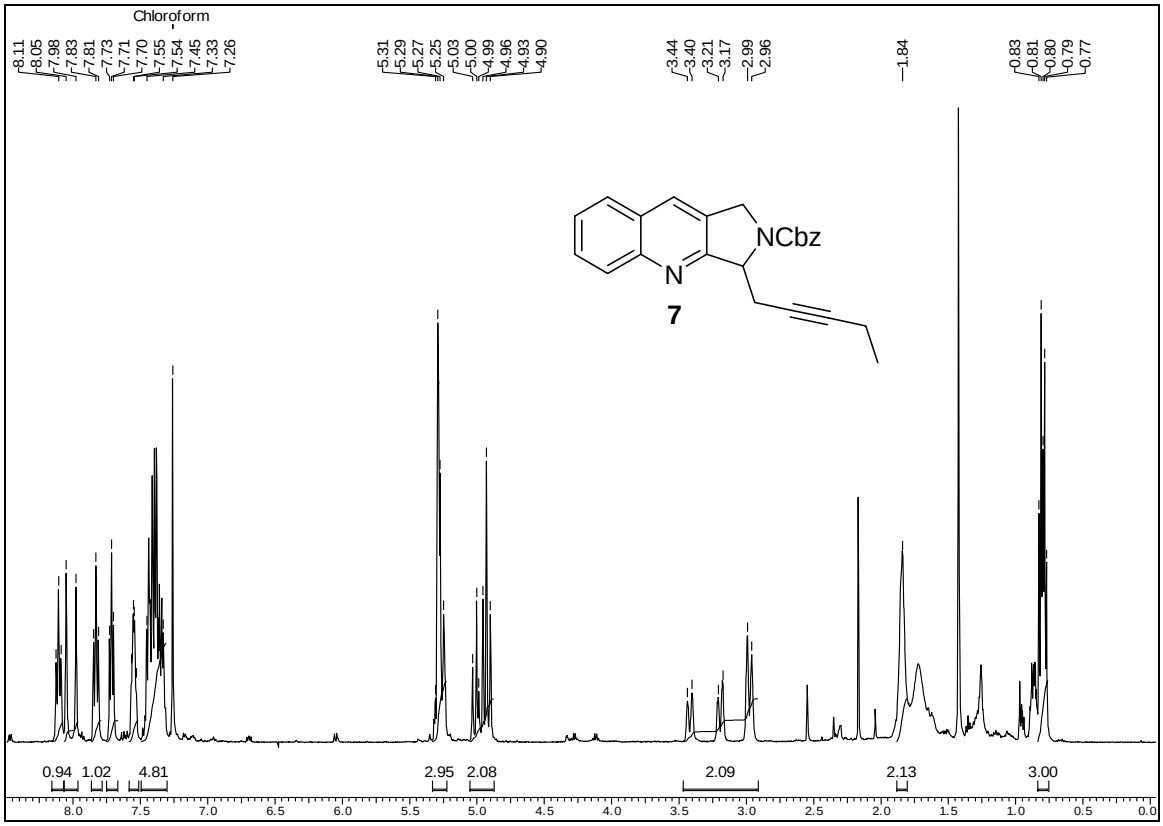
^{1}H NMR spectrum of compound 8 ($CDCl_3$ + CCl_4, 200 MHz)



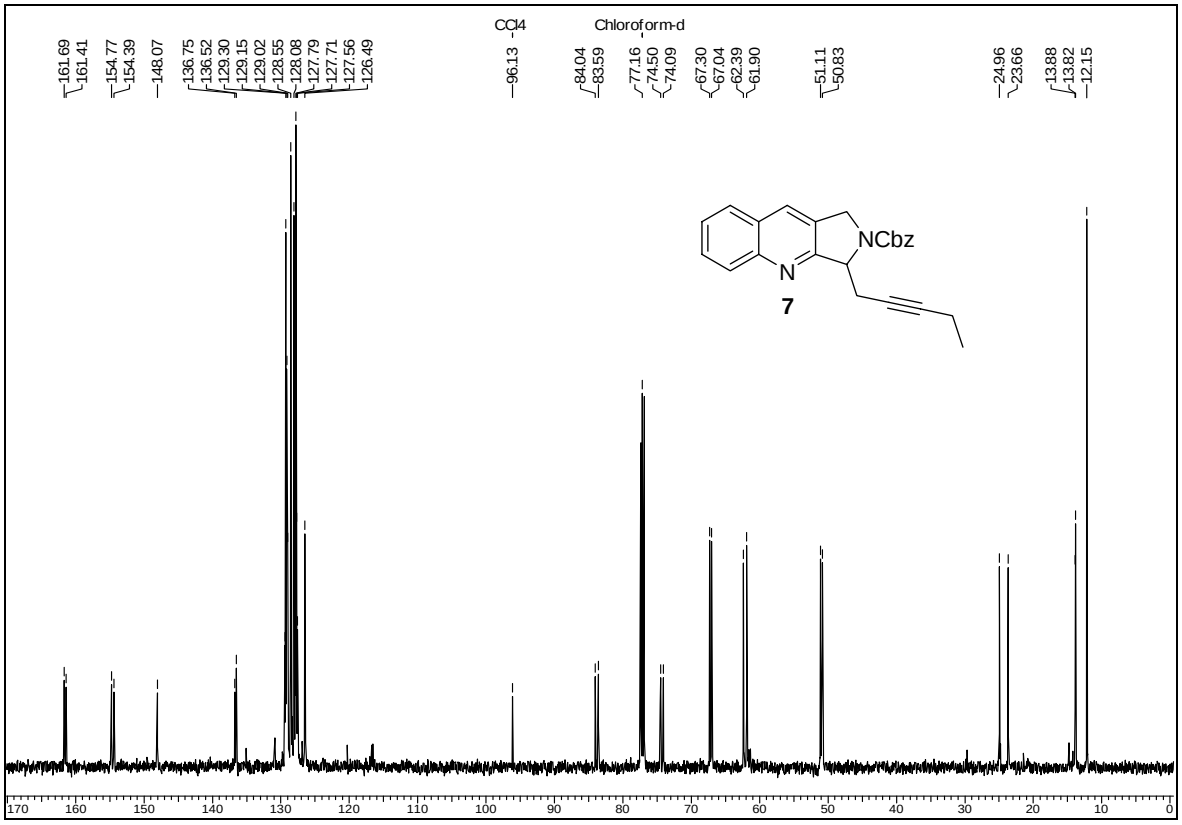
^{13}C NMR spectrum of compound 8 ($CDCl_3$ + CCl_4, 50 MHz)



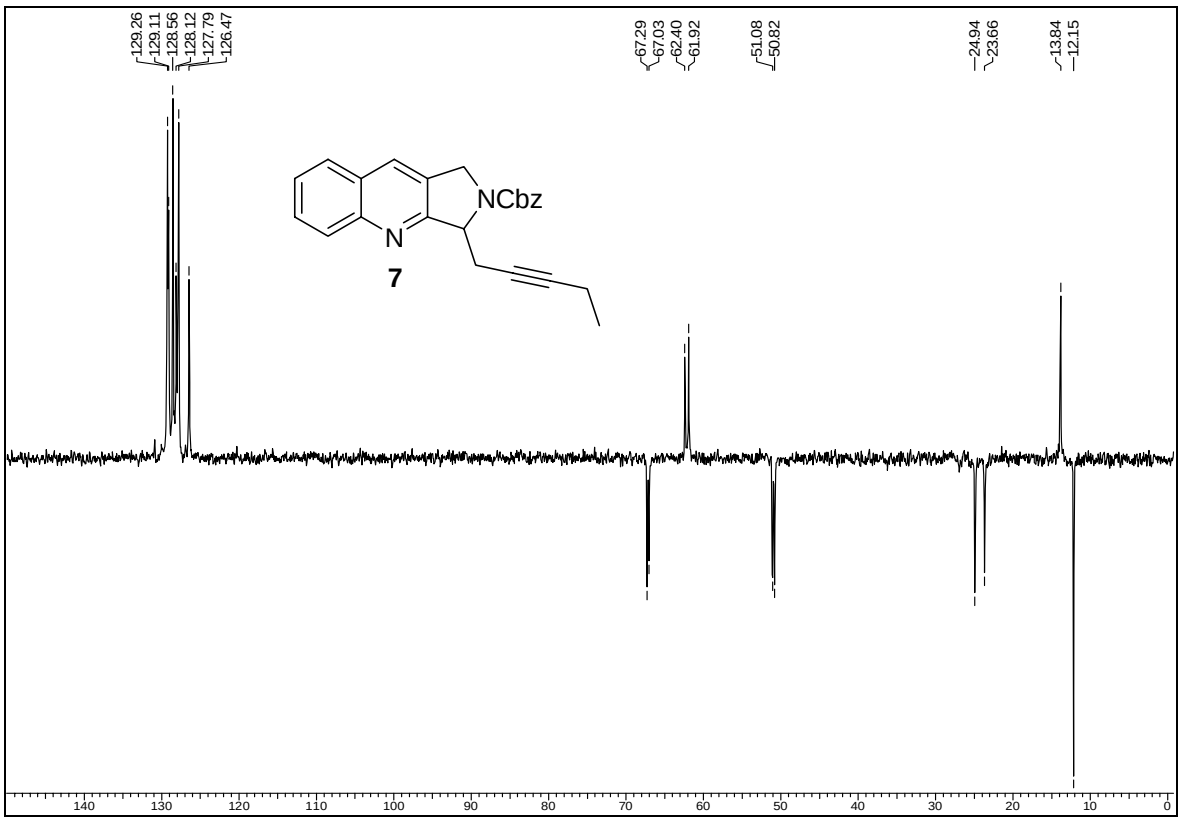
DEPT spectrum of compound 8 ($CDCl_3$ + CCl_4, 50 MHz)



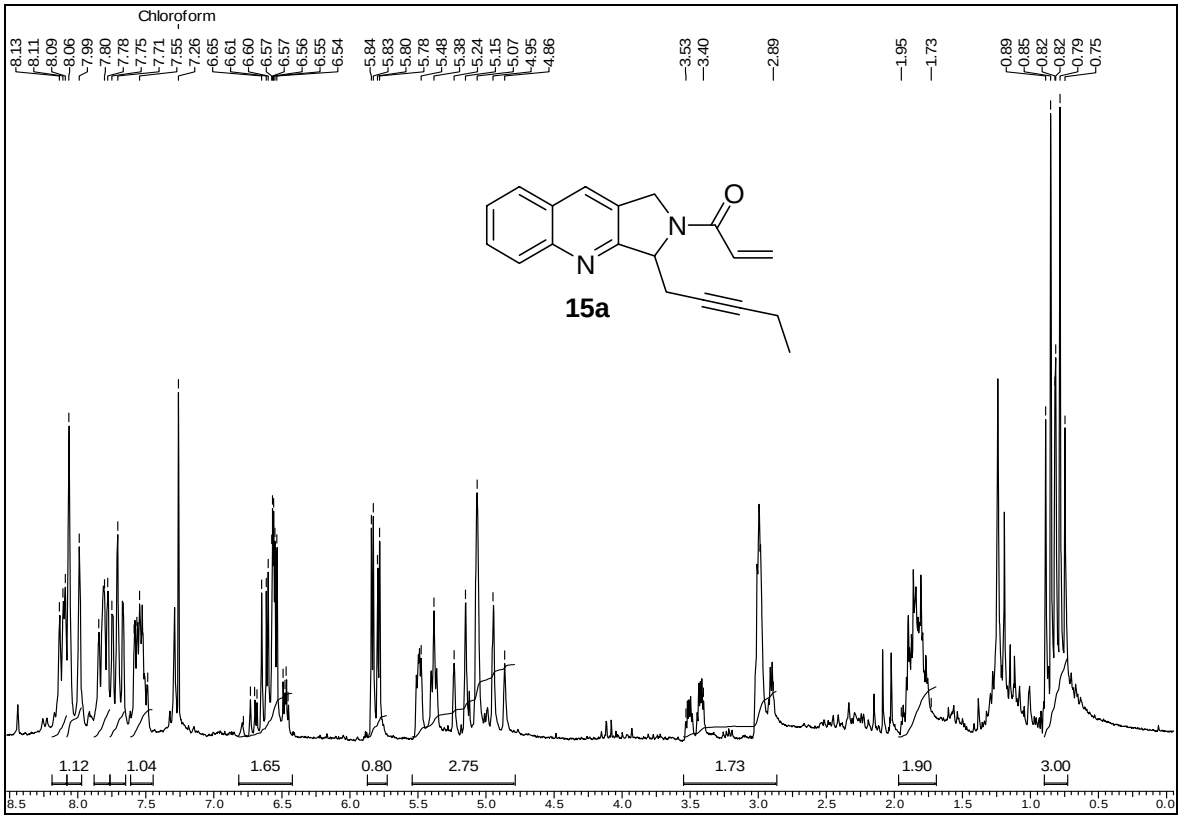
^{1}H NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 200 MHz)



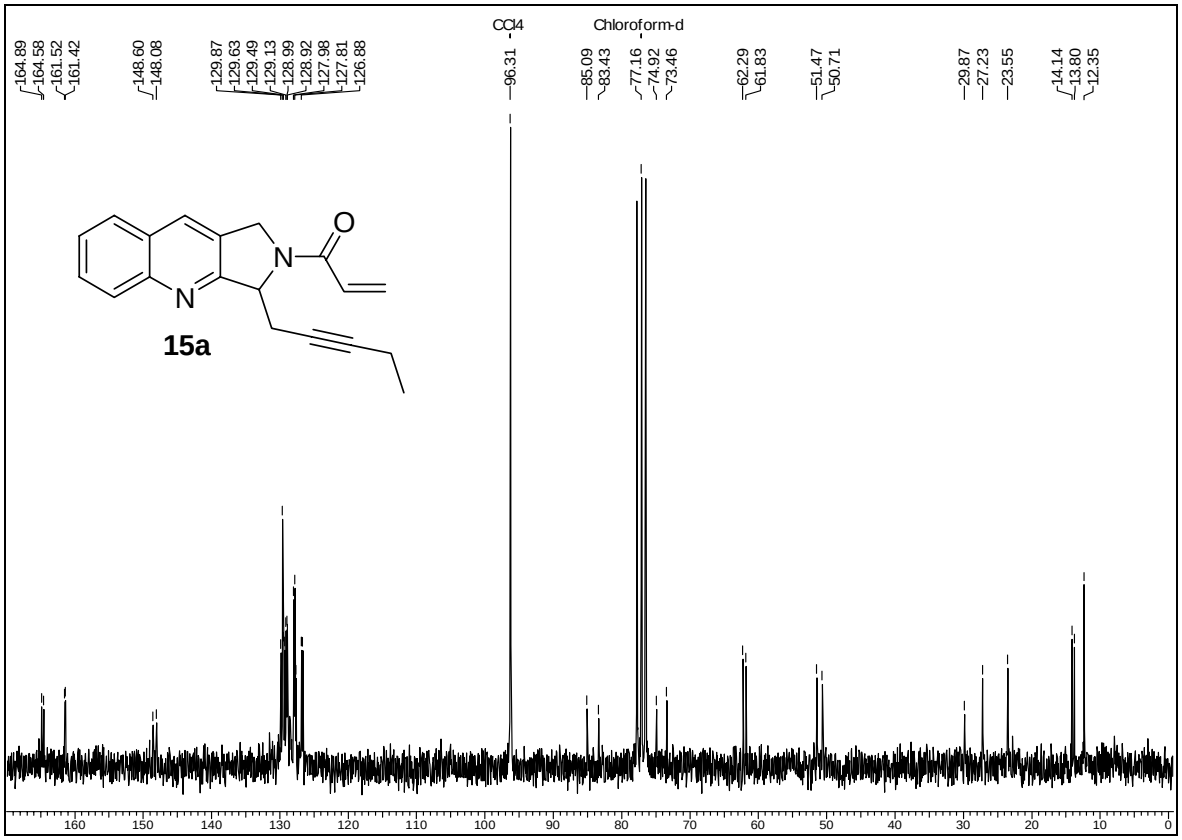
^{13}C NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 100 MHz)



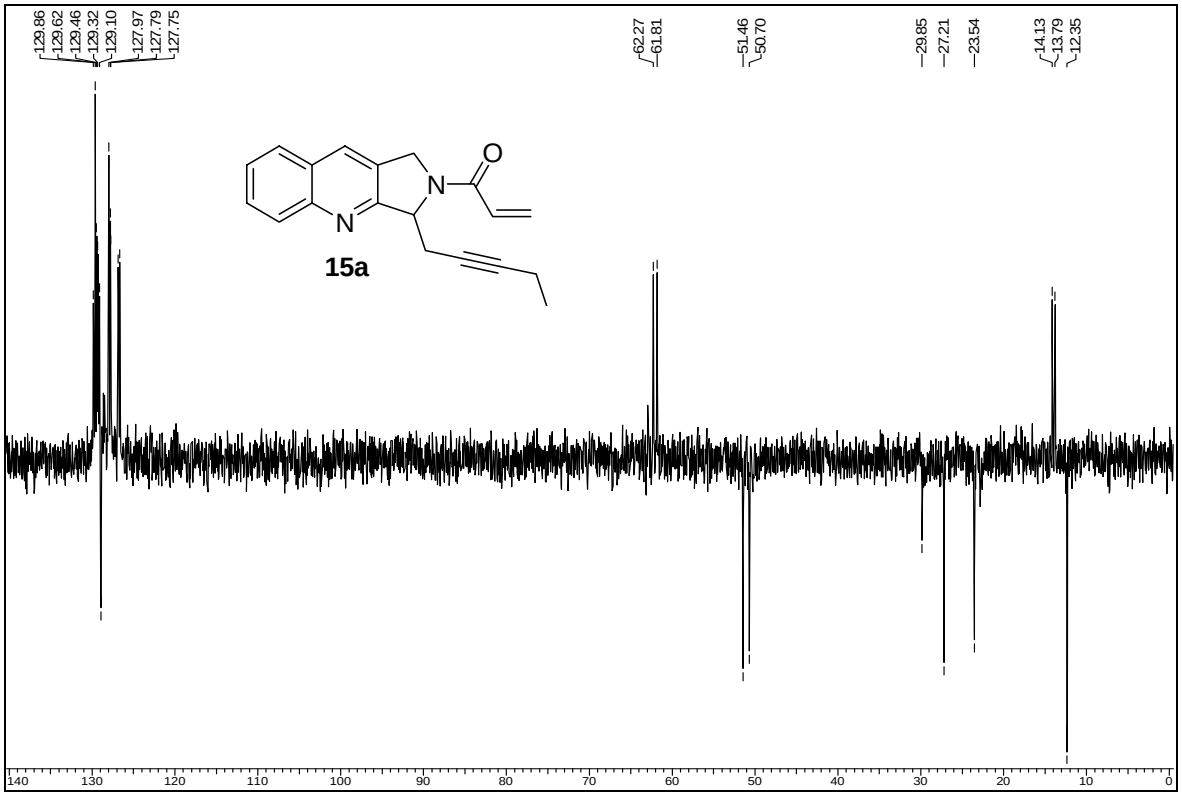
DEPT spectrum of compound 7 ($CDCl_3$ + CCl_4, 100 MHz)



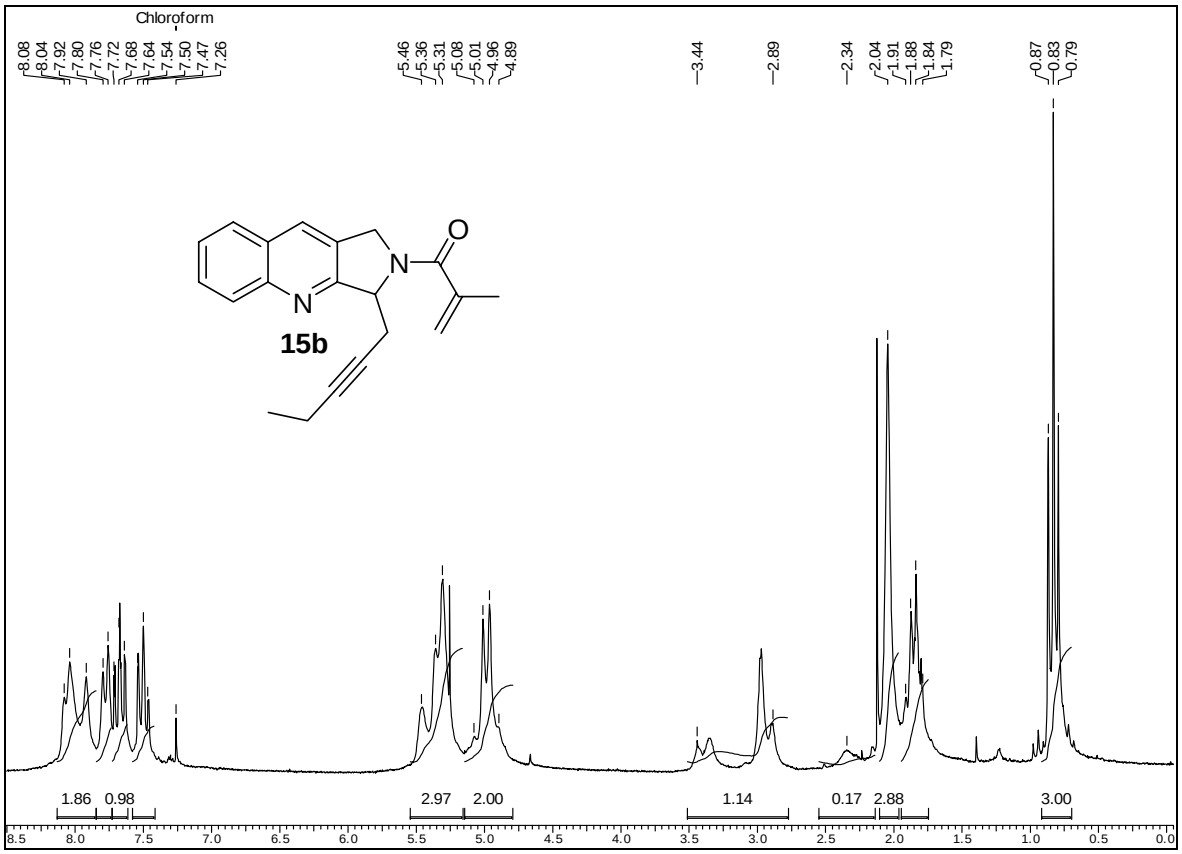
^{1}H NMR spectrum of compound 15a ($CDCl_3$ + CCl_4, 200 MHz)



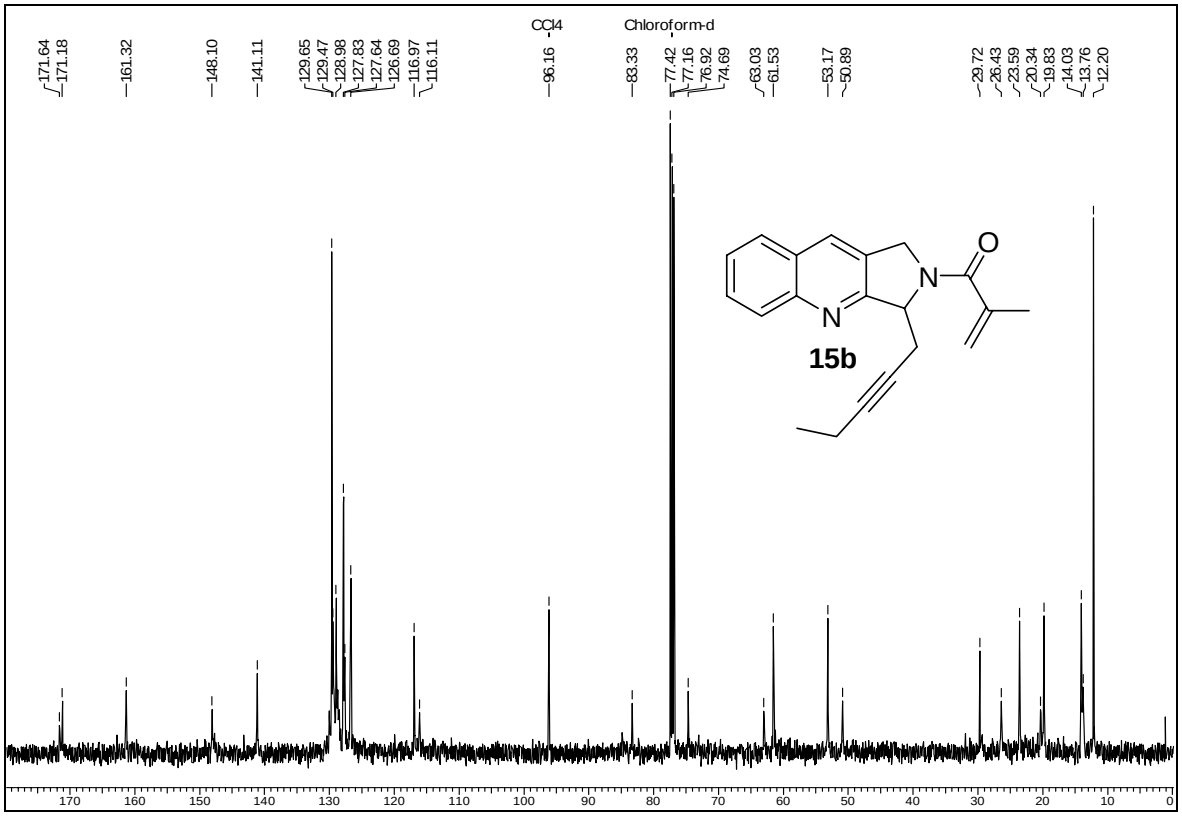
^{13}C NMR spectrum of compound 15a ($CDCl_3$ + CCl_4, 50 MHz)



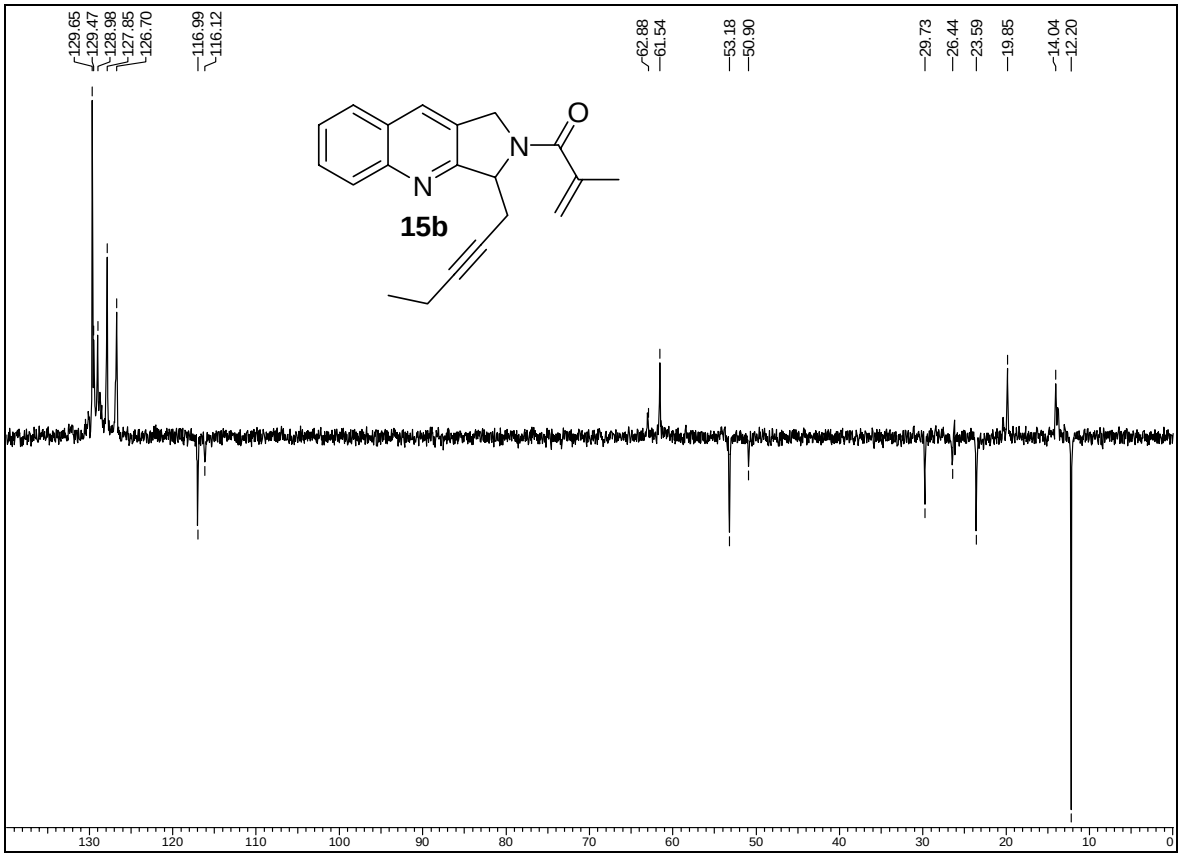
DEPT spectrum of compound 15a ($CDCl_3$ + CCl_4, 50 MHz)



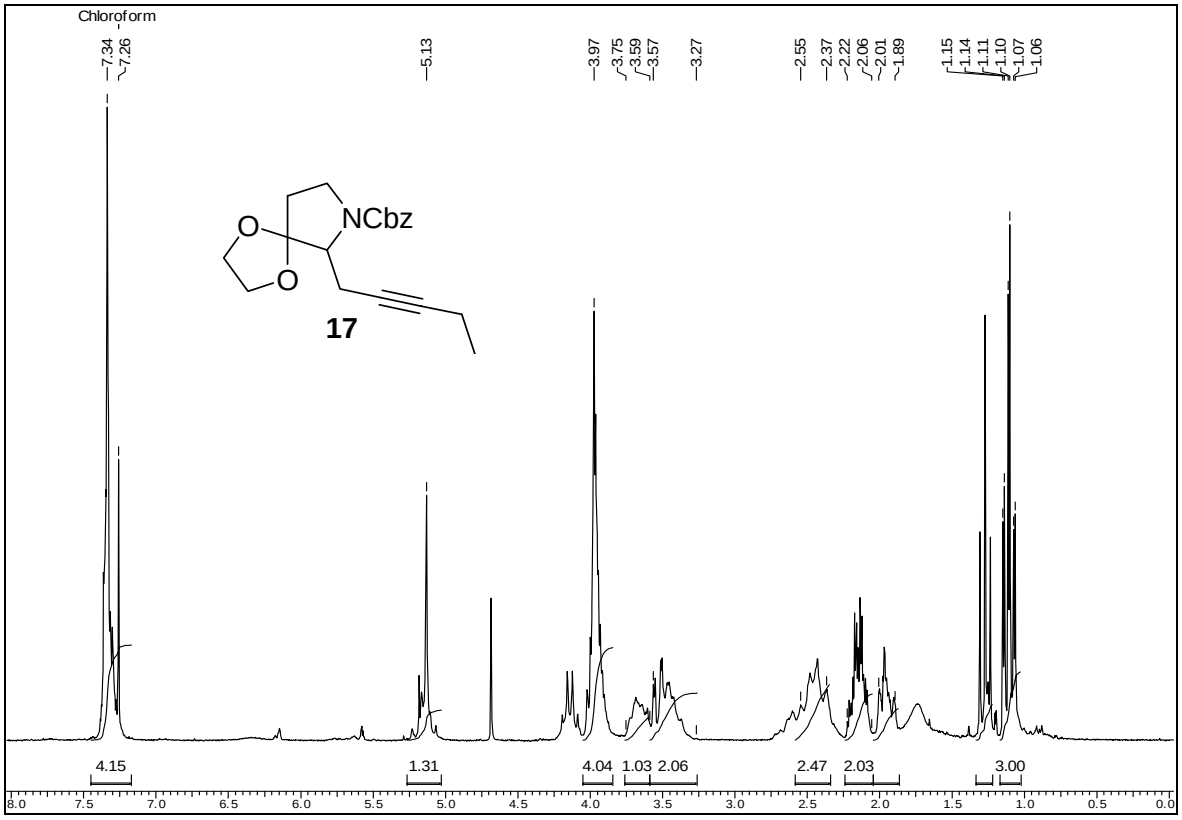
^{1}H NMR spectrum of compound 15b ($CDCl_3$ + CCl_4, 200 MHz)



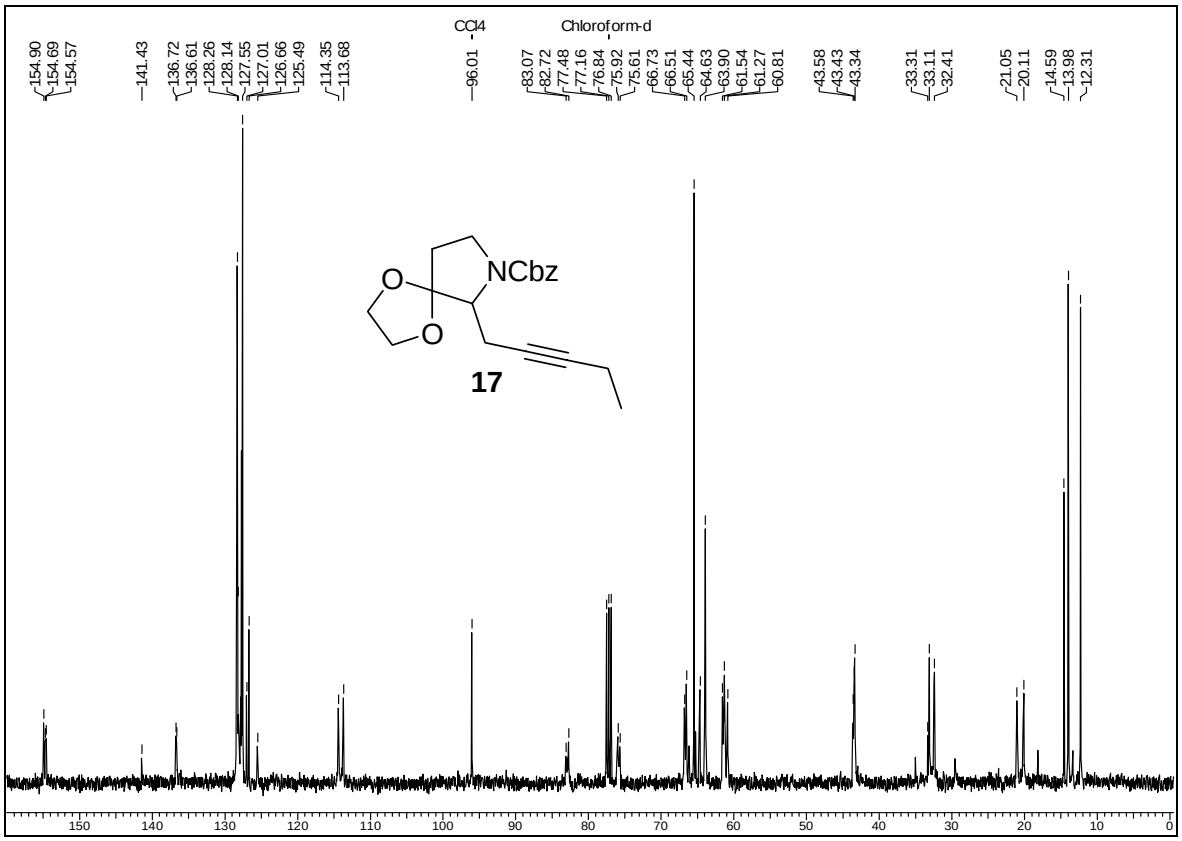
^{13}C NMR spectrum of compound 15b ($CDCl_3$ + CCl_4, 100 MHz)



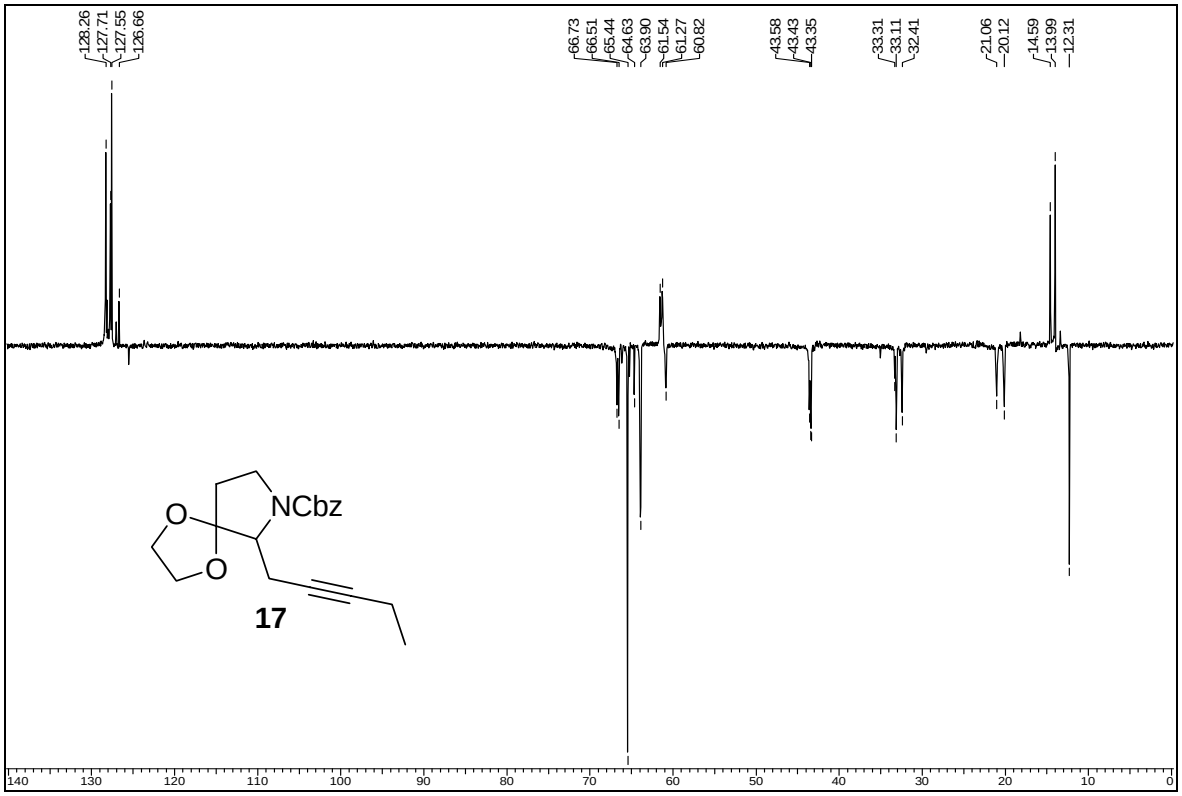
DEPT spectrum of compound 15b ($CDCl_3$ + CCl_4, 100 MHz)



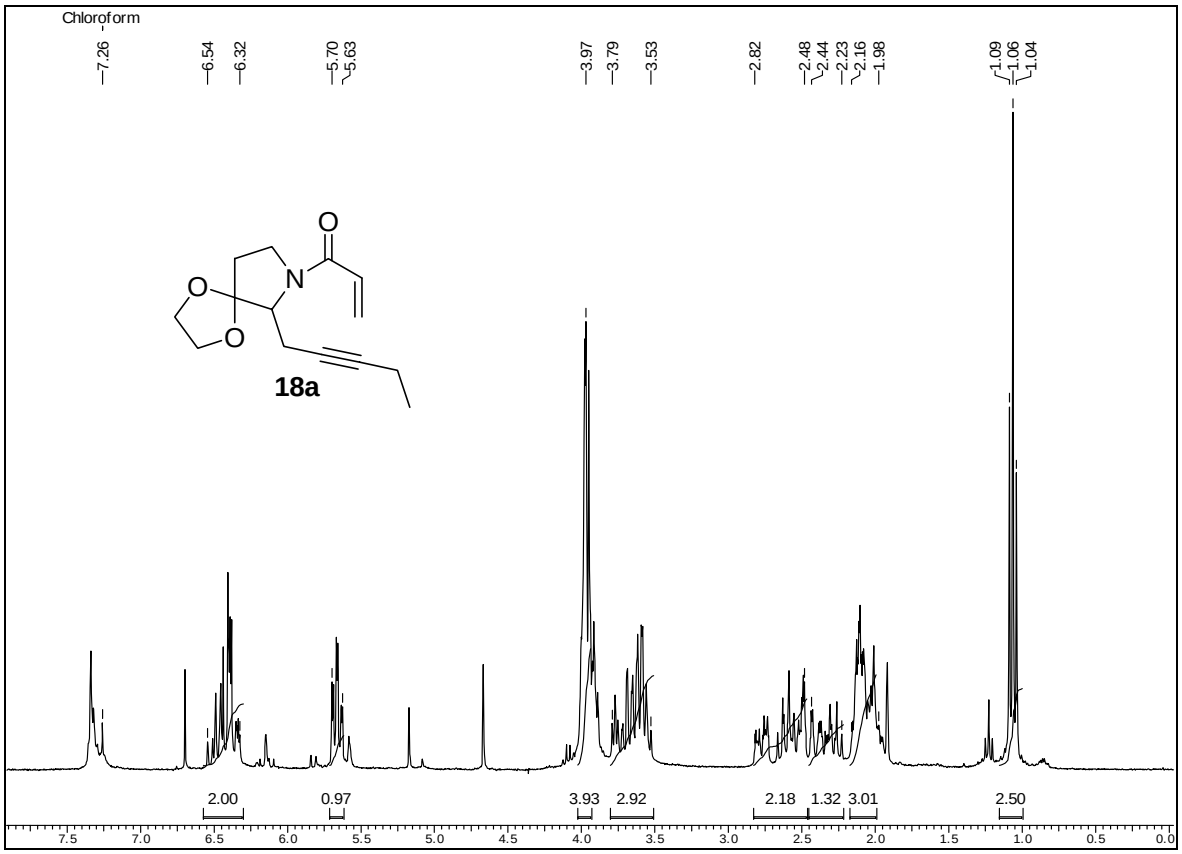
^{1}H NMR spectrum of compound 17 ($CDCl_3$ + CCl_4, 200 MHz)



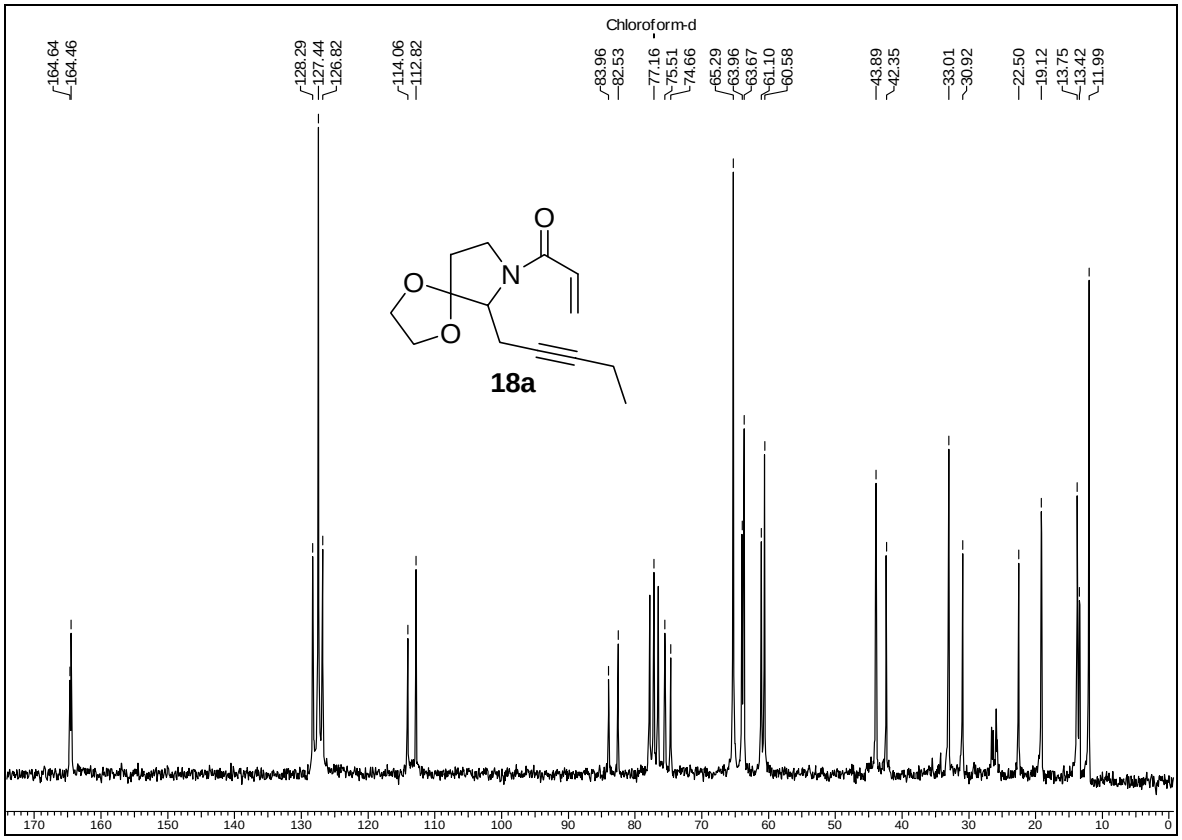
^{13}C NMR spectrum of compound 17 ($CDCl_3$ + CCl_4, 100 MHz)



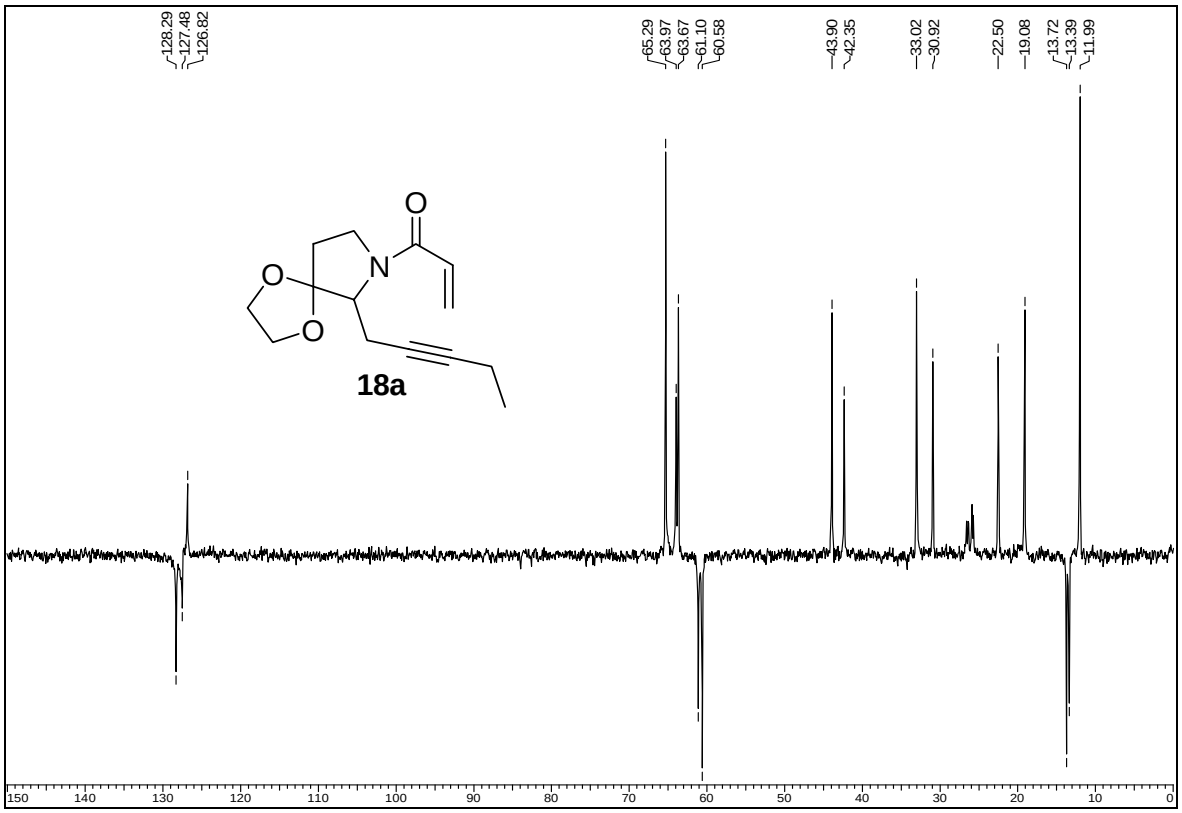
DEPT spectrum of compound 17 ($CDCl_3$ + CCl_4, 100 MHz)



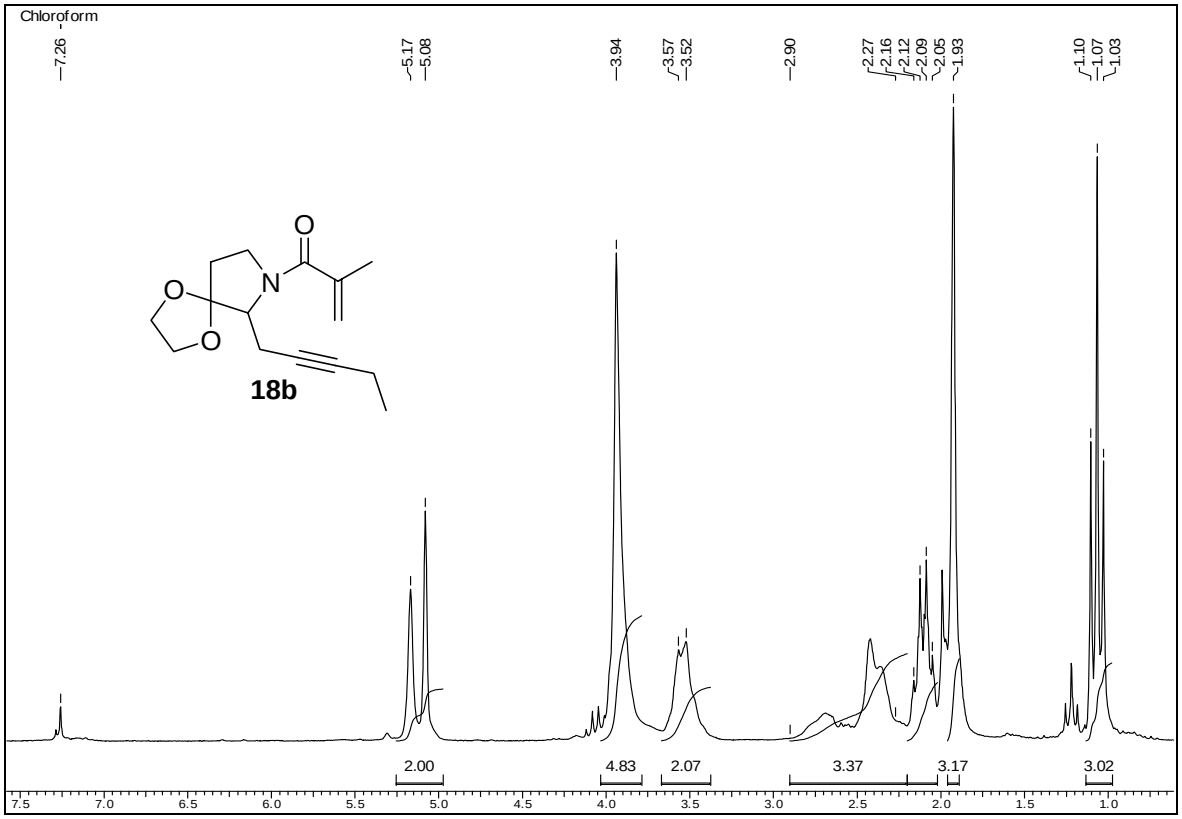
^{1}H NMR spectrum of compound 18a ($CDCl_3$ + CCl_4, 200 MHz)



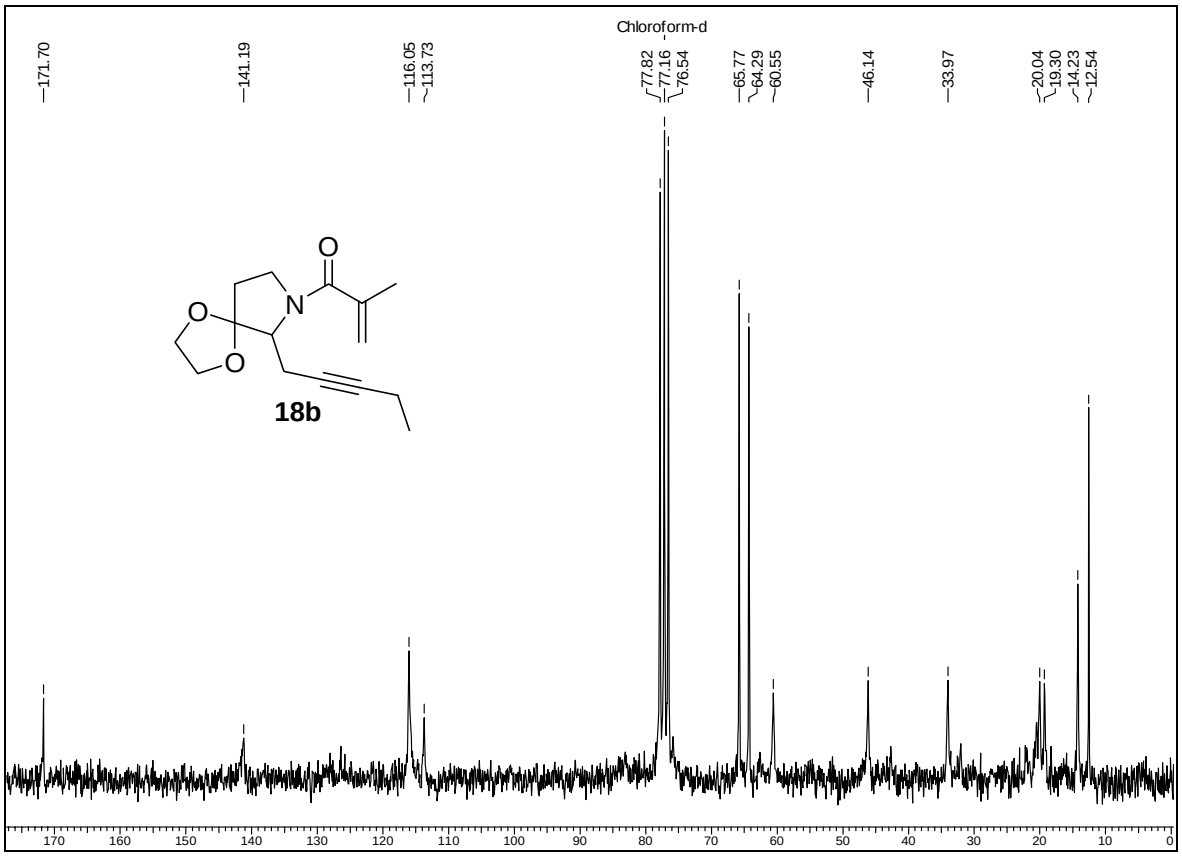
^{13}C NMR spectrum of compound 18a ($CDCl_3$, 50 MHz)



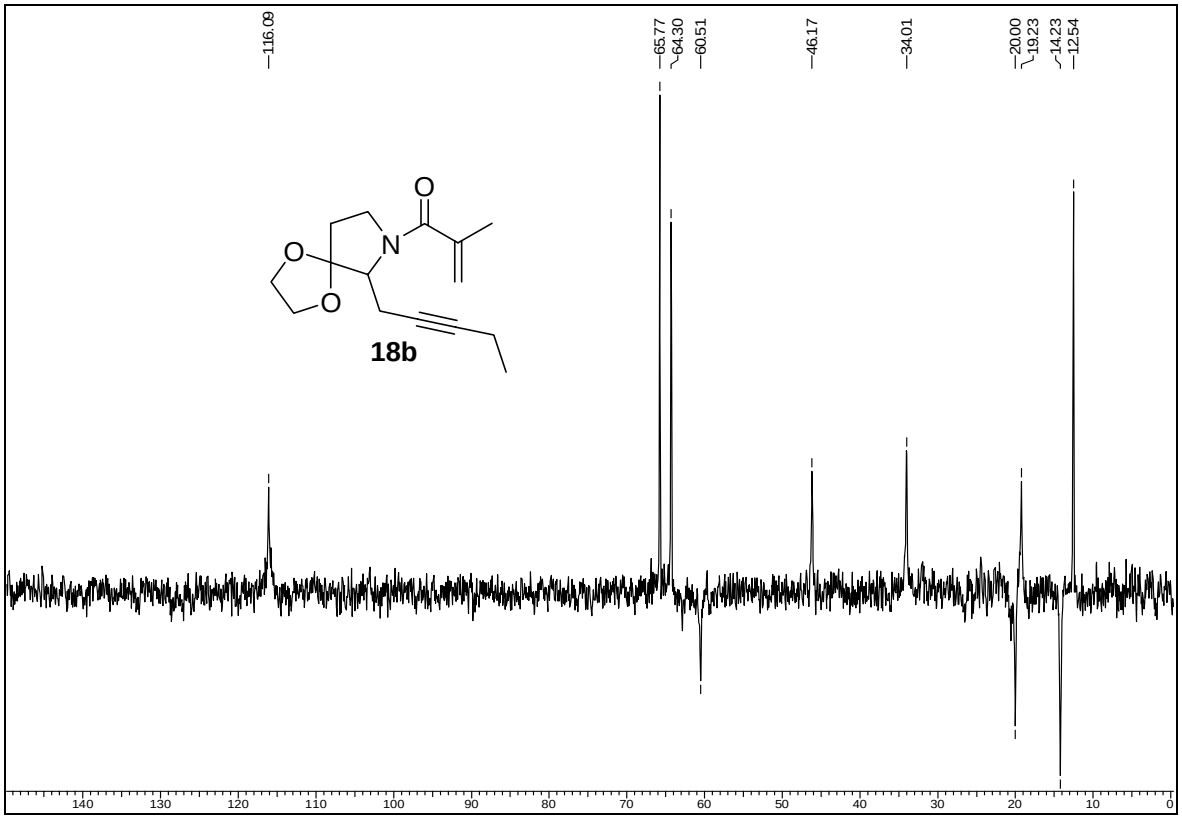
DEPT spectrum of compound 18a ($CDCl_3$, 50 MHz)



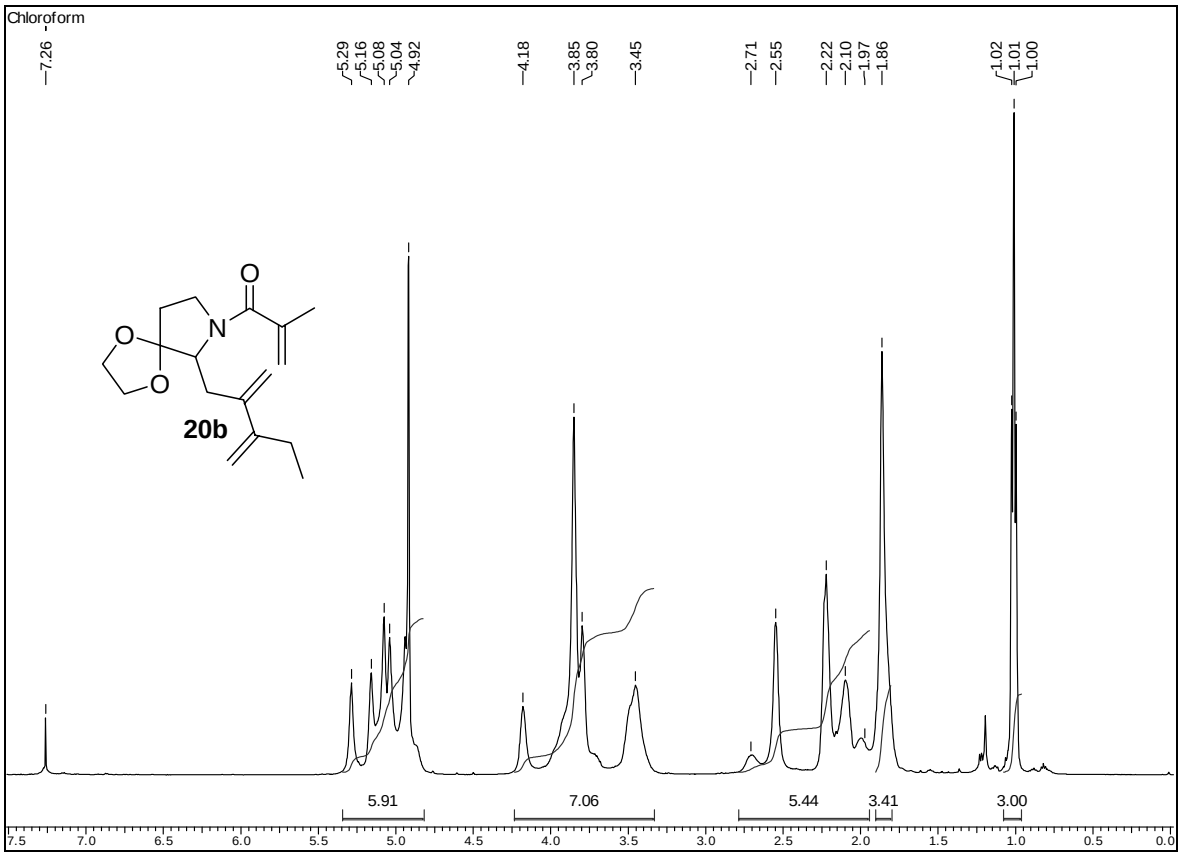
^{1}H NMR spectrum of compound 18b ($CDCl_3$, 200 MHz)



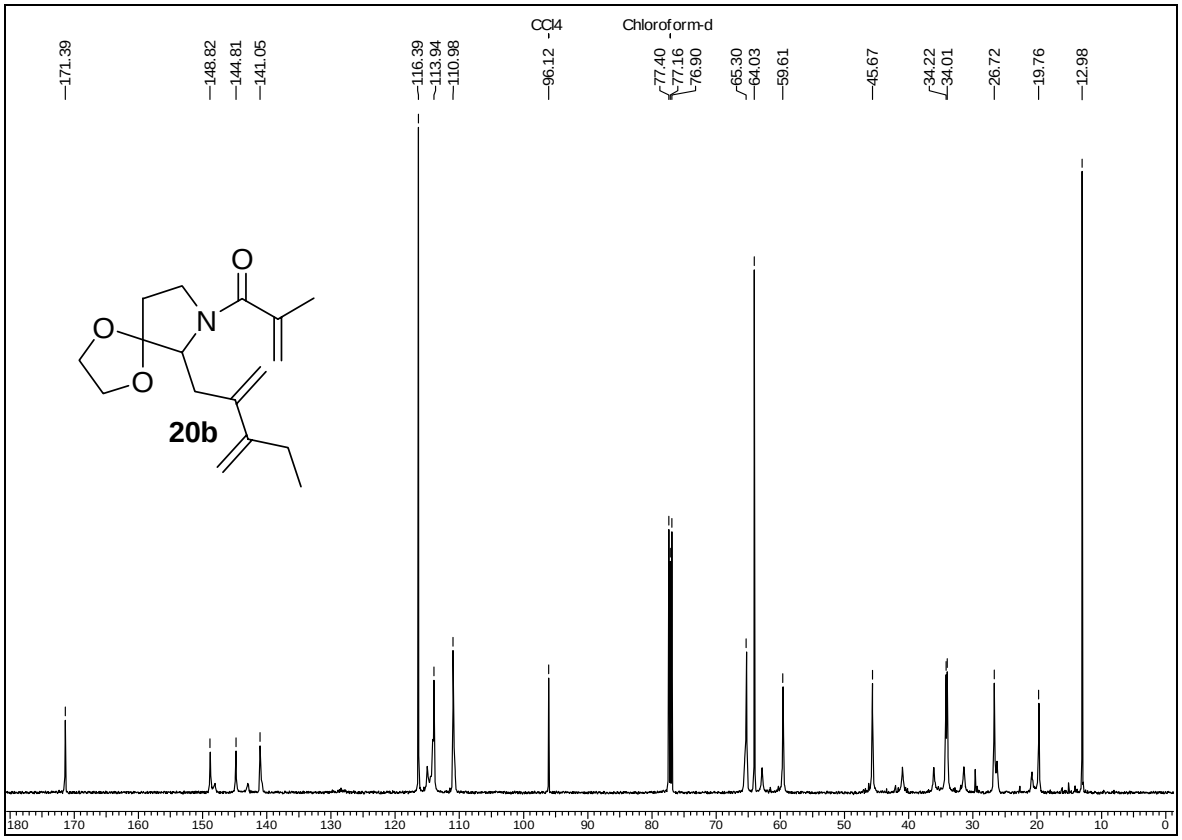
^{13}C NMR spectrum of compound 18b ($CDCl_3$, 50 MHz)



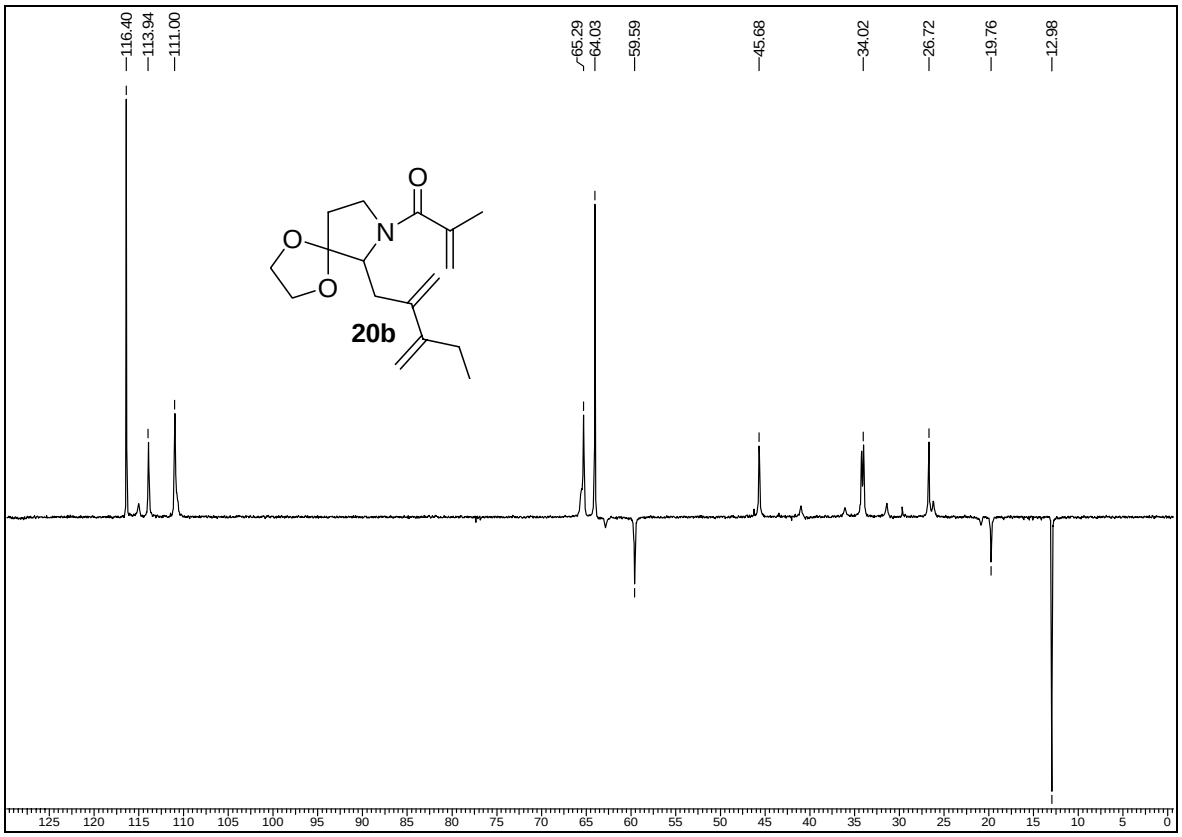
DEPT spectrum of compound 18b ($CDCl_3$, 50 MHz)



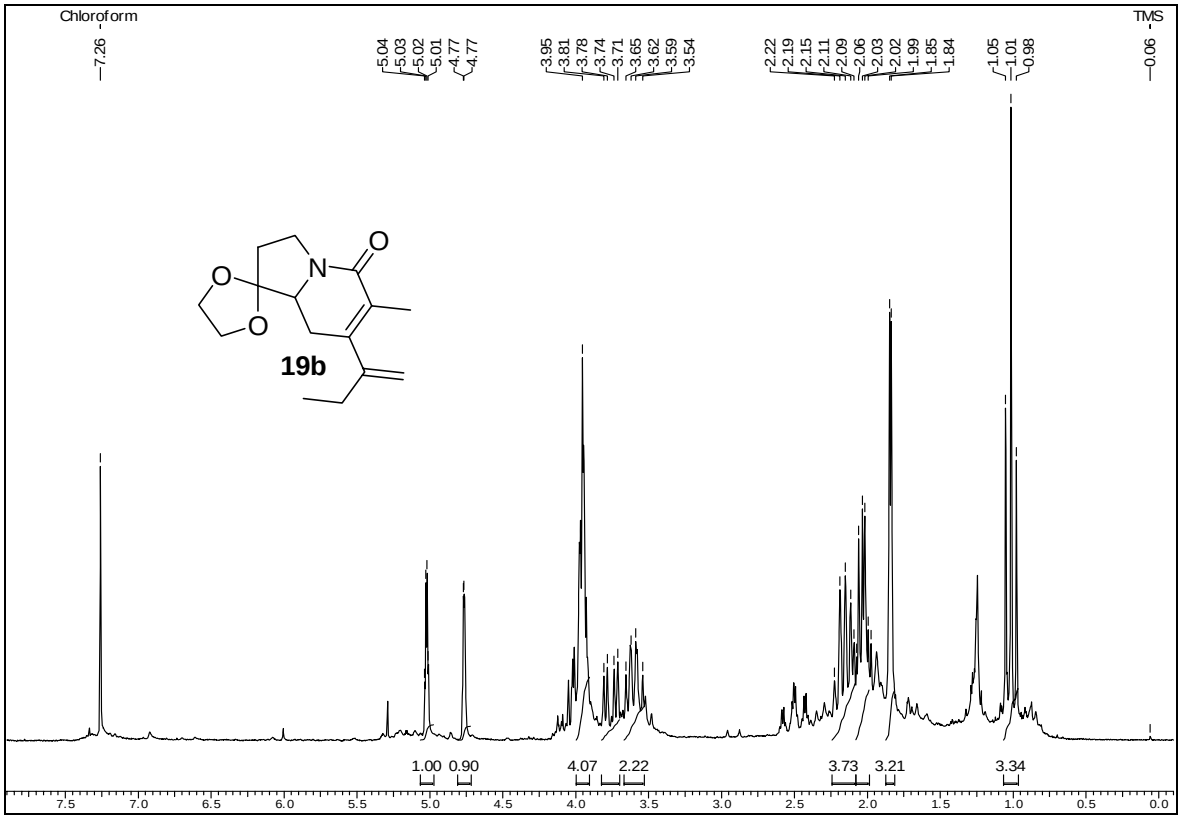
^{1}H NMR spectrum of compound 20b ($CDCl_3$ + CCl_4, 200 MHz)



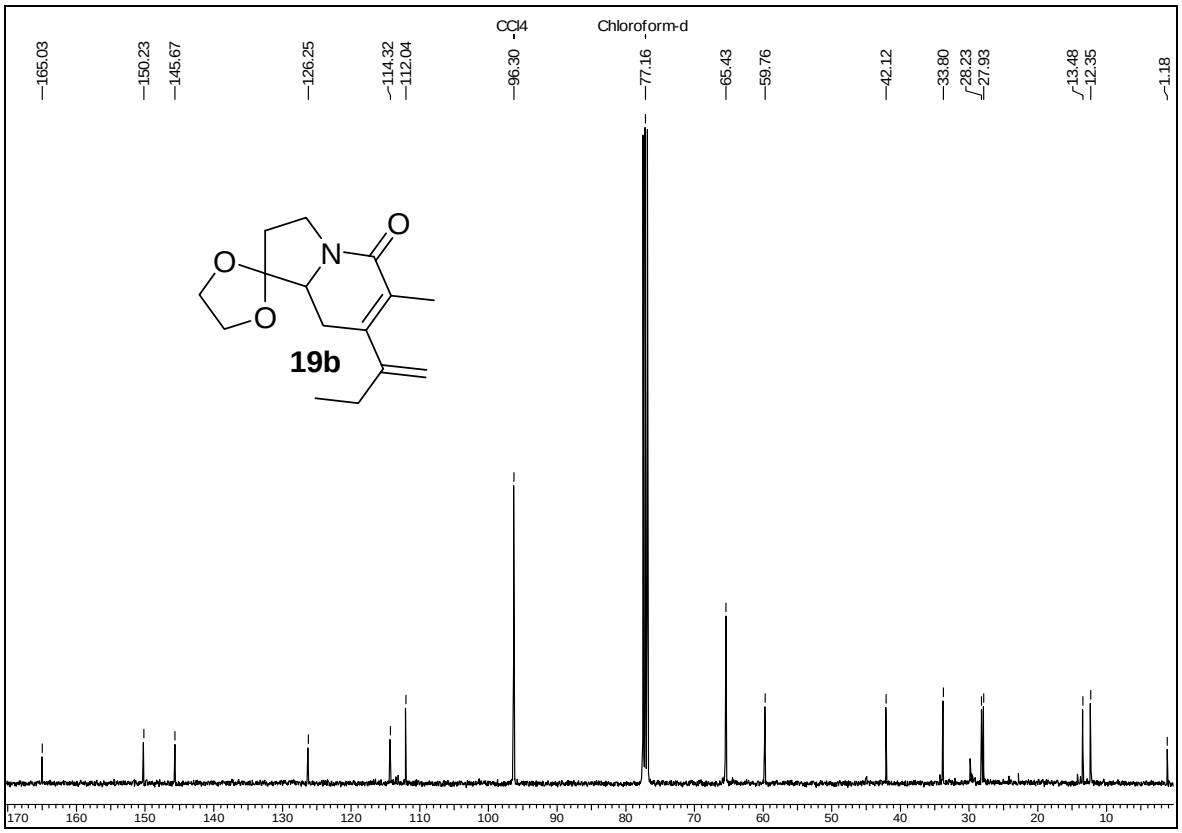
^{13}C NMR spectrum of compound 20b ($CDCl_3$ + CCl_4, 100 MHz)



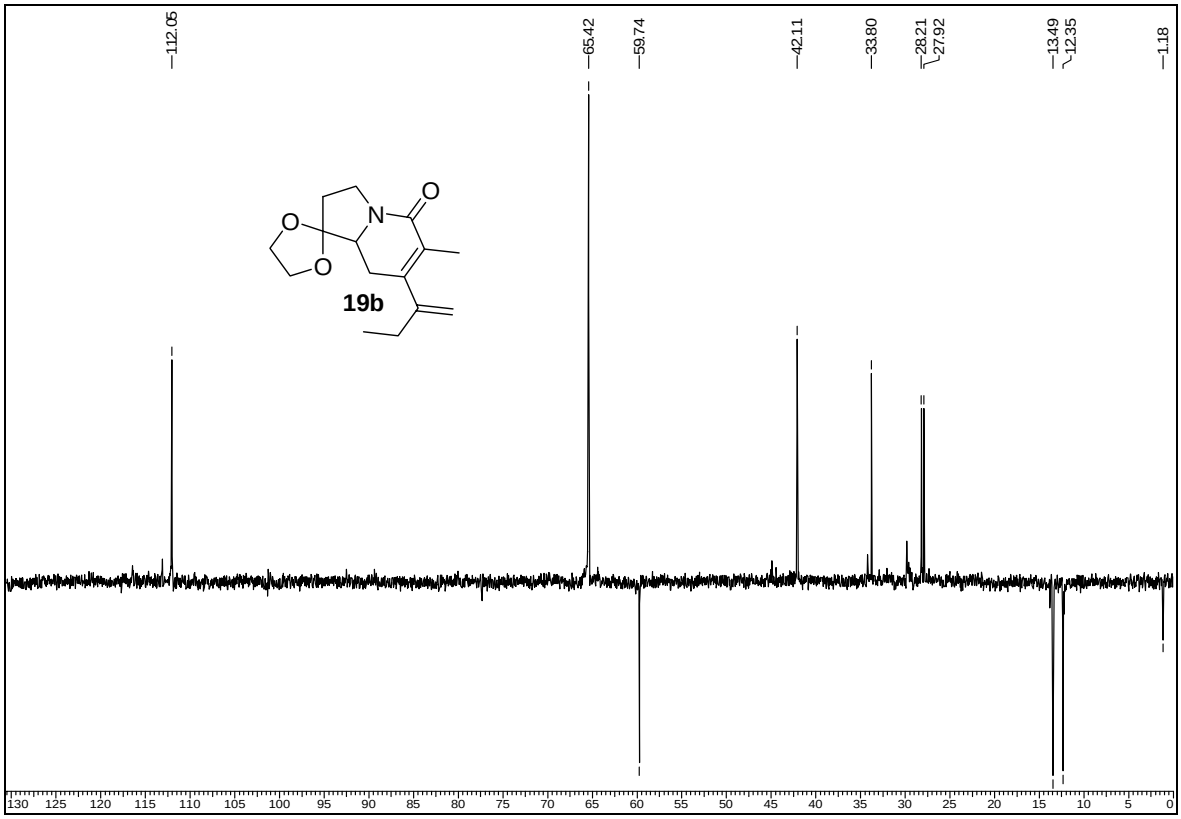
DEPT spectrum of compound 20b ($CDCl_3$ + CCl_4, 100 MHz)



^{1}H NMR spectrum of compound 19b ($CDCl_3$ + CCl_4, 200 MHz)



^{13}C NMR spectrum of compound 19b ($CDCl_3$ + CCl_4, 100 MHz)



DEPT spectrum of compound 19b ($CDCl_3$ + CCl_4, 100 MHz)

1.3.7 References

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Chapter 2, Section I

Total synthesis of (±)-camptothecin employing tandem Knoevenagel condensation and Michael addition

2.1.1 Introduction:

The Reformatsky reaction[1-4] is very well known reaction for the carbon-carbon bond formation under mild reaction conditions. An aldehyde or ketone is treated with zinc and α-halo ester, vinylog of an α-halo ester, α-halo nitriles, α-halo ketones and α-halo *N,N*-disubstituted amides in ethers (*viz*. Et_2O, THF and 1,4-dioxane) gives β-hydroxy ester (figure 1) or sometimes eliminated compound α,β-unsaturated ester (in case of aryl aldehydes) and this sometimes becomes alternative to Wittig reaction.

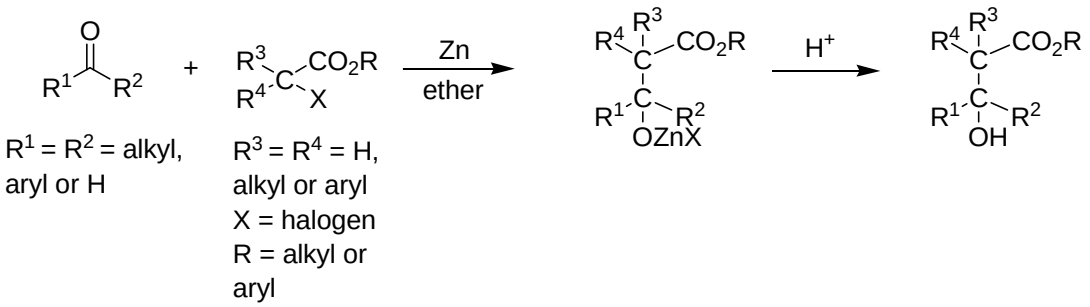


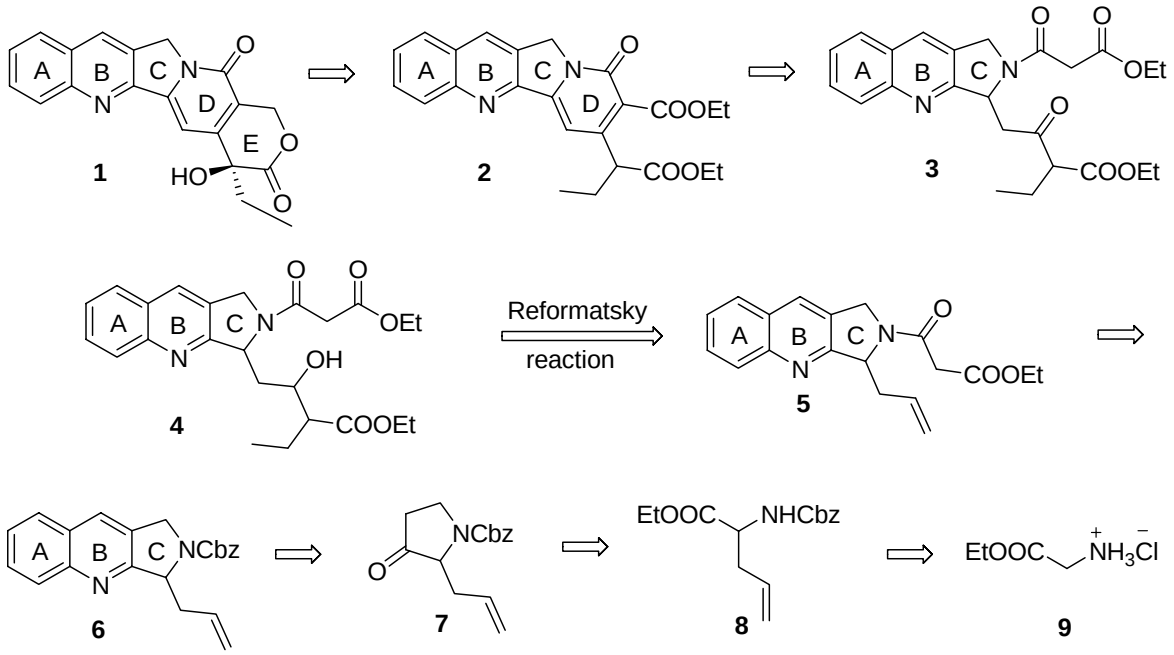
Figure 1.

2.1.2 Present work:

After achieving the synthesis of advanced intermediate of camptothecin and its analogues employing tandem ethylene cross enyne metathesis followed by ring-closing metathesis strategy, as a part of the ongoing programme to synthesize the camptothecin and its analogues which exhibited impressive anticancer activity, this group has been synthesizing the camptothecin and its analogues by different protocols.[5] In this section the feasibility of mild intermolecular Reformatsky reaction as well as intermolecular Michael reaction of carbon nucleophile on an activated tetracyclic dihydropyridone substrates is described.

As per retrosynthetic plan 1 depicted in scheme 1 the CPT **1** could be synthesized from diester **2** by selective reduction followed by lactonization and enantioselective hydroxylation, the diester **2** could be accessed from keto ester **3** by intramolecular Knoevenagel condensation and aromatization. The β-keto ester **3** could be obtained from hydroxy compound **4** by oxidation; the hydroxy compound **4** in turn would be realized from amide **5** by oxidative cleavage followed by Reformatsky reaction. The amide **5** in turn could be prepared from carbamate **6** by Cbz deprotection followed by condensation with ethyl malonyl chloride. The carbamate **6** can be readily obtained from keto compound **7** by Friedlander condensation. Keto compound **7** in turn could be prepared from

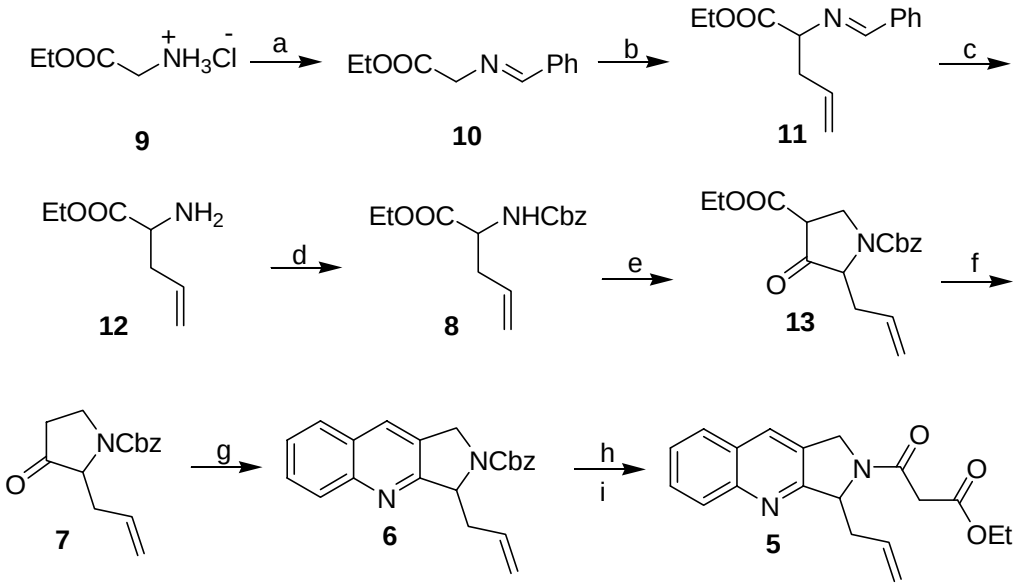
carbamate **8** and carbamate **8** could be synthesized from commercially available ethyl ester of glycine hydrochloride salt **9** by sequence of simple transformation.



Scheme 1. *Retrosynthetic plan 1.*

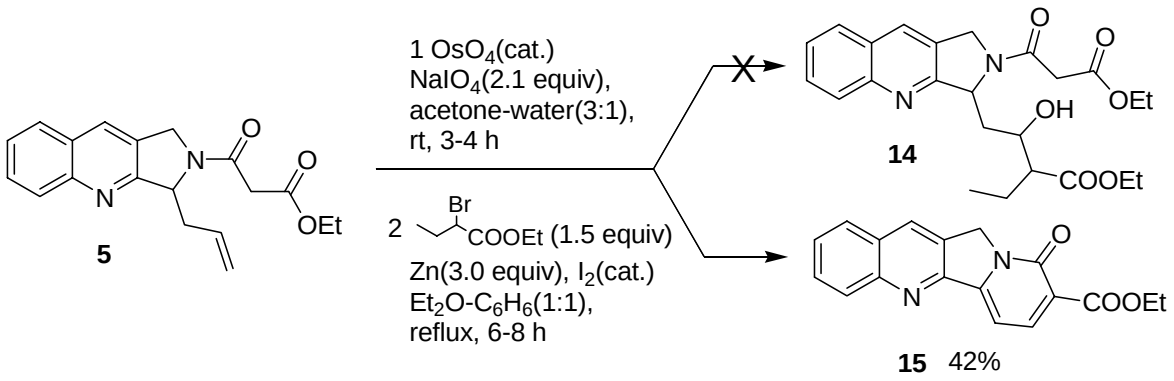
2.1.3 Results and discussion:

According to planned retrosynthetic analysis (scheme 1) the amide **5** which is the precursor for Reformatsky reaction was synthesized from commercially available ethyl ester of glycine hydrochloride salt **9** as per procedure[5a] developed by this group as shown in scheme 2.



Scheme 2. *Reagents and conditions: (a) Et_3N (1.2 equiv), PhCHO (0.9 equiv), MS, dry CH_2Cl_2, 0 ^oC, 1 h, 98%. (b) 10% NaOH (1.5 equiv), allyl bromide (1.2 equiv), $TBAHSO_4$ (0.1 equiv), CH_2Cl_2, rt 2 h, 96%. (c) 10% HCl (1.5 equiv), rt, 0.5 h, 92%. (d) K_2CO_3 (3.0 equiv), benzylchloroformate (1.1 equiv), anhydrous CH_2Cl_2, 0 ^oC, 1h, 91%. (e) NaH (1.2 equiv), ethyl acrylate (1.2 equiv), C_6H_6, rt 1h, refluxed 2-3 h, 72%. (f) NaCl (4.0 equiv), DMSO-H_2O (3:1), 120-130 ^oC, 6 h, 78%. (g) N-(o-aminobenzilidine)-p-toluidine (1.2 equiv), PTSA (cat), anhydrous toluene, reflux, 6 h 86%. (h) KOH, EtOH, reflux, 8h; (i) K_2CO_3 (1.2 equiv), ethyl malonyl chloride (1.2 equiv), dry CH_2Cl_2, 0 ^oC 1-2 h, 67% in two steps.*

The amide **5** was treated with catalytic amount of OsO_4 and 2.1 equivalent of $NaIO_4$ in acetone-water at room temperature furnished the corresponding aldehyde. This resultant aldehyde was subsequently subjected to Reformatsky reaction with 1.5 equivalents of ethyl 2-bromobutyrate, 3.0 equivalents of Zinc powder and catalytic amount of iodine in the mixture of diethyl ether and benzene (1:1) and was refluxed for 6-8 h but unfortunately it did not yield the desired product **14**. Instead a complex reaction mixture along with traces of aromatic compound **15** was observed**.**

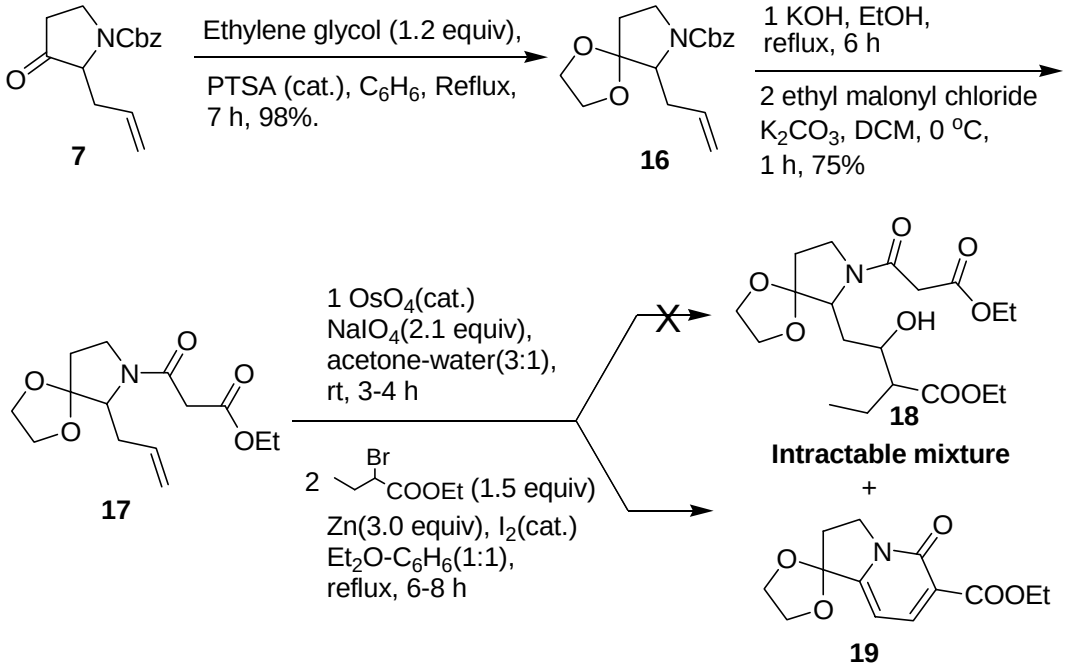


Scheme 3.

The formation of compound **15** was confirmed by spectral analysis. ^1H NMR spectrum of **15** displayed the triplet and quartet at δ 1.43 & 4.43 (J = 7.1 Hz) corresponding to three and two protons indicated the presence of ethyl ester functionality. Singlet at δ 5.35 for two protons were observed which were assigned to benzylic protons, doublet at δ 7.35 (J = 8.2 Hz), triplet at δ 7.69 (J = 7.2 Hz), triplet at δ 7.85 (J = 7.2 Hz), doublet at δ 7.96 (J = 8.2 Hz), doublet at δ 8.25 (J = 8.2 Hz), singlet at δ 8.43, doublet at δ 8.51 (J = 8.2 Hz) corresponding to one proton each and were assigned to aromatic protons. Finally the structure of **15** was confirmed by the mass spectral and elemental analysis. The mass

spectrum of **15** showed the *m/z* peaks at 307 $(M + H)^+$, 329 $(M + Na)^+$. Its elemental analysis was also found to be in good agreement with calculated values.

Having failed to obtain the desired product **14** by Reformatsky reaction (scheme 3), it was thought that the same reaction can be performed on protected compound **17** (scheme 4) which was prepared from keto compound **7**. The keto compound **7** was protected as a cyclic acetal **16** using ethylene glycol and catalytic amount of *p*-TSA in benzene with removal of water by azeotropic distillation. The Cbz group of acetal **16** was deprotected by employing KOH in ethanol at reflux temperature for 8 h to furnish amine[6] and the resultant crude amine was subsequently condensed with ethyl malonyl chloride utilizing potassium carbonate as a base in anhydrous dichloromethane at 0 ^oC yielded the amide **17** in 68% yield in two steps.



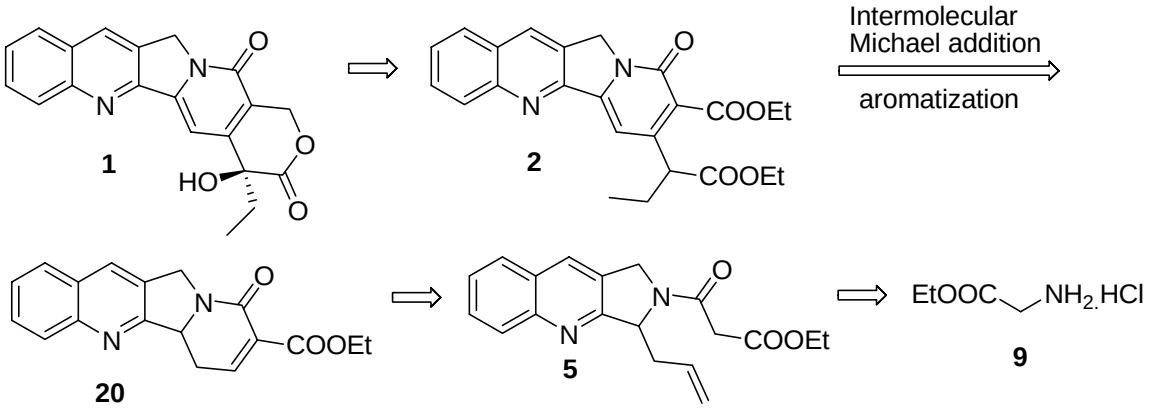
Scheme 4.

The structure of amide **17** was confirmed by spectroscopic data. IR spectrum of **17** showed the disappearance of the absorption band corresponding to Cbz group while appearance of the strong absorption bands at 3457, 1736 and 1647 cm^{-1} indicated the conversion of **16** to **17**. ^1H NMR spectrum of **17** displayed the disappearance the signals corresponding to Cbz group while the triplet and quartet appeared at δ 1.28 (J = 7.1 Hz) & 4.19 (J = 7.1 Hz) which integrated for three and two protons respectively corresponding to ethoxy moiety of the ester. The singlet at δ 3.26 for two protons clearly suggested the introduction of ethyl malonyl moiety. ^{13}C NMR along with DEPT spectra of **17** also confirmed structural

assignment of **17**. The mass spectrum of **17** revealed the *m/z* peak at 284 and 306 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively and by its elemental analysis, which was in good agreement with calculated values.

Thus the compound **17** was converted into corresponding aldehyde by oxidative cleavage of the olefin and was subjected to the Reformatsky reaction under identical conditions as mentioned in scheme 3. But again the intractable mixture along with trace amounts of aromatic compound **19** was observed instead of expected product **18.**

The formation of compound **19** was confirmed by spectral study. ^{1}H NMR spectrum of **19** displayed the triplet and quartet at δ 1.38 & 4.36 (J = 7.1 Hz) respectively integrating for three and two protons corresponding to the presence of ethyl ester functionality. Triplet at δ 2.39 (J = 6.8 Hz) integrating for two protons, triplet at δ 4.02 (J = 6.8 Hz) integrated for two protons, singlet at δ 4.25 integrated for four protons. Two doublets resonated at δ 6.24 & 8.21 (J = 7.3 Hz) integrated for one proton each, were assigned to aromatic protons. Further the structure of **19** was confirmed by the mass spectral and elemental analysis. The mass spectrum of **19** showed the *m/z* peaks at 266 $(M + H)^+$, 288 $(M + Na)^+$, 304 $(M + K)^+$ and further it was confirmed by elemental analysis which was in good agreement with the calculated values.

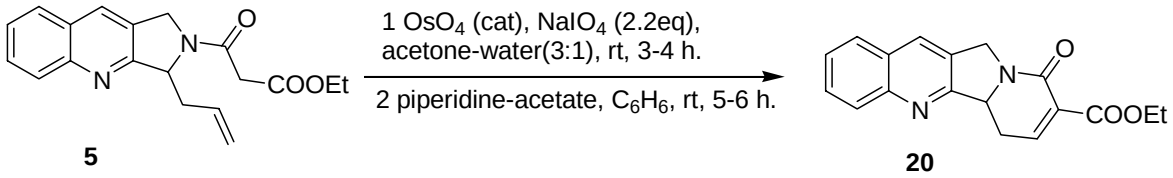


Scheme 5. *Retrosynthetic plan 2.*

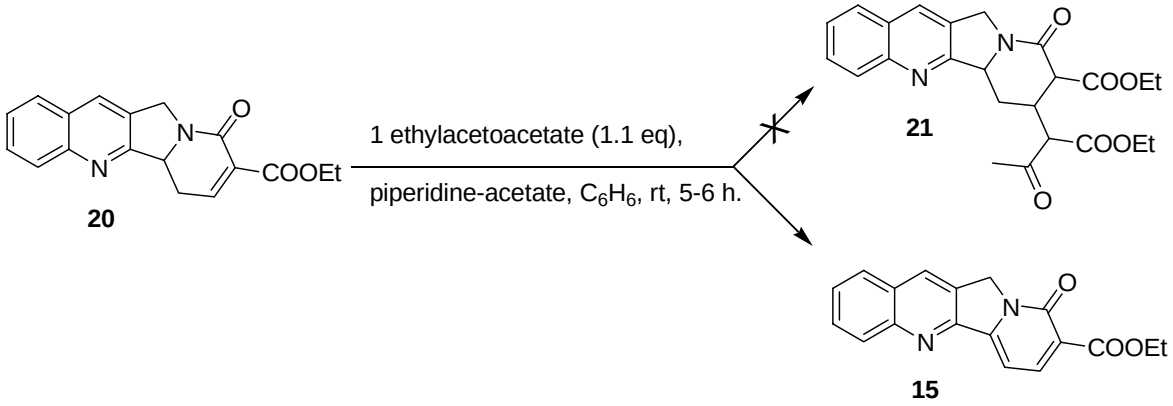
Having failed to obtain the compounds **14** & **18** employing Reformatsky reaction (schemes 3 & 4), it was decided to construct the pyridone ring by Knoevenagel condensation[6-8] and Michael reaction[9-12] as delineated in modified retrosynthetic pathway in scheme 5.

The oxidative cleavage of **5** was accomplished employing similar conditions as shown in scheme 3 to furnish aldehyde and the resultant aldehyde was further treated with piperidine-acetate in benzene at room temperature, delivered dihydropyridone **20** (scheme

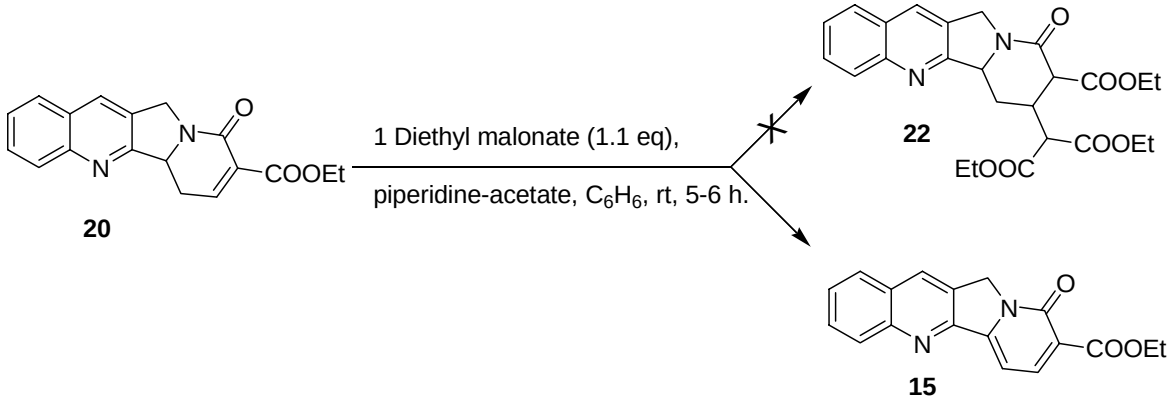
6). The dihydropyridone **20** was unstable therefore it was immediately subjected to intermolecular Michael addition with ethyl acetoacetate using piperidine-acetate as the base gave aromatic compound **15** instead of anticipated Michael adduct **21.** Similarly 1,4-addition with diethyl malonate under identical conditions resulted in formation of **15** instead of desired compound **21**. The formation of aromatic compound **15** instead of desired compounds **21** & **22** can be explained by logical way. There are two possibilities: one is aromatization reaction is competing with intermolecular Michael reaction and rate of aromatization is more than conjugate addition. Second is initially the Michael adduct might be formed but it was further converted into aromatic compound **15**.



Scheme 6.

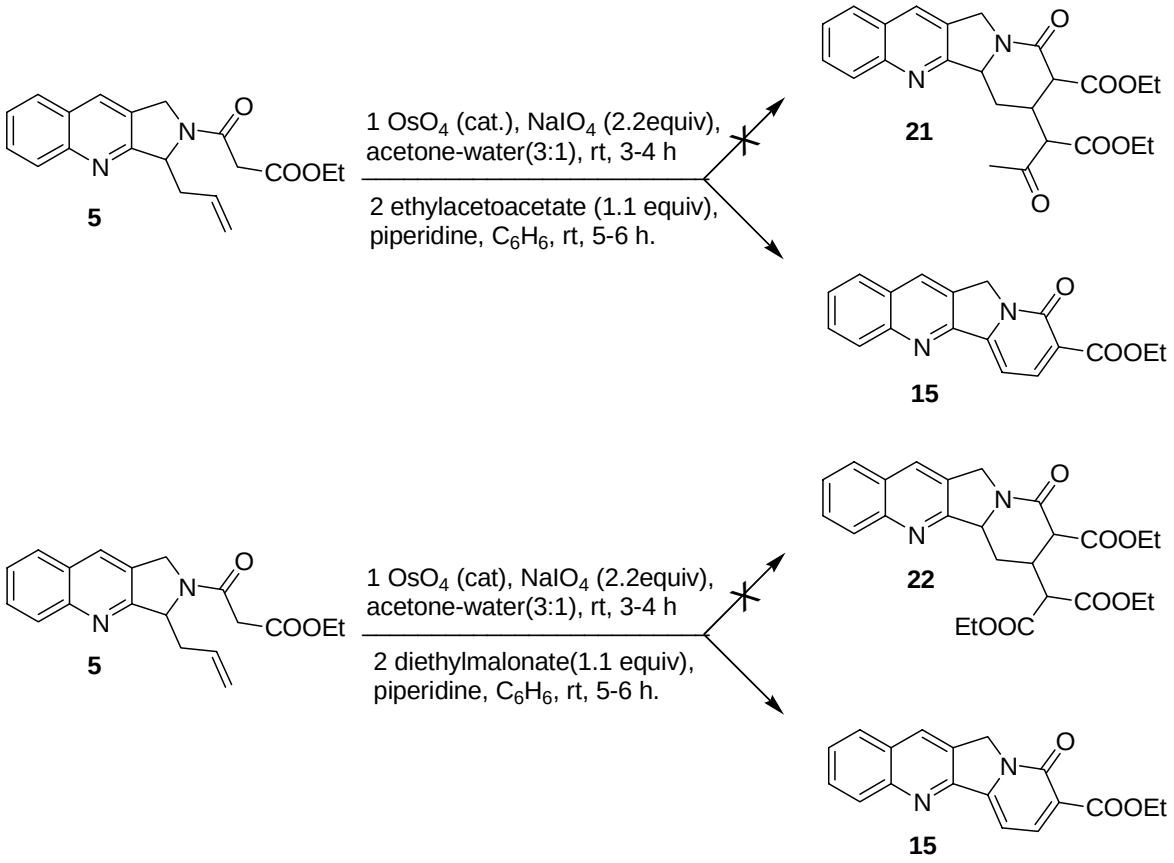


Scheme 7.



Scheme 8.

Having failed to obtain the Michael adducts **21** & **22**, it was thought that the simultaneous addition of the piperidine-acetate and ethyl acetoacetate to the solution of aldehyde and progress of reaction was monitored by TLC. And it indicated that the formation aromatic compound **15** goes through Michael adduct **21.** The formation of intermediate **21** was confirmed by spectral data analysis. ^{1}H NMR spectrum of **21** showed the disappearance of signals corresponding to three olefinic protons while multiplet appeared at δ 1.19-136 corresponding to the six protons ($OCOCH_2C\underline{H_3}$). The signal at δ 2.09 for three protons was assigned to acetyl protons and the multiplet at δ 4.06-4.44 corresponding to four protons was assigned to methylene protons of acetal ($OCOC\underline{H_2}CH_3$). The ^{13}C NMR along with DEPT spectra of **21** displayed it to be the mixture of diastereomers. Finally the formation of intermediate **21** was confirmed by mass spectrum. The mass spectrum of **21** showed *m/z* peak at 439, 461 & 477 corresponding to $(M + 1)^+$, $(M + Na)^+$ and $(M + K)^+$ respectively.

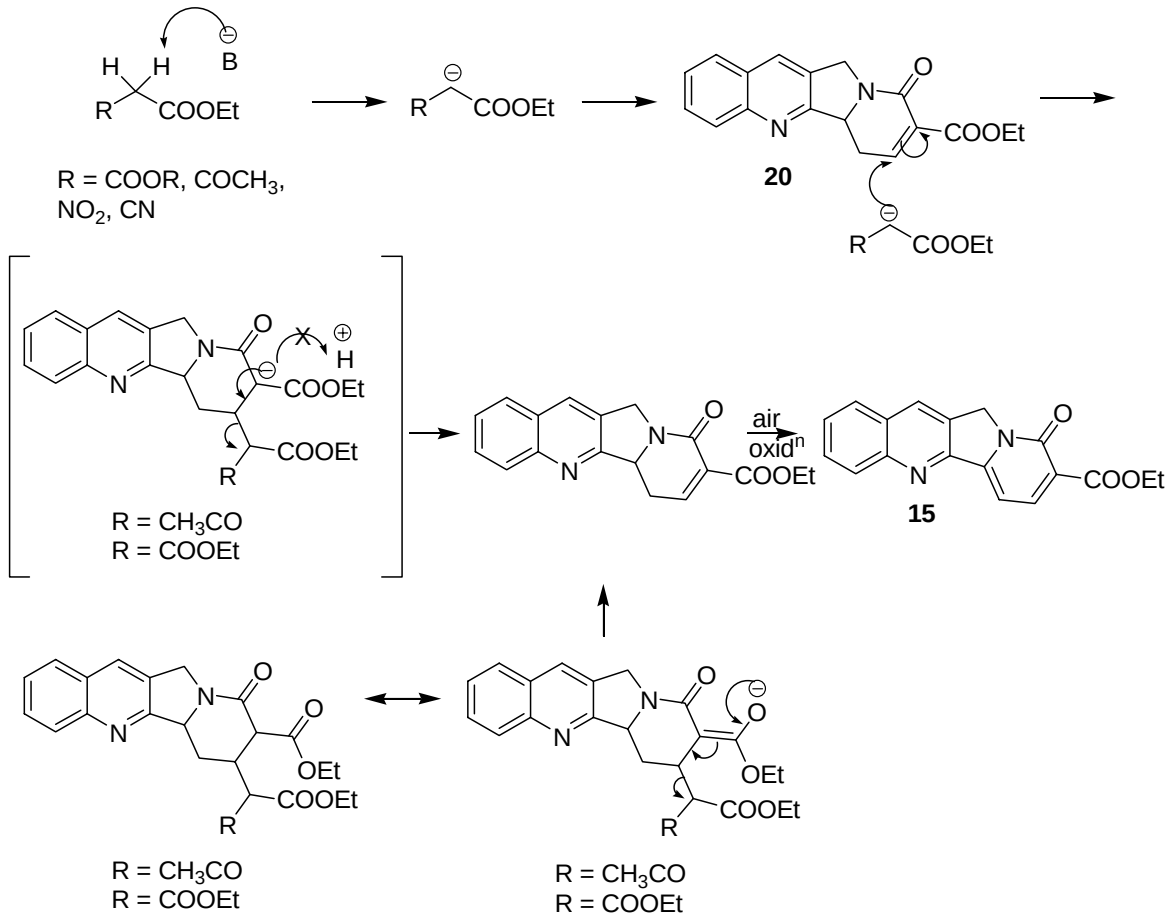


Scheme 9.

Similarly the formation of compound **22** was also confirmed by spectral study. ^{1}H NMR spectrum of **22** showed the disappearance of the signals corresponding to three olefinic protons. While new multiplet appeared at δ 1.20-1.37 integrated for nine protons that were

assigned to methyl protons ($OCOCH_2C\underline{H_3}$), multiplet that appeared at δ 2.83-4.00 integrating for five protons and multiplet appeared at δ 4.06-4.47 integrated for six protons were assigned to methylene ester protons ($OCOC\underline{H_2}CH_3$). The ^{13}C NMR along with DEPT spectra of **22** showed the presence of diastereomers. Lastly the formation of **22** was confirmed by mass spectral analysis which revealed the *m/z* peaks at 369, 391 & 507 corresponding to $(M + 1)^+$, $(M + Na)^+$ and $(M + K)^+$ respectively. It suggests that the generated Michael adduct of ethyl acetoacetate or diethylmalonate may be unstable and it was further converted into aromatized compound. This may be due to the tendency of stabilised nucleophiles to undergo retro Michael reaction due to resonance.

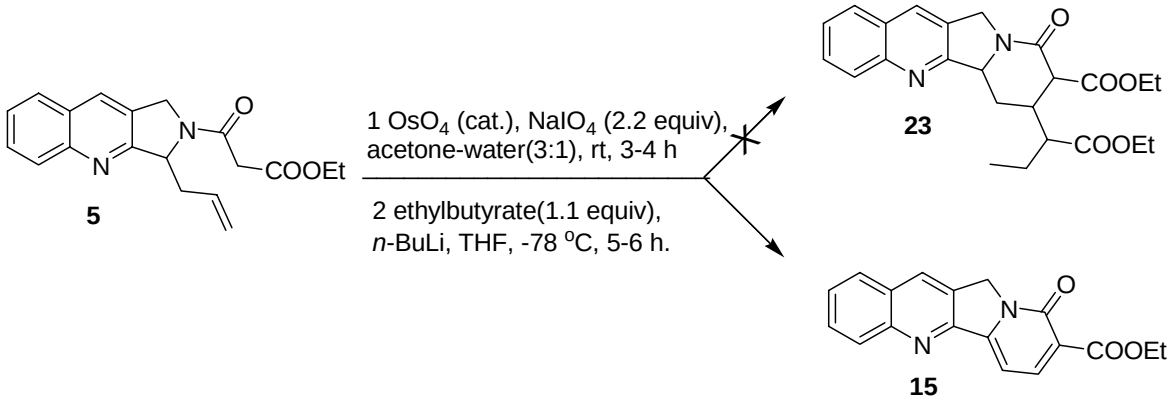
The formation of aromatic compound **15** can be explained by the probable mechanism described in scheme 10.



Scheme 10. *Probable mechanism.*

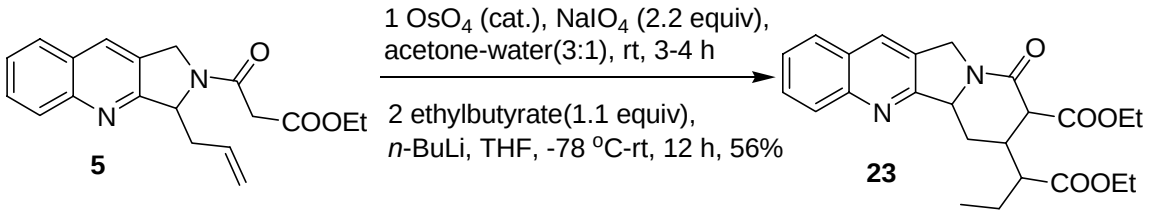
After the unsuccessful tandem Knoevenagel condensation and conjugate addition to aldehyde with ethyl acetoacetate and diethyl malonate, it was decided to use the reactive nucleophile *viz.* ethyl butyrate and strong base like n-BuLi. When aldehyde was treated

with ethyl butyrate using n-BuLi in THF at -78 ^{o}C for 5-6 h, the reaction was monitored by TLC which showed the formation of dihydropyridone **20** but it failed to provide the desired product **23**, instead furnished the aromatic compound **15**. This indicates that the Michael addition is not favored at low temperature and the generated dihydropyridone **20** may have been converted into aromatic compound **15** by air oxidation.



Scheme 11.

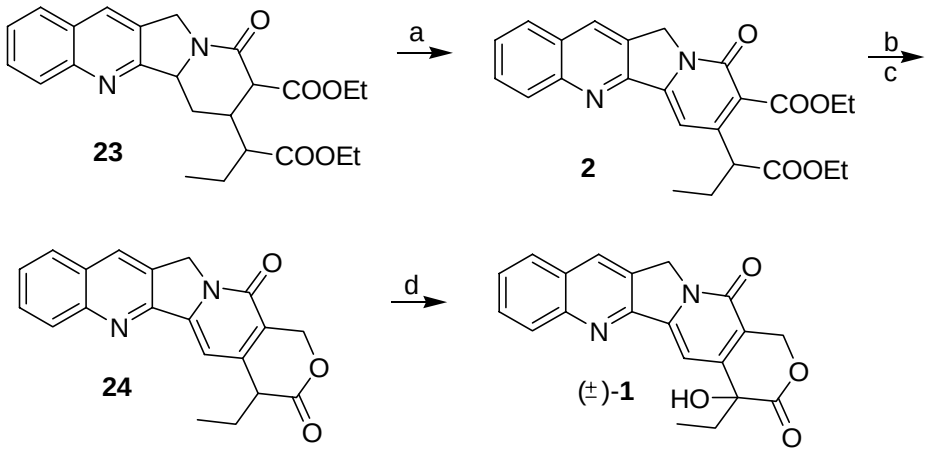
Considering to vary the temperature parameter, the same reaction was carried out at -78 ^{o}C and allowed to warm to room temperature. It was indeed gratifying to note that the desired diester **23** was obtained in 56% yield along with aromatized compound **15** in 36% yield. The formation of compound **23** was confirmed by spectral analysis and it is in complete agreement with data reported by this group earlier.[5a]



Scheme 12.

The tetrahydropyridone **23** was aromatized using DDQ in refluxing 1,4-dioxane for 2 h furnished desired aromatized product **2** and the structure of **2** was confirmed by spectral data which exactly matched with reported data.[5a] The selective hydrolysis of aliphatic ester in presence of heteroaromatic ester was carried out using LiOH in EtOH at room temperature for 7-8 h furnished its lithium salt which subsequently was converted into deoxycamptothecin **24** in 43% yield employing lithium borohydride.[13] Finally the hydroxy group was installed at the α-carbon of the lactone ring on deoxycamptothecin **24** using $CuCl_2$, catalytic amount of Me_2NH in DMF under oxygen atmosphere at room temperature

for 24 h furnished (±)-camptothecin **1** in 87%.[14] Thus, the total synthesis of camptothecin was achieved employing tandem Knoevenagel condensation followed by Michael addition.



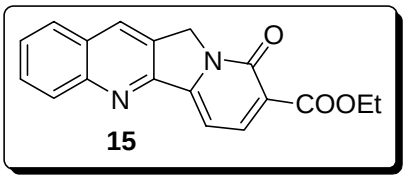
Scheme 13. *Reagent and conditions: (a) DDQ (2.1 equiv), 1,4-dioxane, reflux, 3-4 h, 97%. (b) LiOH (1.0 equiv), EtOH, rt, 7-8 h; (c) $LiBH_4$ (0.3 equiv), THF, 0 ^oC-rt, 6 h, 43% in two steps (d) $CuCl_2.7H_2O$, Me_2NH, O_2, DMF, rt, 24 h, 87%.*

2.1.4 Conclusion:

The intermolecular Michael addition versus aromatization reaction on tetracyclic activated dihydropyridone was studied. The total synthesis of (±)-camptothecin **1** was achieved employing tandem Knoevenagel condensation followed by Michael addition and selective hydrolysis of aliphatic ester in the presence of heteroaromatic ester was accomplished.

2.1.5 Experimental

Ethyl 9-oxo-9,11-dihydroindolizino[1,2-*b*]quinoline-8-carboxylate (15)



15

To a well stirred solution of olefin **5** (0.5 g, 1.54 mmol) in acetone-water (12 mL, 3:1) was added catalytic amount of OsO_4 at room temperature and stirred for 10 minutes. The reaction mixture become black coloured, then $NaIO_4$ (0.69 g, 3.71 mmol) was added portion wise and resultant reaction mixture was allowed to stir at rt for 3-4 h. After the completion of reaction (TLC), the acetone was removed on rotary evaporator under reduced pressure and the residue obtained was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*, to furnish aldehyde. A mixture of crude aldehyde ((assuming 100% conversion)), Zinc power (0.302 g, 4.62 mmol) and ethyl 2-bromobutyrate (0.45 g, 0.34 mL, 2.31 mmol) and I_2 (cat.) in C_6H_6-Et_2O (1:1) (20 mL) was refluxed for 6-8 h and the progress of reaction was monitored by (TLC). The reaction mixture was allowed to cool at room temperature and quenched with addition of 10% HCl and extracted with Et_2O (3 x 10 mL). The organic phase was washed with saturated $NaHCO_3$ solution, brine, dried over anhydrous sodium sulphate, filtered and concentrated under diminished pressure. The residue was purified by flash column chromatography eluting with ethyl acetate-petroleum ether (4:1) gave **15** as a pale yellow solid (0.094 g, 20%) yield.

MF: $C_{18}H_{14}N_2O_3$, **MW**: 306

M.P.: 141-143 ^oC

IR ($CHCl_3$) ν_{max}: 3373, 1728, 1216, 754, 666 cm^{-1}

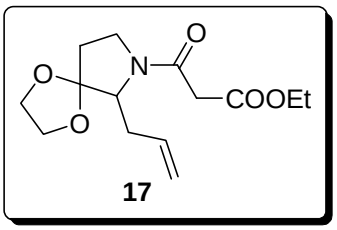
^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.43 (t, *J* = 7.1 Hz, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 5.35 (s, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.85 (t, *J* = 7.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.43 (s, 1H), 8.51 ppm (d, *J* = 8.2 Hz, 1H).

MS (ESI) *m/z*: 307 $(M + H)^+$, 329 $(M + Na)^+$.

Elemental analysis Calculated: C, 70.58; H, 4.61; N, 9.15%.

Found: C, 70.39; H, 4.84; N, 8.87%.

Compound (17)



17

To a well stirred solution of carbamate **16** (5.0 g, 16.5 mmol) in ethanol (50 mL) was added KOH (13.0 g, 231 mmol) in ethanol (40 mL) and the solution was degassed under N_2 atmosphere and resultant yellow solution was refluxed under N_2 atmosphere till the completion of reaction (8 h, TLC). The dark brown solution was concentrated *in vacuo*, and the residue was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulted the crude amine. To a well stirred mixture of crude amine (assuming 100% conversion) at 0 ^oC, K_2CO_3 (2.73 g, 19.8 mmol) in anhydrous CH_2Cl_2 (50 mL) was dropwise added ethyl malonyl chloride (2.97 g, 2.5 mL, 19.8 mmol) under argon and allowed to stir for 1 h. After the completion of reaction (TLC), the reaction mixture was filtered and residue was washed with CH_2Cl_2 (3 x 20 mL). The filtrate was washed with H_2O (50 mL), brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The resulted residue was purified by flash column chromatography (SiO_2) eluting with mixture of ethyl acetate-petroleum ether (2:3) as a solvent system afforded the compound **17** as a viscous liquid (3.17 g, 68% yield).

MF: $C_{14}H_{21}NO_5$, **MW**: 283

IR ($CHCl_3$) ν_{max}: 3458, 1736, 1647, 1436, 755, 667 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.28 (t, *J* = 7.1 Hz, 3H), 1.93-2.59 (m, 4H), 3.26 (s, 2H), 3.34-3.46 (m, 2H), 3.71-397 (m, 4H), 4.19 (q, *J* = 7.1 Hz, 2H), 5.01-5.18 (m, 2H), 5.72-5.93 ppm (m, 1H).

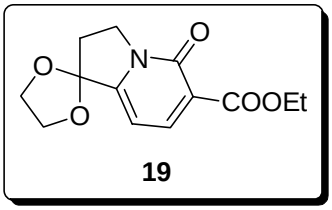
^{13}C NMR (CDCl3 + CCl4, 50 MHz) δ: 13.7, 31.1, 32.8, 33.7, 36.1, 41.2, 41.6, 42.1, 43.8, 60.7, 61.4, 62.6, 63.5, 63.7, 64.9, 113.1, 114.0, 116.9, 118.2, 133.4, 134.3, 164.5, 166.8 ppm (mixture of rotamers).

MS (ESI) *m/z*: 284 $(M + H)^+$, 306 $(M + Na)^+$.

Elemental analysis Calculated: C, 59.35; H, 7.47; N, 4.94%.

Found: C, 59.44; H, 7.33; N, 5.19%.

Compound (19)



19

The title compound **19** (0.05 g, 27%) was observed from **17** (0.2 g, 0.70 mmol) as per the procedure of compound **15**.

MF: $C_{13}H_{15}NO_5$, **MW**: 265

IR ($CHCl_3$) ν_{max}: 3451, 1733, 1655 cm^{-1}

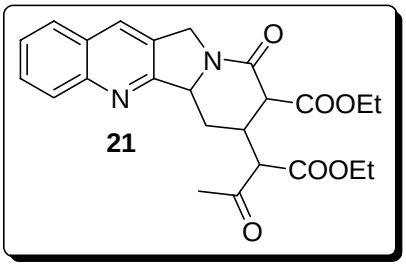
^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.38 (t, *J* = 7.1 Hz, 3H), 2.39 (t, *J* = 6.8 Hz, 2H), 4.02 (t, *J* = 6.8 Hz, 2H), 4.25 (s, 4H), 4.36 (q, *J* = 7.1 Hz, 2H), 6.24 (d, *J* = 7.3 Hz, 1H), 8.21 ppm (d, *J* = 7.3 Hz, 1H).

MS (ESI) *m/z*: 266 $(M + H)^+$, 288 $(M + Na)^+$, 304 $(M + K)^+$.

Elemental analysis Calculated: C, 58.86; H, 5.70; N, 5.28%.

Found: C, 59.17; H, 5.43; N, 5.13%.

Ethyl 7-(1-ethoxy-1,3-dioxobutan-2-yl)-9-oxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-b]quinoline-8-carboxylate (21)



21

To a well stirred solution of olefin **5** (0.5 g, 1.54 mmol) in acetone-water (12 mL, 3:1) was added catalytic amount of OsO_4 at room temperature and stirred for 10 minutes. The reaction mixture become black coloured, then $NaIO_4$ (0.69 g, 3.24 mmol) was added portion wise and resultant reaction mixture was allowed to stir at room temperature for 6-7 h. After the completion of reaction (TLC), the acetone was removed on rotary evaporator under reduced pressure and the residue obtained was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*, to furnish aldehyde. The solution of crude aldehyde (assuming 100% conversion) in anhydrous benzene (5.0 mL) was gradually added to the well stirred mixture of ethyl acetoacetate (0.22 g, 1.69 mmol) and piperidine (0.14 g, 0.16 mL, 1.69 mmol) in anhydrous benzene (5.0 mL) at room temperature and left to stir till to completion of reaction (5-6 h, TLC). The reaction was quenched by the addition of 10% HCl and the organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (3:2)

as eluent furnished the compound **21** in 0.45 g, 67% but it was not stable and converted into aromatic compound **15**.

MF: $C_{24}H_{26}N_2O_6$, **MW**: 438

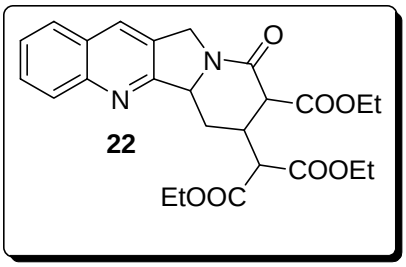
IR ($CHCl_3$) ν_{max}: 1659, 1651, 1602, 1453, 1410, 1216 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.19-1.36 (m, 6H), 2.09 (s, 3H), 2.17-2.57 (m, 2H), 3.14-3.28 (m, 1H), 3.49-3.64 (m, 2H), 4.06-4.44 (m, 4H), 4.71-5.36 (m, 2H), 7.57-8.57 ppm (m, 5H).

^{13}C NMR (CDCl3, 50 MHz) δ: 14.0, 14.2, 20.4, 20.8, 22.5, 22.7, 29.6, 33.8, 34.3, 34.8, 37.4, 37.9, 38.9, 48.95, 49.2, 50.55, 51.0, 54.9, 58.1, 58.2, 59.9, 60.8, 60.9, 61.7, 75.35, 84.3, 85.0, 85.8, 126.75, 127.3, 127.85, 128.0, 128.2, 128.9, 130.1, 131.1, 131.3, 147.5, 159.2, 159.4, 164.2, 164.5, 169.6, 170.1, 170.5, 171.0, 172.2, 174.1 ppm (mixture of isomers).

MS (ESI) *m/z*: 439 $(M + H)^+$, 461 $(M + Na)^+$, 392, 329, 307.

Diethyl 2-(8-(ethoxycarbonyl)-9-oxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-b]quinolin-7-yl)malonate (22)



22

The title compound **22** (0.51 g, 71%) was prepared from **5** (0.5 g, 1.54 mmol) as per the procedure outlined for the preparation of compound **21**

MF: $C_{25}H_{28}N_2O_7$, **MW**: 468

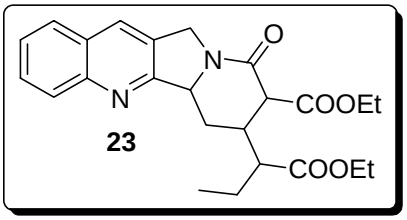
IR ($CHCl_3$) ν_{max}: 1657, 1648, 1450, 1411, 1216 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.20-1.37 (m, 9H), 2.83-4.0 (m, 5H), 4.06-4.47 (m, 6H), 4.69-5.34 (m, 3H), 7.55-8.33 ppm (m, 5H).

^{13}C NMR (CDCl3, 50 MHz) δ: 13.9, 29.6, 29.8, 31.1, 33.4, 36.3, 36.7, 41.6, 48.1, 48.4, 48.9, 51.2, 51.4, 53.0, 54.2, 54.4, 54.7, 59.2, 61.2, 61.9, 126.7, 127.5, 127.6, 127.9, 128.5, 128.7, 129.6, 129.95, 130.3, 139.25, 147.9, 148.4, 152.45, 160.8, 164.5, 165.9, 167.3, 167.4, 167.6, 167.8, 168.9, 169.3, 170.1 ppm (mixture of isomers).

MS (ESI) *m/z*: 469 $(M + H)^+$, 491 $(M + Na)^+$, 507 $(M + K)^+$.

Ethyl 7-(1-ethoxy-1-oxobutan-2-yl)-9-oxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (23)



23

To a well stirred solution of olefin **5** (0.5 g, 1.54 mmol) in acetone-water (12 mL, 3:1) was added catalytic amount of OsO_4 at room temperature and stirred for 10 minutes, the reaction mixture become black coloured, then $NaIO_4$ (0.69 g, 3.24 mmol) was added portion wise and resultant reaction mixture was allowed to stir at rt for 6-7 h. After the completion of reaction (TLC), the acetone was removed on rotary evaporator under reduced pressure and the residue obtained was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*, to furnish aldehyde. The solution of crude aldehyde in anhydrous THF (assuming 100% conversion) was dropwise added to the well stirred mixture ethyl butyrate (0.214 g, 1.85 mmol) and 1.6 M *n*-BuLi (0197 g, 1.93 mL, 3.08 mmol) in anhydrous THF (10 mL) at -78 ^{o}C and reaction mixture was allowed to warm to room temperature. The progress of reaction was monitored by TLC. After the completion of reaction (12 h) the reaction was quenched with addition of saturated ammonium chloride solution and organic phase was separated and aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (3:2) as eluent furnished the tetrahydropyridone **23** as pale yellow solid (0.366 g, 56% yield) along with aromatic compound **15** (0.17 g, 36% yield).

MF: $C_{24}H_{24}N_2O_5$, **MW**: 424

M.P.: 157-159 ^{o}C

IR ($CHCl_3$) ν_{max}: 1736, 1729, 1659, 1451, 1412, 1215 cm^{-1}

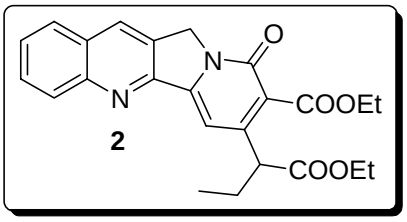
^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.98 (t, *J* = 7.5 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 6H), 1.46-2.15 (m, 3H), 2.20-2.98 (m, 2H), 3.49 (dd, *J* = 13.0, 6.0 Hz, 1H), 4.01-4.35 (m, 4H), 4.57-5.25 (m, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 8.07 ppm (s, 1H).

^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 11.8, 12.1, 12.2, 14.2, 14.3, 21.8, 23.2, 23.5, 29.1, 30.1, 35.6, 38.7, 39.1, 48.4, 48.9, 49.6, 50.5, 52.2, 53.8, 59.4, 60.6, 60.7, 61.4, 61.7, 61.8,

126.9, 127.8, 127.9, 129.0, 129.6, 129.7, 130.4, 130.5, 147.9, 148.1, 161.2, 161.6, 164.8, 164.9, 166.6, 169.7, 170.1, 170.5, 173.4, 173.7, 173.9, 174.2 ppm (mixture of isomers).

MS (ESI) *m/z*: 425 $(M + H)^+$, 447 $(M + Na)^+$.

Ethyl 7-(1-ethoxy-1-oxobutan-2-yl)-9-oxo-9,11-dihydroindolizino[1.2-*b*]quinoline-8-carboxylate (2)



2

To a well stirred solution of tetrahydropyridone **23** (0.2 g, 0.47 mmol) in anhydrous 1,4-dioxane (10 mL) was added DDQ (0.235 g, 1.03 mmol) and the resultant reaction mixture was refluxed under N_2 atmosphere for (3-4 h, TLC). After the completion of reaction, the reaction mixture was diluted with benzene and quenched with addition of 10% $NaHCO_3$ solution. The organic layer was separated and aqueous layer was extracted with benzene (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (4:1) as eluent afforded the compound **2** as a pale yellow solid (0.197 g, 97% yield).

MF: $C_{24}H_{24}N_2O_5$, **MW**: 420

M.P.: 172-174 ^oC (Lit. 172-173 ^oC)

IR ($CHCl_3$) ν_{max}: 1735, 1727, 1649, 1215, 757, 668 cm^{-1}

^1H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.98 (t, *J* = 7.4 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.91-2.29 (m, 2H), 3.72 (t, *J* = 7.7 Hz, 1H), 4.04-4.30 (m, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 5.24 (s, 2H), 7.42 (s, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 8.35 ppm (s, 1H).

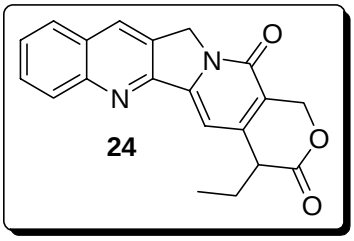
^{13}C NMR ($CDCl3$ + CCl_4, 100 MHz) δ:12.2, 14.3, 14.4, 25.9, 50.1, 50.2, 61.3, 61.7, 99.8, 125.4, 128.0, 128.1, 129.0, 129.7, 130.6, 131.1, 146.2, 148.7, 150.5, 152.2, 158.2, 165.9, 171.8 ppm.

MS (ESI) *m/z*: 421 $(M + H)^+$, 443 $(M + Na)^+$.

Elemental analysis Calculated: C, 68.56; H, 5.75; N, 6.66%.

Found: C, 68.61; H, 5.68; N, 6.71%.

Deoxycamptothecin (24)



To a well stirred solution of diester **2** (0.2 g, 0.44 mmol) in EtOH (10 mL) was added LiOH (0.012 g, 0.44 mmol) and resultant reaction mixture was allowed to stir at room temperature till the completion of reaction (7-8 h, TLC). The ethanol was removed on rotary evaporator under diminished pressure and salt obtained was dissolved in THF (10 mL) was added $LiBH_4$ (0.003 g, 0.11 mmol) at 0 ^oC and left to stir till the completion of reaction (6 h, TLC), H_2O (10 mL) was added and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (SiO_2) using $CHCl_3$ as eluent furnished deoxy camptothecin **24** as a pale yellow solid (0.067 g, 43% yield).

MF: $C_{20}H_{16}N_2O_3$, **MW**: 332

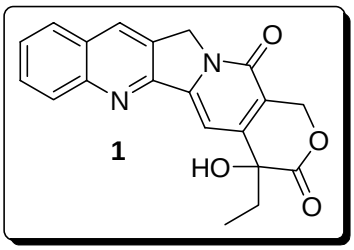
M.P.: 257-261 ^oC

IR ($CHCl_3$) ν_{max}: 1736, 1658, 1601, 1051, 1217, 758 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.1 (t, *J* = 7.4 Hz, 3H), 2.15 (m, 2H), 3.65 (t, *J* = 6.2, 1H), 5.35 (s, 2H), 5.5 (dd, *J* = 16.4, 7.0 Hz, 2H), 7.2 (s, 1H), 7.7 (t, *J* = 7.2 Hz, 1H), 7.85 (t, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.45 ppm (s, 1H).

MS (ESI) *m/z*: 333 $(M + H)^+$, 355 $(M + Na)^+$, 371 $(M + K)^+$.

Camptothecin (1)



The mixture of compound **24** (0.030 g, 0.09 mmol), $CuCl_2$ (0.040 g, 0.29 mmol) and 25% aqueous dimethylamine (4-5 drops) in anhydrous DMF (10 mL) was allowed to stir at room temperature under oxygen atmosphere. The progress of reaction was monitored by TLC, after the completion of reaction (24 h), H_2O (10 mL) was added and the pH was adjusted to 6.5 with addition of dilute HCl, and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated on rotary evaporator under diminished pressure. The residue obtained was purified by flash column chromatography (SiO_2) using 2% methanol in chloroform as eluent resulted (±)-camptothecin **1** as white solid (27 mg, 87% yield).

MF: $C_{20}H_{16}N_2O_4$; **MW**: 348

M.P.: 265 ^oC (Lit. 264-266 ^oC)

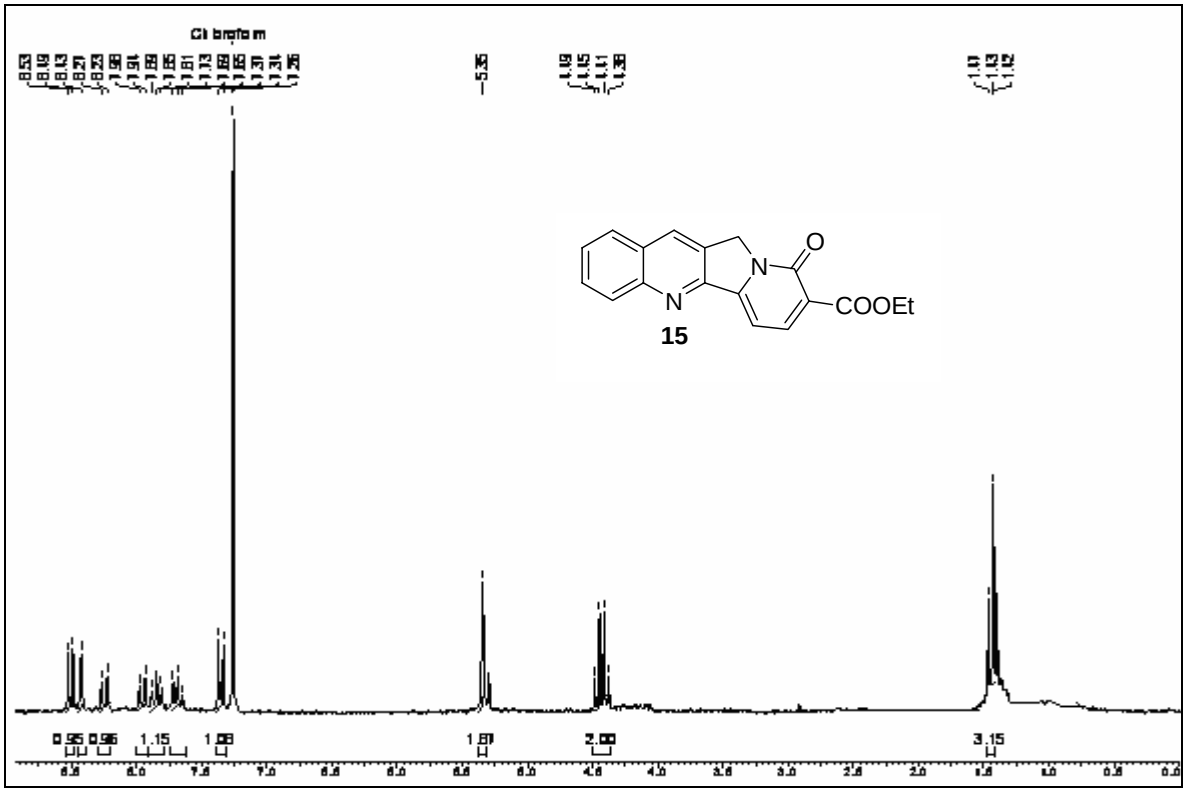
IR ($CHCl_3$) ν_{max}: 1735, 1659, 1602, 1051, 1215, 758 cm^{-1}

^1H NMR (DMSO-d_6, 400 MHz) δ: 0.89 (t, *J* = 7.1 Hz, 3H), 1.89 (q, *J* = 7.1 Hz, 2H), 5.31 (s, 2H), 5.44 (dd, *J* = 16.4, 7.0 Hz, 2H), 7.46 (s, 1H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.90 (t, *J* = 7.4 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.70 ppm (s, 1H).

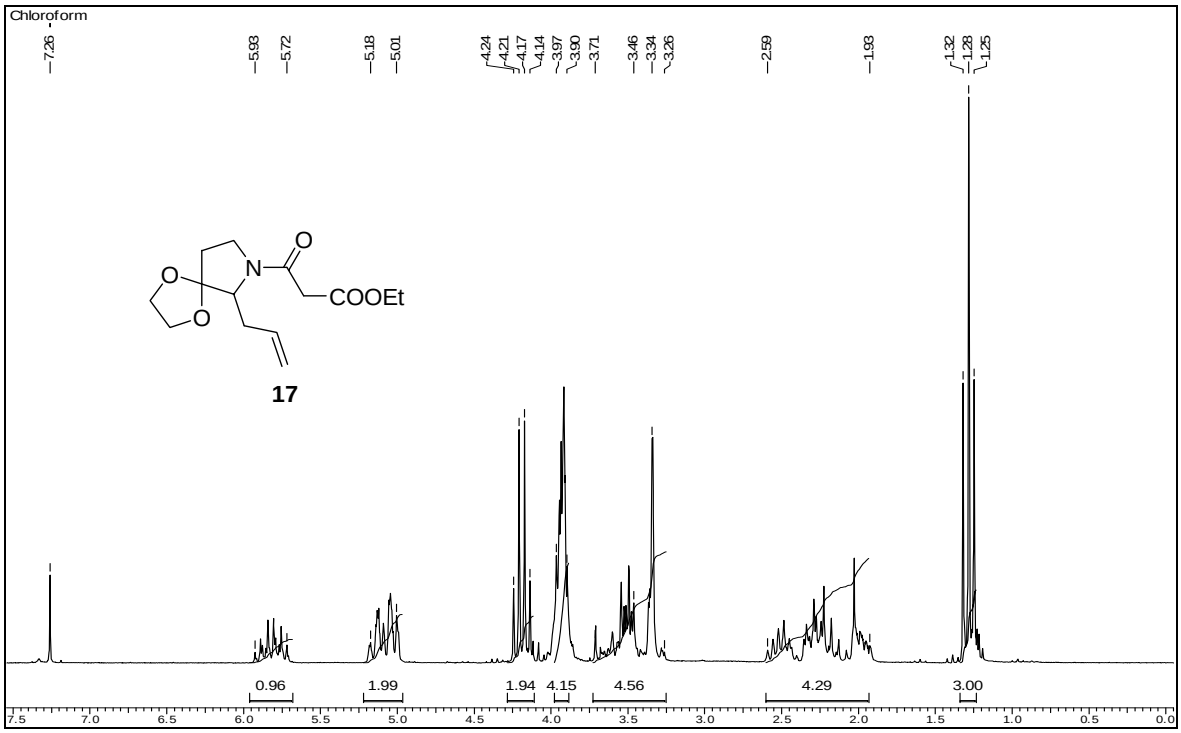
^{13}C NMR (DMSO-d_6, 100 MHz) δ: 8.3, 31.0, 51.0, 65.9, 73.2, 98.2, 119.7, 128.7, 129.3, 129.4, 130.3, 131.4, 132.6, 146.2, 148.6, 151.0, 153.2, 157.9, 171.0 ppm.

MS (ESI) *m/z*: 349 $(M + H)^+$, 371 $(M + Na)^+$.

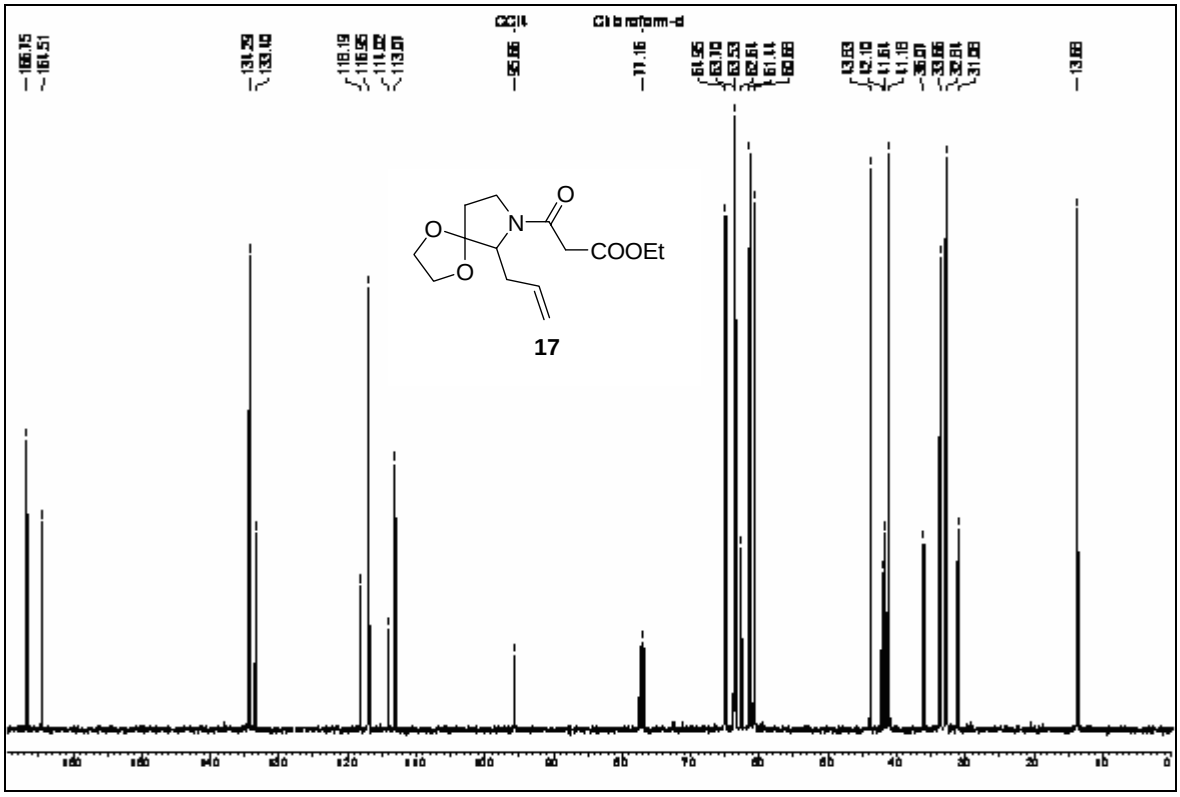
2.1.6 Spectra



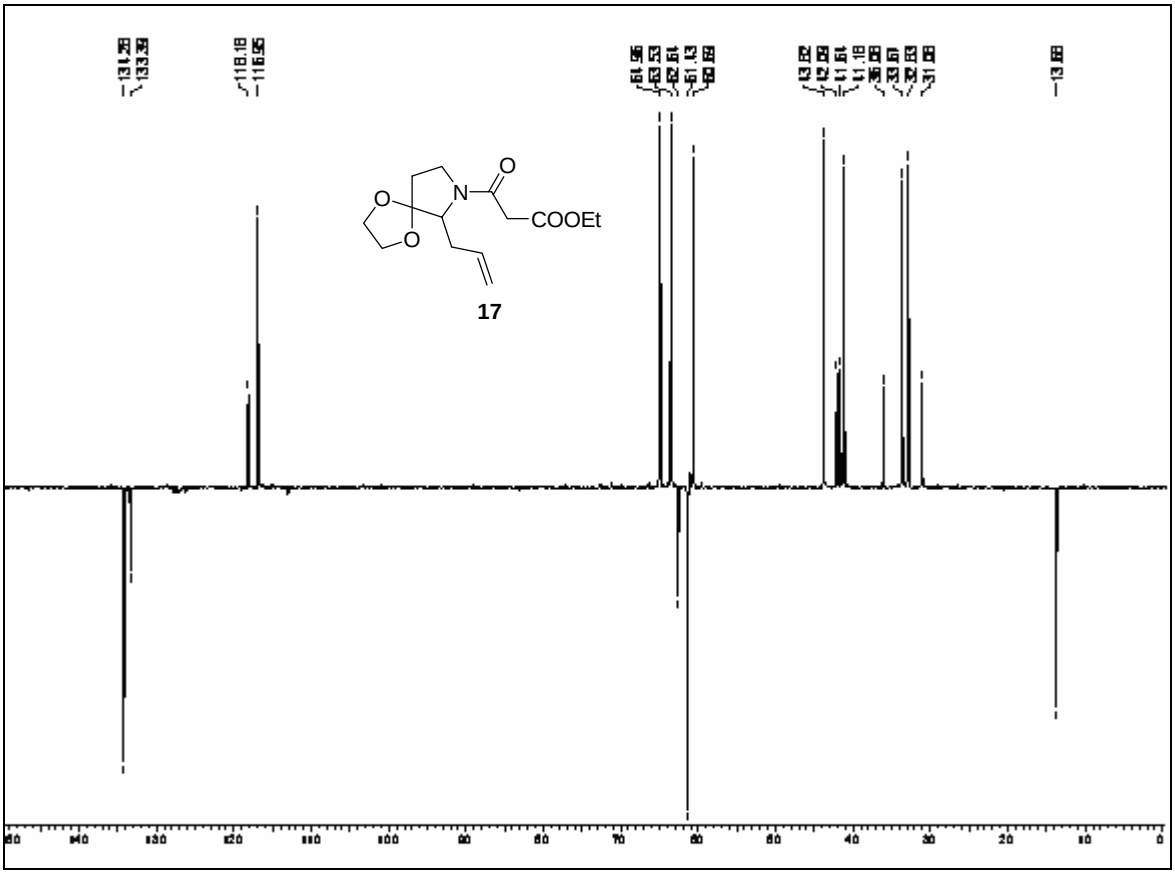
^{1}H NMR spectrum of compound 15 ($CDCl_3$, 200 MHz)



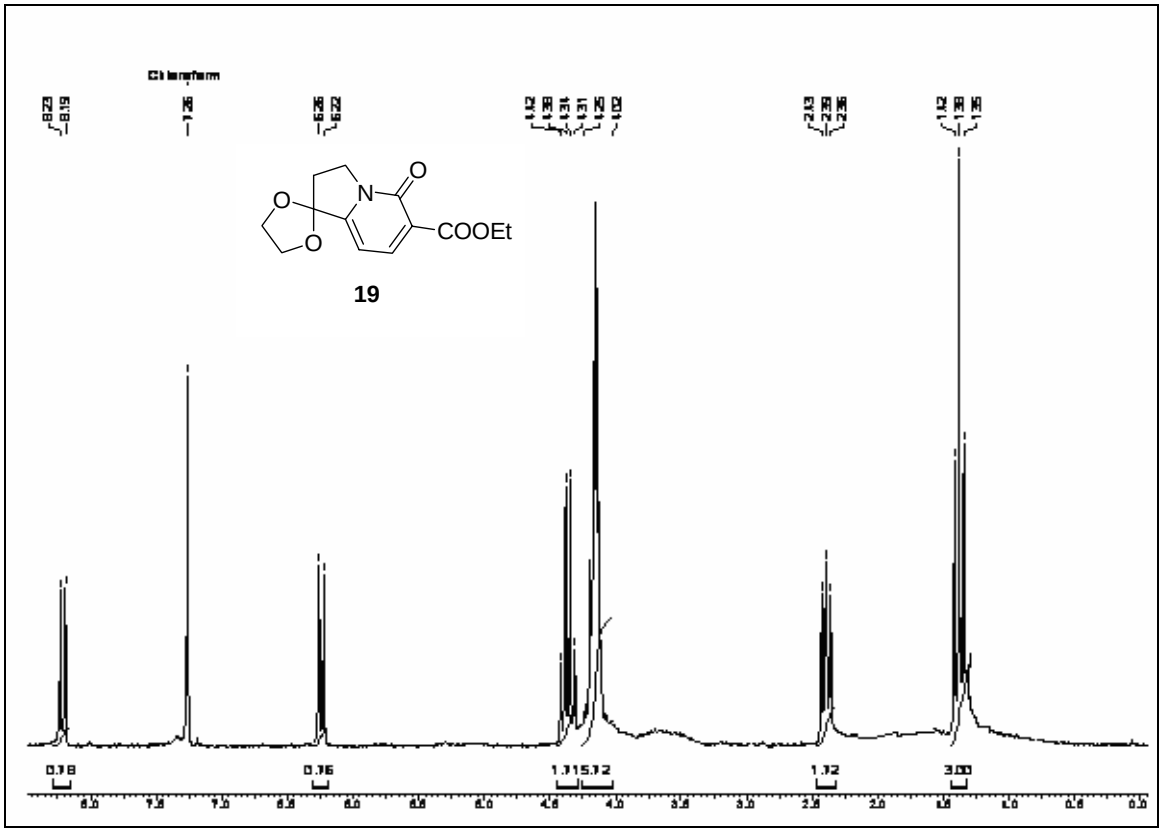
^{1}H NMR spectrum of compound 17 ($CDCl_3$ + CCl_4, 200 MHz)



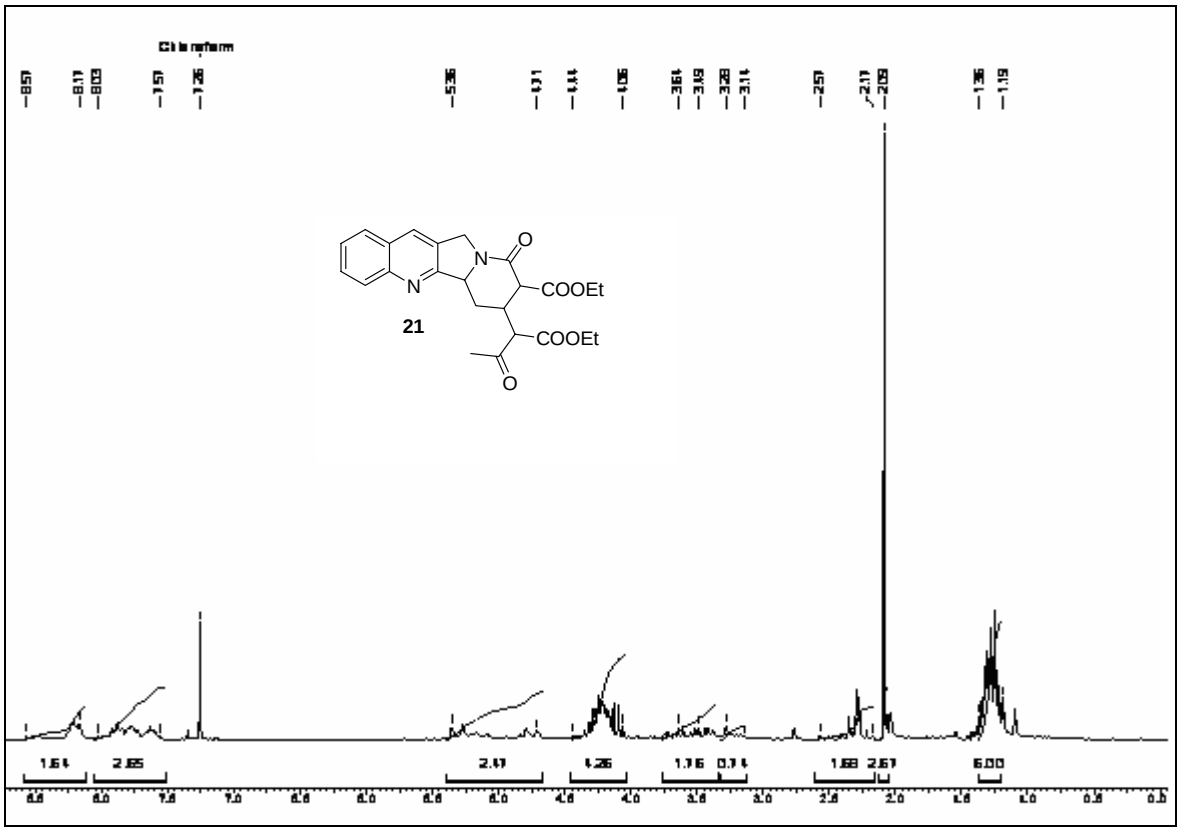
^{13}C NMR spectrum of compound 17 ($CDCl_3$ + CCl_4, 50 MHz)



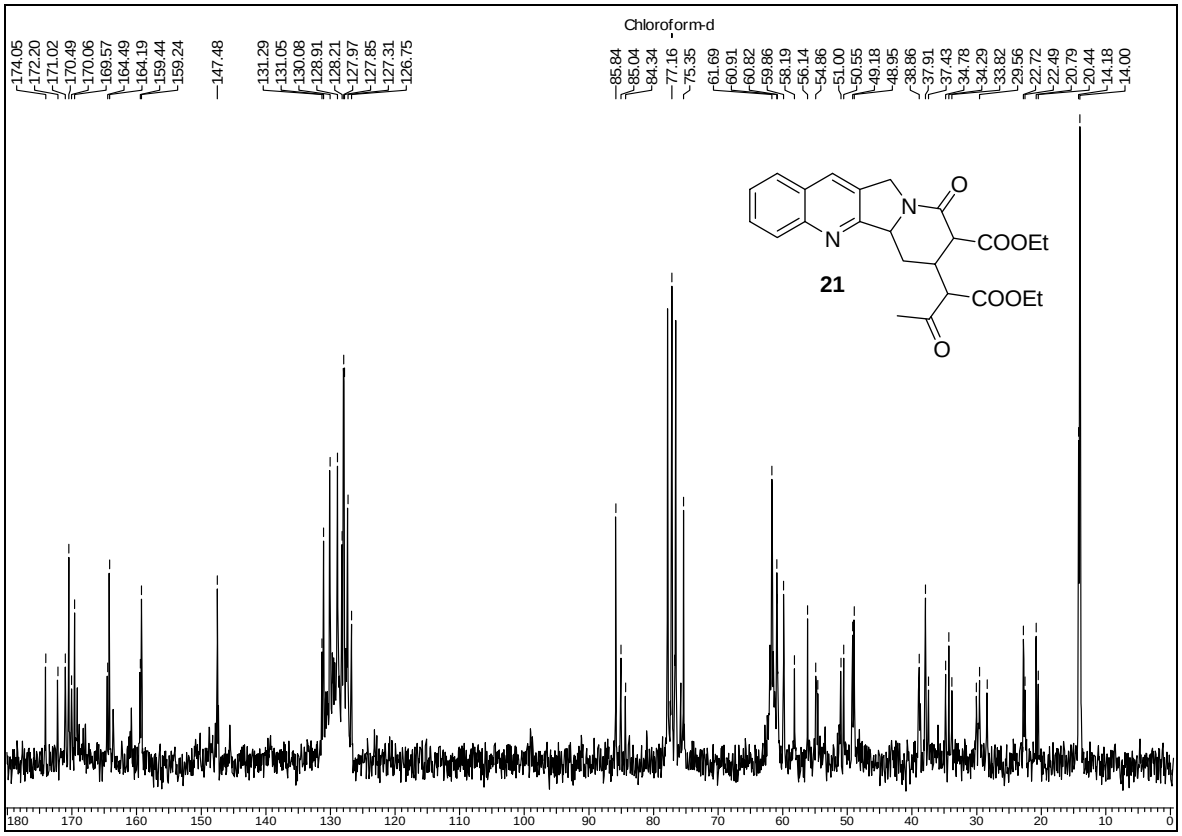
DEPT spectrum of compound 17 ($CDCl_3$ + CCl_4, 50 MHz)



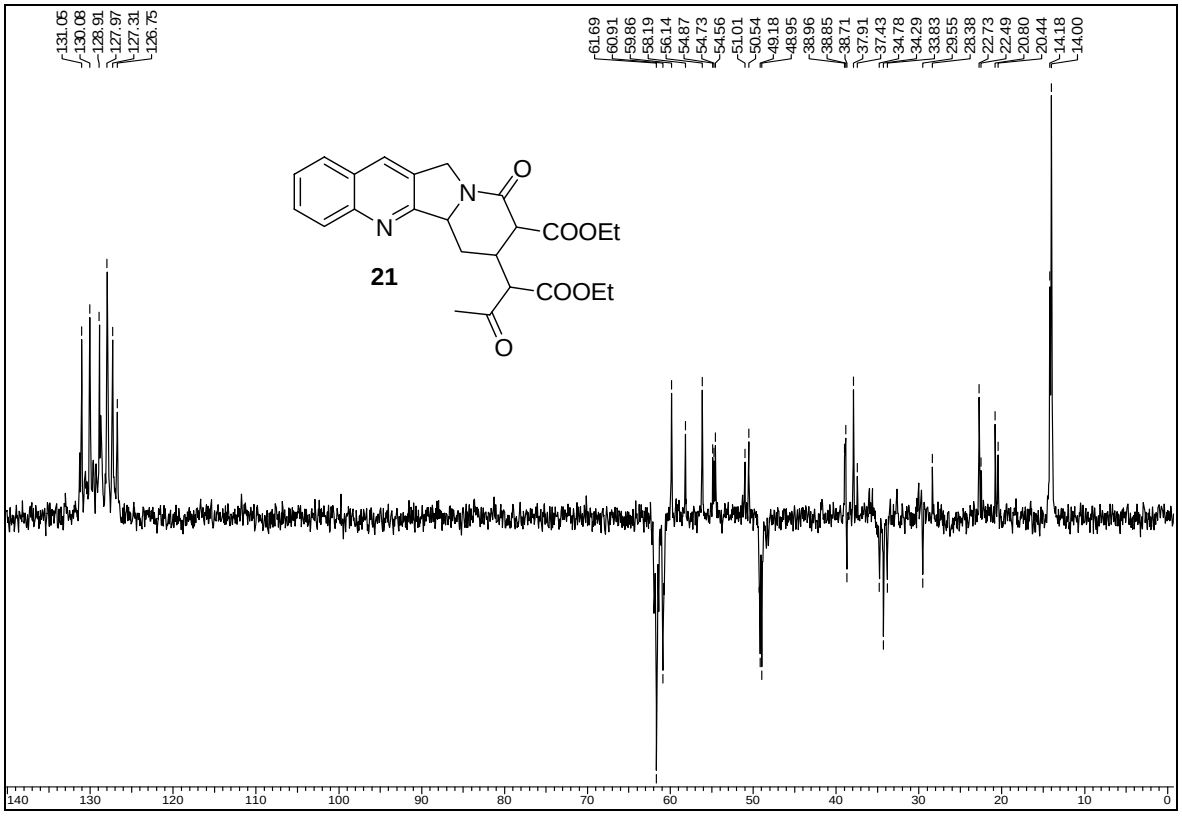
^{1}H NMR spectrum of compound 19 ($CDCl_3$ + CCl_4, 200 MHz)



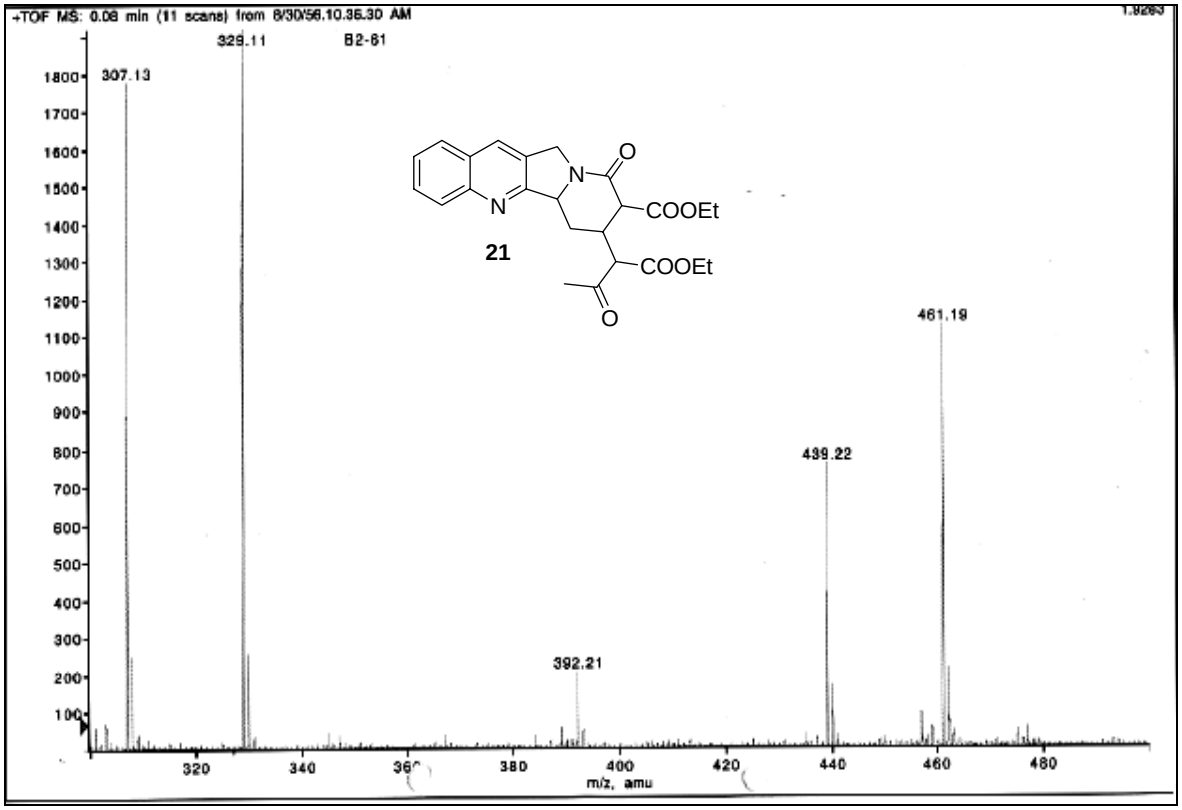
^{1}H NMR spectrum of compound 21 ($CDCl_3$ + CCl_4, 200 MHz)



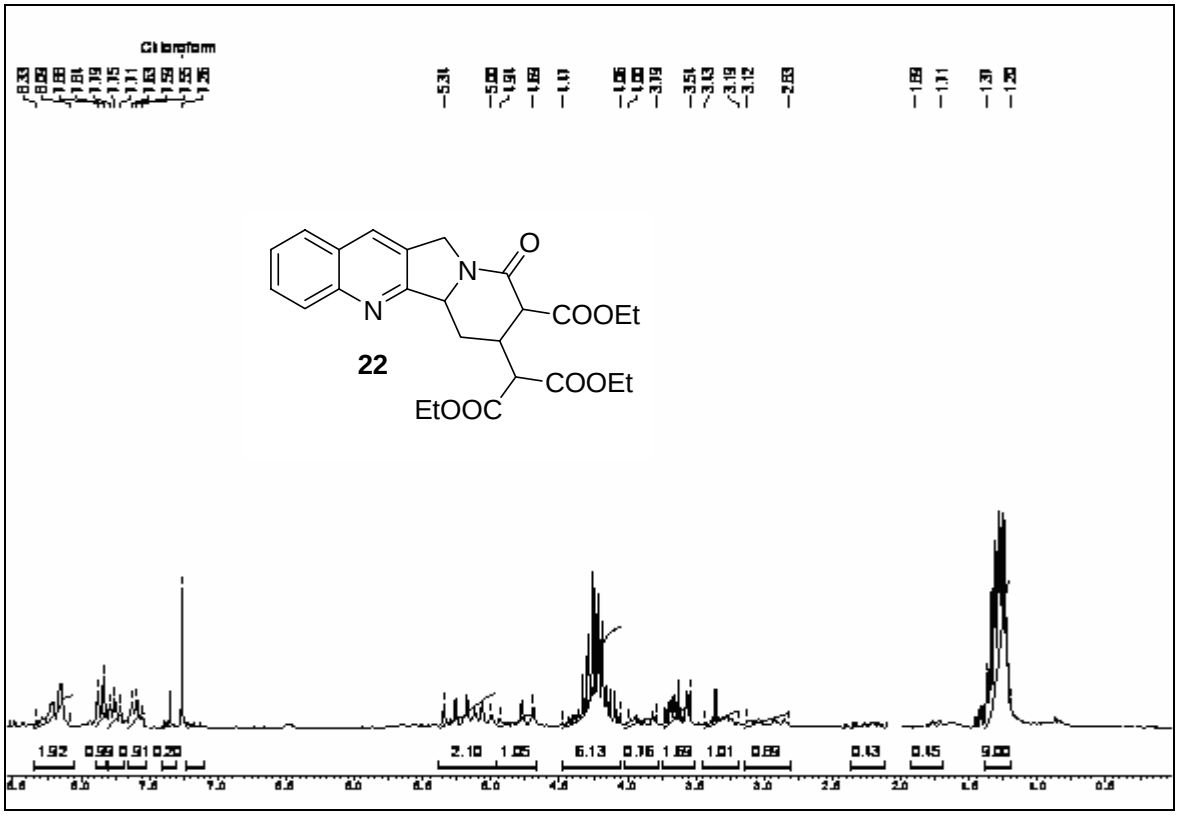
^{13}C NMR spectrum of compound 21 ($CDCl_3$ + CCl_4, 50 MHz)



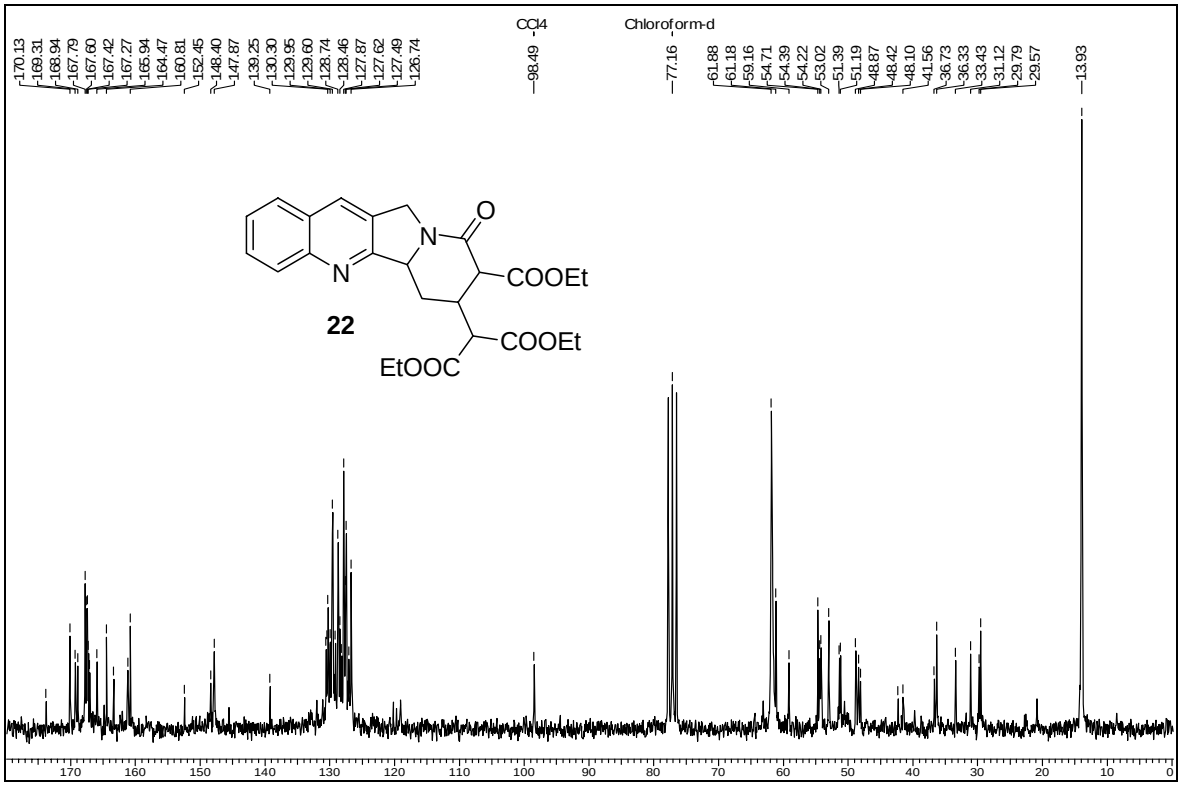
DEPT spectrum of compound 21 ($CDCl_3$ + CCl_4, 50 MHz)



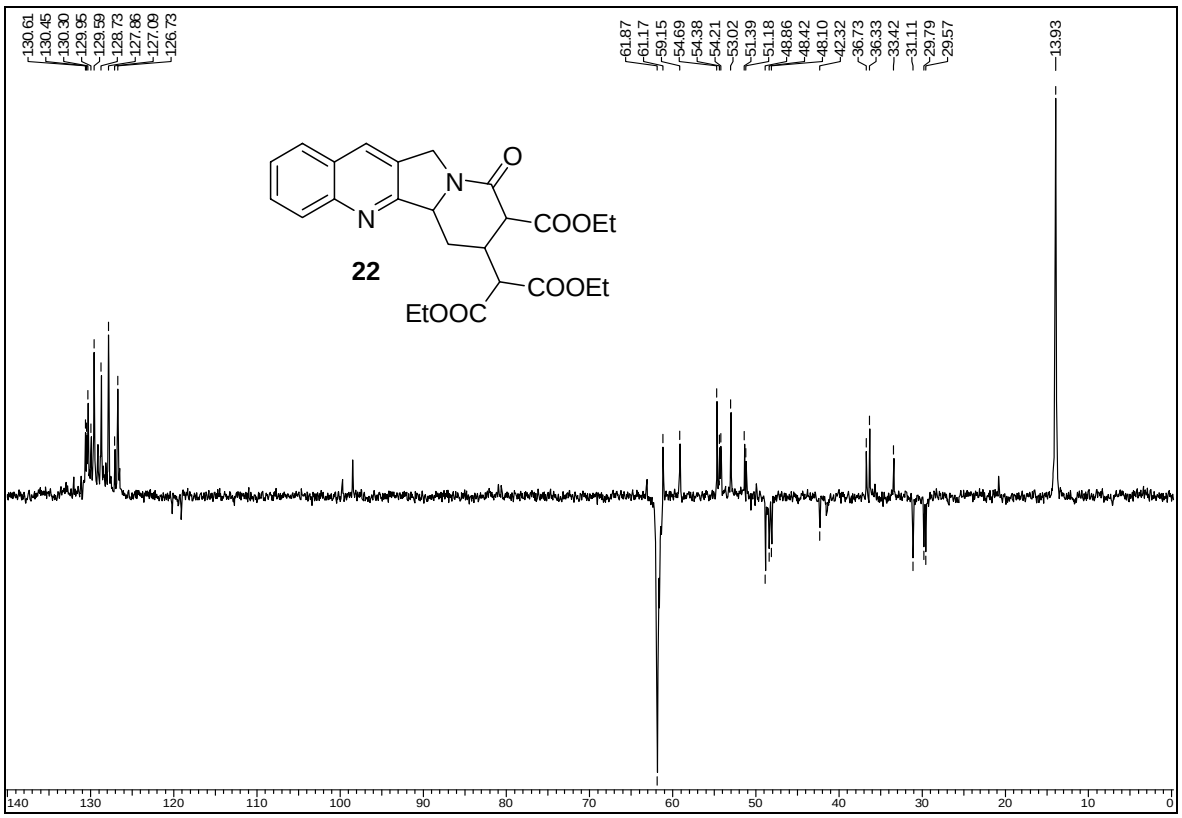
Mass spectrum of compound 21 (ESI)



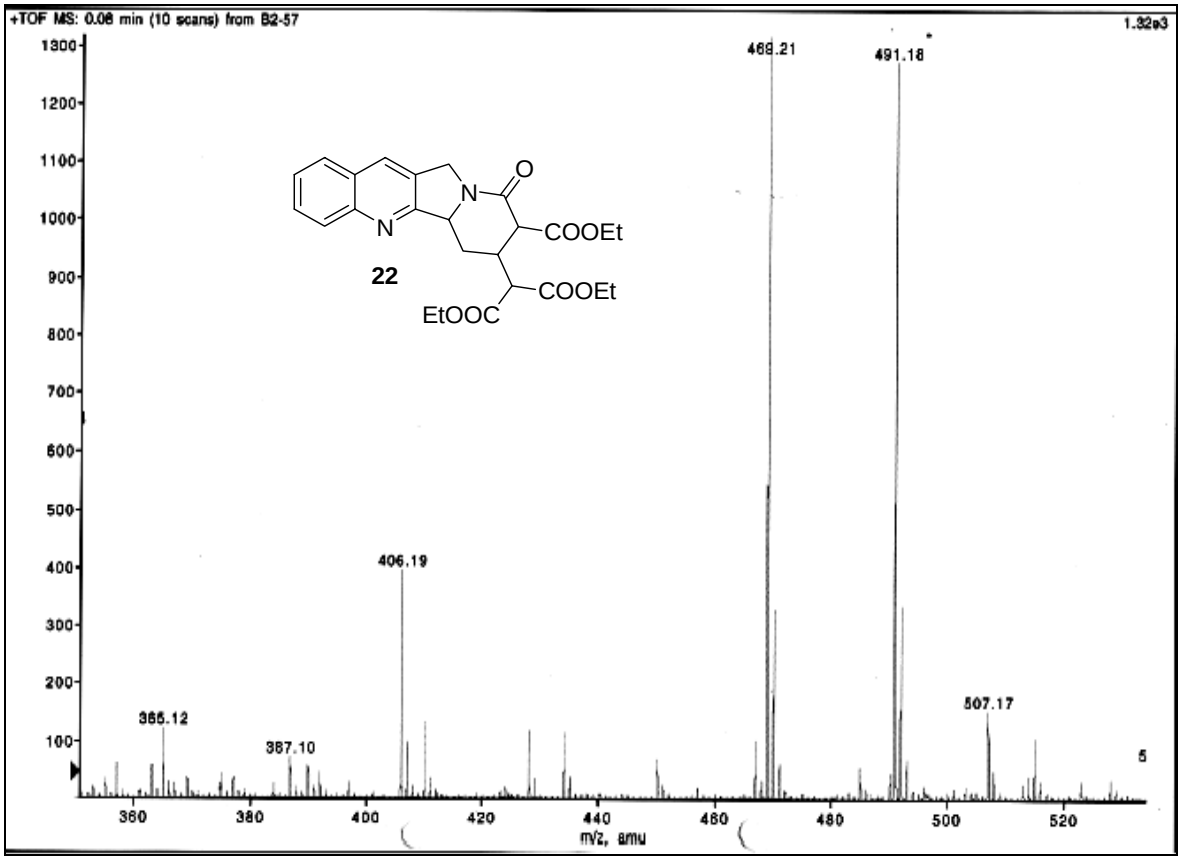
^{1}H NMR spectrum of compound 22 ($CDCl_3$ + CCl_4, 200 MHz)



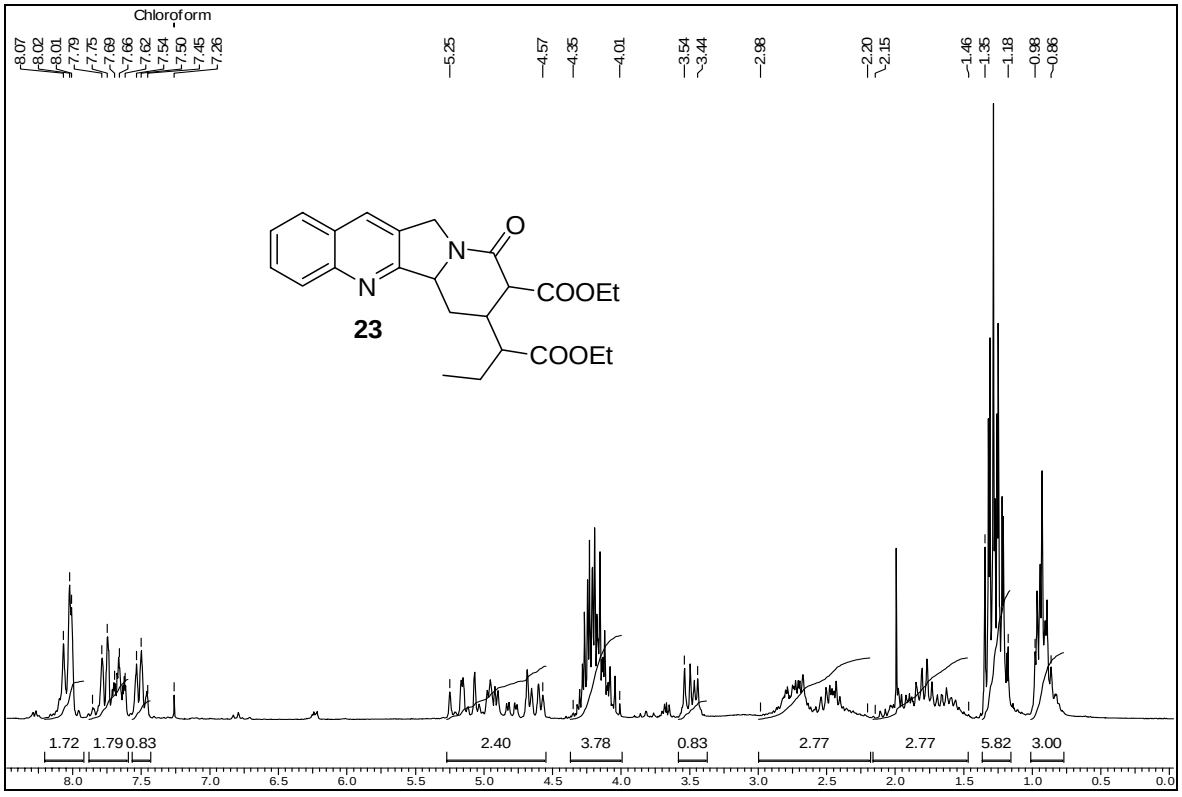
^{13}C NMR spectrum of compound 22 ($CDCl_3$ + CCl_4, 50 MHz)



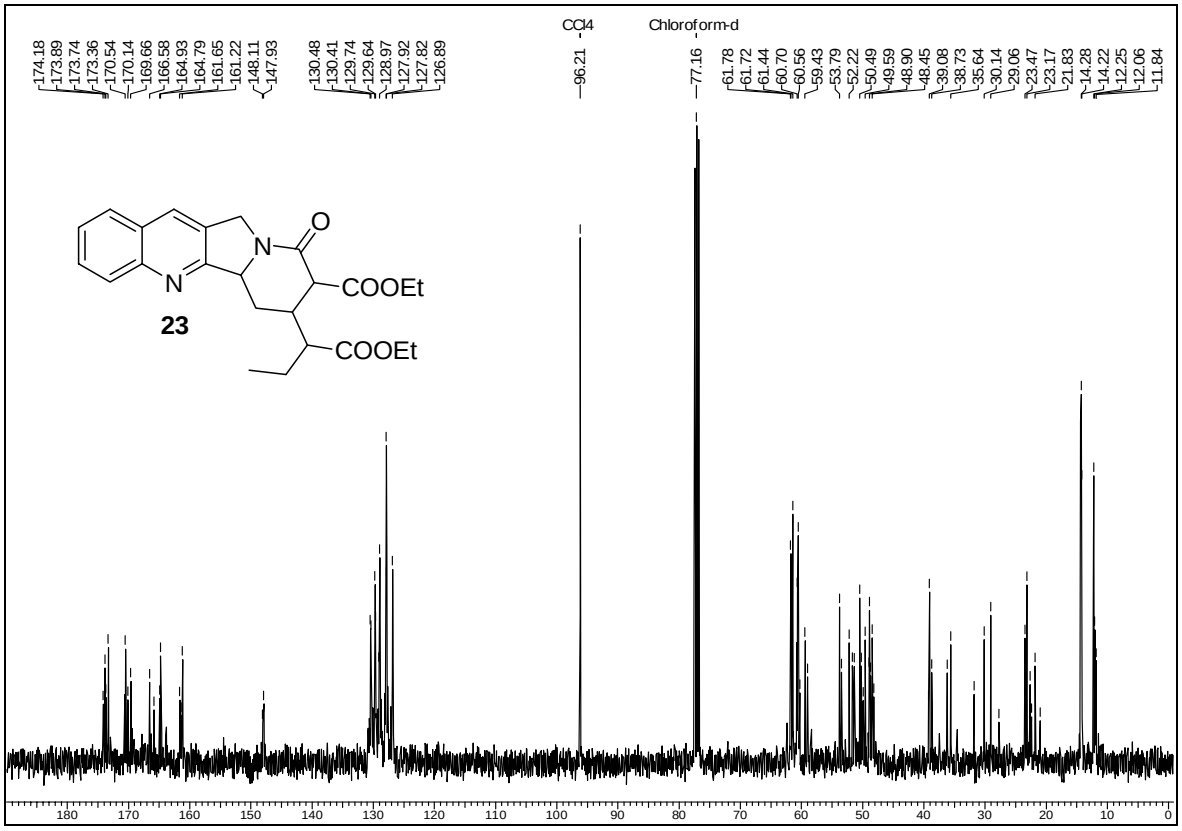
DEPT spectrum of compound 22 ($CDCl_3$ + CCl_4, 50 MHz)



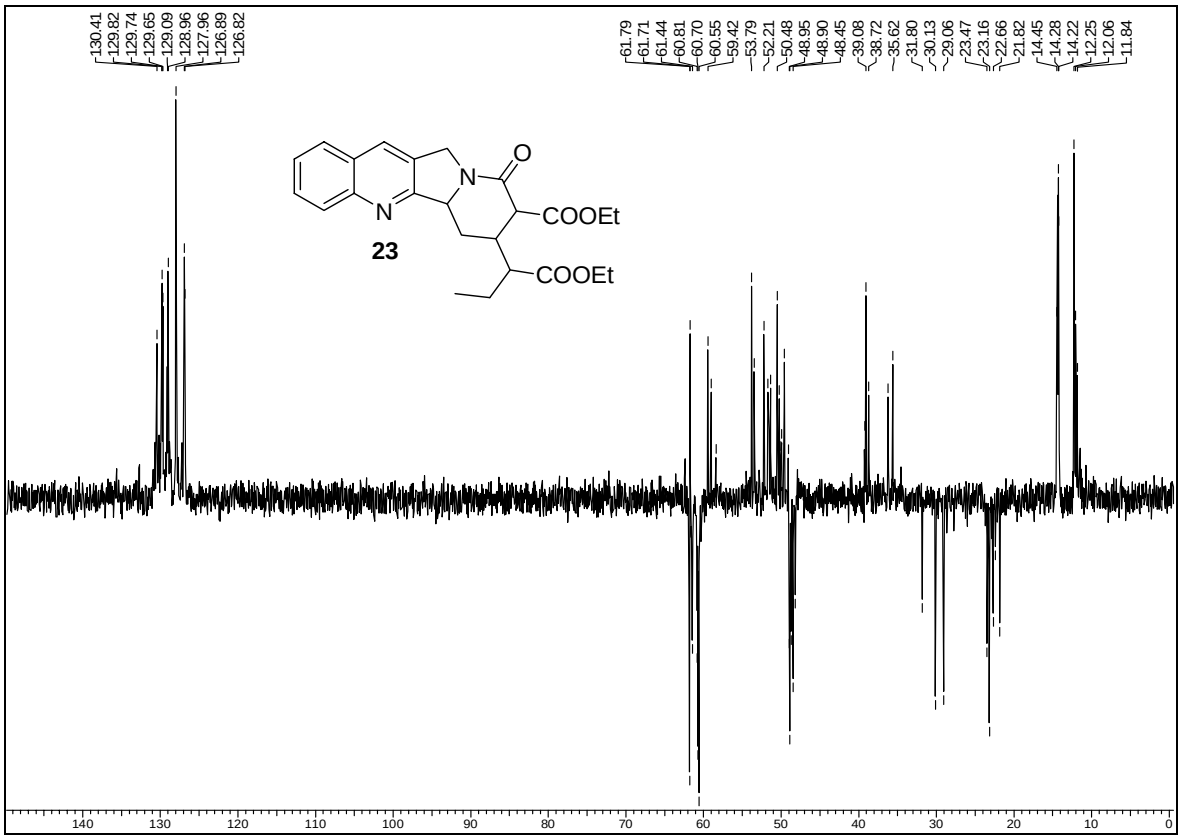
Mass spectrum of compound 22 (ESI)



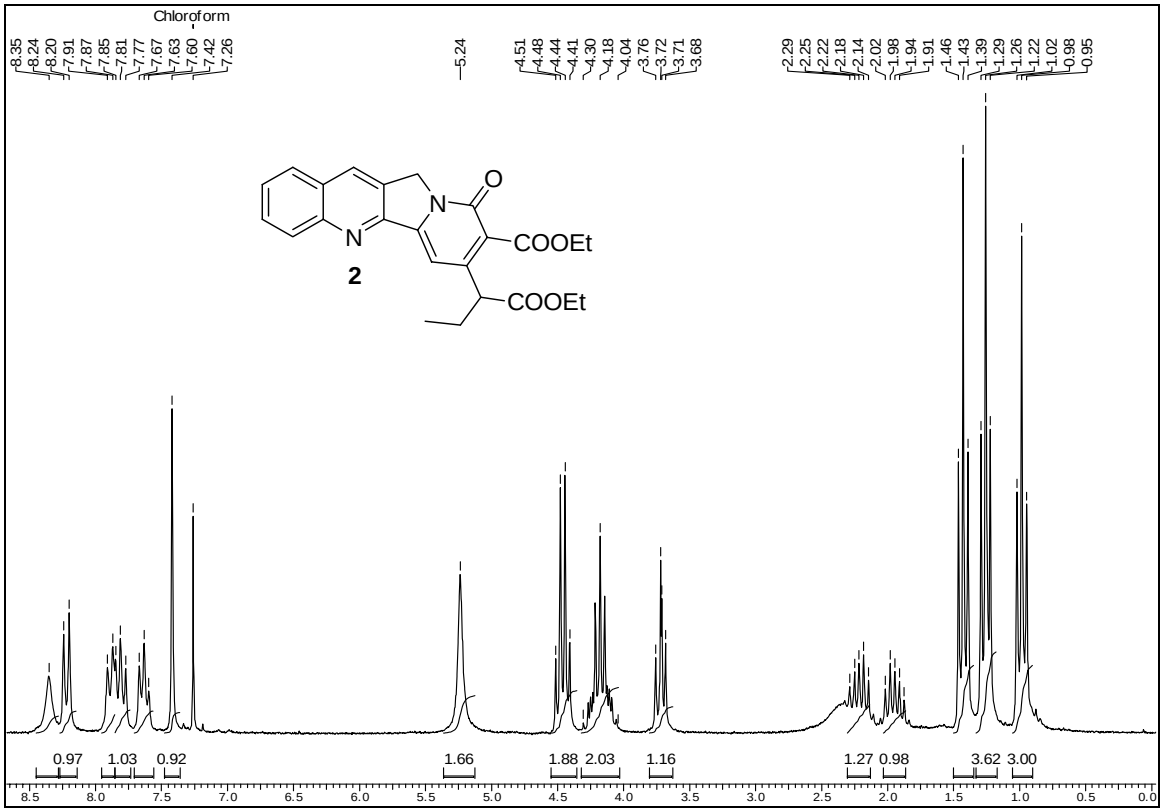
^{1}H NMR spectrum of compound 23 ($CDCl_3$ + CCl_4, 200 MHz)



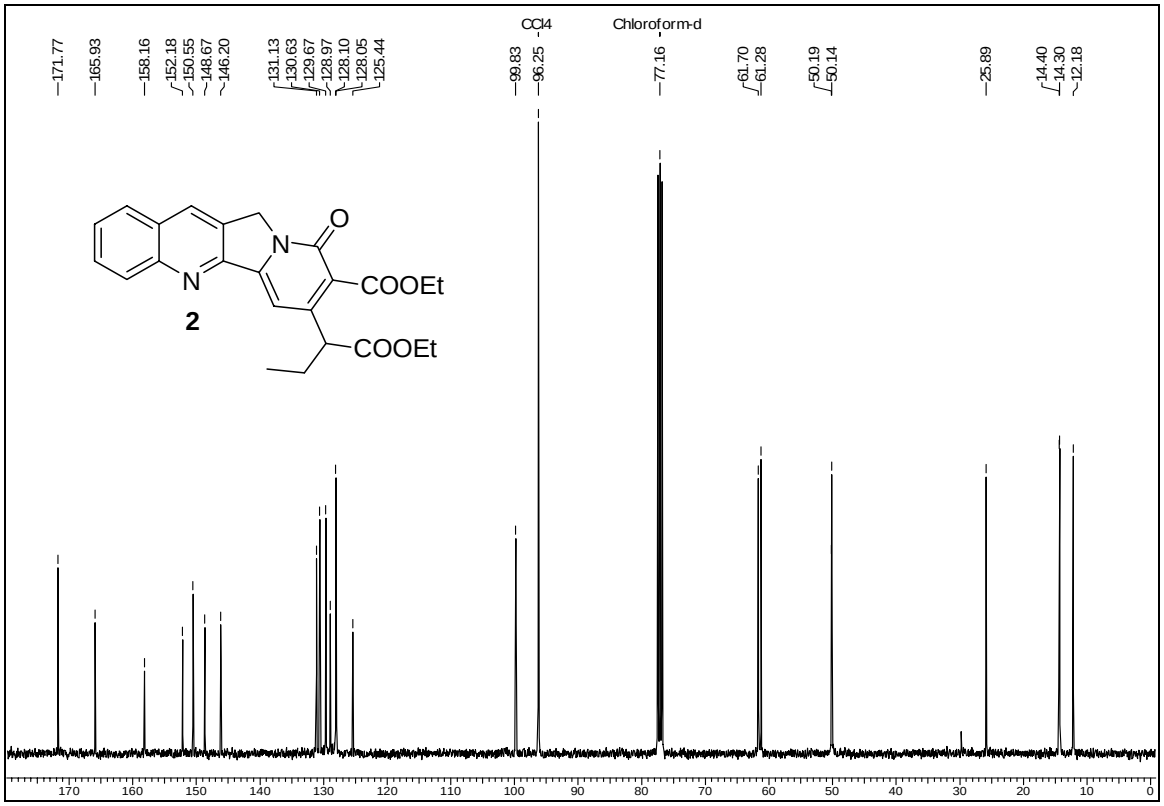
^{13}C NMR spectrum of compound 23 ($CDCl_3$ + CCl_4, 100 MHz)



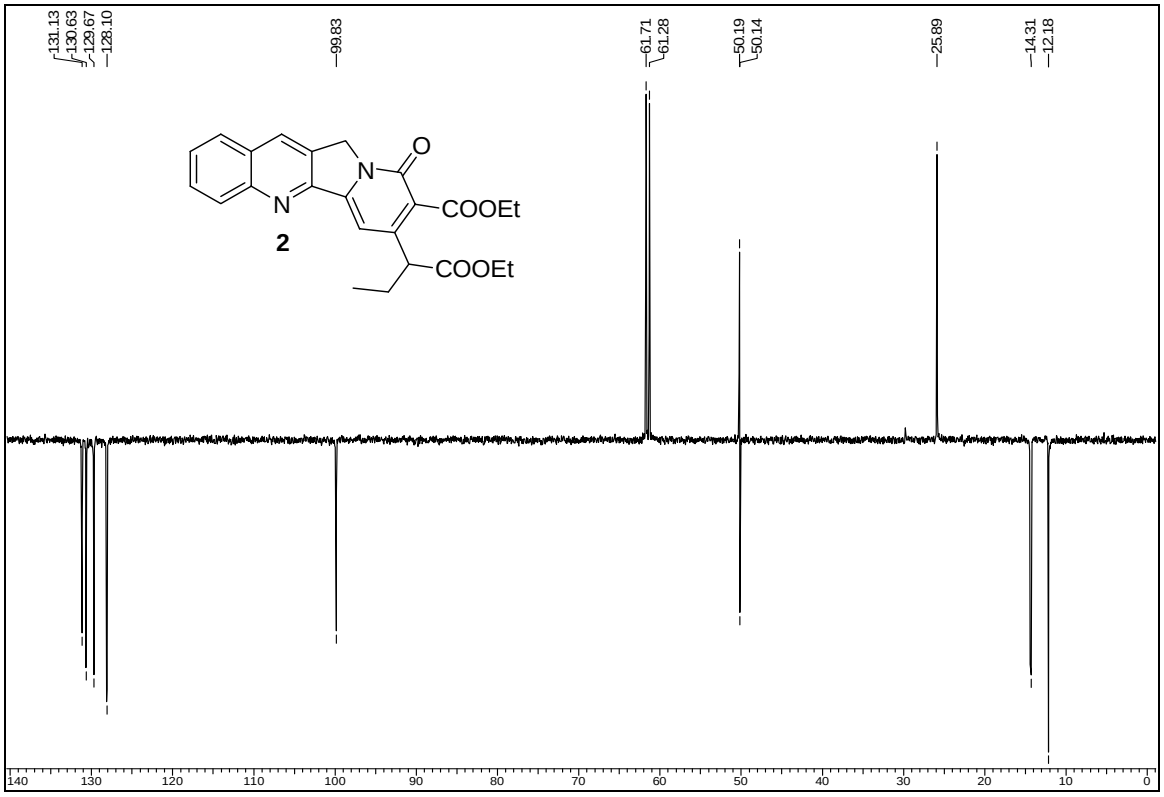
DEPT spectrum of compound 23 ($CDCl_3$ + CCl_4, 100 MHz)



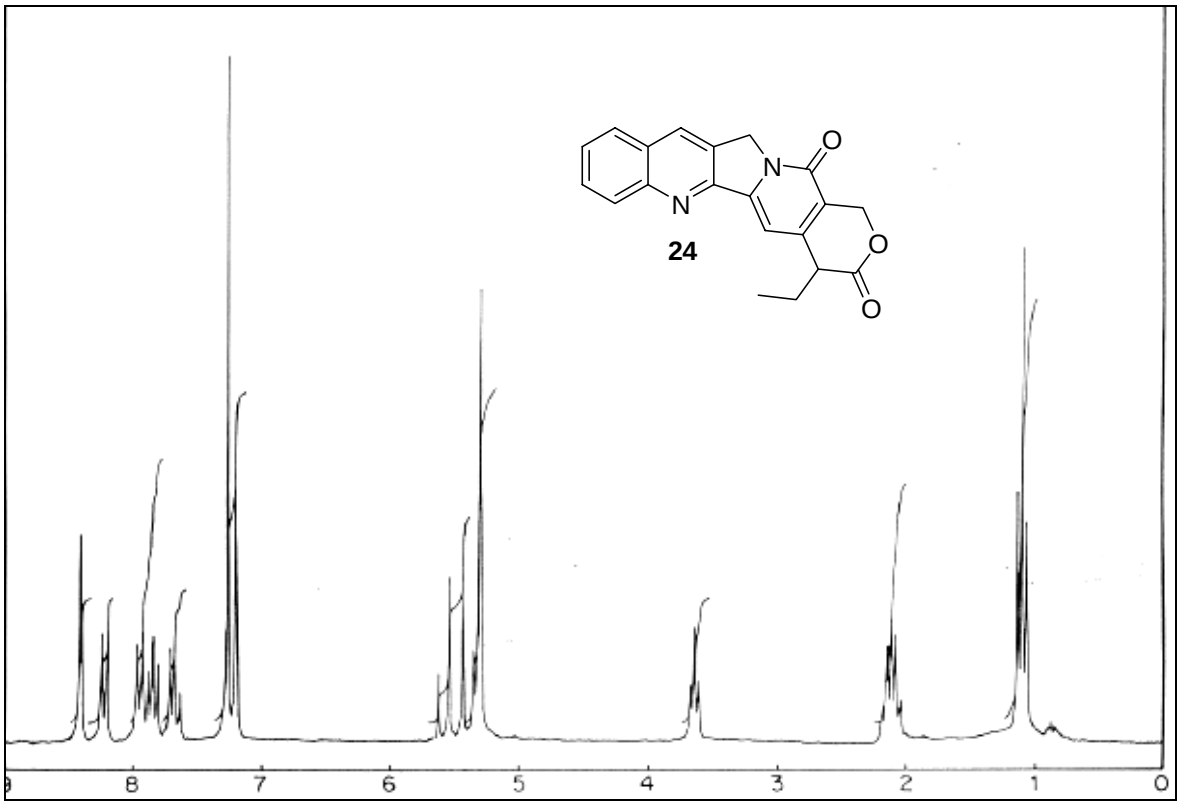
^{1}H NMR spectrum of compound 2 ($CDCl_3$ + CCl_4, 200 MHz)



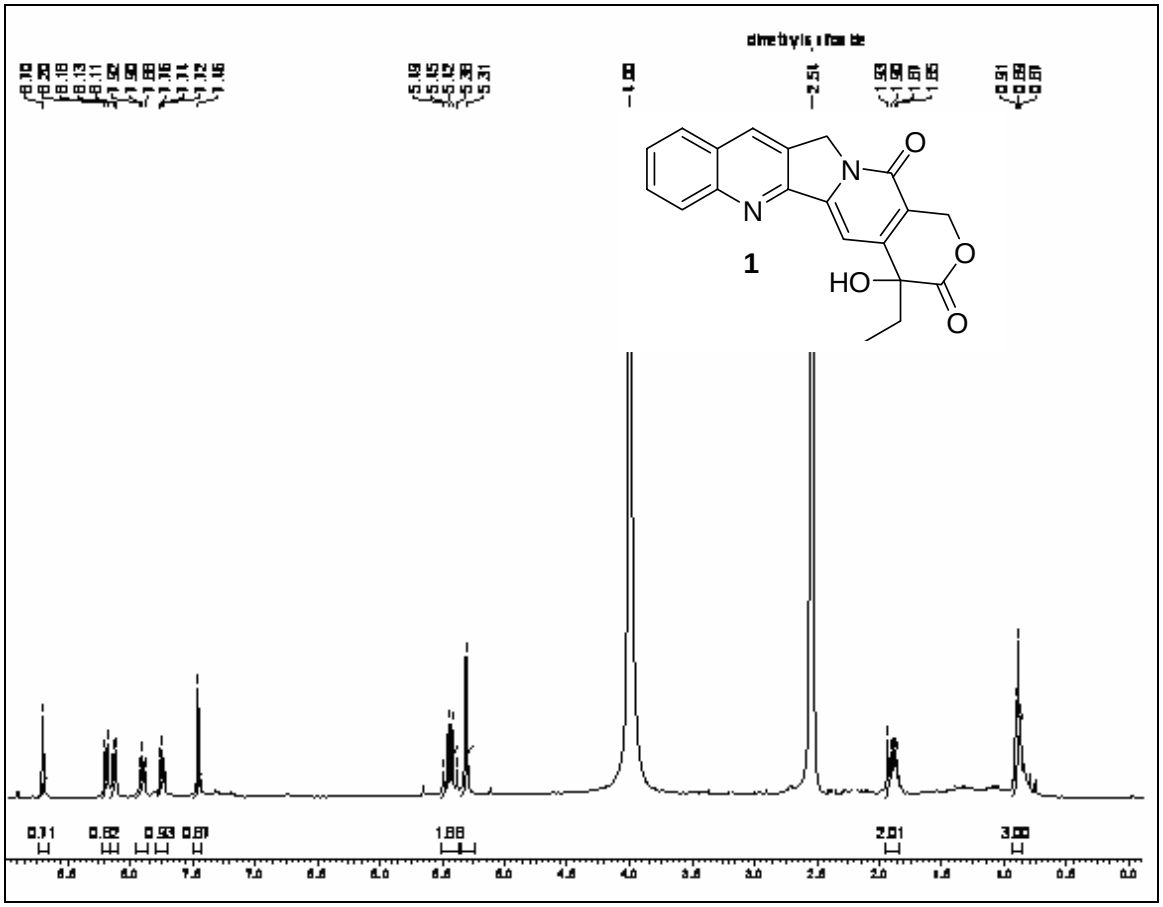
^{13}C NMR spectrum of compound 2 ($CDCl_3$ + CCl_4, 100 MHz)



DEPT spectrum of compound 2 ($CDCl_3$ + CCl_4, 100 MHz)



^{1}H NMR spectrum of compound 24 ($CDCl_3$ + CCl_4, 200 MHz)



^{1}H NMR spectrum of compound 1 (DMSO-d_6, 400 MHz)

2.1.7 References

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Chapter 2, Section II

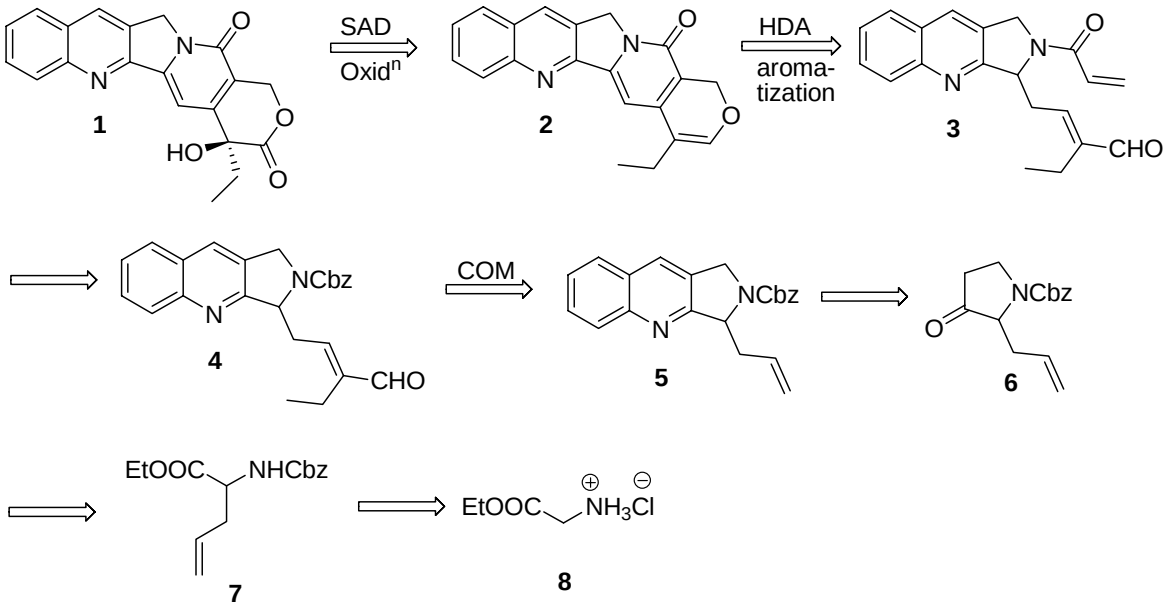
Total synthesis of (+)-camptothecin employing Pd-catalyzed cyclization strategy

2.2.1 Introduction:

Cross olefin metathesis is a very powerful tool for the C=C formation[1-2] in the synthetic organic chemistry and it is the very good alternative to various intermolecular alkene formation reactions, *viz*. palladium-catalyzed methods (e.g. Heck coupling, Suzuki-Miyaura coupling and Stille coupling) as well as non-metal-mediated reactions like Wittig reaction, Peterson olefination and various other methods. Hetero-Diels-Alder reaction is also very efficient method for the construction heterocyclic rings[3] generally which are present in natural and unnatural products and which show broad spectrum of biological activity against numerous diseases.

The camptothecin **1** and its analogues were synthesized by intramolecular enyne metathesis and tandem Knoevenagel condensation followed by Michael addition as mentioned in earlier section. As a part of ongoing program to synthesize the camptothecin family alkaloids and utilization of metathesis protocols this group has been employing different protocols particularly for the construction of D-ring of camptothecins which have been reported.[4] In this section attempted utilization of the cross olefin metathesis for C=C formation is described.

2.2.2 Present work:



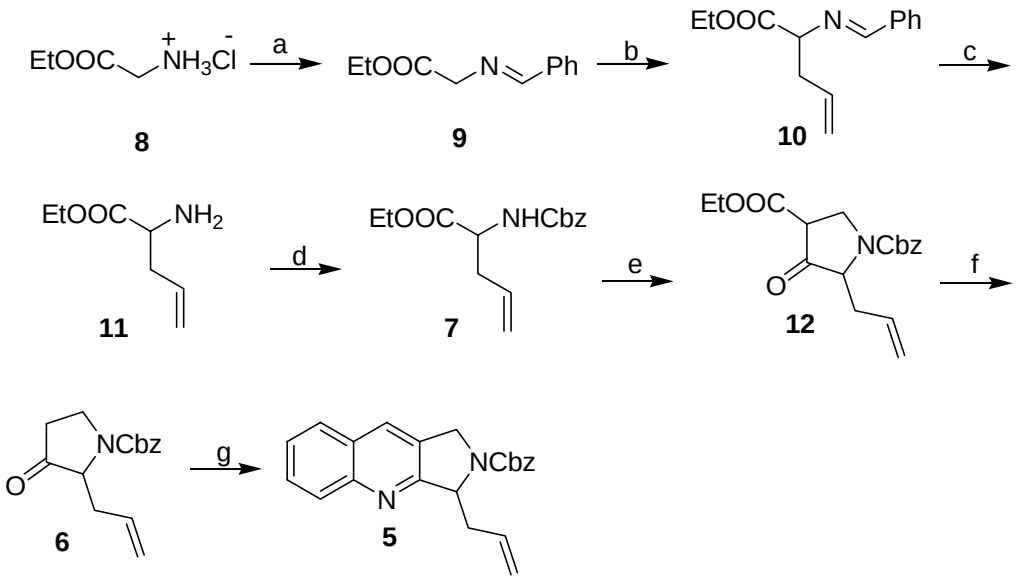
Scheme 1. *Retrosynthetic plan 1.*

The planned retrosynthetic analysis (scheme 1) revealed that the (+)-camptothecin **1** could be derived from enol ether **2** by Sharpless asymmetric dihydroxylation followed by

oxidation. Enol ether **2** could be realized from compound **3** by hetero Diels-Alder reaction, compound **3** can be accessed from compound **4** by Cbz group deprotection and condensation. Compound **4** would be realized from urethane **5** by cross olefin metathesis and urethane **5** in turn could be obtained from readily available ethyl ester glycine hydrochloride salt **8** *via*. Intermediates **6** and **7**.

2.2.3 Results and discussion:

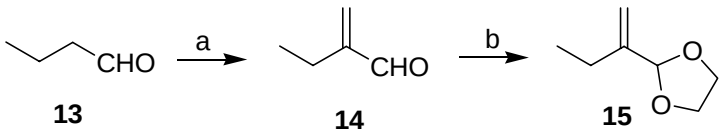
According to planned retrosynthetic analysis the key precursor **5** which is a substrate for cross olefin metathesis was synthesized from readily available ethyl ester of glycine hydrochloride **8** as per reported procedure[4a] described by this group as shown in scheme 2.



Scheme 2. *Reagents and conditions: (a) Et_3N (1.2 equiv), PhCHO (0.9 equiv), MS, dry CH_2Cl_2, 0 ^oC, 1 h, 98%. (b) 10% NaOH (1.5 equiv), allyl bromide (1.2 equiv), $TBAHSO_4$ (0.1 equiv), CH_2Cl_2, rt 2 h, 96%. (c) 10% HCl (1.5 equiv), rt, 0.5 h, 92%. (d) K_2CO_3 (3.0 equiv), benzylchloroformate (1.1 equiv), anhydrous CH_2Cl_2, 0 ^oC, 1h, 91%. (e) NaH (1.2 equiv), ethyl acrylate (1.2 equiv), C_6H_6, rt 1h, refluxed 2-3 h, 72%. (f) NaCl (4.0 equiv), DMSO-H_2O (3:1), 120-130 ^oC, 6 h, 78%. (g) N-(o-aminobenzilidine)-p-toluidine (1.2 equiv), PTSA (cat), anhydrous toluene, reflux, 6 h 86%.*

After the synthesis of tricyclic carbamate **5** which is one partner of cross metathesis another partner i.e. 2-ethyl acrolein **14** or its cyclic acetal **15** was prepared from

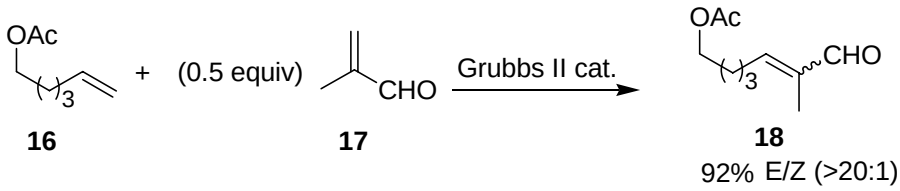
commercially available *n*-butyraldehyde **13** as per literature procedure[5,6] depicted in scheme 3.



Scheme 3. *Reagents and conditions: (a) preheated mixture of Et_2NH-CH_2Br_2 (1:3), 55 ^oC, 2 h, 76%. (b) Ethylene glycol (1.2 equiv), H_2SO_4 adsorbed on silica gel (cat.), C_6H_6-Et_2O (67:33), reflux, 6-8 h, 81%.*

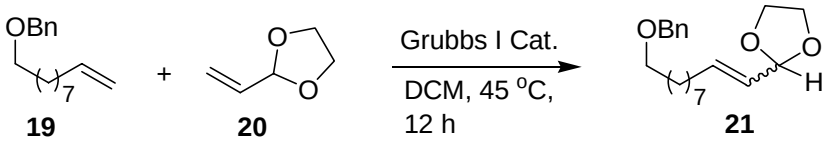
There are several reports of cross olefin metathesis well documented in the literature some of them are described here.

Chatterjee, A. K.; Morgan, J. P.; Scholl, M. and Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 3783-3784.[7]



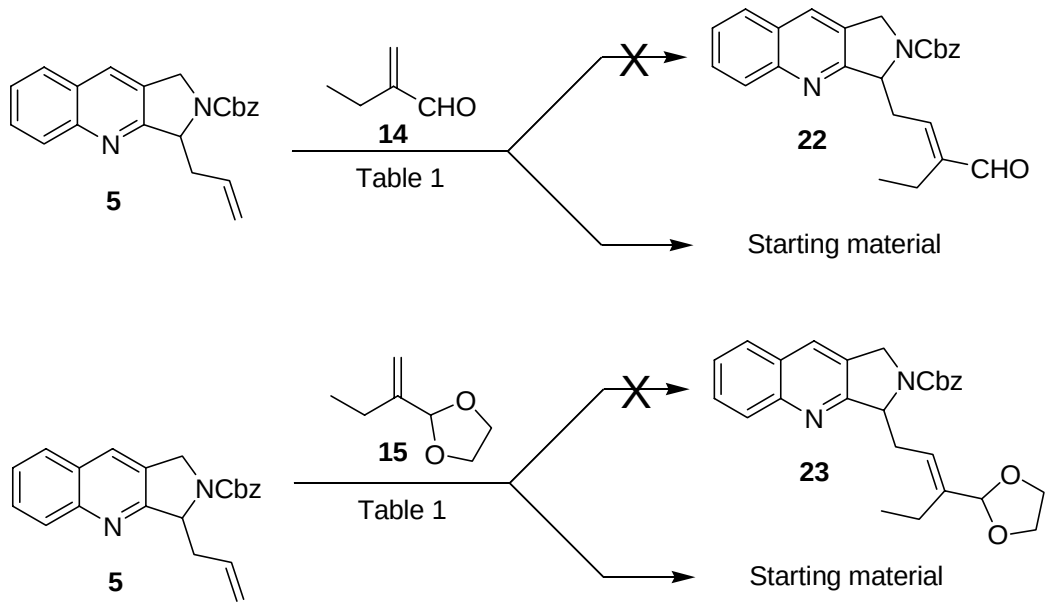
Scheme 4.

O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K and Grubbs, R. H. *Tetrahedron Letters* **1999**, *40*, 1091-1094.[8]



Scheme 5.

Having the required literature support for the cross olefin metathesis as shown in schemes 4 and 5 and in accordance with the planned retrosynthesis, the carbamate **5** was subjected to cross olefin metathesis with 2-ethyl acrolein **14** under different reaction conditions shown in tabulated form in table 1. But unfortunately all efforts were not fruitful and the anticipated compound **22** could not be accessed, instead the starting material was recovered.



Scheme 6.

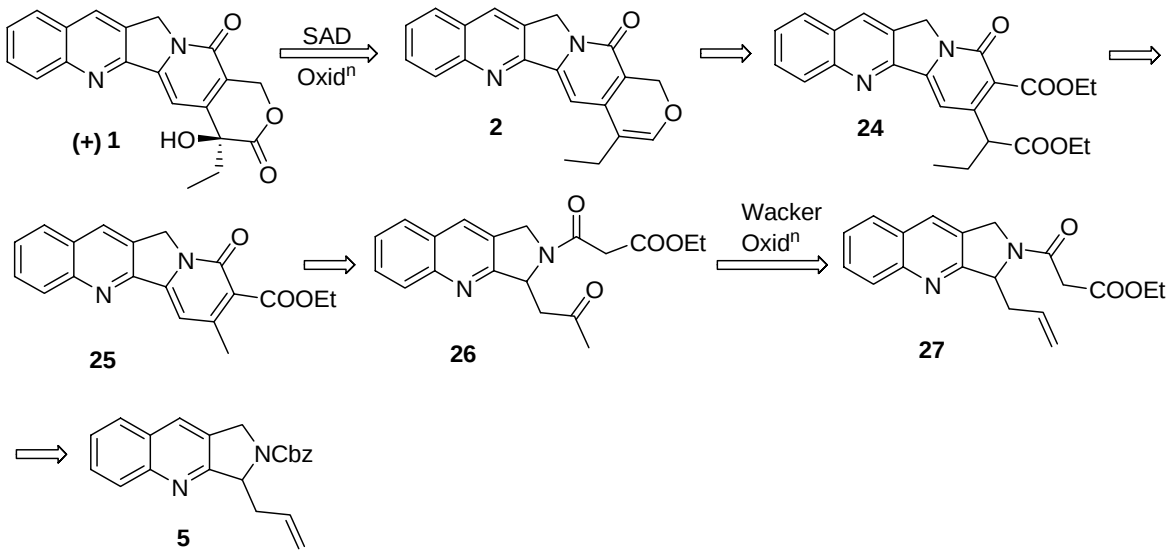
Table 1

Sr. No.	Reagents	Solvents	Temperature	Time	Observation
1	Grubbs I gen. cat. (10 mol %)	CH_2Cl_2	rt	12 h	SM
2	Grubbs I gen. cat. (10 mol %)	CH_2Cl_2	reflux	15 h	SM
3	Grubbs I gen. cat. (10 mol %) 2 eq $Ti(OiPr)_4$	CH_2Cl_2	reflux	15 h	SM
4	Grubbs II gen. cat. (10 mol %)	C_6H_6	reflux	10 h	SM
5	Grubbs II gen. cat. (10 mol %)	toluene	80 ^oC	12 h	SM
6	Grubbs II gen. cat. (10 mol %) 2 eq $Ti(OiPr)_4$	toluene	80 ^oC	15 h	SM

After the failure in cross olefin metathesis of **5** with **14**, **5** was again subjected to cross olefin metathesis with cyclic acetal **15** under various reaction conditions mentioned in table 1 but again the desired could not be realized. This might be probably due to less reactive geminal disubstituted olefins towards cross olefin metathesis.

Having failed to obtain the desired products **22** and **23** via cross olefin metathesis as mentioned in scheme 6, it was decided to modify the strategy for the synthesis of (+)-camptothecin **1** by another protocol employing mild and very well known reaction *viz*. Wacker oxidation as a key step.

Palladium plays a very important role in organic synthesis, Pd in its different oxidation states is a very useful catalyst in effecting critical C-C, C=C and C-X bond forming reactions and is utilized in different coupling reactions.[9-15] Pd (II) catalyst finds use in Wacker oxidation and in different types of cyclization reactions. The Wacker oxidation is the well known reaction for the conversion of an olefin into ketone employing $PdCl_2$ as the catalyst and CuCl, $CuCl_2$, *p*-benzoquinone or H_2O_2 as a reoxidants.[16]



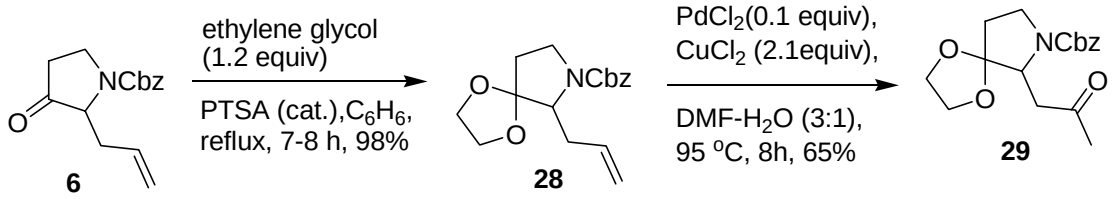
Scheme 7. *Retrosynthetic plan 2.*

The retrosynthetic plan 2 (scheme 7) revealed that, the (+)-camptothecin **1** could be accessed from enol ether **2** by Sharpless asymmetric dihydroxylation followed by oxidation; the enol ether **2** in turn could be obtained from diester **24** by sequence of transformations. The diester **24** in turn could be synthesized from ester **25** by acylation followed by alkylation. Ester **25** could be obtained from keto compound **26** by intramolecular Knoevenagel condensation; the ketone **26** would be realized from olefin **27**

by Wacker oxidation, the olefin **27** in turn could be accessed from carbamate **5** and which in turn could be obtained from commercially avaiable ethyl ester of glycine hydrochloride **8**.

According to retrosynthetic analysis (scheme 7), it was thought that the hypothesis (Wacker oxidation) can be tested on simple substrate, accordingly the substrate required for Wacker oxidation **28** was prepared from ethyl ester of glycine hydrochloride **8** by reported procdure in literature.[4c] When the Wacker oxidation was performed on compound **28** employing catalytic amount of $PdCl_2$ and 2.1 equivalents $CuCl_2$ as a reoxidant in (DMF-H_2O, 3:1) at 95 ^oC it afforded anticipated keto compound **29** in 65% yield.[16g]

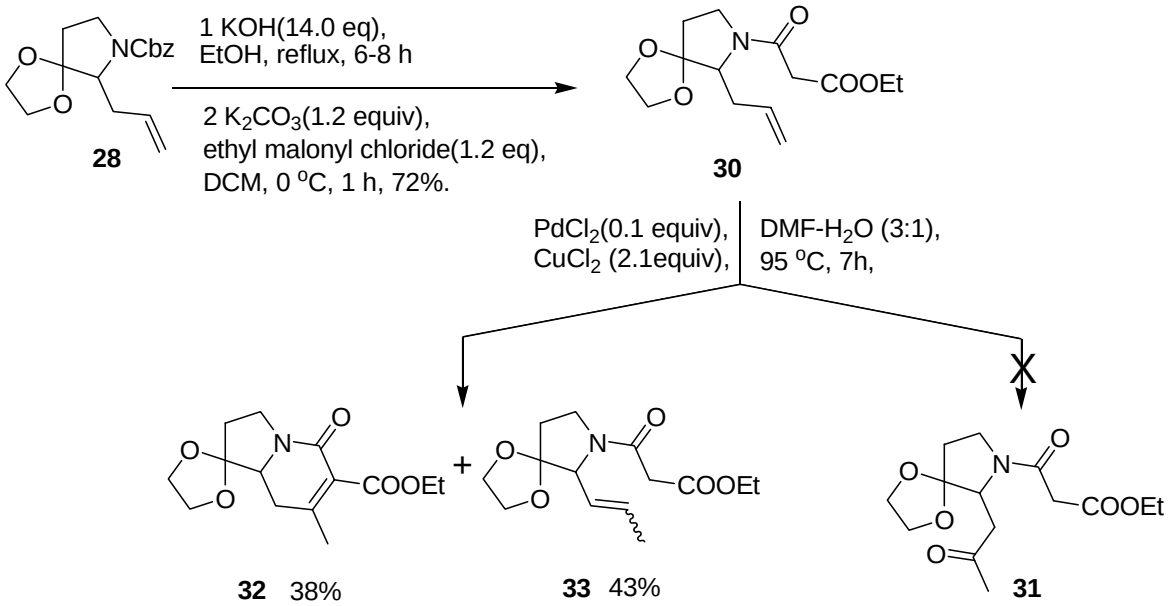
The formation of keto compound **29** was confirmed by spectroscopic data. IR spectrum of **29** displayed strong absorption band at 1717 cm^{-1} indicated the presence of ketone functionality. ^1H NMR spectrum of **29** showed the disappearance the olefinic signals, while new two singlets appeared at δ 2.08 and 2.15 integrating for three protons which were attributed to methyl protons attached to ketone. ^{13}C NMR spectrum of **29** also exhibited the absence of signals of olefinic carbons and new signals appeared at 30.6, 30.8 and δ 205.5, 205.6 which were assigned to methyl and carbonyl carbon of ketone. DEPT spectrum of **29** revealed it to be a mixture of rotamers, and finally the structure of **29** was confirmed by mass spectral and elemental analysis. The mass spectrum of **29** showed the *m/z* peak at 320 $(M + 1)^+$ and 342 $(M + Na)^+$. Elemental analysis was also found to be in good agreements with calculated values.



Scheme 8.

After the successful Wacker reaction on compound **28** (scheme 8), it was decided to perform the Wacker oxidation under identical reaction conditions on compound **30** containing olefin and active methylene in the same molecule. Accordingly compound **30** was subjected to Wacker reaction under identical conditions like compound **28**. Surprisingly the formation of a cyclic product **32** in 38% yield along with isomer of starting material **33** in 43% yield were observed instead of anticipated ketone **31**. It is

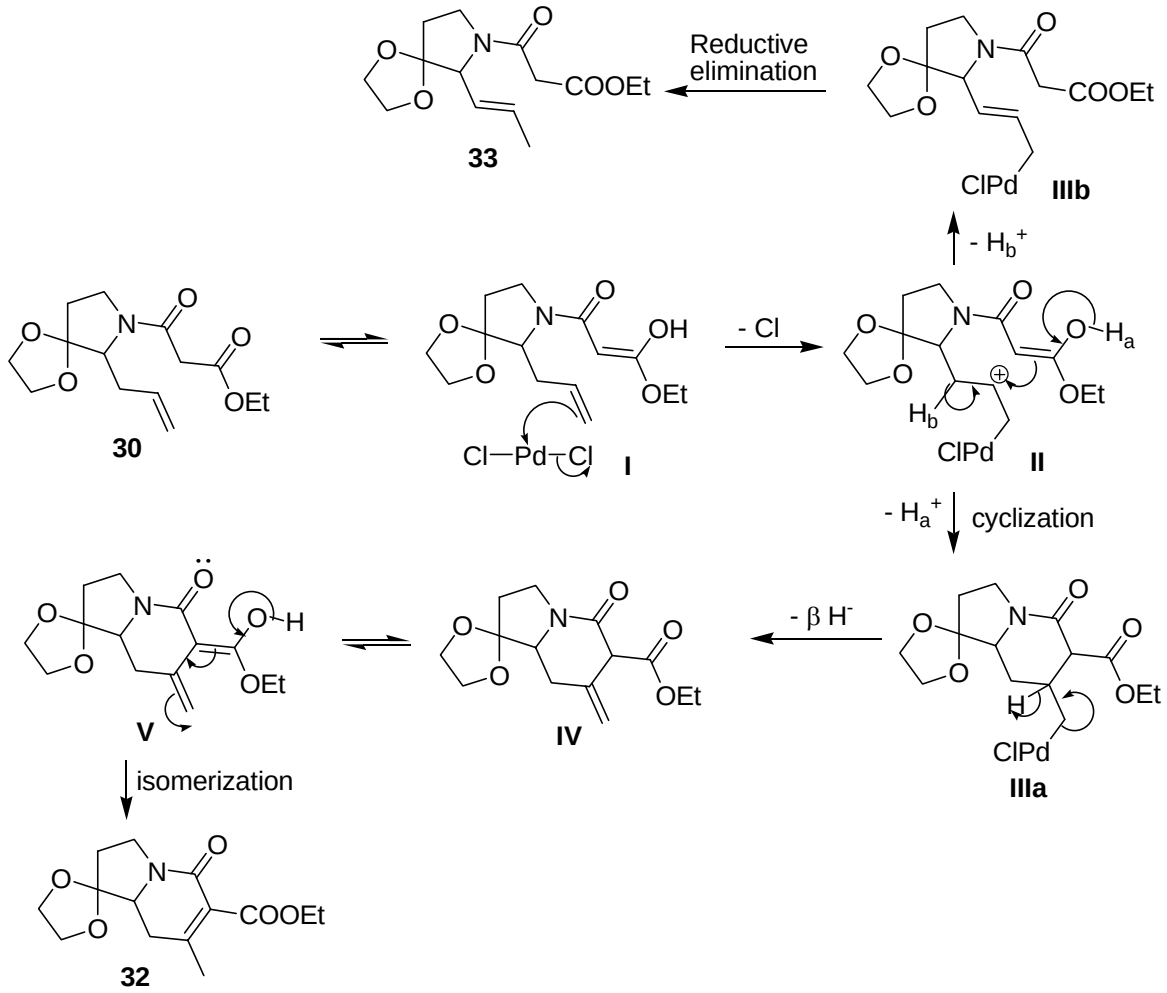
pertinent to mention that earlier Hegedus and coworkers have reported Pd(II) catalyzed intermolecular alkylation of olefin and intramolecular Pd (II)-mediated heterocyclic ring formation.[17] Trost *et al* also reported the formation of rings from the substrate having olefin and β-sulfonyl ester in same subtrate[18] and most recently Widenhoefer *et al* have also observed similar intramolecular cyclizations were observed when 1,3-diketo and β-ketoester olefin were subjected to the treatment with catalyst $PdCl_2(MeCN)_2$ in DME as the solvent.[19] Other reports of Pd-mediated alkylation and cyclization have been reported by various authors.[20-22]



Scheme 9.

The structure of **32** was confirmed by analysis of spectral data. ^{1}H NMR spectrum of **32** displayed the disappearances of the signals corresponding to active methylene and olefinic protons respectively while new singlet appeared at δ 2.00 was ascribed to vinylic methyl protons. This indicated the absence of olefin and active methylene functionality. ^{13}C NMR spectrum of **32** also indicated the absence of signals corresponding to active methylene and olefinic carbons while new signals appeared at δ 21.1, 127.15 and 149.2 characteristic of vinyl methyl carbon and two quaternary olefinic carbons. DEPT spectrum of **32** was also in accordance with the proposed structure. Finally structure of **32** was confirmed by mass spectrum and elemental analysis. The mass spectrum of **32** revealed the *m/z* peaks at 284 $(M + H)^+$, 304 $(M + Na)^+$ and its elemental analysis was in good agreement with calculated values. The compound **32** is the common intermediate in the Shamma's approach and the spectral data is in complete agreement with reported data.[23]

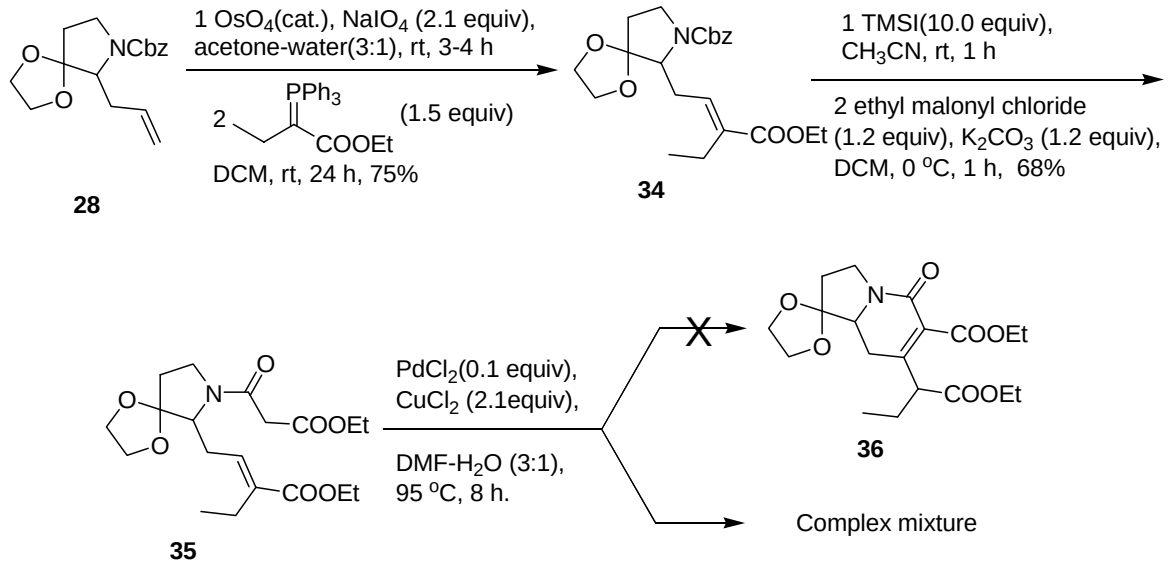
The formation of compound **33** was also characterized by spectroscopic methods. ^{1}H NMR spectrum of **33** displayed the absence of signals corresponding to terminal olefin while presence of doublet at δ 1.76 integrating for three protons (CH=CH-C<u>H</u>$_3$) and multiplet at δ 5.25-5.75 integrated for two protons which was assigned to internal olefinic protons (-C<u>H</u>=C<u>H</u>-CH$_3$). ^{13} C NMR spectrum of **33** showed the disappearance of the signals of terminal olefinic carbon while new signals appeared at δ 17.9 and δ 18.0 corresponding to allylic carbon. Signals which appeared at δ 125.8, 127.4, 127.6, and 128.9 correspond to internal olefinic carbons. ^{1}H, ^{13}C and DEPT spectrum of **33** showed it to be the mixture of rotamers. Lastly the structure of **33** was confirmed by mass spectral and elemental analysis. The mass spectrum of **33** showed the *m/z* peaks at 284 $(M + H)^+$, 306 $(M + Na)^+$ and elemental analysis was also found to be in good agreement with the calculated values. The formation of cyclic compound **32** and isomer **33** can be explained by the mechanism depicted in scheme 10.



Scheme 10. *Probable mechanism.*

The Pd catalyst forms complex with electron rich olefin. This complex formation is followed by attack of the malonate carbanion as an internal nucleophile even in the presence of another nucleophile (i. e. water). After the β-H elimination the Pd catalyst is regenerated and isomerisation of exocyclic double bond into endocyclic double bond takes place, which results the formation of **32**, a competing elimination of H_b results in the formation of isomeric olefin **33**.

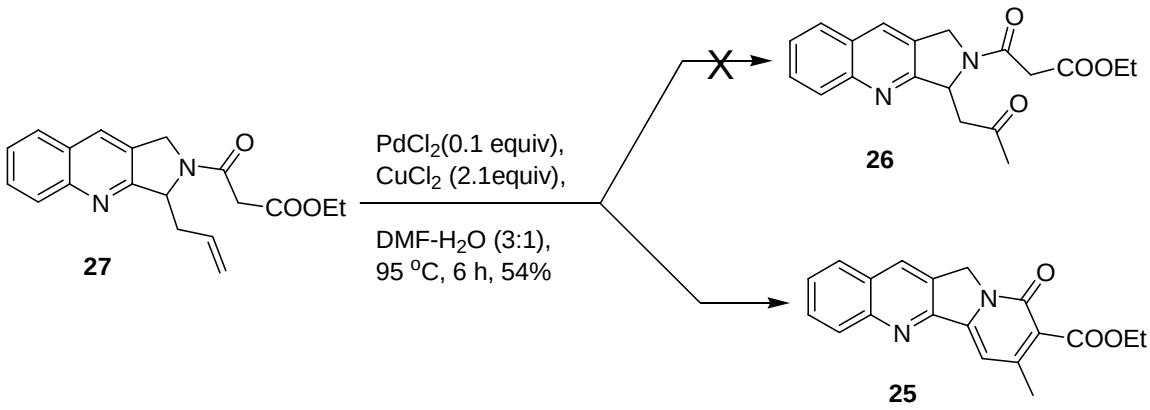
Encouraged by the above results, i.e. cyclization of **30** to **32** (scheme 9) and some similar literature reports[24] it was assumed that similar reaction could also performed on advanced compound **35** under identical reaction conditions. The compound **35** was prepared by reported procedure[4a] as shown in scheme 11. When same reaction was performed on compound **35** under Wacker conditions an intractable mixture was observed instead of anticipated cyclized product **36**. The failure of this reaction may be attributed to the electron deficient olefin, which fails to the complex with the catalyst and hence the reaction is not very clean.



Scheme 11.

After failure of olefin **35** to undergo with Pd-mediated cyclization (scheme 11), it was thought that, by taking the advantage of unusual result of monosubstituted undergoing cyclization (scheme 9), the synthesis of S-(+)-camptothecin **1** could be achieved**.** Accordingly this methodology was employed on tricyclic compound **27** which was synthesized from carbamate **5** by Cbz deprotection followed by condensation with ethyl

malonyl chloride. Accordingly the tricyclic compound **27** was subjected to Wacker oxidation reaction employing catalytic amount of $PdCl_2$ and 2.1 equivalents $CuCl_2$ in DMF-H_2O (3:1) at 95-100 ^oC for 5-6 h. Surprisingly the aromatized product **25** was observed in 54% yield and no isomer of starting material or keto compound **26** was formed. Formation of **25** might be due to the driving force for aromatization. Here the Pd-catalyzed oxidative cyclization followed by concomitant aromatization was accomplished in one-pot.

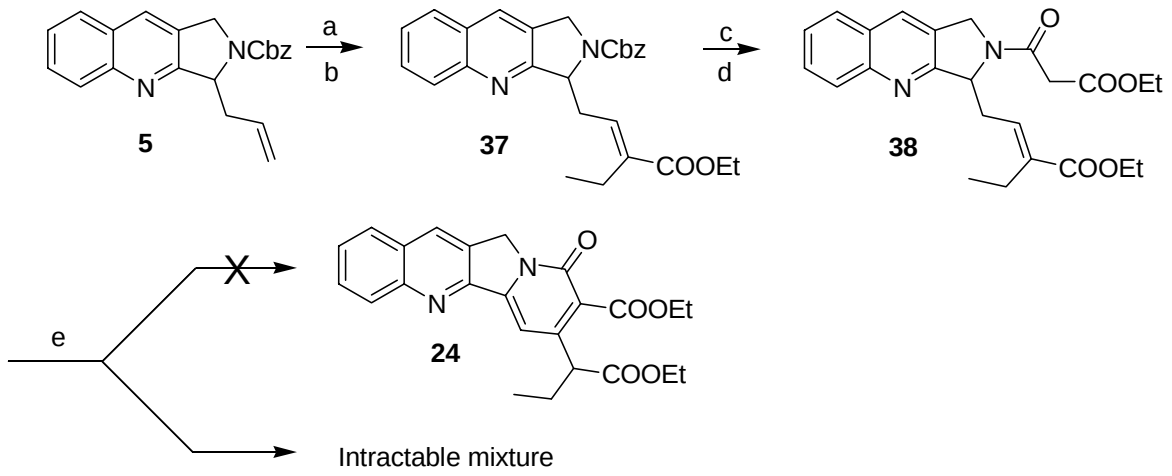


Scheme 12.

The formation of compound **25** was confirmed by spectral techniques. ^1H NMR spectrum of **25** displayed the disappearance of signals corresponding to two active methylene protons and three olefinic protons respectively. While new singlet appeared at δ 2.45 integrating for three protons which was assigned to methyl protons and singlet at δ 7.20 integrated for one proton was assigned to aromatic proton. ^{13}C NMR spectrum of **25** showed new signals that resonated at δ 20.5, 103.6, 128.1, 128.3, 149.1 and 151.2. DEPT spectrum of **25** exhibited the two signals for methylene carbons at δ 50.3 and 61.65. Finally the structure of **25** was confirmed by mass spectral and elemental analysis. The *m/z* peak at 321 $(M + 1)^+$ and 343 $(M + Na)^+$ in mass spectrum confirmed the structure of **25** and elemental analysis of compound **25** was in good agreement with the calculated values.

By taking the inspiration from scheme 12, it was believed that Wacker oxidation would work on substrate **38** which contains the α,β-unsaturated ester and ester amide functionality to form the known advanced intermediated **24** in one-pot. Thus the compound **38** was synthesized as per reported procedure[4a] and it was subjected to Wacker oxidation under identical conditions but unfortunately the desired compound **24** could not be

obtained instead the intractable mixture was observed. This again might be presumably due to the electron deficient olefin's inability to complex with Pd.



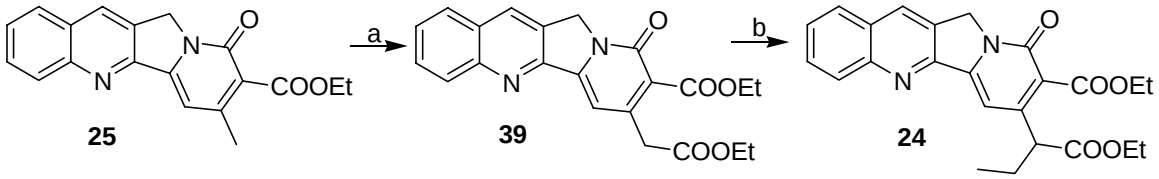
Scheme 13. *Reagents and conditions: (a) OsO_4 (cat.), $NaIO_4$ (2.1 equiv), acetone-water (3:1), rt, 6-8 h (b)* $\overset{PPh_3}{\underset{COOEt}{\diagup\!\!\diagdown}}$(1.5 equiv)*, dry DCM, rt, 48 h, 73%. (c) TMSI (10.0 equiv), dry CH_3CN, rt, 1 h (d) Ethyl malonyl chloride (1.2 equiv), K_2CO_3 (1.2 equiv), dry DCM, 0 ^oC, 1 h, 67%. (e) $PdCl_2$ (0.1 equiv), $CuCl_2$ (2.1 equiv), DMF-H_2O (3:1), 95 ^oC, 12 h*

Having failed in synthesis of advanced intermediate **24** by employing Pd-mediated cyclization followed by aromatization (scheme 13), it was decided that the known intermediate **24** can be obtained by stepwise manner from **25**. Thus the compound **25** was treated with diethyl carbonate using LDA as the base at -78 ^{o}C for 3-4 h furnished diester compound **39** in 70% yield.[25]

The structure of **39** was confirmed by spectral analysis. ^{1}H NMR spectrum of **39** showed the disappearance of the singlet corresponding to methyl protons while appearance of the triplet at δ 1.29 and quartet at δ 4.20 integrated for three and two protons respectively. Singlet at δ 3.78 integrated for two protons, suggested the introduction of ester functionality. ^{13}C NMR spectrum of **39** displayed new signals at δ 14.2, 39.7 and 61.5 indicated the presence of ethyl ester group. DEPT spectrum of **39** revealed the presence of ten quaternary carbons and four methylene carbons that resonated at δ 39.6, 50.2, 61.4 and 61.6. The mass spectrum of **39** displayed the *m/z* peak at 393, 415 and 431 corresponding to $(M + H)^+$, $(M + Na)^+$ & $(M + K)^+$ respectively which confirmed the structure of

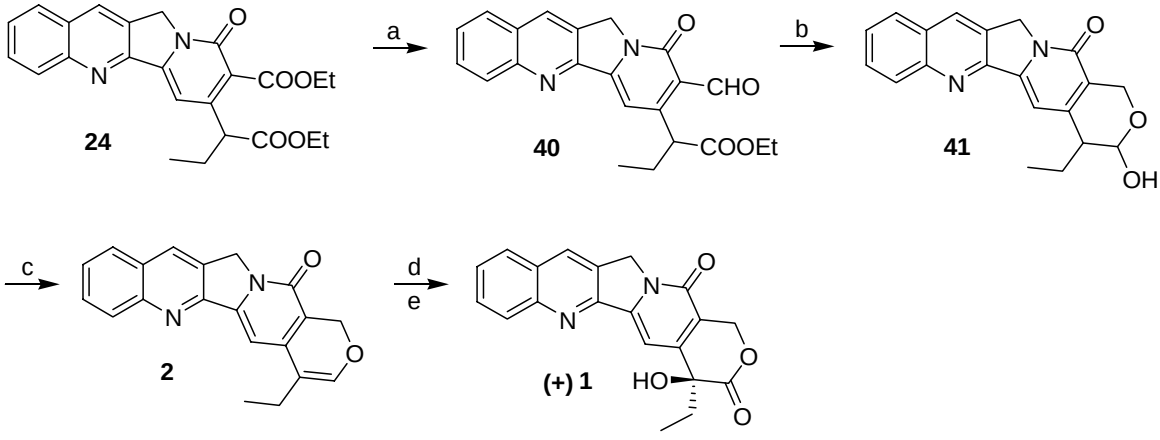
compound **39** and in the elemental analysis the observed values were in good agreement with calculated values.

The compound **39** was alkylated with ethyl iodide using sodium hydride as the base in anhydrous DME. It was gratifying to note that the desired compound **24** was obtained in 64% yield.[26] The formation of compound **24** was confirmed by spectral data which was in complete agreement with the literature data.[4a] The compound **24** is a common key intermediate in our previous approach.[4a]



Scheme 14. *Reagents and conditions: (a) LDA (1.1 equiv), Diethyl carbonate (1.0 equiv), THF, -78 ^{o}C, 3-4 h, 70%. (b) NaH (1.1 equiv), EtI (1.1 equiv), anhydrous DME, 0 ^{o}C- rt, 3-4 h, 64%.*

After obtaining the diester compound **24**, the remaining job was to construct the E-ring having chiral centre. The selective reduction of aromatic ester of diester **24** to aldehyde **40** was accomplished in 90% yield using DIBAL-H in THF at 60 ^{o}C and further the aldehyde was converted into lactol **41** *via* the lactonization using two equivalents of $NaBH_4$. The lactol **41** was converted into enol ether **2** in 92% yield *via O*-mesylation followed by elimination using Et_3N as the base in THF at ambient temperature.



Scheme 15. *Reagents and conditions: (a) DIBAL-H (3.0 equiv), dry THF, -60 ^{o}C, 2 h, 83%. (b) $NaBH_4$ (2.0 equiv), THF-H_2O (5:1), 0 ^{o}C, 0.5 h, 90%. (c) MsCl (4.0 equiv), Et_3N (8.0 equiv), anhydrous THF, rt, 24 h, 92%. (d) $(DHQD)_2$-PYR (cat.), OsO4 (cat.), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $CH_3SO_2NH_2$ (1.0 equiv), t-BuOH-H_2O (1:1), 0 ^{o}C, 7 h (e) I_2 (12.5 equiv), $CaCO_3$ (12.5 equiv), CH_3OH-H_2O (10:1), rt, 24 h, 33% in two steps.*

A short account on Sharpless asymmetric dihydroxylation (AD):

The stereospecific cis-dihydroxylation of olefins achieved by OsO_4, is one of the most important transformation for introducing functionality into organic molecules. Initially the AD using derivatives of cinchona alkaloids was performed under stoichiometric conditions. Lateron with the advent of (i) use of two phase of conditions with $K_3Fe(CN)_6$ as reoxidant (ii) $MeSO_2NH_2$ for rate acceleration and (iii) second generation ligands (phthalazine and diphenylpyrimidine with two independent cinchona alkaloid units) by sharpless et al. catalytic AD came into focus. The enantioselectivity in the AD reaction is due to the enzyme-like binding pocket present in the dimeric cinchona alkaloid ligands. The cinchona alkaloid backbone is ideally suited for providing high ligand acceleration and enantioselectivity. The reaction rates are influenced by the nature of O-9 substituent of the cinchona alkaloid (figure 1).

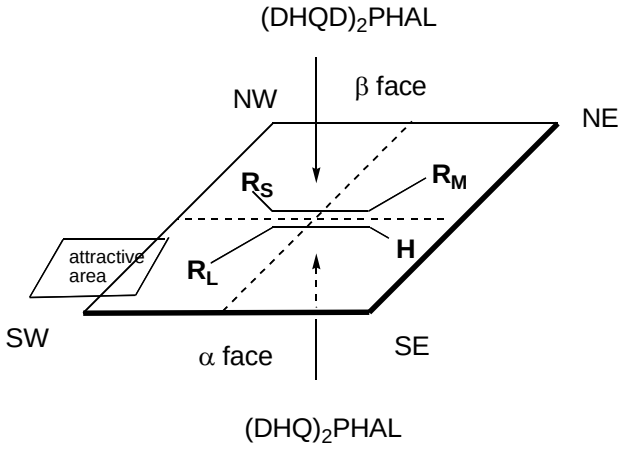


Figure 1. *Mnemonic diagram* (S = small group, L = large group, M = medium group, H = hydrogen.

The rate enhancement is caused by a stabilization of the transition state due to aromatic stacking interactions. Although this kind of stabilization is operative even in monomeric first generation ligand, it is most effective in the dimeric second-generation ligands due to the presence of a binding with respect to rates and enantioselectivities can be readily explained by an especially good transition state stabilization resulting from offset-parallel interactions between the aromatic substituent of the olefin and the phthalazine floor of the ligand, as well as favorable edge-to-face interactions with the bystander methoxyquinoline ring.

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

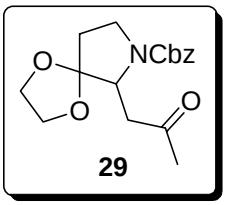
Having the enol ether **2** in hand the last and important task was to install the enantiomerically pure α-hydroxy lactone by Sharpless asymmetric dihydroxylation followed by oxidation. Thus enol ether **2** was treated with catalytic amount of OsO_4 and $(DHQD)_2$-PYR, 3.0 equivalent $K_3Fe(CN)_6$ as a re-oxidant, 3.0 equivalent K_2CO_3, 1.0 equivalent $CH_3SO_2NH_2$ as an additive to enhance the rate of reaction in t-BuOH-H_2O (1:1) at 0 ^oC for 7 h to furnish the diol. Subsequently the resultant diol was oxidized into target *S*-(+)-camptothecin **1** in 33% yield using $CaCO_3$ and I_2 in MeOH-H_2O (10:1) at room temperature for 24 h. However, it can be improved upto 83% by changing the ratio of MeOH-H_2O from 10:1 to 2:1 which was recently reported by Yao *et al*.[27] The formation of compounds **24** to (+)-**1** were confirmed by spectral analysis and which were in complete agreement with literature data.[4e]

2.2.4 Conclusion:

The total synthesis of (+)-camptothecin **1** was achieved employing novel tandem Pd-catalyzed cyclization followed by aromatization under Wacker reaction conditions as a crucial step to construct the pyridone ring.

2.2.5 Experimental

Compound (29):



29

To a well stirred solution of **28** (0.2 g, 0.66 mmol) in DMF-H_2O (8.0 mL, 3:1) was added $PdCl_2$ (0.007 g, 0.066 mmol) and $CuCl_2.2H_2O$ (0.236 g, 1.38 mmol) under oxygen atmosphere. The dark green reaction mixture was heated at 95 ^oC for 8 h. After the completion of reaction (TLC) reaction mixture was cooled to room temperature H_2O (20 mL) was added and extracted with Et_2O (3 x 25 mL). The organic phase was washed with H_2O (3 x 20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with 20% ethyl acetate in petroleum ether yielded compound **29** as a viscous liquid (0.136 g, 65% yield).

MF: $C_{17}H_{21}NO_5$**, MW**: 319

IR ($CHCl_3$) ν_{max}: 1717, 1697, 1216, 758 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.93 (t, *J* = 9.5 Hz, 2H), 2.07, 2.14 (s, s, 3H), 2.49-2.85 (m, 2H), 3.33-3.57 (m, 2H), 3.80, 4.00 (s, s, 4H), 4.18 (dd, *J* =9.35 & 3.8 Hz, 1H) 5.06, 5.19 (d, d, *J* = 12.5 Hz, 2H), 7.32 ppm (s, 5H) (mixture of rotamers).

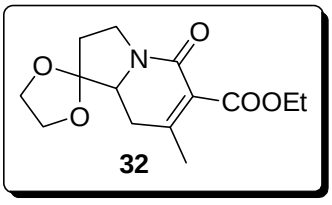
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 30.6, 30.8, 32.2, 33.0, 43.2, 44.5, 45.4, 59.1, 59.4, 64.5, 65.4, 66.8, 113.8, 114.4, 127.95, 128.0, 128.5, 136.7, 154.45, 154.6, 205.5, 205.6 ppm (mixture of rotamers).

MS (ESI) *m/z*: 320 $(M + H)^+$, 342 $(M + Na)^+$.

Elemental analysis Calculated: C, 63.94; H, 6.63; N, 4.39%.

Found: C, 64.02.19; H, 6.69; N, 4.66%.

Compound (32):



32

To a well stirred mixture of **30** (0.5 g, 1.7 mmol), $PdCl_2$ (0.020 g, 0.17 mmol) and $CuCl_2.2H_2O$ (0.632 g, 3.7 mmol) in DMF-H_2O (16.0 mL, 3:1) and the resultant dark green solution was heated at 95 ^oC. The progress of reaction was monitored by TLC. After the completion of reaction (7 h), reaction mixture was cooled to room temperature, H_2O (30 mL) was added and extracted with Et_2O (3 x 30 mL). The organic phase was washed with H_2O (3 x 30 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and solvent was removed *in vacuo*. The residue obtained was

purified by flash column chromatography (SiO_2) eluting with ethyl acetate-petroleum ether (2:3) yielded mixture of compound **32** (0.188 g, 38%) and **33** (0.215 g, 43%) as a viscous liquid.

MF: $C_{14}H_{19}NO_5$**, MW**: 281

IR ($CHCl_3$) ν_{max}: 1731, 1659, 1651, 1213, 759 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.33 (t, *J* = 7.1 Hz, 3H), 1.68-2.37 (m, 7H), 2.60 (t, *J* = 7.5 Hz, 1H), 3.44-388 (m, 3H), 3.96 (s, 4H), 4.30 ppm (q, *J* = 7.1 Hz, 2H).

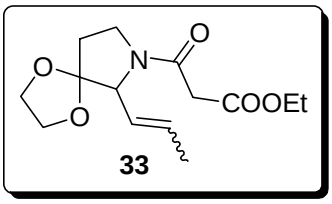
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 14.3, 21.1, 29.9, 33.6, 41.8, 59.2, 61.2, 65.4, 113.75, 127.15, 149.2, 160.45, 166.1 ppm.

MS (ESI) *m/z*: 282 $(M + H)^+$, 304 $(M + Na)^+$.

Elemental analysis Calculated: C, 59.78; H, 6.81; N, 4.98%.

Found: C, 59.72.19; H, 6.79; N, 5.06%.

Compound (33):



33

MF: $C_{14}H_{21}NO_5$**, MW**: 283

IR ($CHCl_3$) ν_{max}: 1728, 1667, 1651, 1216, 754 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.28 (t, *J* = 7.1 Hz, 3H), 1.75 (d, *J* = 5.9 Hz, 3H), 1.91-2.18 (m, 2H), 3.30-3.39 (m, 2H), 3.52-3.77 (m, 3H), 3.96 (s, 4H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.25-5.75 ppm (m, 2H).

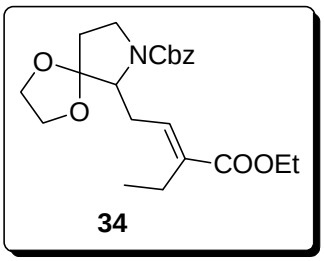
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ:14.2, 17.9, 18.0, 29.2, 31.35, 32.3, 36.6, 40.2, 41.7, 42.1, 43.2, 44.2, 50.3, 52.7, 61.25, 62.0, 62.95, 64.2, 64.5, 65.2, 65.4, 112.45, 113.3, 114.7, 125.8, 127.4, 127.6, 128.9, 164.8, 165.5, 167.4 ppm (mixture of rotamers).

MS (ESI) *m/z*: 284 $(M + H)^+$, 306 $(M + Na)^+$.

Elemental analysis Calculated: C, 59.35; H, 7.47; N, 4.94%.

Found: C, 59.39; H, 7.41; N, 4.89%.

Compound (34):



34

To the stirred solution of olefin **28** (2.0 g, 6.6 mmol) in acetone-water (40 mL, 3:1) was added catalytic amount of OsO_4 at room temperature and stirred for 10 minutes, the reaction mixture became black coloured, then $NaIO_4$ (2.96 g, 13.86 mmol) was added portion wise and reaction mixture was left to stir for 3-4 h. After the completion of reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure and the resultant

residue was dissolved in H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*, to furnish aldehyde. The generated crude aldehyde (assuming 100% conversion) was treated with Wittig salt (3.72 g, 9.9 mmol) in CH_2Cl_2 (20 mL) under argon atmosphere and allowed to stir at room temperature. After the completion of reaction (24 h, TLC) the DCM was removed *in vacuo* and purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:4) as eluent yielded the gum like compound **34** (2.07 g, 78% yield).

MF: $C_{22}H_{29}NO_6$, **MW**: 403

IR ($CHCl_3$) ν_{max}, 1701, 1621, 1217, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.76-0.94 (m, 3H), 1.13-1.21 (m, 3H), 1.78-2.49 (m, 6H), 3.36-3.42 (m, 2H), 3.47-3.90 (m, 5H), 3.97-4.16 (m, 2H), 4.58 (s, 1H), 5.03 (s, 1H), 6.67 (dd, *J* = 15.8, 7.8 Hz, 1H), 7.24 ppm (s, 5H).

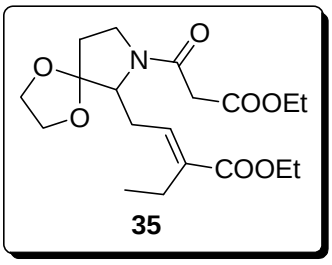
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 13.6, 14.2, 20.0, 43.4, 60.2, 62.0, 62.3, 64.1, 64.9, 65.4, 66.8, 67.1, 114.0, 114.6, 126.8, 127.3, 127.8, 128.0, 128.4, 135.5, 136.4, 136.6, 137.3, 137.5, 141.2, 155.0 167.7 ppm (mixture of isomers).

MS (ESI) *m/z*: 404 $(M + H)^+$, 421 $(M + NH_4)^+$, 426 $(M + Na)^+$.

Elemental analysis Calculated: C, 65.49; H, 7.24; N, 3.47%.

Found: C, 65.53; H, 7.19; N, 3.51%.

Compound (35):



35

To a well stirred mixture of carbamate **34** (1.0 g, 2.48 mmol) in anhydrous acetonitrile (10 mL) was added TMSCl (2.67 g, 24.8 mmol) dropwise at room temperature and allowed to stir at room temperature till completion of reaction (1 h, TLC). The reaction was quenched with addition of 20% sodium thiosulphate solution and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure delivered amine. To a well stirred mixture of the obtained crude amine (0.67 g, 2.48 mmol), K_2CO_3 (0.41 g, 2.97 mmol) in anhydrous CH_2Cl_2 (20 mL) was added ethyl malonyl chloride (0.45 g, 2.97 mmol) gradually under nitrogen atmosphere at 0 ºC over a period of 10 minutes and left to stir till completion of reaction (3 h, TLC). After the completion of reaction the reaction

mixture was filtered and residue was washed with CH_2Cl_2 (3 x 10 mL), the filtrate was washed with H_2O (50 mL), brine (30 mL) and organic phase was dried over anhydrous Na_2SO_4,filtered and concentrated on rotary evaporator under reduced pressure. The residue thus obtained was purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (2:3) afforded the compound **35** as a viscous liquid (0.62 g, 65% yield).

MF: $C_{19}H_{29}NO_7$, **MW**: 383

IR ($CHCl_3$) ν_{max}, 1736, 1705, 1650, 1215, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.0 (t, *J* = 7.5 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 6H), 1.93-2.66 (m, 6H), 3.34 (s, 2H), 3.48-3.57 (m, 2H), 3.60-3.73 (m, 1H), 3.86-4.00 (m, 4H), 4.12-4.25 (m, 4H), 6.61-6.75 ppm (m, 1H).

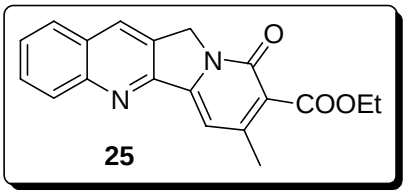
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 13.9, 14.3, 20.1, 28.8, 36.7, 41.5, 43.7, 60.5, 61.4, 61.7, 113.9, 137.9, 165.4, 166.9, 167.2 ppm (mixture of isomers).

MS (ESI) *m/z*: 384 $(M + H)^+$, 401 $(M + NH_4)^+$, 406 $(M + Na)^+$, 422 $(M + K)^+$.

Elemental analysis Calculated: C, 59.52; H, 7.62; N, 3.65%.

Found: C, 59.49; H, 7.66; N, 3.61%.

Ethyl7-methyl-9-oxo-9,11-dihydroindolizino[1,2-b]quinoline-8-carboxylate (25)



25

To a stirred solution of **27** (2.0 g, 6.17 mmol) in DMF (15.0 mL) and H_2O (5.0 mL) was added $PdCl_2$ (0.072 g, 0.61 mmol) and $CuCl_2.2H_2O$ (2.20 g, 12.95 mmol). The resultant reaction mixture became dark green which was heated at 95 ^oC and the progress of reaction was monitored by TLC. After the completion of reaction (6 h), the reaction mixture was allowed to cool to room temperature, H_2O (50 mL) was added and it was extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with H_2O (3 x 50 mL), brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (4:1) as eluent furnished compound **25** as a pale yellow solid (1.06 g, 54% yield).

MF: $C_{19}H_{16}N_2O_3$, **MW**: 320

M.P.: 147-150 ^oC

IR ($CHCl_3$) ν_{max}: 1728, 1658 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 400 MHz) δ: 1.43 (t, *J* = 7.1 Hz, 3H), 2.45 (s, 3H), 4.45 (q, *J* = 7.1 Hz, 2H), 5.26 (s, 2H), 7.20 (s, 1H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.81 (t, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 8.36 ppm (s, 1H).

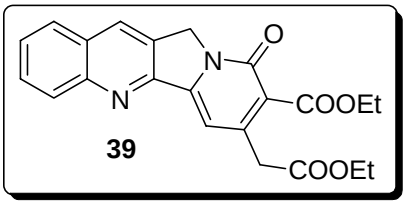
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ:14.5, 20.5, 50.3, 61.6, 103.6, 128.1, 128.3, 129.3, 130.0, 130.7, 131.2, 145.9, 149.1, 151.2, 152.5, 158.55, 166.5 ppm.

MS (ESI) *m/z*: 321 $(M + H)^+$, 343 $(M + Na)^+$.

Elemental analysis Calculated: C, 71.24; H, 5.03; N, 8.74%.

Found: C, 71.19; H, 5.11; N, 8.69%.

Ethyl7-(2-ethoxy-2-oxoethyl)-9-oxo-9,11-dihydroindolizino[1,2-*b*]quinoline-8-carboxylate (39)



39

To a well stirred solution of diisopropyl amine (0.378 g, 3.75 mmol) in anhydrous THF (10.0 mL) was added 1.6 M *n*-BuLi (0.24 g, 2.3 ml, 3.75 mmol) at 0 ^oC for 40 minutes and then cooled to -78 ^oC. Compound **25** (1.0 g, 3.12 mmol) in THF (5.0 mL) was added dropwise over 10 minutes and allowed to stir for 30 minutes at -78 ^oC followed by dropwise addition of diethyl carbonate (0.442 g, 3.75 mmol) in THF (5.0 mL) and reaction mixture was allowed to stir at -78 ^oC for further 3-4 h. After the completion of reaction (TLC) the reaction was quenched with the addition of saturated NH_4Cl solution at -78 ^oC and reaction mixture was allowed to warm to room temperature, the organic phase was separated and aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and solvent was removed *in vacuo*. The residue obtained was purified by flash column chromatography (SiO_2, 230-400 mesh) using ethyl acetate-petroleum ether (4:1) as eluent rendered the **39** as a pale yellow solid (0.85 g, 70% yield).

MF: $C_{22}H_{20}N_2O_5$, **MW**: 392

M.P.: 244-246 ^oC

IR ($CHCl_3$) ν_{max}: 1736, 1727, 1658 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.29 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 3.78 (s, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 5.17 (s, 2H), 7.21 (s, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.32 ppm (s, 1H).

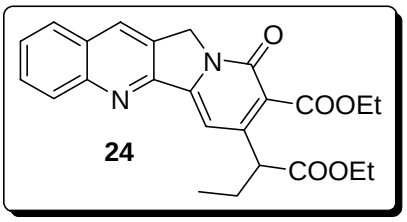
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 14.2, 39.8, 50.3, 61.5, 61.7, 103.2, 124.0, 128.2, 129.05, 129.7, 130.7, 131.1, 146.55, 147.6, 148.9, 152.1, 158.35, 165.9, 169.2 ppm

MS (ESI) *m/z*: 393 $(M + H)^+$, 415 $(M + Na)^+$, 431 $(M + K)^+$.

Elemental analysis Calculated: C, 67.34; H, 5.14; N, 7.14%.

Found: C, 66.94; H, 4.91; N, 7.43%.

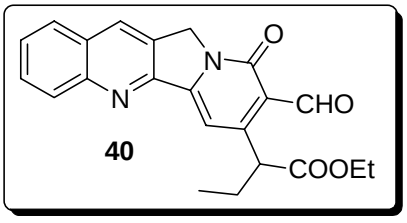
Ethyl 7-(1-ethoxy-1-oxobutan-2-yl)-9-oxo-9,11-dihydroindolizino[1,2-*b*]quinoline-8-carboxylate (24):



24

To a 60% NaH (0.097 g, 2.4 mmol) prewashed with anhydrous petroleum ether (3 x 10 mL), anhydrous THF (10 mL) was added. Compound **39** (0.8 g, 2.0 mmol) in anhydrous THF (10 mL) was added slowly at 0 ^oC and stirred for 15 minutes followed by dropwise addition of ethyl iodide (0.350 g, 2.24 mmol) in anhydrous THF (5 mL) at 0 ^oC and the reaction mixture was allowed to stir till the completion of reaction (3 h, TLC). The reaction was quenched by addition of saturated NH_4Cl solution, the organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (4:1) as eluent resulted compound **24** as a yellow solid (0.548 g, 64% yield). The m.p. and spectral data of **24** has mentioned in chapter 2, section II

8-(formyl)-7-[1-(ethoxycarbonyl)propyl]-9,11-dihydroindolizino[1,2*b*]-quinoline-9-one (40)



40

To a well stirred solution of **24** (0.11 g, 0.261 mmol) in anhydrous THF (25 mL) was added 3 M solution in toluene of DIBAL-H (0.257 mL, 0.785 mmol) dropwise at -60°C under argon atmosphere. The resultant reaction mixture was allowed to stir at -60 °C for an additional 2 h. The reaction was quenched with addition of MeOH (0.257 mL) and H_2O (0.05 mL) and warmed to room temperature. The gelatinous precipitate was filtered through celite and the celite washed thoroughly with THF (3 x 10 mL). The filtrate was concentrated on rotary evaporator under reduced pressure the resultant residue was purified by flash column

chromatography (SiO_2) using ethyl acetate-petroleum ether (1:4) as eluent to furnish pure aldehyde **40** (0.081 g, 83% yield).

MF: $C_{22}H_{20}N_2O_4$, **MW**: 376

M.P.: 181-182 ^oC

IR (KBr) ν_{max}: 1725, 1680, 1635, 1590, 1510 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.05 (t, *J* = 7.5 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.9 (m, 1H), 2.25 (m, 1H), 4.2 (m, 2H), 5.15 (t, *J* = 6.4 Hz, 1H), 5.35 (s, 2H), 7.7 (t, *J* = 7.4 Hz, 1H), 8.85 (t, *J* = 7.4 Hz, 1H), 8.95 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.42 (s, 1H), 10.65 ppm (s, 1H).

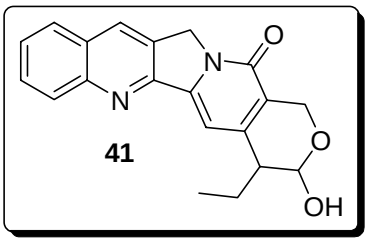
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 12.2, 14.3, 26.0, 47.3, 50.4, 61.3, 101.7, 121.5, 128.3, 128.5, 128.7, 129.5, 130.0, 131.0, 131.4, 149.1, 150.2, 151.8, 158.4, 162.6, 172.5, 192.3 ppm.

MS (ESI) *m/z*: 377 $(M + H)^+$, 394 $(M + NH_4)^+$, 399 $(M + Na)^+$.

Elemental analysis Calculated: C, 70.3; H, 5.1; N, 7.4%

Found: C,69.7; H, 4.5; N, 8.05%

4-ethyl-3hydroxy-3,4,12,14-tetrahydro-1H-pyrano[3',4',6,7]indolizino[1,2*b*]quinoline-14-one (41) :



41

To a stirred solution of aldehyde **40** (0.079 g, 0.2 mmol) in THF-H_2O (6 mL, 5:1) was added $NaBH_4$ (0.015 g, 0.4 mmol) at 0 ^oC and the reaction mixture allowed to stir at 0 °C for 0.5 h. After the completion of reaction (TLC), 10% HCl was added and the mixture extracted with $CHCl_3$ (3 x 25 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* the residue obtained was purified by column flash chromatography over silica gel using 5% methanol in chloroform as eluent furnished lactol **41** (0.063 g, 90% yield).

MF: $C_{20}H_{16}N_2O_4$, **MW**: 334

M.P.: 212-214°C

IR (Neat) ν_{max}: 3400; 1660; 1600 cm^{-1}.

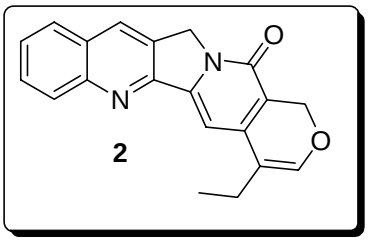
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.1 (t, *J* = 7.5 Hz, 3H), 1.7 (m, 2H), 2.7 (m, 1H), 4.85 (dd, 2H), 5.25 (s, 2H), 5.45 (s, 1H), 7.15 (s, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.85 (t, *J* = 7.4 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 8.2 (d, *J* = 8.5 Hz, 1H), 8.35 ppm (s, 1H).

MS (ESI) *m/z*: 335 $(M + H)^+$, 357 $(M + Na)^+$ and 373 $(M + K)^+$.

Elemental analysis Calculated: C, 72.0; H, 5.1; N, 8.4%.

Found: C, 71.83; H, 5.05; N, 7.96%.

4-ethyl-12,14-dihydro-1H-pyrano[3',4',6,7]indolizino[1,2*b*]quinoline-14-one (2)



2

To a well stirred solution of lactol **41** (0.06 g, 0.17 mmol) in anhydrous THF (10 mL) was added Et_3N (0.145 g, 1.4 mmol) followed by mesyl chloride (0.082 g, 0.7 mmol) at 0°C. The resultant reaction mixture was left to stir at room temperature till the completion of reaction (24 h, TLC). Water (15 mL) was added and aqueous phase extracted with $CHCl_3$ (3 x 15 mL). The combined organic phase was dried over anhydrous sodium sulphate, filtered and concentrated on rotary evaporator under diminished pressure. The residue thus obtained was purified by flash column chromatography (SiO_2) using $CHCl_3$ as eluent furnished enol ether **2** (0.052 g, 92% yield).

MF: $C_{20}H_{14}NO_3$, **MW**: 316

IR (Neat) ν_{max}: 1660; 1620; 1540; 1020 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.25 (t, *J* = 7.5 Hz, 3H), 2.45 (q, *J* = 7.5 Hz, 2H), 5.2 (s, 2H), 5.25 (s, H), 6.65 (s, 1H), 7.2 (s, 1H), 7.6 (t, *J* = 7.4 Hz, 1H), 7.8 (t, *J* = 7.4 Hz, 1H), 7.9 (d, *J* = 8.5 Hz, 1H), 8.2 (d, *J* = 8.5 Hz, 1H), 8.35 ppm (s, 1H).

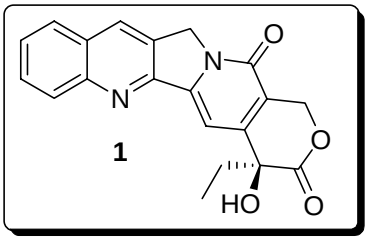
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 13.7, 20.6, 49.7, 63.3, 95.5, 114.8, 115.6, 127.5, 127.9, 128.7, 129.4, 130.2, 130.7, 143.5, 145.6, 146.9, 148.8, 153.6, 158.6 ppm.

MS (ESI) *m/z*: 317 $(M + H)^+$, 334 $(M + NH_4)^+$, 339 $(M + Na)^+$ and 355 $(M + K)^+$.

Elemental analysis Calculated: C, 75.90; H, 4.70; N, 8.90%.

Found: C, 75.84; H, 5.09; N, 9.38%

4(S)-4-ethyl-4-hydroxy-1H-pyrano[3',4',6,7]indolizino[1,2*b*]quinoline-3,14(4H,12H)-dione (1)



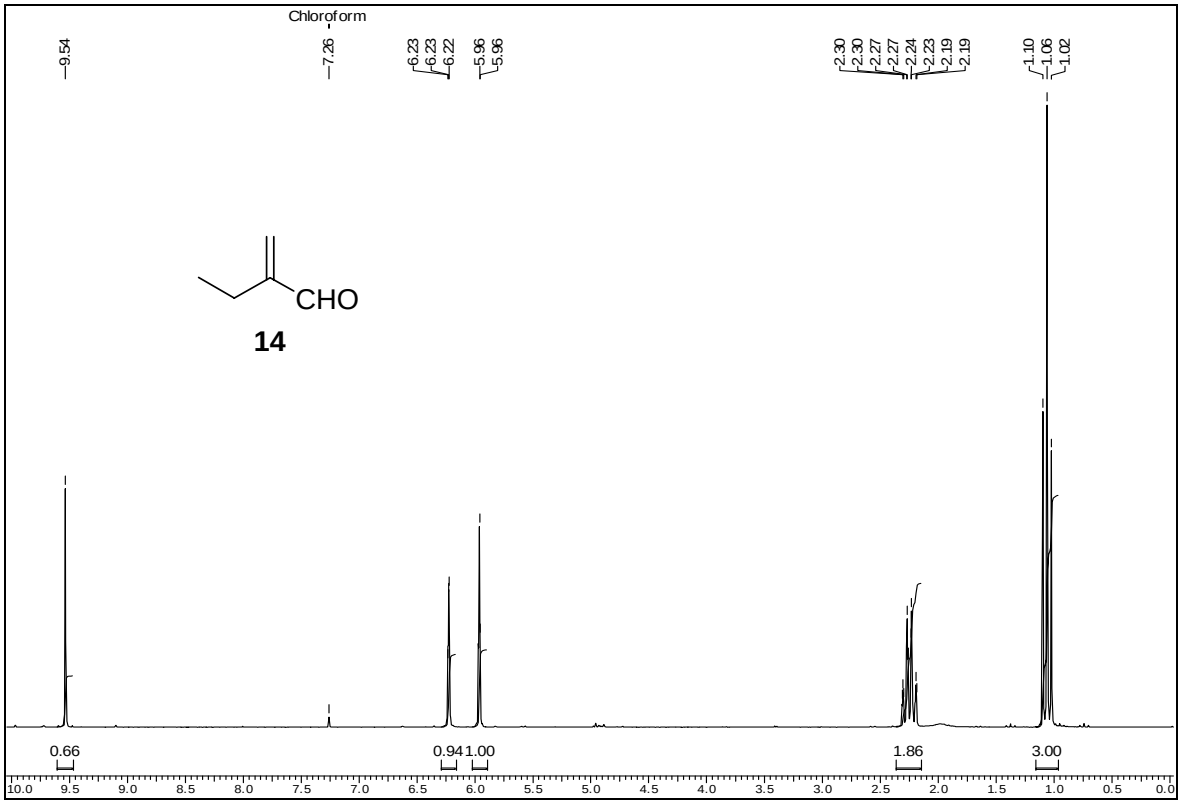
1

A mixture of $K_3[Fe(CN)_6]$ (0.063 g, 0.18 mmol), K_2CO_3 (0.026 g, 0.18 mmol) and $MeSO_2NH_2$ (0.006 g, 0.06 mmol) was dissolved in t-BuOH-H_2O (2 mL, 1:1). To this slurry was added a precomplexed mixture of $(DHQD)_2$ PYR and catalytic OsO_4 (0.005 g, 0.0006 mmol) in t-BuOH (0.5 mL) and the mixture was stirred for 10 minutes at 0 °C. The enol ether **2** (0.020 g, 0.06 mmol) in t-BuOH (1 mL) was added to the above reaction mixture. The resultant reaction mixture was allowed to stir at 0 °C till the completion of reaction (7 h, TLC). The t-BuOH was removed under reduced pressure and the mixture was extracted with $CHCl_3$ (3 x 20 mL). The combined organic layers were washed with 10% HCl. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* rendered crude diol (0.016 g). The crude diol was dissolved in MeOH-H_2O (11 mL, 10:1). Calcium carbonate (0.145 g, 0.57 mmol) was added followed by Iodine (0.140 g, 0.57 mmol) and the reaction mixture stirred at room temperature for 24 h. After the completion of reaction (TLC) the methanol was removed on rotary evaporator under reduced pressure. The mixture was extracted with $CHCl_3$ (5 x 20 mL), the combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography (SiO_2) using 2% MeOH in chloroform furnished (+)-**1** (0.007 g 33% yield).

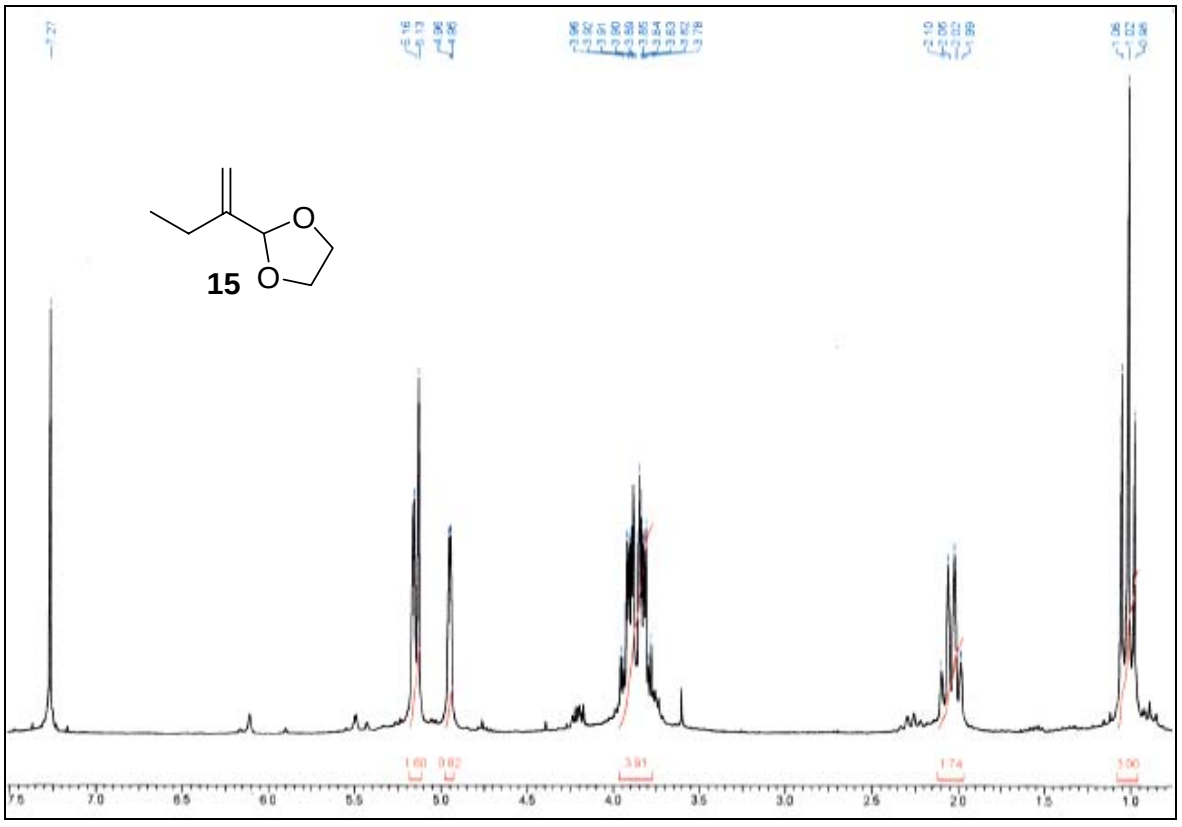
$[\alpha]^{25}_{D}$ +39 (C 0.142, $CHCl_3$; MeOH 4:1) (lit. + 41.2; + 42.1; + 36).

The m.p. and spectral data of camptothecin **1** has mentioned in chapter 1, section II.

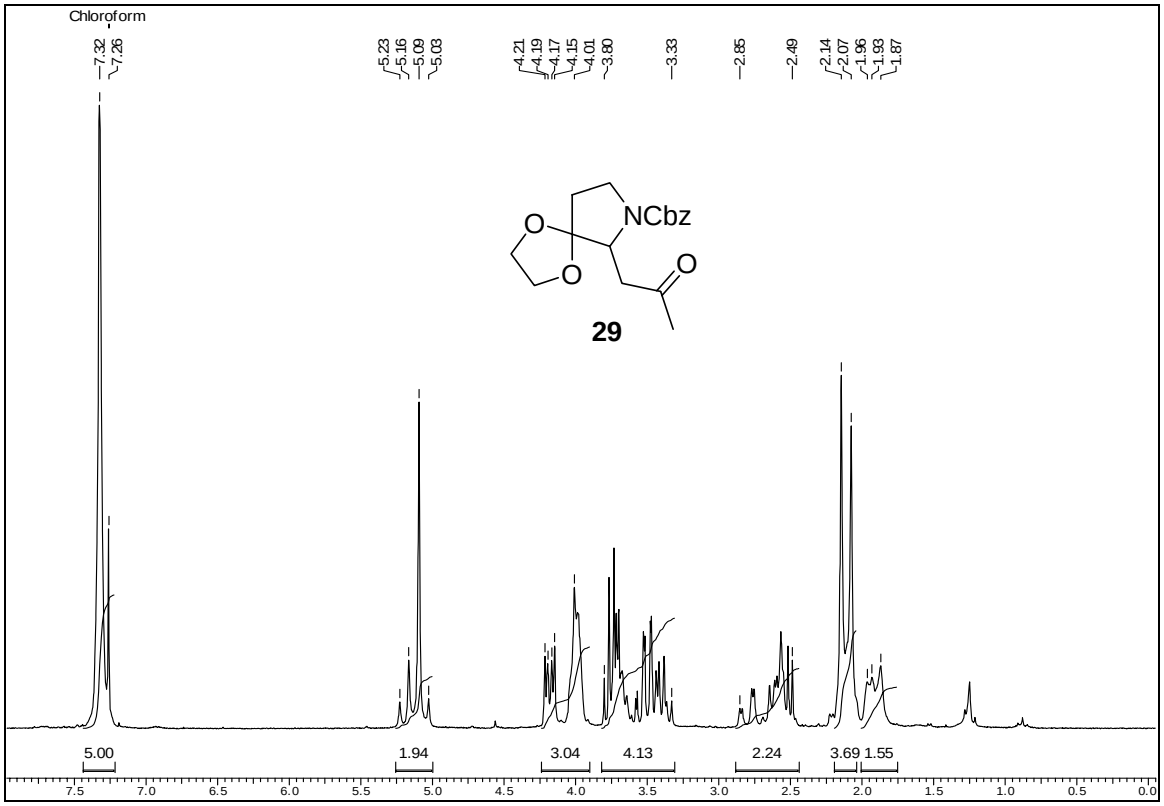
2.2.6 Spectra:



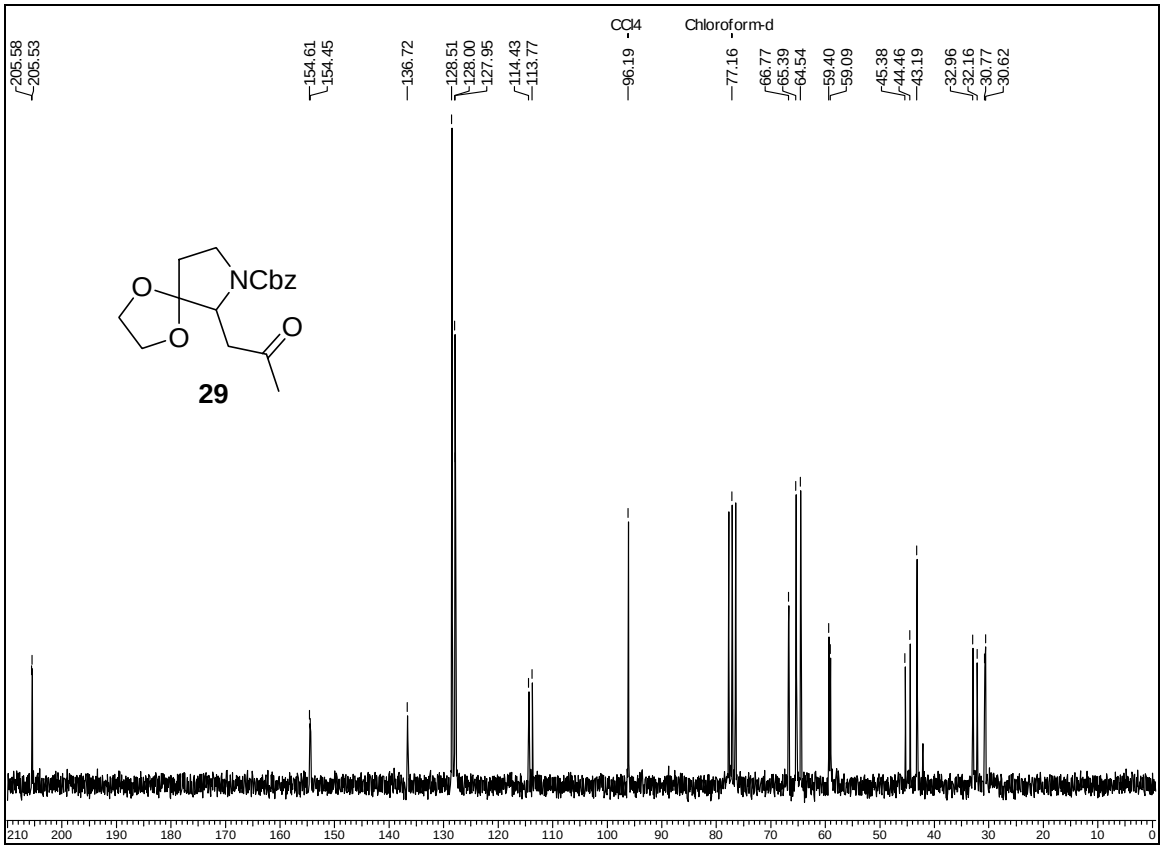
^{1}H NMR spectrum of compound 14 ($CDCl_3$ + CCl_4, 200 MHz)



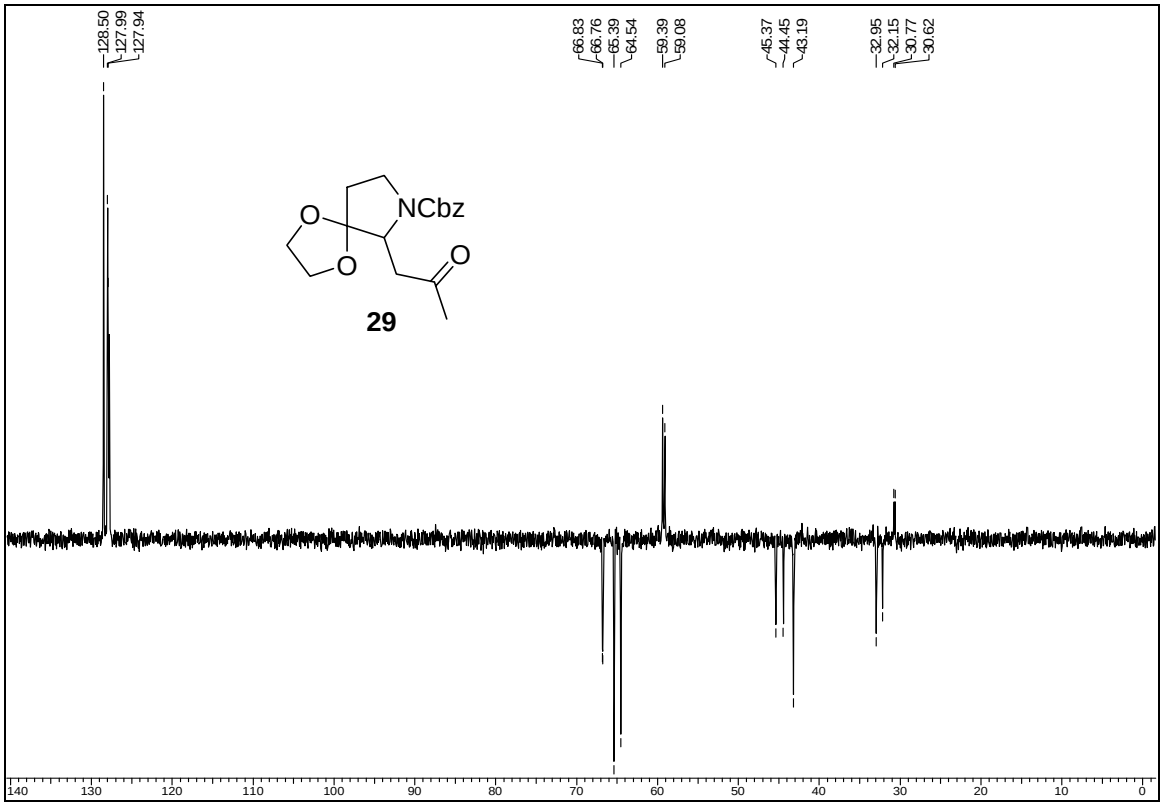
^{1}H NMR spectrum of compound 15 ($CDCl_3$ + CCl_4, 200 MHz)



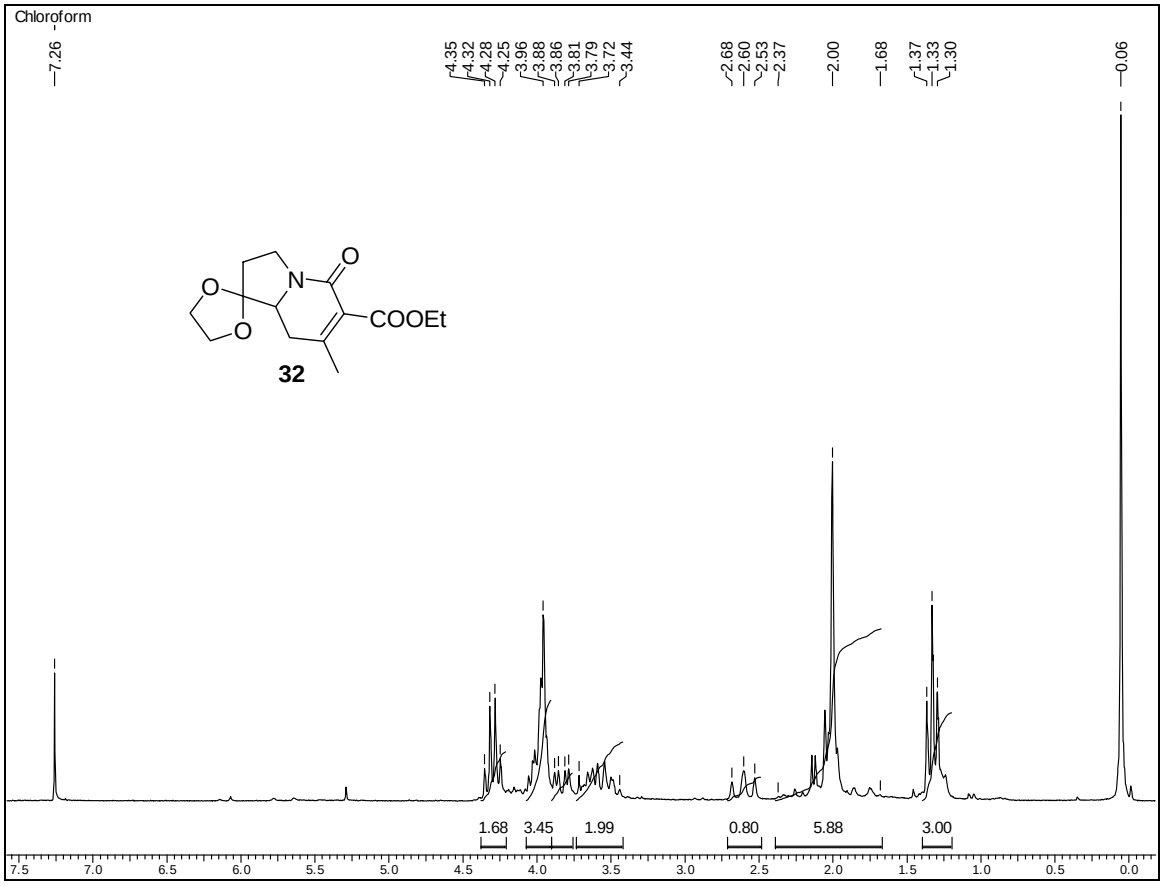
^{1}H NMR spectrum of compound 29 ($CDCl_3$ + CCl_4, 200 MHz)



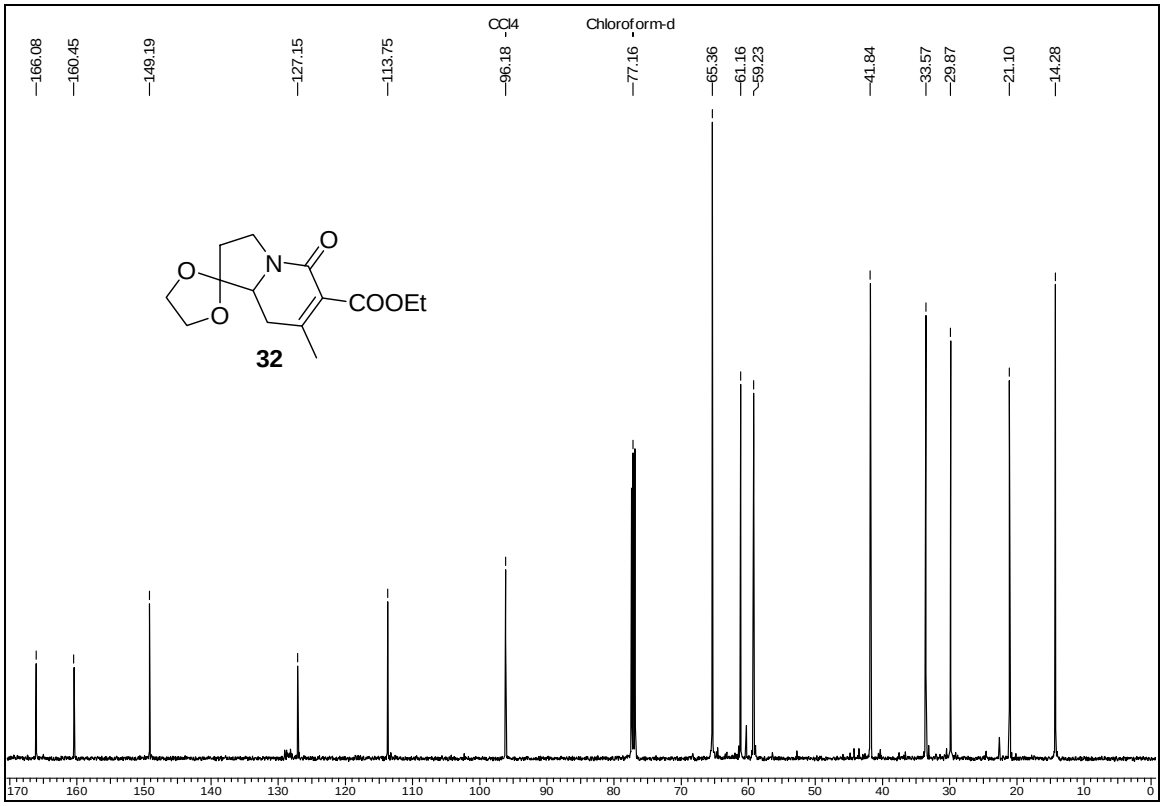
^{13}C NMR spectrum of compound 29 ($CDCl_3$ + CCl_4, 50 MHz)



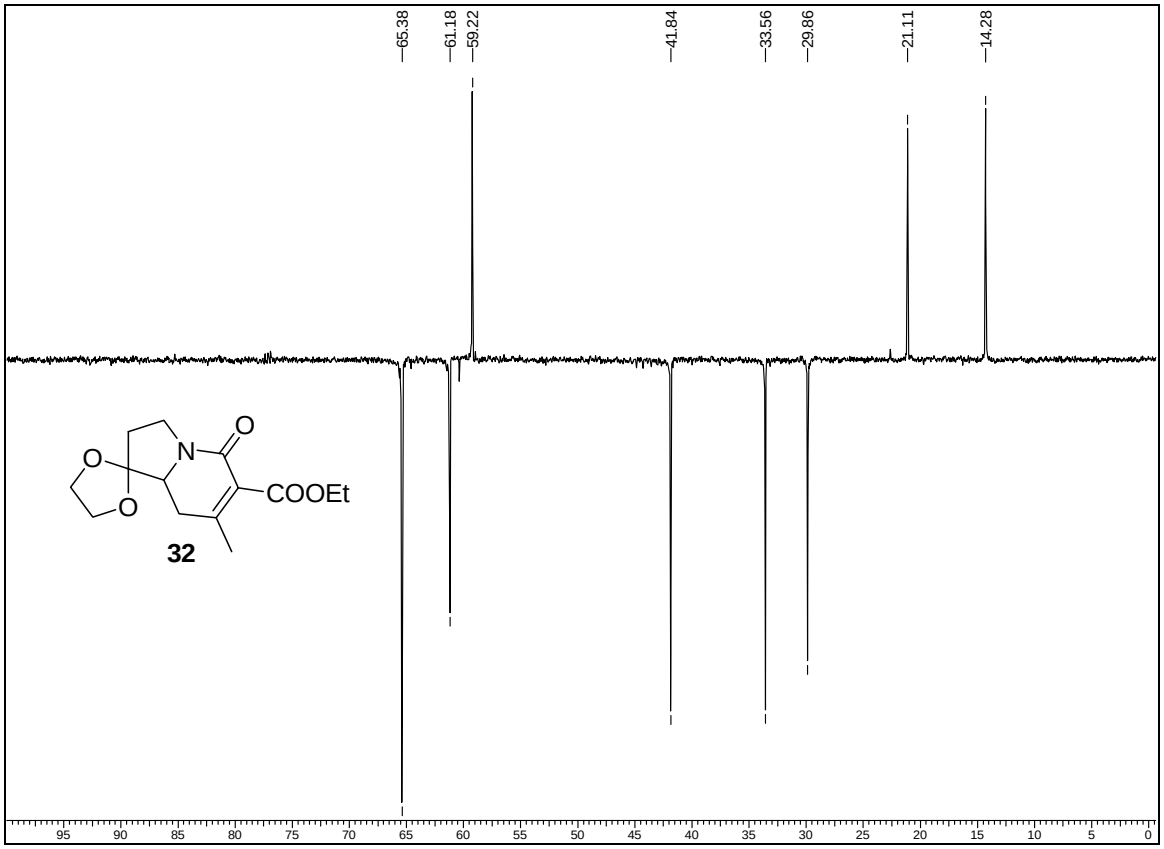
DEPT spectrum of compound 29 ($CDCl_3$ + CCl_4, 50 MHz)



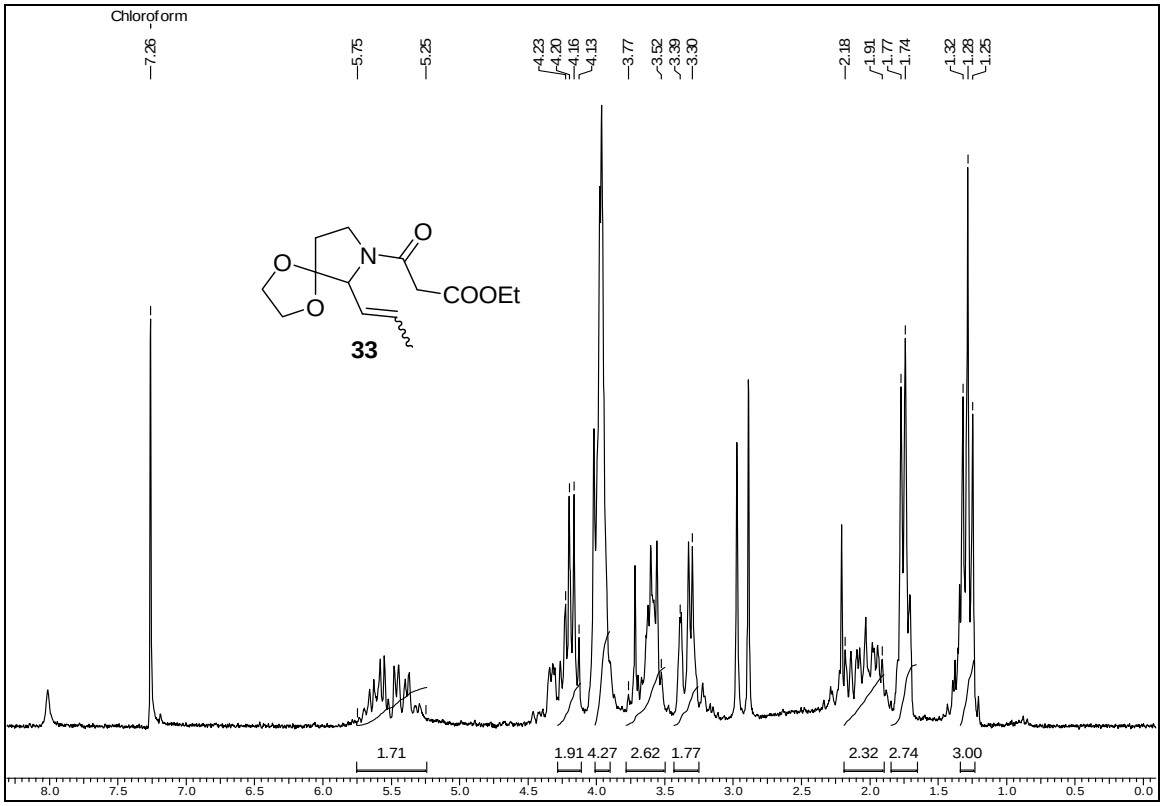
^{1}H NMR spectrum of compound 32 ($CDCl_3$ + CCl_4, 200 MHz)



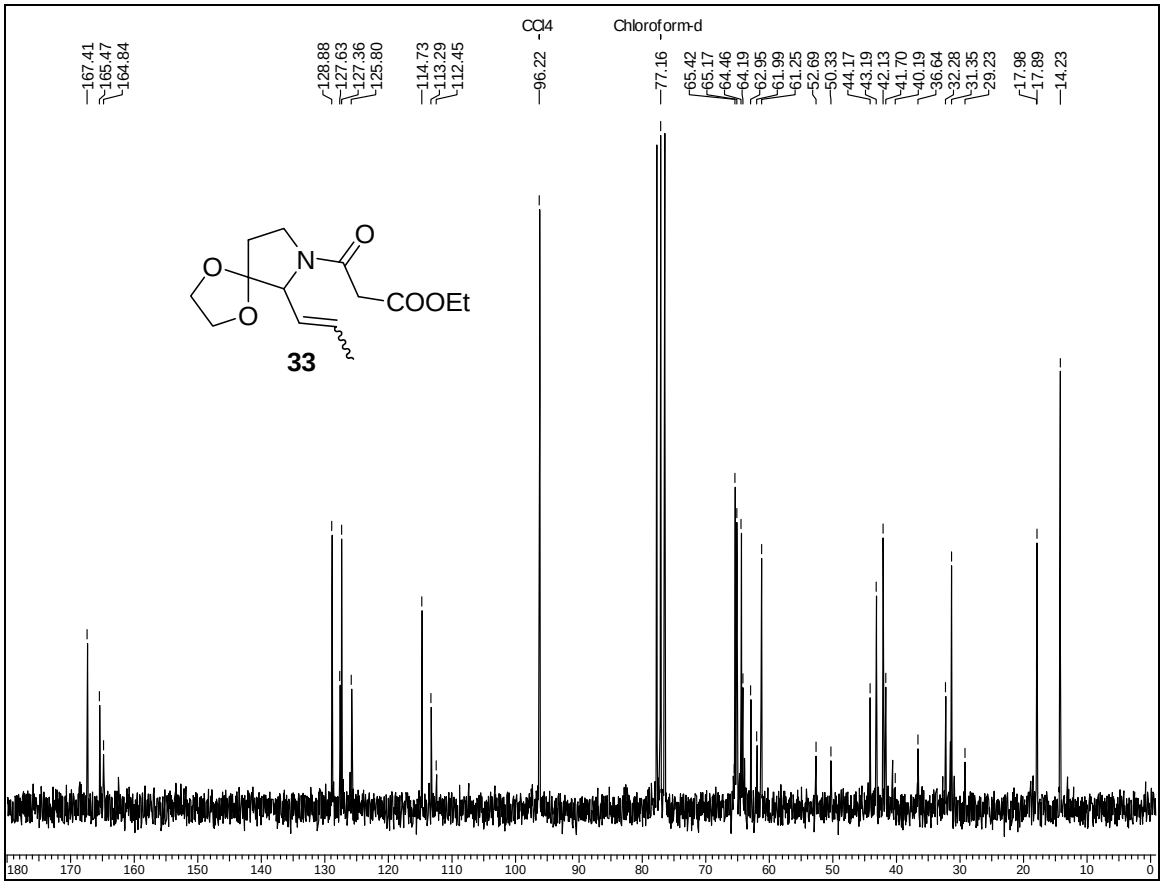
^{13}C NMR spectrum of compound 32 ($CDCl_3$ + CCl_4, 50 MHz)



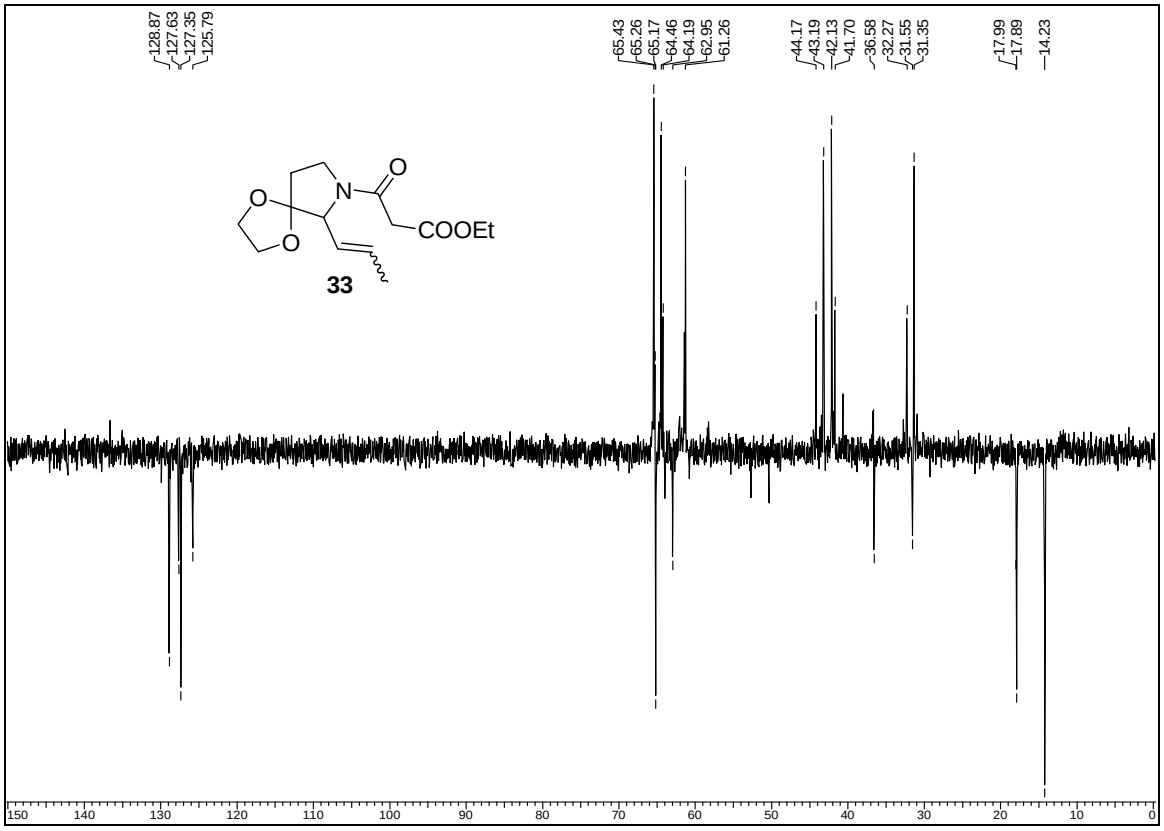
DEPT spectrum of compound 32 ($CDCl_3$ + CCl_4, 50 MHz)



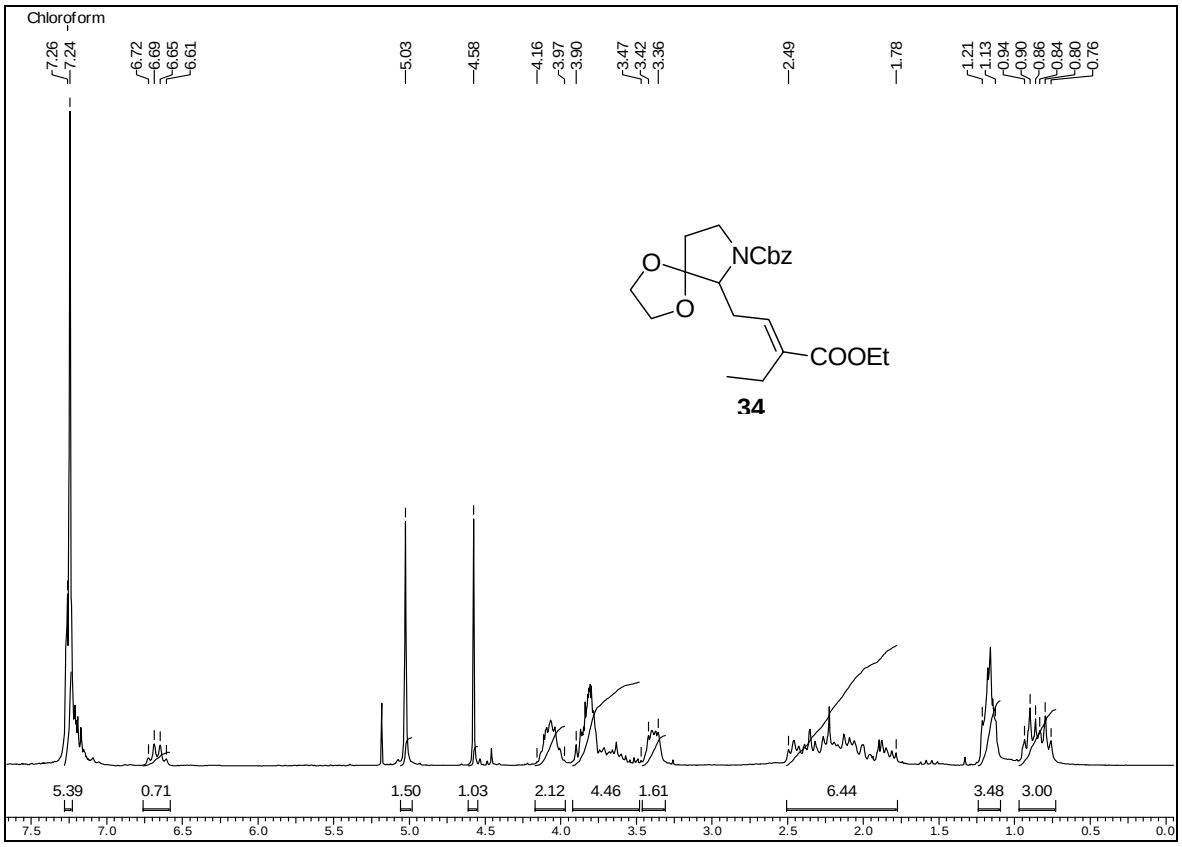
^{1}H NMR spectrum of compound 33 ($CDCl_3$ + CCl_4, 200 MHz)



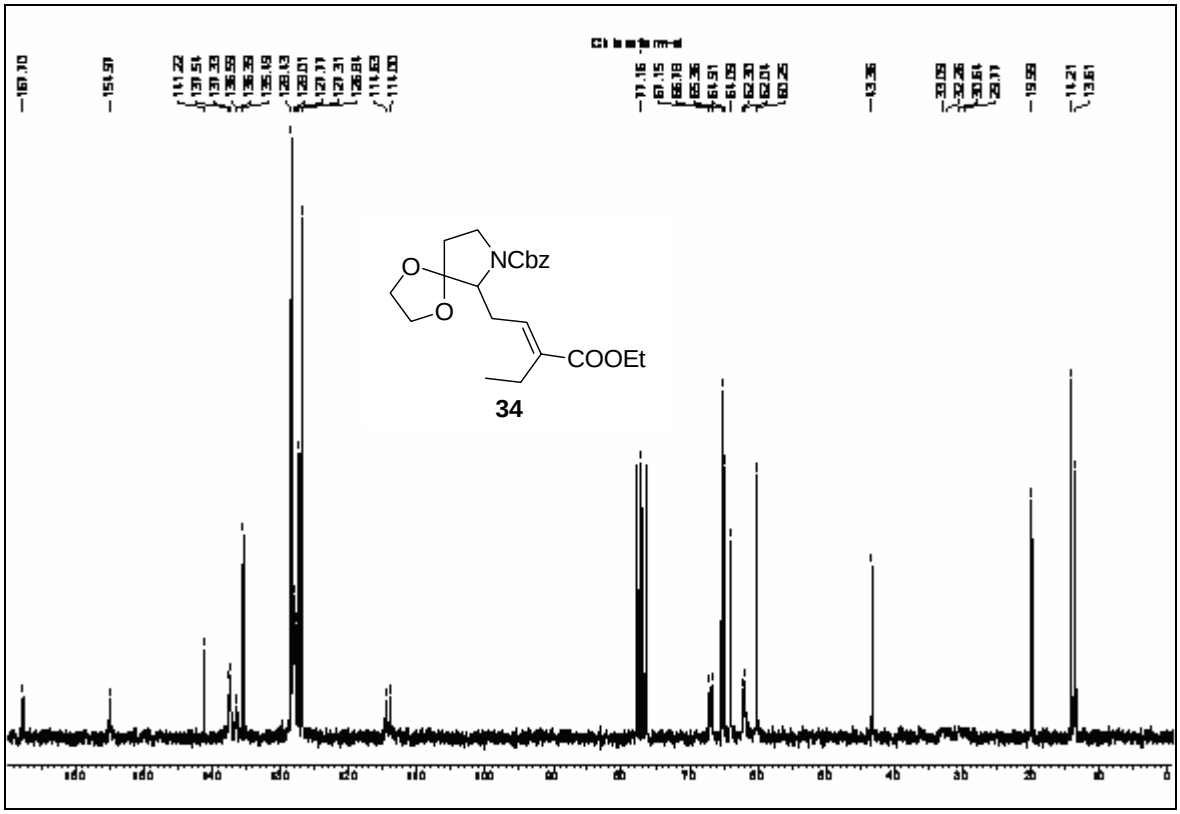
^{13}C NMR spectrum of compound 33 ($CDCl_3$ + CCl_4, 50 MHz)



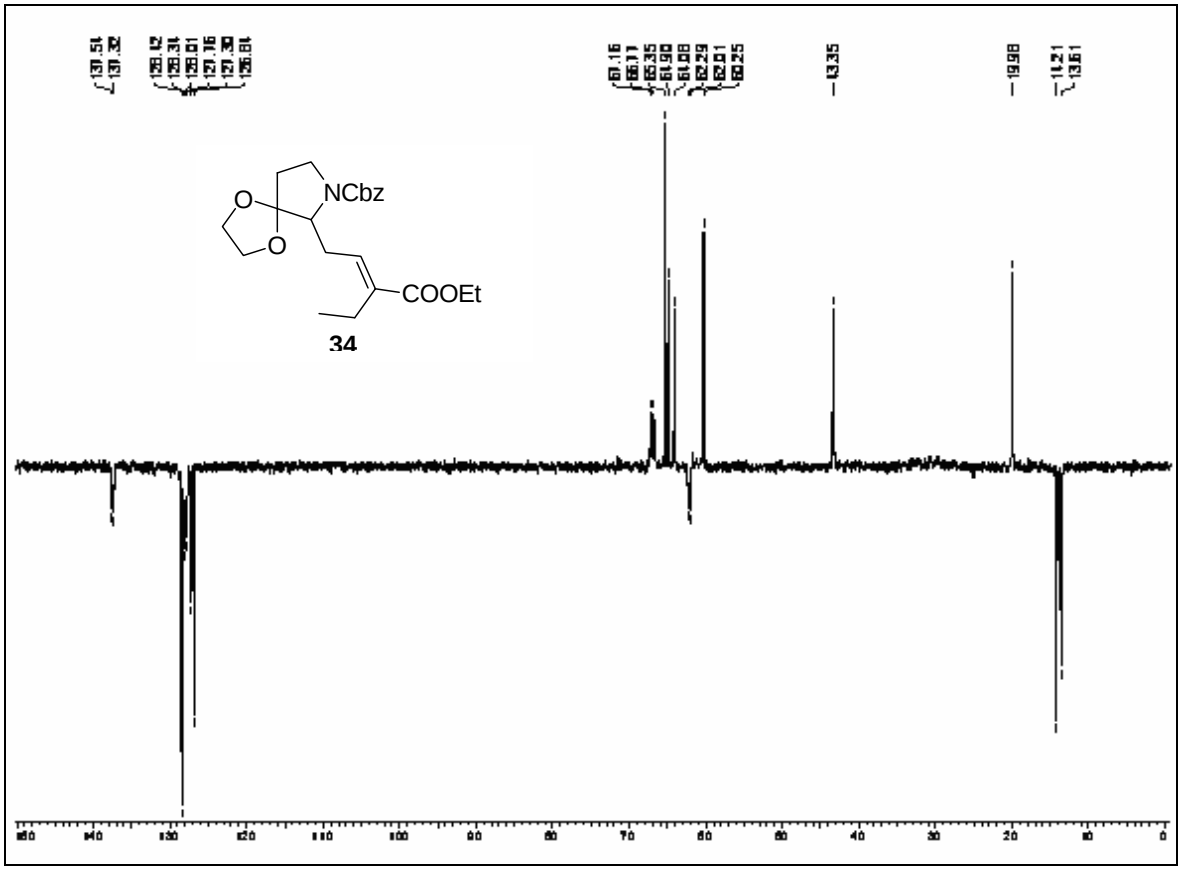
DEPT spectrum of compound 33 ($CDCl_3$ + CCl_4, 50 MHz)



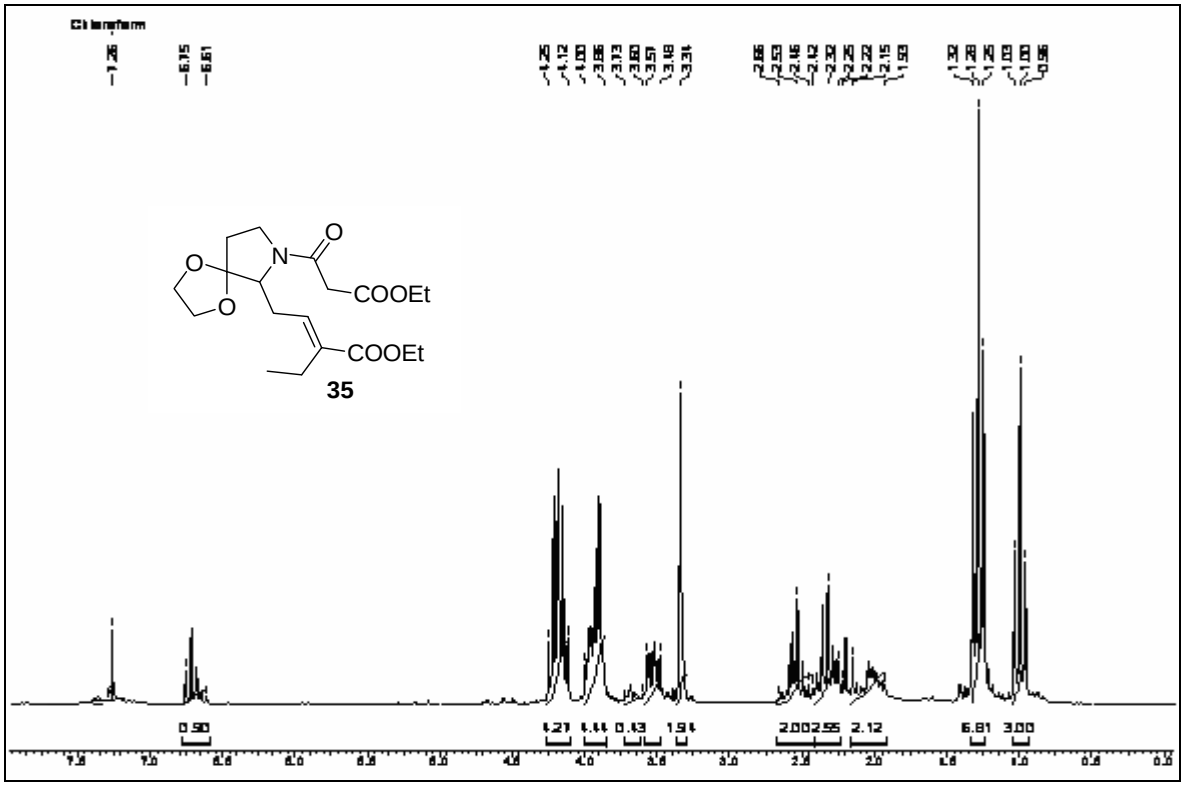
^{1}H NMR spectrum of compound 34 ($CDCl_3$, 200 MHz)



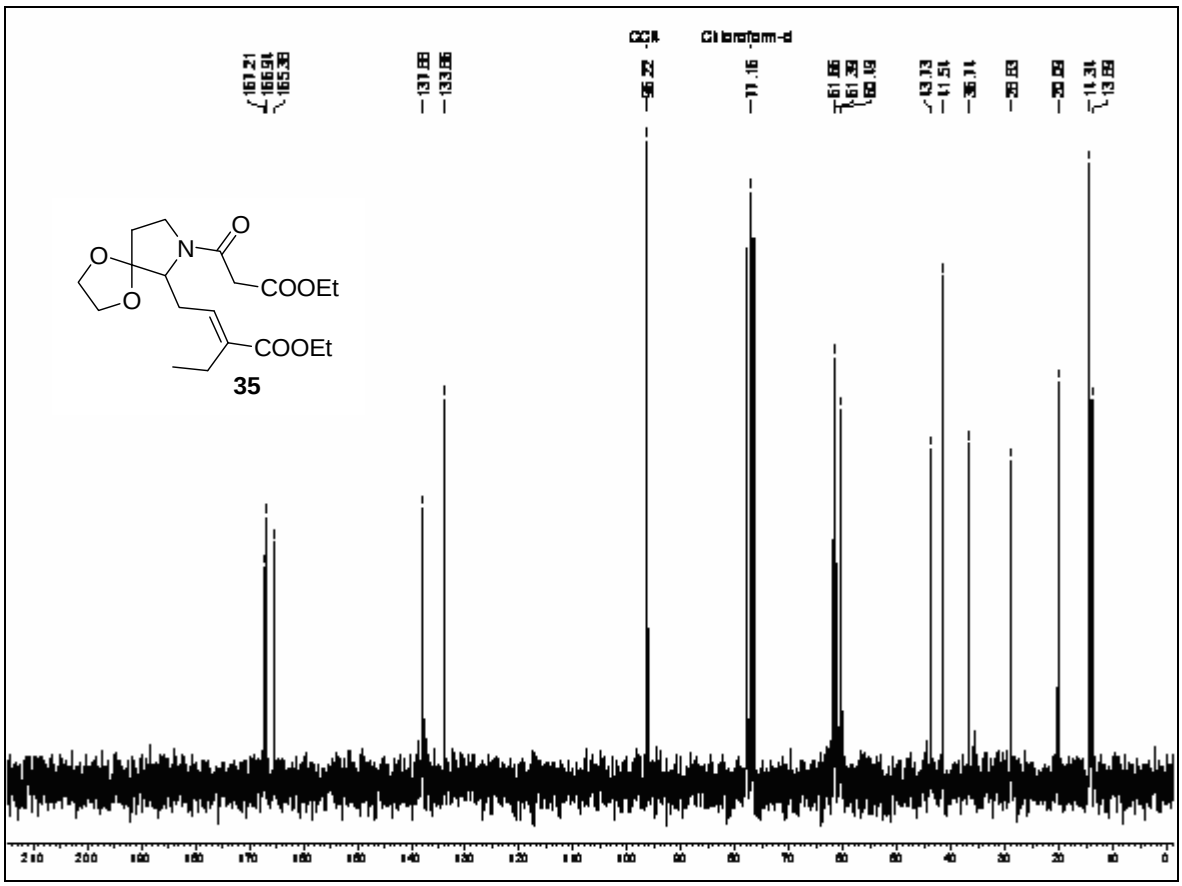
^{13}C NMR spectrum of compound 34 ($CDCl_3$, 50 MHz)



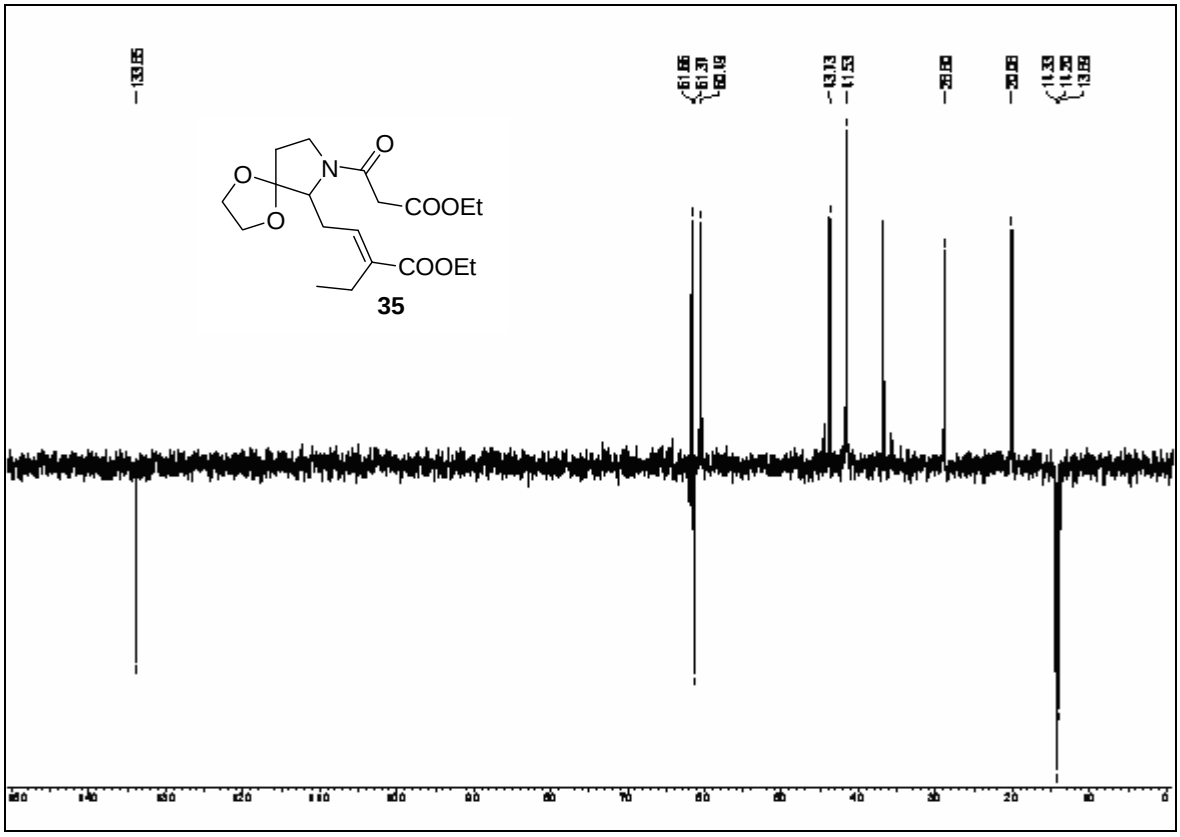
DEPT spectrum of compound 34 ($CDCl_3$, 50 MHz)



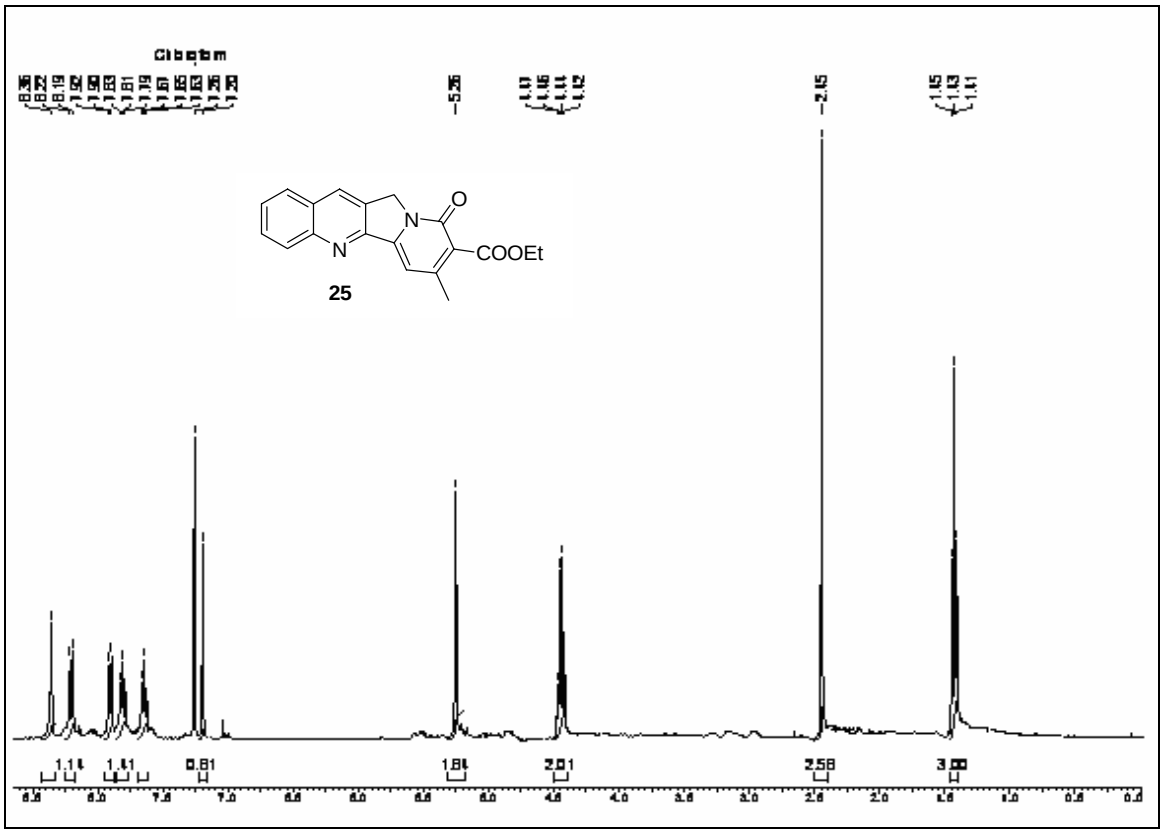
^{1}H NMR spectrum of compound 35 ($CDCl_3$ + CCl_4, 200 MHz)



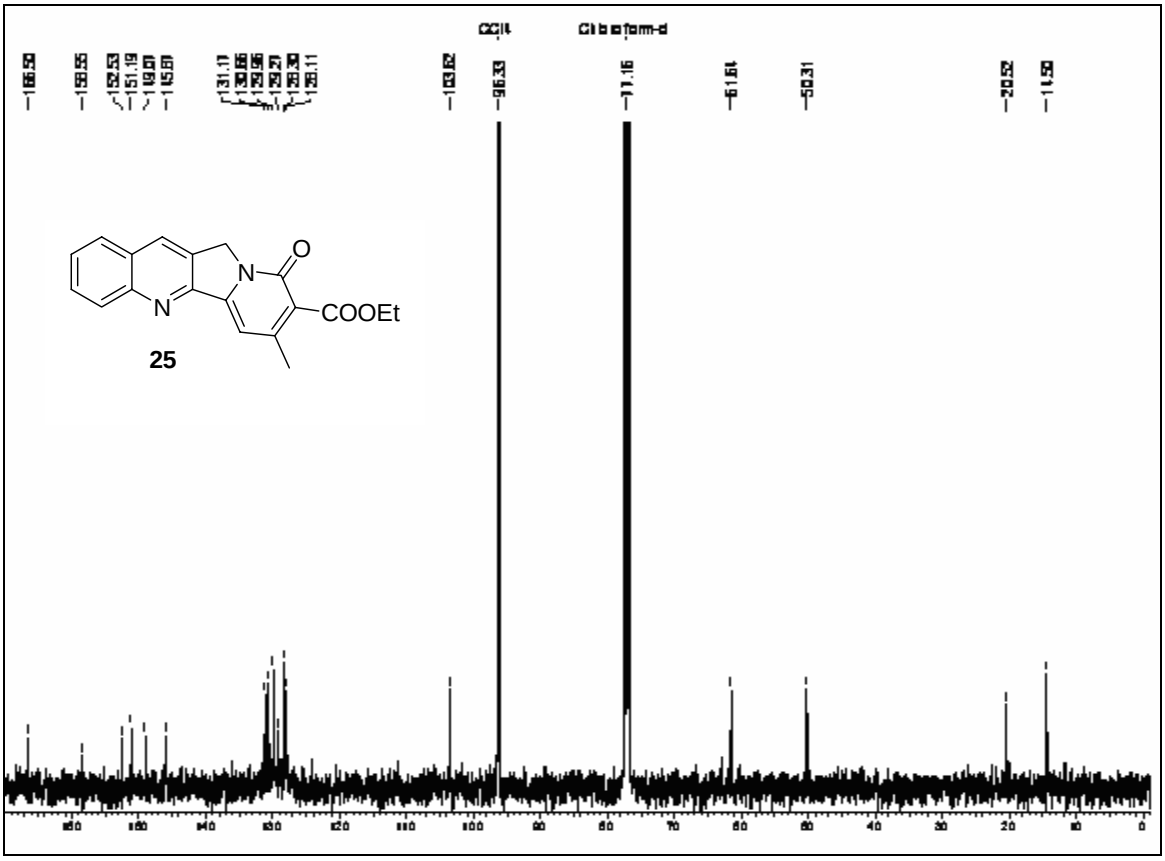
^{13}C NMR spectrum of compound 35 ($CDCl_3$ + CCl_4, 50 MHz)



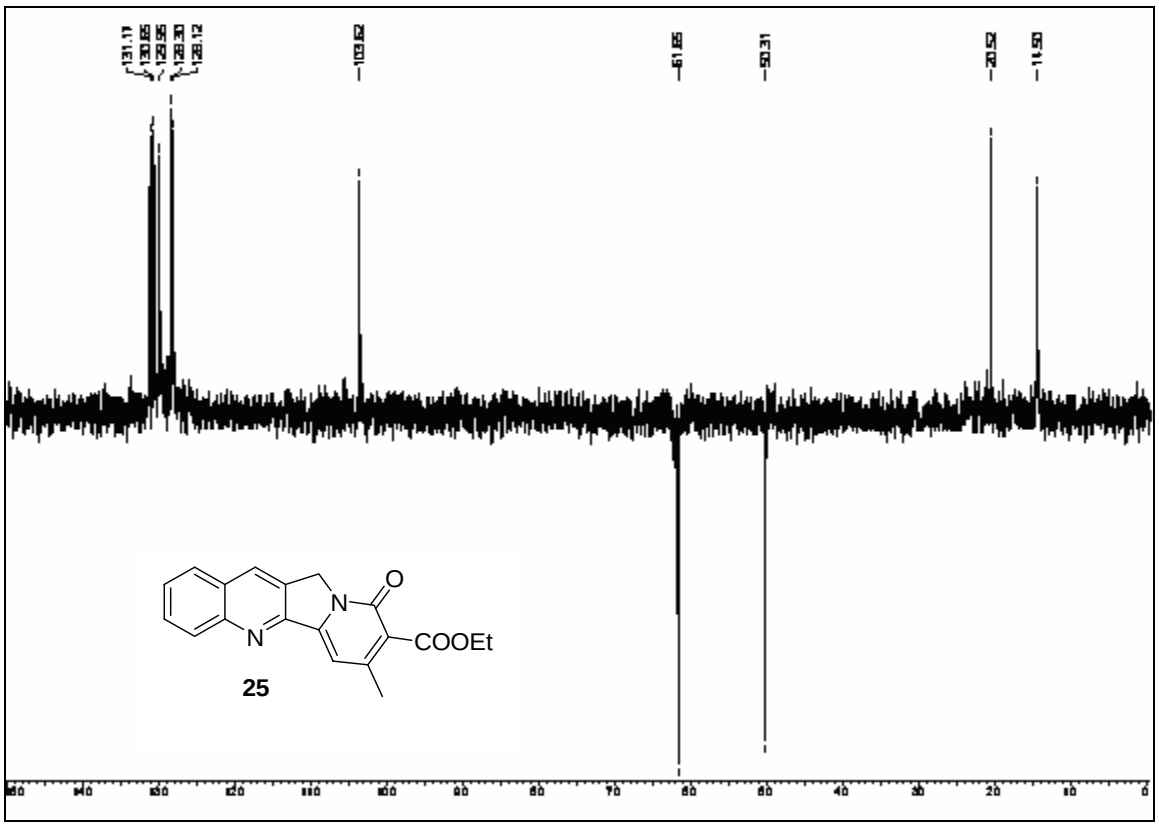
DEPT spectrum of compound 35 ($CDCl_3$ + CCl_4, 50 MHz)



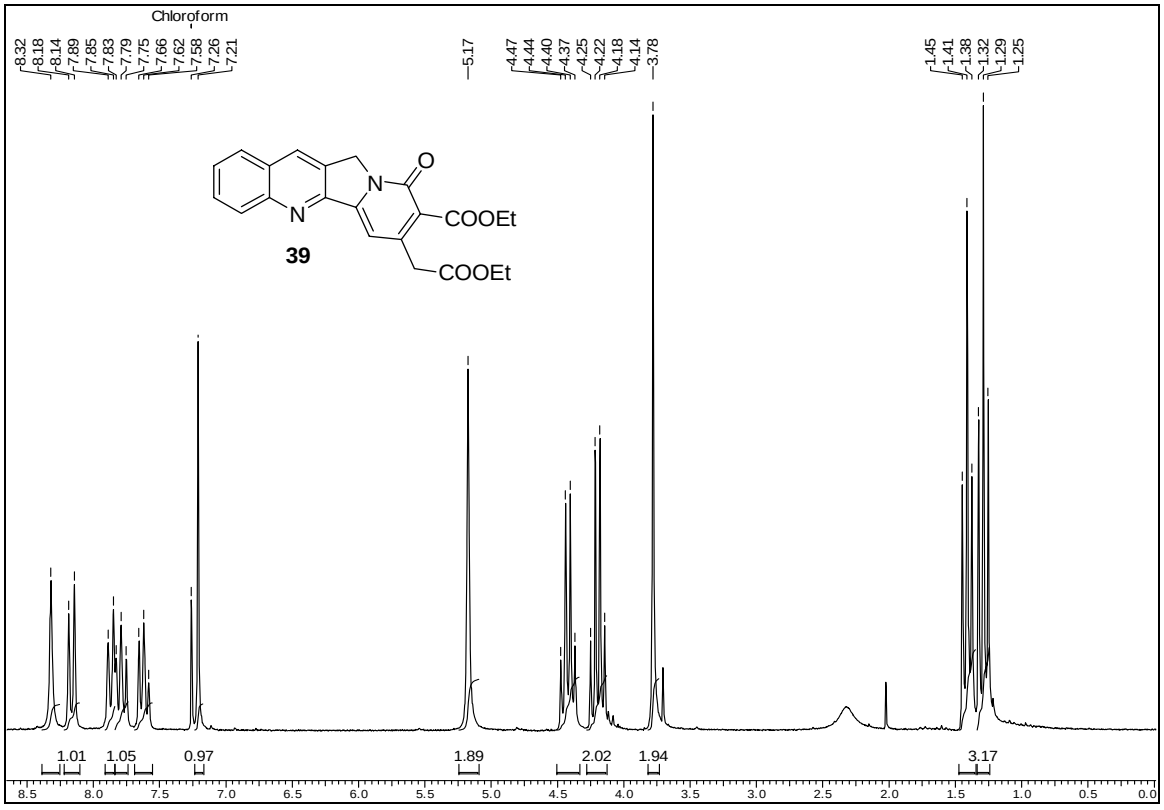
^{1}H NMR spectrum of compound 25 ($CDCl_3$ + CCl_4, 400 MHz)



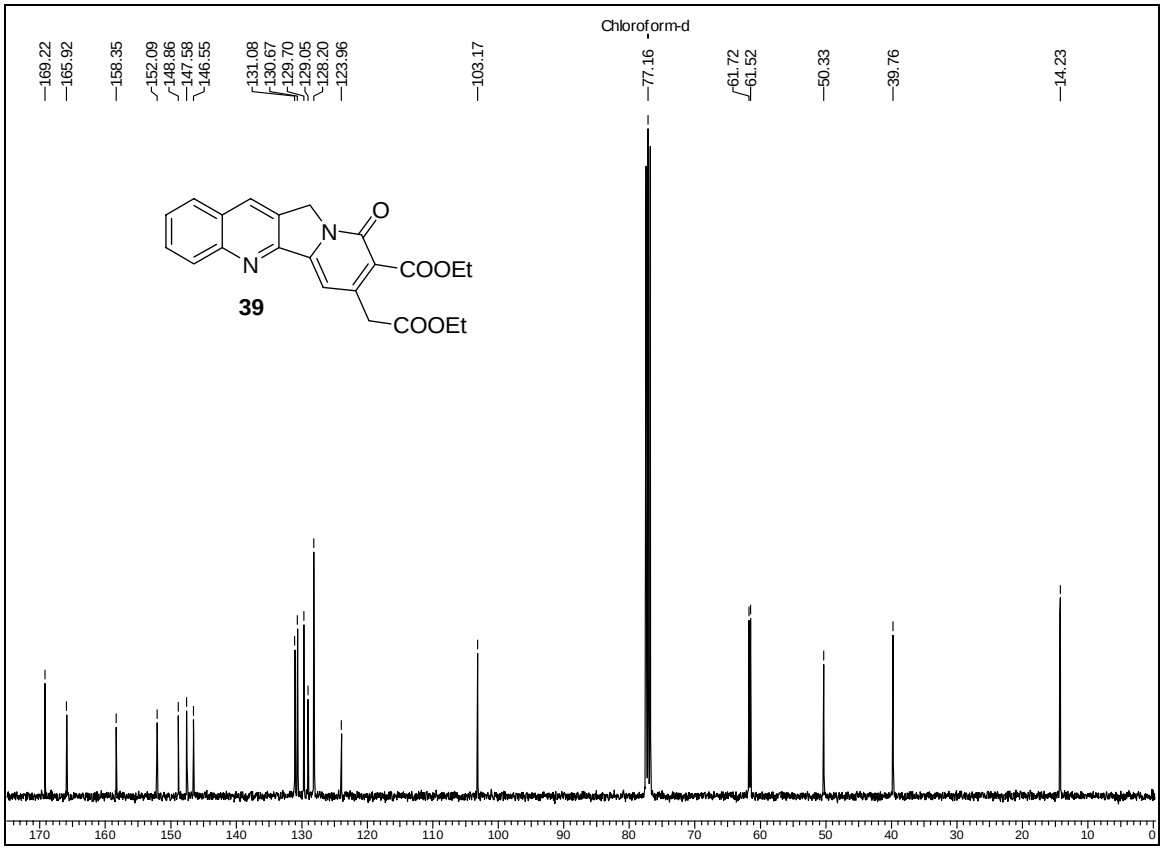
^{13}C NMR spectrum of compound 25 ($CDCl_3$ + CCl_4, 100 MHz)



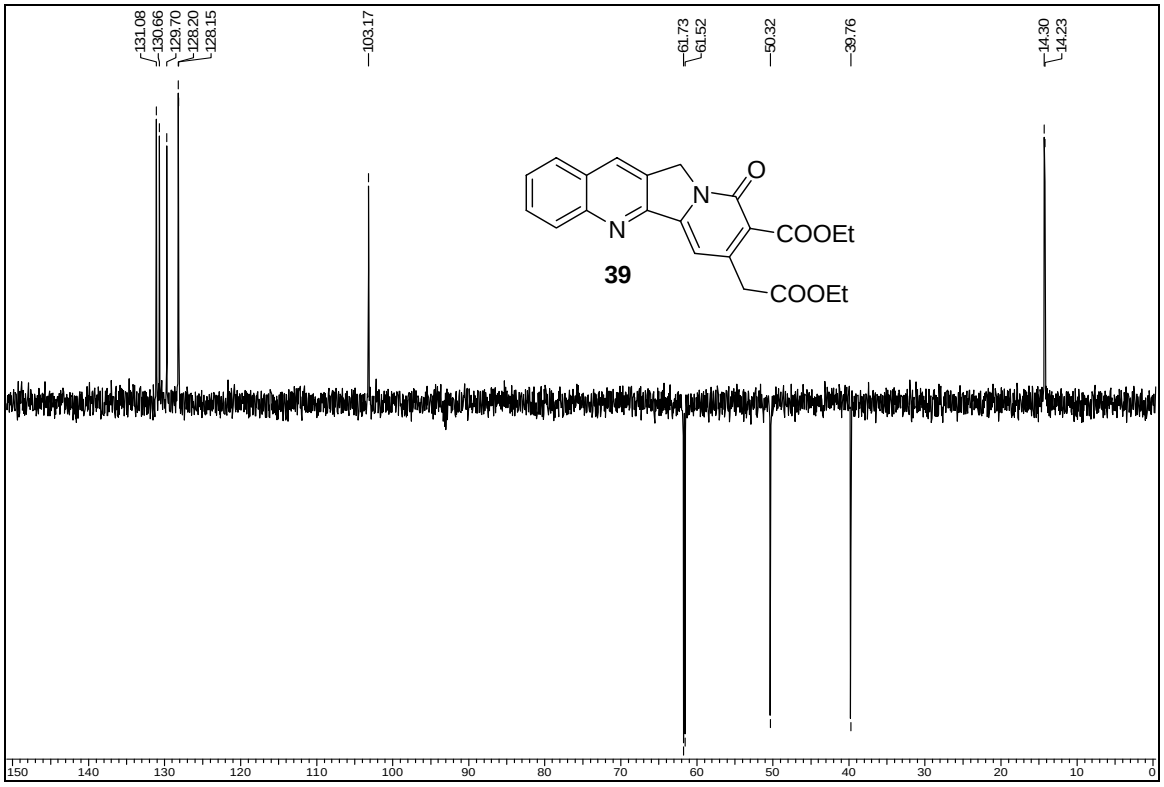
DEPT spectrum of compound 25 ($CDCl_3$ + CCl_4, 100 MHz)



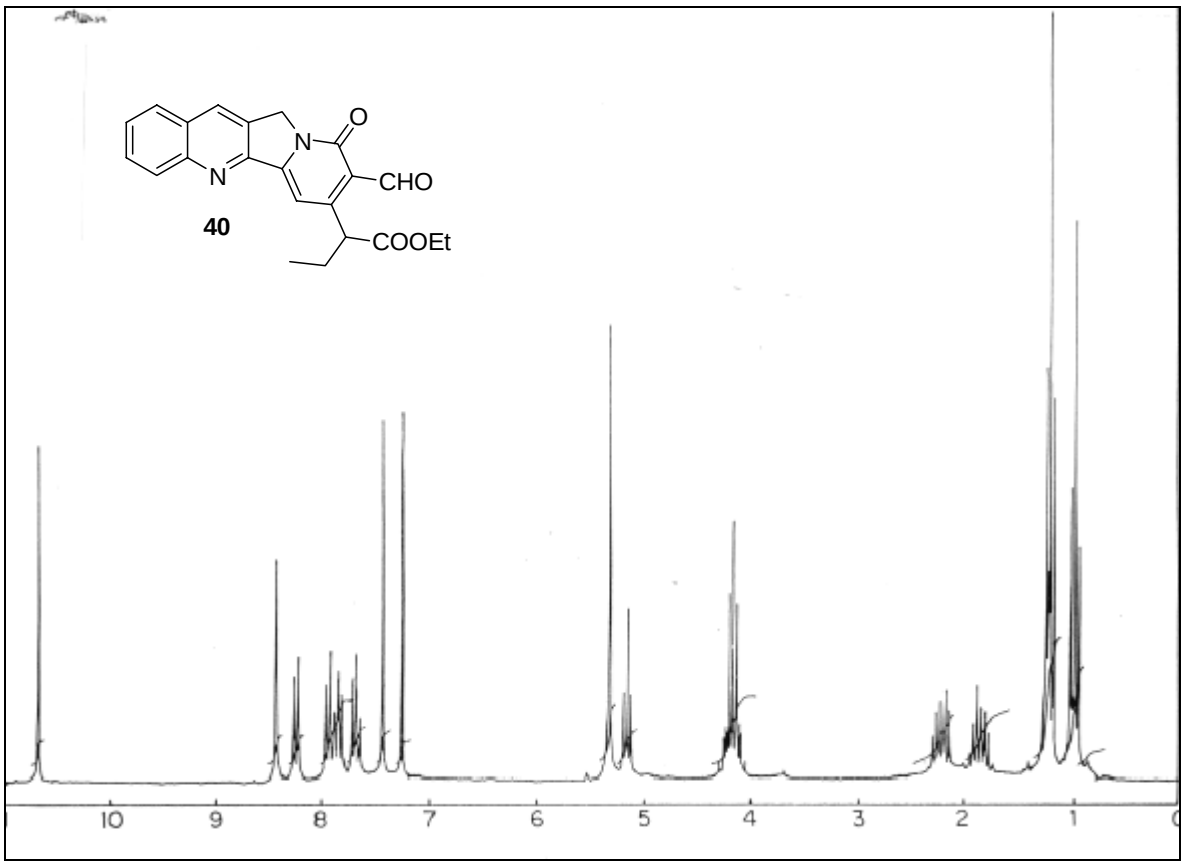
^{1}H NMR spectrum of compound 39 ($CDCl_3$, 200 MHz)



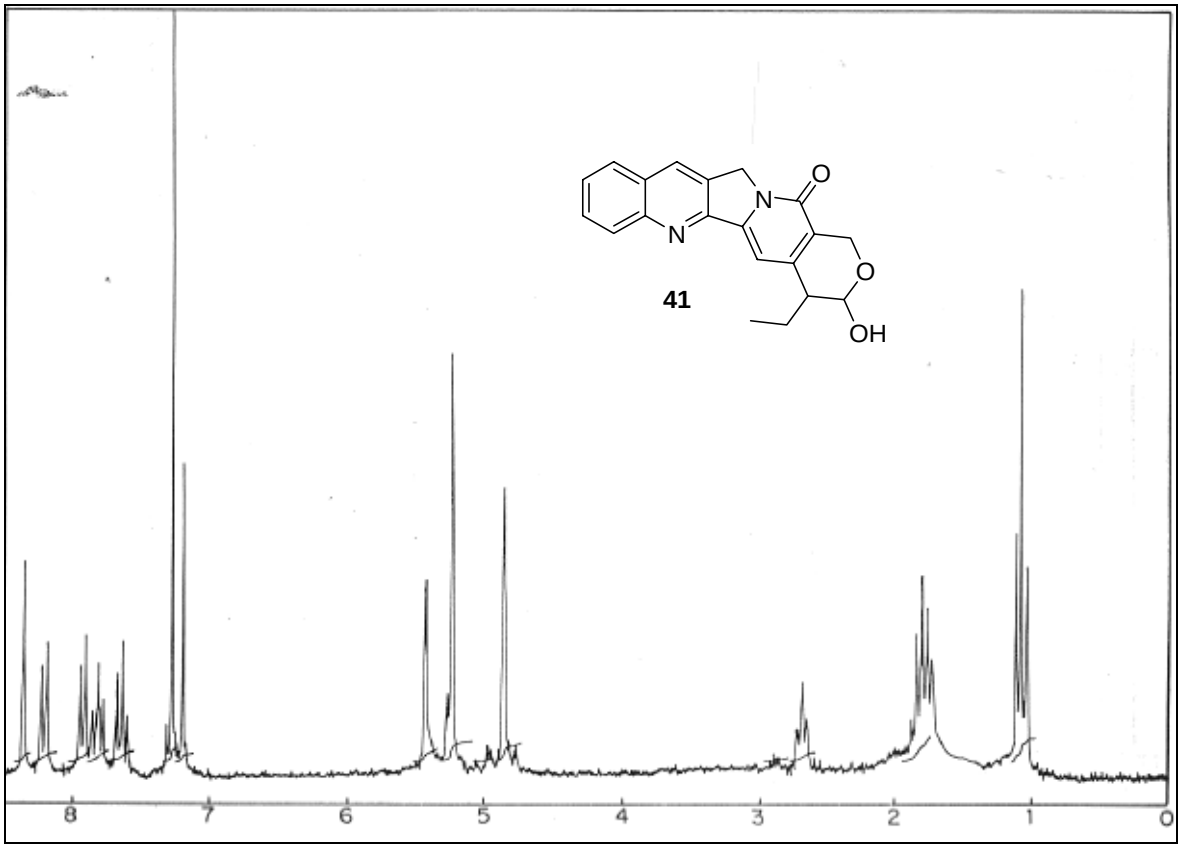
^{13}C NMR spectrum of compound 39 ($CDCl_3$, 100 MHz)



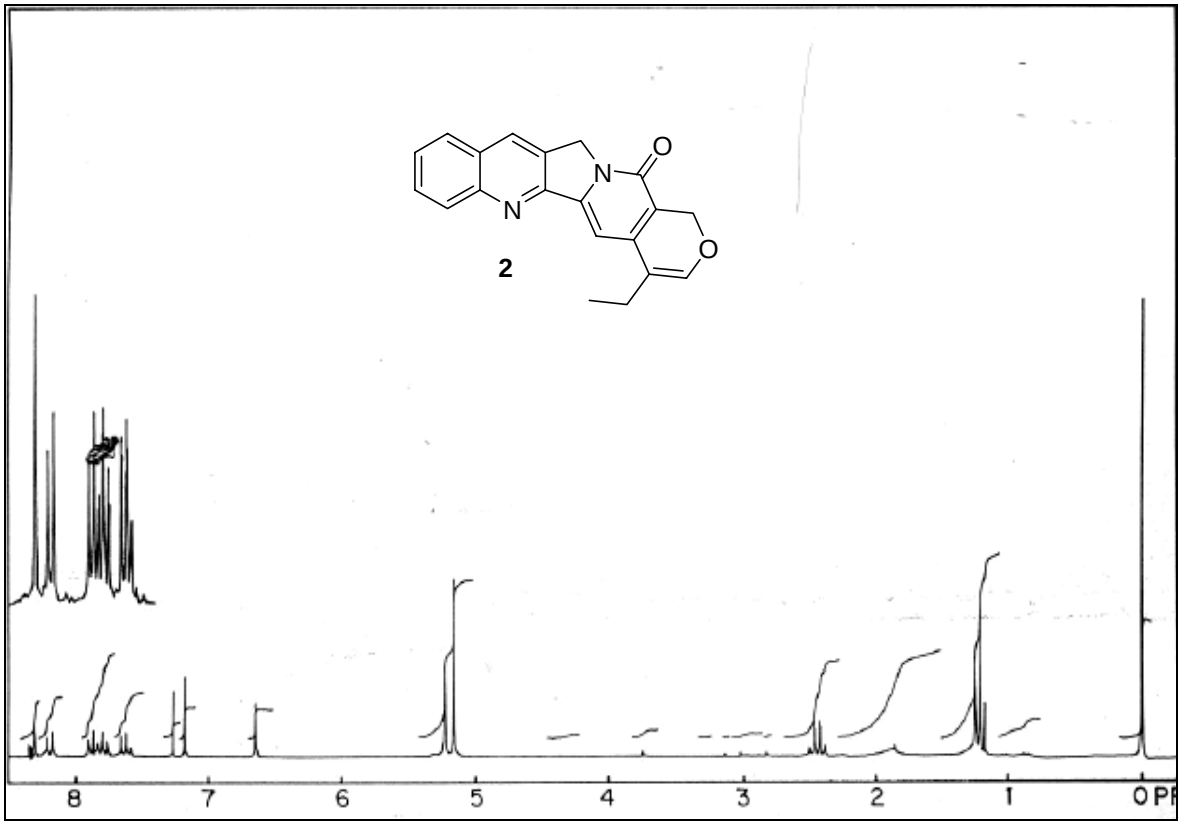
DEPT spectrum of compound 39 ($CDCl_3$, 100 MHz)



^{1}H NMR spectrum of compound 40 ($CDCl_3$, 200 MHz)



^{1}H NMR spectrum of compound 41 ($CDCl_3$, 200 MHz)



^{1}H NMR spectrum of compound 2($CDCl_3$, 200 MHz)

2.2.7 References

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Chapter 2, Section III

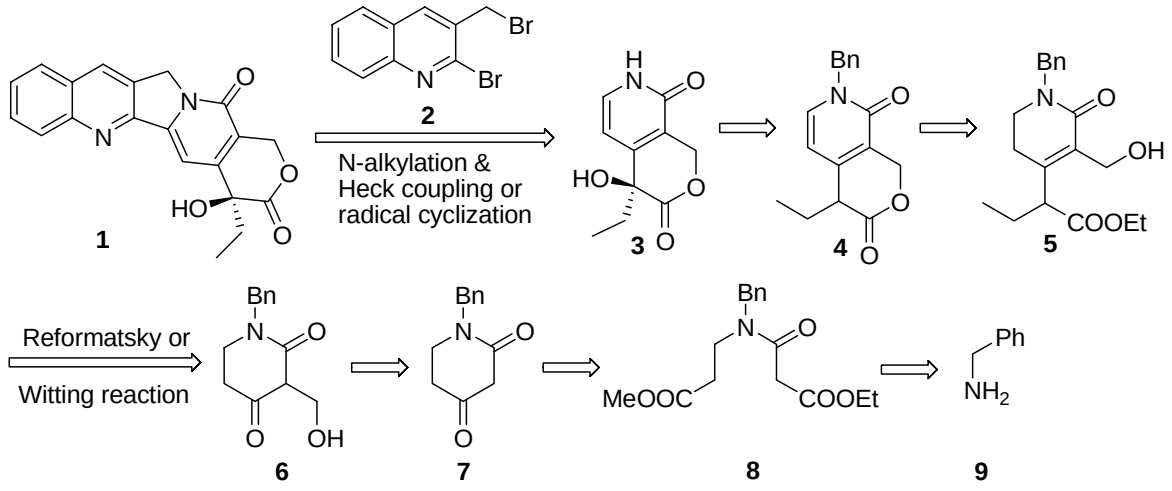
Formal synthesis of (±)-camptothecin

2.3.1 Introduction:

Although camptothecin was synthesized more than 4 decades ago, it faced considerable limitation in the clinical use.[1] Due to its poor solubility and toxicity associated within the biosystem. Several of its analogues can be derived from camptothecin in a convergent manner. Alternative synthetic approaches for these analogues typically involve the synthesis of suitably functionalized CDE-rings[2] or DE-rings[3] or relevant synthons followed by coupling with suitable AB-ring counter parts either predominantly through Friedlander coupling or by radical or Heck cyclization respectively. Thinking on these lines, it was envisioned to synthesize first the DE-ring fragment with suitable functionality and then condense with AB-ring fragment by radical or Heck cyclization to complete the synthesis of target molecule camptothecin.

2.3.2 Present work:

Having the successful synthesis of racemic as well as chiral camptothecin **1** and its analogues by different strategies viz. intramolecular enyne metathesis, tandem Knoevenagel condensation followed by Michael addition and novel tandem Pd-mediated cyclization followed by aromatization but these are linear approaches. In this section the formal synthesis of (±)-camptothecin **1** (DE-ring fragment) by convergent manner which is efficient than linear one is described.



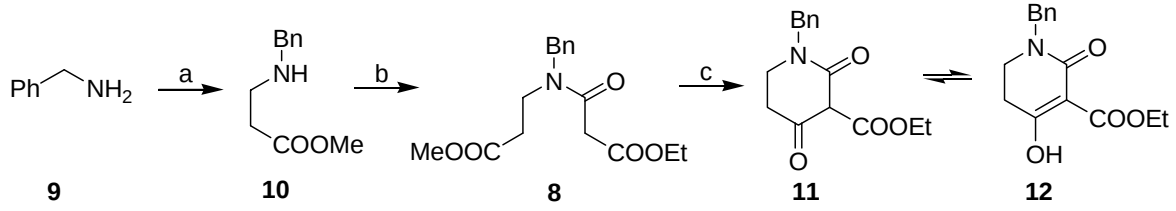
Scheme 1. *Retrosynthetic analysis.*

The planned retrosynthetic strategy depicted in scheme 1 which shows the (+)-camptothecin **1** could be accessed from DE-ring synthon **3** by *N*-alkylation with **2** followed

by Heck coupling or radical cyclization. The DE ring synthon **3** can be synthesized from lactone **4** by hydroxylation and *N*-debenzylation. The lactone **4** could be obtained from compound **5** by aromatization followed by lactonization. The compound **5** could be realized from alcohol **6** by Reformatsky reaction or Wittig reaction. Alcohol **6** can be prepared from β-keto lactam **7** by hydroxymethylation. Compound **7** could be synthesized from amide **8** by Dieckmann condensation followed by decarboxylation and amide **8** could be readily obtained from inexpensive and commercially available benzyl amine **9** by Michael addition and *N*-acylation.

2.3.3 Results and discussion:

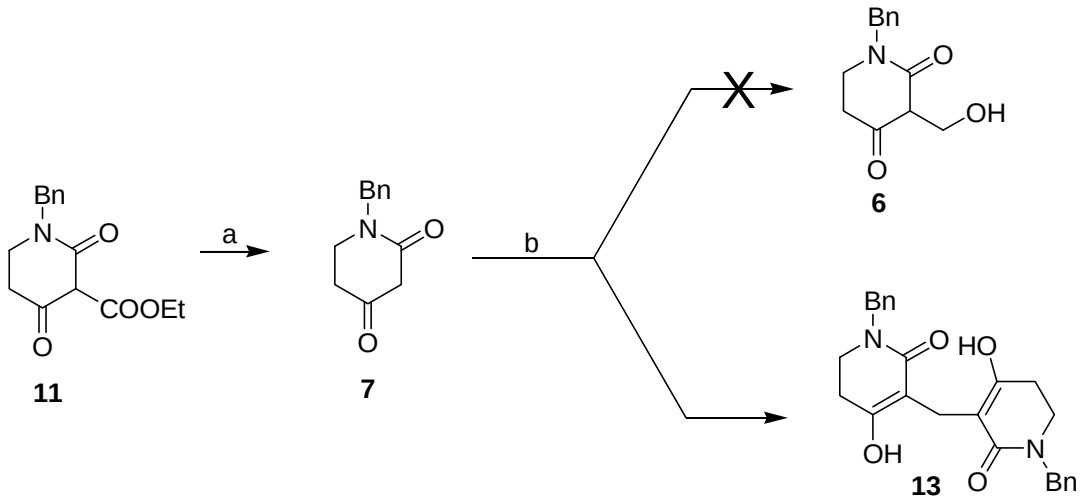
The Michael addition of benzyl amine **9** on methyl acrylate was smoothly accomplished to furnish the amine **10** in 97% yield. The amine **10** was further condensed with ethyl malonyl chloride, afforded the amide **8** in very good yield (86%). Amide **8** was treated with sodium hydride in ethanol at 0 ^{o}C yielded the cyclised compound which existed in tautomeric form as the keto **11** and enol **12** in 91% yield (scheme 2). The formation of **10** to **12** was confirmed by spectral analysis which was in complete agreement with literature data.[4]



Scheme 2. *Reagents and conditions: (a) methyl acrylate (1.0 equiv), rt, 12 h, 97%. (b) K_2CO_3 (3.0 equiv), ethyl malonyl chloride (1.2 equiv), CH_2Cl_2, 0 ^{o}C, 1 h, 86%. (c) NaH (1.2 equiv), EtOH, rt, 3 h, 91%.*

The mixture of **11** and **12** was decarboxylated using 10% HCl to furnish compound **7** in very good yield (87%), which was confirmed by spectral analysis. IR spectrum of **7** displayed strong absorption bands at 1731 and 1651 cm^{-1} corresponding to β-keto lactam functionality. ^{1}H NMR spectrum of **7** displayed a triplet at δ 2.44 integrated for two protons were assigned to methylene adjacent to carbonyl of ketone. Singlet at δ 3.32 integrating for two protons which was assigned to methylene protons flanked between two carbonyl groups, triplet at δ 3.40 integrated for two protons adjacent to amide nitrogen. Singlet at δ 4.60 integrated for two benzylic protons and multiplet at δ 7.15-7.31

integrating for five aromatic protons. ^{13}C NMR spectrum of **7** revealed signals at δ 38.5, 42.3, 48.7 and 49.9 which were assigned to aliphatic methylene carbons. The signals that appeared at δ 127.8, 128.0, 128.8 and 136.3 corresponded to aromatic carbons while the signals at δ 166.4 and 203.1 corresponded to amide and ketone carbonyl carbons respectively. Finally structure of **7** was confirmed by mass spectral and elemental analysis. The mass spectrum of **7** showed the $(M + 1)^+$ peak at *m/z* 204 and its elemental analysis was also found to be in good agreement with theoretical values. The next task was to introduce the hydroxymethyl group at active methylene site.[5]



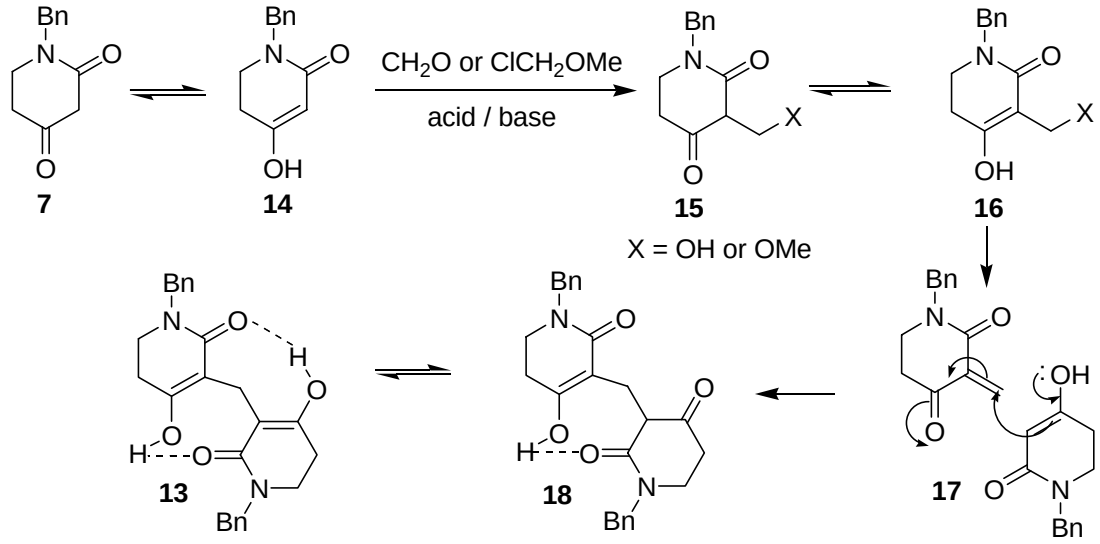
Scheme 3. *Reagents and conditions: (a) 10% HCl, reflux, 4-5 h, 87%. (b) Reaction conditions mentioned in table 1.*

Table 1

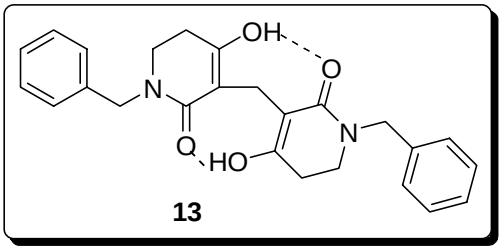
Sr.No.	Reagents	Solvent	Temperature	Time	Product
1	$KHCO_3$/Formalin	CH_3OH	rt	2 h	13
2	Et_3N / $(CH_2O)_n$	THF	0 ^oC-rt	15 h	13
3	K_2CO_3/ $(CH_2O)_n$	THF	0 ^oC-rt	15 h	13
4	NaH/ MOMCl	DMF	0 ^oC	3 h	13
5	Et_3N, TMSCl, $TiCl_4$, $(CH_2O)_n$	CH_3CN	-78 ^oC	3-4 h	13
6	Et_3N, TMSCl, $TiCl_4$, MOMCl	CH_3CN	-78 ^oC	3 h	13

A number of reactions were performed on compound **7** under basic as well as acidic conditions using the formalin, paraformaldehyde and MOMCl but unfortunately instead of desired product **6** formation of compound **13** was observed (scheme 3). The formation of compound **13** was confirmed by spectral techniques. ^{1}H NMR spectrum of **13** showed the signal as multiplet at δ 2.25-2.33 integrating for two protons, multiplet at δ 2.54-2.61 integrated for two protons. The multiplet at δ 3.16-3.20 integrating for two protons, and singlet at δ 3.23 integrated for two protons which were attributed to bridged methylene protons. The multiplet at δ 3.31-3.44 integrated for two protons, doublets of doublets at δ 4.63 (J = 16.8, 14.9 Hz) integrated for four protons which were assigned to benzylic protons. The multiplet at 7.28-7.30 integrated for ten aromatic protons appeared as broad singlet at δ 12.34 integrated for two enolic protons. ^{13}C NMR, DEPT, COSY and HETCOR spectra of **13** were also used to ascertain the structure of **13**. The structure of compound **13** was further supported by mass spectral and elemental analysis. The *m/z* peak at 419 $(M + H)^+$ and 441 $(M + Na)^+$ in the mass spectrum, its elemental analysis was in good agreement with theoretical values and finally the structure of **13** was unambiguously confirmed by single crystal X-ray analysis.

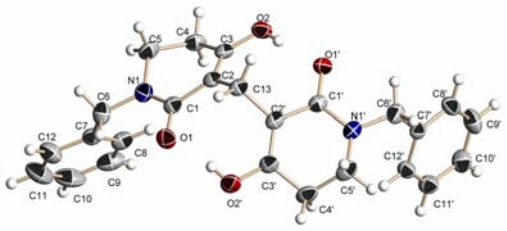
The formation of compound **13** can be rationalized by the probable mechanism which is depicted in scheme 4.



Scheme 4. *Probable mechanism.*



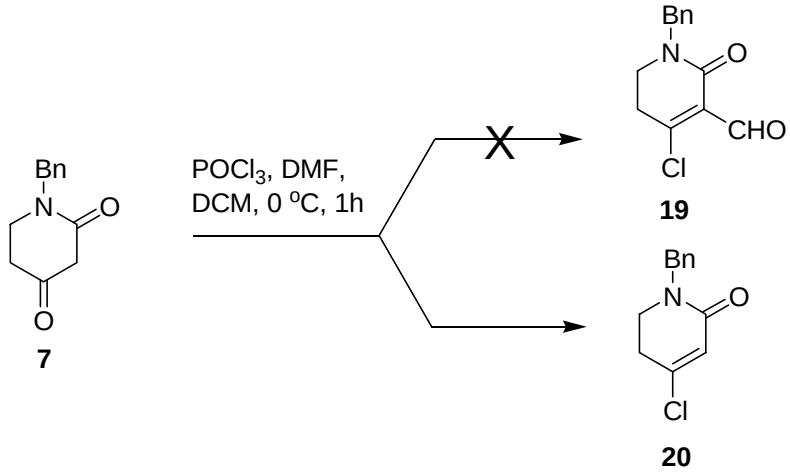
13



ORTEP Diagram of 13

The β-keto lactam **7** in its enolic form **14** when treated with formalin, paraformaldehyde or methoxy methyl chloride under acidic or basic condition forms a mixture of compounds **15** and **16**. However the tautomeric mixture **15** and **16** are unstable which immediately lose water molecule or HCl and is converted into enone **17**. Enol **14** reacts with this enone **17** in a Michael fashion to give compound **18** which exists as its enolic form **13** which is stabilized by intramolecular hydrogen bonding.

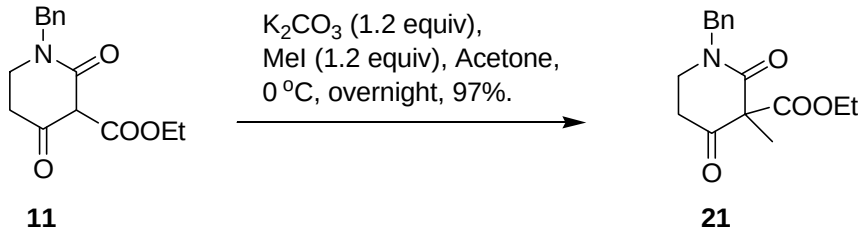
After the failure in introduction of CH_2OH functionality at C-3, it was thought that same moiety can be installed *via* aldehyde **19.** The aldehyde **19** can be obtained by Vilsmeier-Haack reaction.[5] Thus compound **7** was treated with $POCl_3$ and DMF in anhydrous CH_2Cl_2 at 0 ^oC to room temperature for 1 h. The formation of compound **20** was observed in very poor yield (27%) instead of the desired aldehyde **19**.



Scheme 5.

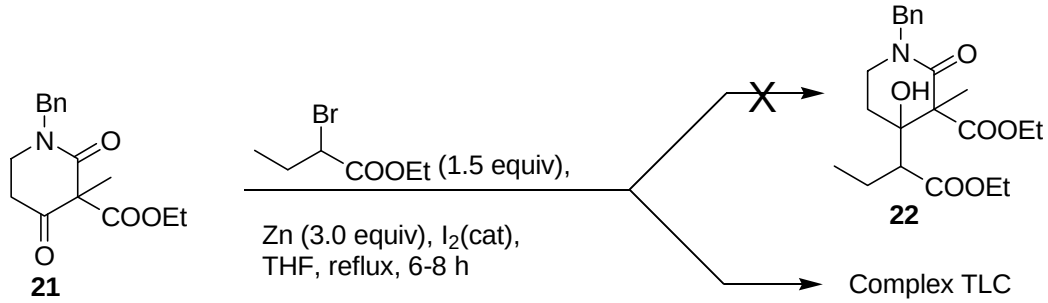
The formation of chloro compound **20** was confirmed by spectral data. ^{1}H NMR spectrum of **20** showed appearance of a triplet at δ 2.64 integrated for two allylic protons, triplet at δ 3.38 integrating for two protons which were assigned to methylene protons adjacent to amide *N* and the singlet at δ 6.15 integrating for one olefinic proton. The mass spectrum of **20** displayed the *m/z* peak 222, 244 corresponding to $(M + H)^{+}$ and $(M + Na)^{+}$ respectively.

After the failure of Vilsmeier-Haack reaction on compound **7** (scheme 5)**,** the compound **11** was alkylated with methyl iodide using potassium carbonate as the base to give compound **21** in very good yield (97%), which was confirmed by spectral methods. ^{1}H NMR spectrum of **21** displayed the triplet at 1.21 and quartet at 4.17 (J = 7.1 Hz) integrated for three and two protons corresponding to ethyl ester functionality and the singlet at 1.60 integrating for three methyl protons. ^{13}C NMR spectrum of **21** revealed the thirteen signals, DEPT spectrum of **21** exhibited the four methylene carbons and finally the structure of **21** was confirmed by mass spectral and elemental analysis. The mass spectrum of **21** showed the *m/z* peak at 290 & 312 corresponding to $(M + H)^{+}$ & $(M + Na)^{+}$ respectively and in elemental analysis the experimental values were in good agreement with calculated values.



Scheme 6.

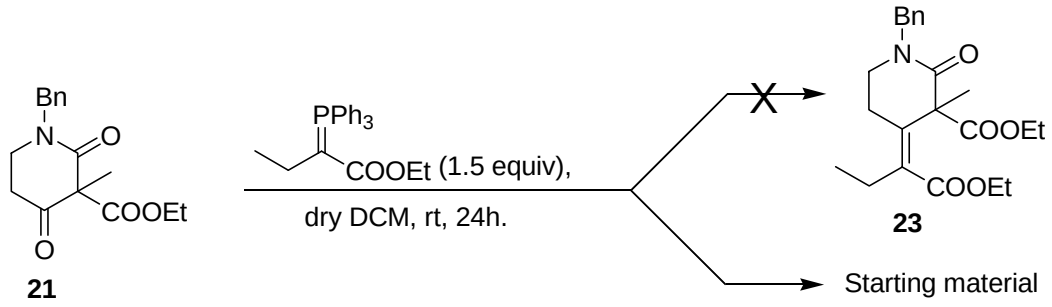
After obtaining the compound **21** (scheme 6), it was thought to perform the Reformatsky reaction[6] on **21**.



Scheme 7.

Accordingly the compound **21** was treated with zinc and ethyl 2-bromo butyrate in THF under reflux conditions, complex reaction mixture was observed on TLC instead of desired product **22**.

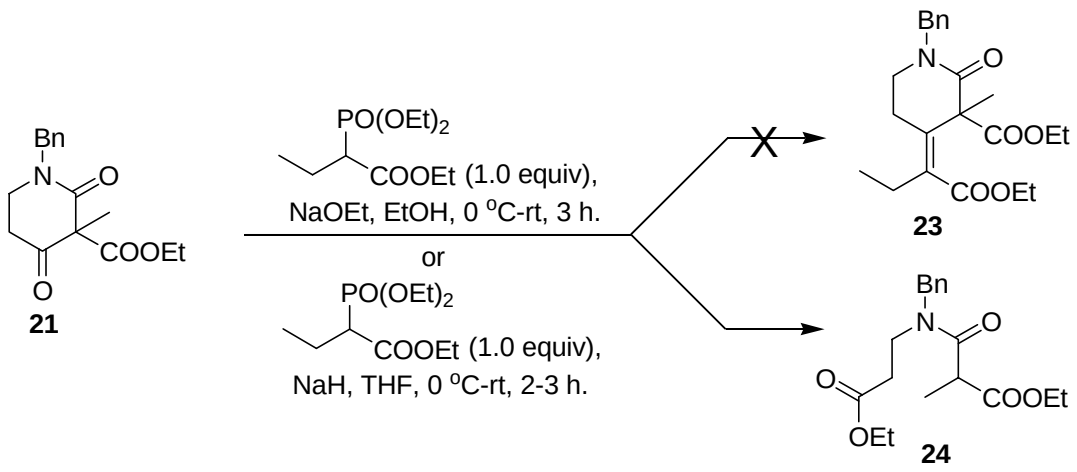
Having failed to obtain the hydroxy compound **22** by Reformatsky reaction mentioned in scheme 7, it was decided to perform the Wittig reaction on compound **21.** Wittig reaction on ketone at high pressure or in sealed tube is reported in literature.[7] When Wittig reaction on **21** was attempted it did not provide the desired product **23,** instead the starting material was recovered. It was presumably due to the steric crowding of the ketone and the less reactivity of the Wittig reagent.



Scheme 8.

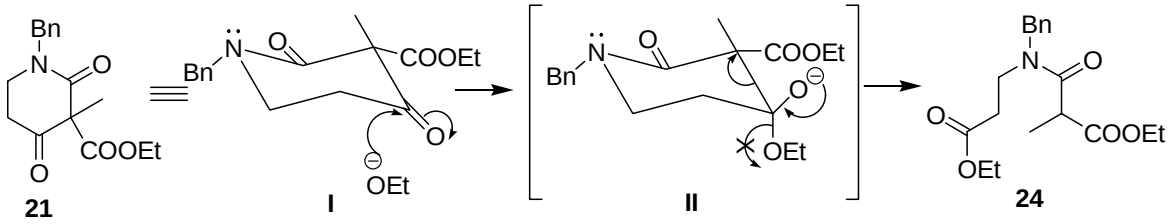
After failure of the Wittig reaction on compound **21** (scheme 8), it was thought to perform the Wittig-Horner reaction[8] in which Wittig reagent is more reactive.

Accordingly compound **21** was subjected to Wittig-Horner reaction using sodium ethoxide as base in ethanol, NaH as base in THF but again the desired product **23** was not obtained, instead the ring was opened and compound **24** was formed in 87% yield. The formation of **24** was confirmed by spectral analysis. IR spectrum of **24** showed the disappearance of absorption band that corresponded to ketone functionality. ^{1}H NMR spectrum of **24** displayed the disappearance of singlet while appearance of two doublets at δ 1.36 and 1.46 (J = 6.0 Hz) of three methyl protons. Triplet and quartet appeared at δ 1.25 and 4.14 (J = 7.1 Hz) integrated for six and four protons respectively corresponding to ester functionality. This suggested the formation of ethyl ester group during reaction and a multiplet appeared at δ 3.36-3.92 integrated for three protons. ^{13}C NMR along with DEPT spectra of **24** revealed the mixture of rotamers due to ring opening. The mass spectrum of **24** shows *m/z* peak at 336, 353 and 358 corresponding to $(M + H)^+$, $(M + H_2O)^+$ and $(M + Na)^+$ respectively which confirmed the structure of **24**.



Scheme 9.

The formation of compound **24** can be explained by the probable mechanism outlined in (scheme 10). Sodium ethoxide acts as a nucleophile instead of base and it attacks on electrophilic ketonic carbonyl of compound **21** and then the bond between ketone and ester functionality breaks because the resulting carbanion is stabilized and the resulting compound **24** became free from steric crowding may be the driving force for retro-Dieckmann condensation.



Scheme 10. *Probable mechanism.*

After the failure of Wittig-Horner reaction on compound **21** as shown in scheme 9, a totally different approach for the E ring construction as delineated in scheme 11 was devised.

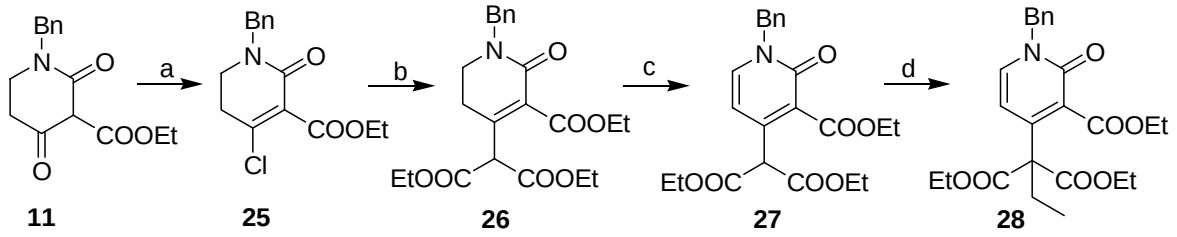
Accordingly the compound **11** was treated with $POCl_3$ in anhydrous dichloromethane at reflux temperature to furnish chloro compound **25** in excellent yield (96%). The resulting compound **25** was unstable so immediately the addition elimination reaction of diethyl malonate was carried out on crude chloro compound **25** using sodium hydride as a base in

anhydrous benzene at room temperature for overnight, afforded the product **26** in very good yield (85%).[8]

The structure of compound **26** was confirmed by spectral studies. IR spectrum of **26** showed a strong absorption band at 1732 cm^{-1} indicating the presence of ester functionality. The ^{1}H NMR spectrum of **26** displayed triplet at δ 1.28 integrating for nine protons, two triplets at δ 2.57 and δ 3.35 integrating for two protons each, multiplet at δ 4.11-4.37 integrating for seven protons. ^{13}C NMR along with DEPT spectra of **26** showed six methylene carbons. Finally the structure of **26** was confirmed by mass spectral and elemental analysis. The mass spectrum of compound **26** showed the *m/z* peak at 418 $(M + H)^{+}$ and 440 $(M + Na)^{+}$ and elemental analysis was in good agreement with calculated values.

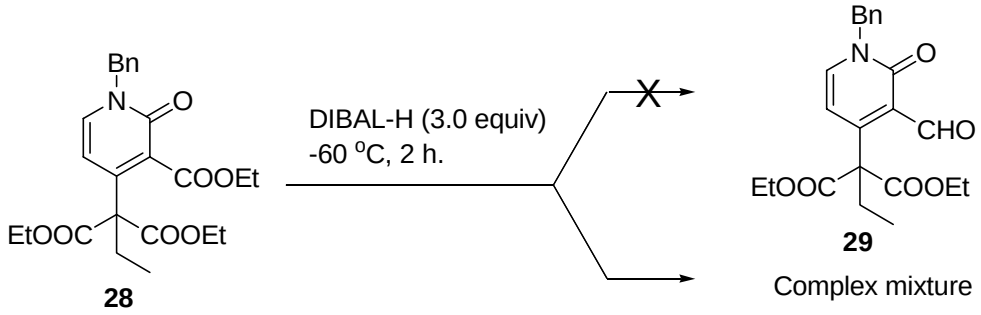
The compound **26** was aromatized by DDQ in refluxing 1,4-dioxane for 6 h, afforded aromatized product **27** in excellent yield (96%). The formation of pyridone **27** was confirmed by spectral study. The ^{1}H NMR spectrum of **27** showed the disappearance of two triplet integrating for two protons each and appearance of two new doublets at δ 6.29 and δ 7.23 for one proton each (J = 7.2 Hz). ^{13}C NMR along with DEPT spectra of **27** revealed the presence of three methylene carbons and lastly structure of compound **27** was confirmed by mass spectral and elemental analysis. The mass spectrum of compound **27** displayed the *m/z* peak at 416 $(M + 1)^{+}$ and its elemental analysis was also found to be in good agreement with calculated values.

The alkylation of pyridone **27** was accomplished with ethyl iodide using K_2CO_3 as the base in anhydrous acetone at 0 ^{o}C to room temperature for overnight to furnish the alkylated product **28** in (91%) yield. The compound **28** was characterized by spectral analysis. In the ^{1}H NMR spectrum of **28** the triplet and quartet appeared at δ 0.94 and δ 2.27 (J = 7.5 Hz) integrating for three and two protons respectively which suggest the incorporation of ethyl moiety. ^{13}C NMR spectrum of **28** revealed two extra carbons at δ 10.0 and δ 28.6. DEPT spectrum of **28** showed five methylene carbons and finally the structure of the compound **28** was confirmed by mass spectral and elemental analysis. The mass spectrum of **28** displayed the *m/z* peak at 444 $(M + H)^{+}$ and 466 $(M + Na)^{+}$ and in an elemental analysis the experimental values were in good agreement with the theoretical values.



Scheme 11. *Reagents and conditions: (a) $POCl_3$ (1.2 equiv), CH_2Cl_2, reflux, 3h, 96.5%. (b) NaH (1.2 equiv), diethylmalonate (1.2 equiv), benzene, rt, overnight, 85%. (c) DDQ (1.2 equiv), anhydrous 1,4 dioxane, reflux, 6 h, 96%. (d) K_2CO_3 (3.0 equiv), ethyl iodide (1.2 equiv), anhydrous acetone, reflux, 12 h, 91%.*

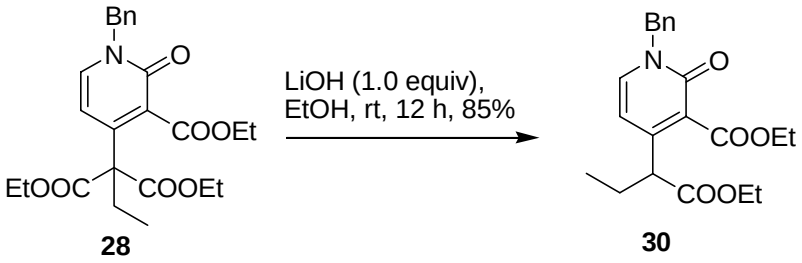
After achieving the synthesis of compound **28** in scheme 11, the selective reduction of heteroaromatic ester in presence of aliphatic ester employing DIBAL-H was accomplished by this group.[9] Therefore pyridone **28** was treated with DIBAL-H under reported reaction conditions, but unfortunately complex TLC pattern was observed instead of desired product **29**.



Scheme 12.

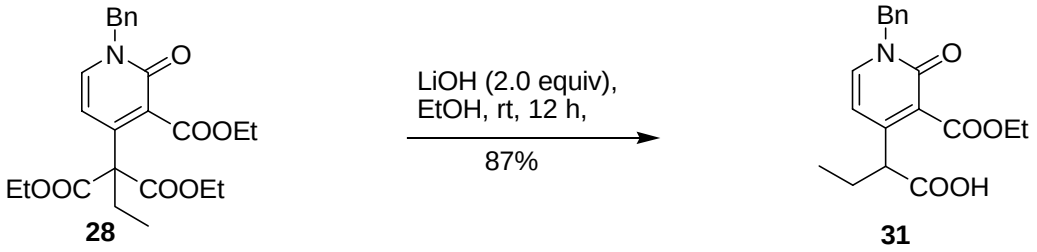
After failing to convert aromatic ester to aldehyde in scheme 12, the compound **28** was subjected to the treatment with one equivalent lithium hydroxide in ethanol at ambient temperature to furnish diester compound **30** in very good yield (85%). The compound **30** was formed *via* selective hydrolysis of aliphatic ester followed by decarboxylation. It can be explained on the basis of hard-soft acid base theory. In DIBAL-H hydride is soft nucleophile it reacts with carbonyl of aromatic ester (soft electrophile) while in LiOH hydroxyl anion is hard nucleophile and it react with carbonyl of aliphatic ester (hard electrophile). The structure of diester compound **30** was confirmed by spectral data. The

^{1}H NMR spectrum of **30** displayed the absence of triplet and quartet corresponding to aliphatic ester while appearance of a new triplet at δ 3.49 integrating for one proton which suggests the loss of one aliphatic ethyl ester group. The compound **30** was also confirmed by mass spectrum which revealed the *m/z* peak at 372 $(M + 1)^+$ along with 394 $(M + Na)^+$ respectively.



Scheme 13.

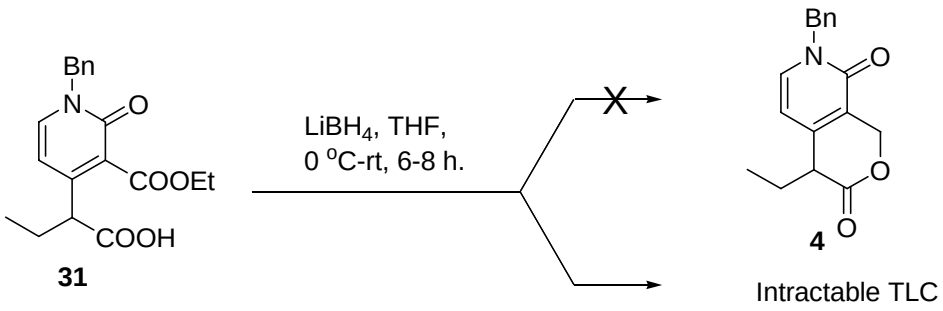
After the selective hydrolysis followed by decarboxylation of aliphatic ester was accomplished (scheme 13), then 2.0 equiv LiOH was used under identical reaction conditions which afforded the anticipated acid **31** in very good yield. The structure of acid **31** was confirmed by spectral analysis. IR spectrum of **31** showed a very broad absorption band at 2500-3300 cm^{-1} which is characteristic of carboxylic acid. The ^{1}H NMR spectrum of **31** displayed the absence of peaks corresponding to aliphatic ester, and new triplet appeared at δ 3.51 integrating for one proton. The structure of compound **31** was also confirmed by mass spectrum which shows the *m/z* peaks at 344 $(M + H)^+$ and 366 $(M + Na)^+$.



Scheme 14.

After achieving the synthesis of acid **31** in scheme 14, the next task was to construct E-ring *via* lactonization. There are some reports in literature[10] for cyclization using lithium

borohydride in THF at 0 ^{o}C to room temperature for 6-8 h. But in this case compound **31** did not furnish the desired lactone **4** under the literature reaction conditions.

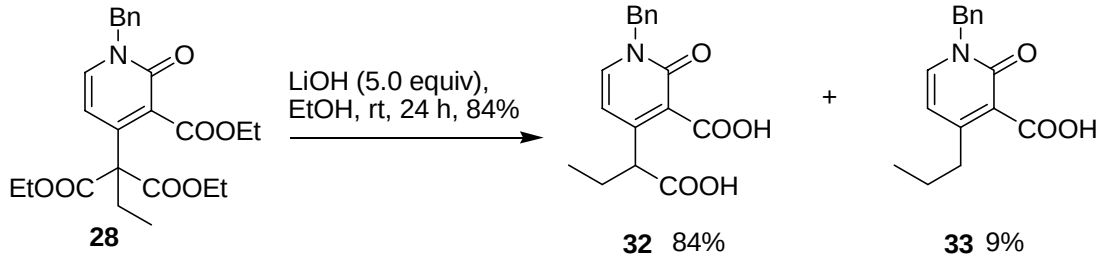


Scheme 15.

After failure to obtain lactone by reduction of ester **31** (scheme 15), the compound **28** was subjected to global hydrolysis and was treated with excess (5.0 equiv) of lithium hydroxide in ethanol at room temperature to deliver expected diacid **32** in good yield (76%) along with decarboxylated compound **33** in 9% yield as depicted in scheme 16.

The diacid **32** was characterized by spectral methods. IR spectrum of **32** showed the disappearance of absorption band corresponding to ester functionality. The ^{1}H NMR spectrum of **32** displayed the absence of the signals corresponding to ester groups. ^{13}C NMR along with DEPT spectra of **32** revealed the two methylene carbons which is indicative of the hydrolysis of all esters and decarboxylation of one of the aliphatic acid. Finally the structure of compound **32** was confirmed by mass spectral and elemental analysis. The mass spectrum of diacid **32** showed the *m/z* peak at 316 and 338 corresponding to $(M + H)^{+}$ and $(M + Na)^{+}$ respectively and in the elemental analysis of **32** the experimental values were in good agreement with calculated values.

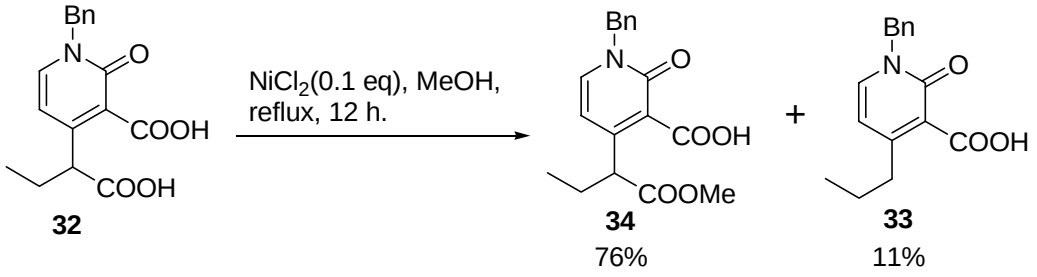
The structure of decarboxylated compound **33** was also confirmed by spectral study. The ^{1}H NMR spectrum of **33** displayed the triplet at δ 3.06 integrated for two protons which was ascribed to methylene adjacent to pyridone ring. The *m/z* peak at 272 and 294 corresponding to $(M + H)^{+}$ and $(M + Na)^{+}$ respectively in mass spectrum of **33** further confirmed the assigned structure.



Scheme 16.

The selective esterification of aliphatic acid in presence of heteroaromatic acid was accomplished using catalytic amount of $NiCl_2$ in anhydrous methanol at reflux temperature to yield monoester compound **34** in good yield (76%)[11] along with decarboxylated compound **33** in 11% yield (scheme 17).

The structure of compound **34** was ascertained by spectral study. IR spectrum of **34** displayed the strong absorption band at 1722 cm^{-1} indicated the presence of ester group. The ^{1}H NMR spectrum of **34** revealed the singlet at δ 3.66 integrating for three protons which was assigned to methyl ester. ^{13}C NMR spectrum of **34** showed the appearance of signal at δ 172.9 corresponding to carbonyl of ester functionality ($O\underline{C}OCH_3$) and a signal at δ 52.25 corresponding to the methyl carbon of ester functionality ($OCO\underline{C}H_3$). The mass spectrum of **34** showed the peaks at *m/z* 330 and 352 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively. The structure of compound **34** was confirmed by its elemental analysis also, which was in good agreements with calculated values.

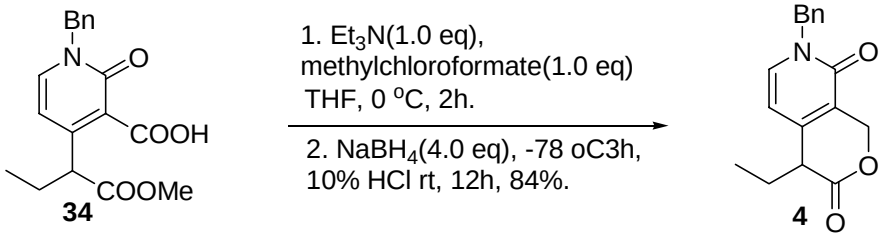


Scheme 17.

Having a compound **34** in hand, the attention was focused towards the E-ring construction. The resultant acid **34** was reacted with methyl chloroformate using triethyl amine as a base delivered the mixed anhydride. The generated mixed anhydride was immediately treated sodium borohydride at -78 ^{o}C followed by addition of 10% HCl at room temperature for 12

h. It was gratifying to note that the desired lactone **4** was obtained in very good yield as shown in scheme 18.[12]

The structure of lactone **4** was confirmed by spectral study. IR spectrum of **4** showed the absorption bands at 1738 and 1660 cm^{-1} corresponding to six-membered lactone and amide functionality respectively. ^{1}H NMR spectrum of **4** showed the presence of two doublets that appeared at δ 5.08 and 5.18 (J = 14.4 Hz) which were attributed for lactone methylene protons. ^{13}C NMR spectrum of **4** displayed the presence of a signal at δ 52.25 while another new signal appeared at δ 66.4 was assigned to the lactone methylene protons. Mass spectrum of **4** showed peak at *m/z* 284 and 306 corresponding to $(M + H)^{+}$ and $(M + Na)^{+}$ respectively. Finally the structure of **4** was confirmed by elemental analysis; the experimental values were in good agreement with its calculated values.

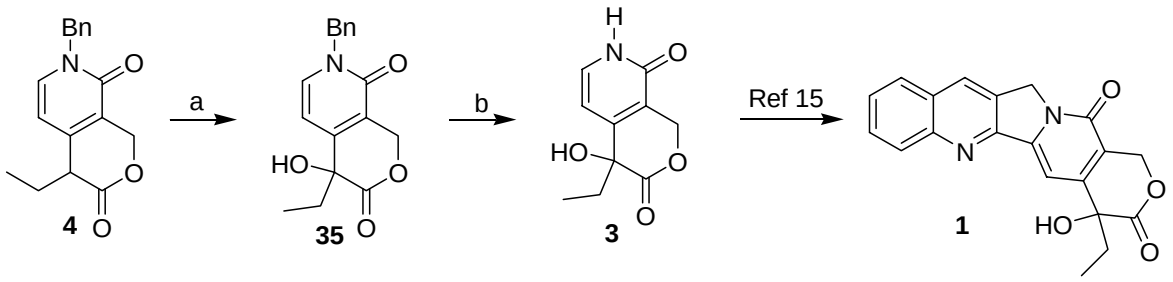


Scheme 18.

The α-hydroxylation on lactone **4** was smoothly carried out using cupric chloride and dimethylamine as a catalyst in DMF under oxygen atmosphere at room temperature for 24 h to furnish α-hydroxy lactone **35** in excellent yield (92%).[13] Compound **35** was characterized by spectral techniques. IR spectrum of **35** showed a broad absorption band at 3530 cm^{-1} indicating the presence of hydrogen bonded hydroxyl functionality. The ^{1}H NMR spectrum of **35** displayed the absence of triplet corresponded to methine proton. ^{13}C NMR spectrum along with DEPT spectra of **35** showed the disappearance of the signal corresponding to methine carbon. The peak at *m/z* 300 and 322 were observed in mass spectrum of **35** corresponding to (M + H) and (M + Na) respectively. The elemental analysis of **35** revealed the experimental values were in good agreement with its calculated values.

The *N*-debenzylation of **35** was successfully carried out using catalytic amount of palladium hydroxide in ethanol under H_2 atmosphere at 50 ^{o}C for 5 h resulted the desired

CD-ring fragment **3** in satisfactory yield (62%) (scheme 19).[14] The structure of 3 was confirmed by spectral study, the spectral data of compound **3** was in complete agreement with the literature data. [15] Compound **3** is a key intermediate in Comins synthesis.[15] The DE-ring can be transformed into (±)-camptothecin **1** or its relevant analogues by coupling with suitable AB-ring counter part.



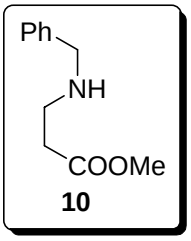
Scheme 19. *Reagents and conditions: (a) $CuCl_2.7H_2O$, Me_2NH, O_2, DMF, rt, 24h, 92%. (b) Pd $(OH)_2$, H_2, EtOH, 50 ^oC, 5h, 68%.*

2.3.4 Conclusion:

The formal total synthesis of (±)-camptothecin **1** (DE-ring) was achieved in twelve-steps in 16.7% overall yield, starting from cheap and commercially available starting material employing the addition elimination reaction and selective esterification of aliphatic acid in presence of heteroaromatic acid as key steps. This also avoided the use of DIBAL-H which is important from practical point of view. This protocol can be also utilized for the construction CDE-ring of CPT.

2.3.5 Experimental:

Methyl 3-(benzylamino) propanoate (10)



To a well stirred benzyl amine **9** (5.0 g, 0.046 mol) was added methyl acrylate (4.6 g, 4.8 mL, 0.046 mol) dropwise at room temperature and allowed to stir for 24 h. After the completion of reaction (TLC), the residue was purified by flash column chromatography (SiO_2) eluting with ethyl acetate-petroleum ether (4:6) to furnish the secondary amine **10** as a colourless liquid (8.7 g, 97% yield).

MF: $C_{11}H_{15}NO_2$, **MW**: 193

IR ($CHCl_3$) $\nu_{max.}$ 3324, 1736, 1361, 737 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.85 (s, 1H), 2.45 (t, *J* = 6.5 Hz, 2H), 2.80 (t, *J* = 6.5 Hz, 2H), 3.58 (s, 3H), 3.71 (s, 2H), 7.21 ppm (s, 5H).

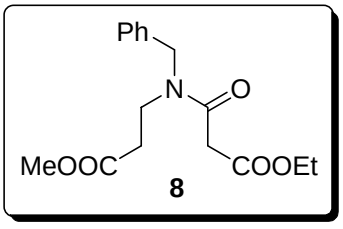
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 34.3, 44.2, 51.02, 53.45, 126.7, 127.8, 128.1, 140.0, 172.8 ppm.

MS (ESI) *m/z*: 194 $(M + H)^+$, 216 $(M + Na)^+$.

Elemental analysis Calculated: C, 68.37; H, 7.82; N, 7.25%.

Found: C, 68.29; H, 7.75; N, 7.09%.

Ethyl 3-(benzyl (3-methoxy-3-oxopropyl) amino)-3-oxopropanoate (8)



To a mixture of amine **10** (8.5 g, 0.044 mol) and K_2CO_3 (7.34 g, 0.052 mol) in anhydrous CH_2Cl_2 (50 mL) was added ethyl malonyl chloride (7.92 g, ml, 0.052 mol) dropwise at 0 ^oC and left to stir at 0 ^oC till the completion of reaction (1 h, TLC). The reaction mixture was filtered and the residue was washed with CH_2Cl_2 (3 x 20 mL). The organic layer was washed with H_2O, brine and organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (4:6) as eluent afforded the tertiary amide **8** as a colourless liquid (11.62 g, 86% yield).

MF: $C_{16}H_{21}NO_5$, **MW**: 307

IR ($CHCl_3$) ν_{max}: 1735, 1654, 1648, 1438, 1216, 1029, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.23, 1.28 (t, t, *J* = 7.2 Hz, 3H), 2.53, 2.64 (t, t, *J* = 6.5 Hz, 2H), 3.43-3.67 (m, 8H), 4.08-4.23 (m, 4H), 4.60, 4.64 (s, s, 2H), 7.16-7.37 ppm (m, 5H) (mixture of rotamers).

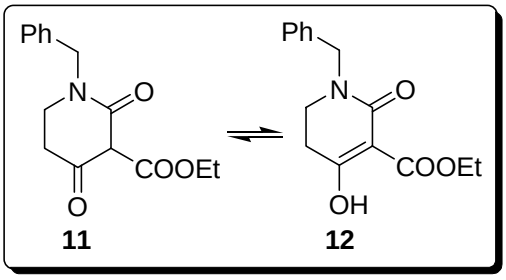
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 13.8, 31.95, 32.6, 40.8, 41.1, 42.7, 42.9, 47.7, 51.4, 51.6, 52.5, 61.2, 126.2, 127.2, 127.4, 127.6, 128.1, 128.4, 128.75, 136.0, 136.6, 166.3, 166.5, 167.2, 167.45, 171.15, 172.0 ppm (mixture of rotamers).

MS (ESI) *m/z*: 308 $(M + H)^+$, 330 $(M + Na)^+$.

Elemental analysis Calculated: C, 62.53; H, 6.89; N, 4.56%.

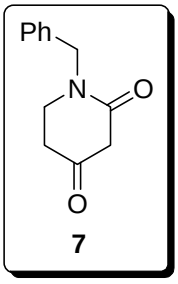
Found: C, 62.49; H, 6.82; N, 4.63%.

Ethyl 1-benzyl-2,4-dioxopiperidine-3-carboxylate (11 or 12)



60% NaH (0.78 g, 0.019 mol) was washed by dry petroleum ether (3 x 5 mL), absolute ethanol (20 mL) was added dropwise at 0 ^oC followed by addition of amide **9** (5.0 g, 0.016 mol) gradually and allowed to stir for 2-3 h at room temperature. After the disappearance of starting material (TLC), the reaction was quenched with addition of 10% HCl and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and solvent was evaporated on rotary evaporator under diminished pressure resulted the mixture of tautomers **11 and 12** as a thick liquid (4.09 g, 91% yield).

1-benzylpiperidine-2, 4-Dione (7)



To a well stirred mixture of **11** & **12** (0.78 g, 0.019 mol) was added 10% HCl (5.8 mL) and refluxed for 6 h till the completion of reaction (TLC). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and the resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (2:8) as eluent rendered the β-keto lactam **7** as a viscous colourless liquid (2.87 g, 87% yield).

MF: $C_{12}H_{13}NO_2$, **MW**: 203

IR ($CHCl_3$) ν_{max}: 1731, 1651, 1428, 1215, 1047, 1029, 928, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 2.44 (t, *J* = 6.2 Hz, 2H), 3.32 (s, 2H), 3.40 (t, *J* = 6.2 Hz, 2H), 4.60 (s, 2H), 7.15-7.31 ppm (s, 5H).

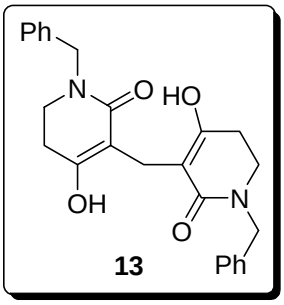
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 38.5, 42.3, 48.7, 49.9, 127.8, 128.0, 128.8, 136.3, 166.4, 203.1 ppm.

MS (ESI) *m/z*: 204 $(M + H)^+$, 226 $(M + Na)^+$.

Elemental analysis Calculated: C, 70.92; H, 6.45; N, 6.89%.

Found: C, 71.03; H, 6.39; N, 6.87%.

3, 3 methylenebis(1-benzyl-4-hydroxy-5,6-dihydroxypyridin-2(*1H*)-one) (13)



13

To a well stirred solution of compound **7** (0.2 g, 0.98 mmol) in anhydrous THF (10 mL) was added Et_3N (0.099 g, 0.137 mL, 0.98 mmol) to the above solution at 0 ^oC and stirred for 5 minutes. Paraformaldehyde (0.029 g, 0.98 mmol) was added to the above reaction mixture at 0 ^oC and allowed to stir till completion of reaction (15 h, TLC), solvent was evaporated *in vacuo* and residue was dissolved in H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure the residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:9) as eluent resulted compound **13** as a white crystalline solid (0.191 g, 93% yield).

MF: $C_{25}H_{26}N_2O_4$, **MW**: 418

M.P.: 153-155 ^oC

IR ($CHCl_3$) ν_{max}: 1647, 1556, 1486, 1447, 1215, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 2.25-2.33 (m, 2H), 2.54-2.61 (m, 2H), 3.16-3.20 (m, 2H), 3.23 (s, 2H), 3.31-3.44 (m, 2H), 4.63 (dd, *J* = 16.8, 14.9 Hz, 4H), 7.28-7.30 (m, 10H), 12.34 ppm (bs, 2H).

^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 19.3, 28.2, 43.6, 50.25, 104.7, 127.5, 128.0, 128.7, 137.3, 165.6, 171.3 ppm.

MS (ESI) *m/z*: 419 $(M + H)^+$, 442 $(M + Na)^+$.

Elemental analysis Calculated: C, 71.75; H, 6.26; N, 6.69%.

Found: C, 71.79; H, 6.31; N, 6.73%.

Table 1 Crystal data and structure refinement for J26.

Identification code	j26
Empirical formula	$C_{25}H_{26}N_2O_4$
Formula weight	418.48
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.042(2) Å, α = 82.097(4)º. b = 11.037(3) Å, β = 74.061(4)º. c = 11.629(3) Å, γ = 75.413(4)º.
Volume	1077.1(4) $Å^3$
Z, Calculated density	2, 1.290 Mg/m^3
Absorption coefficient	0.088 mm^{-1}
F(000)	444
Crystal size	0.64 x 0.49 x 0.29 mm
Theta range for data collection	2.55 to 25.00º.
Limiting indices	-10<=h<=10, -13<=k<=13, -13<=l<=13
Reflections collected / unique	15708 / 3783 [R(int) = 0.0266]
Completeness to theta = 25.00º	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9750 and 0.9459
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3783 / 0 / 283
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0414, wR2 = 0.1098
R indices (all data)	R1 = 0.0461, wR2 = 0.1145

Largest diff. peak and hole 0.182 and -0.181 e. $Å^{-3}$

Table 2 Bond lengths [Å] and angles [º] for J26.

O(1)-C(1)	1.2534(18)
O(2)-C(3)	1.3361(18)
O(1')-C(1')	1.2521(18)
O(2')-C(3')	1.3358(19)
N(1)-C(1)	1.3473(19)
N(1)-C(6)	1.451(2)
N(1)-C(5)	1.465(2)
N(1')-C(1')	1.3485(19)
N(1')-C(6')	1.455(2)
N(1')-C(5')	1.458(2)
C(1)-C(2)	1.462(2)
C(2)-C(3)	1.348(2)
C(2)-C(13)	1.5178(19)
C(3)-C(4)	1.493(2)
C(4)-C(5)	1.505(2)
C(6)-C(7)	1.508(2)
C(7)-C(8)	1.382(2)
C(7)-C(12)	1.394(2)
C(8)-C(9)	1.387(3)
C(9)-C(10)	1.373(3)
C(10)-C(11)	1.385(4)
C(11)-C(12)	1.376(3)
C(13)-C(2')	1.5144(19)
C(1')-C(2')	1.466(2)
C(2')-C(3')	1.346(2)
C(3')-C(4')	1.497(2)
C(4')-C(5')	1.503(3)
C(6')-C(7')	1.512(2)
C(7')-C(12')	1.381(2)
C(7')-C(8')	1.385(2)
C(8')-C(9')	1.385(3)
C(9')-C(10')	1.373(3)
C(10')-C(11')	1.362(2)
C(11')-C(12')	1.380(2)
C(1)-N(1)-C(6)	120.81(13)
C(1)-N(1)-C(5)	119.64(13)
C(6)-N(1)-C(5)	117.31(13)
C(1')-N(1')-C(6')	120.46(13)
C(1')-N(1')-C(5')	119.34(13)
C(6')-N(1')-C(5')	118.74(13)
O(1)-C(1)-N(1)	120.53(14)
O(1)-C(1)-C(2)	120.74(13)
N(1)-C(1)-C(2)	118.73(13)
C(3)-C(2)-C(1)	119.55(13)

C(3)-C(2)-C(13)	123.39(14)
C(1)-C(2)-C(13)	117.02(12)
O(2)-C(3)-C(2)	124.83(14)
O(2)-C(3)-C(4)	114.23(13)
C(2)-C(3)-C(4)	120.92(14)
C(3)-C(4)-C(5)	110.43(13)
N(1)-C(5)-C(4)	111.35(12)
N(1)-C(6)-C(7)	115.09(13)
C(8)-C(7)-C(12)	118.73(17)
C(8)-C(7)-C(6)	123.16(15)
C(12)-C(7)-C(6)	118.08(16)
C(7)-C(8)-C(9)	120.17(19)
C(10)-C(9)-C(8)	120.5(2)
C(9)-C(10)-C(11)	120.0(2)
C(12)-C(11)-C(10)	119.5(2)
C(11)-C(12)-C(7)	121.1(2)
C(2')-C(13)-C(2)	117.72(11)
O(1')-C(1')-N(1')	120.56(14)
O(1')-C(1')-C(2')	120.75(13)
N(1')-C(1')-C(2')	118.69(13)
C(3')-C(2')-C(1')	119.21(13)
C(3')-C(2')-C(13)	123.68(14)
C(1')-C(2')-C(13)	117.05(12)
O(2')-C(3')-C(2')	124.81(14)
O(2')-C(3')-C(4')	114.52(13)
C(2')-C(3')-C(4')	120.67(15)
C(3')-C(4')-C(5')	110.20(14)
N(1')-C(5')-C(4')	110.76(13)
N(1')-C(6')-C(7')	114.98(12)
C(12')-C(7')-C(8')	118.04(14)
C(12')-C(7')-C(6')	122.89(14)
C(8')-C(7')-C(6')	119.06(14)
C(9')-C(8')-C(7')	120.59(16)
C(10')-C(9')-C(8')	120.38(17)
C(11')-C(10')-C(9')	119.32(17)
C(10')-C(11')-C(12')	120.74(16)
C(11')-C(12')-C(7')	120.88(15)

Symmetry transformations used to generate equivalent atoms:

Table 3 Torsion angles [°] for J26.

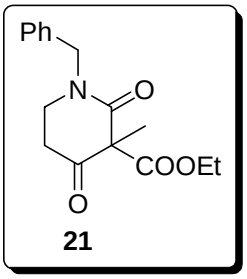
C(6)-N(1)-C(1)-O(1)	8.6(2)
C(5)-N(1)-C(1)-O(1)	171.13(14)
C(6)-N(1)-C(1)-C(2)	-171.38(13)
C(5)-N(1)-C(1)-C(2)	-8.8(2)
O(1)-C(1)-C(2)-C(3)	162.99(13)

N(1)-C(1)-C(2)-C(3)	-17.0(2)
O(1)-C(1)-C(2)-C(13)	-14.71(19)
N(1)-C(1)-C(2)-C(13)	165.26(12)
C(1)-C(2)-C(3)-O(2)	-171.57(12)
C(13)-C(2)-C(3)-O(2)	6.0(2)
C(1)-C(2)-C(3)-C(4)	6.9(2)
C(13)-C(2)-C(3)-C(4)	-175.55(13)
O(2)-C(3)-C(4)-C(5)	-155.54(13)
C(2)-C(3)-C(4)-C(5)	25.83(19)
C(1)-N(1)-C(5)-C(4)	41.84(19)
C(6)-N(1)-C(5)-C(4)	-155.02(14)
C(3)-C(4)-C(5)-N(1)	-48.15(18)
C(1)-N(1)-C(6)-C(7)	-118.96(16)
C(5)-N(1)-C(6)-C(7)	78.10(18)
N(1)-C(6)-C(7)-C(8)	4.9(2)
N(1)-C(6)-C(7)-C(12)	-172.88(15)
C(12)-C(7)-C(8)-C(9)	-1.0(2)
C(6)-C(7)-C(8)-C(9)	-178.76(16)
C(7)-C(8)-C(9)-C(10)	0.2(3)
C(8)-C(9)-C(10)-C(11)	0.9(3)
C(9)-C(10)-C(11)-C(12)	-1.2(4)
C(10)-C(11)-C(12)-C(7)	0.4(3)
C(8)-C(7)-C(12)-C(11)	0.7(3)
C(6)-C(7)-C(12)-C(11)	178.58(19)
C(3)-C(2)-C(13)-C(2')	-84.53(18)
C(1)-C(2)-C(13)-C(2')	93.07(16)
C(6')-N(1')-C(1')-O(1')	4.5(2)
C(5')-N(1')-C(1')-O(1')	170.49(14)
C(6')-N(1')-C(1')-C(2')	-175.73(12)
C(5')-N(1')-C(1')-C(2')	-9.70(19)
O(1')-C(1')-C(2')-C(3')	162.04(14)
N(1')-C(1')-C(2')-C(3')	-17.8(2)
O(1')-C(1')-C(2')-C(13)	-15.14(19)
N(1')-C(1')-C(2')-C(13)	165.05(12)
C(2)-C(13)-C(2')-C(3')	-83.94(18)
C(2)-C(13)-C(2')-C(1')	93.10(16)
C(1')-C(2')-C(3')-O(2')	-171.07(14)
C(13)-C(2')-C(3')-O(2')	5.9(2)
C(1')-C(2')-C(3')-C(4')	7.8(2)
C(13)-C(2')-C(3')-C(4')	-175.20(14)
O(2')-C(3')-C(4')-C(5')	-154.83(14)
C(2')-C(3')-C(4')-C(5')	26.2(2)
C(1')-N(1')-C(5')-C(4')	43.93(19)
C(6')-N(1')-C(5')-C(4')	-149.79(14)
C(3')-C(4')-C(5')-N(1')	-49.99(18)
C(1')-N(1')-C(6')-C(7')	-105.61(16)
C(5')-N(1')-C(6')-C(7')	88.28(17)
N(1')-C(6')-C(7')-C(12')	-24.0(2)
N(1')-C(6')-C(7')-C(8')	156.19(14)

C(12')-C(7')-C(8')-C(9')	-1.7(2)
C(6')-C(7')-C(8')-C(9')	178.16(16)
C(7')-C(8')-C(9')-C(10')	-0.2(3)
C(8')-C(9')-C(10')-C(11')	1.8(3)
C(9')-C(10')-C(11')-C(12')	-1.4(3)
C(10')-C(11')-C(12')-C(7')	-0.5(3)
C(8')-C(7')-C(12')-C(11')	2.0(2)
C(6')-C(7')-C(12')-C(11')	-177.84(15)

Symmetry transformations used to generate equivalent atoms:

Ethyl 1-benzyl-3-methyl-2, 4-dioxopiperidine-3-carboxylate (21)



21

To a stirred solution of β-keto ester **11** (1.0 g, 3.6 mmol) in anhydrous acetone (10 mL) was added K_2CO_3 (0.60 g, 4.36 mmol) at 0 ^oC stirred for 15 minutes and then methyl iodide (0.62 g, 4.36 mmol) was added dropwise and left to stir at room temperature for overnight. After the completion of reaction (TLC), solvent was removed *in vacuo* and residue obtained was dissolved in H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with mixture ethyl acetate-petroleum ether (2:8) as a solvent system furnished the compound **21** as a viscous colourless liquid (0.96 g, 92% yield).

MF: $C_{16}H_{19}NO_4$, **MW**: 289

IR ($CHCl_3$) ν_{max}: 1755, 1723, 1655, 1216, 756 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.21 (t, *J* = 7.1 Hz, 3H), 1.60 (s, 3H), 2.52-2.82 (m, 2H), 3.27-3.57 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.52 (d, *J* = 14.7 Hz, 1H), 4.89 (d, *J* = 14.7 Hz, 1H), 7.28 ppm (s, 5H).

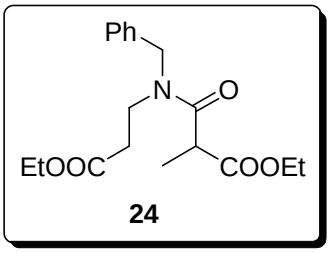
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 13.7, 17.7, 37.2, 41.4, 50.8, 62.1, 127.7, 127.9, 128.6, 136.1, 167.1, 201.8 ppm.

MS (ESI) *m/z*: 290 $(M + 1)^+$, 312 $(M + Na)^+$.

Elemental analysis Calculated: C, 66.42; H, 6.62; N, 4.84%.

Found: C, 66.47; H, 6.51; N, 4.79%.

Ethyl 3-(benzyl (3-ethoxy-3-oxopropyl)amino)-2-methyl-3-oxopropanoate (24)



24

To a well stirred mixture of Wittig reagent (0.43 g, 1.7 mmol) and NaOEt (0.11 g, 1.7 mmol) in anhydrous EtOH (15 mL) was dropwise added the solution of **21** (0.5 g, 1.7 mmol) in anhydrous EtOH (2 mL) at room temperature and left to stir till completion of reaction (6 h, TLC). The EtOH was removed *in vacuo* and the resultant residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:4) as eluent afforded compound **24** as colourless syrup (0.512 g, 89% yield).

MF: $C_{18}H_{25}NO_5$, **MW**: 335

IR ($CHCl_3$) ν_{max}: 1737, 1729, 1655, 1648, 1438, 1216, 1029, 738, 669 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.19-1.28 (m, 6H), 1.35-1.48 (m, 3H), 2.52-2.66 (m, 2H), 3.36-3.92 (m, 3H), 4.04-4.24 (m, 4H), 4.34-4.94 (m, 2H), 7.16-7.36 ppm (m, 5H) (mixture of rotamers).

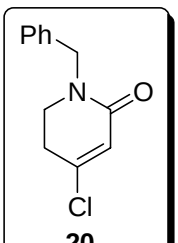
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 14.0, 14.1, 32.45, 33.5, 42.8, 43.3, 48.3, 52.3, 60.5, 61.0, 61.3, 61.4, 126.3, 127.4, 127.7, 127.8, 128.6, 128.9, 136.6, 137.1, 170.3, 170.5, 170.9, 171.95 ppm (mixture of rotamers).

MS (ESI) *m/z*: 336 $(M + H)^+$, 358 $(M + Na)^+$.

Elemental analysis Calculated: C, 64.46; H, 7.51; N, 4.18%.

Found: C, 64.47; H, 7.57; N, 4.23%.

1-benzyl-4-chloro-5, 6-dihydropyridin-2(1*H*)-one (20)



20

To a well stirred mixture of compound **7** (0.2 g, 0.98 mmol) and DMF (0.071 g, 0.076 mL, 0.98 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise $POCl_3$ (0.15 g, 0.09 mL, 0.98 mmol) at 0 ^oC and the progress of reaction was monitored by TLC. After the disappearance of starting material (3 h), the reaction was quenched with the addition of saturated $NaHCO_3$ solution. Organic phase was separated and aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo and the resultant residue was

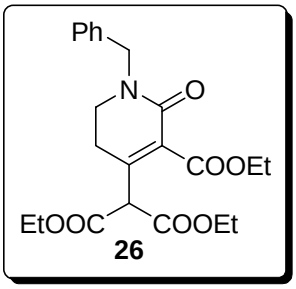
purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1: 6) as eluent rendered the compound **20** as pale yellow syrup (0.045 g, 21% yield)

MF: $C_{12}H_{12}NOCl$, **MW**: 221

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 2.64 (t, *J* = 7.1 Hz, 2H), 3.38 (t, *J* = 7.1 Hz, 2H), 4.59 (s, 2H), 6.15 (t, *J* = 1.4 Hz, 1H), 7.19-7.39 ppm (m, 5H).

MS (ESI) *m/z*: 222 $(M + 1)^+$, 244 $(M + Na)^+$.

Diethyl 2-(1-benzyl-3-(ethoxycarbonyl)-2-oxo-1, 2, 5, 6-tetrahydropyridine-4-yl) malonate (26)



26

To a well stirred solution of keto enol mixture **11** & **12** (1.0 g, 3.6 mmol) in anhydrous CH_2Cl_2 (15 mL) was dropwise added $POCl_3$ (0.67 g, 0.40 mL, 4.3 mmol) at rt and the resultant mixture was refluxed under argon atmosphere till the completion of reaction (3 h, TLC). After the completion of reaction, the reaction mixture was cooled to rt and reaction was quenched by the addition of saturated $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and solvent was removed on rotary evaporator under diminished pressure afforded the crude chloro compound **25** in 1.03 g, 96.5% yield. To a stirred suspension of 60% NaH (0.16 g, 4.0 mmol) was prewashed with anhydrous petroleum ether (3 x 10 mL), dry benzene (50 mL) was added followed by gradual addition of diethyl malonate (0.65 g, 4.1 mmol) over 15 minutes at room temperature and stirred for 30 minutes. The chloro compound **25** (1.0 g, 3.4 mmol) was added dropwise over 15 minutes initially formed yellow coloured solution and then which turned into orange colour, the reaction mixture was allowed to stir at room temperature for overnight. After the completion of reaction (TLC), reaction was quenched by addition of saturated NH_4Cl solution (50 mL), the organic layer was separated and aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and solvent was removed *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1: 4) as eluent furnished the compound **26** as viscous yellow liquid (1.2 g, 85% yield).

MF: $C_{22}H_{27}NO_7$, **MW**: 417

IR ($CHCl_3$) ν_{max}: 1732, 1584, 1506, 1215, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.28 (t, *J* = 7.1 Hz, 6H), 1.41 (t, *J* = 7.1 Hz, 3H), 2.57 (t, *J* = 6.9 Hz, 2H), 3.35 (t, *J* = 6.9 Hz, 2H), 4.11-4.37 (m, 7H), 4.62 (s, 2H), 7.29 ppm (s, 5H).

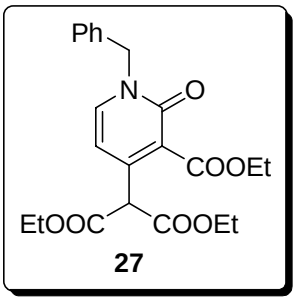
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 13.9, 14.1, 26.1, 43.85, 47.6, 49.7, 53.4, 55.02, 55.5, 61.6, 61.8, 61.9, 62.1, 124.4, 125.8, 127.5, 127.9, 128.1, 128.6, 130.9, 136.1, 136.8, 143.2, 161.0, 163.5, 164.9, 165.9, 166.7, 167.8 ppm.

MS (ESI) *m/z*: 418 $(M + H)^+$, 440 $(M + Na)^+$.

Elemental analysis Calculated: C, 63.30; H, 6.52; N, 3.36%.

Found: C, 63.34; H, 6.59; N, 3.33%.

Diethyl 2-(1-benzyl-3-(ethoxycarbonyl)-2-oxo-1, 2-dihydropyridine-4-yl) malonate (27)



27

To a mixture of dihydropyridone **26** (1.0 g, 2.3 mmol) and DDQ (0.598 g, 2.6 mmol) in anhydrous 1, 4-dioxane (10 mL) was refluxed till the completion of reaction (6 h, TLC). The reaction mixture was diluted with benzene and quenched with addition of 10% $NaHCO_3$ solution, the organic phase was separated and aqueous phase was extracted with benzene (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The generated residue was purified by flash column chromatography (SiO_2) eluting with 30% ethyl acetate-petroleum ether as a solvent system yielded pyridone **27** as a pale yellow liquid (0.95 g, 96% yield).

MF: $C_{22}H_{25}NO_7$, **MW**: 415

IR ($CHCl_3$) ν_{max}: 1736, 1651, 1606, 1508, 1215, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.27 (t, *J* = 7.1 Hz, 6H), 1.39 (t, *J* = 7.1 Hz, 3H), 4.17-4.26 (2q, *J* = 7.1 Hz, 4H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.74 (s, 1H), 5.11 (s, 2H), 6.29 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.26 ppm (s, 5H).

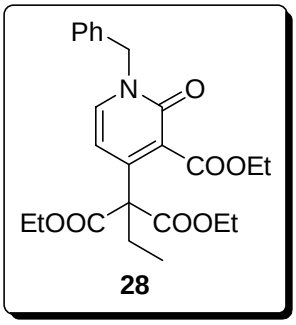
^{13}C NMR ($CDCl_3$ + CCl_4, 100 MHz) δ: 13.8, 14.0, 52.1, 54.4, 61.6, 62.1, 106.0, 125.7, 128.1, 128.5, 128.8, 135.4, 137.9, 143.3, 159.0, 165.3, 166.1 ppm.

MS (ESI) *m/z*: 416 $(M + H)^+$, 438 $(M + Na)^+$.

Elemental analysis Calculated: C, 63.60; H, 6.07; N, 3.37%.

Found: C, 63.57; H, 6.11; N, 3.41%.

Diethyl 2-(1-benzyl-3-(ethoxycarbonyl)-2-oxo-1, 2-dihydropyridine-4-yl) -2-ethylmalonate (28)



28

To a well stirred solution of pyridine **27** (0.9 g, 2.1 mmol) in anhydrous acetone (10 mL), K_2CO_3 (0.36 g, 2.6 mmol) was added at 0 ^oC and stirred for 15 minutes and ethyl iodide (0.40 g, 0.20 mL, 2.6 mmol) was added dropwise over 15 minutes and refluxed for 12 h. After the completion of reaction (TLC), the reaction mixture was filtered and residue was washed with acetone (3 x 10 mL). The filtrate was concentrated *in vacuo* and the resultant residue was diluted with CH_2Cl_2 (20 mL), organic phase was washed with H_2O, brine dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:3) as eluent afforded the alkylated product **28** as a colourless viscous liquid (0.87 g, 91% yield).

MF: $C_{24}H_{29}NO_7$, **MW**: 443

IR ($CHCl_3$) ν_{max}: 1735, 1647, 1601, 1258, 1216, 1128, 1022, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.94 (t, *J* = 7.5 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 6H), 1.37 (t, *J* = 7.1 Hz, 3H), 2.27 (q, *J* = 7.5 Hz, 2H), 4.10-4.43 (m, 6H), 5.10 (s, 2H), 6.19 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.33 ppm (s, 5H).

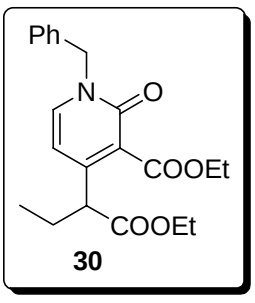
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 10.0, 14.0, 28.6, 52.1, 61.7, 61.95, 63.3, 107.3, 128.45, 128.8, 129.1, 135.5, 135.9, 147.05, 160.15, 166.0, 168.8 ppm.

MS (ESI) *m/z*: 444 $(M + H)^+$, 466 $(M + Na)^+$.

Elemental analysis Calculated: C, 65.00; H, 6.59; N, 3.16%.

Found: C, 65.07; H, 6.61; N, 3.19%.

Ethyl 1-benzyl-4-(1-ethoxy-1-oxobutan-2-yl)-2-oxo-1,2-dihydropyridine-3-carboxylate (30)



30

To a stirred solution triester **28** (2.0 g, 4.5 mmol) in EtOH (20 mL), LiOH (0.108 g, 4.5 mmol) was added and the resultant reaction mixture was allowed to stir at room temperature for 24 h. After the disappearance of starting materials (TLC), ethanol was evaporated *in vacuo* and the resultant residue was extracted with CH_2Cl_2 (3 x 25 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered

and concentrated on rotary evaporator under reduced pressure. The residue thus obtained was purified by flash column chromatography (SiO_2) eluting with mixture of ethyl acetate-petroleum ether as a solvent system delivered compound **30** as colourless oil (1.42 g, 85% yield).

MF: $C_{21}H_{25}NO_5$, **MW**: 371

IR ($CHCl_3$) ν_{max}: 1736, 1718, 1681, 1629, 1566, 1521, 1477, 1217, 769 cm^{-1}.

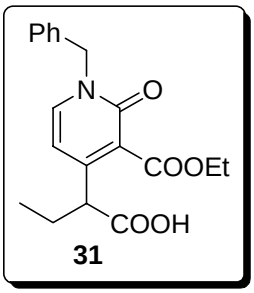
^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.91 (t, *J* = 7.5 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.69-1.83 (m, 1H), 1.89-2.11 (m, 1H), 3.49 (t, *J* = 7.6 Hz, 1H), 4.00-4.25 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 5.09 (d, *J* = 1.6 Hz, 2H), 6.27 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.32 ppm (s, 5H).

MS (ESI) *m/z*: 372 $(M + H)^+$, 394 $(M + Na)^+$.

Elemental analysis Calculated: C, 67.91; H, 6.78; N, 3.77%.

Found: C, 68.04; H, 6.71; N, 3.79%.

2-(1-benzyl-3-(ethoxycarbonyl)-2-oxo-1,2-dihydropyridin-4-yl) butanoic acid (31)



31

The triester **28** (2.0 g, 4.5 mmol) in EtOH (20 mL) was treated with LiOH (0.216 g, 9.0 mmol) and the resultant reaction mixture was allowed to stirred at room temperature for 24 h. After the disappearance of starting materials (TLC), ethanol was removed on rotary evaporator under diminished pressure. The residue thus obtained was acidified with addition of 10 % HCl till neutralization and extracted EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* furnished compound **31** as colourless syrup (1.35 g, 87% yield).

MF: $C_{19}H_{21}NO_5$, **MW**: 343

IR ($CHCl_3$) ν_{max}: 3020, 1718, 1681, 1629, 1566, 1521, 1477, 1217, 769 cm^{-1}.

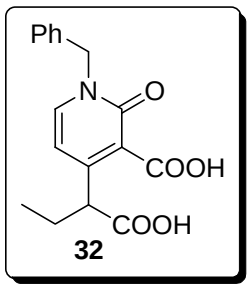
^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.91 (t, *J* = 7.5 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.62-1.80 (m, 1H), 1.92-2.10 (m, 1H), 3.51 (t, *J* = 7.6 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 5.09 (s, 2H), 6.25 (d, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.31 ppm (s, 5H).

MS (ESI) *m/z*: 344 $(M + H)^+$, 366 $(M + Na)^+$.

Elemental analysis Calculated: C, 66.46; H, 6.16; N, 4.08%.

Found: C, 66.49; H, 6.13; N, 3.99%.

1-benzyl-4-(1-carboxypropyl)-2-oxo-1, 2-dihydropyridine-3-carboxylic acid (32)



32

To a well stirred mixture of triester **28** (2.0 g, 4.5 mmol) and LiOH (0.541 g, 22.5 mmol) in EtOH (20 mL) was stirred at room temperature for 24 h. After the completion of reaction (as per TLC), ethanol was evaporated *in vacuo* and the resultant residue was treated with 10 % $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 25 mL). The aqueous layer was acidified with 10 % HCl up to neutralization and extracted EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure afforded compound **32** as a white solid (1.19 g, 84% yield).

MF: $C_{17}H_{17}NO_5$, **MW**: 315

M.P.: 130 ^oC

IR ($CHCl_3$) ν_{max}: 3018, 1718, 1681, 1629, 1566, 1521, 1477, 1217, 769 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.64 (t, *J* = 7.5 Hz, 3H), 1.30-1.52 (m, 1H), 1.68-1.81 (m, 1H), 4.94 (s, 2H), 6.30 (d, *J* = 7.1 Hz, 1H), 7.05 (s, 5H), 7.49 ppm (d, *J* = 7.1 Hz, 1H).

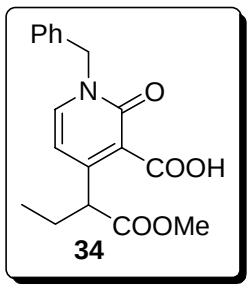
^{13}C NMR ($CDCl_3$ + CCl_4 + DMSO-d_6, 100 MHz) δ: 11.8, 25.3, 48.1, 52.9, 109.4, 115.7, 128.05, 128.6, 134.2, 139.5, 160.4, 164.2, 165.3, 173.2 ppm.

MS (ESI) *m/z*: 316 $(M + H)^+$, 338 $(M + Na)^+$.

Elemental analysis Calculated: C, 64.75; H, 5.43; N, 4.44%.

Found: C, 64.77; H, 5.38; N, 4.39%.

1-benzyl-4-(1-methoxy-1-oxobutan-2-yl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (34)



34

To a well stirred solution of dicarboxylic acid **32** (0.5 g, 1.58 mmol) in MeOH (10 mL) was added $NiCl_2$ $6H_2O$ (0.037 g, 0.158 mmol) and reaction mixture was refluxed for 12 h. The progress of reaction was monitored by TLC, after the completion of reaction, methanol was removed *in vacuo* and the residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (3:2) as eluent gave compound **34** as a gum (0.396 g, 76% yield).

MF: $C_{18}H_{19}NO_5$, **MW**: 329

IR ($CHCl_3$) ν_{max}: 3025, 1736, 1691, 1630, 1568, 1479, 1456, 1215, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.95 (t, *J* = 7.5 Hz, 3H), 1.59-1.83 (m, 1H), 1.93-2.21 (m, 1H), 3.66 (s, 3H), 5.21 (s, 2H), 5.52 (t, *J* = 7.2 Hz, 1H), 6.54 (d, *J* = 7.2 Hz, 1H), 7.45 (s, 5H), 7.51 ppm (d, *J* = 7.2 Hz, 1H).

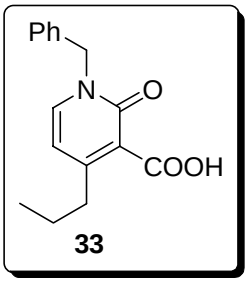
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 12.3, 26.2, 48.3, 52.25, 53.6, 109.8, 116.1, 128.8, 129.1, 129.4, 134.3, 139.45, 160.8, 165.05, 165.6, 172.9 ppm.

MS (ESI) *m/z*: 330 $(M + H)^+$, 352 $(M + Na)^+$.

Elemental analysis Calculated: C, 65.64; H, 5.81; N, 4.25%.

Found: C, 65.67; H, 5.78; N, 4.24%.

1-benzyl-2-oxo-4-propyl-1, 2-dihydropyridine-3-carboxylic acid (33)



33

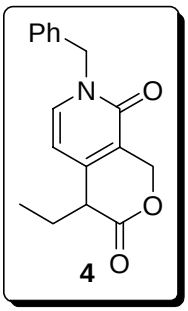
MF: $C_{16}H_{17}NO_3$, **MW**: 271

IR ($CHCl_3$) ν_{max}: 3023, 1687, 1636, 1567, 1459, 1214, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.94 (t, *J* = 7.5 Hz, 3H), 1.47-166 (m, 2H), 3.06 (t, *J* = 7.1 Hz, 2H), 5.14 (s, 2H), 6.29 (d, *J* = 7.2 Hz, 1H), 7.28 (s, 5H), 7.42 ppm (d, *J* = 7.2 Hz, 1H).

MS (ESI) *m/z*: 272 $(M + H)^+$, 294 $(M + Na)^+$.

1-benzyl-4-ethyl-1H-pyrano [3, 4-*c*] pyridine-3, 8(4H, 7*H*)-dione (4)



4

To a well stirred mixture of **5** (0.2 g, 0.60 mmol) and Et_3N (0.060 g, 0.082 mL, 0.60 mmol) in anhydrous THF (10 mL) was added methyl chloroformate (0.057 g, 0.60 mmol) dropwise at 0 ^oC and left to stir till the completion of reaction (1 h, TLC). The reaction mixture was filtered and precipitate was washed with dry THF (3 x 5 mL). The resultant filtrate was cooled to -78 ^oC and $NaBH_4$ (0.92 g, 2.4 mmol) was added portionwise followed by dropwise addition of methanol (10 mL) over 30 minutes and allowed to stir at -78 ^oC for 1 h. The cooling bath was removed and 10% HCl solution was added slowly until no residual $NaBH_4$ remained, and further stirred for additional 12 h at room temperature. After the completion of reaction (TLC), the solvent was evaporated on rotary evaporator under diminished pressure and residue obtained diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (2:3) as eluent yielded lactone **4** as a gum (0.144 g, 84% yield).

MF: $C_{17}H_{17}NO_3$, **MW**: 283

IR ($CHCl_3$) ν_{max}: 1720, 1651, 1567, 1523, 1477, 1215, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.01 (t, *J* = 7.5 Hz, 3H), 1.84-2.08 (m, 2H), 3.36 (t, *J* = 6.4 Hz, 1H), 5.08 & 5.18 (2d, *J* = 14.4 Hz, 2H), 5.25 & 5.43 (2d, *J* = 16.2 Hz, 2H), 6.01 (d, *J* = 7.1 Hz, 1H), 7.31 (d, *J* = 7.1 Hz, 1H), 7.33 ppm (s, 5H).

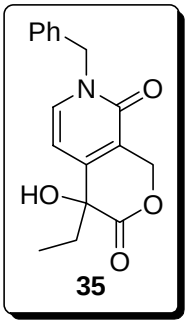
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 11.4, 25.3, 45.1, 52.1, 66.4, 105.2, 121.3, 128.5, 129.2, 135.9, 136.95, 145.75, 159.0, 170.5 ppm.

MS (ESI) *m/z*: 284 $(M + H)^+$, 306 $(M + Na)^+$.

Elemental analysis Calculated: C, 72.07; H, 6.05; N, 4.94%.

Found: C, 72.11; H, 6.03; N, 4.97%.

7-benzyl-4-ethyl-4-hydroxy-*1H pyrano* [3, 4-*c*] pyridine-3, 8 (*4H, 7H*)-dione (35)



35

The mixture of lactone **4** (0.1 g, 0.35 mmol), $CuCl_2$ (0.19 g, 1.4 mmol) and 25% aqueous dimethyl amine (0.5 mL) in anhydrous DMF (10 mL) under oxygen atmosphere was stirred at room temperature till the completion of reaction (24 h, TLC). After the completion of reaction, H_2O (10 mL) was added and the pH was adjusted to 6.5 with addition of dilute HCl, and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under diminished pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with the mixture of ethyl acetate-petroleum ether (2:3) as a solvent system delivered the hydroxyl compound **35** as white solid (0.103 g, 98% yield).

MF: $C_{17}H_{17}NO_4$, **MW**: 299

M.P.: 139-141 ^oC (Lit. 140 ^oC)

IR ($CHCl_3$) ν_{max}: 3350, 1741, 1655, 1604, 1563, 1512, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 0.97 (t, *J* = 7.5 Hz, 3H), 1.78 (q, *J* = 7.5 Hz, 2H), 5.08 & 5.18 (2d, *J* = 14.4 Hz, 2H), 5.17 & 5.61 (2d, *J* = 16.2 Hz, 2H), 6.49 (d, *J* = 7.1 Hz, 1H), 7.33 (s, 5H), 7.36 ppm (d, *J* = 7.1 Hz, 1H).

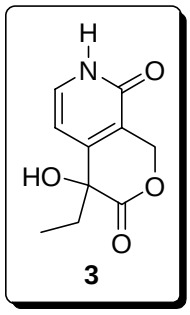
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 7.9, 31.7, 52.3, 66.7, 72.2, 103.2, 119.3, 128.4, 129.2, 135.8, 137.5, 148.7, 158.8, 173.7 ppm.

MS (ESI) *m/z*: 300 $(M + H)^+$, 322 $(M + Na)^+$.

Elemental analysis Calculated: C, 68.21; H, 5.72; N, 4.68%.

Found: C, 68.28; H, 5.69; N, 4.63%.

4-ethyl-4-hydroxy -*1H pyrano*[3, 4-*c*] pyridine-3, 8(*4H, 7H*)-dione (3)



To a well stirred solution of compound **35** (0.1 g, 0.33 mmol) in EtOH (10 mL) was added 10% Pd $(OH)_2$ (0.0046 g, 0.03 mmol) and the reaction mixture was allowed to stir at 50 ^oC under hydrogen atmosphere. The progress of reaction was monitored by TLC (5 h), after the disappearance of starting material, the reaction mixture was filtered on celite and residue was washed with EtOH (3 x 10 mL). The solvent was removed *in vacuo* and resultant crude compound was purified by flash column chromatography (SiO_2) using the ethyl acetate-petroleum ether (3:2) as eluent furnished the desired DE-ring fragment **3** as a white solid (0.047 g, 68% yield).

MF: $C_{10}H_{11}NO_4$, **MW**: 209

M.P.: 225 ^oC (Lit. 227 ^oC)

IR ($CHCl_3$) ν_{max}: 3273, 1754, 1651, 1255, 837 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 400 MHz) δ: 0.97 (t, *J* = 7.5 Hz, 3H), 1.80 (q, *J* = 7.5 Hz, 2H), 5.14 (d, *J* = 16.1 Hz, 1H), 5.54 (d, *J* = 16.1 Hz, 1H), 6.66 (d, *J* = 6.8 Hz, 1H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.58 ppm (d, *J* = 6.8 Hz, 1H).

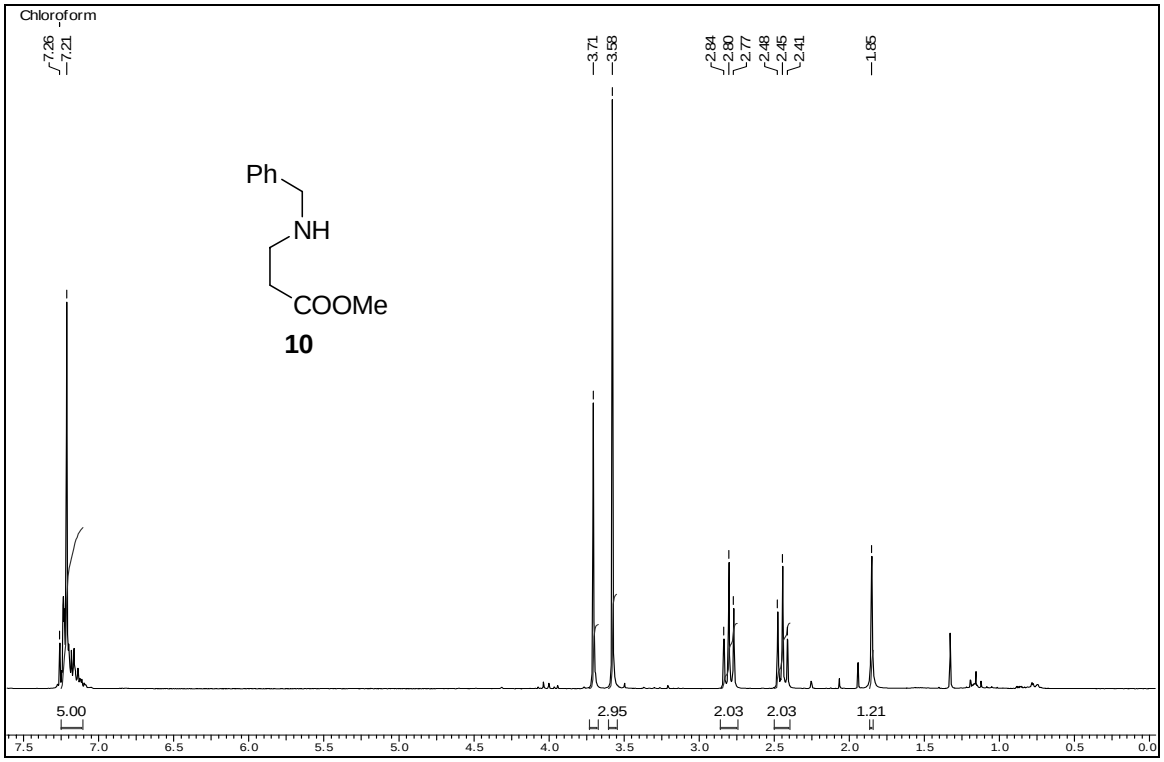
^{13}C NMR ($CDCl_3$ + CCl_4 + DMSO-d_6, 100 MHz) δ: 7.85, 31.7, 65.91, 104.6, 115.3, 134.6, 151.5, 175.0 ppm.

MS (ESI) *m/z*: 210 $(M + 1)^+$, 232 $(M + Na)^+$.

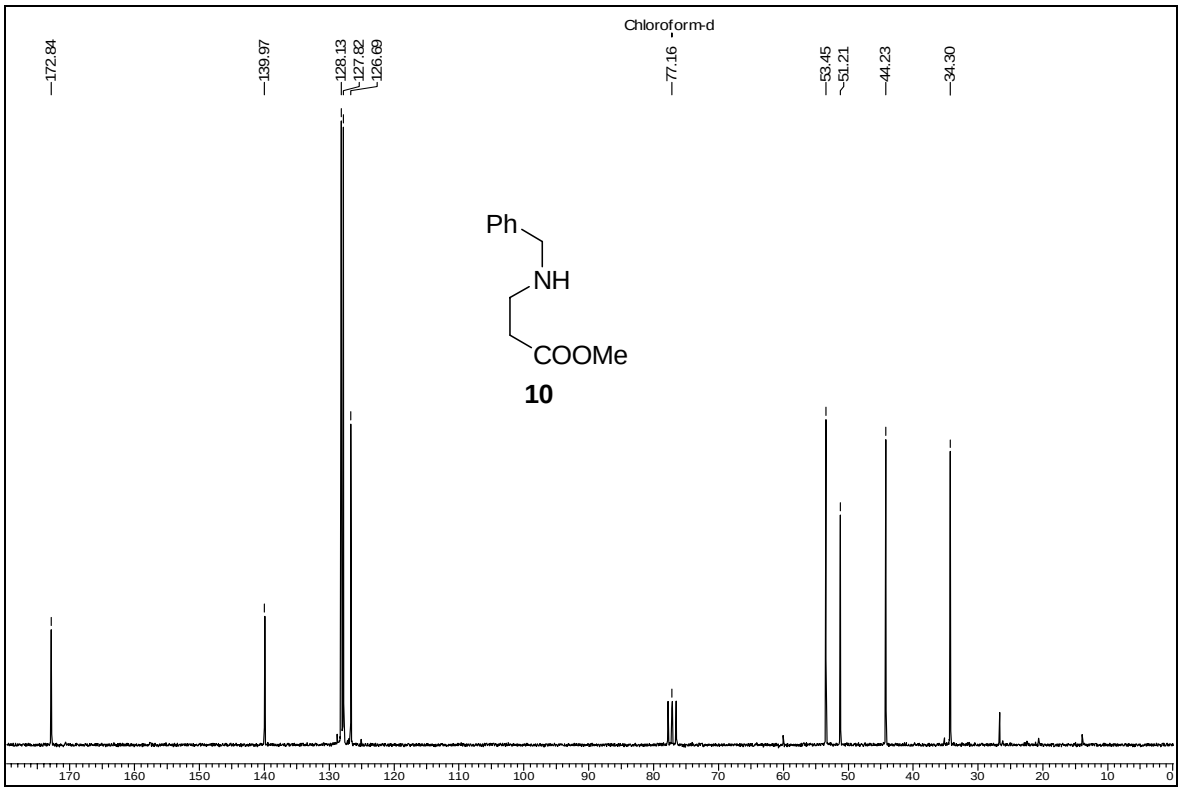
Elemental analysis Calculated: C, 57.41; H, 5.30; N, 6.70%.

Found: C, 57.39; H, 5.34; N, 6.73%.

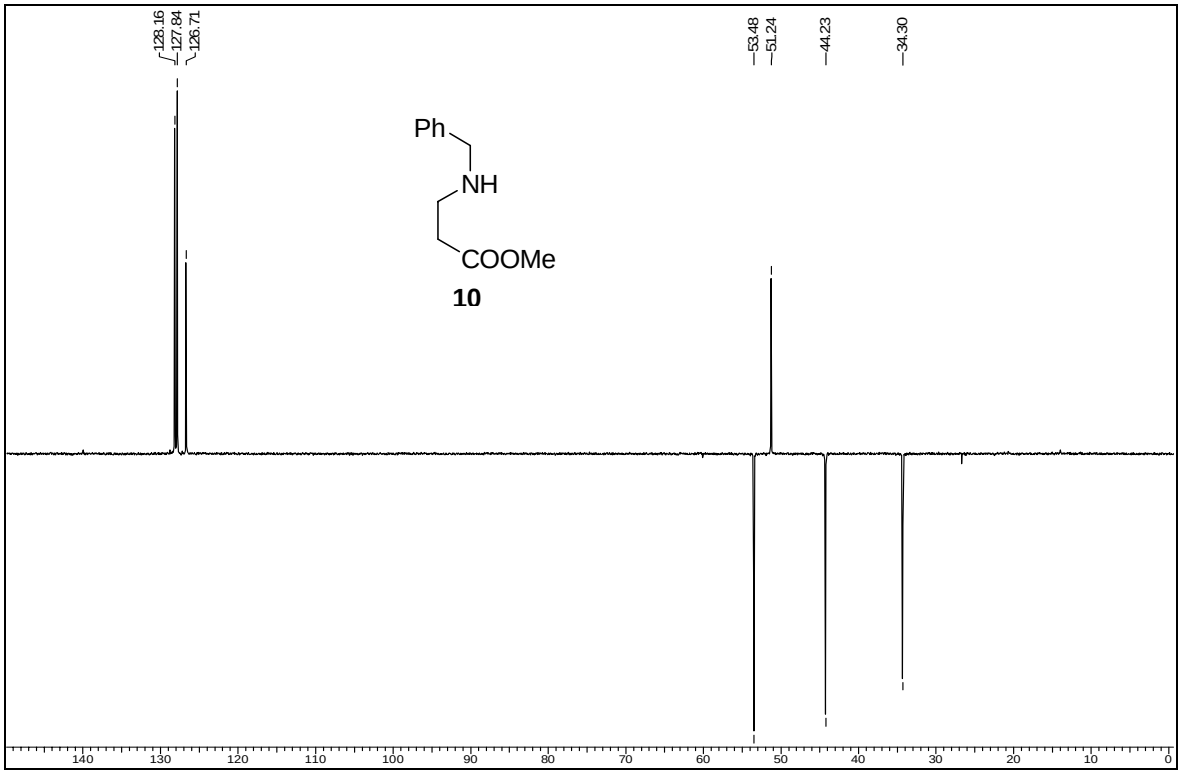
2.3.6 Spectra:



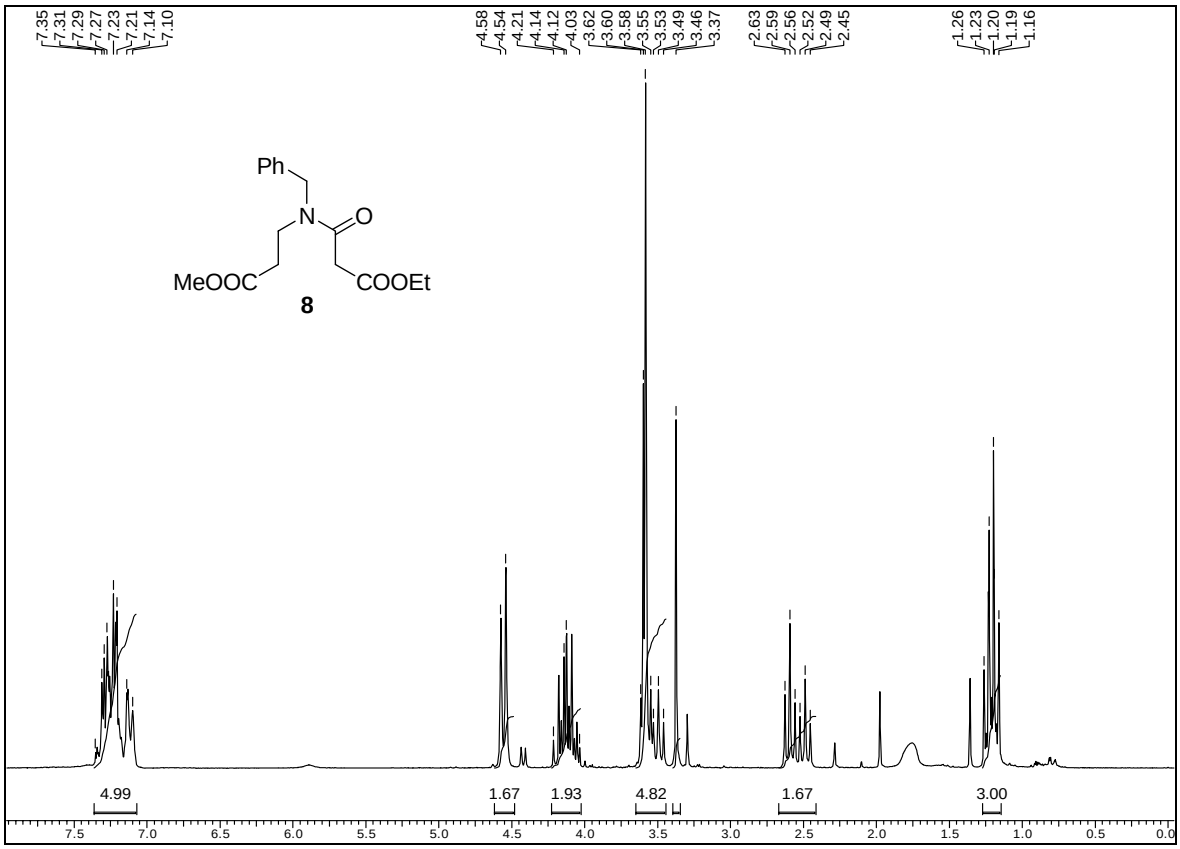
^{1}H NMR spectrum of compound 10 ($CDCl_3$ + CCl_4, 200 MHz)



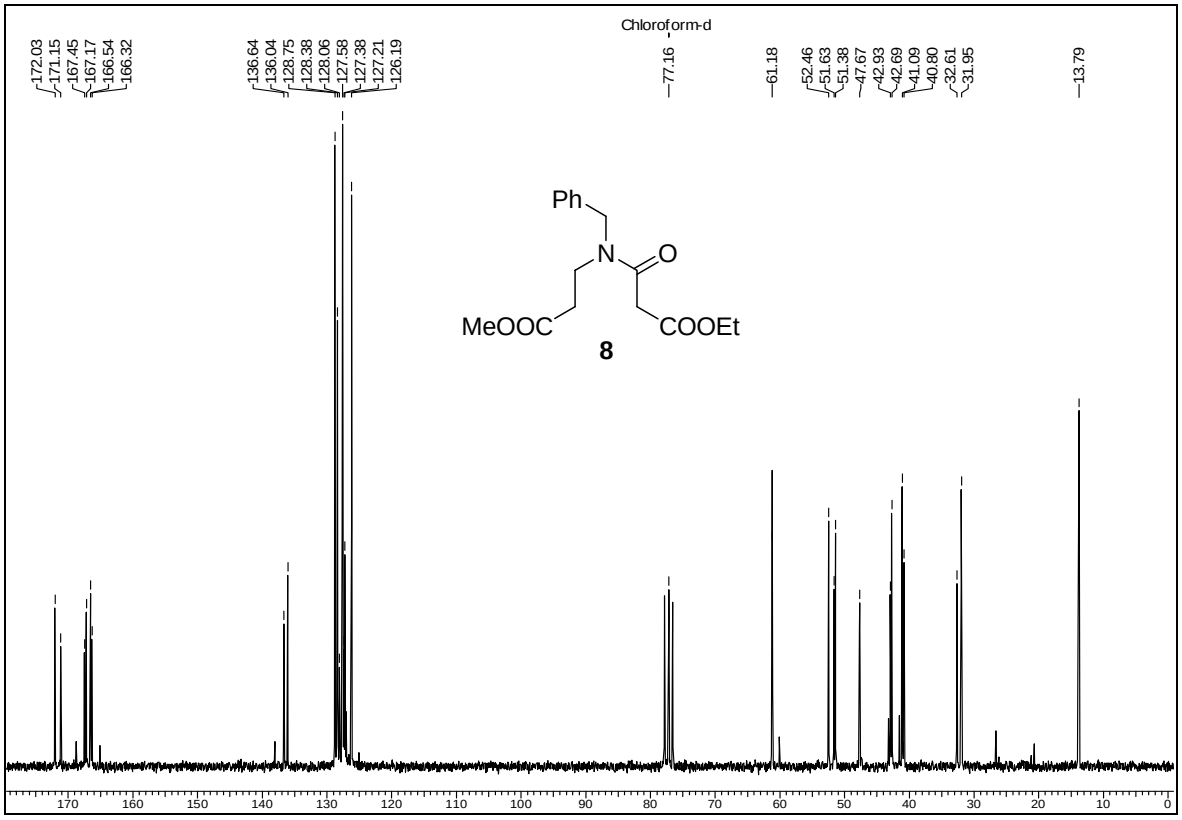
^{13}C NMR spectrum of compound 10 ($CDCl_3$ + CCl_4, 50 MHz)



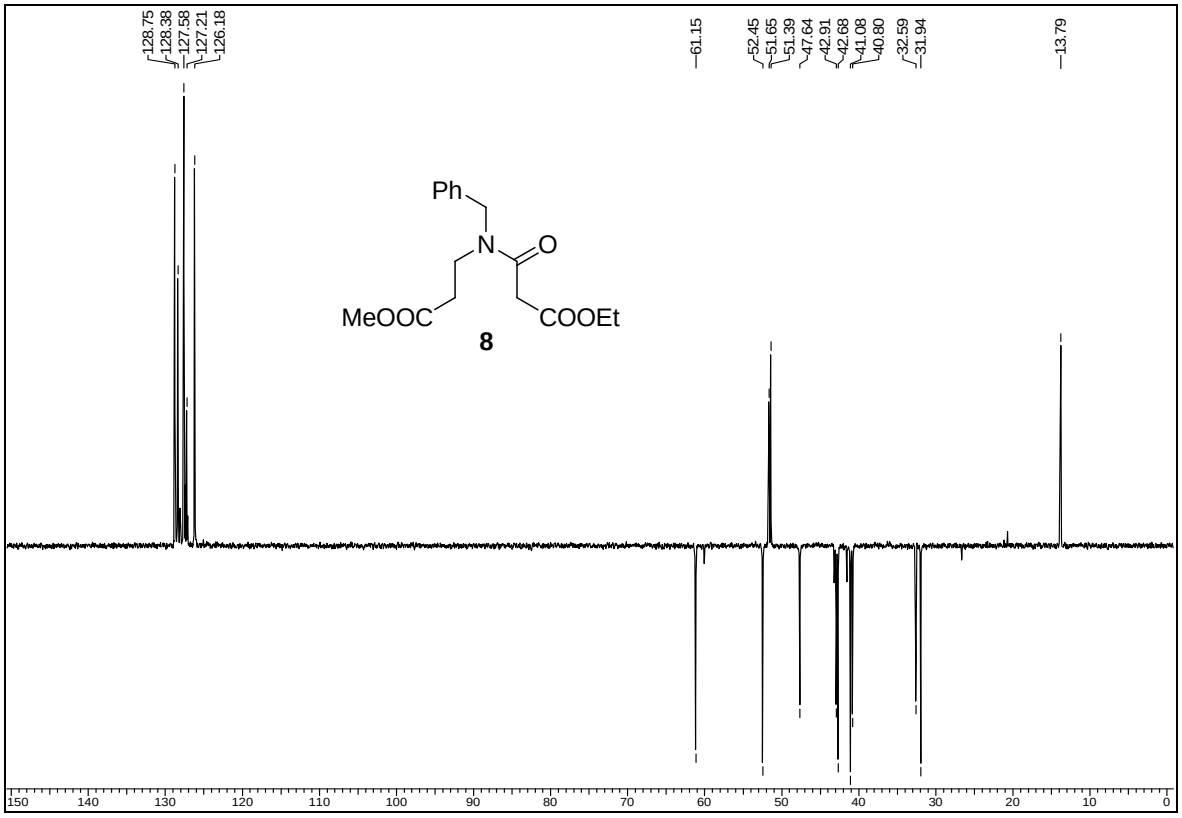
DEPT spectrum of compound 10 ($CDCl_3$ + CCl_4, 50 MHz)



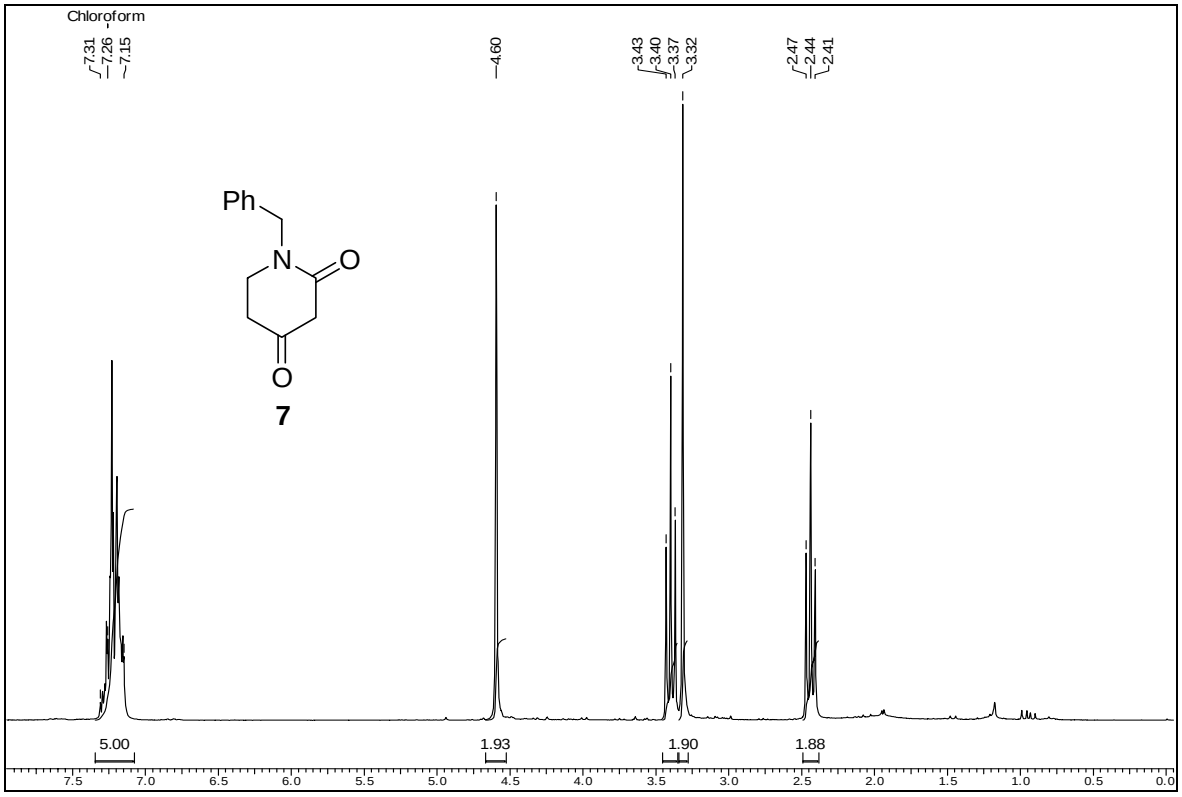
^{1}H NMR spectrum of compound 8 ($CDCl_3$ + CCl_4, 200 MHz)



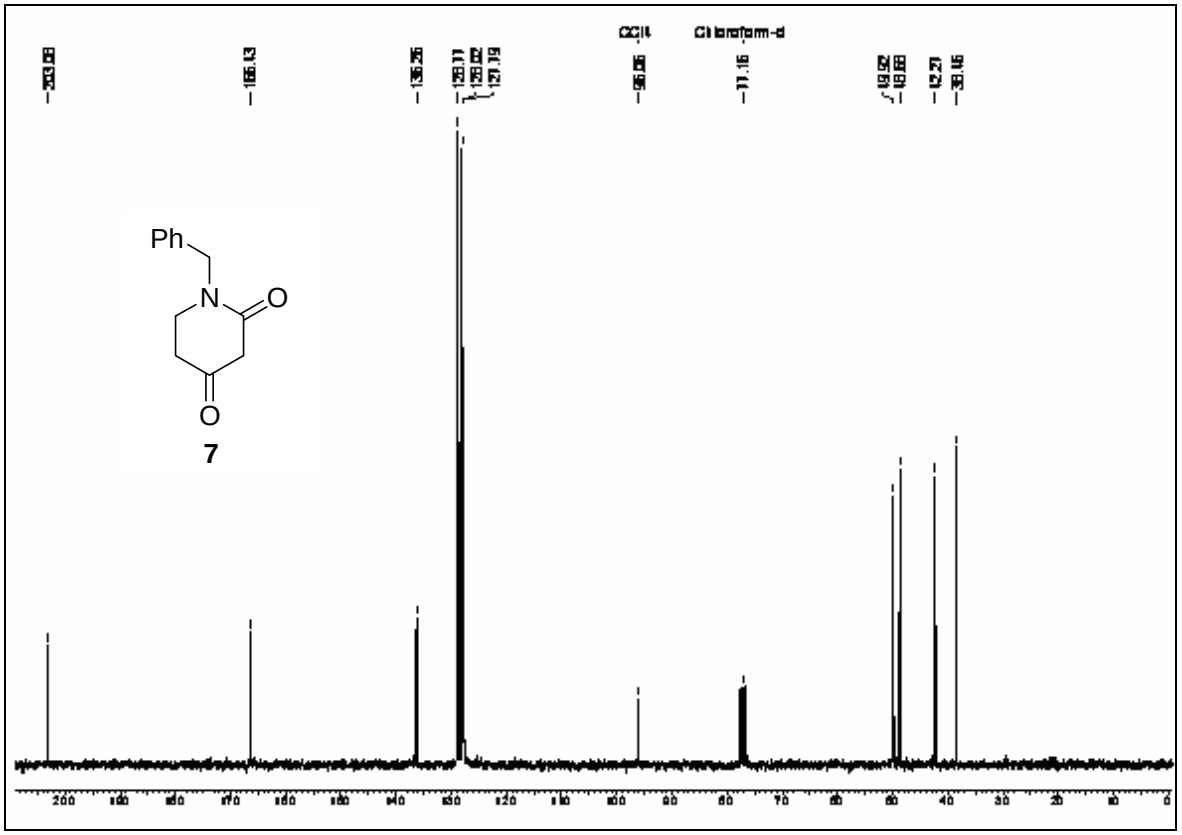
^{13}C NMR spectrum of compound 8 ($CDCl_3$ + CCl_4, 50 MHz)



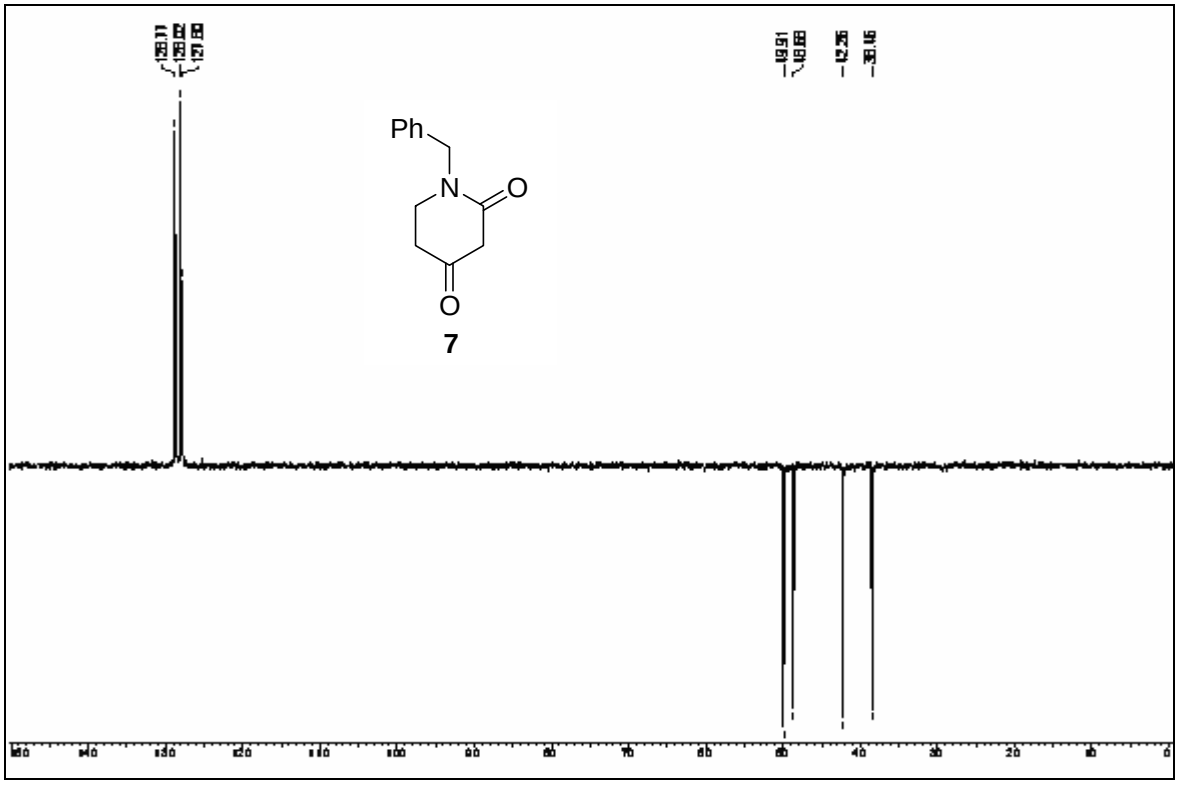
DEPT spectrum of compound 8 ($CDCl_3$ + CCl_4, 50 MHz)



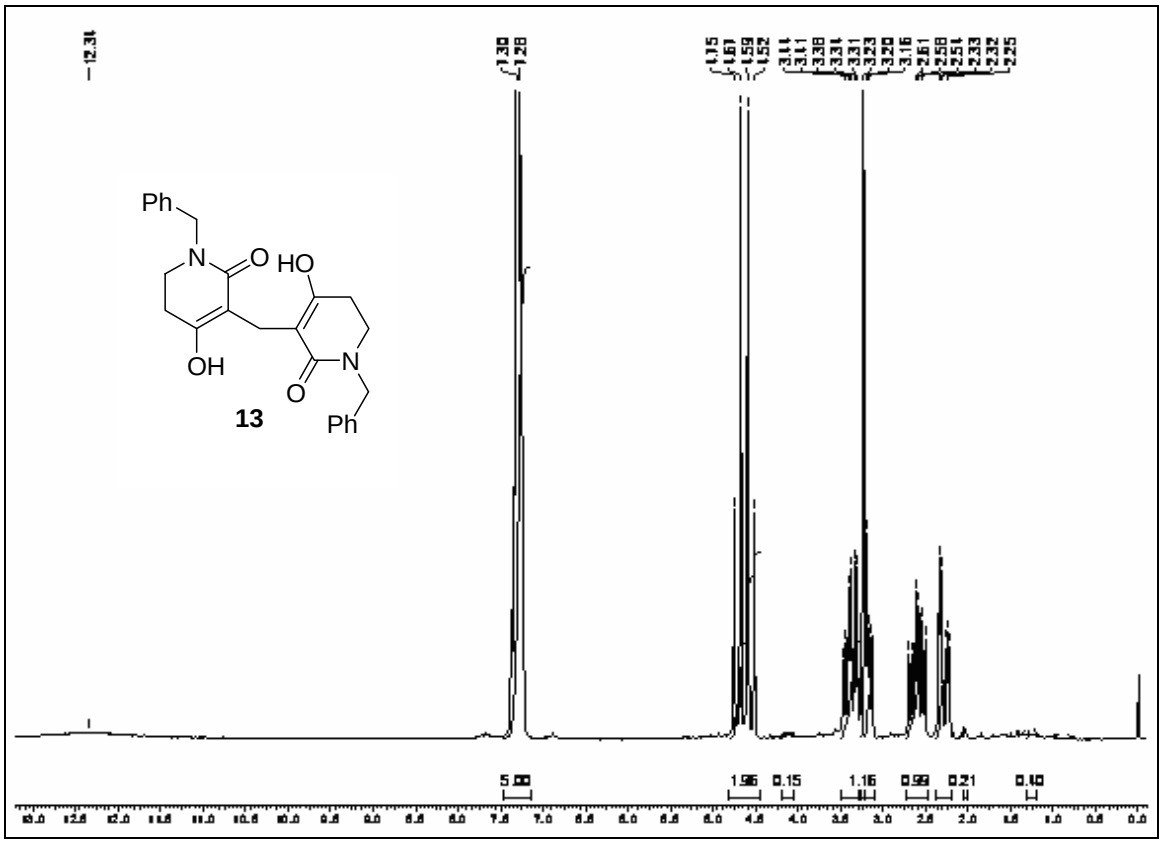
^{1}H NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 200 MHz)



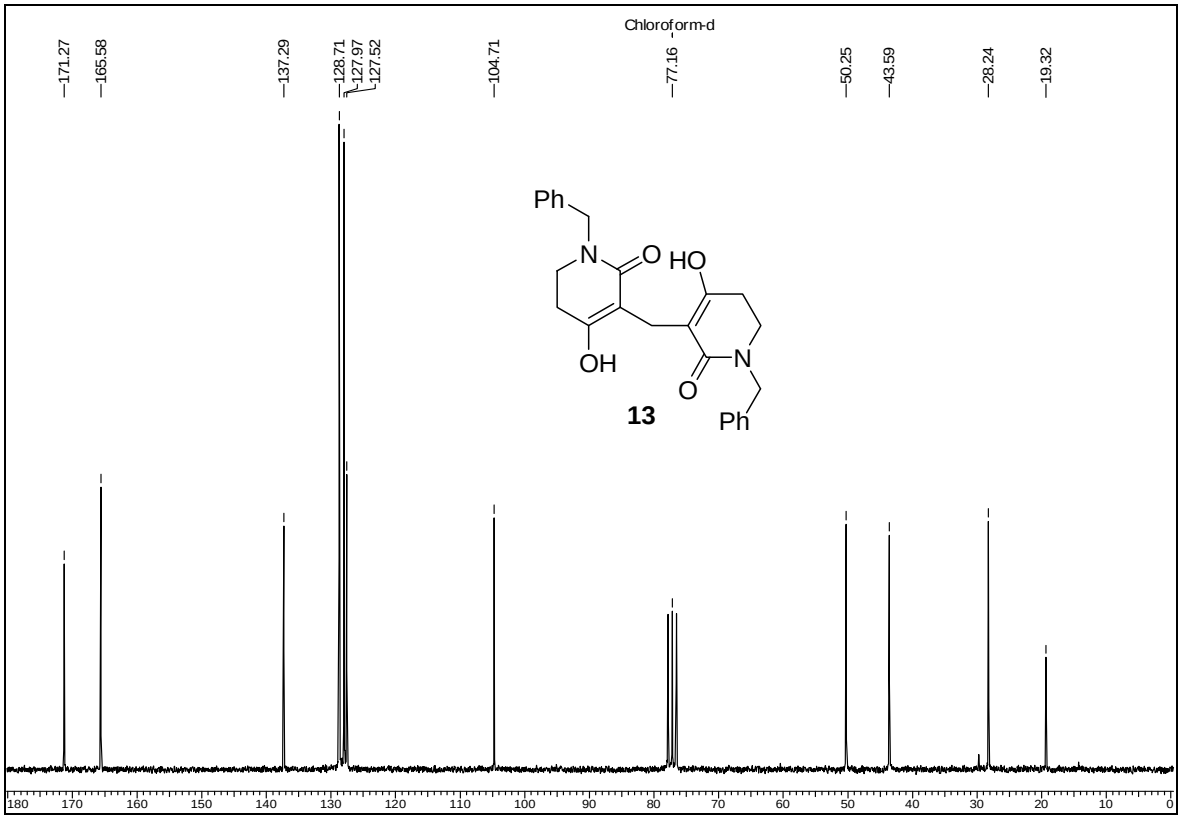
^{13}C NMR spectrum of compound 7 ($CDCl_3$ + CCl_4, 50 MHz)



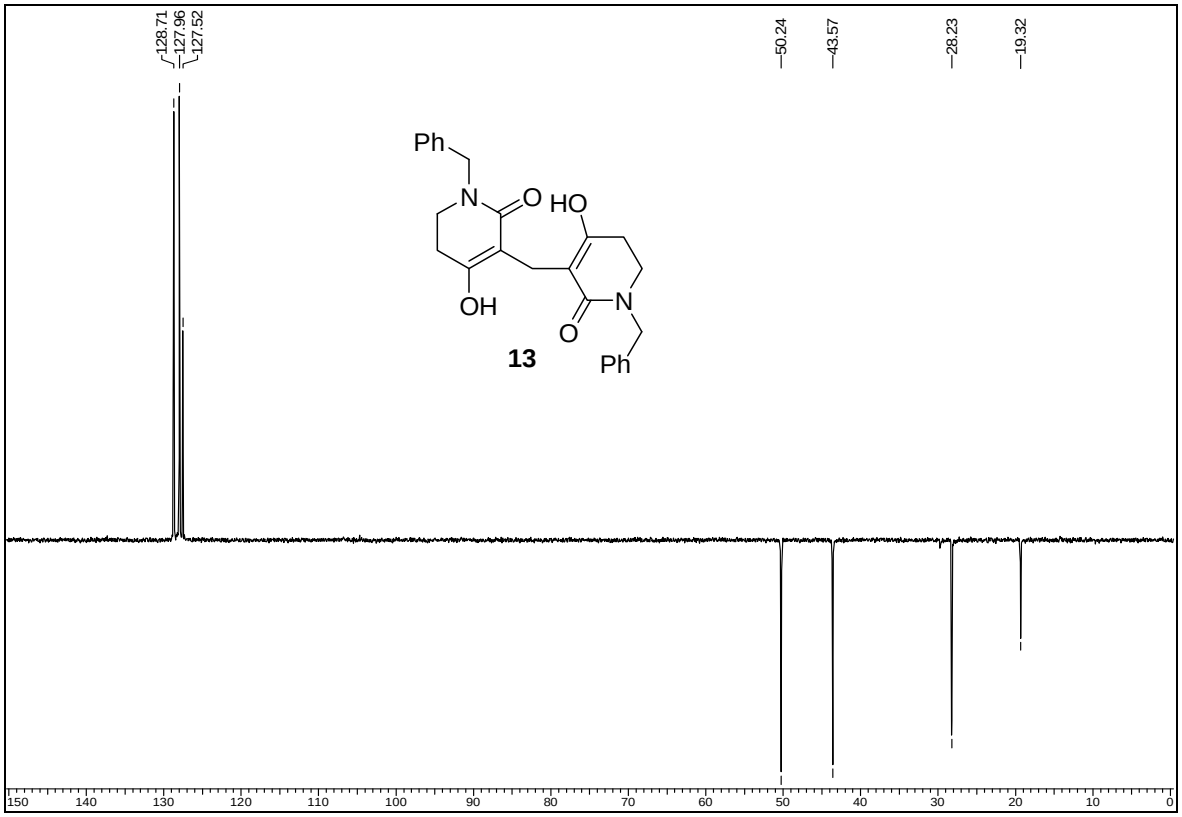
DEPT spectrum of compound 7 ($CDCl_3$ + CCl_4, 50 MHz)



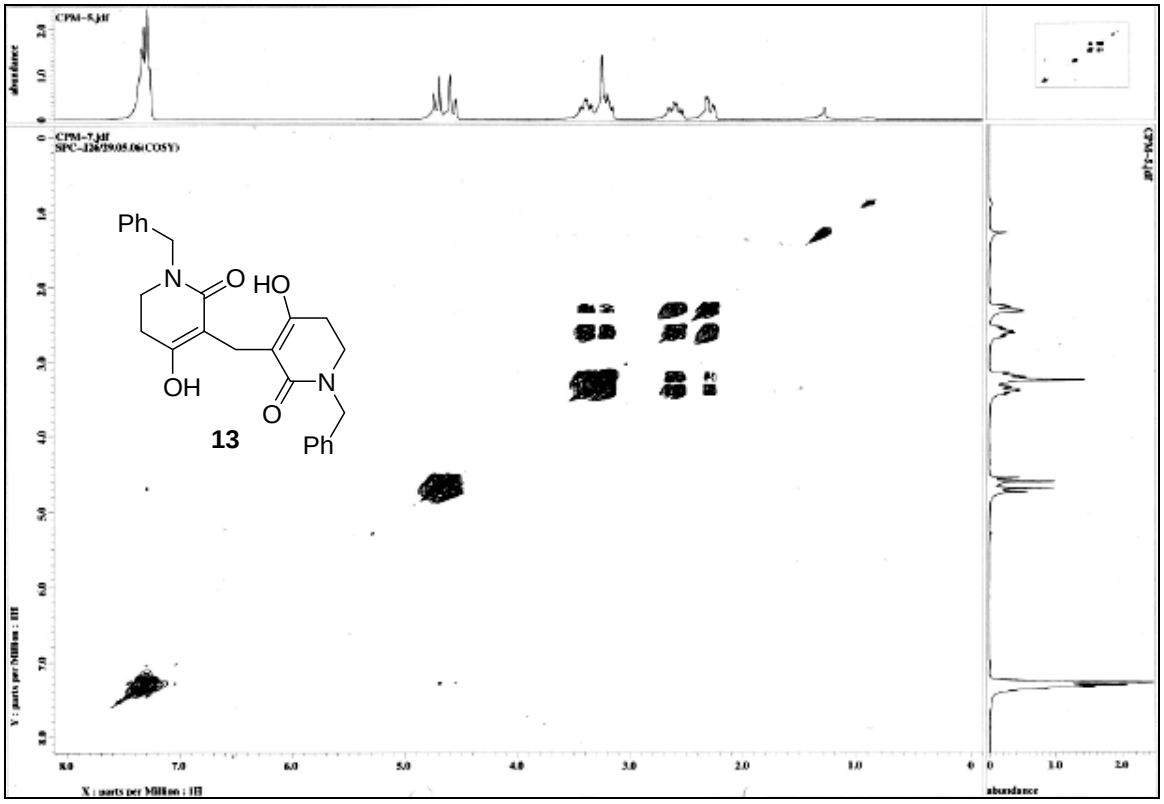
^{1}H NMR spectrum of compound 13 ($CDCl_3$ + CCl_4, 200 MHz)



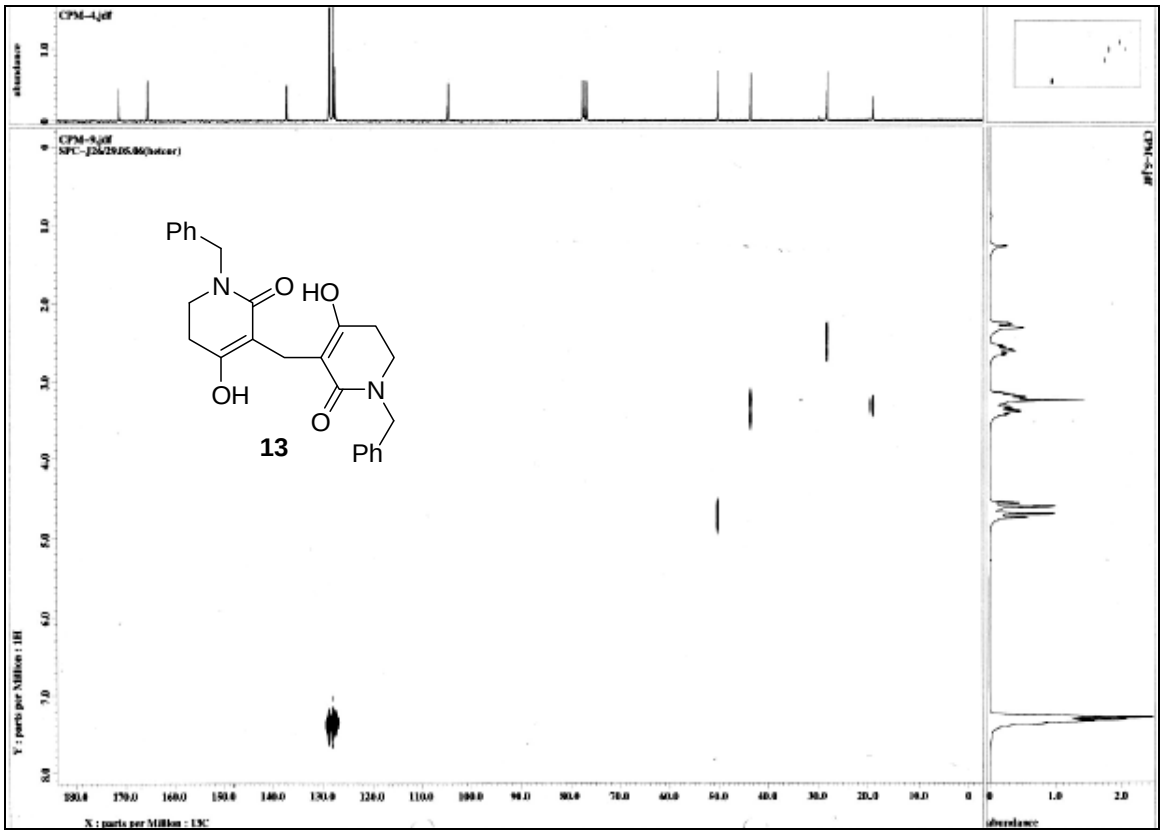
^{13}C NMR spectrum of compound 13 ($CDCl_3$ + CCl_4, 50 MHz)



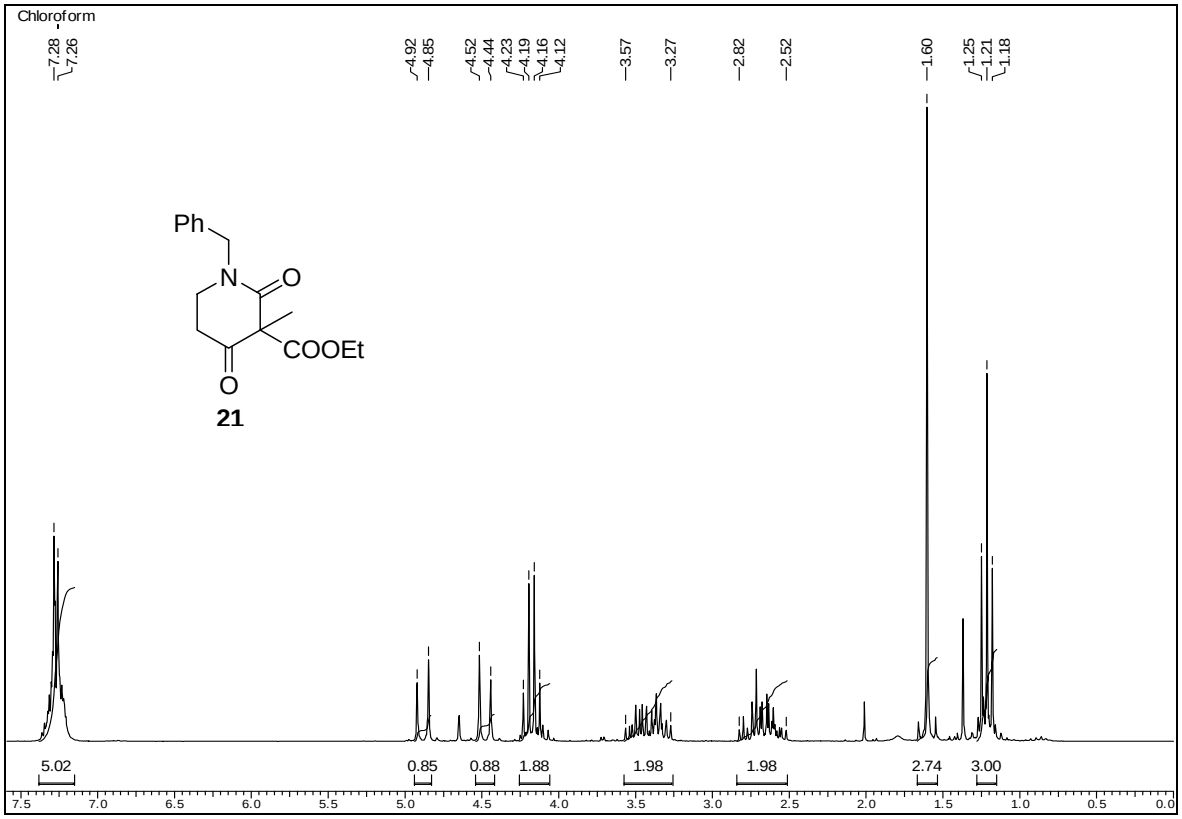
DEPT spectrum of compound 13 ($CDCl_3$ + CCl_4, 50 MHz)



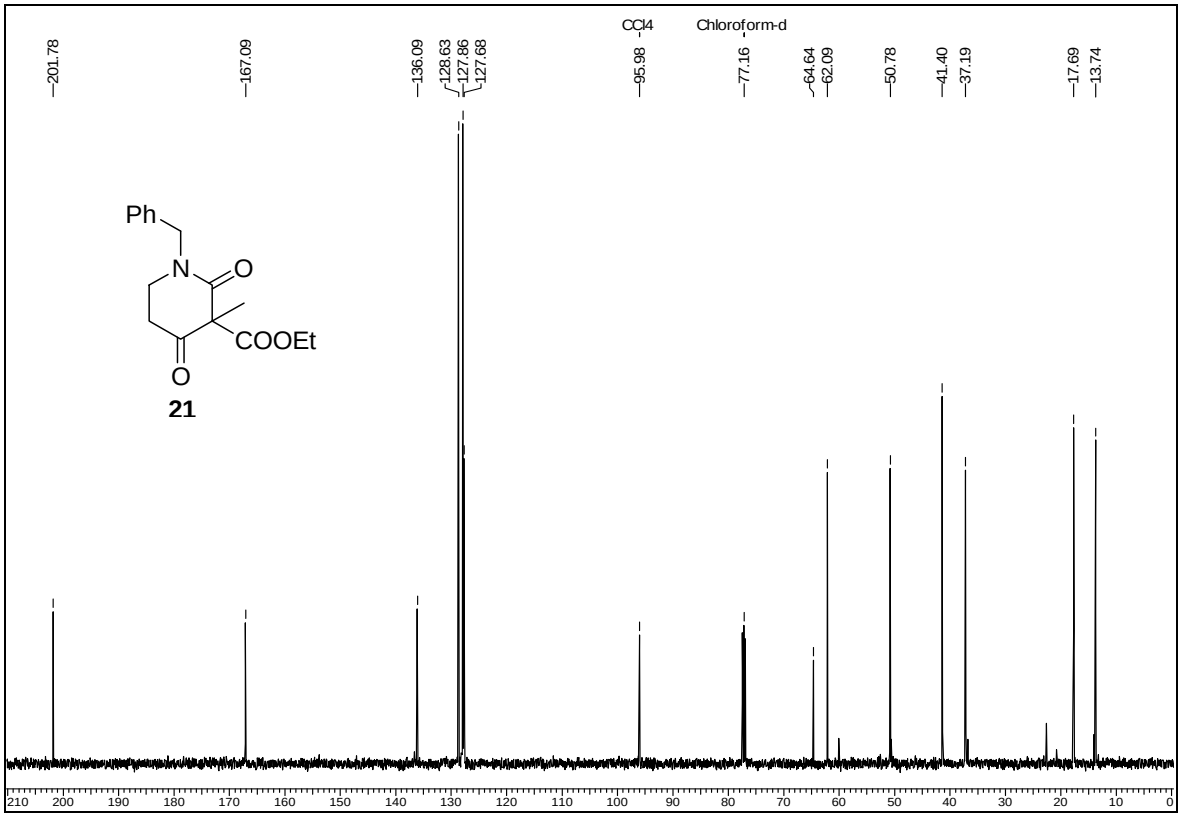
COSY spectrum of compound 13 ($CDCl_3$ + CCl_4, 200 MHz)



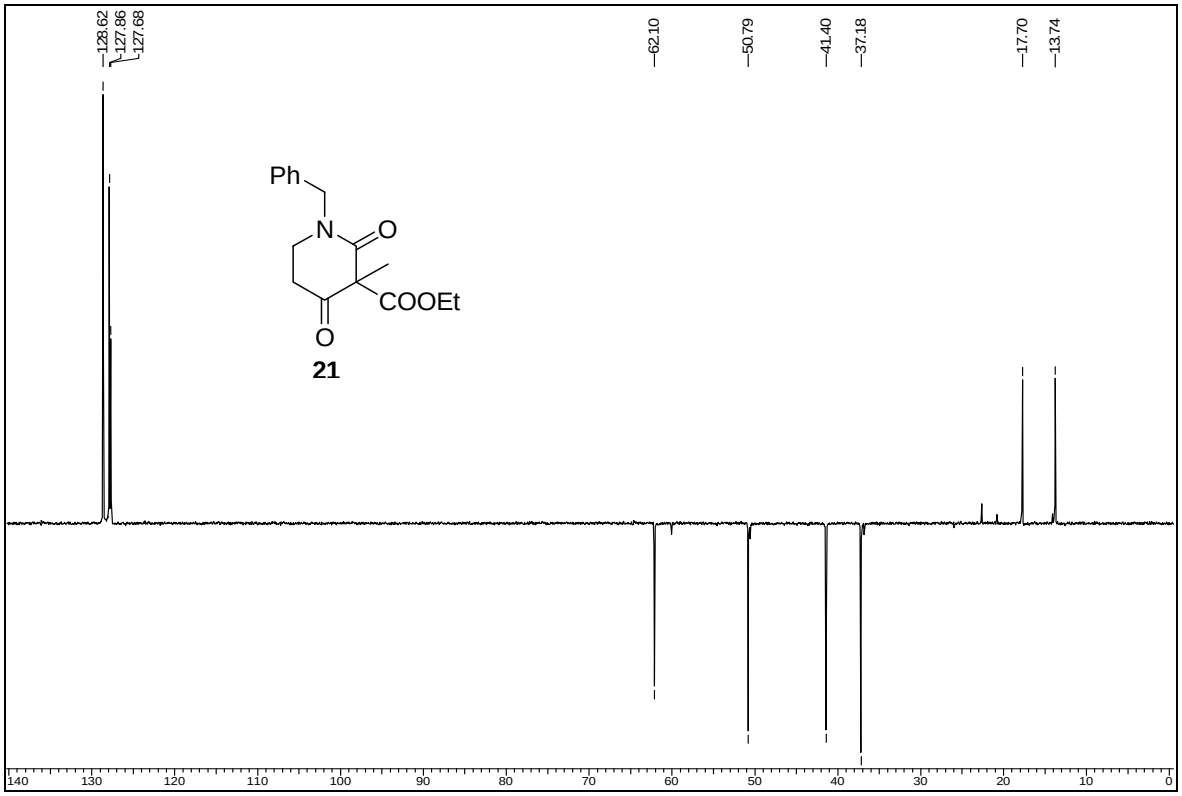
HETCOR spectrum of compound 13 ($CDCl_3$ + CCl_4, 200 MHz)



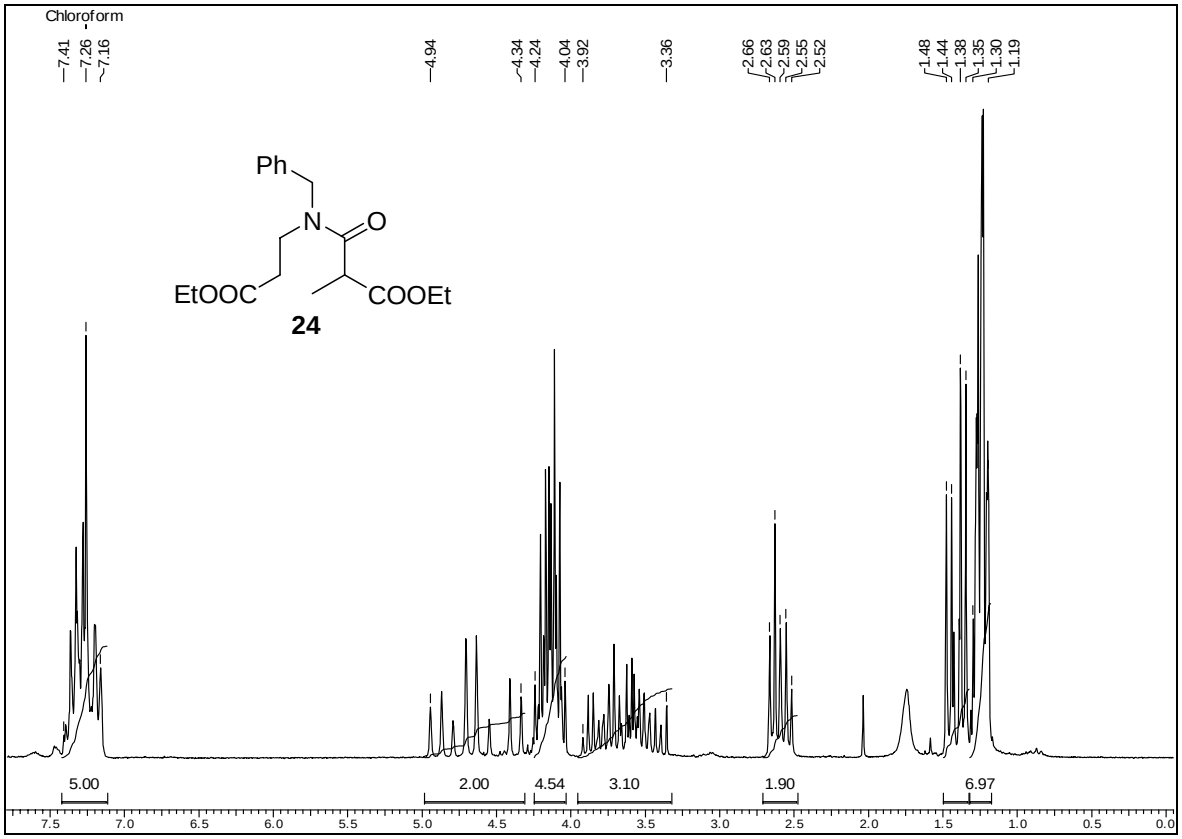
^{1}H NMR spectrum of compound 21 ($CDCl_3$ + CCl_4, 200 MHz)



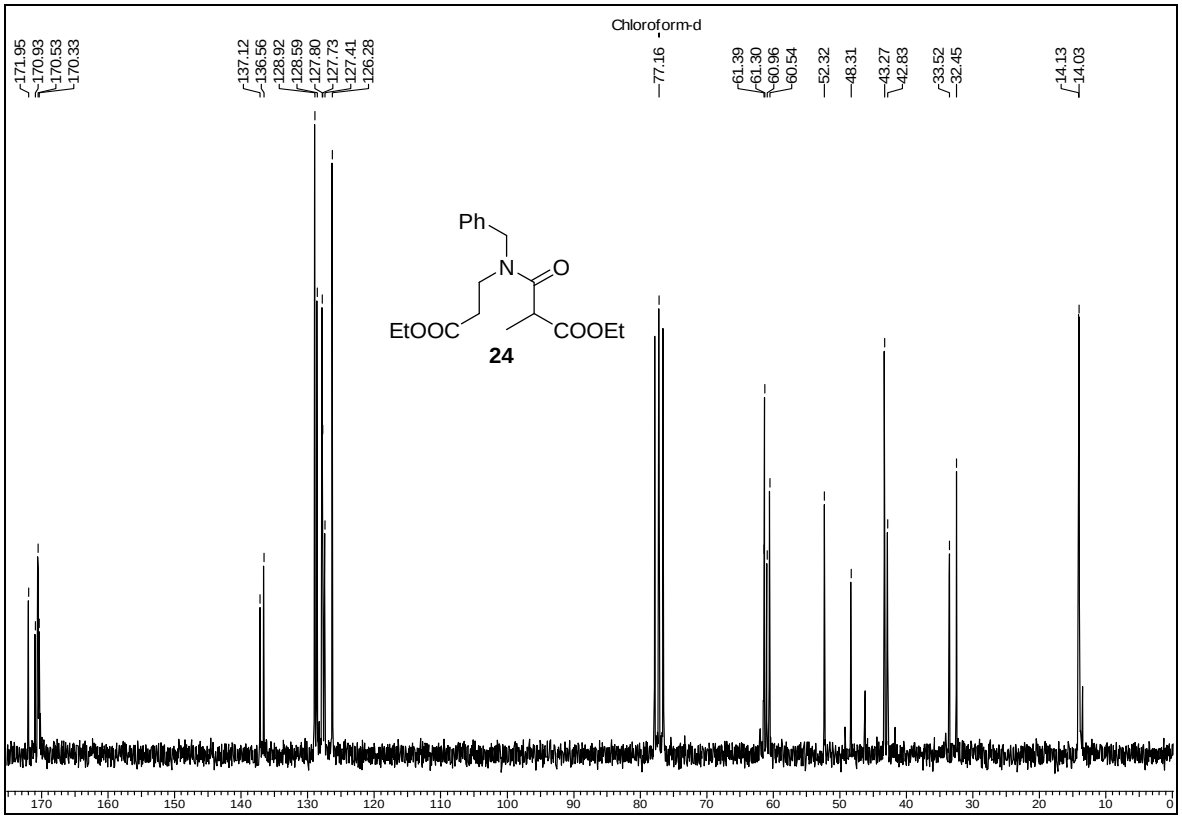
^{13}C NMR spectrum of compound 21 ($CDCl_3$ + CCl_4, 100 MHz)



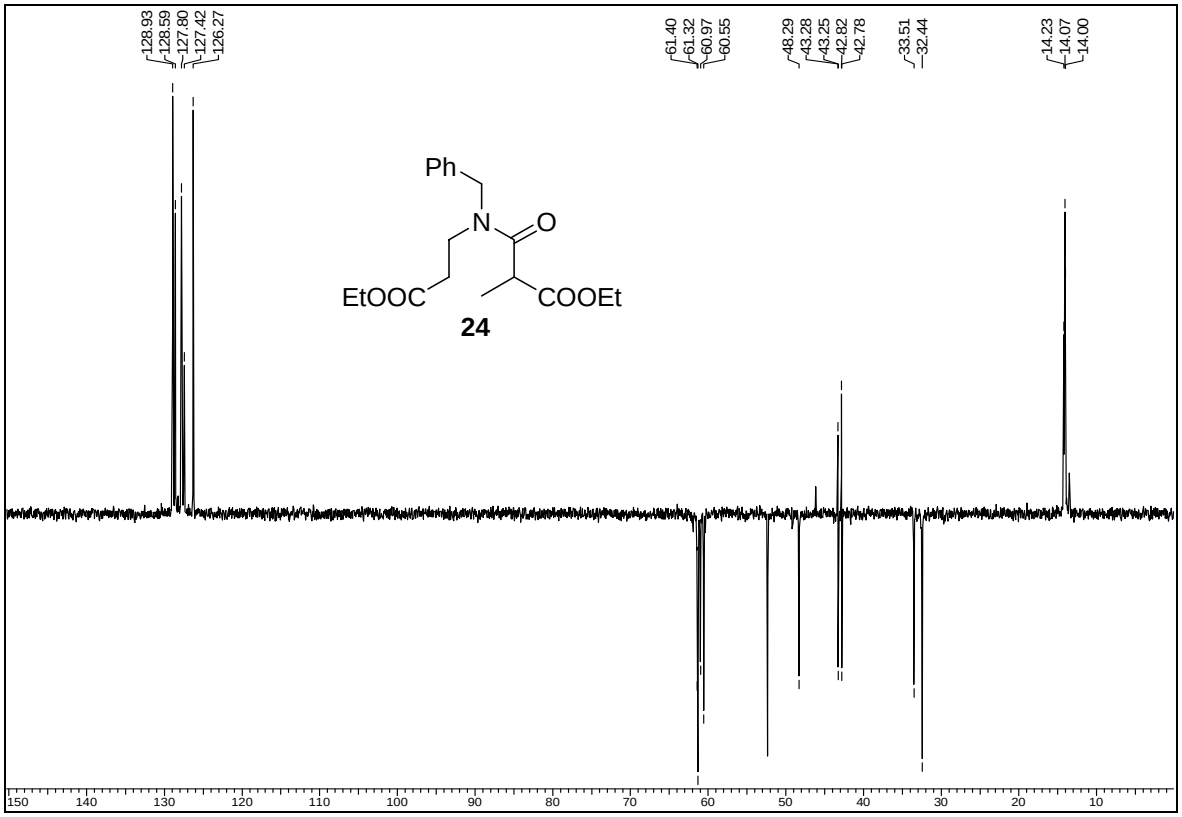
DEPT spectrum of compound 21 ($CDCl_3$ + CCl_4, 100 MHz)



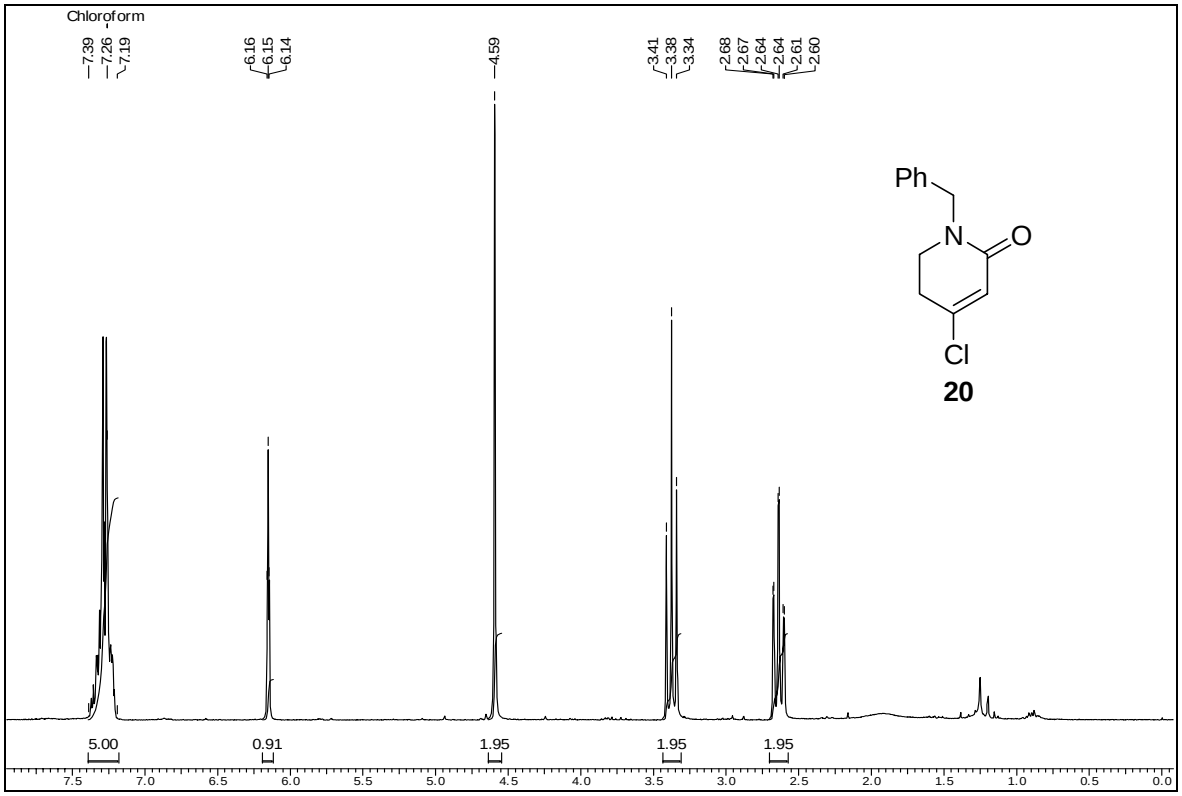
^{1}H NMR spectrum of compound 24 ($CDCl_3$ + CCl_4, 200 MHz)



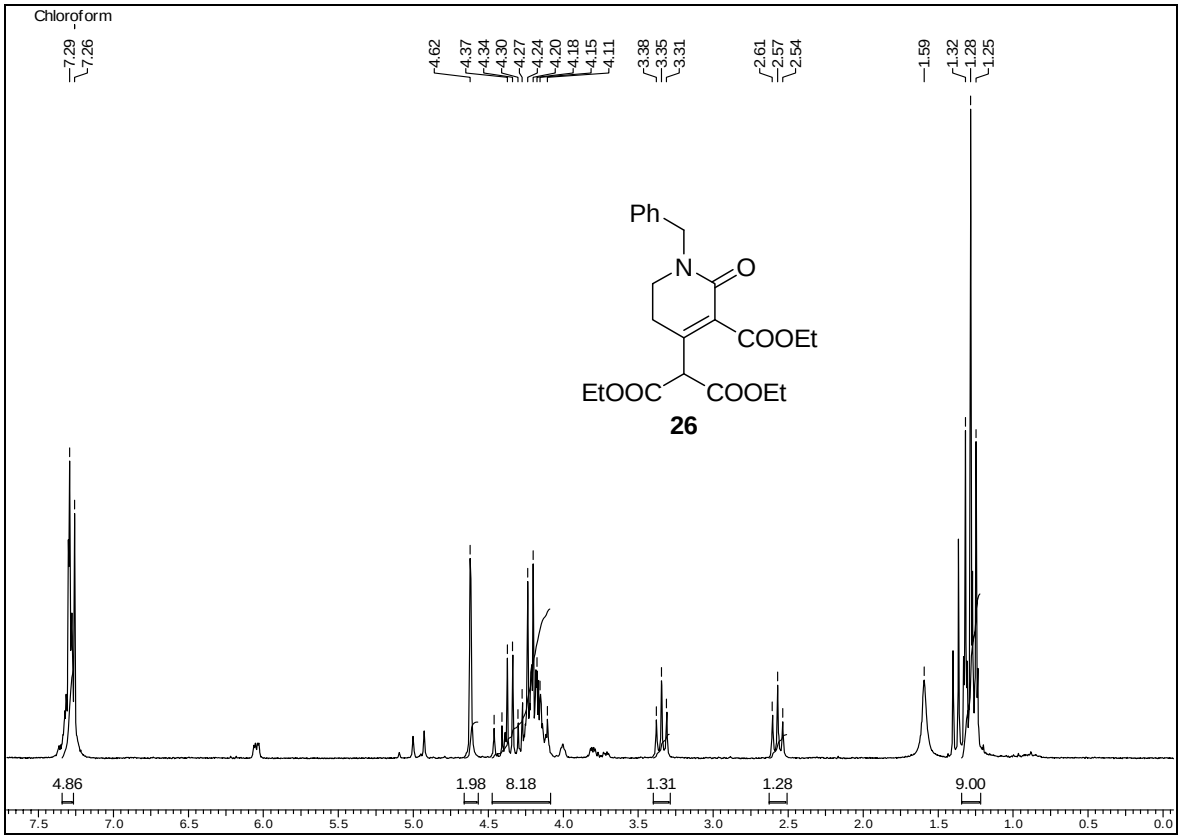
^{13}C NMR spectrum of compound 24 ($CDCl_3$, 50 MHz)



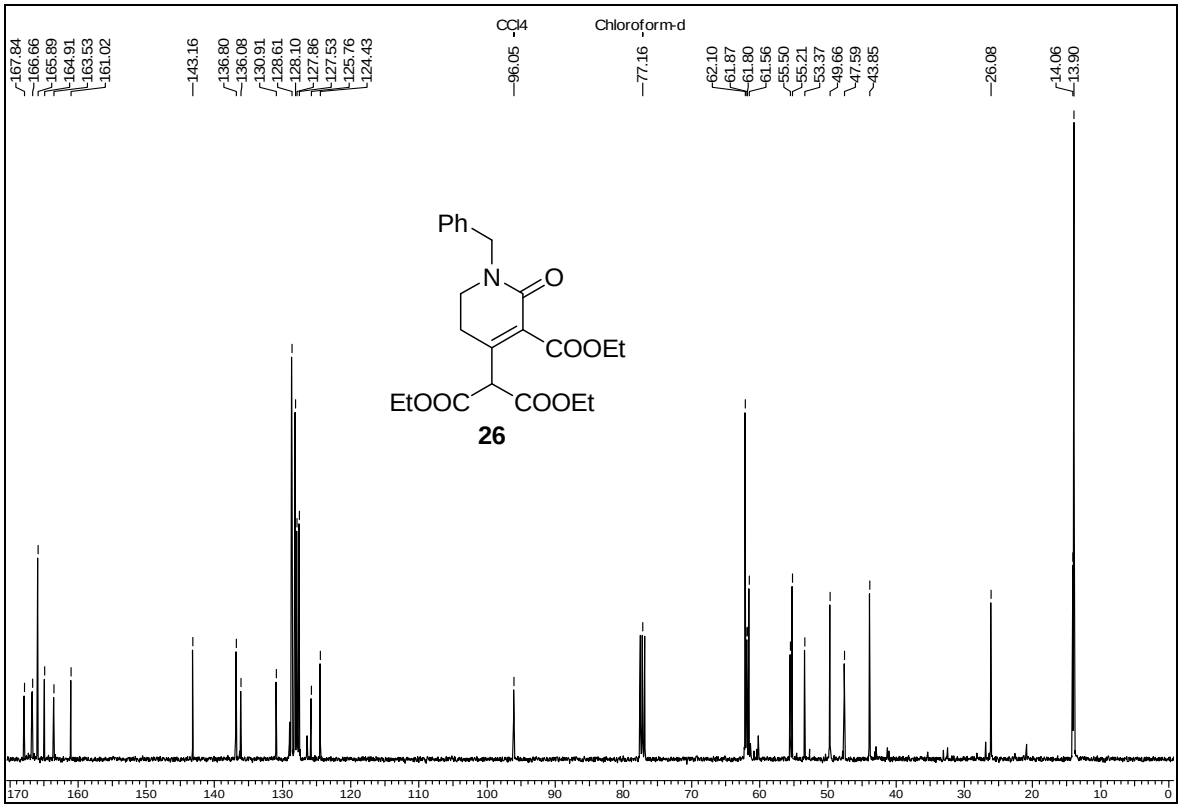
DEPT spectrum of compound 24 ($CDCl_3$, 50 MHz)



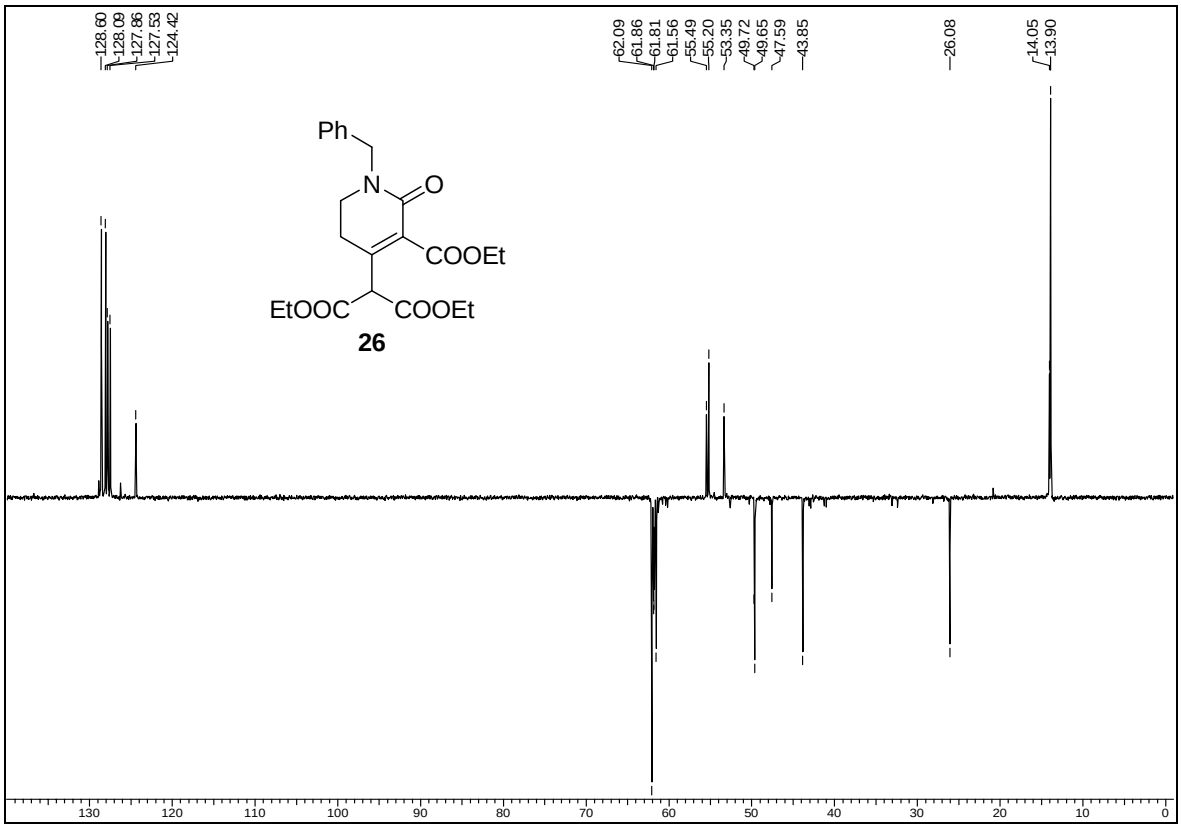
^{1}H NMR spectrum of compound 20 ($CDCl_3$ + CCl_4, 200 MHz)



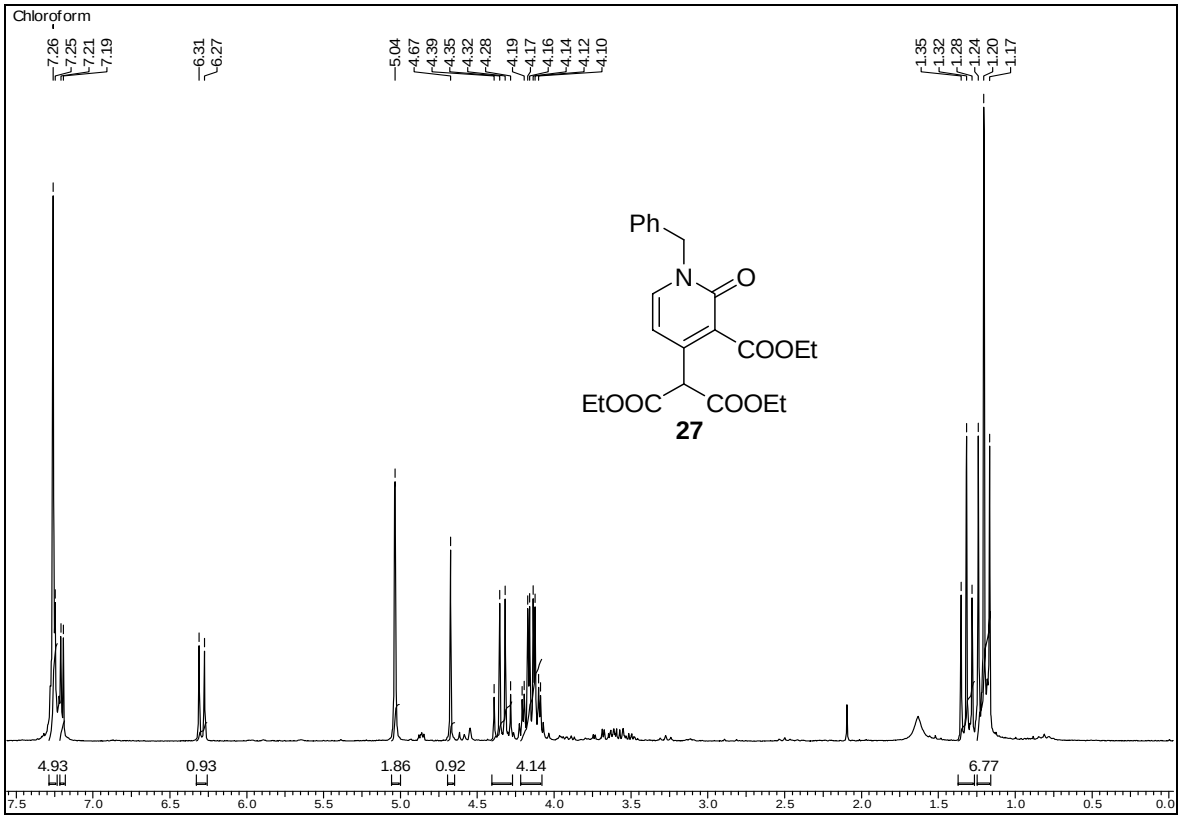
^{1}H NMR spectrum of compound 26 ($CDCl_3$ + CCl_4, 200 MHz)



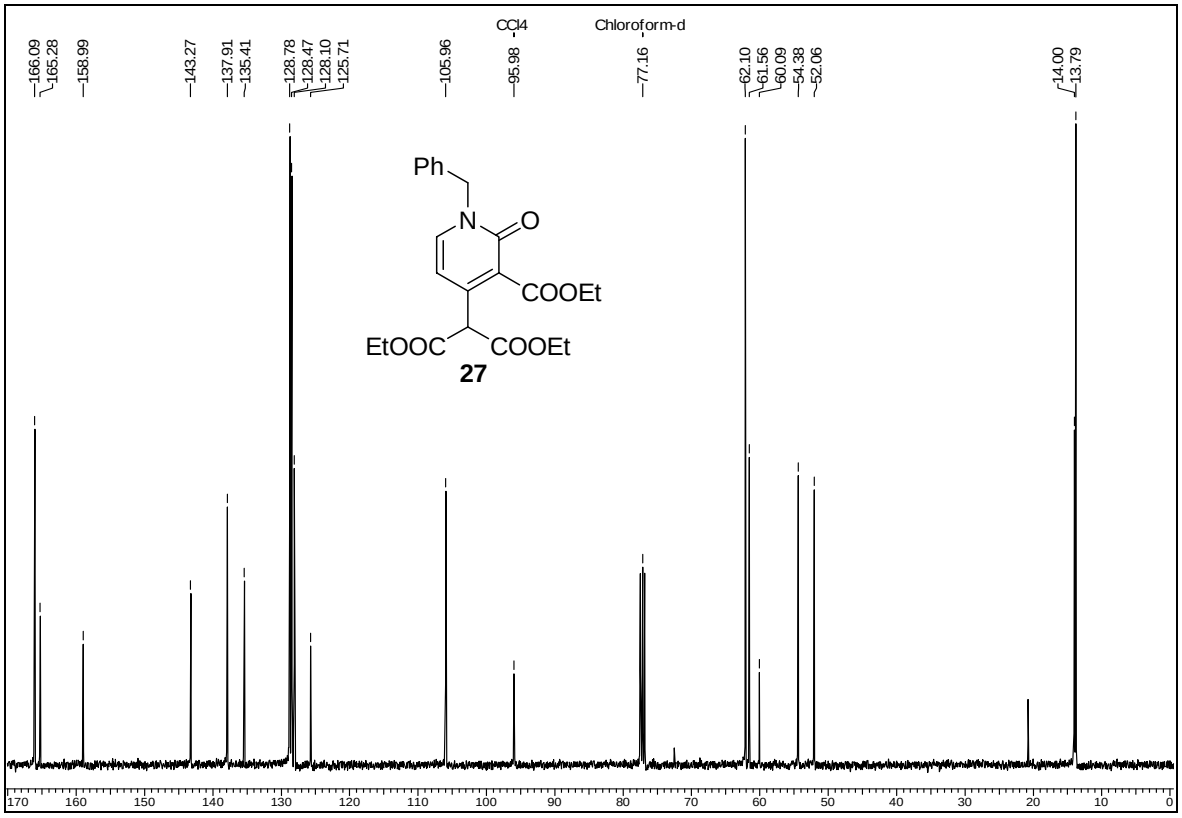
^{13}C NMR spectrum of compound 26 ($CDCl_3$ + CCl_4, 100 MHz)



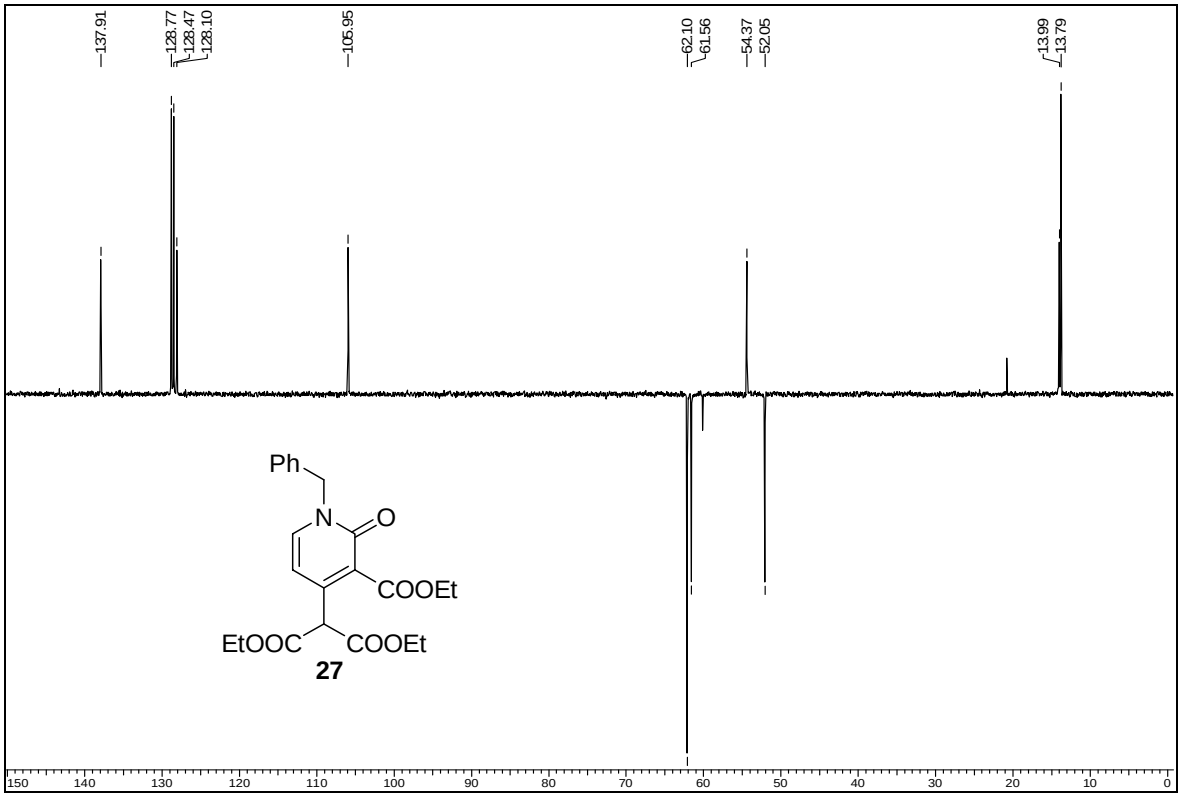
DEPT spectrum of compound 26 ($CDCl_3$ + CCl_4, 100 MHz)



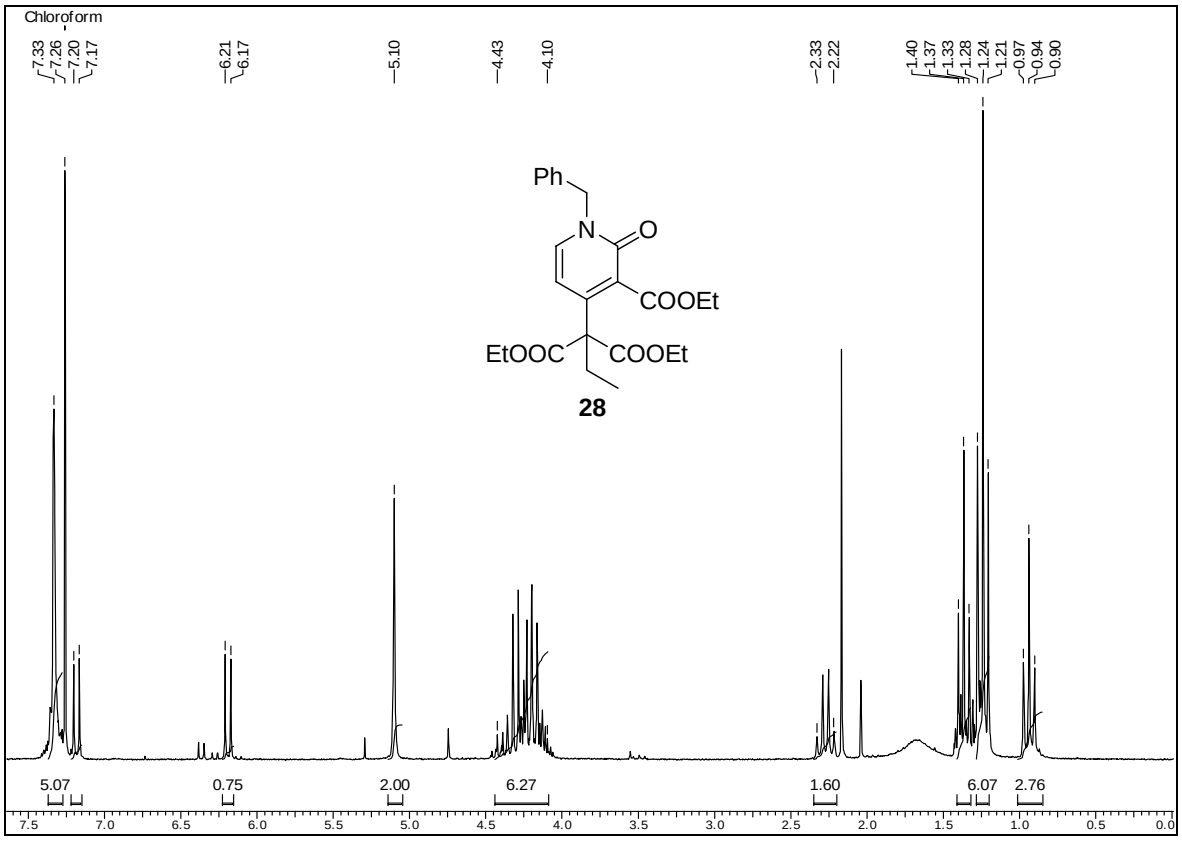
^{1}H NMR spectrum of compound 27 ($CDCl_3$ + CCl_4, 200 MHz)



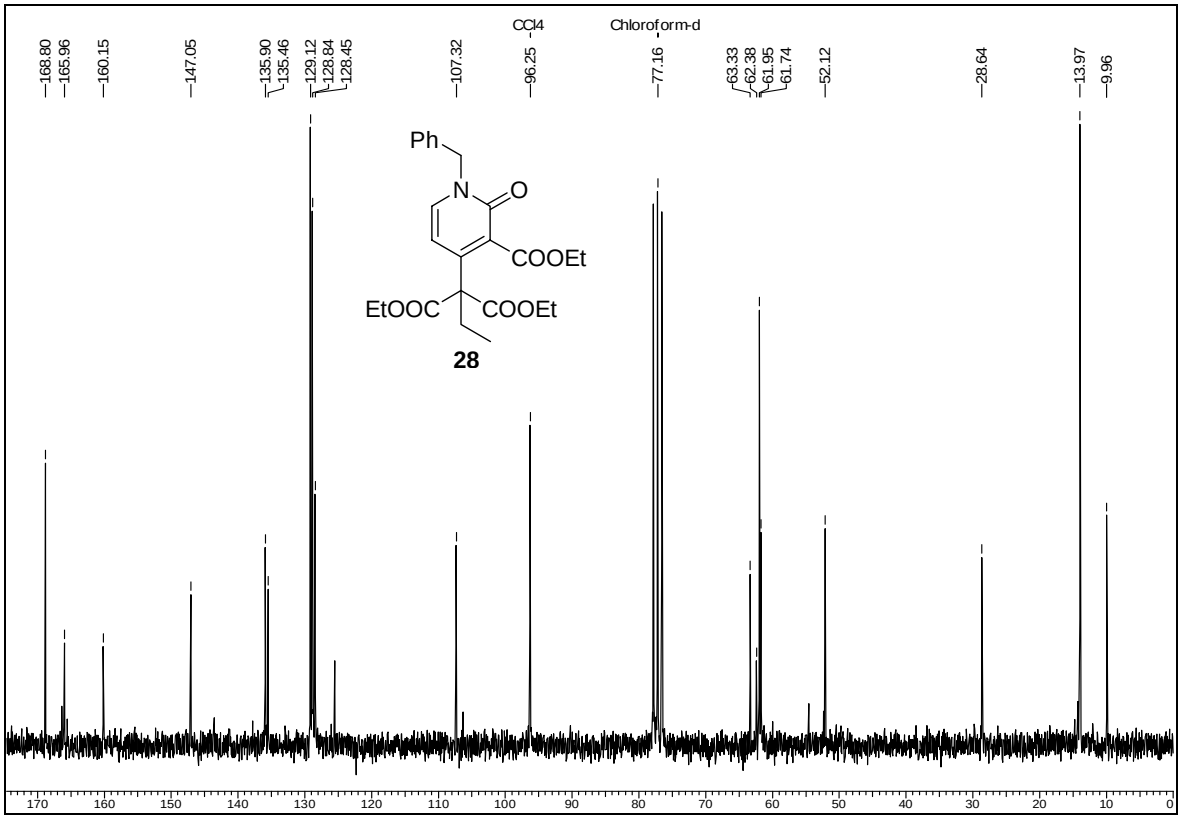
^{13}C NMR spectrum of compound 27 ($CDCl_3$ + CCl_4, 100 MHz)



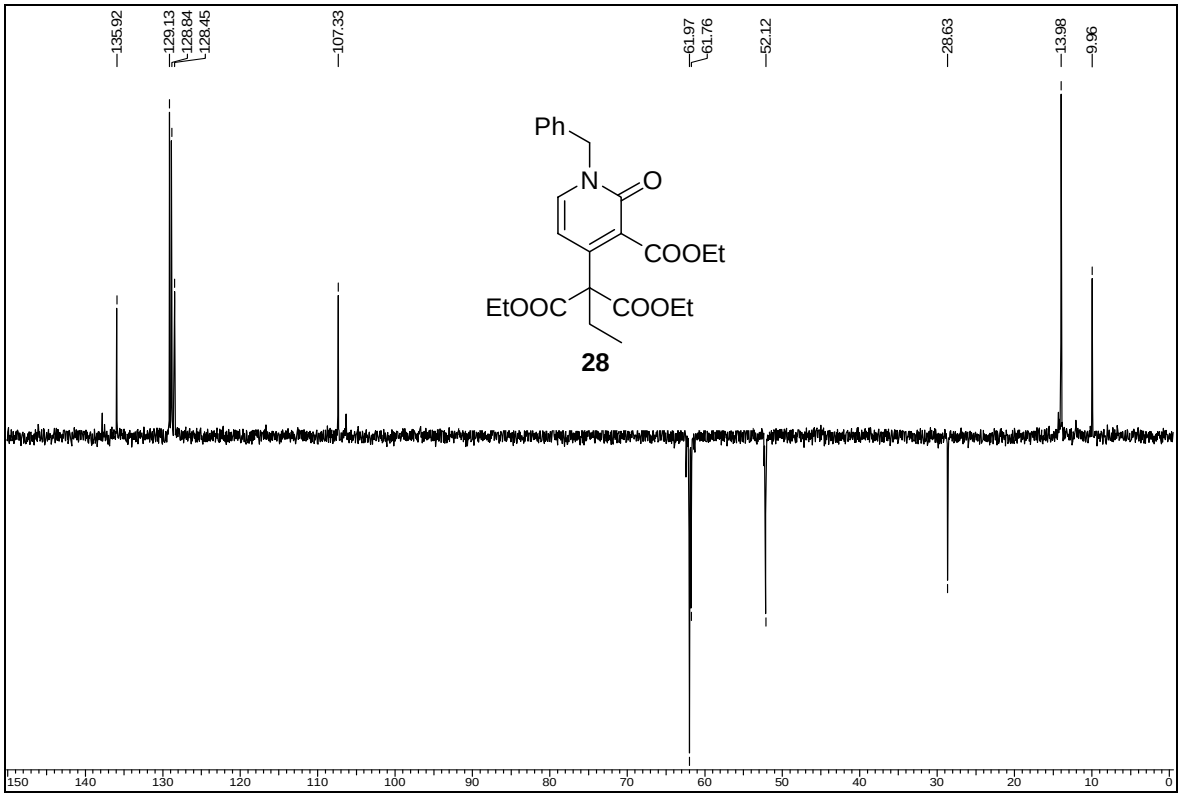
DEPT spectrum of compound 27 ($CDCl_3$ + CCl_4, 100 MHz)



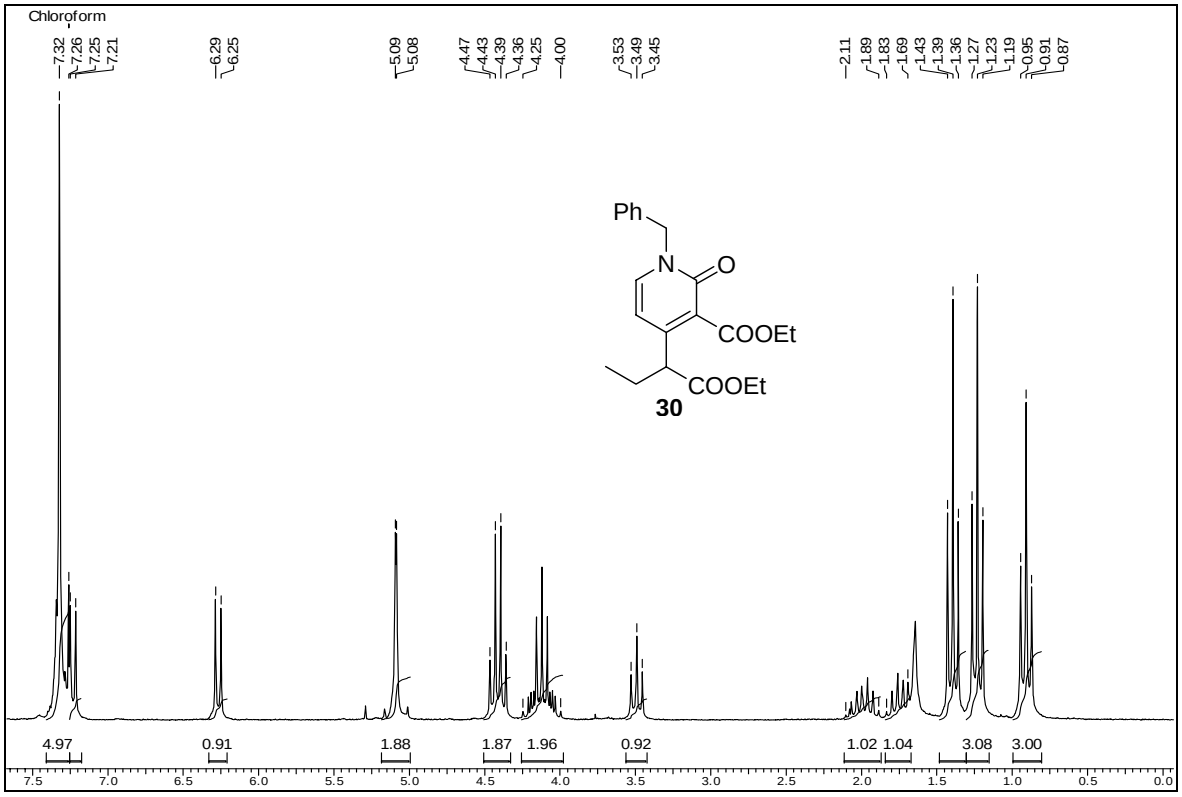
^{1}H NMR spectrum of compound 28 ($CDCl_3$ + CCl_4, 200 MHz)



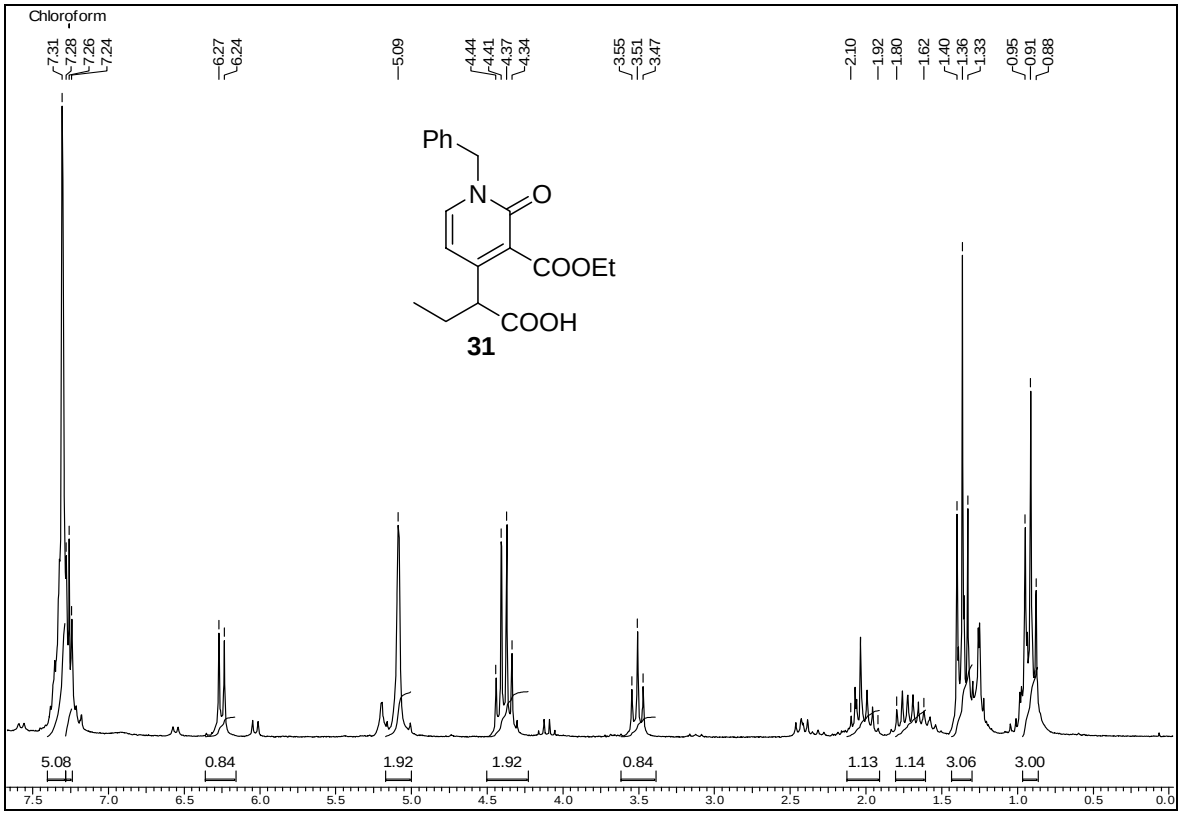
^{13}C NMR spectrum of compound 28 ($CDCl_3$ + CCl_4, 50 MHz)



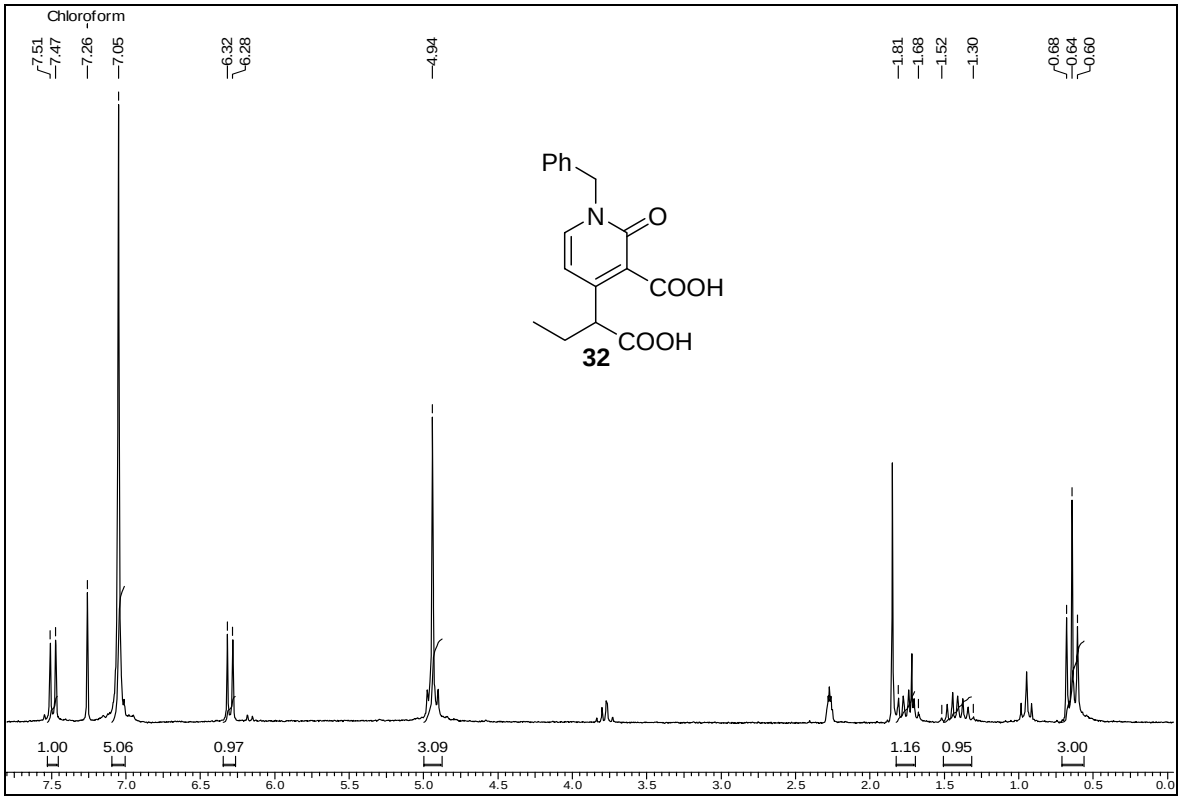
DEPT spectrum of compound 28 ($CDCl_3$ + CCl_4, 50 MHz)



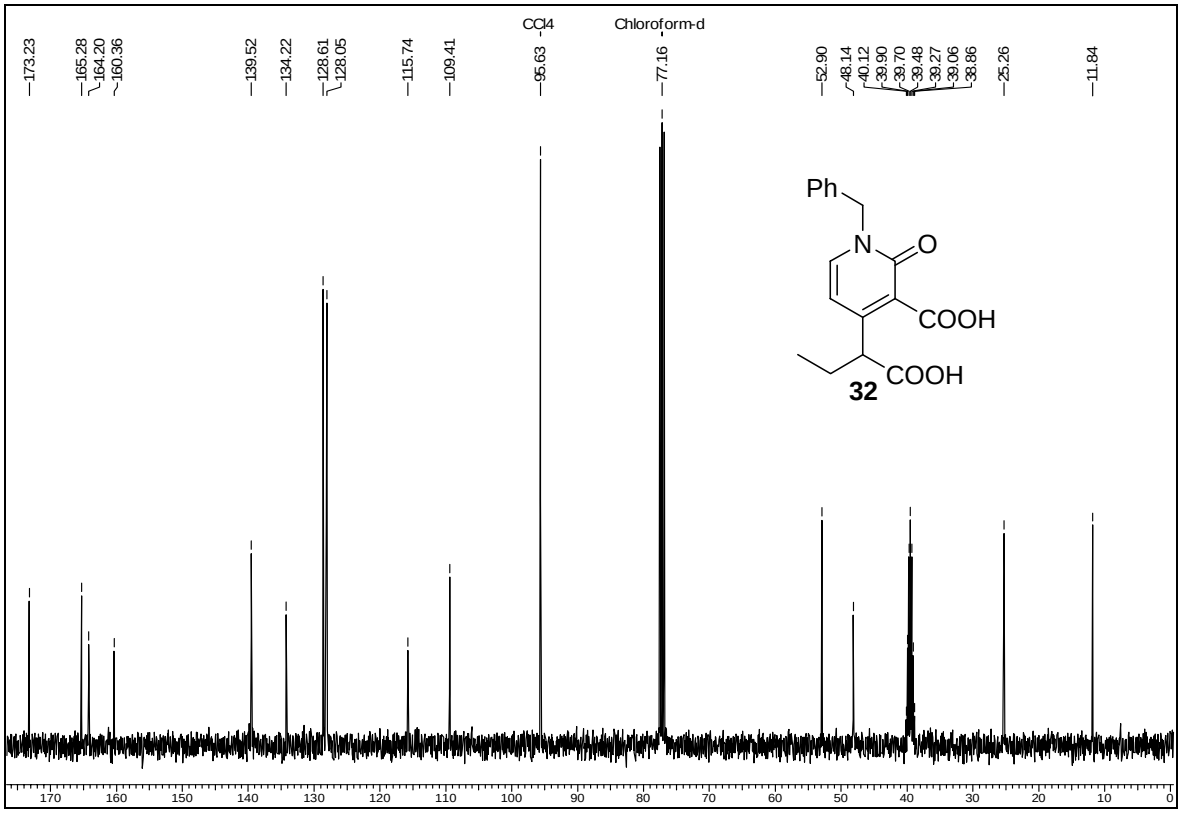
^{1}H NMR spectrum of compound 30 ($CDCl_3$ + CCl_4, 200 MHz)



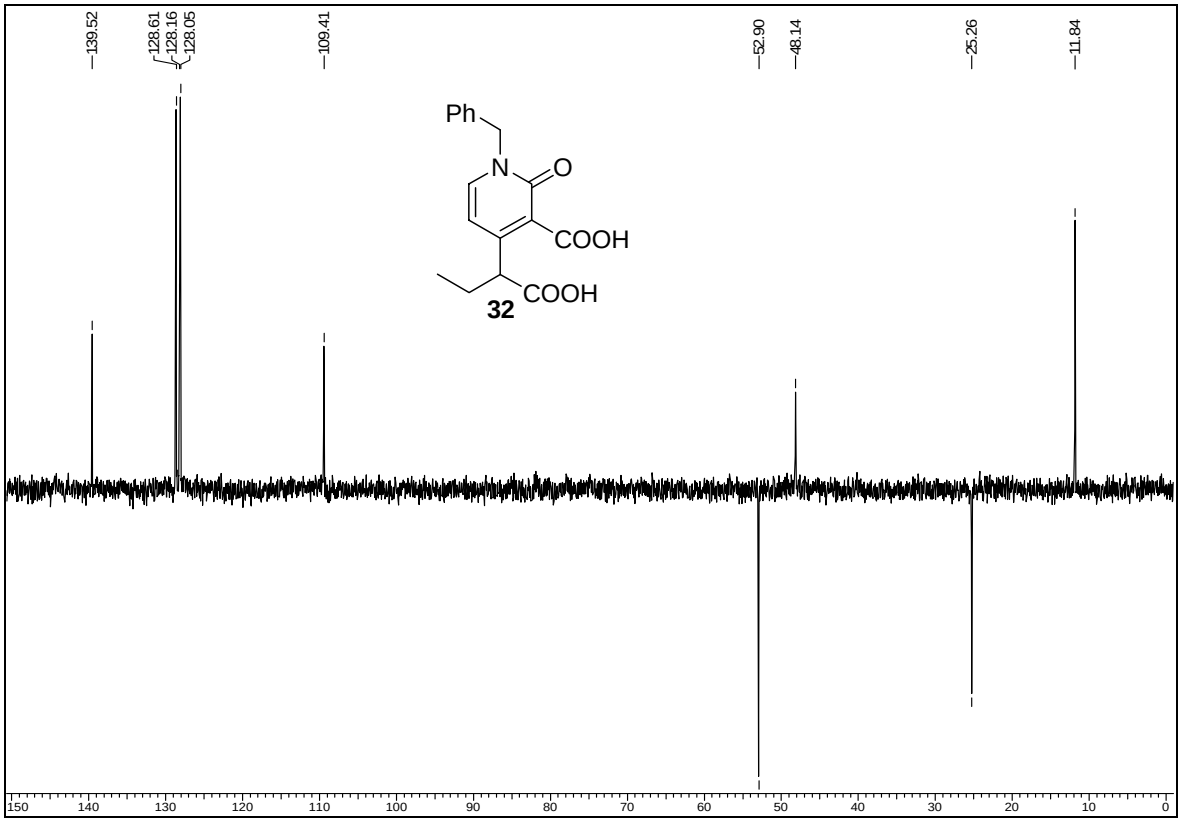
^{1}H NMR spectrum of compound 31 ($CDCl_3$ + CCl_4, 200 MHz)



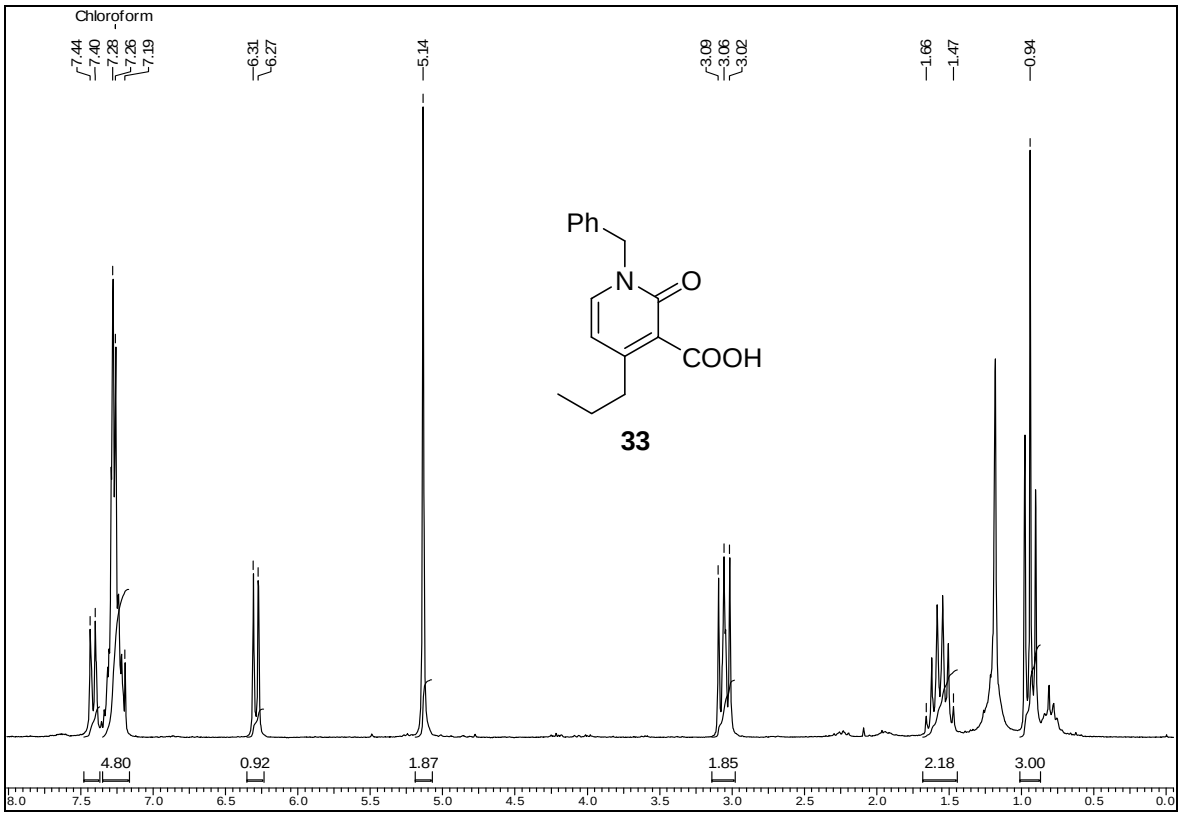
^{1}H NMR spectrum of compound 32 ($CDCl_3$ + CCl_4 + DMSO-d_6, 200 MHz)



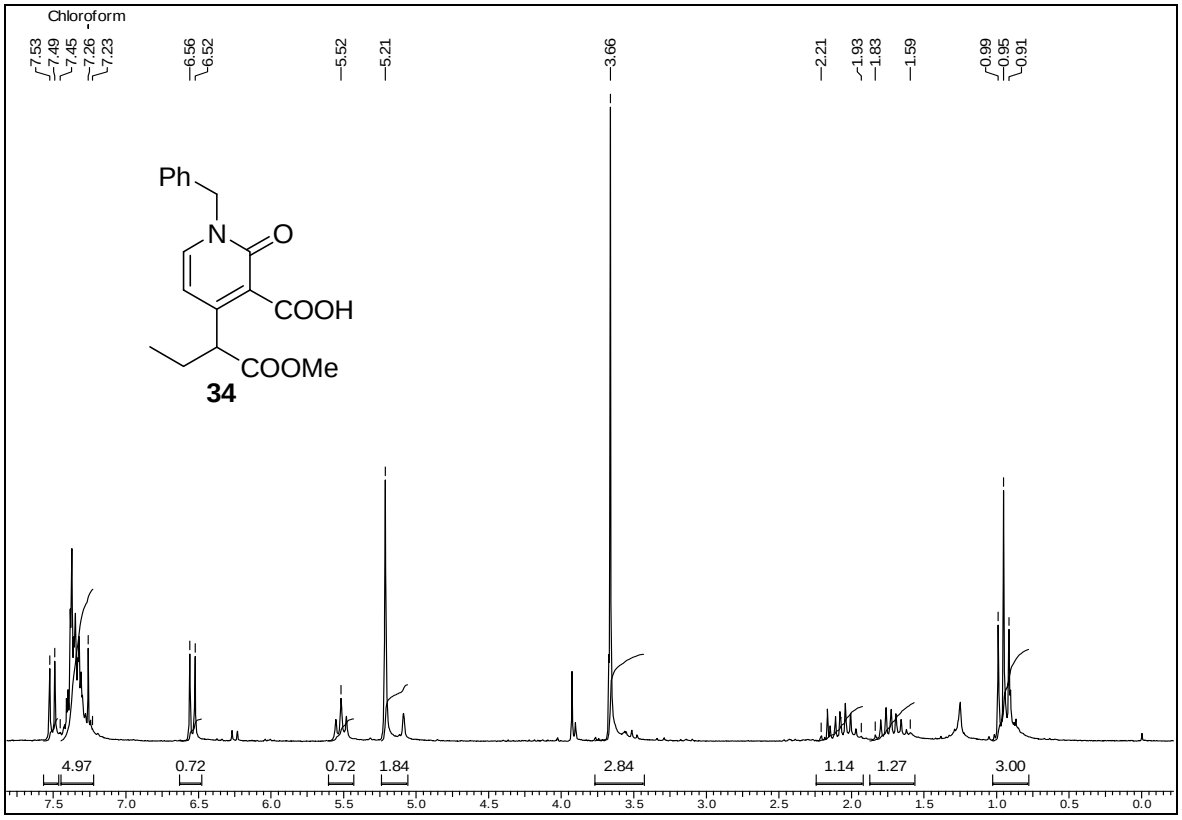
^{13}C NMR spectrum of compound 32 ($CDCl_3$ + CCl_4 + DMSO-d_6, 100 MHz)



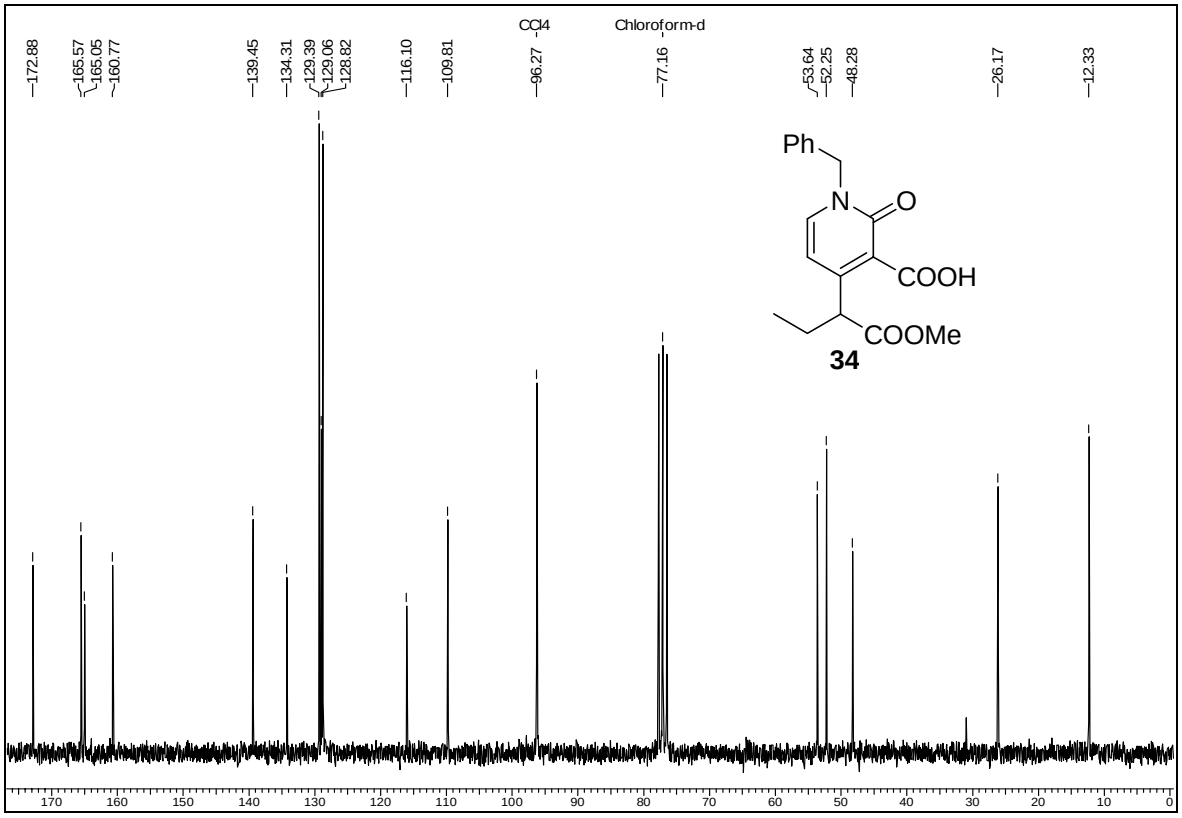
DEPT spectrum of compound 32 ($CDCl_3$ + CCl_4 + DMSO-d_6, 100 MHz)



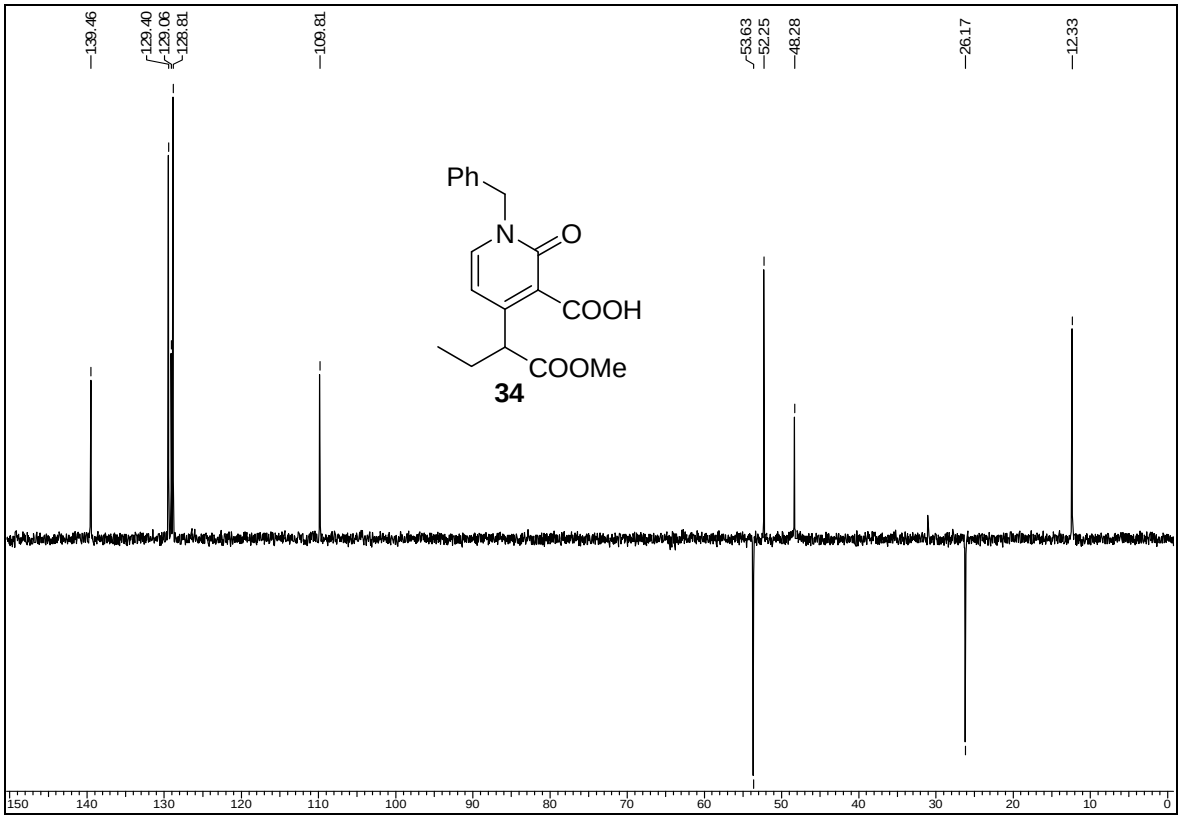
^{1}H NMR spectrum of compound 33 ($CDCl_3$ + CCl_4 + DMSO-d_6, 200 MHz)



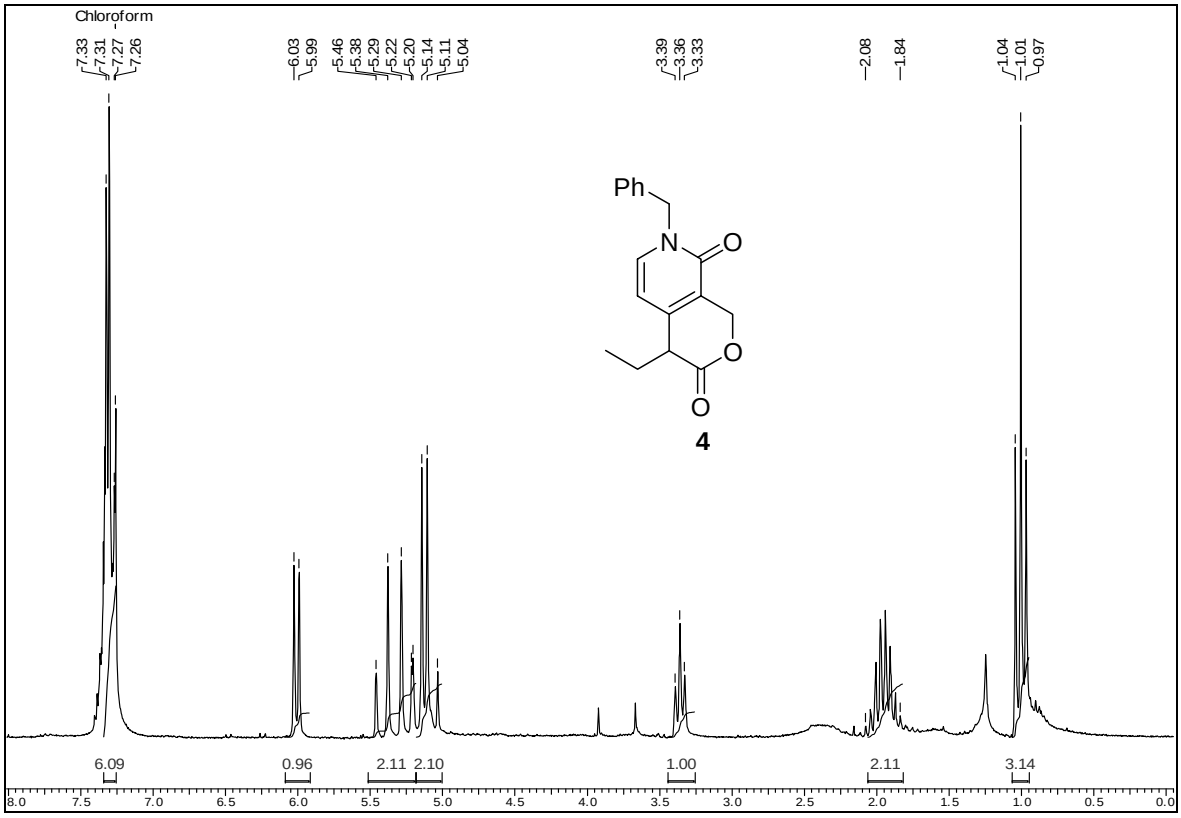
^{1}H NMR spectrum of compound 34 ($CDCl_3$ + CCl_4, 200 MHz)



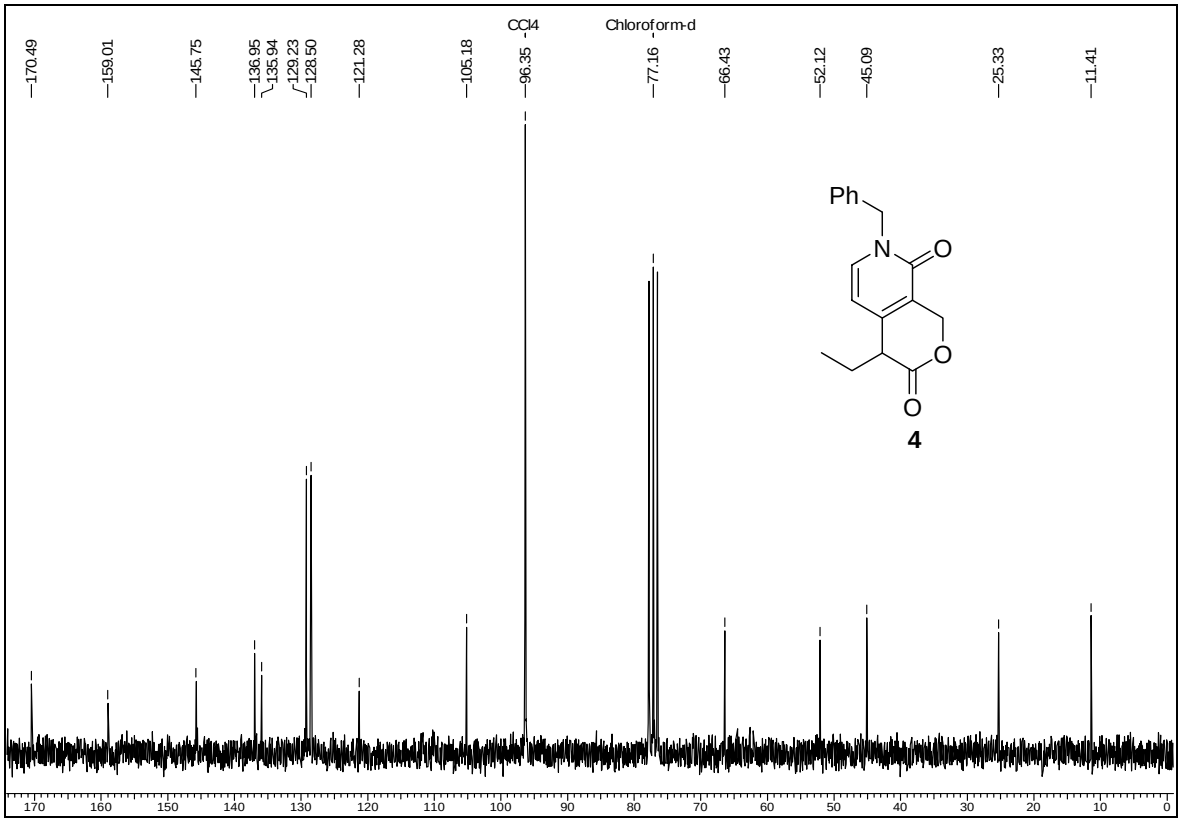
^{13}C NMR spectrum of compound 34 ($CDCl_3$ + CCl_4, 50 MHz)



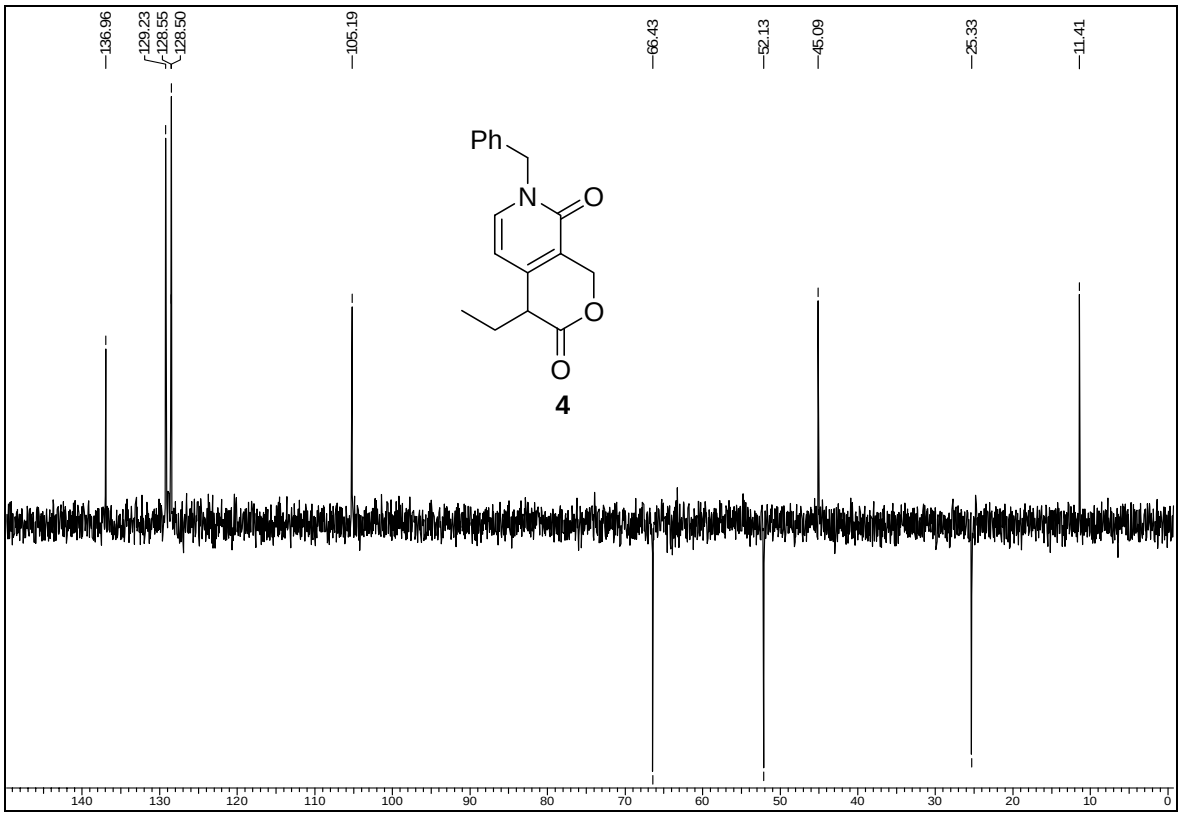
DEPT spectrum of compound 34 ($CDCl_3$ + CCl_4, 50 MHz)



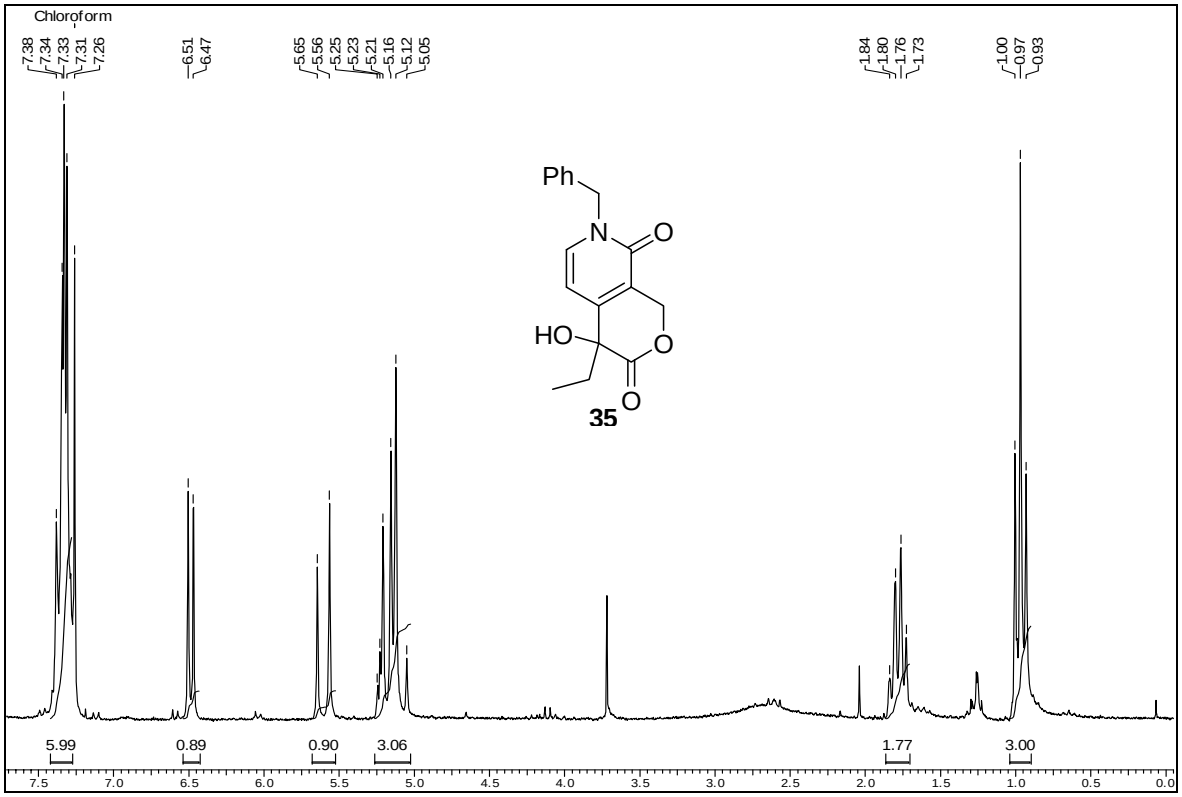
^{1}H NMR spectrum of compound 4 ($CDCl_3$ + CCl_4, 200 MHz)



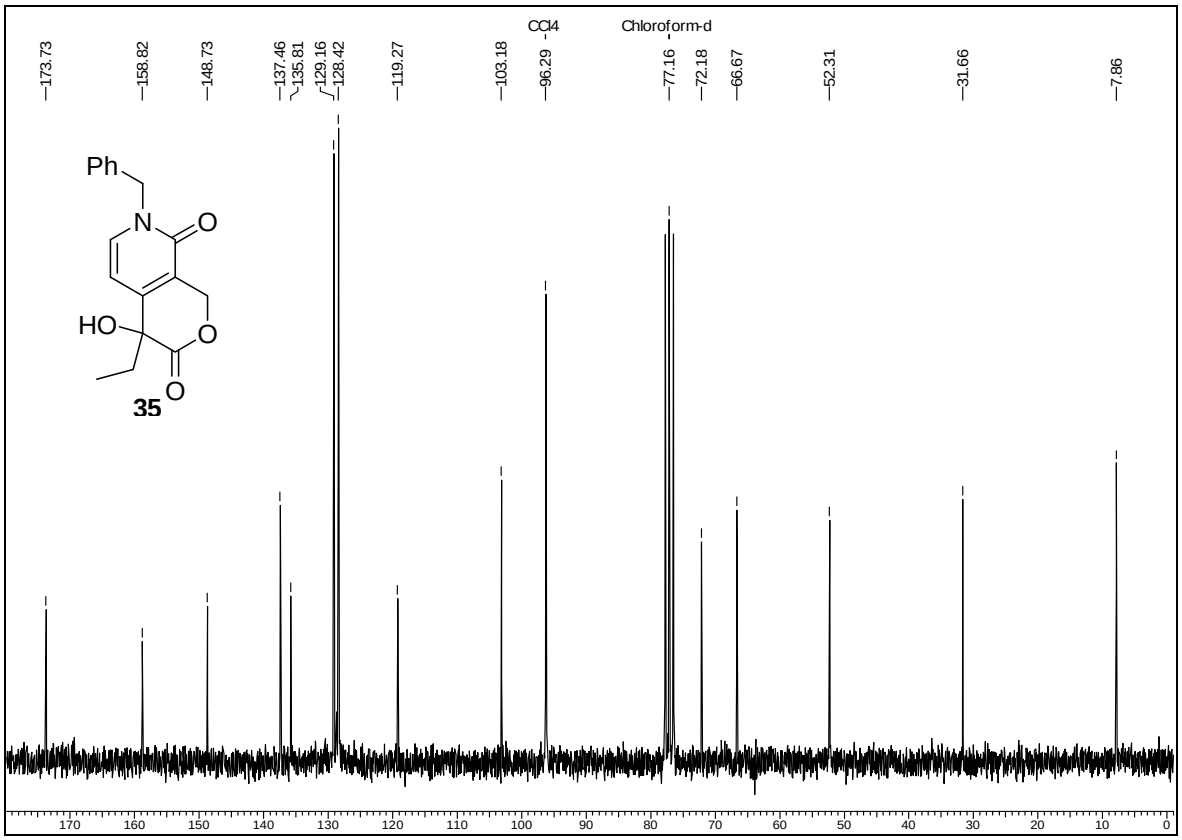
^{13}C NMR spectrum of compound 4 ($CDCl_3$ + CCl_4, 50 MHz)



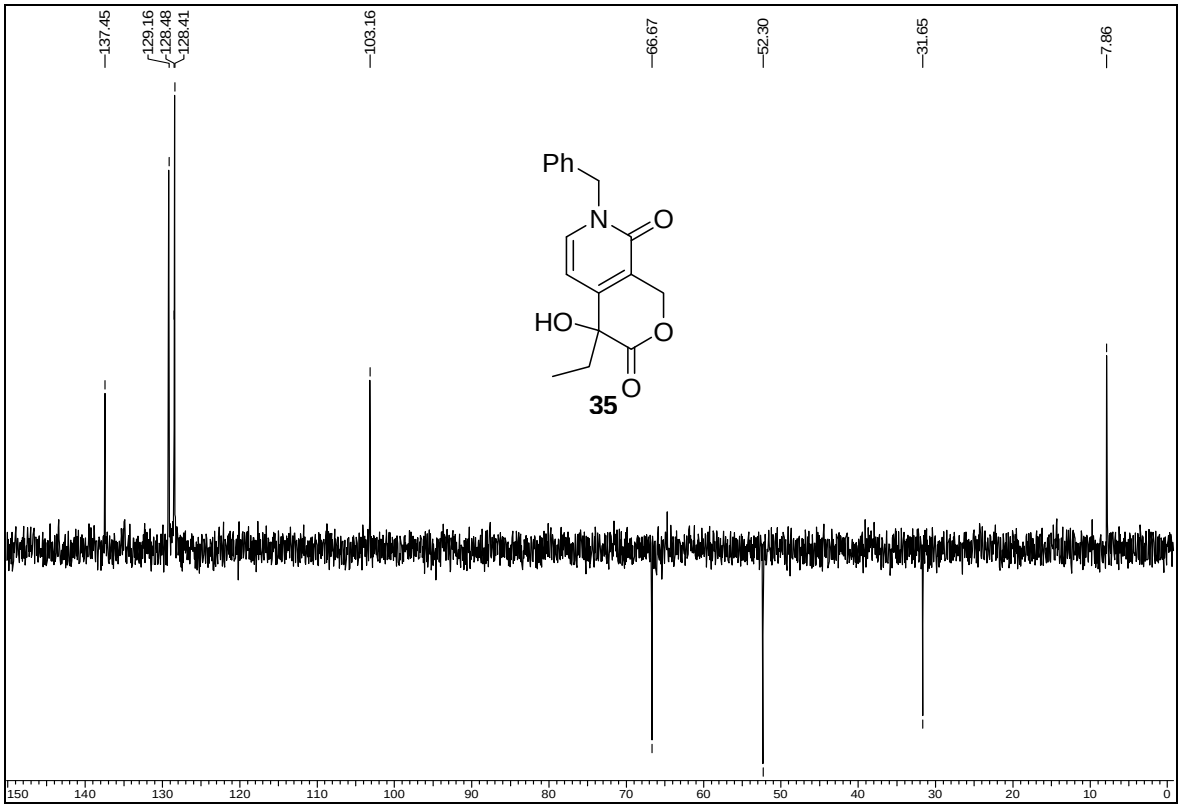
DEPT spectrum of compound 4 ($CDCl_3$ + CCl_4, 50 MHz)



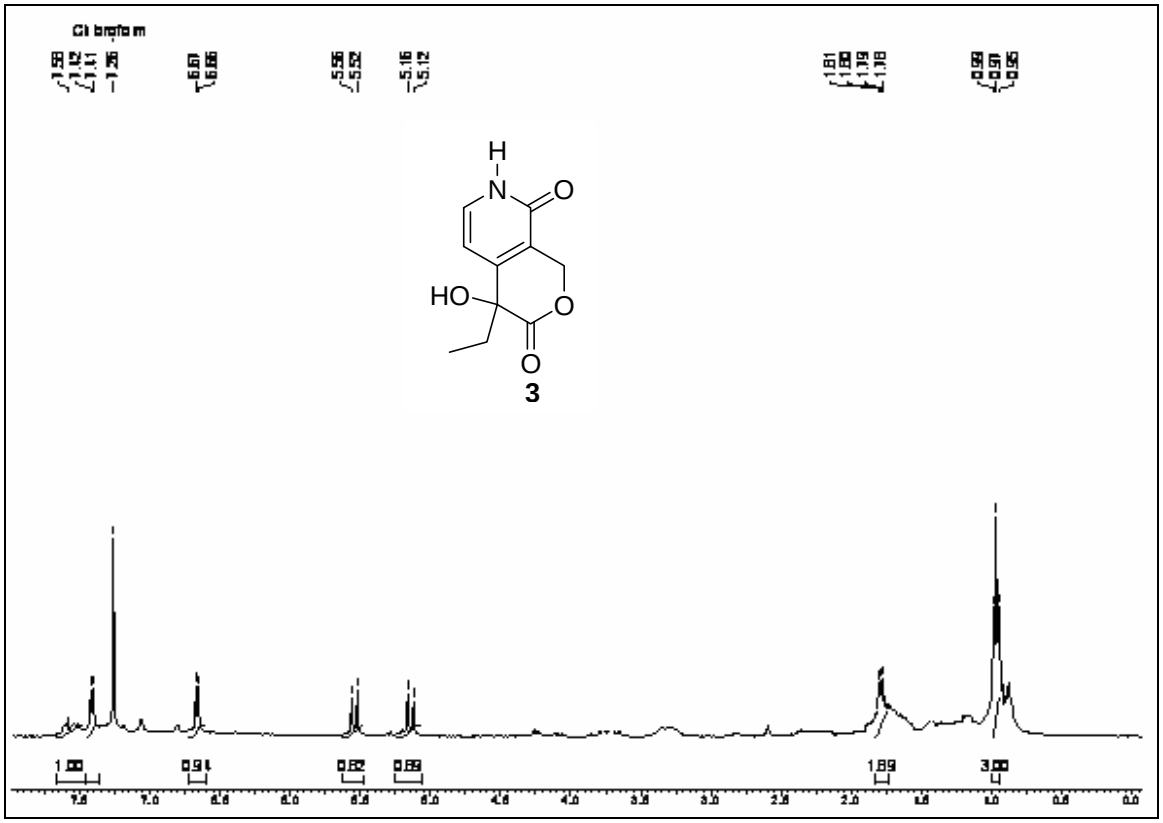
^{1}H NMR spectrum of compound 35 ($CDCl_3$ + CCl_4, 200 MHz)



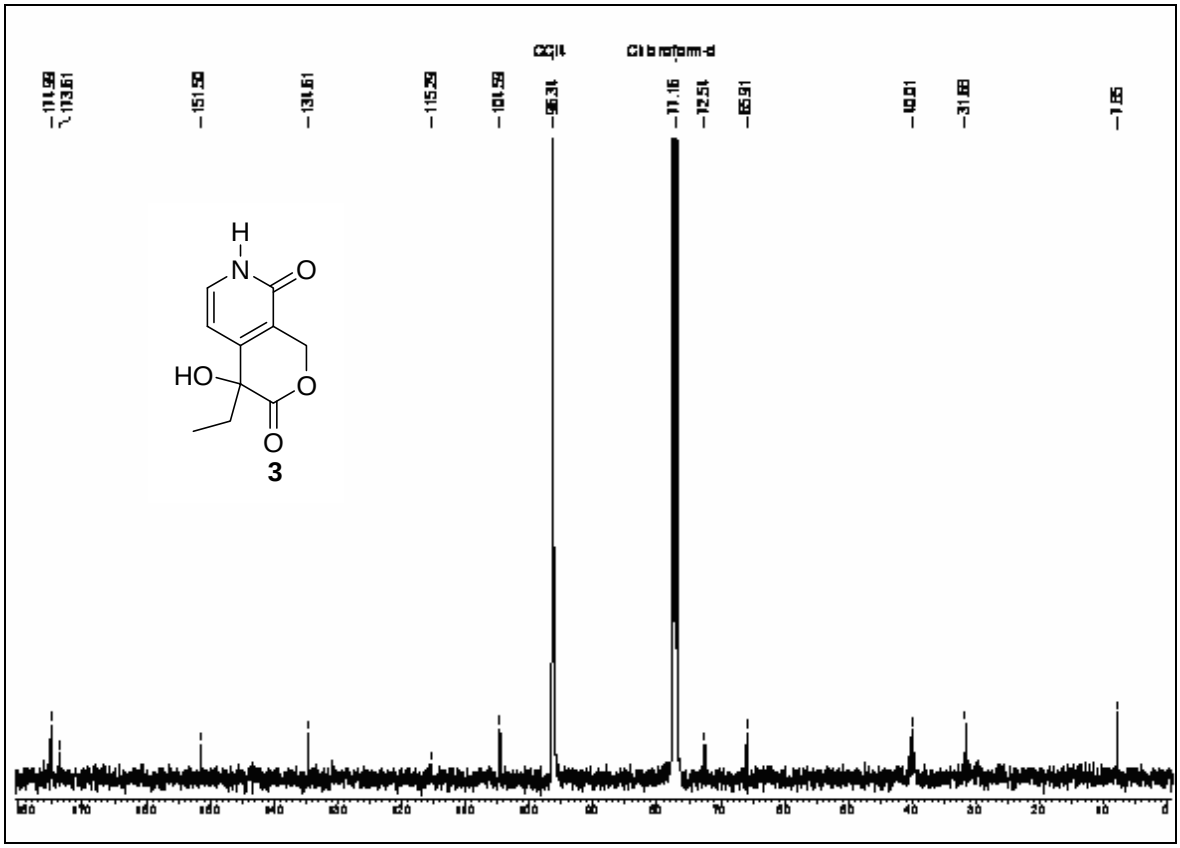
^{13}C NMR spectrum of compound 35 ($CDCl_3$ + CCl_4, 50 MHz)



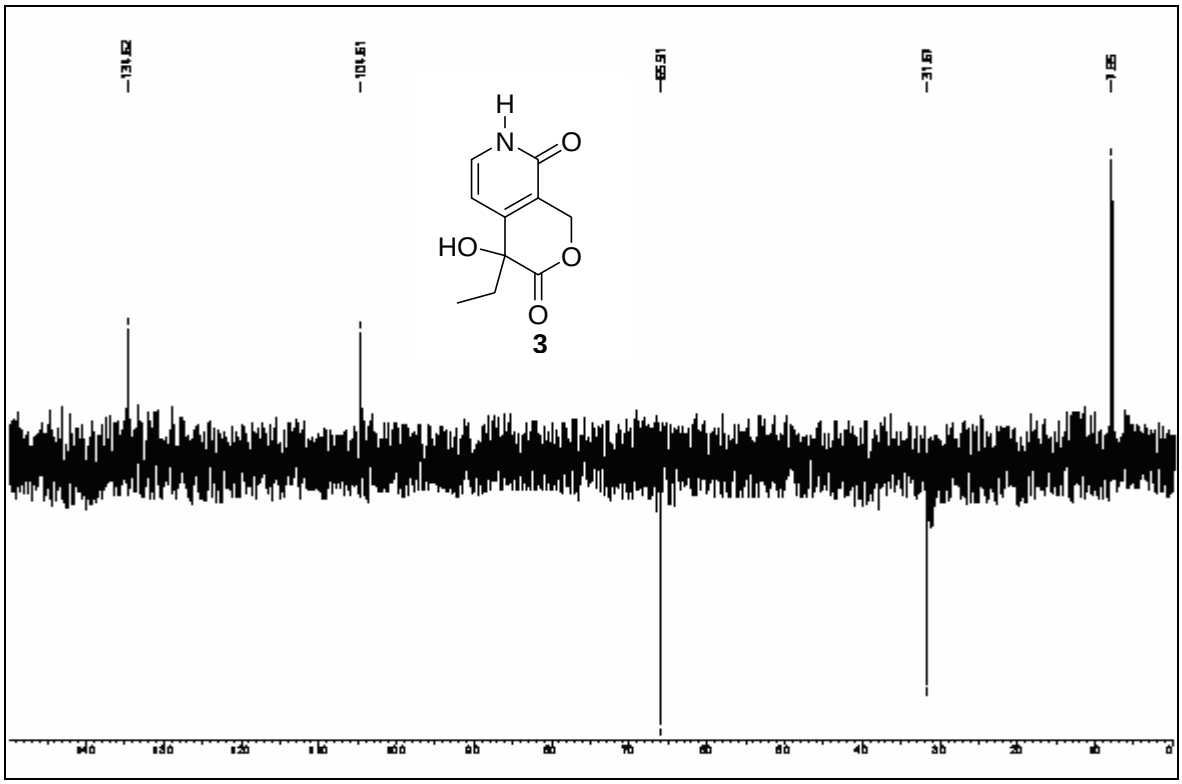
DEPT spectrum of compound 35 ($CDCl_3$ + CCl_4, 50 MHz)



^{1}H NMR spectrum of compound 3 ($CDCl_3$ + CCl_4, 400 MHz)



^{13}C NMR spectrum of compound 3 ($CDCl_3$ + CCl_4 + DMSO-d_6, 100 MHz)



DEPT spectrum of compound 3 ($CDCl_3$ + CCl_4 + DMSO-d_6, 100 MHz)

2.3.7 References

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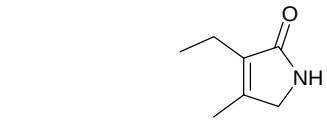
Chapter 3, Section I

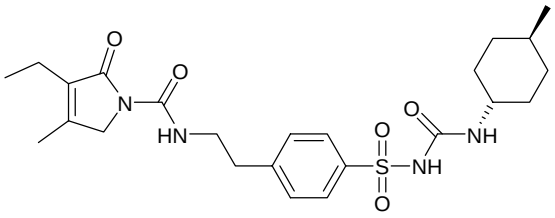
Synthesis of 3-ethyl-4-methyl pyrroline-2-one

3.1.1 Introduction:

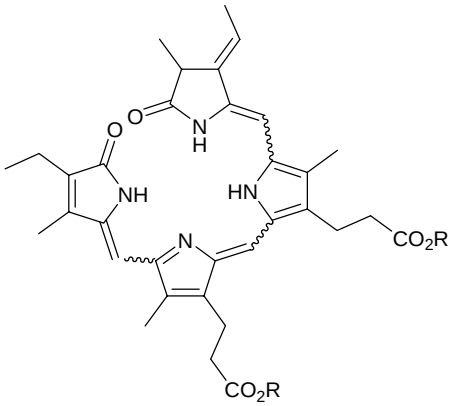
Today diabetes is increasingly common, potentially devastating, treatable yet incurable, lifelong disease and becoming a major and serious problem in society. It is leading cause of other diseases like blindless, kidney failure and amputation. According to recent estimation USA have a treatment of diabetes cost is $90 billion dollar annually it is more than the heart, cancer and AIDS diseases. In India also this disease is increasingly at an alarming rate and it is estimated that India will soon become the diabetic capital of the world.



3-ethyl-4-methyl-3-pyrrolin-2-one **1**



Glimepiride **2**



C-phycocyanin **3**

Figure 1

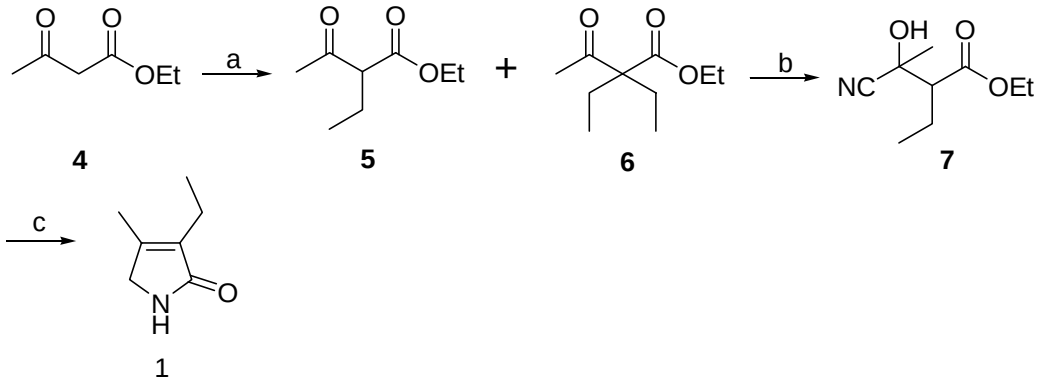
Five-and six-membered lactones and lactams are widely present as key building blocks in several natural products showing promising biological activity. 3- Ethyl –4- methyl –3-pyrroline –2- one **1** is an important heterocyclic building block of anti-diabetic drug *viz*. Glimepiride (**2**) and its derivative, which belongs to sulfonylurea drug and show potent activity against diabetic diseases a metabolite of glimepiride The synthesis of *trans*-hydroxyglimepiride a metabolite of the drug glimepiride was reported by Gurjar *et al*.[1] Pyrrolinone **1** is also present as main precursor in bile pigments (the blue protein C-phycocyanin **3**), which is depicted in figure 1 which was isolated from the blue-green algae *Synechococcus sp*. 6301. Bile pigment takes part in the very useful photosynthesis reaction.

Following lines describe the reported syntheses of 3-ethyl-4-methyl-3-pyrroline-2-one.

3.1.2 Literature survey

Henry's approach[2] **(***J. Am. Chem. Soc*. **1991**, *113*, 8024**)**

Henry and co workers reported the synthesis of **1** from ethyl acetoacetate **4,** which was alkylated with ethyl iodide using sodium ethoxide in ethanol at reflux temperature to give the mixture of monoalkylated compound **5** and dialkylated compound **6** in 52% yield and 15-20% yield respectively. Monoalkylated compound **5** was subjected to treatment with sodium bisulphite and sodium cyanide to furnish cyanohydrin **7** whose further the reduction followed by cyclization of cyanohydrin nitrile **7** employing Raney nickel in H_2 atmosphere under 50 psi at 33 ^oC and dehydration using sodium carbonate afforded desired intermediate **1** in 29%.

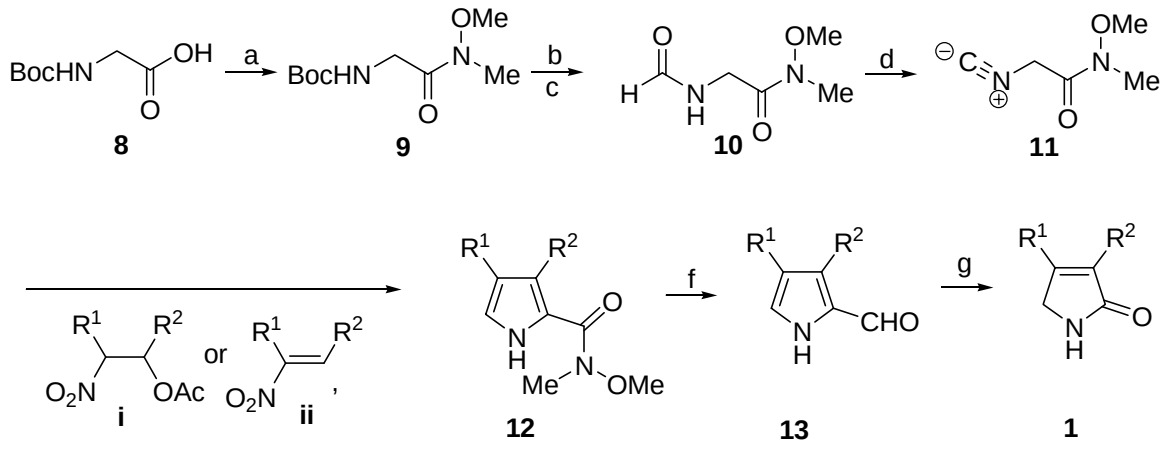


Scheme 1. *Reagents and conditions: (a) NaOEt (1.0 equiv) , EtI (1.0 equiv), EtOH, 80 ^oC, 4 h, 52% (b) $NaHSO_3$ (1.23 equiv), NaCN (1.05 equiv), H_2O, 0 ^oC, 3 h (c) H_2, T-1 Ra-Ni, Ac_2O, 50 psi, 33 ^oC, 12 h , reflux, 8 h (ii) Na_2CO_3, H_2O, reflux, 4 h 29%.*

Pelkey's approach[3] (*J. Org. Chem*. **2006**, *71*, 6678)

After completion of the work described in this thesis recently, Pelkey and co workers accomplishd the synthesis of **1** in seven-steps in 14% overall yield starting his synthesis from Boc-glycine **8**. DCC coupling of **8** with *N,O*-dimethylhydroxylamine gave **9** in 78% yield. Deprotection of Boc group group followed by formylation furnished compound **10** in 65% yield (two steps). Dehydration of formamide **10** with $POCl_3$ to afford the key intermediate isocynide **11** in 70% yield. The cyclocondensation reaction between isocynide **11** with β-nitroacetate or α-nitroalkenes in the presence of DBU led to the corresponding pyrrole Weinreb amide **12** in good yield. The pyrrole Weinreb amides **12** were then converted into the corresponding pyrrole -2-carboxaldehyde **13** by reduction with lithium aluminium hydride in THF at 0 ^oC to give 65% yield. Finally, oxidation of the pyrrole-2-

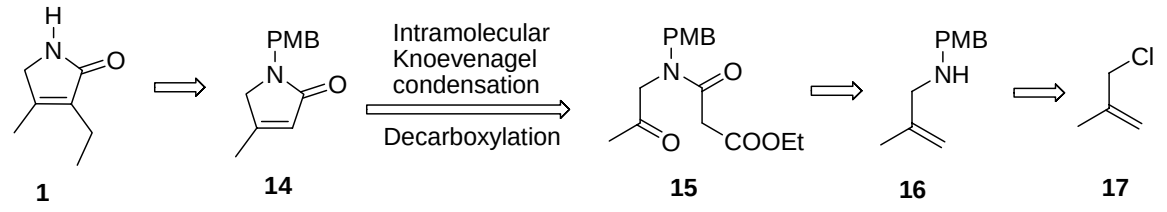
carboxaldehyde **13** to corresponding 3-pyrrolin-2-ones **1** was accomplished employing H_2O_2 and $NaHCO_3$.



Scheme 2. *Reagents and conditions: (a) MeONHMe, DCC, CH_2Cl_2, 0 ^oC-rt, 78%; (b)HCO_2H, 80 ^oC; (c) HCO_2Et, Et_3N, heat, (65%, two steps); (d) $POCl_3$, Et_3N, THF, 70%; (e)* ***i*** *or* ***ii****, DBU, THF, 0 ^oC-rt, 90%; (f) $LiAlH_4$, THF, 0 ^oC, 65%; (g) H_2O_2, $NaHCO_3$, MeOH, rt, 67%.*

3.1.3 Present work:

Owing to its impressive pharmaceutical importance, very poor yield and the ongoing programme on synthesis of biologically active compounds and generalization of RCM protocol for C=C formation, interest to devise the practical routes of bioactive compounds, it was decided to explore the intramolecular Knoevenagel condensation and catalytic Pd-mediated cyclization and ring-closing metathesis protocols.



Scheme 3. *Retrosynthetic plan 1.*

From the retrosynthetic analysis (scheme 3) it is clear that the target intermediate **1** can be accessed from lactam **14** by alkylation followed by deprotection; the lactam **14** could be realized from keto compound **15** by intramolecular Knoevenagel condensation followed by

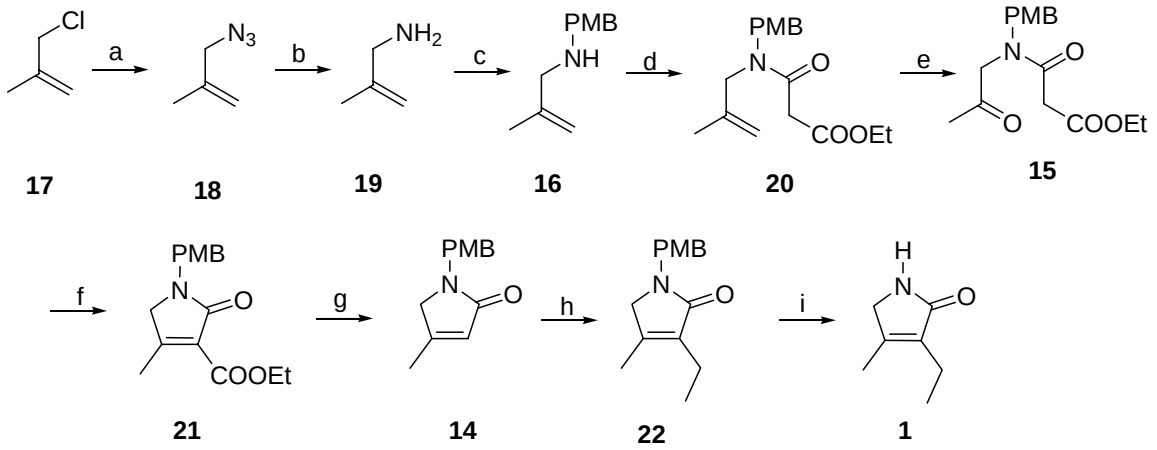
decarboxylation. The ketone **15** can be readily obtained from amine **16**, and amine **16** in turn could be accessed from commercially available methallyl chloride **17** by different transformations.

3.1.4 Results and discussion:

According to retrosynthetic plan 1 (scheme 3), the synthesis began from the commercially available methallyl chloride **17**, which was converted into corresponding amine **16** in 61% yield in three steps.[4] The structure of the generated amine **16** was confirmed by spectroscopic techniques. IR spectrum of **16** exhibited broad absorption band at 3436 cm^{-1} indicating the presence of amino group. ^{1}H NMR spectrum of **16** displayed a singlet at δ 1.78 integrated for three protons and which was assigned to vinyl methyl, singlet at δ 3.18 integrating for two protons assigned to methylene adjacent to nitrogen, singlet at δ 3.70 integrated for two benzyl protons, singlet at δ 3.80 integrated for three protons (Ar-OC$\underline{H_3}$) two olefinic protons resonated as two singlets at δ 4.86 and δ 4.90 while the four aromatic protons appeared as two doublets at δ 6.85 and 7.25 (J = 8.7 Hz). ^{13}C NMR spectrum of **16** revealed nine signals. DEPT spectrum of **16** displayed three methylene carbons. The structure of **16** was further confirmed by mass spectral and elemental analysis. The mass spectrum of **16** revealed the $(M + H)^+$ peak at *m/z* 192. The elemental analysis revealed that the experimental values were found to be in good agreement with the calculated values.

The amine **16** was further subjected to the treatment with ethyl malonyl chloride using potassium carbonate as the base in anhydrous dichloromethane at 0 ^{o}C to give tertiary amide **20** in 86% yield. The formation of amide **20** was confirmed by spectral data analysis. IR spectrum of **20** displayed strong absorption band at 1735 and 1654 cm^{-1} characteristic of ester and amide functionality respectively. ^{1}H NMR spectrum of **20** displayed three extra signals which appeared as triplet and quartet at δ 1.29 and δ 4.20 (J = 7.1 Hz) integrating for three and two protons respectively and were assigned to ethyl ester suggesting the presence of ethyl ester group and incorporation of malonyl moiety, two singlets in ratio (2:1) appeared at δ 3.66 and δ 3.96 due to presence of rotamers. ^{13}C NMR along with DEPT spectra of **20** revealed the presence of rotamers and finally mass spectrum and elemental analysis confirmed the structure of **20.** Mass spectrum of **20** displayed the *m/z* peak at 306 $(M + H)^+$, 328 $(M + Na)^+$, while the elemental analysis the observed values were in good agreement with the theoretical values.

The oxidative cleavage of **20** was carried out using catalytic amount of OsO_4 and 2.1 equivalents $NaIO_4$ to furnish its corresponding keto compound **15** in very good yield (89%). The structure of compound **15** was confirmed by spectral data. IR spectrum of **15** displayed the strong absorption band at 1717 cm^{-1} which indicated the presence of ketone functionality. The ^1H NMR spectrum of **15** exhibited the disappearance of signals corresponding to two olefinic protons suggesting the absence exomethylene moiety. ^{13}C NMR spectrum of **15** also supported the absence of signals characteristic of alkene terminal and quaternary carbons while new signal appeared at δ 202.2 and 202.5 due to rotamers which also the indication of the transformation of olefin to ketone functionality. Finally the structure of **15** was ascertained by mass spectral and elemental analysis, the mass spectrum of **15** showed the *m/z* peak at 308 $(M + H)^+$ and 330 $(M + Na)^+$, the experimental values were found to be in good agreement with the calculated values in an elemental analysis.



Scheme 4. *Reagents and conditions: (a) NaN_3 (1.5 equiv), dry DMSO, 70 ^oC, 12h. (b) PPh_3 (1.1 equiv), Et_2O, 0 ^oC, 15h. (c) (i) Anisaldehyde (1.2 equiv), dry MeOH, 0 ^oC, 1h. (ii) $NaBH_4$ (1.0 equiv), MeOH, 0 ^oC, 1h, 61% over four steps (d) K_2CO_3 (3.0 equiv), dry DCM, ethyl malonyl chloride (1.2 equiv), 0 ^oC, 3h, 86%. (e) OsO_4 (cat), $NaIO_4$ (2.2 equiv), acetone-water (3:1), rt, 3h, 89%. (f) NaH (2.0 equiv), dry THF, 0 ^oC, 3h, 81%. (g) NaCl (4.0 equiv), DMSO-H_2O (3:1), 120-130 ^oC, 12h, 87% (h) NaH (1.2 equiv), ethyl iodide (1.2 equiv), dry THF, 0 ^oC-rt, 3h, 71%. (i) CAN (2.5 equiv), acetonitrile: water (5:1), rt, 2h, 80%.*

The intramolecular Knoevenagel condensation was successfully carried out on **15** using NaH as a base in THF to furnish α,β-unsaturated lactam **21** in 81% yield. The formation of compound **21** was confirmed by spectral study. IR spectrum of **21** showed the absence the peak corresponding to ketone functionality. ^{1}H NMR spectrum of **21** displayed the disappearance of the methylene protons and showed the single signals from these two observations it suggested the formation of **21**, the *m/z* peak at 290, 312 and 328 corresponding to $(M + H)^+$, $(M + Na)^+$ and $(M + K)^+$ respectively in the mass spectrum and finally the structure of **21** was further ascertained by its elemental analysis as well.

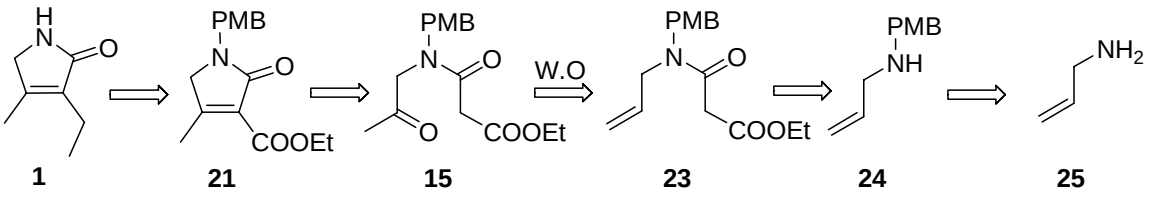
The smooth decarboxylation of ester group was accomplished under Krapcho's condition furnished corresponding decarboxylated α,β-unsaturated lactam **14** in very good yield (87%).[5] The formation of **14** was confirmed by spectral data. IR spectrum of **14** revealed the absence of absorption band corresponding to ester group and appearance of absorption band at 1672 cm^{-1} characteristic of α,β-unsaturated lactam. ^{1}H NMR spectrum of **14** displayed the disappearance of the signals corresponding to ethyl ester and a new singlet appeared at δ 5.85 indicated that the ethyl ester at α -carbon in α,β -unsaturated lactam was decarboxylated. ^{13}C NMR spectrum of **14** showed twelve signals, DEPT spectrum of **14** revealed two methylene carbons which also supported the structure. Additionally the mass spectrum of **14** showed a *m/z* peak at 218 (M + H), $^{+}$ 240 $(M + Na)^+$ and 256 $(M + K)^+$. Finally the formation of compound **14** was further ascertained by its elemental analysis as well**.**

The regioselective alkylation at α -carbon over γ-carbon was accomplished with ethyl iodide utilizing sodium hydride as a base in dry THF delivered the anticipated desired product **22** in 71% yield.[6] The structure of **22** was ascertained by its spectral study. ^{1}H NMR spectrum of **22** showed the disappearance the olefinic proton while triplet and quartet appeared at δ 1.07 and 2.28 (J = 7.6 Hz) integrating for three and two protons respectively which indicated the introduction of ethyl group at α-carbon. ^{13}C NMR spectrum of **22** displayed the disappearance of the signal corresponding to α-carbon of α,β-unsaturated lactam while appearance of the new signals at δ 12.6 and 16.8 which suggested the incorporation of ethyl functional group. DEPT spectrum of **22** revealed the presence of three methylene carbons supported the structure of **22**. Finally the structure of **22** was confirmed by its mass spectral and elemental analysis. The mass spectrum exhibited the *m/z* peaks at 246 $(M + H)^+$, 268 $(M + Na)^+$ and 274 $(M + K)^+$ and in an

elemental analysis the experimental values were found to be in good agreement with the calculated values.

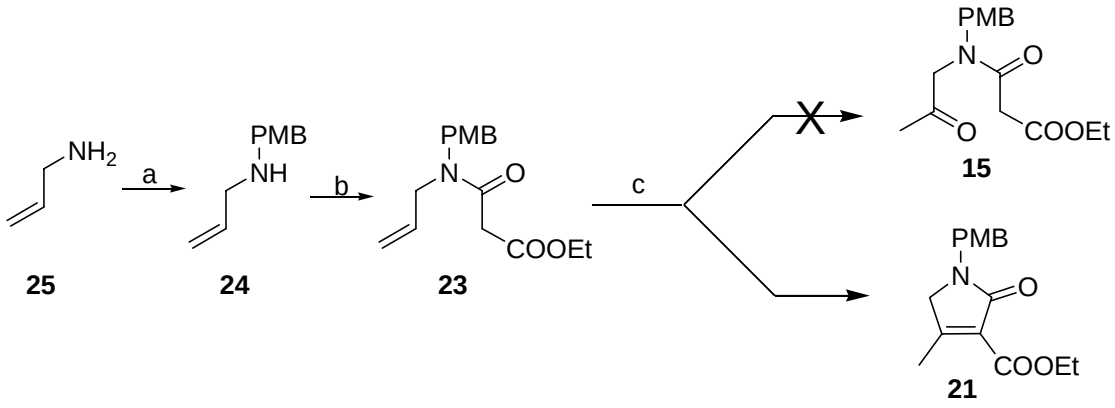
The last step was the deprotection of PMB group and which was achieved by employing the two equivalents CAN in acetonitrile at room temperature resulted in the formation target **1** in 80% yield.[7] The structure of **1** was confirmed by spectral analysis. IR spectrum of **1** shows the strong absorption bands at 3226 cm^{-1} and 1681 cm^{-1} corresponding to N-H and C=O stretching frequency of α,β-unsaturated lactam. ^{1}H NMR spectrum of **1** revealed the disappearance of the peaks corresponding to PMB group and a new broad singlet appeared at δ 8.04 characteristic of amide proton suggesting the removal of PMB group. ^{13}C NMR spectrum of **1** also revealed the absence of signals due to PMB group, clearly indicated that the compound **1** does not contain the PMB moiety, DEPT spectrum of **1** displayed two methylene carbons which also supported the structure of **1** and finally the structure of **1** was confirmed by mass spectral and elemental analysis. The mass spectrum of **1** showing the *m/z* peak at 126 and 148 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively, in an elemental analysis the experimental values were found to be in good agreement with theoretical values. The spectral data of **1** exactly matched with the reported data.

After the successful synthesis of **1** employing intramolecular Knoevenagel condensation (scheme 4), it was thought to synthesize it by following an alternative approach including cheap and commercially available starting material containing less number of steps and employing novel Pd-catalysed cyclization step under Wacker reaction conditions which is delineated in scheme 5. The target intermediate **1** could be obtained from compound **21**, the lactam **21** can be readily accessed from keto compound **15**, which in turn would be realized from amide **23** by Wacker oxidation and cyclization. The amide **23** in turn could be synthesized from amine **24** and amine **24** can be easily obtained from cheap and readily available allyl amine **25**.



Scheme 5. *Retrosynthetic plan 2.*

Accordingly the synthesis started from cheap and readily available starting material *viz.* allyl amine **25**. Allyl amine **25** was converted into secondary amine **24** in excellent yield (97%) by reductive amination with *p*-anisaldehyde, using triethyl amine in methanol followed by reduction of the resultant imine by sodium borohydride in methanol at 0 ^{o}C. The formation of **24** was confirmed by spectral analysis. ^{1}H-NMR spectrum of **24** revealed the doublet at δ 3.28 that integrated for two protons and was assigned to allylic protons, singlet at δ 3.78 integrating for three protons was ascribed to (Ar-OC<u>H</u>$_3$), singlet at δ 4.65 for two benzylic protons was attributed to multiplet at δ 5.14-5.28 was assigned to terminal olefinic protons, multiplet at δ 5.6-6.1 integrating for one proton was ascribed to internal olefinic doublet that appeared at δ 6.87 two aromatic protons was attributed to ortho to methoxy group, doublet at δ 7.28 for two aromatic protons meta to methoxy group. The structure of **24** was also ascertained by mass spectral and elemental analysis. The mass spectrum of **24** displayed the $(M + H)^{+}$ peak at 177.



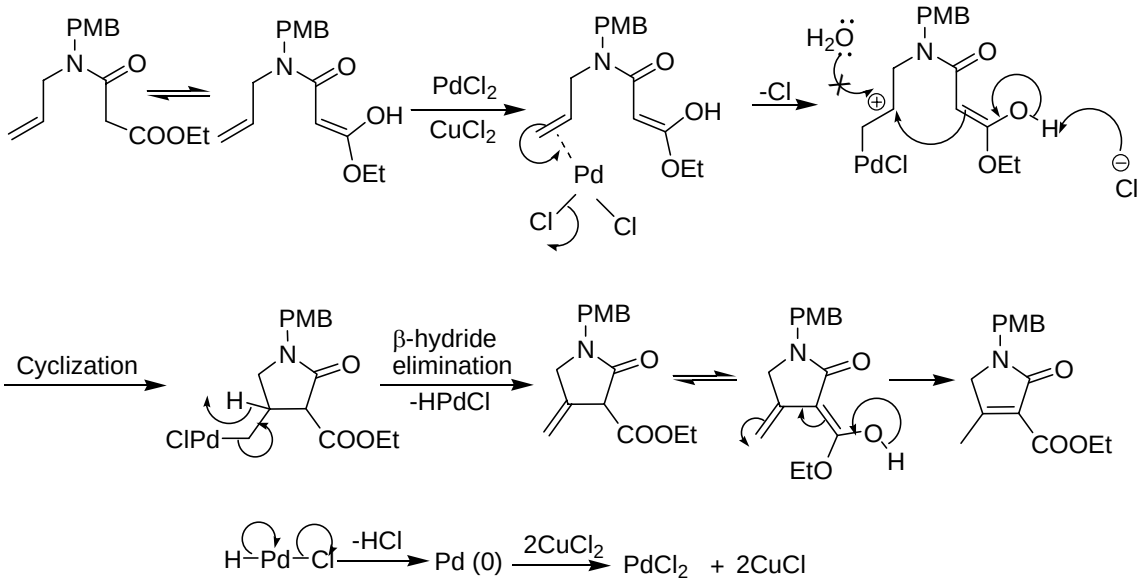
Scheme 6. *Reagents and conditions: (a) (i) p-anisaldehyde (1.0 equiv), MeOH, 0 ^{o}C, 1h. (ii) $NaBH_4$, MeOH, 0 ^{o}C, 1h, 97%. (b) K_2CO_3 (3.0 equiv), ethyl malonyl chloride (1.2 equiv), CH_2Cl_2, 0 ^{o}C, 1h. 86%. (c) $PdCl_2$ (10 mol %), $CuCl_2$ (2.1 equiv), DMF-H_2O (3:1), 95 ^{o}C, 6 h, 62%.*

The treatment of **24** with ethyl malonyl chloride using K_2CO_3 as a base in anhydrous dichloromethane furnished the amide **23** in 86% yield. The structure of amide **23** was confirmed by spectroscopic techniques. IR spectrum of **25** revealed the strong absorption bands at 1735 and 1654 cm^{-1} characteristic of ester and amide functionality respectively which indicate the introduction of ethyl malonyl moiety in **23**. ^{1}H NMR spectrum of **23**

revealed the triplet at δ 1.28 integrating for three protons a singlet at δ 3.78 for two methylene protons and a quartet at δ 4.23 integrating for two protons also supported the installment of ethyl malonyl group. ^{13}C NMR spectrum along with DEPT spectrum of **23** showed the presence of rotamers. The formation of **23** was confirmed by mass spectral and elemental analysis. The mass spectrum of **23** exhibited the molecular ion peak at *m/z* 292 corresponding to its molecular weight. The elemental analysis of **23**, the experimental values were found to be in good agreement with the theoretical values.

With **23** was in hand, attention was towards the crucial Wacker oxidation. When **23** was subjected under Wacker reaction conditions[8] employing catalytic amount of palladium chloride (10 mol %) and two equivalent $CuCl_2$ as a co-oxidant in DMF-H_2O (6:1) at 95 ^oC for 6 hrs, surprisingly cyclized product **21** was observed in 62% yield, instead of anticipated Wacker product **15.** The cyclized product **21** is common intermediate in scheme 4 and which was already manipulated into desired target **1.**

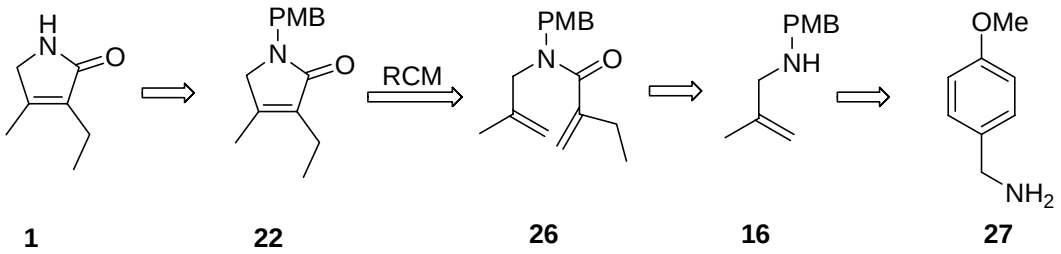
The formation of **21** can be explained by the mechanism delineated in scheme 7.



Scheme 7. *Probable mechanism.*

After the successful synthesis of **1** by two routes i.e. intramolecular Knoevenagel condensation and Pd-catalyzed cyclization, it was also envisioned that **1** can be synthesized in less number of steps employing RCM strategy as shown in scheme 8. The desired key intermediate **1** could be accessed from lactam **22** by deprotection of PMB group, the

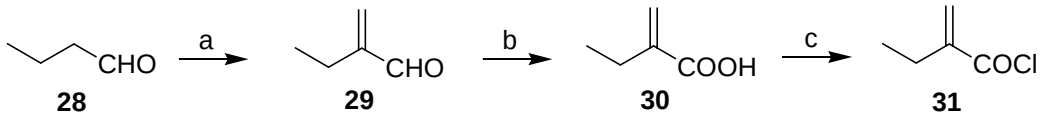
lactam **22** could be realized from acrylamide **26** by RCM, compound **26** could be obtained from amine **16** by *N*-acylation and lastly the amine **16** can be readily accessed from commercially available 4-methoxybenzylamine **27**.



1 **22** **26** **16** **27**

Scheme 8. *Retrosynthetic plan 3.*

According to retrosynthetic plan 3, the synthesis of **1** commenced from the commercially available 4-methoxybenzylamine **27.** The treatment of **27** with 0.33 equivalent of methallyl chloride (in order to prevent the further alkylation) using potassium carbonate as the base & catalytic potassium iodide in anhydrous dichloromethane to furnish the secondary amine **16** in 84% yield (based on the recovery of starting material **27)**. The ethacryloyl chloride **31** is important fragment which was synthesized from commercially available butyraldehyde **28**[9,10] as depicted in scheme 9.



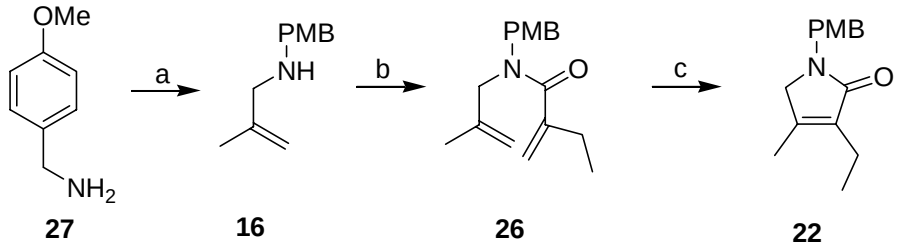
28 **29** **30** **31**

Scheme 9. *Reagents and conditions: (a) preheated mixture of Et_2NH-CH_2Br_2 (1:3), 55 ^oC, 2 h, 76%. (b) $NaClO_2$ (1.0 equiv), NaH_2PO_4 (1.0 equiv), 30% H_2O_2 (1.0 equiv), CH_3CN, rt, 4 h, 92%. (c) $SOCl_2$ (1.1 equiv), C_6H_6, 80 ^oC, 3 h, 68%.*

The treatment of resultant amine **16** with ethacryloyl chloride **31** using K_2CO_3 as the base afforded the acrylamide **26** in excellent yield (91%). The structure of **26** was confirmed by spectral study. The IR spectrum of **26** showed a strong absorption band at 1644 cm^{-1} due to C=O stretching frequency of acrylamide. ^1H NMR spectrum revealed a triplet and quartet at δ 1.08 and 2.33 (J = 7.5 Hz) integrating for three and two protons respectively and singlet at δ 5.10 for two olefinic protons, indicated the presence of the ethacrylamide functionality in **26**. ^{13}C-NMR spectrum displayed signals at δ 11.4, 26.9 corresponding to

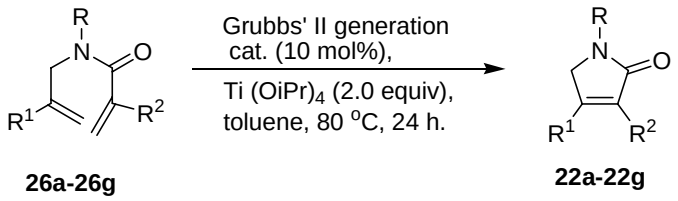
ethyl group, signals that appeared at δ 111.9, 112.2 and 146.0 were assigned to olefinic carbons while signal at δ 172.1 was assigned to acrylamide carbonyl carbon. DEPT spectrum of **26** showed methylene carbons at δ 26.9, 45.25, 47.7, 49.8, 52.3, 111.9 and 112.2, which give the support for structure of **26**. The *m/z* peak at 274 $(M + H)^+$ and base peak observed at 192 in mass spectrum which confirmed the structure of **26**. Finally the structure of **26** was ascertained by its elemental analysis also, which was found to be in good agreement with the calculated values.

After getting **26** in hand, the next task was to perform the crucial ring-closing metathesis transformation. Accordingly **26** was subjected to Grubbs 2nd generation catalyst (10 mol %) in anhydrous toluene at 80 °C for 12 h, it was gratifying to note that the desired lactam **22** was obtained in 40% yield[11-13] (90% yield based on the recovery of starting material). The yield of RCM step was very poor presumably due steric hindrance of substituents at olefin and ring strain of resulting ring it was decided to study the substituent effect in the RCM reaction.



27 **16** **26** **22**

Scheme 10. *Reagents and conditions: (a) methallyl chloride (0.33 equiv), K_2CO_3 (1.2 equiv), KI (cat), dry DCM, 0 °C-rt, 12h, 84%. (b) K_2CO_3 (1.2 equiv), ethacryloyl chloride* ***6*** *(1.2 equiv), dry DCM, 0 °C – rt, 3h, 91%. (c) Grubbs' catalyst 2nd generation (10 mol %), dry toluene, 80 °C, 12h, 90%.*



26a-26g **22a-22g**

Scheme 11.

Table 1. RCM reactions of allyl and acrylamide in toluene at 80 °C.

entry	substrate	R	R^1	R^2	product	Yield (%)
1	**26a**	PMB	H	H	**22a**	98
2	**26b**	PMB	Me	H	**22b**	45
3	**26c**	PMB	Me	Et	**22c**	40
4	**26d**	Bn	Me	Me	**22d**	45
5	**26e**	Bn	Me	Et	**22e**	43
6	**26f**	BOC	Me	H	**22f**	37
7	**26g**	alkyl	H	CO_2Et	**22g**	92

From the results in table 1 it is observed that the substituent present on allyl moiety (electron rich olefin) has a profound influence on the rate of reaction as well as yield and not the substituent present on acrylamide (electron deficient olefin).

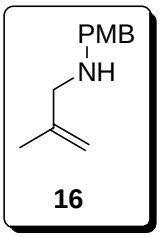
3.1.5 Conclusion:

The synthesis of key intermediate **1** has been achieved by three different synthetic routes, first is intramolecular Knoevenagel condensation as key step for C=C formation in nine-steps in 18% overall yield. Second is novel and efficient Pd-catalyzed cyclization in six-steps in 25% overall yield and third one is the short and efficient by RCM strategy in four-steps in 55% overall yield (based on the recovery of SM), and the generality generalized and the substituent effect on the efficiency of RCM reaction was studied.

3.1.6 Experimental

***N*- (4-Methoxybenzyl)-2- methyl prop –2- en –1- amine (16).**

Method A



16

(i) To the stirred solution of methallyl chloride **17** (1.0 g, 1.08 mL, 11 mmol) in anhydrous DMSO (15 mL), was added NaN_3 (1.07 g, 16.05 mmol) and the resultant reaction mixture was heated at 70 ^oC under inert atmosphere for 15 h. After the completion of the reaction (TLC), the DMSO was removed by water wash and extracted with Et_2O (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure furnished the corresponding azide **18**. (ii) To a well stirred solution of the above crude methallyl azide **18** (assuming 100% conversion) in Et_2O (20 mL), PPh_3 (3.18 g, 12.1 mmol) was added at 0 ^oC, after 1 h H_2O (2 mL) was added and reaction mixture was allowed stir at room temperature till the completion of the reaction (14 h, TLC). The reaction mixture was poured into ice-water and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* yielded the crude methallyl amine **19**. (iii) A mixture of crude methallyl amine **19** (assuming 100 % conversion) and *p*-anisaldehyde (1.79 g, 1.59 mL, 13.2 mmol) in anhydrous MeOH (20 mL) was stirred at 0 ^oC for 1 h and after the completion of reaction (TLC), $NaBH_4$ (0.5 g, 13.2 mmol) was added portion wise at 0 ^oC and allowed to stir till the completion of reaction (TLC). After the completion of reaction, methanol was removed *in vacuo* and residue was quenched with the addition of cold H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (2:3) as eluent to furnish amine **16** as colourless oil (1.28 g, 61% yield).

Method B

To the stirred solution of 4-methoxybenzylamine **27** (1.0 g, 7.2 mmol) in anhydrous CH_2Cl_2 (10 mL), K_2CO_3 (3.03 g, 21.6 mmol) was added at 0 ^oC and stirred for 30 minutes and a solution methallyl chloride (0.217 g, 0.234 mL, 2.37 mmol) in CH_2Cl_2 (5 mL) was added drop wise over 10 minutes at 0 ^oC under N_2 atmosphere. The reaction mixture was allowed to stir for 3 h and the progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was quenched by the addition of saturated

ammonium chloride solution and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (2:3) as eluent furnished amine **16** as a colourless oil (0.384 g, 84% yield), 0.670 g starting material was recovered.

MF: $C_{12}H_{17}NO$, **MW**: 191

IR ($CHCl_3$) ν_{max}: 1611, 1512, 1216, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.78 (s, 3H), 1.85 (s, 1H), 3.18 (s, 2H), 3.70 (s, 2H), 3.80 (s, 3H), 4.86 (s, 1H), 4.90 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.25 ppm (d, *J* = 8.7 Hz, 2H).

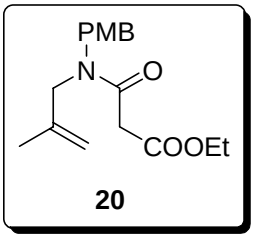
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 20.5, 52.1, 54.5, 54.6, 110.6, 113.3, 128.9, 132.1, 143.4, 158.3 ppm.

MS (ESI) *m/z*: 192 $(M + H)^+$.

Elemental analysis Calculated: C, 75.35; H, 8.96; N, 7.32%.

Found: C, 75.23; H, 9.07; N, 7.27%.

Ethyl 3- (4-methoxybenzyl) (2-methylallyl) amino –3- oxopropanoate (20)



20

To a stirred solution of **16** (1.25 g, 0.65 mmol) in anhydrous CH_2Cl_2 (15 mL), K_2CO_3 (2.72 g, 1.2 mmol) was added and stirred for 15 minutes at 0 ^oC and then ethyl malonyl chloride (1.17 g, 0.98 mL, 0.78 mmol) was added drop wise over 10-15 minutes at 0 ^oC. The progress of reaction was monitored on TLC. After the completion of reaction, the reaction mixture was filtered and residue was washed with CH_2Cl_2 (3 x 15 mL). The filtrate was concentrated *in vacuo* and resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:4) as eluent to render the amide **20** as colourless oil (1.71 g, 86% yield).

MF: $C_{17}H_{23}NO_4$, **MW**: 305

IR ($CHCl_3$) ν_{max}: 3461, 3007, 1735, 1654, 1512, 1248, 1035, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.29 (t, *J* = 7.1 Hz, 3H), 1.70, 1.72 (s, s, 3H), 3.43, 3.48 (s, s, 2H), 3.66, 3.96 (s, s, 2H), 3.79, 3.80 (s, s, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.41, 4.53 (s, s, 2H), 4.82, 4.93 (d, d, (1:2), *J* = 12.4 Hz, 2H), 6.82, 6.86 (d, d, *J* = 8.7 Hz, 2H), 7.75, 7.18 ppm (d, d, *J* = 8.7 Hz, 2H) (mixture of rotamers).

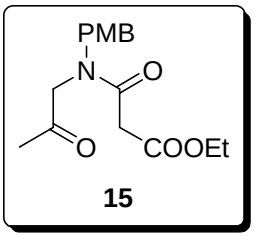
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 14.0, 20.0, 41.0, 41.15, 47.7, 49.6, 50.1, 52.2, 55.0, 61.2, 111.6, 112.65, 113.8, 114.25, 127.5, 127.8, 128.9, 129.3, 139.5, 140.1, 158.9, 159.1, 166.1, 166.5, 167.4 ppm (mixture of rotamers).

MS (ESI) *m/z*: 306 $(M + H)^+$, 328 $(M + Na)^+$.

Elemental analysis Calculated: 66.86; H, 7.59; N, 4.59%.

Found: C, 67.09; H, 7.42; N, 4.35%.

Ethyl 3 (4-methoxybenzyl) (2-oxopropyl) amino) –3- oxopropanoate (15)



15

To the stirred solution of olefin **20** (1.6 g, 5.2 mmol) in (15 mL acetone & 5 mL H_2O), catalytic amount of OsO_4 was added at room temperature and stirred for 10 minutes. The reaction mixture became black coloured, then $NaIO_4$ (2.46 g, 11.5 mmol) was added portion wise and reaction mixture was allowed to stir for 3-4 h. After the completion of reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure and the residue was dissolved in H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*, the residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (3:7) as eluent furnished compound **15** as a thick colourless syrup (1.43 g, 89% yield).

MF: $C_{16}H_{21}NO_5$, **MW**: 307

IR ($CHCl_3$) ν_{max}: 3450, 2982, 2937, 1735, 1651, 1513, 1248, 1174, 1033, 818, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.26, 1.29 (t, t, *J* = 7.1 Hz, 3H), 2.06 (t, *J* = 5.9 Hz 3H), 3.32, 3.56 (s, s, 2H), 3.78, 3.80 (s, s, 3H), 4.05 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.51, 4.54 (s, s, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.11 ppm (d, *J* = 8.8 Hz, 2H) (mixture of rotamers).

^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 14.1, 21.0, 27.1, 27.2, 41.1, 41.6, 49.2, 52.3, 54.65, 55.2, 56.5, 60.3, 61.5, 114.1, 114.4, 127.2, 128.4, 129.7, 159.5, 166.6, 167.2, 202.2, 202.5 ppm (mixture of rotamers).

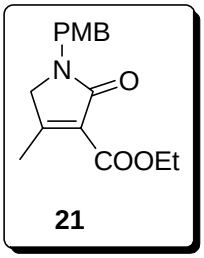
MS (ESI) *m/z*: 308 $(M + H)^+$, 330 $(M + Na)^+$.

Elemental analysis Calculated: C, 62.53; H, 6.89; N, 4.56%.

Found: C, 62.42; H, 7.03; N, 4. 67%.

Ethyl 1-(4-methoxybenzyl) -4- methyl -2- Oxo – 2, 5-dihydro -1H pyrrole -3-carboxylate (**21)**

Method A:



21

60 % NaH (0.195 g, 4.8 mmol) was washed by dry pet ether, (3 x 10 mL) of dry THF was added and cooled the solution at 0 ^{o}C, amide **15** (1.25 g, 4.0 mmol) in anhydrous THF (10 mL) was added dropwise 0 ^{o}C and the reaction mixture was allowed to stir at 0 ^{o}C for 1 hour. After the completion of reaction (TLC), the reaction was quenched by the addition of saturated ammonium chloride solution and the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and solvent was removed on rotary evaporator under diminished pressure. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:2) as eluent afforded compound **21** as pale yellow syrup (0.98 g, 84% yield).

Method B:

To a stirred solution of ester olefin **23** (0.2 g, 0.68 mmol) in DMF-H_2O, (12 mL, 3:1), $PdCl_2$, (0.011 g, 0.068 mmol) and $CuCl_2.2H_2O$ (0.24 g, 1.4 mmol) was added and the resultant solution was heated at 95 ^{o}C. The progress of reaction was monitored by TLC (6-8 h) and the reaction mixture was cooled to room temperature and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was remover on rotary evaporator under diminished pressure and the residue obtained was purified by flashed column chromatography (SiO_2) eluting with the mixture of ethyl acetate-petroleum ether (2:3) as eluent furnished cyclized product **21** (0.122 g, 62% yield) as a pale yellow syrup.

MF: $C_{16}H_{19}NO_4$, **MW**: 289

IR ($CHCl_3$) ν_{max}: 1721, 1687, 1214, 757 cm^{-1}

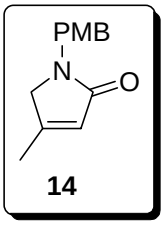
^{1}H NMR ($CDCl_3$ + CCl_4, 300 MHz) δ: 1.38 (t, *J* = 7.1 Hz, 3H), 2.29 (s, 3H), 3.74 (s, 2H), 3.78 (s, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.52 (s, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.15 ppm (d, *J* = 8.8 Hz, 2H).

MS (ESI) *m/z*: 290 $(M + H)^+$, 312 $(M + Na)^+$.

Elemental analysis Calculated: C, 66.42; H, 6.62; N, 4.84%.

Found: C, 66.56; H, 6.45; N, 4. 77%.

1- (4- methoxybenzyl) -4- methyl -1H pyrrol -2 (5H) – one (14)



To the stirred solution of **21** (0.5 g, 1.7 mmol) in DMSO-H_2O (20 mL, 3:1), NaCl (0.4 g, 6.8 mmol) was added and resultant reaction mixture was heated at 120-130 ^oC for 6-7 h. After the disappearance of starting material (TLC), the reaction mixture was allowed to cool at room temperature, diluted with water (25 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (4:6) as eluent gave compound **14** as a pale yellow solid (0.326 g, 87% yield).

MF: $C_{13}H_{15}NO_2$, **MW**: 217

M. P.: 122 ^oC

IR ($CHCl_3$) ν_{max}: 3347, 1672, 1513, 1247, 1216, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 300 MHz) δ: 2.01 (s, 3H), 3.68 (s, 2H), 3.78 (s, 3H), 4.50 (s, 2H), 5.85 (s, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.14 ppm (d, *J* = 8.8 Hz, 2H).

^{13}C NMR ($CDCl_3$ + CCl_4, 75 MHz) δ: 15.05, 45.05, 54.7, 55.0, 114.0, 122.7, 129.1, 129.5, 154.9, 159.0, 171.6 ppm.

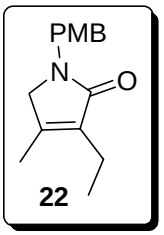
MS (ESI) *m/z*: 218 $(M + H)^+$, 240 $(M + Na)^+$.

Elemental analysis Calculated: C, 71.87; H, 6.96; N, 6.45%.

Found: C, 71.61; H, 6.98; N, 6.69%.

4.1.4 3-Ethyl-1-(-4-methoxy-benzyl)-4-methyl-1, 5-dihydro-pyrrol-2-one (22)

Method A



To a 60% NaH (0.044 g, 1.08 mmol) prewashed with anhydrous petroleum ether (3 x 10 mL) was added **14** (0.2 g, 0.9 mmol) in anhydrous THF (10 mL) slowly at 0 ^oC stirred for 15 minutes followed by ethyl iodide (0.158 g, 0.081 mL, 0.99 mmol) in anhydrous THF (5 mL) dropwise addition at 0 ^oC and the reaction mixture was allowed stir for 2-3 h. The progress of reaction was monitored by TLC. The reaction was quenched with addition of saturated ammonium chloride solution and organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and solvent was evaporated *in vacuo* and the resultant residue

was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:4) as eluent furnished lactam **22** as a yellow solid mp- 127-131 ^oC (0.160 g, 71% yield).

Method B

To a degassed homogeneous solution of **26** (0.2 g, 0.7 mmol) in anhydrous toluene (20 mL), Grubbs' second generation catalyst (0.062 g, 10 mol %) was added under an argon atmospheres. The resultant reaction mixture was heated at 80 ^oC for 12 h and after the completion of reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure and residue thus obtained was purified by flash column chromatography (SiO_2) eluting with ethyl acetate-petroleum ether (1:4) to provide lactam **22 (22C)** as a yellow solid (0.072 g, 40% yield) and 0.11 g of starting material was recovered.

MF: $C_{15}H_{19}NO_2$, **MW**: 245

M.P.: 127-131 ^oC

IR ($CHCl_3$) ν_{max}: 1671, 1515, 1248, 1212, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.07 (t, *J* = 7.6 Hz, 3H), 1.91 (s, 3H), 2.28 (q, *J* = 7.6 Hz, 2H), 3.56 (s, 2H), 3.77 (s, 3H), 4.51 (s, 2H), 5.85 (s, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.14 ppm (d, *J* = 8.8 Hz, 2H).

^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 12.9, 12.95, 18.9, 46.1, 53.2, 54.3, 113.8, 128.1, 128.6, 135.0, 144.95, 158.7, 171.7 ppm.

MS (ESI) *m/z*: 246 $(M + H)^+$, 268 $(M + Na)^+$.

Elemental analysis Calculated: C, 73.44; H, 7.81; N, 5.71%.

Found: C, 73.47; H, 7.78; N, 5.76%.

(22a) ^{1}H NMR (CDCl3, 200 MHz) δ: 3.79 (s, 3H), 3.85 (s, 2H), 4.57 (s, 2H), 6.20 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.17 ppm (d, *J* = 8.0 Hz, 2H).

(22b) ^{1}H NMR (CDCl3, 200 MHz) δ: 1.98 & 1.99 (2s, 3H), 3.67 (s, 2H), 3.75 & 3.77 (2s, 3H), 4.50 (s, 2H), 5.83 & 5.84 (2s, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 7.15 ppm (d, *J* = 8.0 Hz, 2H).

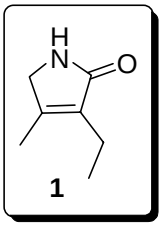
(22d) ^{1}H NMR (CDCl3, 200 MHz) δ: 1.82 (s, 3H), 1.91 (s, 3H), 3.59 (s, 2H), 4.59 (s, 2H), 7.35 ppm (s, 5H).

(22e) ^{1}H NMR (CDCl3, 200 MHz) δ: 1.03 (t, *J* = 7.3 Hz, 3H), 1.86 (s, 3H), 2.24 (q, *J* = 7.3 Hz, 2H), 3.52 (s, 2H), 4.52 (s, 2H), 7.15-7.26 ppm (m, 5H).

(22f) Spectral data of compound **22f** has mentioned in Ch. 3, Sec II, compound **5**.

(22g) ^{1}H NMR (CDCl3, 200 MHz) δ: 1.28 (t, *J* = 7.2 Hz, 3H), 1.95-2.04 (m, 2H), 2.22-2.61 (m, 2H), 3.45-3.71 (m, 2H), 3.80 (dd, *J* = 14.0 & 6.0 Hz, 1H), 3.93 (s, 4H), 4.24 (q, *J* = 7.2 Hz, 2H), 7.31 ppm (dd, *J* = 6.0 & 2.0 Hz).

3- Ethyl –4- methyl –3- pyrrolin –2- one (2)



To a stirred solution of lactam **22** (0.1 g, 0.40 mmol) in CH_3CN (10 mL) and H_2O (2 mL), Cerium ammonium nitrate (0.447 g, 0.80 mmol) was added. The reaction mixture was allowed to stir at room temperature till the completion of reaction (2 h) by TLC. The solvent was removed on rotary evaporator under diminished pressure, the resultant residue was diluted with H_2O (40 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:2) as eluent furnished target **1** as a pale yellow solid (0.036 g, 80% yield).

MF: $C_7H_{11}NO$, **MW**: 124

M.P.: 102 ^oC

IR ($CHCl_3$) ν_{max}: 3326, 2974, 1681, 1451, 1216 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.02 (t, *J* = 7.4 Hz, 3H), 1.95 (s, 3H), 2.22 (q, *J* = 7.4 Hz, 2H), 3.76 (s, 2H), 8.04 ppm (bs, 1H).

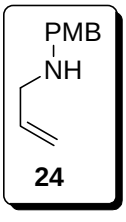
^{13}C NMR ($CDCl_3$, 75 MHz) δ: 12.3, 12.5, 16.0, 49.7, 133.4, 148.2, 175.9 ppm.

MS (ESI) *m/z*: 125 $(M)^+$.

Elemental analysis Calculated: C, 67.17; H, 8.86; N, 11.19%.

Found: C, 66.93; H, 9.11; N, 11.38%.

***N*- (4-methoxybenzyl) prop -2- en -1-amine (24)**



To the stirred solution of allyl amine **25** (1.0 g, 1.3 mL, 17.5 mmol) in dry methanol (20 mL), was added *p*-anisaldehyde (2.62 g, 2.34 mL, 19.25 mmol) at 0 ^oC and stirred for 1 h. After the disappearance of starting material (TLC), $NaBH_4$ (0.66 g, 17.5 mmol) was added portion wise at 0 ^oC and stirred for additional 0.5 h. After the completion of reaction (TLC), the reaction mixture was concentrated *in vacuo* and residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and solvent was evaporated on rotary evaporator under reduced

pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with mixture of ethyl acetate-petroleum ether (4:6) solvent system resulted secondary amine **24** as pale yellow liquid (3.0 g, 97% yield).

MF: $C_{11}H_{15}NO$, **MW**: 177

IR ($CHCl_3$) ν_{max}: 3393, 3019, 1613, 1215, 758 cm^{-1}.

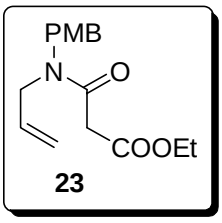
^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.94 (s, 1H), 3.28 (d, *J* = 4.0 Hz, 2H), 3.78 (s, 3H), 4.65 (s, 2H), 5.14-5.28 (m, 2H), 5.91 (m, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 7.26 ppm (d, *J* = 9.0 Hz, 2H).

MS (ESI) *m/z*: 178 $(M + H)^+$.

Elemental analysis Calculated: C, 74.54; H, 8.53; N, 7.90%.

Found: C, 74.59; H, 8.47; N, 7.87%.

Ethyl 3- (allyl (4-methoxybenzyl) amino) -3- oxopropanoate (23)



23

To the stirred solution of **24** (1.0 g, 5.6 mmol) in anhydrous CH_2Cl_2 (10 mL) was added K_2CO_3 (2.3 g, 16.8 mmol) at 0 ^oC and stirred for 15 minutes and then ethyl malonyl chloride (1.0 g, 0.84 mL, 6.72 mmol) was added drop wise at 0 ^oC and left to stir at 0 ^oC under N_2 atmosphere till the completion of reaction (1 h) by TLC. The reaction mixture was filtered and residue was washed with CH_2Cl_2 (3 x 15 mL), the filtrate was concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:4) as eluent furnished amide **23** as a colorless syrup (1.41 g, 86% yield).

MF: $C_{16}H_{21}NO_4$, **MW**: 293

IR ($CHCl_3$) ν_{max}: 3458, 2982, 2936, 1735, 1654, 1513, 1248, 1032 cm^{-1}.

^{1}H ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.28 (t, *J* = 7.2 Hz, 3H), 3.46 (s, 2H), 3.78 (s, 3H), 3.75, 3.97 (s, s, 2H), 4.2 (q, *J* = 7.2 Hz, 2H), 4.43, 4.5 (s, s, 2H), 5.12-5.25 (m, 2H), 5.72 (m, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.16 ppm (d, *J* = 9.0 Hz, 2H) (mixture of rotamers).

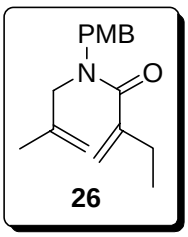
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 14.0, 41.0, 41.1, 47.6, 49.25, 50.1, 55.0, 61.1, 113.8, 114.2, 116.95, 117.4, 127.6, 127.8, 128.9, 129.3, 132.3, 158.9, 159.1, 166.0, 166.2, 167.4 ppm (mixture of rotamers).

MS (ESI) *m/z*: 292 $(M)^+$.

Elemental analysis Calculated: C, 65.96; H, 7.27; N, 4.81%.

Found: C, 66.09; H, 7.19; N, 4.77%.

4.1.2 N-(4-methoxybenzyl)-N- (2-methylallyl) –2- methylenebutanamide (26)



26

To the stirred solution of amine **16** (0.25 g, 1.3 mmol) in anhydrous CH_2Cl_2 (10 mL), K_2CO_3 (0.545 g, 3.9 mmol) was added at 0 ^oC under N_2 atmosphere followed by dropwise addition of ethacryloyl chloride (0.186 g, 1.56 mmol) at 0 ^oC and stirred for 1 h. The progress of the reaction was monitored by TLC, after the completion of reaction, the reaction mixture was filtered and residue washed with CH_2Cl_2 (3 x 10 mL). The filtrate was concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (SiO_2) eluting with mixture of ethyl acetate-petroleum ether (1:4) solvent system to afford compound **26** as a thick colorless oil (0.325 g, 91% yield).

MF: $C_{17}H_{23}NO_2$, **MW**: 273

IR ($CHCl_3$) ν_{max}: 3081, 1970, 1644, 1614, 1512, 1247, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.08 (t, *J* = 7.5 Hz, 3H), 1.65 (s, 3H), 2.33 (q, *J* = 7.5 Hz, 2H), 3.77 (s, 3H), 3.77 (s, 2H), 4.51 (s, 2H), 4.67-4.95 (m, 2H), 5.10 (s, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 7.17 ppm (d, *J* = 8.5 Hz, 2H).

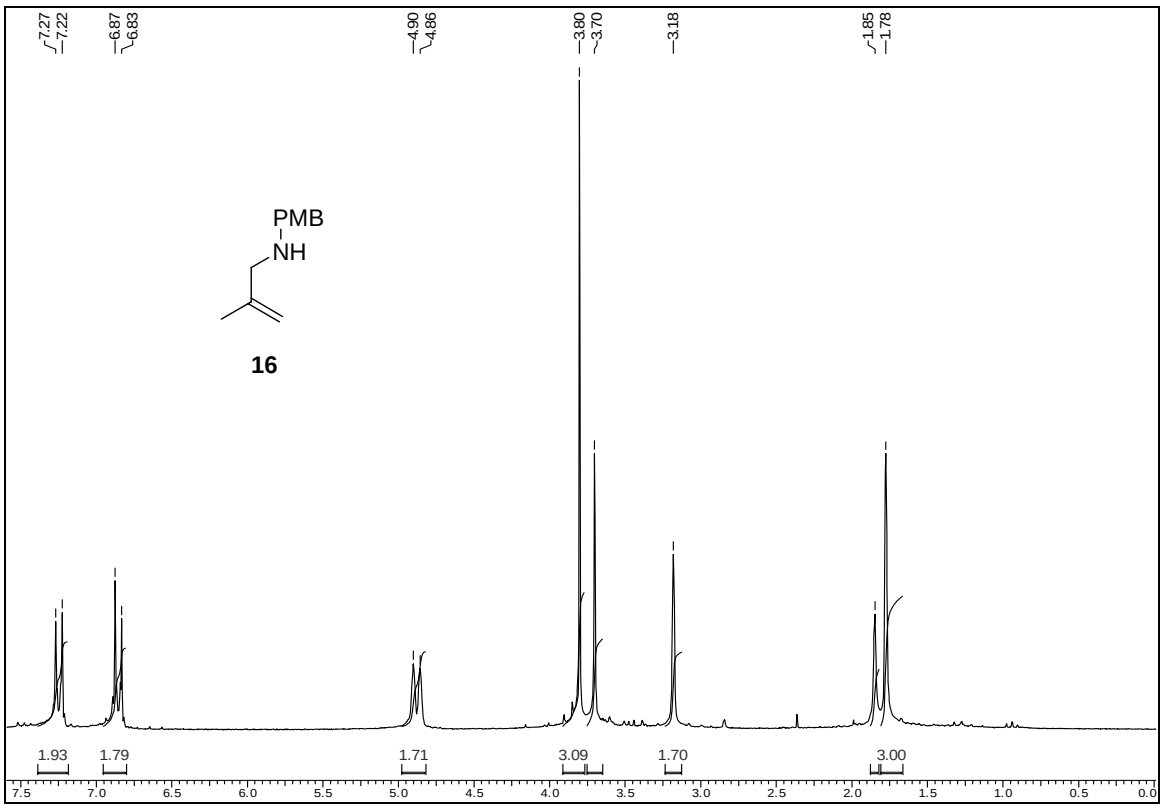
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 11.4, 19.65, 26.9, 45.2, 47.6, 49.8, 52.3, 54.6, 111.9, 112.2, 113.3, 113.6, 127.9, 129.1, 139.9, 146.0, 158.65, 172.3 ppm (mixture of rotamers).

MS (ESI) *m/z*: 274 $(M + H)^+$.

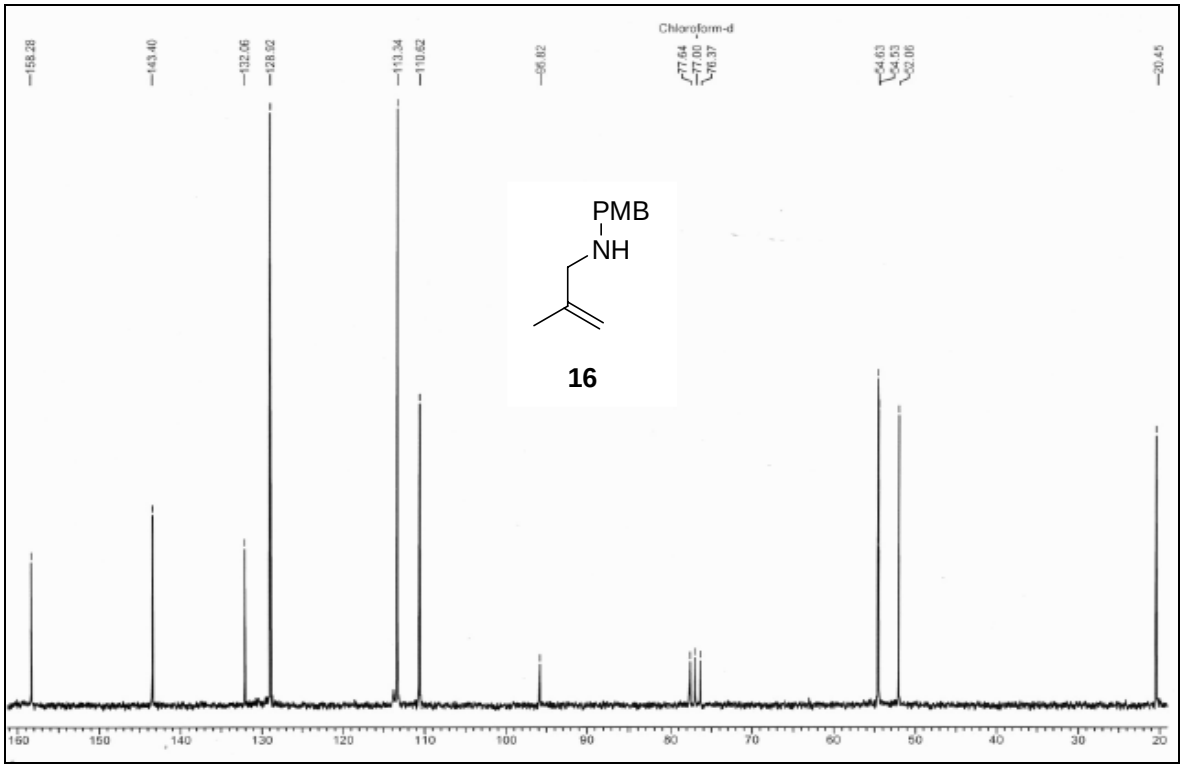
Elemental analysis Calculated: C, 74.69; H, 8.48; N, 5.12%.

Found: C, 74.63; H, 8.37; N, 5.23%.

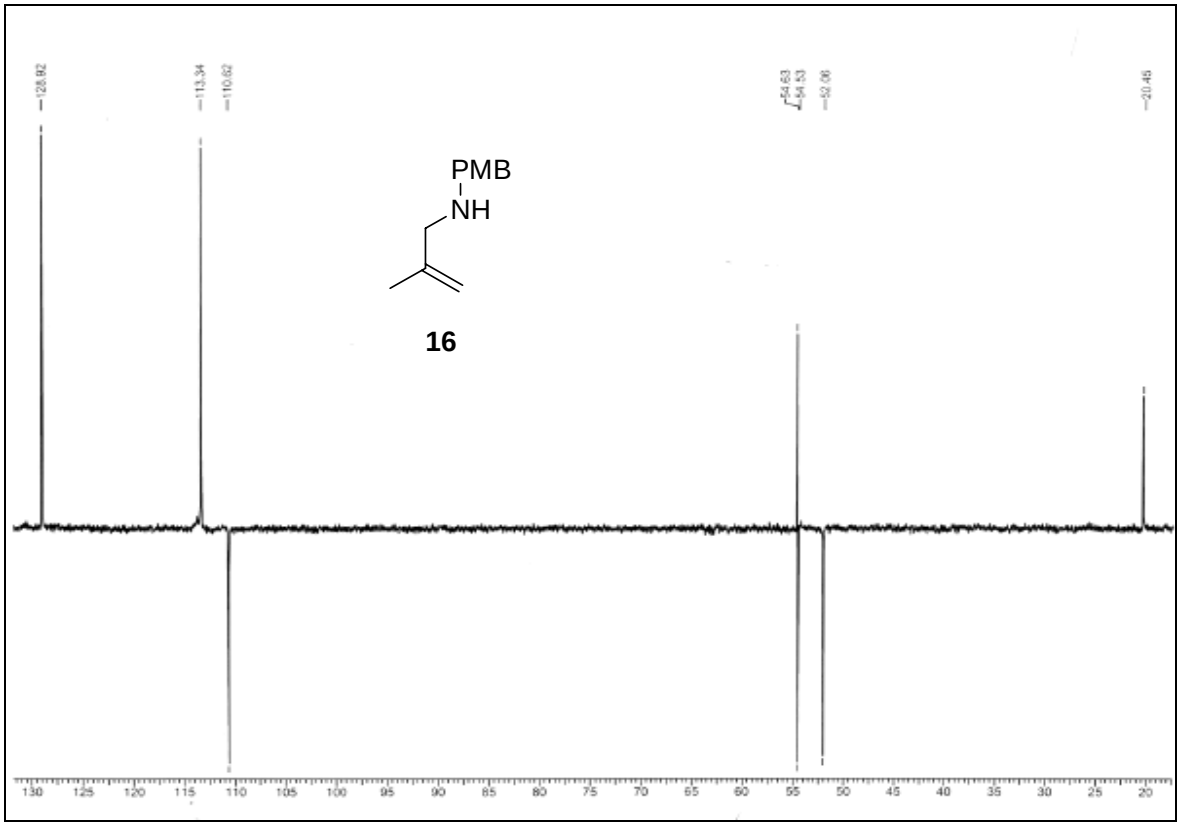
3.1.7 Spectra:



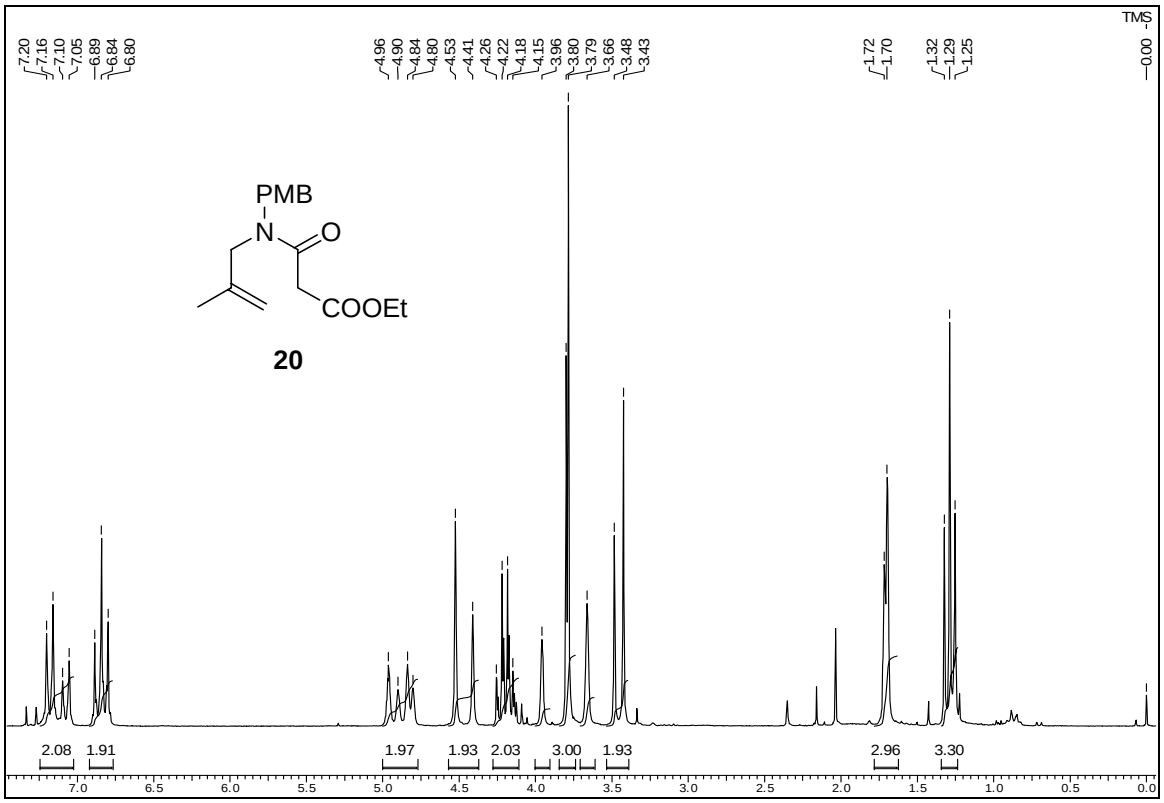
^{1}H NMR spectrum of compound 16 ($CDCl_3$ + CCl_4, 200 MHz)



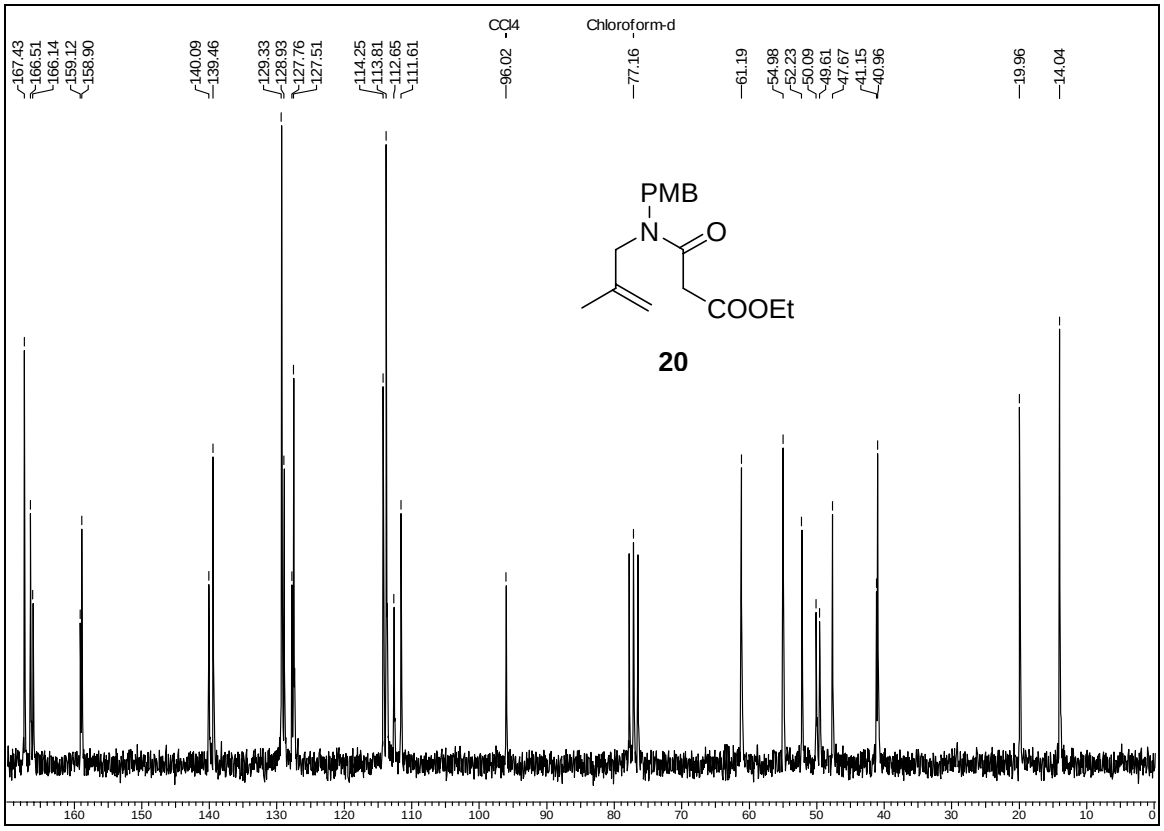
^{13}C NMR spectrum of compound 16 ($CDCl_3$ + CCl_4, 50 MHz)



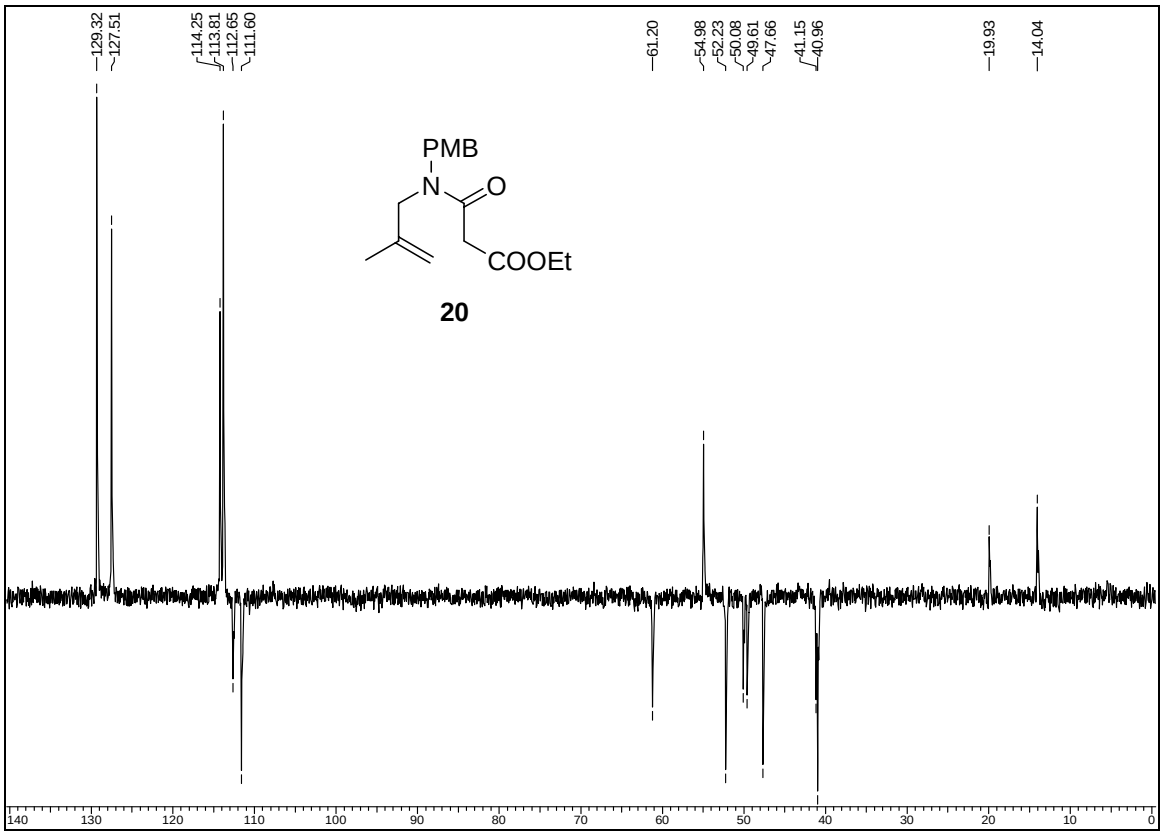
DEPT spectrum of compound 16 ($CDCl_3$ + CCl_4, 50 MHz)



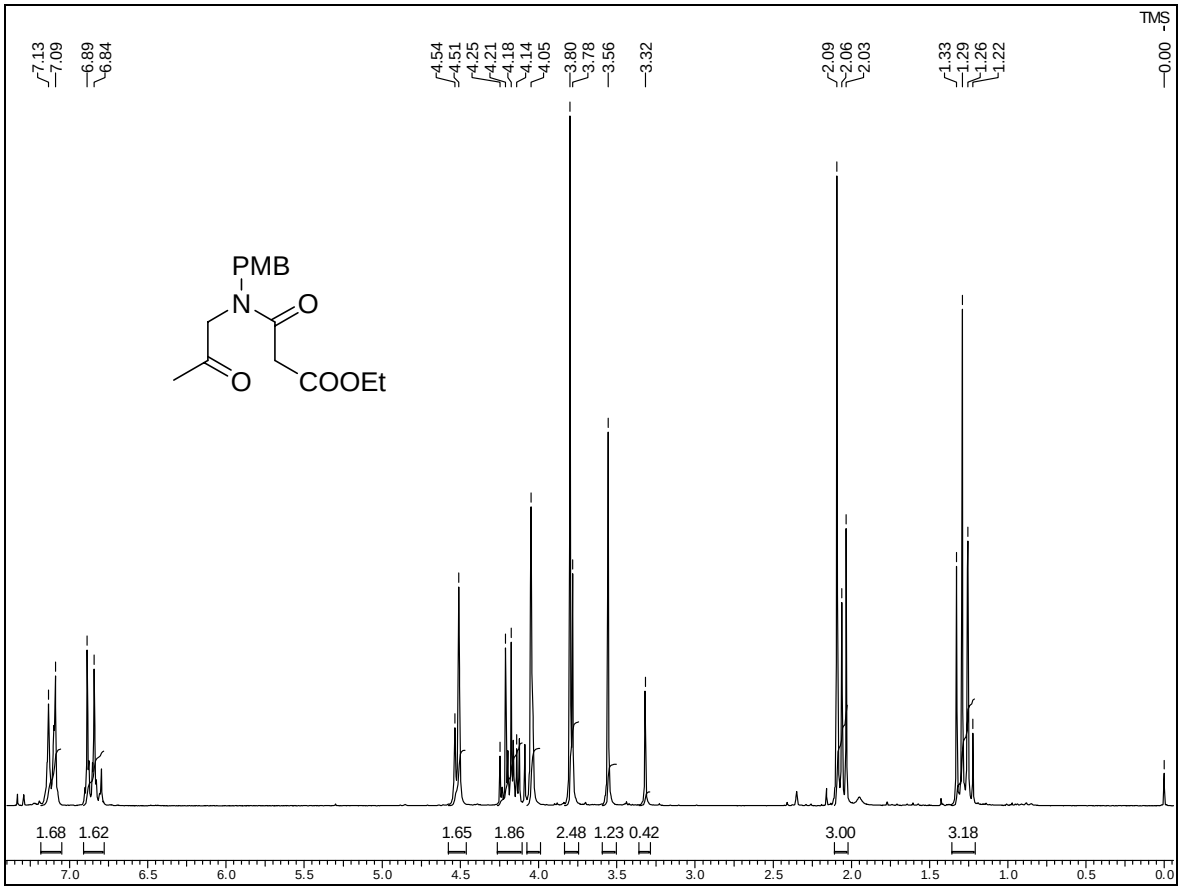
^{1}H NMR spectrum of compound 20 ($CDCl_3$ + CCl_4, 200 MHz)



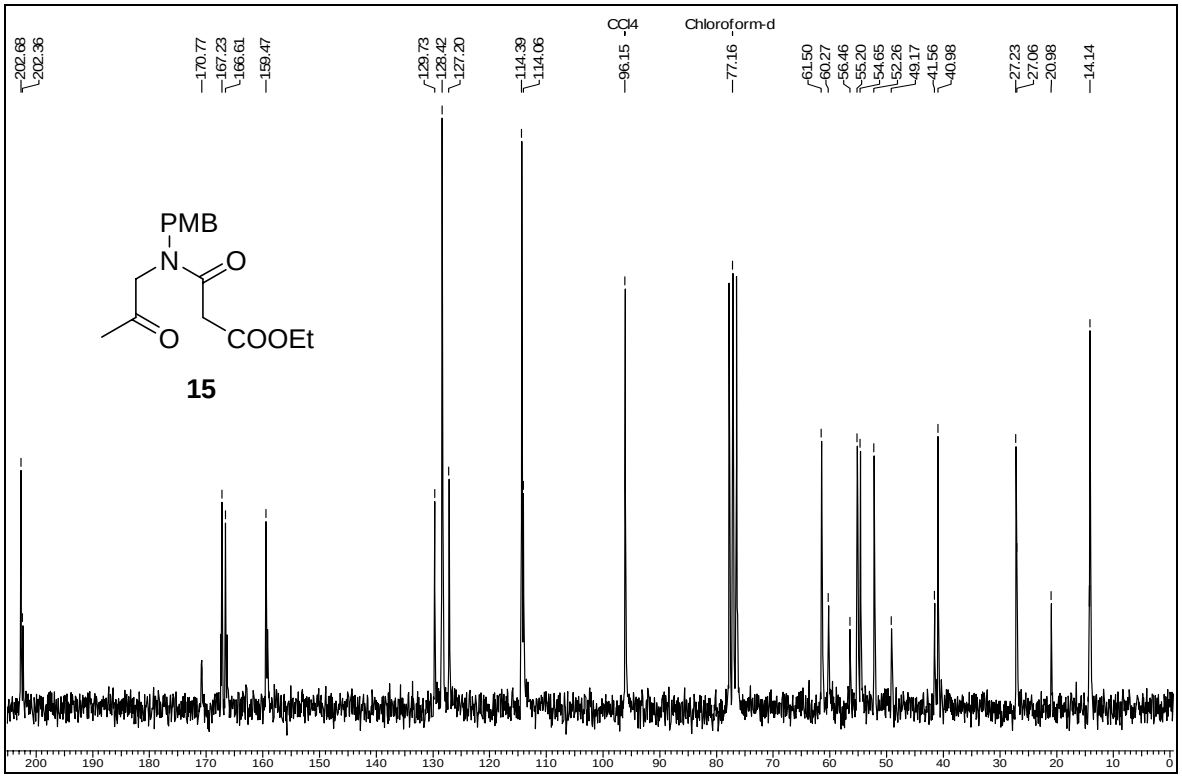
^{13} NMR spectrum of compound 20 ($CDCl_3$ + CCl_4, 50 MHz)



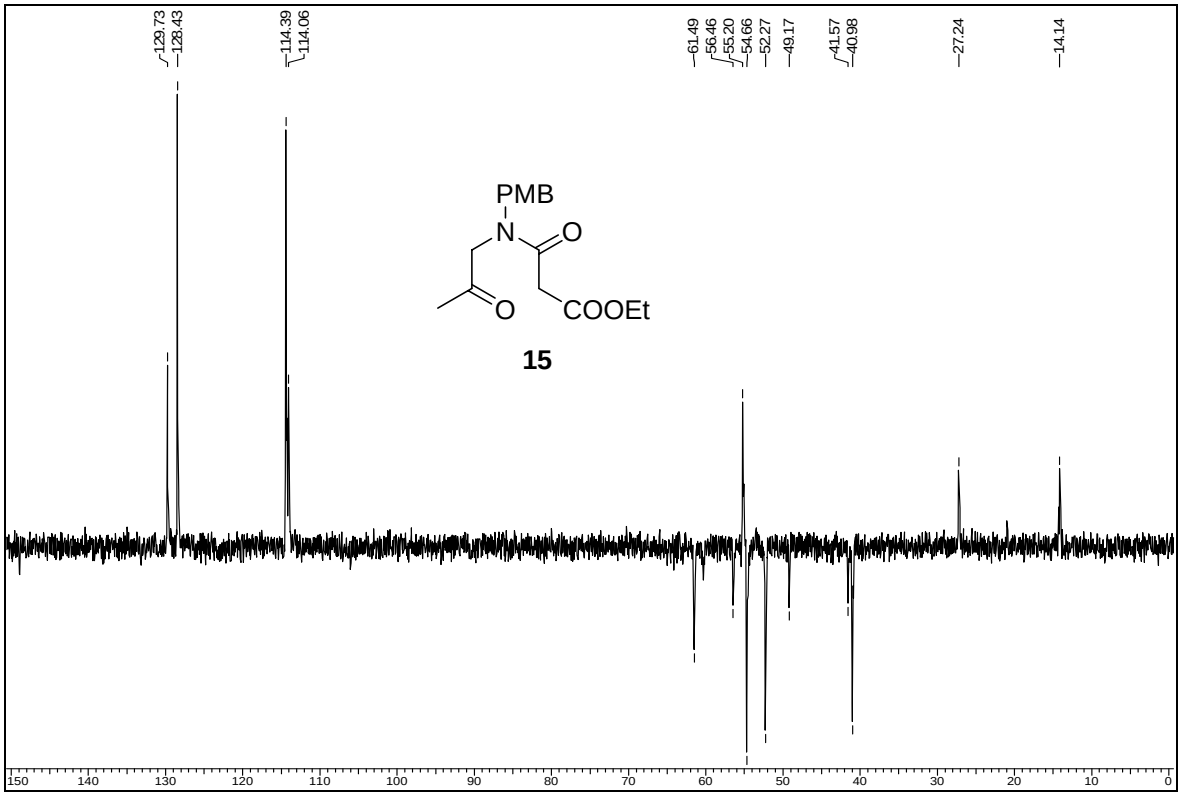
DEPT spectrum of compound 20 ($CDCl_3$ + CCl_4, 50 MHz)



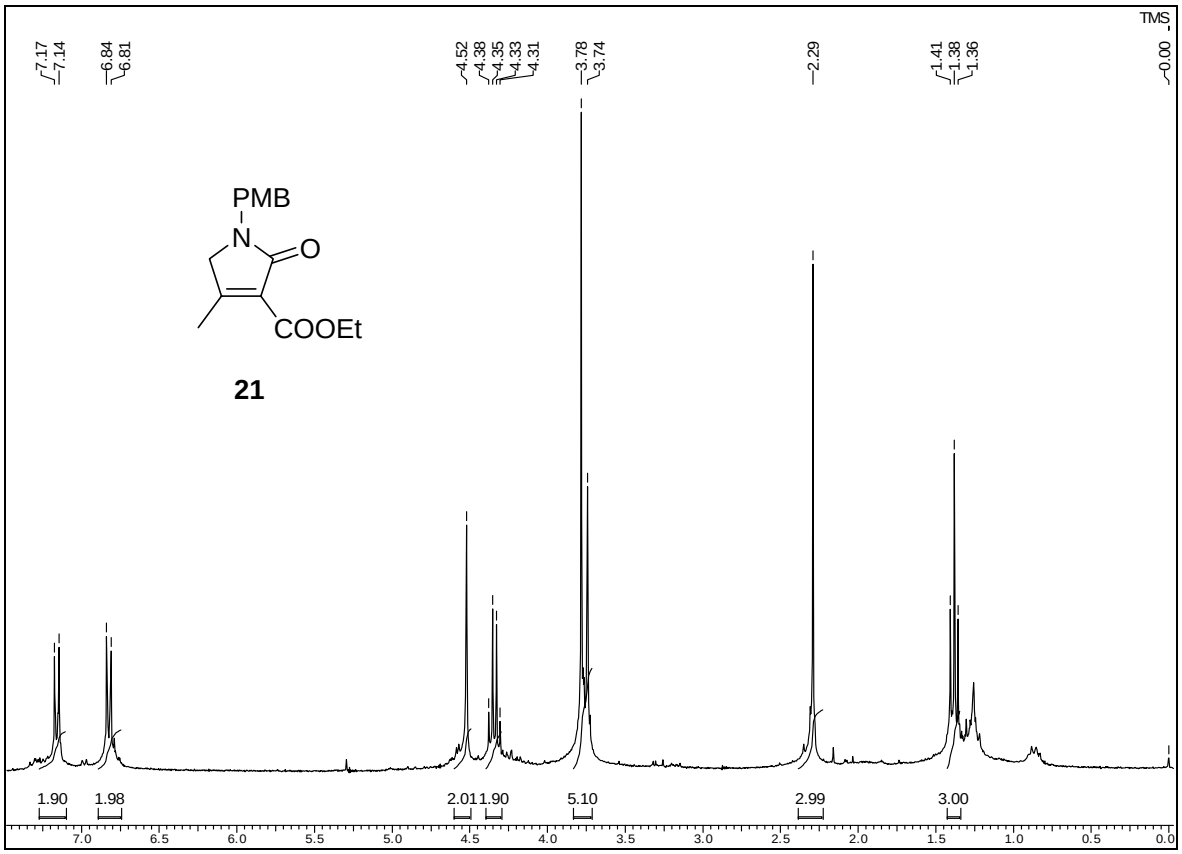
^{1}H NMR spectrum of compound 15 ($CDCl_3$ + CCl_4, 200 MHz)



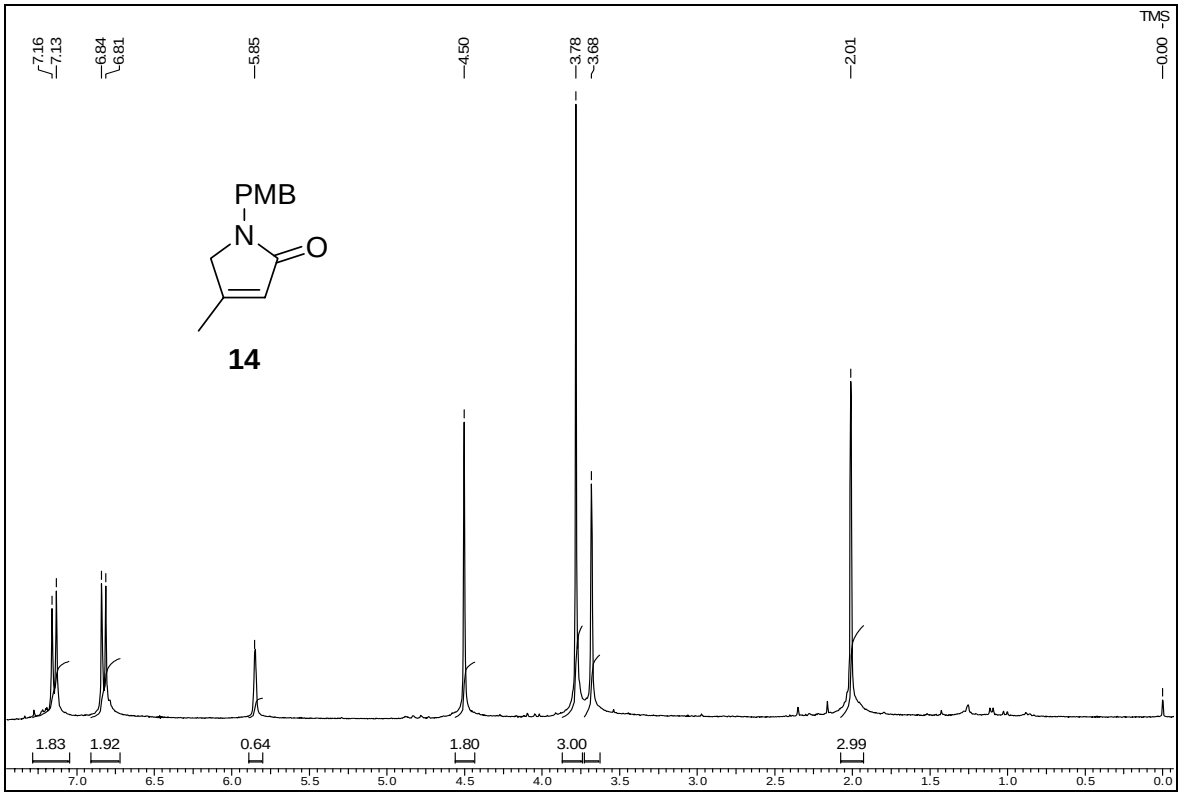
^{13}C NMR spectrum of compound 15 ($CDCl_3$ + CCl_4, 50 MHz)



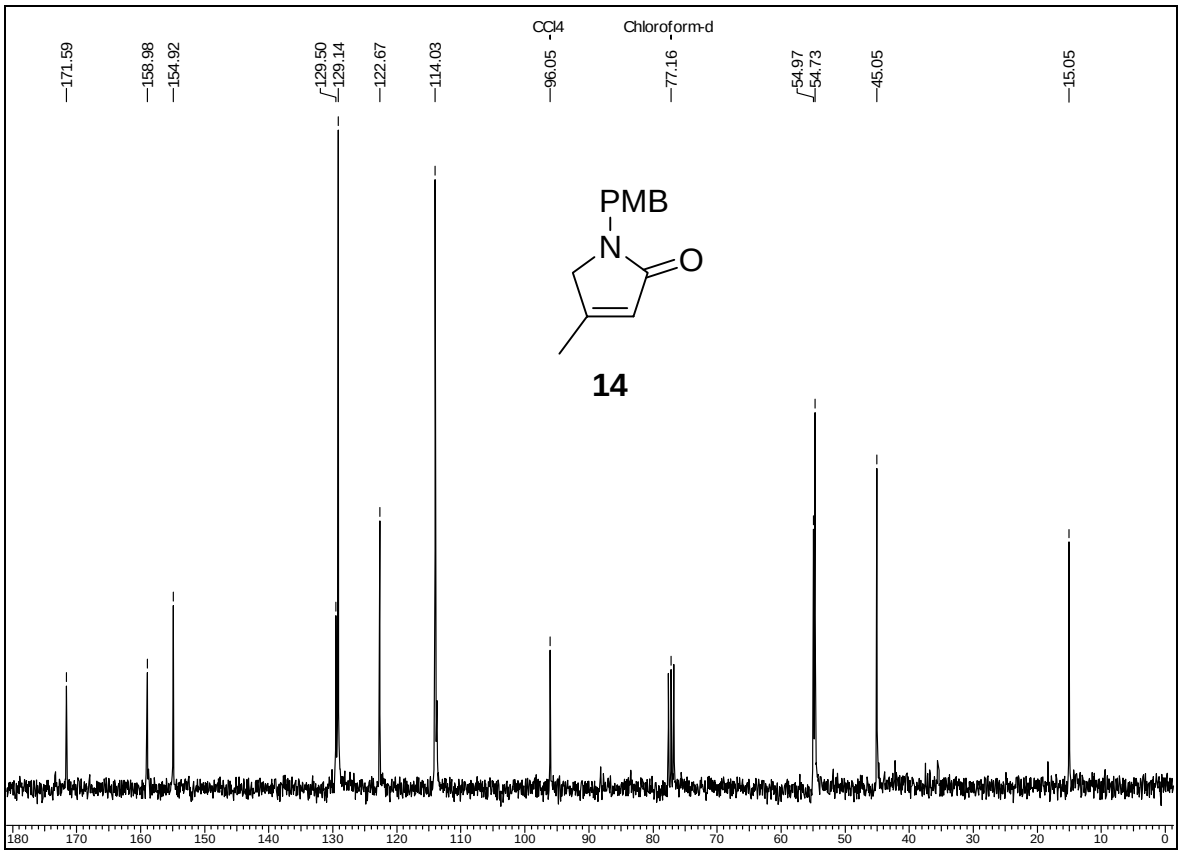
DEPT spectrum of compound 15 ($CDCl_3$ + CCl_4, 50 MHz)



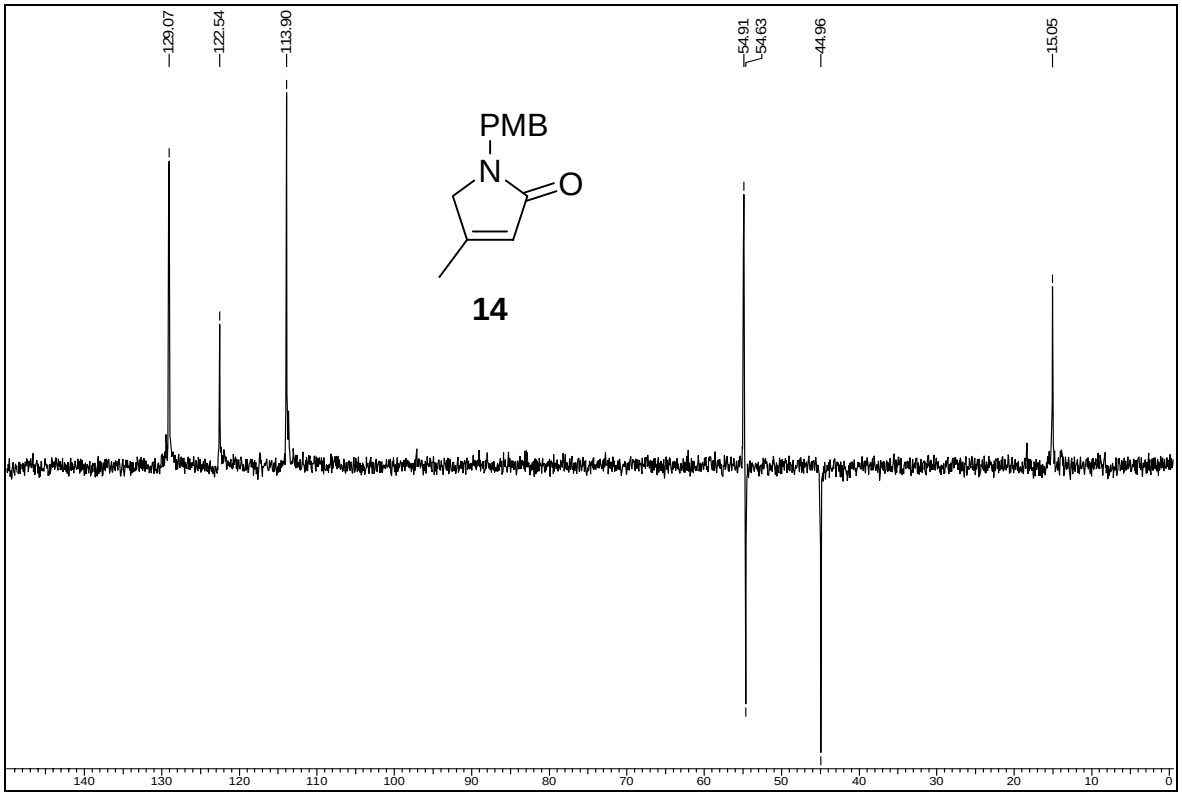
^{1}H NMR spectrum of compound 21 ($CDCl_3$ + CCl_4, 300 MHz)



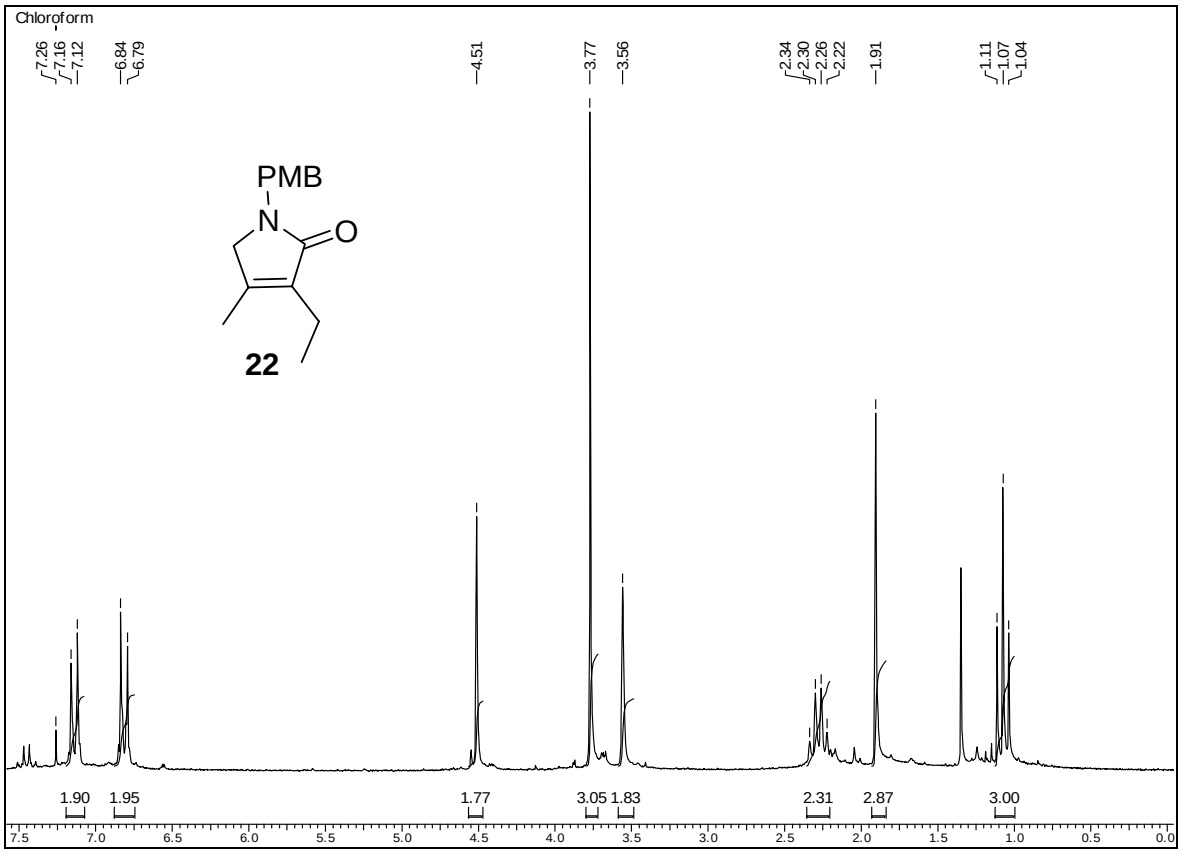
^{1}H NMR spectrum of compound 14 ($CDCl_3$ + CCl_4, 300 MHz)



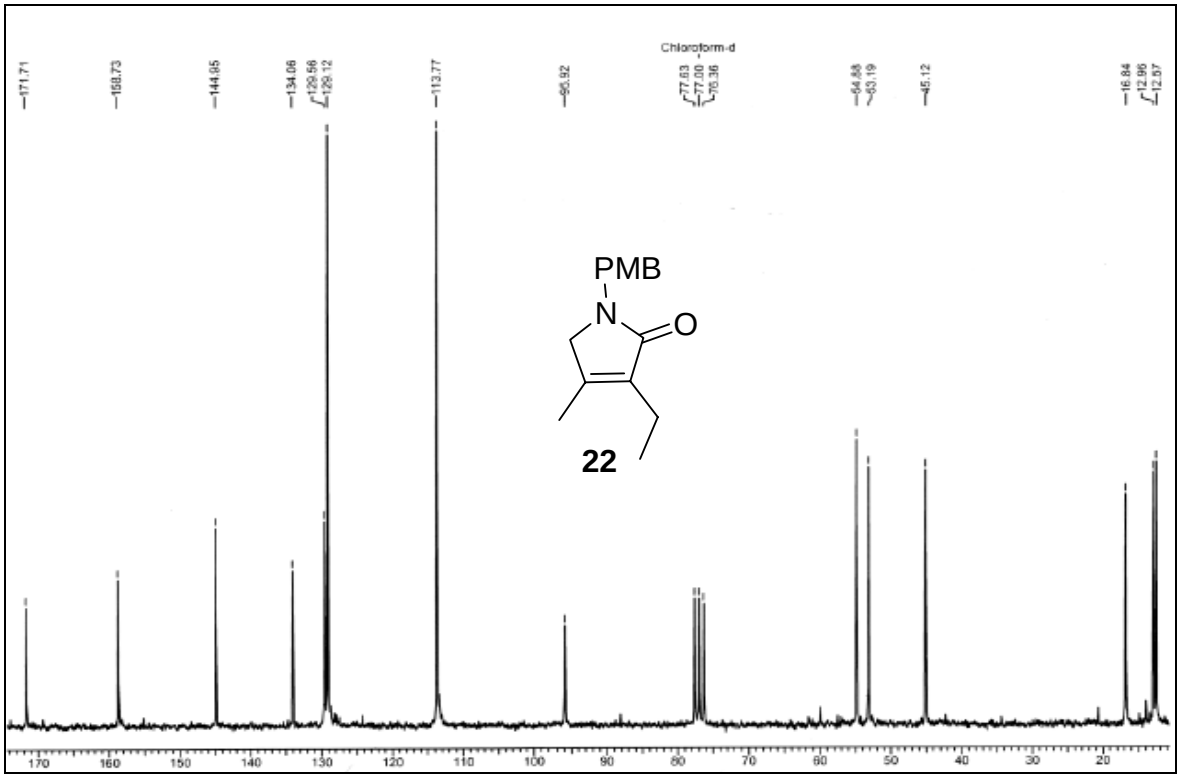
^{13}C NMR spectrum of compound 14 ($CDCl_3$ + CCl_4, 75 MHz)



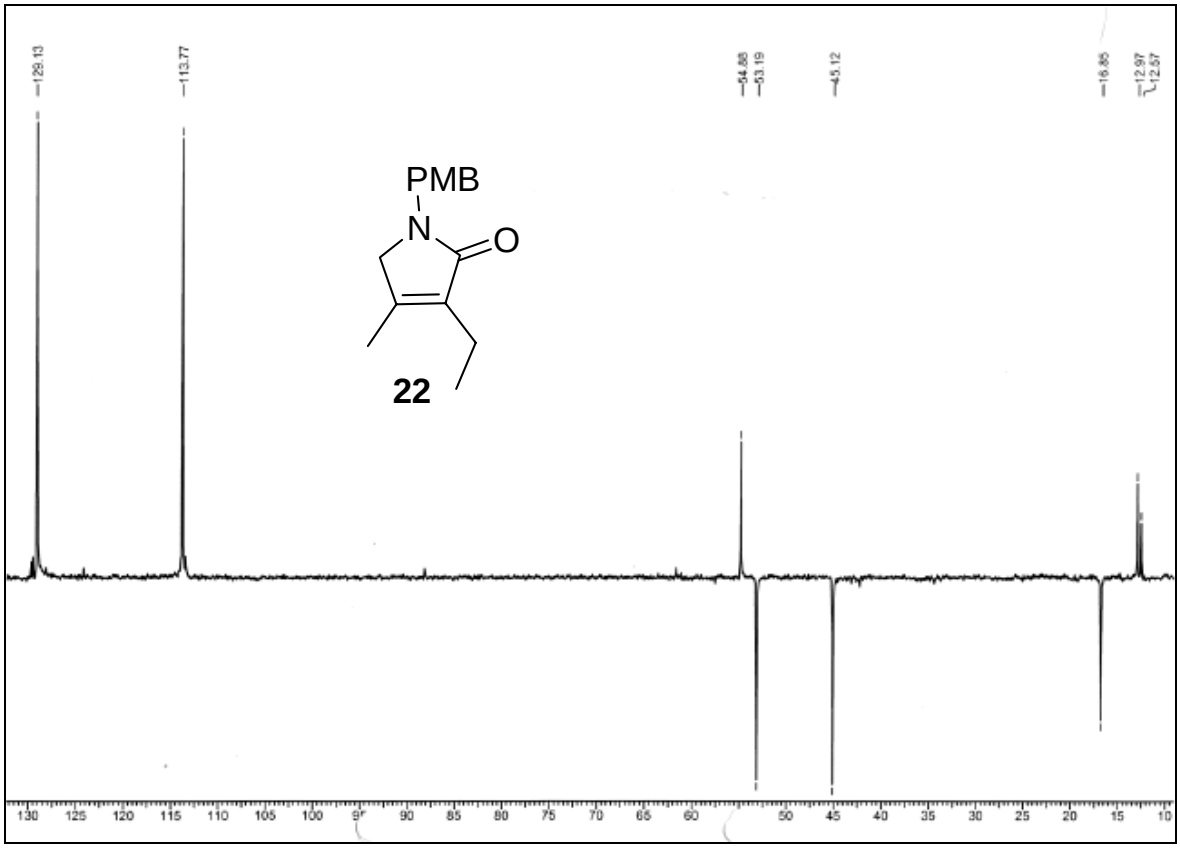
DEPT spectrum of compound 14 ($CDCl_3$ + CCl_4, 75 MHz)



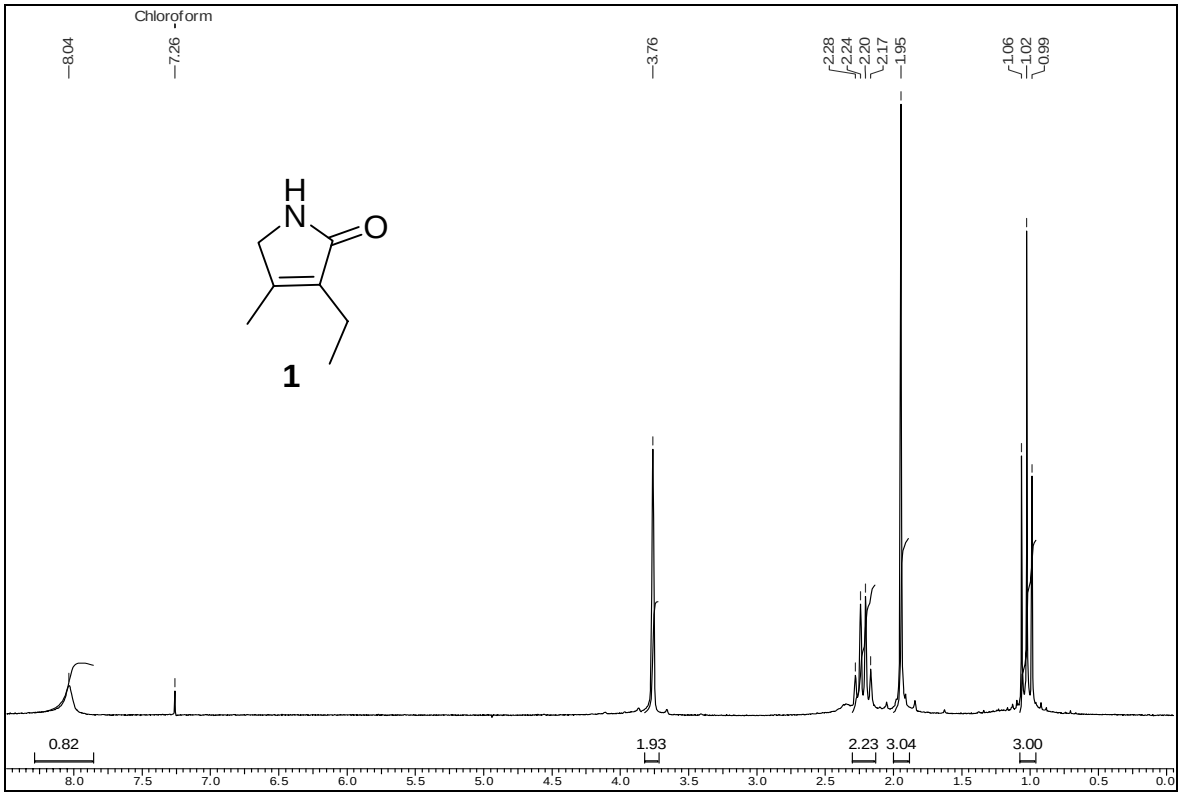
^{1}H NMR spectrum of compound 22 ($CDCl_3$ + CCl_4, 200 MHz)



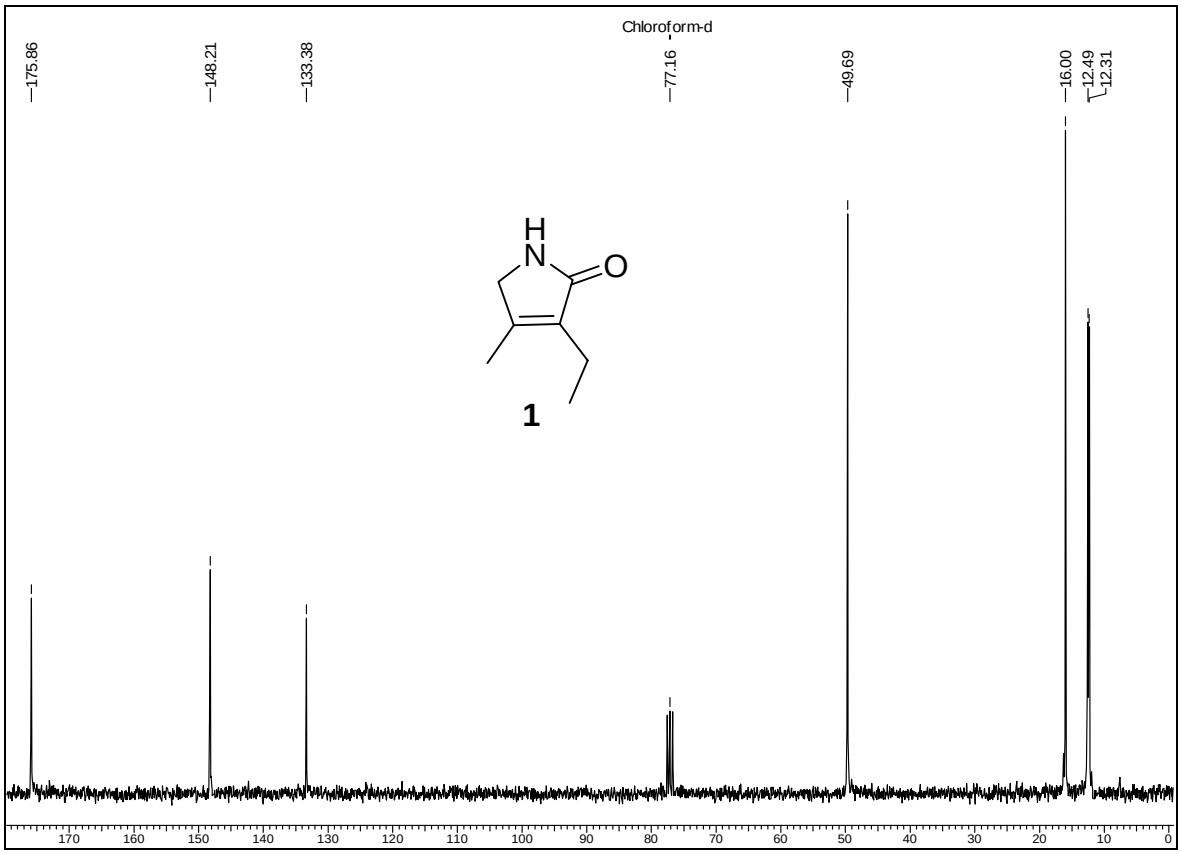
^{13}C NMR spectrum of compound 22 ($CDCl_3$ + CCl_4, 50 MHz)



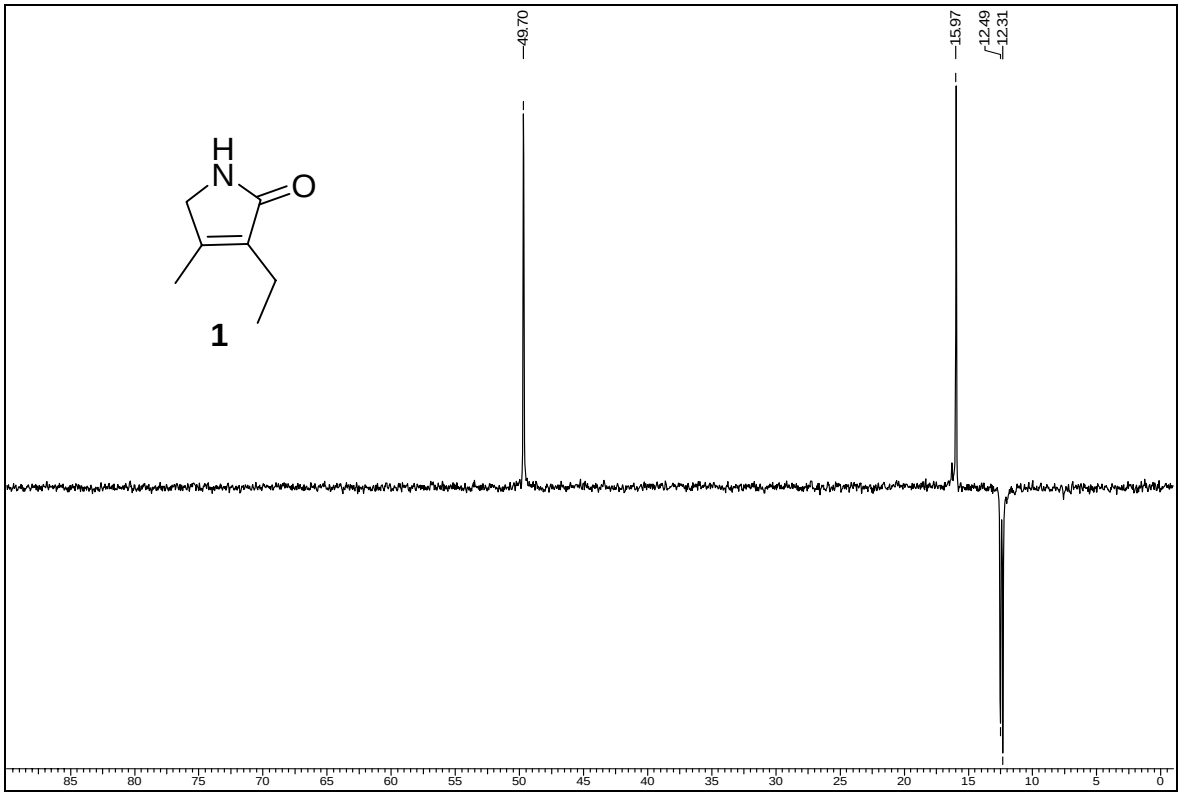
DEPT spectrum of compound 22 ($CDCl_3$ + CCl_4, 50 MHz)



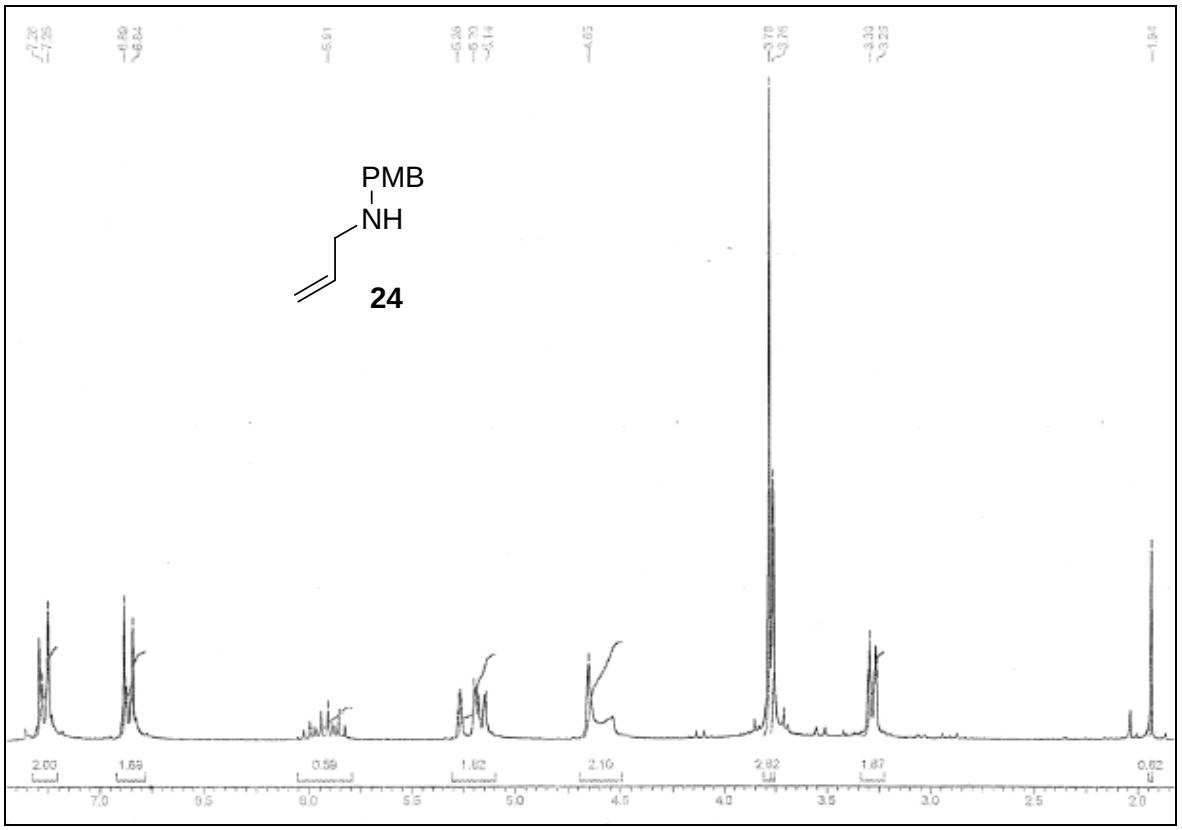
^{1}H NMR spectrum of compound 1 ($CDCl_3$ + CCl_4, 200 MHz)



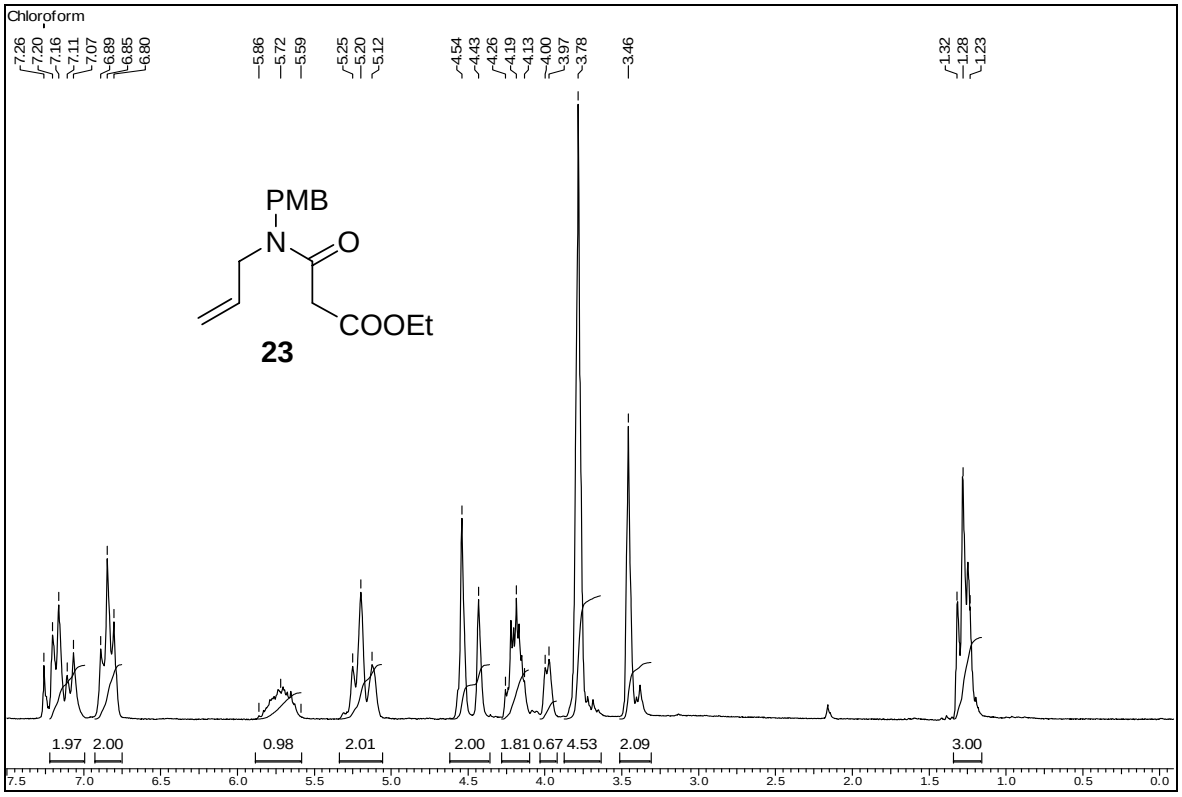
^{13}C NMR spectrum of compound 1 ($CDCl_3$, 75 MHz)



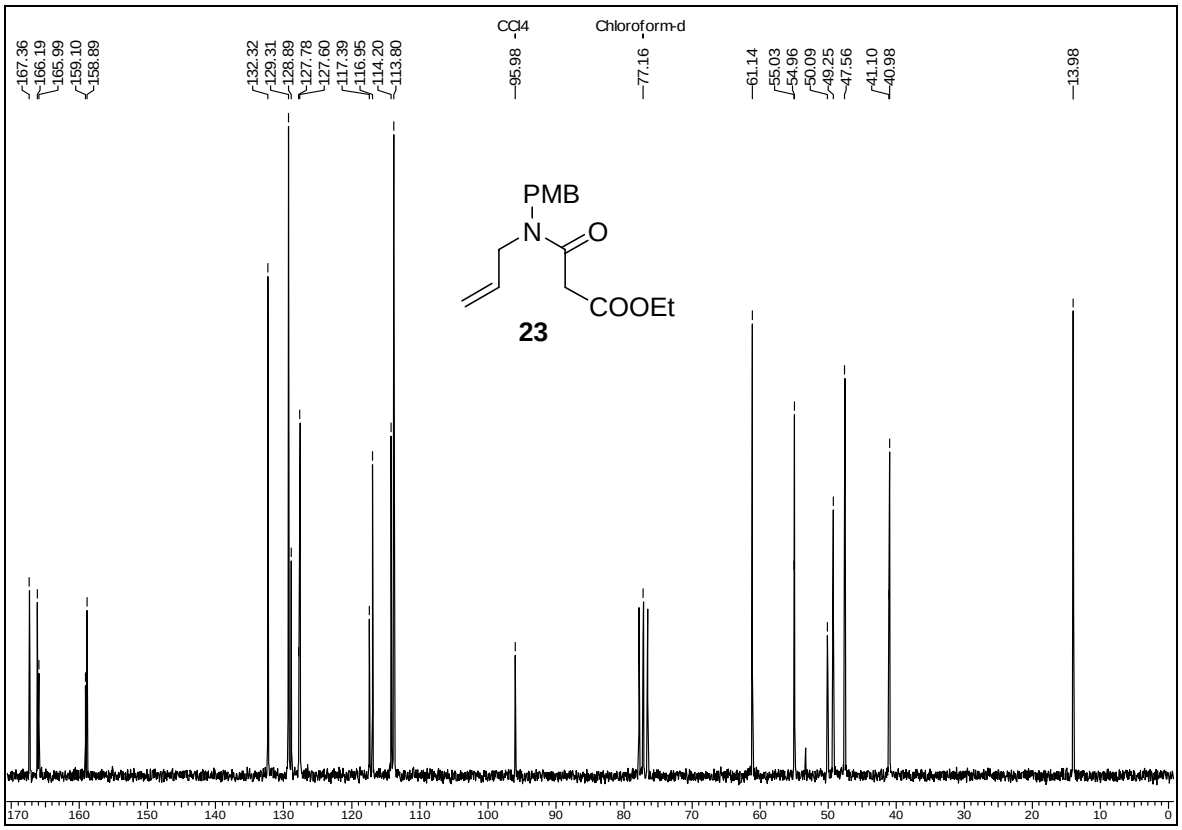
DEPT spectrum compound 1 ($CDCl_3$, 75 MHz)



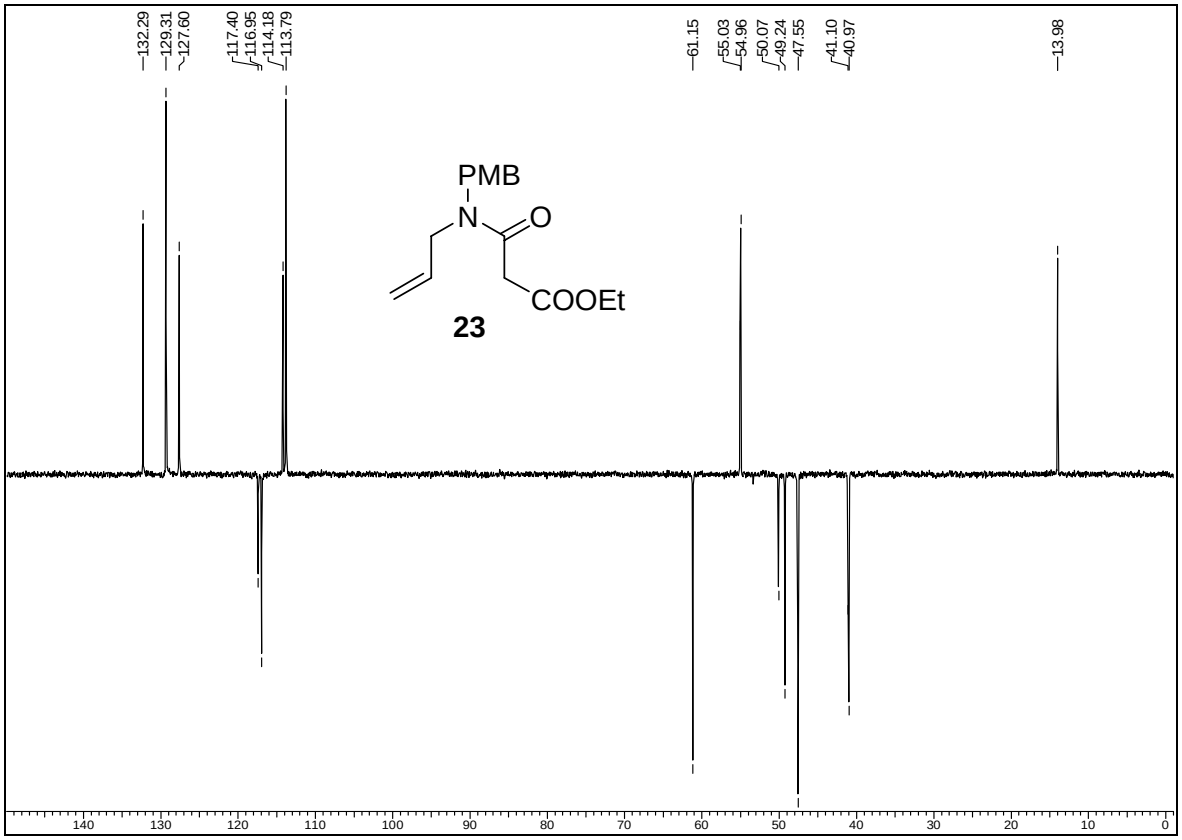
^{1}H NMR spectrum of compound 24 ($CDCl_3$, 200 MHz)



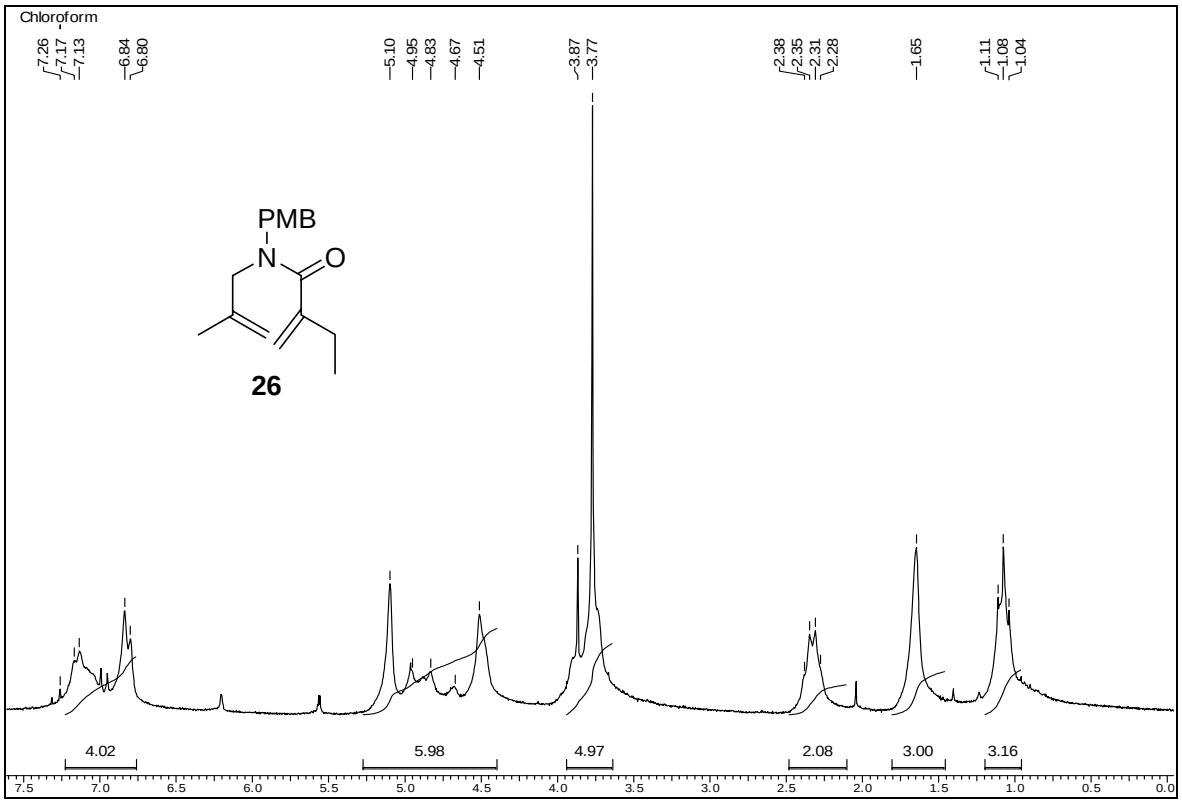
^{1}H NMR spectrum of compound 23 ($CDCl_3$, 200 MHz)



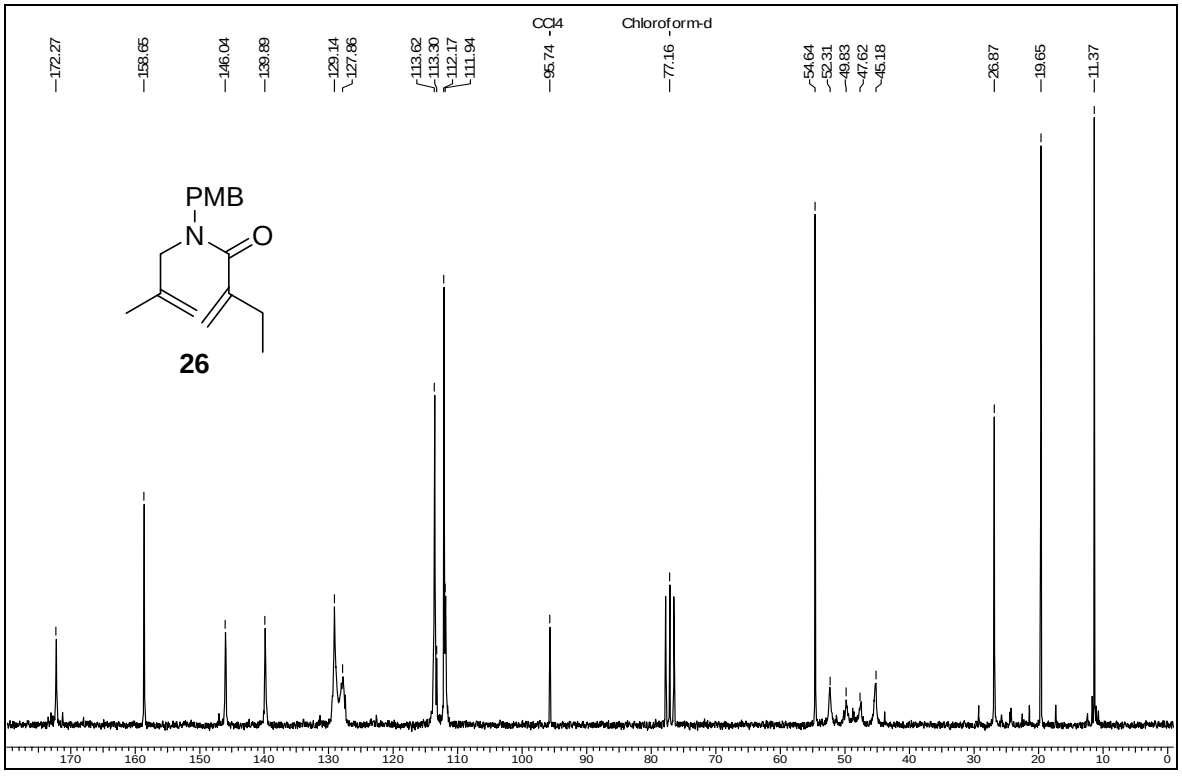
^{13}C NMR spectrum of compound 23 ($CDCl_3$, 50 MHz)



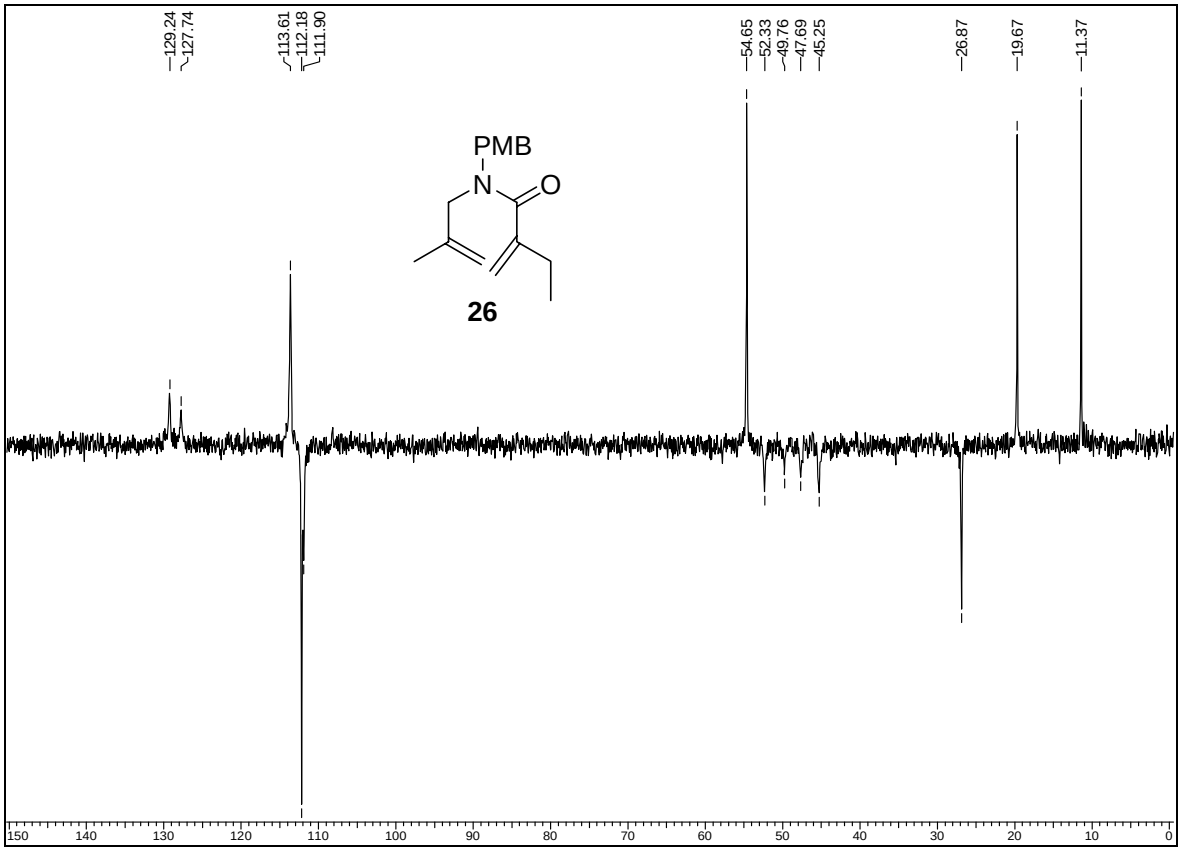
DEPT spectrum of compound 23 ($CDCl_3$, 50 MHz)



^{1}H NMR spectrum of compound 26 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound 26 ($CDCl_3$ + CCl4, 50 MHz)



DEPT spectrum of compound 26 ($CDCl_3$ + CCl4, 50 MHz)

3.1.8 References

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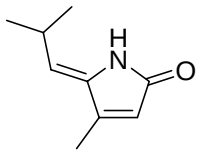
Chapter 3, Section II

Total synthesis of (Z)-pulchellalactam

3.2.1 Introduction

(*Z*)-Pulchellalactam (**1**) a pyrrolidinone was isolated in 1997 from the marine fungus *Corollospora pulchella* by Alvi *et al*.[1] Structurally it is the five-membered α,β-unsaturated lactam having methyl substituents at β-carbon and side chain at γ-carbon. It has been the focus of some attention due to its potent inhibitory action against protein tyrosine phosphatase, (PTP) CD45, which in turn activates B and T cells. Protein tyrosine phosphatase has been a target implicated in autoimmune and anti-inflammatory diseases.[2] The scarcity of effective inhibitors of protein tyrosine phosphatase has led to a search for other small molecule inhibitors. (*Z*) Pulchellalactam (**1**) has been shown to possess remarkable inhibitory action against CD45.



(Z)-Pulchellalactam (**1**)

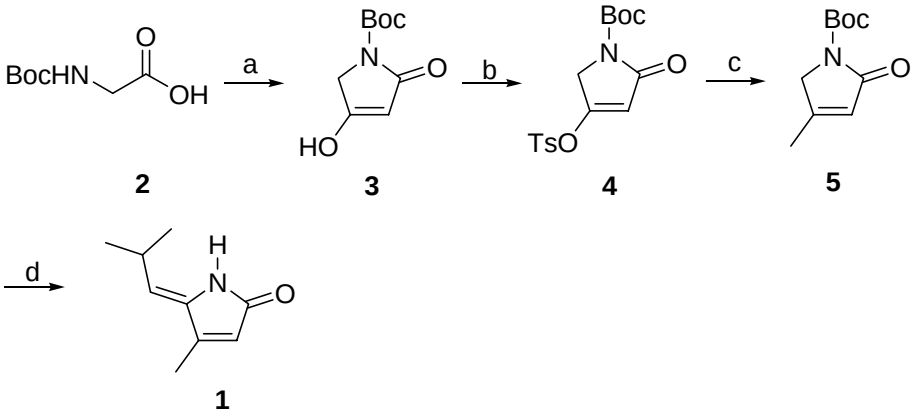
Figure 1.

3.2.2 Literature survey

The literature survey revealed that several syntheses of (*Z*)-pulchellalactam **1** have been achieved by different research group employing various protocols.[3-7]

Li's approach[3] (*J. Org. Chem*. **2002**, *67*, 4702)

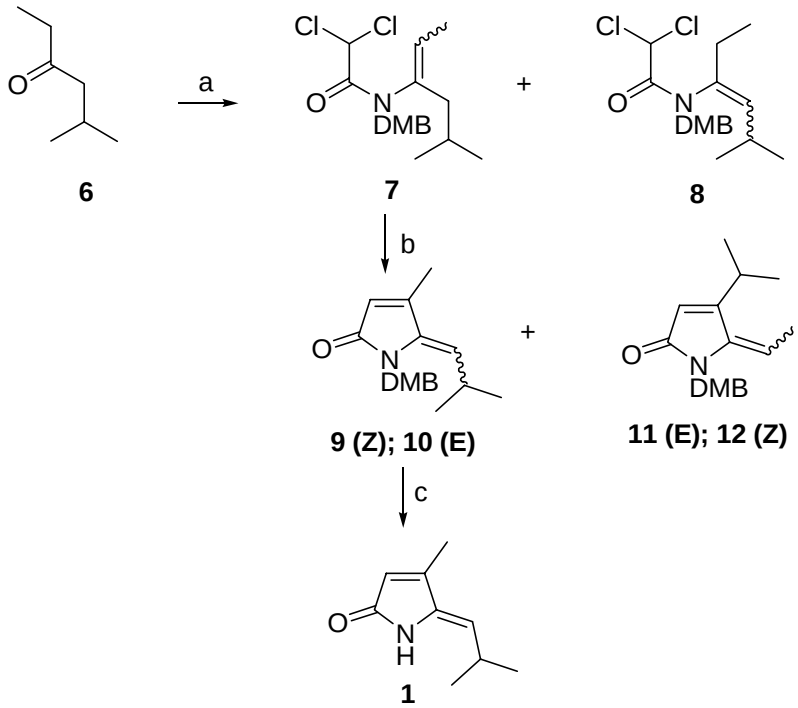
Li *et al.* devised an elegant synthesis of (*Z*) pulchellactam **1** which started with the coupling of Boc-glycine **2** with Meldrum's acid to furnish acylated Meldrum,s acid followed by intramolecular cyclization followed by decarboxylation to provide compound **3.** The hydroxy lactam **3** was converted in to corresponding tosyl compound **4** using tosyl chloride in dichloromethane in 93% yield. The 1,4-addition of Me_2CuLi on **4** and elimination of tosylate was achieved in one pot at 0 ^oC furnished lactam **5** in 70% yield. And finally the condensation of isobutyraldehyde with lactam using sodium hydride in THF followed by Boc deprotection furnished the target molecule (*Z*) pulchellalactam **1** in 86% yield. The synthesis was completed in five-steps in an overall yield of 45%.



Scheme 1. *Reagents and conditions: (a) (i) Meldrum's acid, isopropyl chloroformate, DMAP, CH_2Cl_2 (ii) EtOAc, reflux, 80%. (b) Ts-Cl, DIPEA, CH_2Cl_2, 93%. (c) Me_2CuLi, THF, 70%. (d) NaH, isobutyraldehyde, THF, 86%.*

Parsons's approach[4] (*Tetrahedron*, **2003**, *59*, 6221)

A short and efficient synthesis was disclosed by Parsons and co-workers where they began their synthesis from the reaction of 2,4-dimethoxybenzylamine with ketone **6** followed by treatment of dichloroacetyl chloride provided 1.5:1 mixture of enamide regioisomers **7** and **8** respectively in 32% yield.

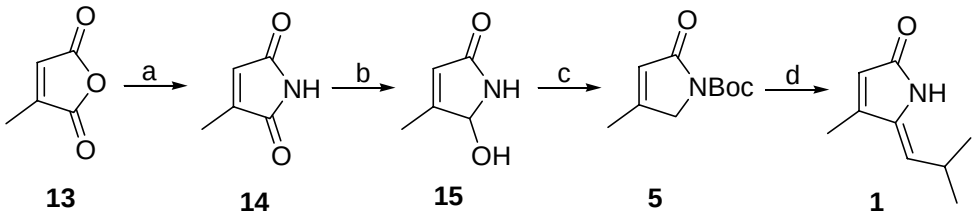


Scheme 2. *Reagents and conditions: (a) (i) $PMBNH_2$ (1.0 equiv), dichloroacetyl chloride (1.1 equiv), toluene, reflux, 32%. (b) $RuCl_2$ $(PPh_3)_3$ (0.5 equiv), toluene, reflux, 4 days, 89% mixture of products. (c) TFA, rt, 15 min, 66%.*

The mixture was heated with $RuCl_2(PPh_3)_3$ in toluene where enamide **7** gave desired dienones **9** and **10** in 32% and 41% yields respectively while **8** gave **11** and **12** in 17% and 14% yields respectively. Dienone **9** was stirred in neat TFA at room temperature afforded desired (*Z*) pulchellalactam **1** in 66%. yield, while dienone **10** gave *E* isomer in 83% yield.

Takabe's Approach[5] (*Heterocycles*, **2004**, *63*, 1013)

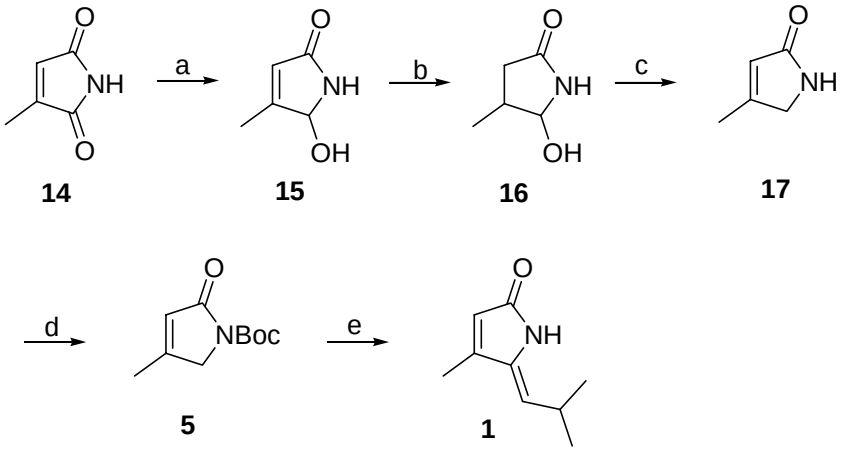
Takabe and co-workers reported the synthesis of **1**. Accordingly the citraconimide **14** was achieved from anhydride **13** by using HMDS as ammonia source in DMF at 100 ^oC. The selective reduction of **14** to **15** was achieved using sodium borohydride in 92% yield. Reductive deoxygenation by employing $BF_3.OEt_2$ and Et_3SiH followed by Boc-protection by Boc-anhydride to provided **5** in 91% yield. The condensation was carried out with isobutyraldehyde using LDA as a base at -78 ^oC to furnish (*Z*) pulchellalactam **1** in 82% yield.



Scheme 3. *Reagents and conditions: (a) HMDS, DMF, 100 ^oC, 80%. (b) $NaBH_4$, 92%. (c)(i) $BF_3.OEt$, Et_3SiH, CH_2Cl_2, -78 ^oC- rt; (ii) $(Boc)_2O$, DMAP, CH_2Cl_2, rt, 91%. (d) LDA, isobutyraldehyde, THF, -78 ^oC-0 ^oC, 24 h, 82%.*

Argade's approach[6] (*Synthesis*, **2004**, 1560)

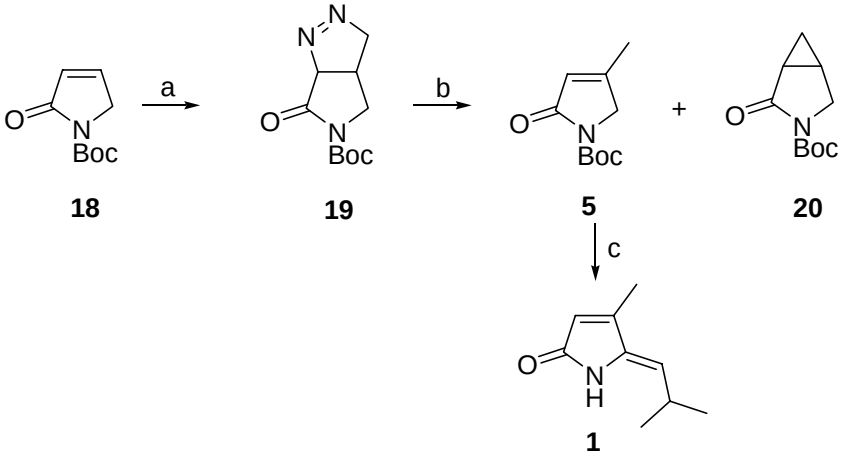
Argade *et al* also commenced their synthesis from citraconimide **14** which underwent regioselective reduction by $NaBH_4$ to give hydroxylactam **15** in quantitative yield. The reduction of olefin was performed by using Pd/C under H_2 to furnish **16** as a mixture of stereoisomers in quantitative yield. Dehydration followed by isomerisation of **16** was carried out by the treatment with mildly acidic amberlyst resin in acetonitrile to furnish α,β-unsaturated lactam **17** in 92% yield. The lactam **17** was protected with Boc-anhydride in acetonitrile at room temperature gave protected lactam **5** in 85% yield. Finally the the aldol condensation of isobutyraldehyde using NaH in THF followed by deprotection of Boc group furnished (*Z*) pulchellalactam **1** in 82% yield. The synthesis was achieved in five-steps with 64% overall yield.



Scheme 4. *Reagents and conditions: (a) $NaBH_4$ (1.0 equiv), EtOH, -40 ^oC, 1 h, quantitative. (b) Pd/C, H_2, MeOH, rt, 2 h, quantitative. (c) (i) p-TSA (cat), C_6H_6, reflux, 3 h, 25-30% (ii) AcOH, 80 ^oC, 1 h, 50-55% (iii)Amberlyst resin, CH_3CN, reflux, 2 h, 92%. (d) $(Boc)_2O$ (1.5 equiv), DMAP, CH_3CN, rt, 3 h, 85%. (e) NaH, THF, isobutyraldehyde, rt, 5 min. 82%.*

Langlois's approach[7] (*Synthetic Communications*, **2006**, *36*, 2253)

Recently Langlois and co-workers disclosed their concise synthesis of **1** from *N*-Boc pyrrolinone **18** which on treatment with diazomethane in diethyl ether at room temperature for 14 h furnished pyrazoline **19** in 68% yield. The pyrazoline **19** was refluxed in toluene for 8 h where thermolysis occurred providing a mixture of compound **5** and cyclopropane **20** in 71% and 9% yields respectively.

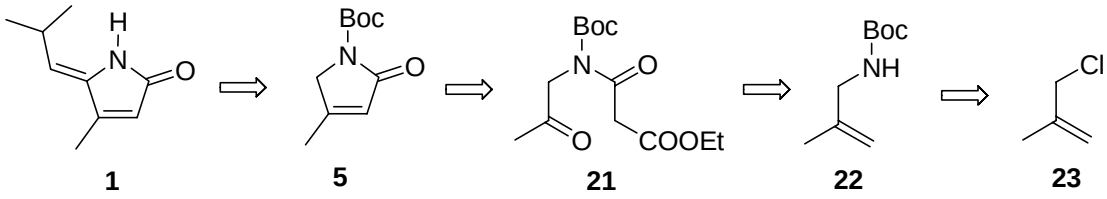


Scheme 5. *Reagents and conditions: (a) CH_2N_2, Et_2O, rt, 14 h, 68%. (b) Toluene, reflux, 8 h, 71%. (c) NaH, isobutyraldehyde, THF, 86%.*

The desired compound **5** was condensed with isobutyraldehyde using sodium hydride as the base in THF followed by Boc deprotection furnished target natural product (*Z*) pulchellalactam **1** in 86% yield. The synthesis has been completed in three-steps in 48% overall yield.

3.2.3 Present work:

In connection with an ongoing programme on the synthesis of biologically and pharmaceutically important natural products, considering its promising biological activity and limited availability from the marine source, it was thought to design a short and feasible route employing RCM protocol for the construction of five-membered α,β-unsaturated lactam present in (*Z*)-pulchellalactam **1**.



1 **5** **21** **22** **23**

Scheme 6. *Retrosynthetic plan 1.*

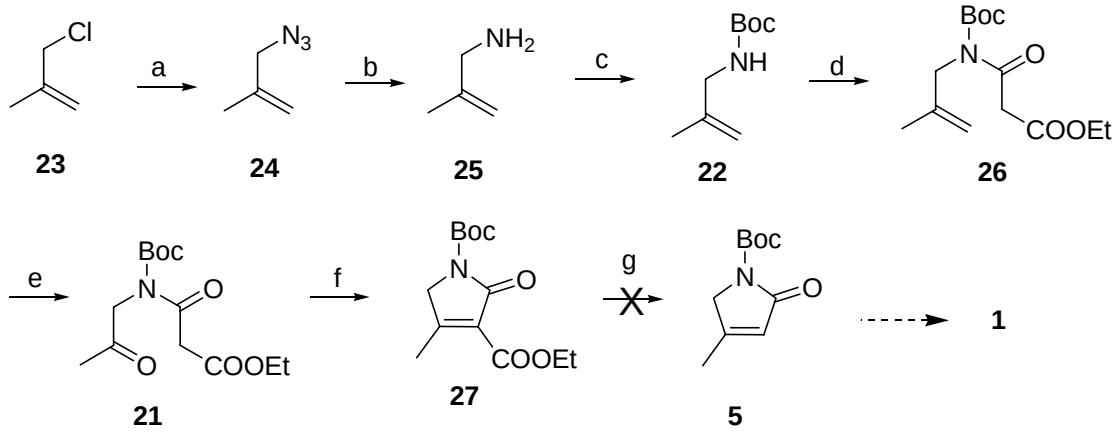
It was surmised that the target molecule (*Z*)-pulchellalactam **1** could be accessed from lactam **5** by intramolecular Knoevenagel condensation followed by deprotection. The lactam **5** in turn could be realized from keto compound **21** by intramolecular Knoevenagel condensation and subsequently decarboxylation. The keto compound **21** can be obtained from carbamate **22** by treatment with ethyl malonyl chloride and carbamate **22** in turn could be accessed from readily available methallyl chloride **23** by simple transformations.

3.2.4 Results and discussion:

According to retrosynthetic plan 1 (scheme 6) synthesis of **1** began with commercially available methallyl chloride **23**. Nucleophilic substitution on **23** with sodium azide furnished corresponding methallyl azide **24** which was subsequently reduced to its corresponding amine **25** using PPh_3 in diethyl ether and catalytic amount of water at ambient temperature,[8] and the amine **25** thus generated on treatment with Boc-anhydride using potassium carbonate as the base in dry dichloromethane furnished carbamate **22** in 59% yield (in three steps).

The structure of **22** was confirmed by spectral analysis. IR spectrum of **22** displayed strong absorption bands at 3352 cm^{-1} and 1701 cm^{-1} characteristic of N-H and C=O stretching

frequency, which indicated the presence of carbamate functionality. ^{1}H NMR spectrum of **22** revealed the singlet at δ 1.45 integrating for nine protons which were assigned to *tert*-butyl group, singlet at δ 1.73 integrated for three protons was ascribed to allylic methyl. A doublet that appeared at δ 3.65 for two protons was attributed to methylene protons adjacent to nitrogen, broad singlet appeared at δ 4.64 for N-H proton, Two singlets at δ 4.80 and δ 4.83 integrated for two olefinic protons. ^{13}C NMR spectrum of **22** displayed the signals at δ 20.0 methyl carbon at δ 28.3 for three equivalent methyl carbons of *tert*-butyl group, δ 46.1 for aliphatic methylene. The signals at δ 78.8 was assigned to quaternary carbon of tert-butyl moiety, while the signal at δ 110.3 was attributed to terminal olefinic carbon, δ 142.5 was assigned to quaternary carbon of olefin and δ 155.75 which was ascribed to the carbonyl carbon of carbamate. DEPT spectrum of **22** displayed the two methylene carbons which resonated at δ 46.1 and 110.3 which also were in agreement with the assigned structure. The mass spectrum showed the *m/z* peak at 172 $(M + H)^+$, 194 $(M + Na)^+$ and 210 $(M + K)^+$ which confirmed the structure of **22**. The structure of **22** was further ascertained by its elemental analysis as well.



Scheme 7. *Reagents & conditions: (a) NaN_3 (1.5 equiv.), DMSO, 70 ^{o}C , 15 h. (b) PPh_3 (1.1 equiv.), Et_2O-H_2O, 0 ^{o}C - rt, 14 h. (c) Boc-anhydride (1.2 equiv.), K_2CO_3 (3.0 equiv.), dry DCM, 0 °C, 3 h, 59% over three-steps. (d) K_2CO_3 (3.0 equiv.), dry DCM, ethyl malonyl chloride (1.2 equiv.), 0 ^{o}C, 3 h, 86%. (e) OsO_4 (cat.), $NaIO_4$ (2.2 equiv.), acetone-water (3:1), rt, 3 h, 89%. (f) NaH (2.0 equiv.), dry THF, 0 ^{o}C, 3 h, 82%. (g) (i) NaCl (4.0 equiv.), DMSO-H_2O (3:1), 120-130 ^{o}C, 12 h. (ii) 10% HCl (1.2 equiv.), reflux, 12 h.*

The carbamate **22** was treated with ethyl malonyl chloride using potassium carbonate as a base in anhydrous dichloromethane to render the compound **26** in very good yield (86%). It was confirmed by spectral analysis. The IR spectrum of **26** displayed the disappearance of absorption band corresponding to N-H stretching frequency of Boc-carbamate while appearance of the strong absorption band at 1741 and 1701 cm^{-1} characteristic of ester and amide functionality which indicate the transformation of **22** to **26**. ^{1}H NMR spectrum of **26** revealed the disappearance of broad singlet corresponding to amide proton and new signals appeared as triplet and quartet at δ 1.29 and 4.19 (J = 7.1 Hz) that integrated for three protons, singlet at δ 3.88 integrating the methylene protons flanked between two carbonyl carbon which clearly indicate the conversion of **22** to **26**. ^{13}C NMR spectrum of **26** showed the additional signals that appeared at δ 14.2, 49.0, 61.0, 167.4 and 168.0 also suggested the introduction of ethyl malonyl moiety. DEPT spectrum of **26** revealed two extra methylene carbons resonating at δ 48.9 and 61.05 which gives support for structural assignment. The *m/z* peak at 286 $(M + H)^+$, 303 $(M + NH_4)^+$, 308 $(M + Na)^+$, 324 $(M + K)^+$ along with peak appeared due to fragmentation 192 and 230 in the mass spectrum of **26** provided strong evidence and it was further confirmed by elemental analysis also which was found to be in good agreement with the calculated values.

The compound **26** was cleaved into corresponding keto compound **21** using catalytic amount of OsO_4 and $NaIO_4$ in acetone-water (3:1) at ambient temperature. The structure of **21** was assigned by spectral techniques. IR spectra of **21** showed the strong absorption band at 1720 cm^{-1}, which indicated the presence of ketone functionality. ^{1}H NMR spectrum of **21** revealed the disappearance of the peak corresponding to two olefinic protons it suggested the absence of olefin functionality. The disappearance of the signals corresponding to olefinic carbons while appearance the new signal at δ 200.9 in the ^{13}C NMR spectrum of **21** clearly indicated the transformation of olefin to ketone. The mass spectrum of **21** revealed the *m/z* peak at 288 $(M + H)^+$, 305 $(M + NH_4)^+$, 310 $(M + Na)^+$ and 326 $(M + K)^+$ also the fragmented peak at 232 and finally it was ascertained by its elemental analysis, the experimental values were found to be in good agreement with the theoretical values.

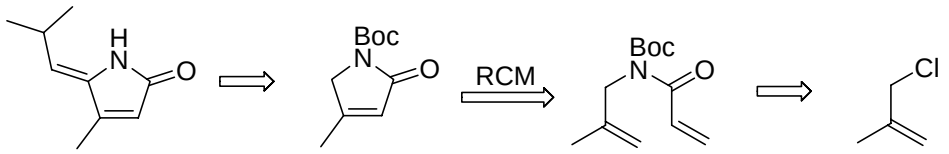
The treatment of keto compound **21** with sodium hydride in THF at low temperature rendered the α,β-unsaturated lactam **27** in 82% yield. The formation of lactam **27** was confirmed by spectral analysis. IR spectrum of **27** displayed the disappearance the

absorption band due to ketone functionality. ^{1}H NMR of **27** displayed the disappearance of the signal corresponding to active methylene protons, which suggested the cyclization. ^{13}C NMR spectrum revealed the signals appearance at δ 124.4 and 161.4 which also indicated the formation of lactam **27**. The *m/z* peak at 270 $(M + H)^+$, 287 $(M + NH_4)^+$, 294 $(M + Na)^+$, 308 $(M + K)^+$ along with fragmentation peak at 170 and 214 in the mass spectrum also gave the support for structural elucidation of **27**. Finally structure of **27** was further confirmed by elemental analysis which showed the experimental values were found to be in good agreement with the calculated values.

The decarboxylation of the ester group of compound **27** was attempted under various reaction conditions but unfortunately all the efforts remained fruitless due to formation intractable mixture.

After the failure in decarboxylation in scheme 7, it was decided to devise the alternative strategy outlined in scheme 8.

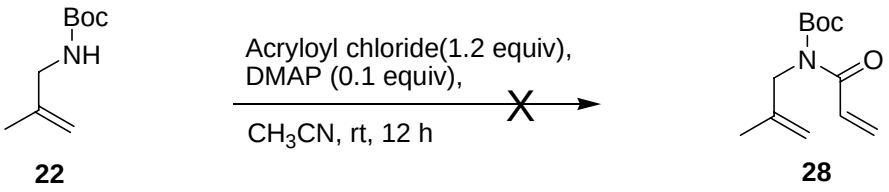
The target molecule (*Z*)-pulchellalactam **1** could be accessed from α,β-unsaturated lactam **5** by Knoevenagel condensation, the lacatm **5** would be realized from acrylamide **21** by RCM and acrylamide **21** in turn can be readily obtained from commercially available methallyl chloride **23**.



1 **5** **21** **23**

Scheme 8. *Retrosynthetic plan 2.*

According to retrosynthetic plan 2 (scheme 8) the carbamate **22** was prepared from commercially available methallyl chloride **23** mentioned in scheme 7. When carbamate **22** was subjected to treatment with acryloyl chloride using sodium hydride as the base in a variety of solvents *viz* THF, DMF did not furnish the desired compound **28**. Performing the acylation reaction by employing DMAP in CH_3CN also did not work. This failure was probably due to the less nucleophilic nature of nitrogen of resultant carbamate **22**, and then it was decided to change the sequence of reagents.



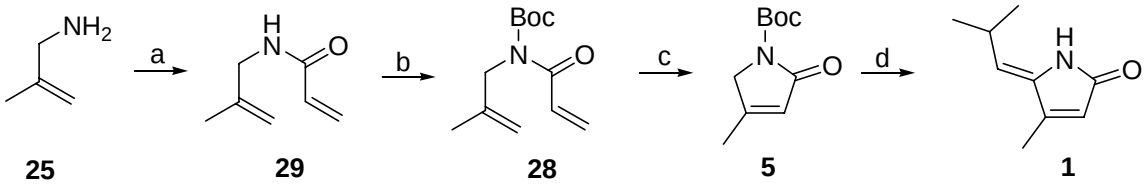
22 **28**

Scheme 9.

After the failure in the conversion of **22** to **28** (scheme 7), the amine **25** was first treated with acryloyl chloride to afford acrylamide **29.** The structure of **29** was confirmed by spectroscopic data. The IR spectrum of **29** displayed the strong absorption bands at 3286 and 1625 cm^{-1} due to stretching frequency of N-H and C=O functional groups of the α,β-unsaturated acrylamide. ^{1}H NMR spectrum of **29** showed the singlet at δ 1.73 integrating for three protons which were attributed to allylic methyl protons, doublet that integrated for two methylene protons appeared at δ 3.86 (J = 6.1 Hz), singlet at δ 4.82 was due to exomethylene protons, doublet of doublet that resonated at δ 5.63 (J = 9.6, 1.8 Hz) integrated for internal olefinic proton of acrylamide, broad singlet appeared at δ 6.07 integrated for N-H proton of acrylamide multiplet that appeared at δ 6.12-6.34 was assigned to two terminal olefinic protons of acrylamide. ^{13}C NMR spectrum of **29** revealed the seven signals matched with its structure. DEPT spectrum of **29** exhibited three methylene carbons that resonated at δ 45.0, 110.95 and 126.1. The mass spectrum of **29** showed the *m/z* peak at 126 $(M + H)^{+}$, 148 $(M + Na)^{+}$ which confirmed the structure of **29**. Finally the structure of **29** was ascertained by its elemental analysis which was also found to be in good agreement with the theoretical values.

When the resultant acrylamide **29** was treated with Boc-anhydride and catalytic amount of DMAP in anhydrous acetonitrile at room temperature to render the desired carbamate **28** in very good yield (82%). Formation of **28** was confirmed by spectral study. IR spectrum of **28** showed the disappearance of the absorption band corresponding to N-H stretching frequency of acrylamide and the new strong absorption bands appeared at 1734 and 1687 cm^{-1} characteristic of C=O stretching frequency of carbamate and acrylamide functional groups respectively. ^{1}H NMR spectrum of **28** revealed the disappearance of broad singlet corresponding to N-H of acrylamide while new singlet appeared at δ 1.48 integrating for nine protons. This observation clearly indicated the conversion of **29** to **28**. ^{13}C NMR spectrum of **28** revealed two additional two signals at δ 28.1 and 83.2 which were assigned

to three methyl carbons and quaternary carbon respectively. The mass spectrum of **28** exhibited the peak at *m/z* 248 $(M + Na)^+$, and lastly the structure of **28** was confirmed by its elemental analysis also.



25 **29** **28** **5** **1**

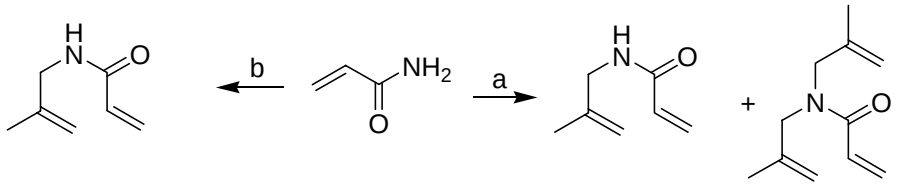
Scheme 10. *Reagents and conditions: (a) acryloyl chloride (1.2 equiv.), K_2CO_3 (1.2 equiv.), dry DCM, 0 °C, 3 h, 59% over three-steps. (b) Boc-anhydride (1.2 equiv.), DMAP (0.1 equiv.), dry CH_3CN, rt, 3 h, 82%. (c) Grubb's catalyst 2nd generation (5 mol %), dry toluene, 80 °C, 12 h, 85%. (d) NaH (1.5 equiv.), isobutyraldehyde (3.0 equiv.), THF, rt, 10 % HCl, 85%.*

With the required compound **28** in the hand the attention was focused towards the key step which was to construct the cyclic α,β-unsaturated lactam by ring-closing metathesis. The compound **28** was subjected with Grubbs' 2 nd generation catalyst (10 mol%) in anhydrous toluene at 80 °C for 12 h delivered the desired α,β-unsaturated lactam **5** in 85% yield (based on the recovery of starting material).[9] The structure of **5** was ascertained by spectroscopic methods. ^{1}H NMR spectrum of **5** revealed the disappearance of signals corresponding to olefinic protons and a new singlet resonated at δ 5.80 integrating for one proton and was ascribed to the α-proton in the α,β-unsaturated lactam. ^{13}C NMR spectrum along with DEPT spectrum of **5** showed the absence of two signals at δ 110.1 and 128.1 corresponding to olefinic methylene carbons which also indicated the formation of lactam **5**. The mass spectrum of **5** showed the peak at *m/z* 198 $(M + H)^+$ and 220 $(M + Na)^+$ and finally the structure of **5** was ascertained by its elemental analysis also, which revealed the experimental values were found to be in good agreement with the calculated values.

After obtaining the lactam **5** by RCM strategy the last job was the condensation with aldehyde and deprotection and thus the treatment of **5** with isobutyraldehyde using NaH as a base in THF at ambient temperature and further treatment of 10% HCl resulted in the target molecule (*Z*)-pulchellalactam **1** in 85% yield.[3] The structure of **1** was elucidated by

analysis of spectral techniques. IR spectrum of **1** showed the disappearance the absorption band corresponding to carbamate carbonyl functionality while the presence of a new strong absorption band at 3287 cm^{-1} which is characteristic of N-H stretching frequency of α,β-unsaturated lactam. This result indicated the deprotection of carbamate. ^{1}H NMR spectrum of **1** revealed the disappearance of the singlet corresponding to two methylene protons at γ position and a new doublet appeared at δ 1.11 integrating for six protons and multiplet at δ 2.57-275 for one proton and doublet at δ 5.14 (J = 9.9 Hz) in olefinic region for one proton that suggested the introduction of isobutyl functionality at C-5 position and the disappearance of the singlet corresponding to nine protons of carbamate while an appearance the broad singlet at δ 8.68 suggested the deprotection of carbamate. ^{13}C NMR spectrum of **1** showed the disappearance of the signals corresponding to Boc-carbamate while new signals resonated at δ 23.0, 27.7, 120.2 and 137.7 indicated the conversion of **5** to **1.** The DEPT spectrum of **1** indicated the absence of methylene carbon at δ 54.1. The mass spectrum of **1** displayed the $(M + 1)^{+}$ peak at *m/z* 152, the structure of **1** was further ascertained by its elemental analysis as well. The spectral data was in good agreement with reported data in literature.[3]

Having achieved the total synthesis of (*Z*)-pulchellalactam **1**, a synthetic route with a view to minimize the number of transformations was examined (scheme 11). The shortened route began from commercially available acrylamide **30** which was alkylated with methallyl chloride **23** using sodium hydride as the base in anhydrous DMF at room temperature to furnish the mixture of desired monoalkylated acrylamide **29** in 59% yield and dialkylated acrylamide **31** in 20% yield (Based on the recovery of acrylamide **30**). The yield of desired compound **29** was improved up to 91% using 0.33 equivalent of methallyl chloride **23** under the same reaction conditions overcame this selectivity problem.



29 **30** **29** **31**

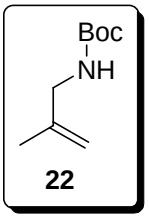
Scheme 11. *Reagents and conditions: (a) methallyl chloride (1.1 equiv.), NaH (1.2 equiv.), dry DMF, 0 ^{o}C-rt, 24 h.59% **29**, 20% **31**. (b) methallyl chloride (0.33 equiv.), NaH (1.2 equiv.), dry DMF, 0 ^{o}C-rt, 30 h, 91%.*

3.2.5 Conclusion:

A short and efficient total synthesis of (*Z*)-pulchellalactam **1** has been achieved in four-steps in 54% overall yield employing ring-closing metathesis as the key step.

3.3.6 Experimental

***Tert*- butyl 2-methylallylcarbamate (22)**



22

(i) To a well stirred mixture of methallyl chloride **23** (1.0 g, 1.08 mL, 11 mmol) and NaN_3 (1.07 g, 16.05 mmol) in anhydrous DMSO (15 mL) under argon atmosphere and the resultant reaction mixture was heated at 70 ^oC for 15 h. After the completion of the reaction (TLC), the DMSO was removed by water wash and extracted with Et_2O (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure afforded corresponding azide **24** as colourless liquid. (ii) To a stirred solution of crude methallyl azide **24** (assuming 100% conversion) in Et_2O (20 mL) was added PPh_3 (3.18 g, 12.1 mmol) at 0 ^oC, after 1 h H_2O (2.0 mL) was added and reaction mixture was left to stir at room temperature for 14 h. After the completion of the reaction (TLC), the reaction mixture was poured into ice-water and extracted with Et_2O (3 x 15 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* furnished methallyl amine **25** as a colourless oil. (iii) To a stirred solution of crude amine **25** (assuming 100% conversion) in DCM (20 mL) was added K_2CO_3 (4.6 g, 33 mmol) at 0 ^oC stirred for 15 minutes followed by the dropwise addition of Boc-anhydride (2.89 g, 3.04 mL, 13.2 mmol) over 10 minutes at 0 ^oC. The progress of reaction was monitored by TLC, after the completion of reaction H_2O (20.0 mL) was added into the reaction mixture and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:4) as eluent yielded compound **22** as colourless oil (1.1 g, 59% yield, in three-steps).

MF: $C_9H_{17}NO_2$, **MW**: 171

IR ($CHCl_3$) ν_{max}: 3352, 3080, 2978, 2932, 1701, 1521, 1366, 1174 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 300 MHz) δ: 1.45 (s, 9H), 1.73 (s, 3H), 3.65 (d, *J* = 5.9 Hz, 2H), 4.64 (bs, 1H), 4.80 (s, 1H), 4.83 ppm (s, 1H).

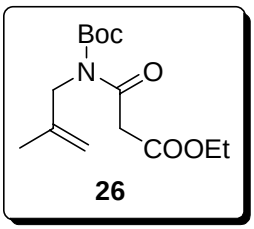
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 20.0, 28.3, 46.1, 78.8, 110.3, 142.5, 155.75 ppm.

MS (ESI) *m/z*: 172 $(M + H)^+$.

Elemental analysis Calculated: C, 63.13; H, 10.01: N, 8.10%.

Found: C, 62.81; H, 9.62; N, 8.36%.

Ethyl 3-(tert-betoxycarbonyl (2-methylallyl) amino) -3- oxopropanoate (26)



26

To a stirred solution of **22** (1.0 g, 5.8 mmol) in anhydrous CH_2Cl_2 (20.0 mL) at 0 ^oC was added K_2CO_3 (0.96 g, 7.0 mmol) and stirred for 15 minutes and ethyl malonyl chloride (1.05 g, 0.88 mL, 7.0 mmol) was added drop wise over 10-15 min at 0 ^oC. The progress of reaction was monitored by TLC and after the completion of reaction the reaction mixture was filtered and the residue was washed with CH_2Cl_2 (3 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and crude product was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether as eluent furnished compound **26** as a colorless oil (1.43 g, 86% yield).

MF: $C_{14}H_{23}NO_5$, **MW**: 285

IR ($CHCl_3$) ν_{max}: 3452, 3080, 2980, 2939, 1741, 1701, 1369, 1240, 1151, 1070, 1033, 855, 777 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.29 (t, *J* = 7.1 Hz, 3H), 1.47 (s, 9H), 1.73 (s, 3H), 3.88 (s, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.25 (s, 2H), 4.79 ppm (d, *J* = 8.0 Hz, 2H).

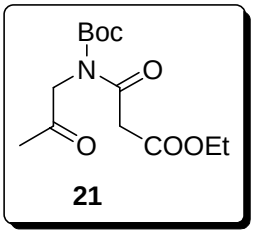
^{13}C NMR ($CDCl_3$ + CCl_4, 75 MHz) δ: 14.2, 20.4, 27.9, 45.9, 49.0, 61.0, 83.4, 110.2, 140.7, 153.0, 167.4, 168.0 ppm.

MS (ESI) *m/z*: 286 $(M + H)^+$, 308 $(M + Na)^+$.

Elemental analysis Calculated: C, 58.93; H, 8.12; 4.90%.

Found: C, 58.76; H, 8.07; N, 4.81%.

Ethyl 3-(tert-butoxycarbonyl (2-oxopropyl) amino) -3-oxopropanoate (21)



21

To the stirred solution of olefin **26** (1.2 g, 4.2 mmol) in acetone-water (20 mL, 3:1), catalytic amount of OsO_4 was added and the reaction mixture became dark black then $NaIO_4$ (1.98 g, 9.2 mmol) was added at room temperature and reaction mixture was allowed to stir for 3-4 h. After the completion of reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure and the residue obtained was

dissolved in H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under diminished pressure. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (2:3) as eluent yielded the keto compound **21** as thick colorless oil (1.07 g, 89% yield).

MF: $C_{13}H_{21}NO_6$, **MW**: 287

IR ($CHCl_3$) ν_{max}: 3455, 2982, 2939, 1744, 1698, 1370, 1151, 1080, 854, 775 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.29 (t, *J* = 7.1 Hz, 3H), 1.47 (s, 9H), 2.17 (s, 3H), 3.93 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.52 ppm (s, 2H).

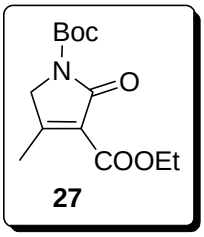
^{13}C NMR ($CDCl_3$ + CCl_4, 75MHz) δ: 13.95, 26.4, 27.6, 45.2, 52.9, 60.9, 84.0, 151.8, 166.9, 167.9, 200.9 ppm.

MS (ESI) *m/z*: 288 $(M + H)^+$, 310 $(M + Na)^+$.

Elemental analysis Calculated: C, 54.34; H, 7.36; N, 4.87%.

Found: C, 54.49; H, 7.16; N, 4.84%.

1- tert-butyl 3-ethyl 4-methyl -2-oxo-2H-pyrrole-1, 3 (*5H*) –dicarboxylate (27)



27

60 % NaH (0.16 g, 4.1 mmol) was washed with anhydrous petroleum ether (3 x 10 mL), anhydrous THF (10 mL) was added and cooled to 0 ^oC and compound **21** (1.0 g, 3.4 mmol) in anhydrous THF (10 mL) was added dropwise at 0 ^oC. After the completion of reaction (1 h, TLC), the reaction mixture was quenched with the addition of saturated ammonium chloride solution and the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and solvent was removed *in vacuo* and the residue thus obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:2) as eluent furnished **27** as pale yellow syrup (0.76 g, 82% yield).

MF: $C_{13}H_{19}NO_5$, **MW**: 269

IR ($CHCl_3$) ν_{max}: 3405, 3019, 2983, 2936, 1781, 1720, 1328, 1159, 1062, 755 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.36 (t, *J* = 7.1 Hz, 3H), 1.55 (s, 9H), 2.38 (s, 3H), 4.25 (s, 2H), 4.33 ppm (q, *J* = 7.1 Hz, 2H).

^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 13.95, 15.3, 27.8, 52.9, 60.7, 82.8, 124.6, 149.2, 161.6, 164.1, 166.4 ppm.

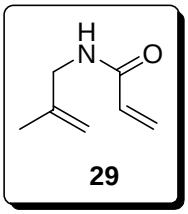
MS (ESI) *m/z*: 270 $(M + H)^+$.

Elemental analysis Calculated: C, 57.98; H, 7.11; N, 5.20%.

Found: C, 58.00; H, 7.56; N, 5.00%.

***N*- (2- methylallyl) acrylamide (29)**

Method A



29

(i) To a stirred solution of methallyl chloride **23** (1.0 g, 1.08 mL, 11 mmol) in DMSO (15 mL), NaN_3 (1.07 g, 16.05 mmol) was added under inert atmosphere and the resultant reaction mixture was heated at 70 ^oC for 15 h. After the completion of reaction (TLC), the DMSO was removed by water washings and extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* afforded corresponding azide **24** as a colourless liquid. (ii) To a stirred solution of crude methallyl azide **24** (assuming 100% conversion) in Et_2O (20 mL), PPh_3 (3.18 g, 12.1 mmol) was added at 0 ^oC, after 1 h H_2O (2 mL) was added and reaction mixture was allowed to stir at room temperature for 14 h. After the completion of reaction (TLC), the reaction mixture was poured into ice-water and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure furnished methallyl amine **25** as a colourless oil. (iii) A mixture of crude amine **25** (assuming 100% conversion) and K_2CO_3 (4.6 g, 33 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 ^oC was stirred and acryloyl chloride (1.2 g, 1.07 mL, 13.2 mmol) was added gradually over 10 minutes at 0 ^oC. The reaction was allowed to stir till the completion of reaction (2 h, TLC), after the completion of reaction cold water (20 mL) was added into the reaction mixture and extracted with CH_2Cl_2 (3 x 15 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and resultant residue was purified by flash column chromatography (SiO_2) eluting with ethyl acetate-petroleum ether (1:4) afforded acrylamide **29** as colourless oil (0.81 g, 59% yield, in three-steps).

Method B

60% NaH (0.67 g, 16.89 mmol) was washed with anhydrous petroleum ether (3 x 10 mL). Anhydrous DMF (10 mL) was added to the above powder followed by the addition of acrylamide (1.0 g, 14.08 mmol) in anhydrous DMF (10 mL) at 0 ^{o}C, stirred for 10 minutes and then methallyl chloride (0.42 g, 0.45 mL, 4.64 mmol) in anhydrous DMF (5 mL) was added dropwise over 20 minutes and reaction mixture was allowed to stir at room temperature for 30 h. After the completion of reaction (TLC), reaction was quenched by addition of saturated ammonium chloride solution and extracted with Et_2O (3 x 20 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:4) as eluent delivered acryl amide **29** as thick colourless oil (0.53 g, 91% yield, based on recovery of starting material).

MF: $C_7H_{11}NO$, **MW**: 125

IR ($CHCl_3$) ν_{max}: 3286, 3080, 2974, 2918, 1916, 1721, 1625, 1550, cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.73 (s, 3H), 3.86 (d, *J* = 6.1 Hz, 2H), 4.82 (s, 2H), 5.63 (dd, *J* = 9.6, 1.8 Hz, 1H), 6.04 (bs, 1H), 6.15 (dd, *J* = 16.9, 9.6 Hz, 1H), 6.30 ppm (dd, *J* = 16.9, 1.8 Hz, 1H).

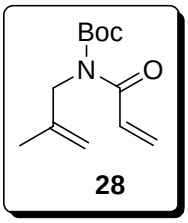
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 20.35, 45.0, 110.95, 126.1, 131.0, 141.6, 165.9 ppm.

MS (ESI) *m/z*: 126 $(M + H)^+$.

Elemental analysis Calculated: C, 67.17; H, 8.86; N, 11.19%.

Found: C, 67.38; H, 8.55; N, 10.84%.

Tert-butyl acryloyl (2-methylallyl) carbamate (28)



28

To a stirred solution of acrylamide **29** (0.5 g, 4 mmol) in anhydrous CH_3CN (5 mL) was added DMAP (0.049 g, 0.4 mmol) followed by the addition of Boc-anhydride (1.05 g, 1.1 mL, 4.8 mmol) in anhydrous CH_3CN (20 mL) at room temperature under argon atmosphere and the reaction mixture was allowed to stir for 3 h. After the completion of reaction (TLC), the acetonitrile was removed on rotary evaporator under reduced pressure

and the resultant residue was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography (SiO_2) eluting with ethyl acetate-petroleum ether (1:6) solvent system furnished carbamate **28** as thick colourless oil (0.74 g, 82% yield).

MF: $C_{12}H_{19}NO_3$, **MW**: 225

IR ($CHCl_3$) ν_{max}: 3364, 2979, 2937, 1734, 1687, 1619, 1404 cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.48 (s, 9H), 1.72 (s, 3H), 4.23 (s, 3H), 4.67-4.80 (2s, 2H), 5.69 (dd, *J* = 10.4, 1.9 Hz, 1H), 6.32 (dd, *J* = 16.8, 1.9 Hz, 1H), 7.04 ppm (dd, *J* = 16.8, 10.4 Hz, 1H).

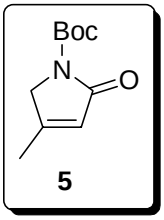
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 20.6, 28.1, 49.5, 83.2, 110.1, 128.1, 131.3, 141.0, 153.2, 168.25 ppm.

MS (ESI) *m/z*: 226 $(M + H)^+$.

Elemental analysis Calculated: C, 63.98; H, 8.50; N, 6.22%.

Found: C, 63.61; H, 8.11; N, 6.53%.

***N*-tert-Butoxycarbonyl-4-methyl-3-pyrrolin-2-one (5)**



5

To a stirred homogeneous solution of **28** (0.7 g, 3.1 mmol) in anhydrous toluene (60 mL) was added Grubbs' 2nd generation catalyst (0.13 mg, 5 mol %) and the solution was degassed with argon and heated at 80 ^oC till to completion of reaction (12 h, TLC). The reaction mixture was concentrated *in vacuo* and the residue obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (2:3) as eluent furnished the α,β-unsaturated lactam **5** as thick colourless oil (0.3 g, 85% yield) and 300 mg of starting material was recovered.

MF: $C_{10}H_{15}NO_3$, **MW**: 197

IR ($CHCl_3$) ν_{max}: 3448, 2980, 1778, 1739, 1712, 1643, 1447, 1293, 1164, 843, 755, cm^{-1}

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ: 1.52 (s, 9H), 2.07 (s, 3H), 4.17 (s, 2H), 5.80 ppm (s, 1H).

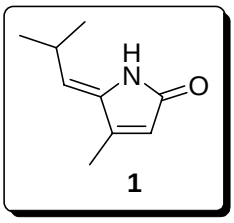
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz) δ: 15.3, 27.9, 54.1, 82.1, 122.6, 149.1, 157.8, 169.0 ppm.

MS (ESI) *m/z*: 198 $(M + H)^+$.

Elemental analysis Calculated: C, 60.90; H, 7.67; N, 7.10%.

Found: C, 61.26; H, 8.06; N, 6.75%.

(*Z*)- Pulchellalactam (1)



1

The NaH (60%, 0.073 g, 1.8 mmol) was washed with anhydrous petroleum ether (3 x 5 mL), the solution of *N*-Boc lactam **6** (0.3 g, 1.5 mmol) in anhydrous THF (5 mL) was added at room temperature and stirred for 5 minutes followed by the addition of isobutyraldehyde (0.33 g, 4.5 mmol) in anhydrous THF (5 mL) and stirred at room temperature for further 0.5 h. After the completion of reaction (TLC), the solvent was removed on rotary evaporator under diminished pressure and the resultant residue was dissolved in CH_2Cl_2 (10 mL) and washed with 5% HCl (10 mL), saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the resultant residue was purified by flash column chromatography (SiO_2) eluting with ethyl acetate-petroleum ether (2:3) resulted the target molecule (*Z*)-pulchellalactam (**1**) as thick colourless oil (0.196 g, 85% yield).

MF: $C_9H_{13}NO$, **MW**: 151

IR ($CHCl_3$) ν_{max}: 3462, 3019, 2400, 1684, 1384, 1215, 843, 669 $cm^{-1.}$

^{1}H NMR ($CDCl_3$ + CCl_4, 200 MHz) δ 1.10 (d, *J* = 6.7 Hz, 6H), 2.07 (s, 3H), 2.57-2.75 (m, 1H), 5.14 (d, *J* = 9.9 Hz, 1H), 5.87 (s, 1H), 8.68 ppm (bs, 1H).

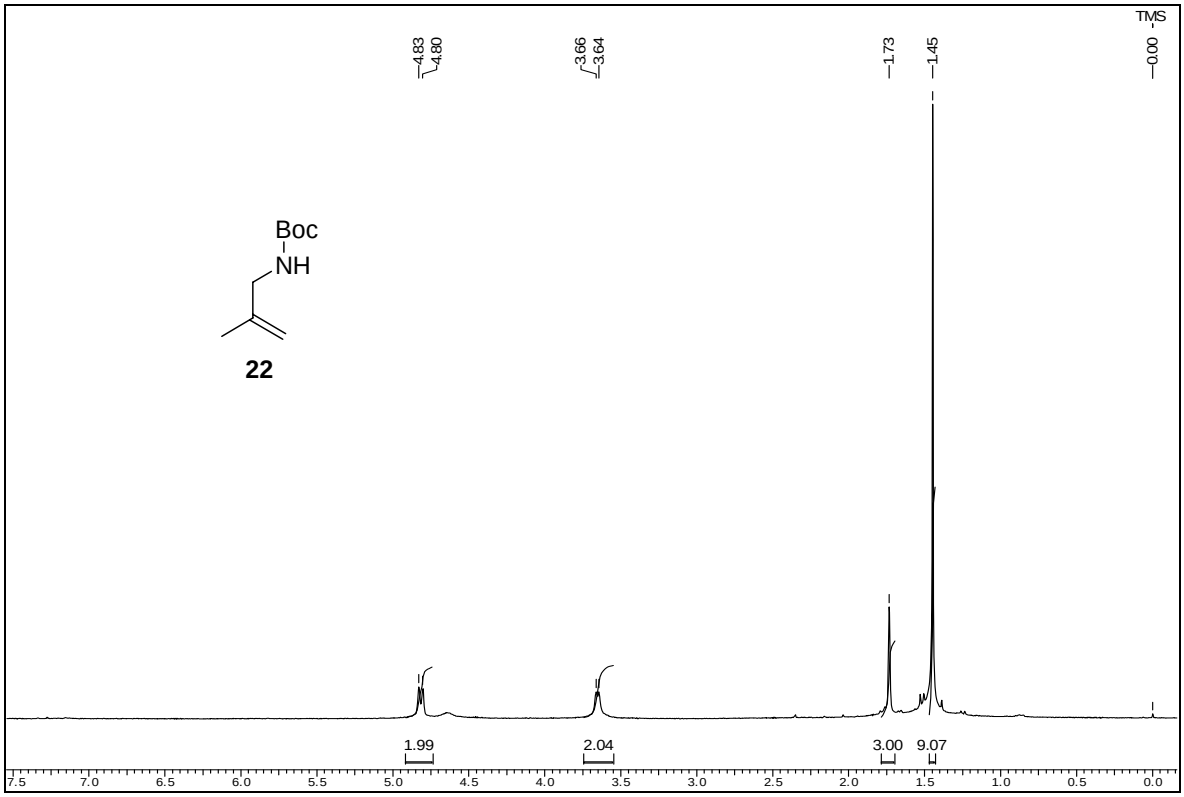
^{13}C NMR ($CDCl_3$ + CCl_4, 75 MHz) δ: 12.0, 23.0, 27.7, 120.2, 121.0, 137.7, 148.9, 172.6 ppm.

MS (ESI) *m/z*: 152 $(M + H)^+$.

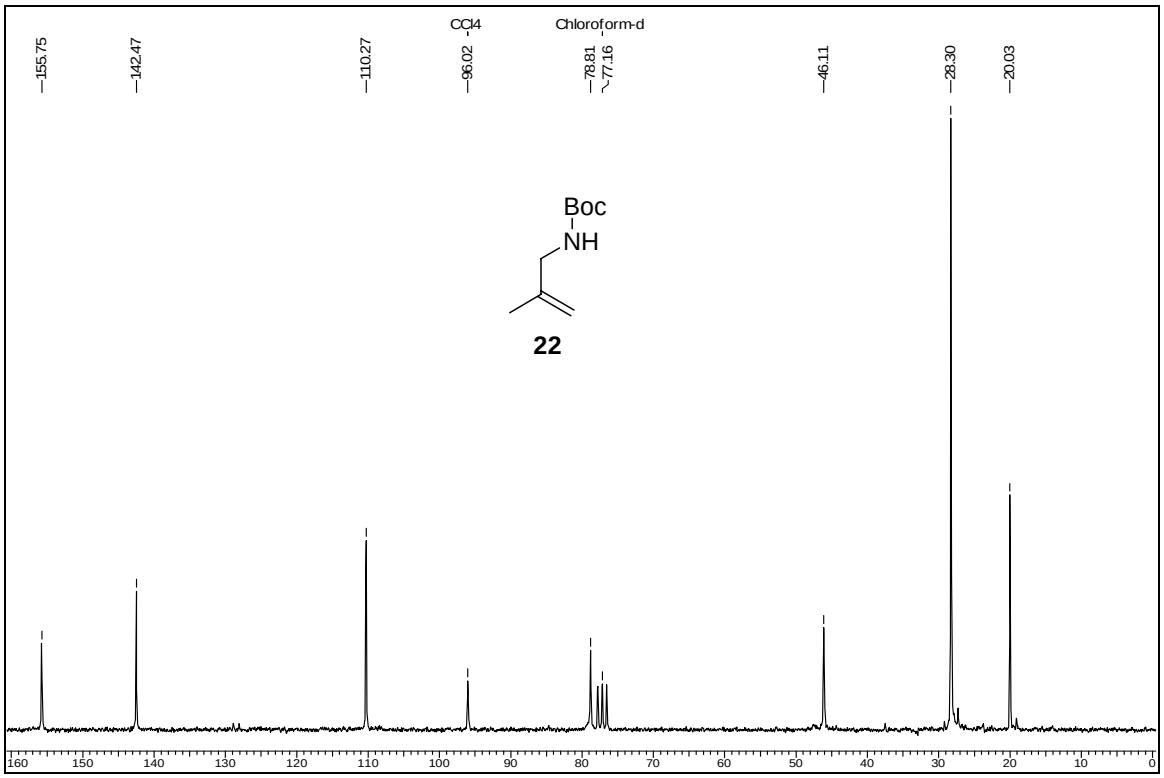
Elemental analysis Calculated: C, 71.49; H, 8.67; N, 9.26%.

Found: C, 71.34; H, 8.68; N, 9.01%.

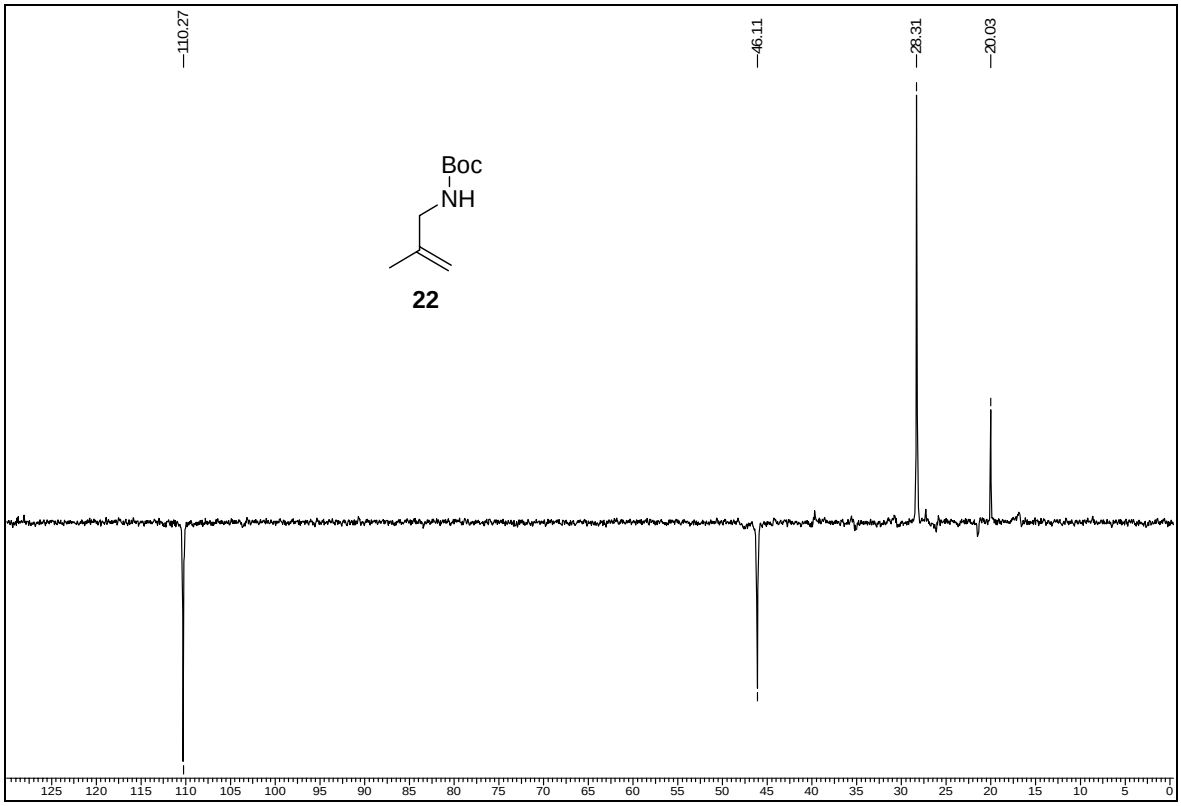
3.2.7 Spectra:



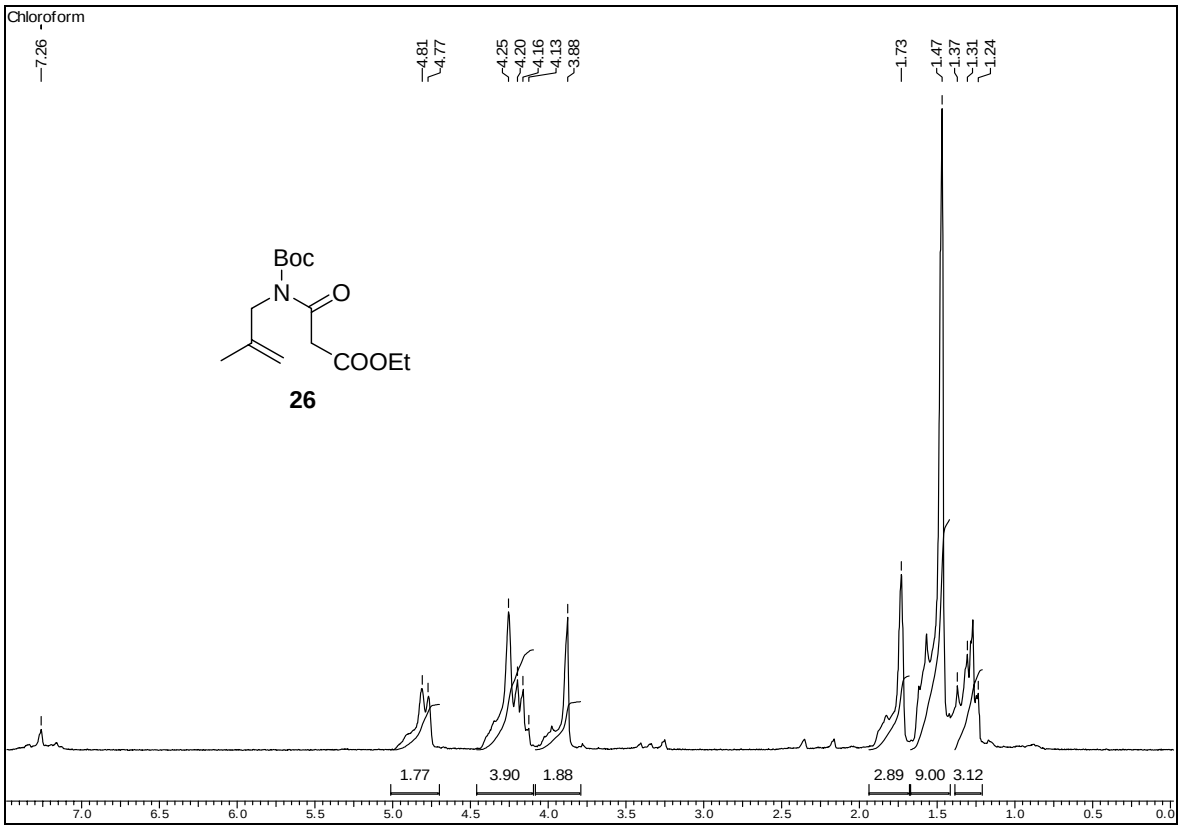
^{1}H NMR spectrum of compound 22 ($CDCl_3$ + CCl_4, 300 MHz)



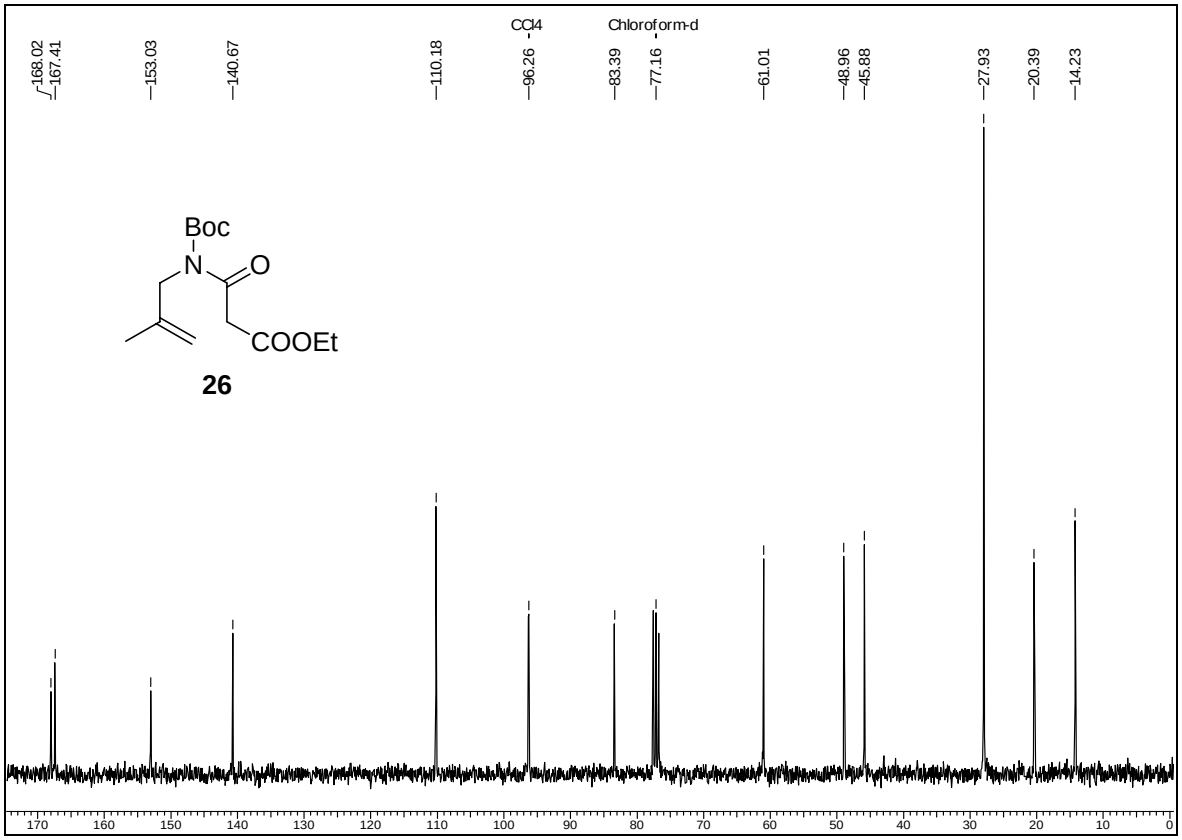
^{13}C NMR spectrum of compound 22 ($CDCl_3$ + CCl_4, 50 MHz)



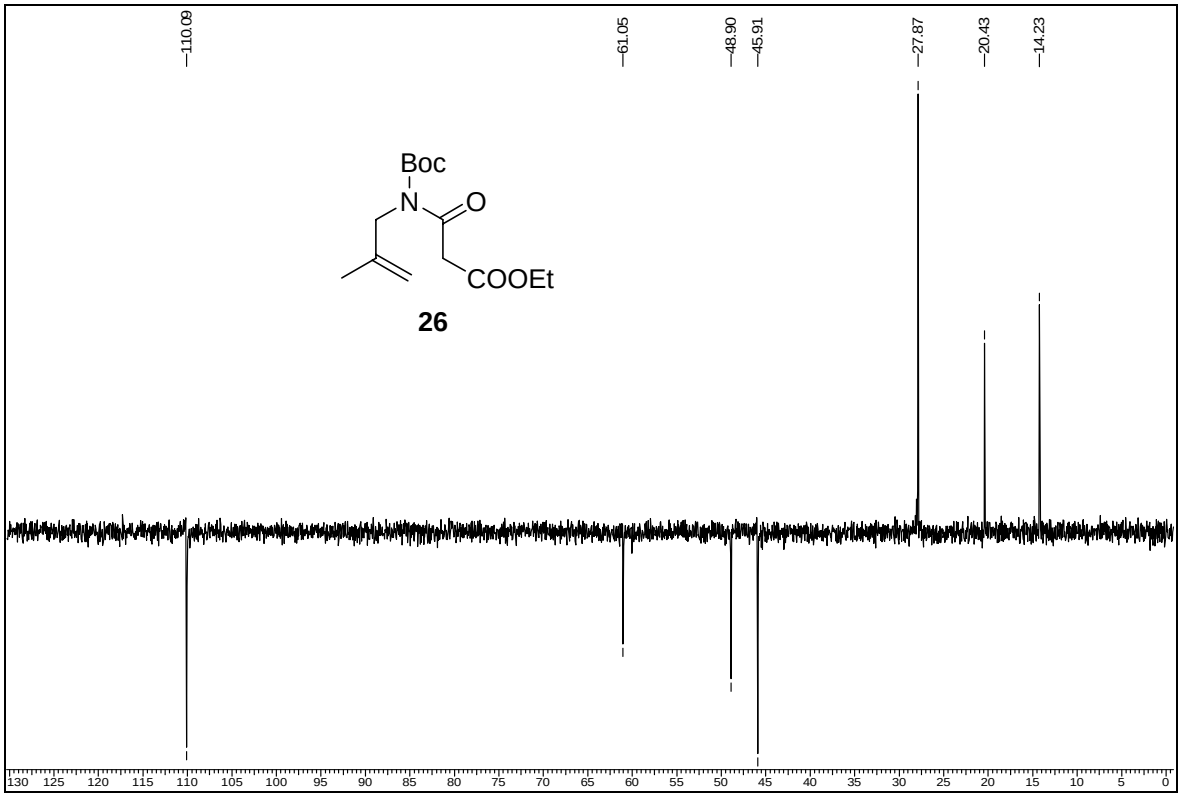
DEPT spectrum of compound 22 ($CDCl_3$ + CCl_4, 50 MHz)



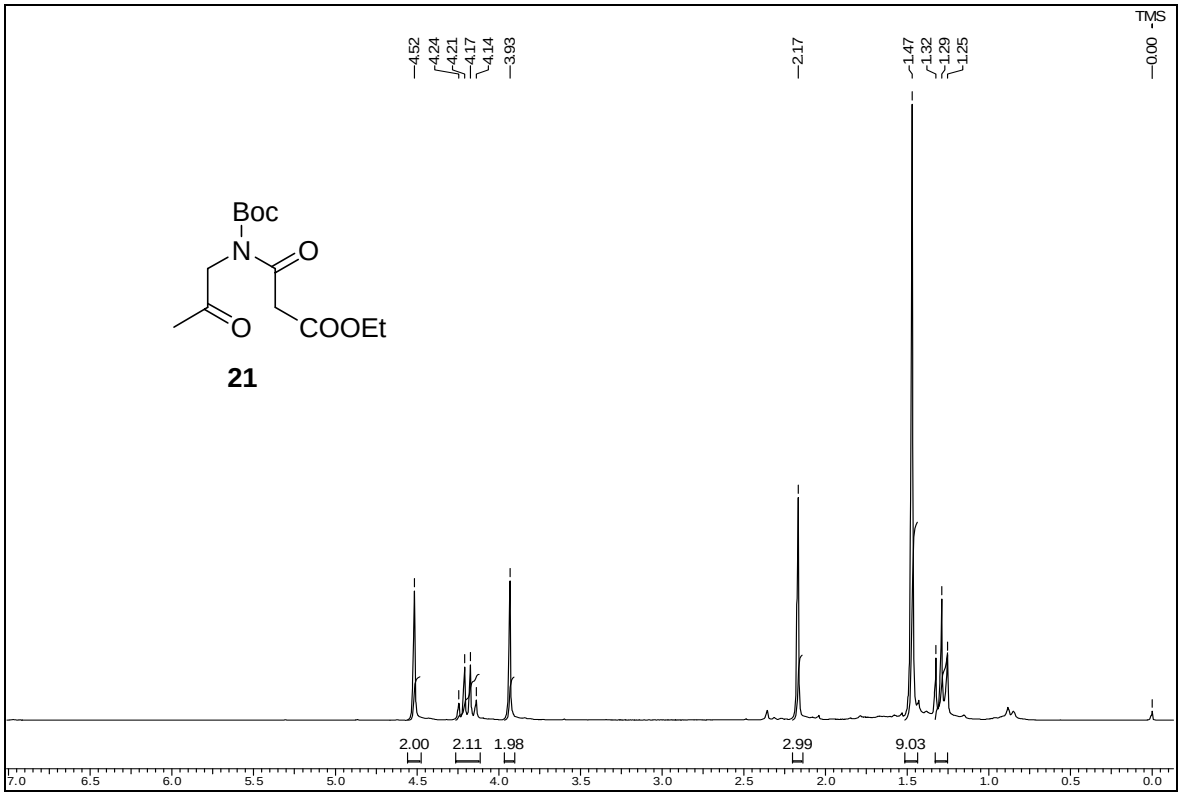
^{1}H NMR spectrum of compound 26 ($CDCl_3$ + CCl_4, 200 MHz)



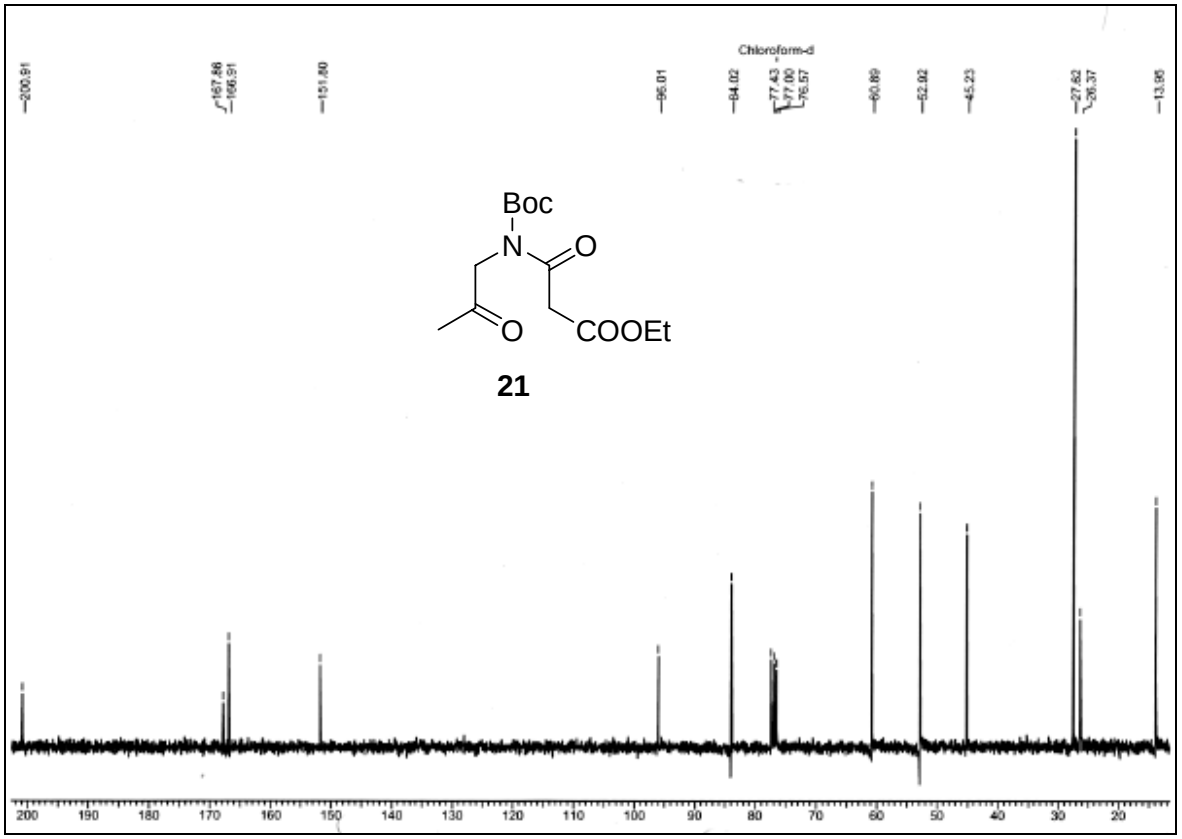
^{13}C NMR spectrum of compound 26 ($CDCl_3$ + CCl_4, 75 MHz)



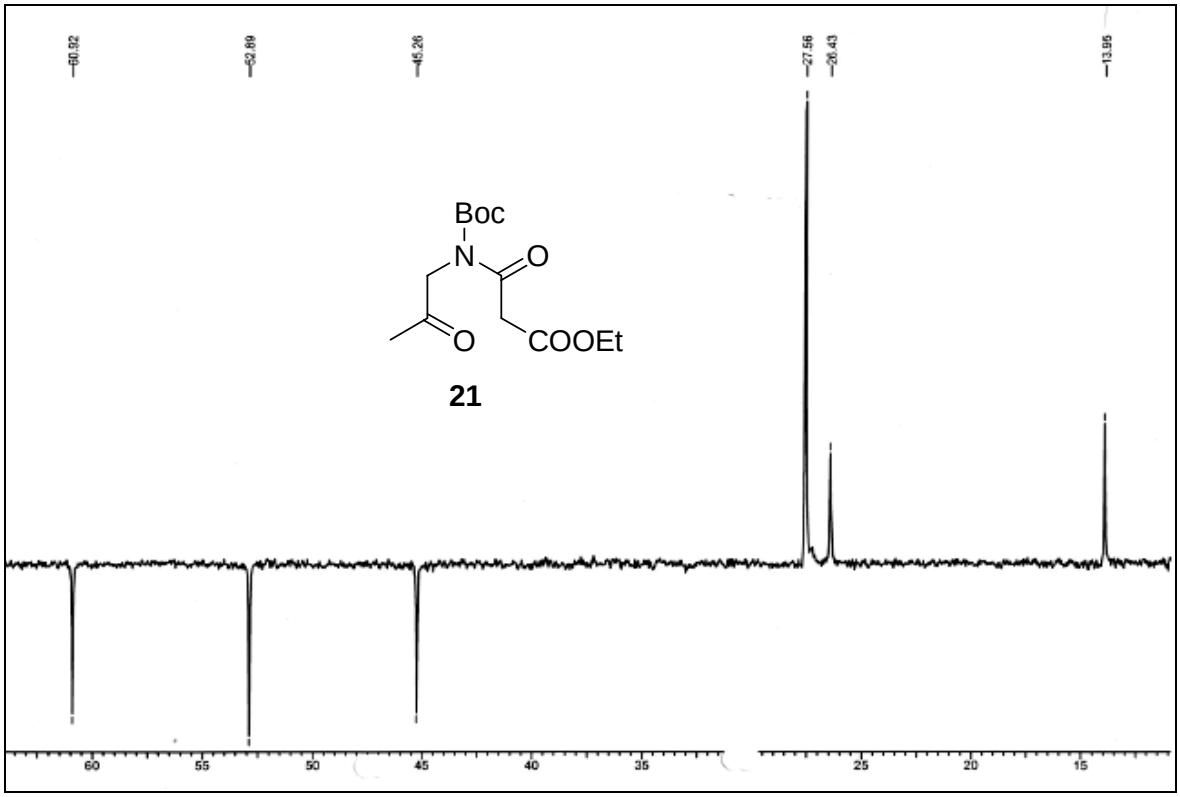
DEPT spectrum of compound 26 ($CDCl_3$ + CCl_4, 75 MHz)



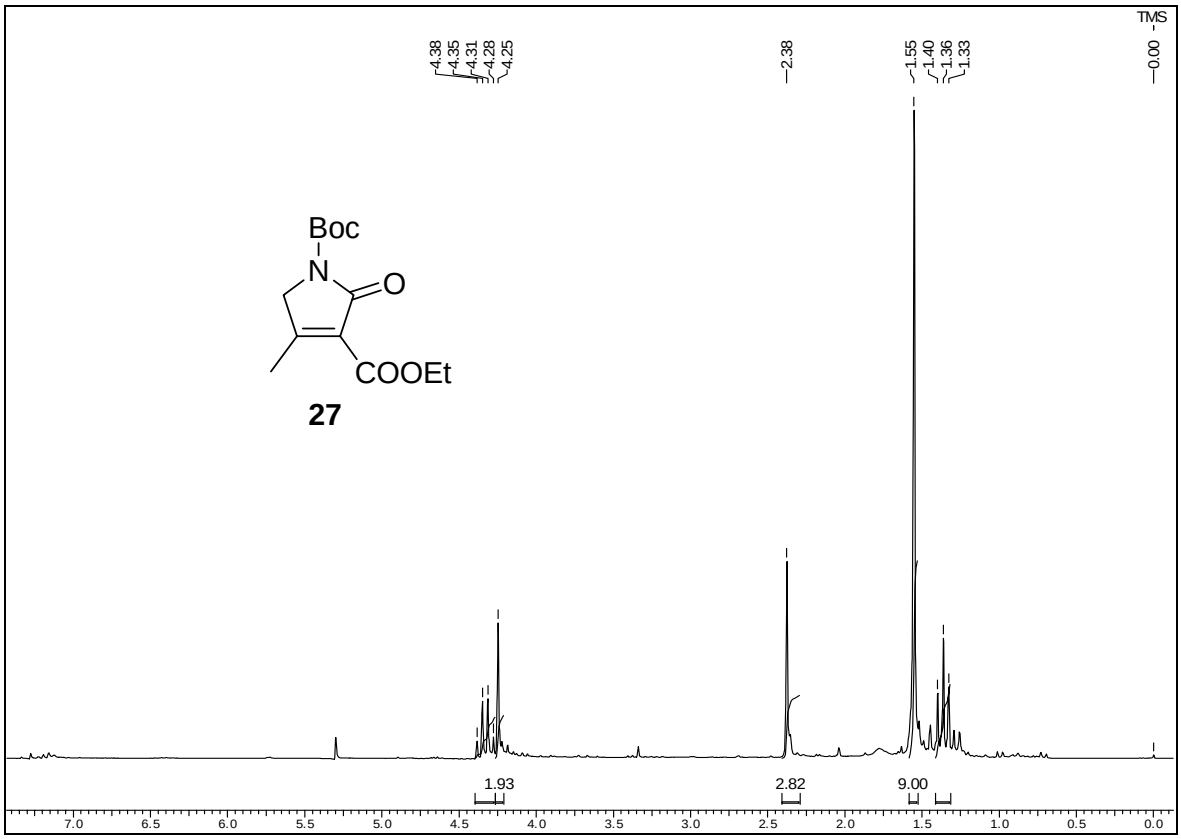
^{1}H NMR spectrum of compound 21 ($CDCl_3$ + CCl_4, 200 MHz)



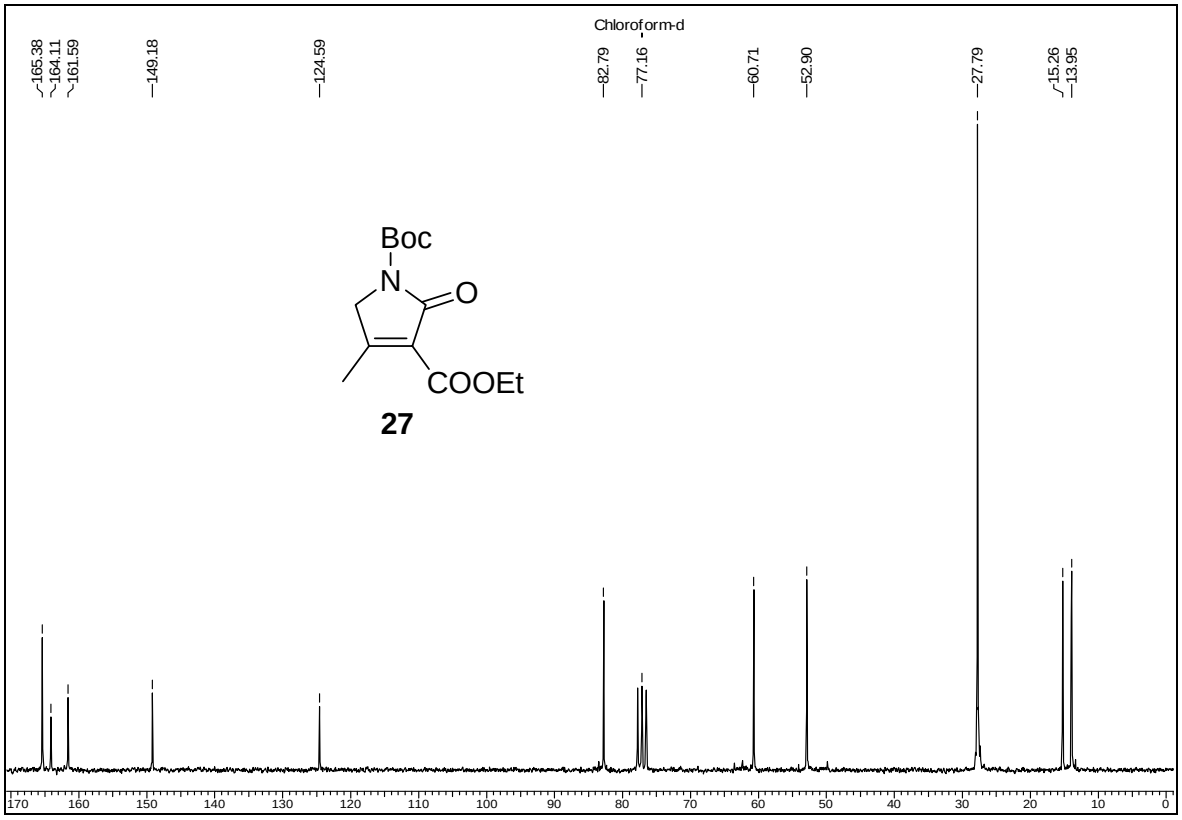
^{13}C NMR spectrum of compound 21 ($CDCl_3$ + CCl_4, 75 MHz)



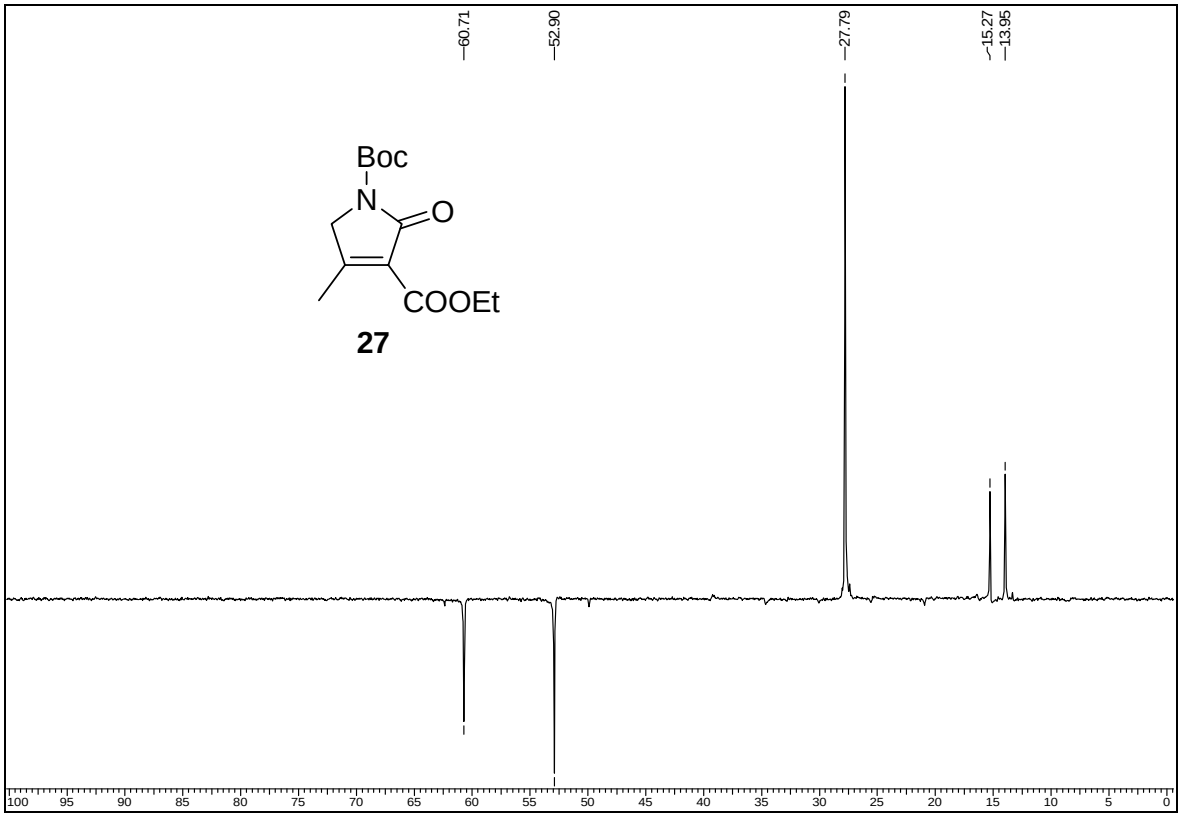
DEPT spectrum of compound 21 ($CDCl_3$ + CCl_4, 75 MHz)



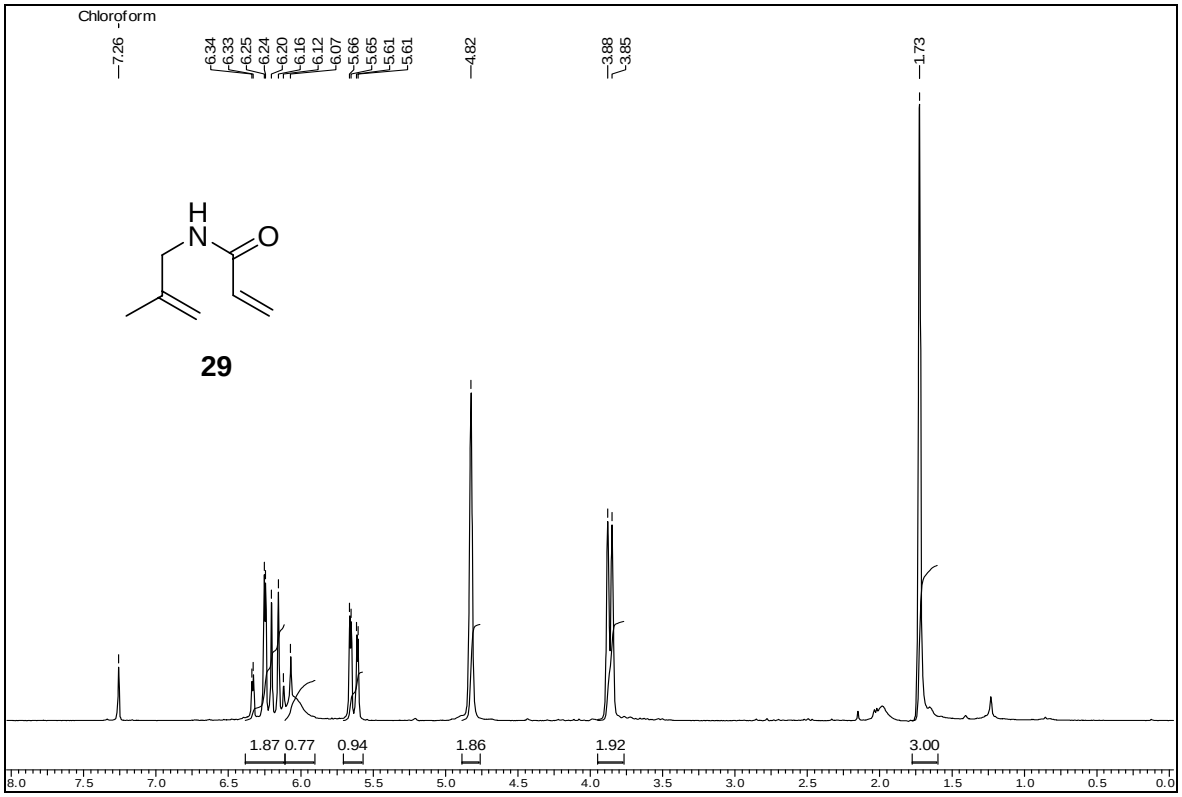
^{1}H NMR spectrum of compound 27 ($CDCl_3$, 200 MHz)



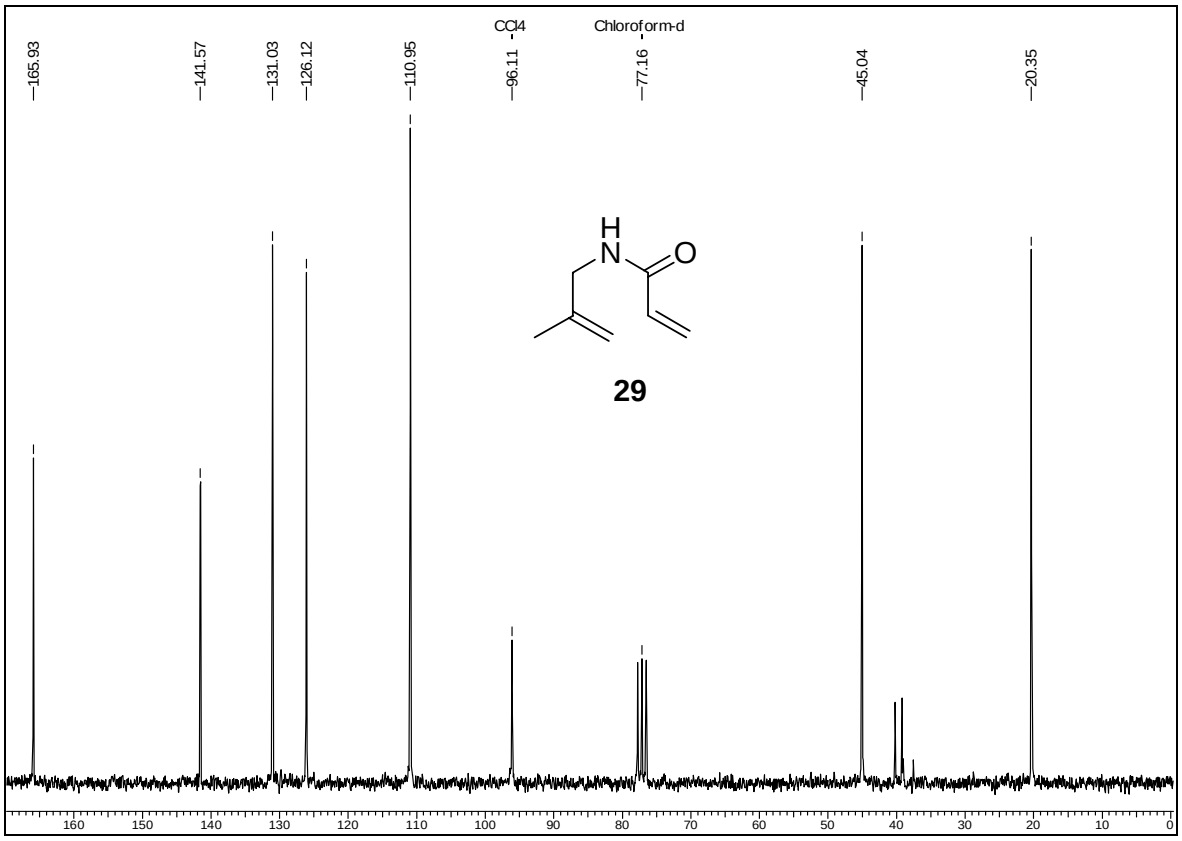
^{13}C NMR spectrum of compound 27 ($CDCl_3$, 50 MHz)



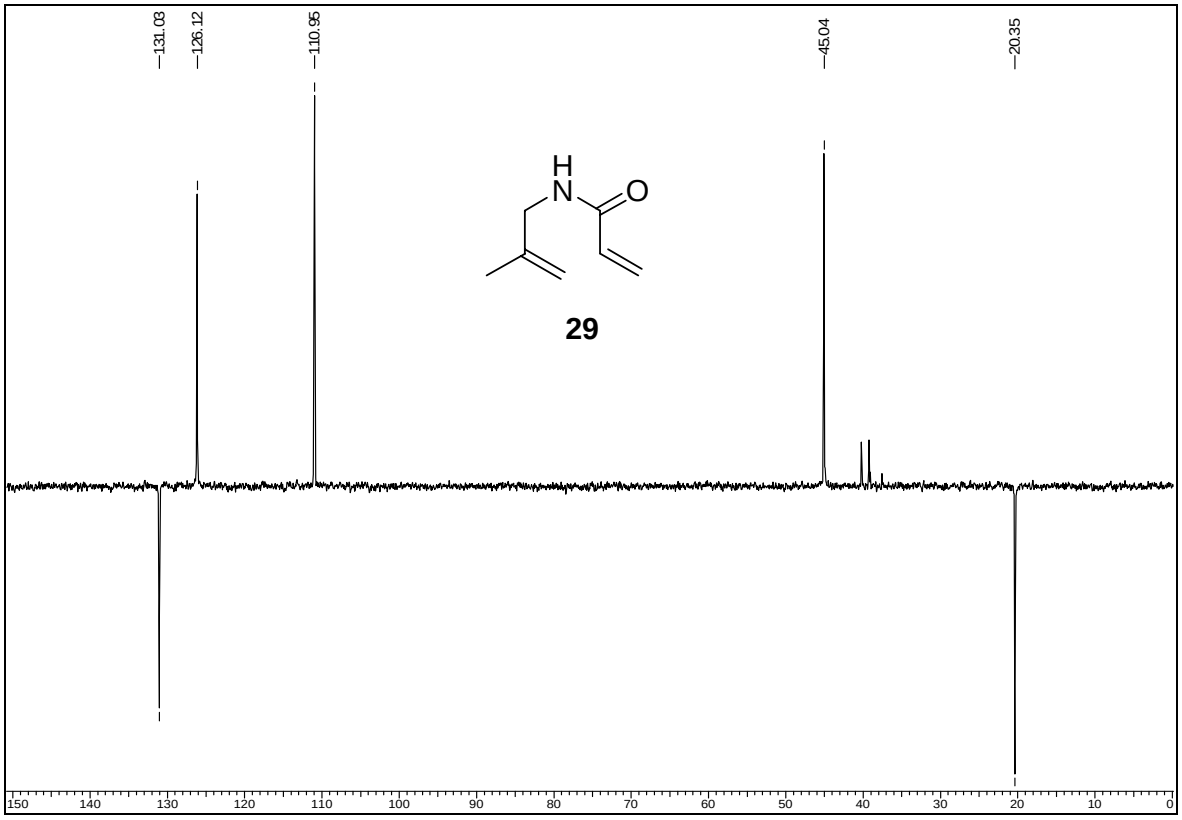
DEPT spectrum of compound 27 ($CDCl_3$, 50 MHz)



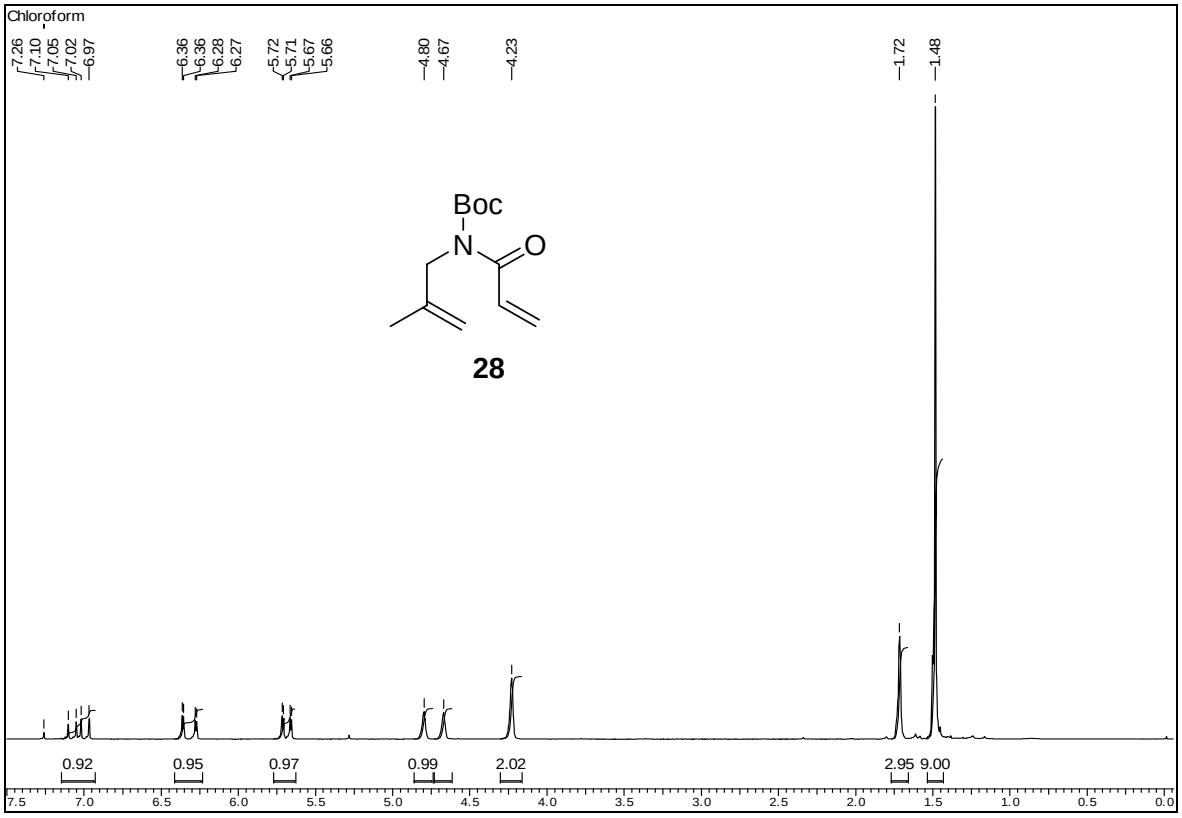
^{1}H NMR spectrum of compound 29 ($CDCl_3$ + CCl_4, 200 MHz)



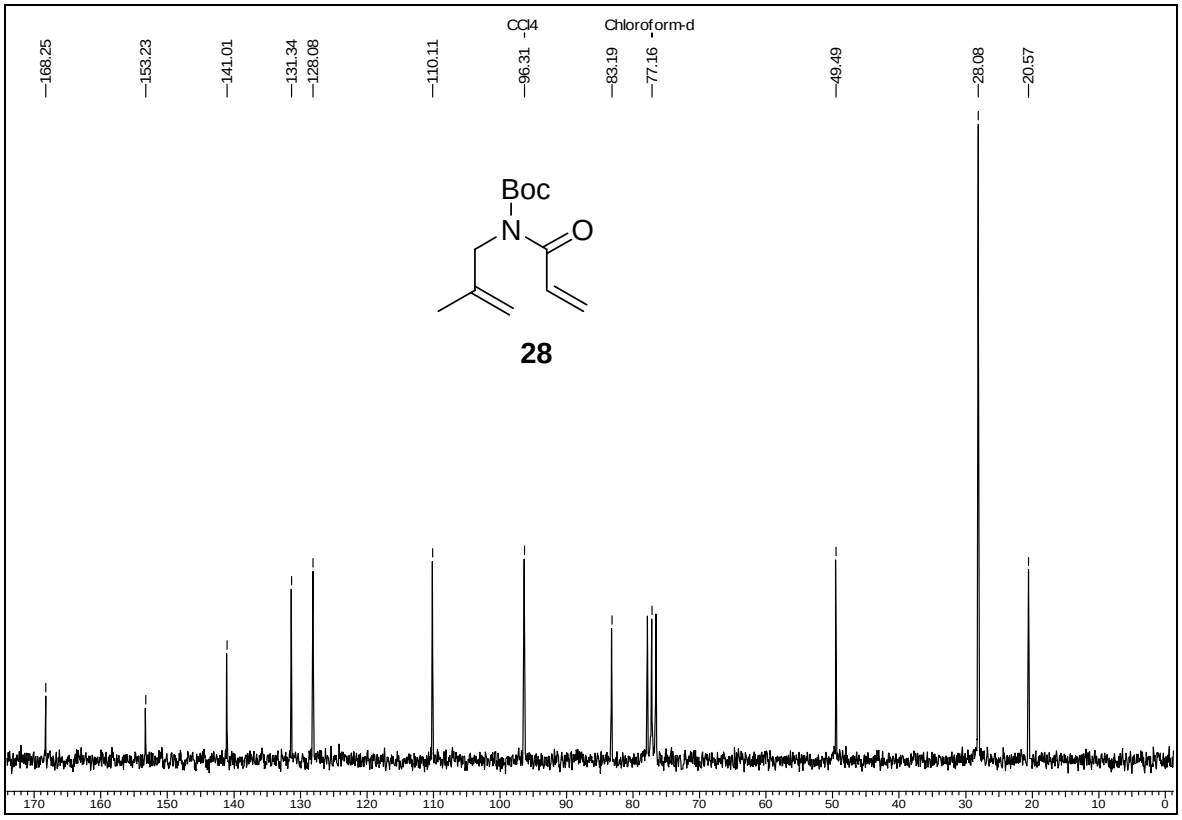
^{13}C NMR spectrum of compound 29 ($CDCl_3$ + CCl_4, 50 MHz)



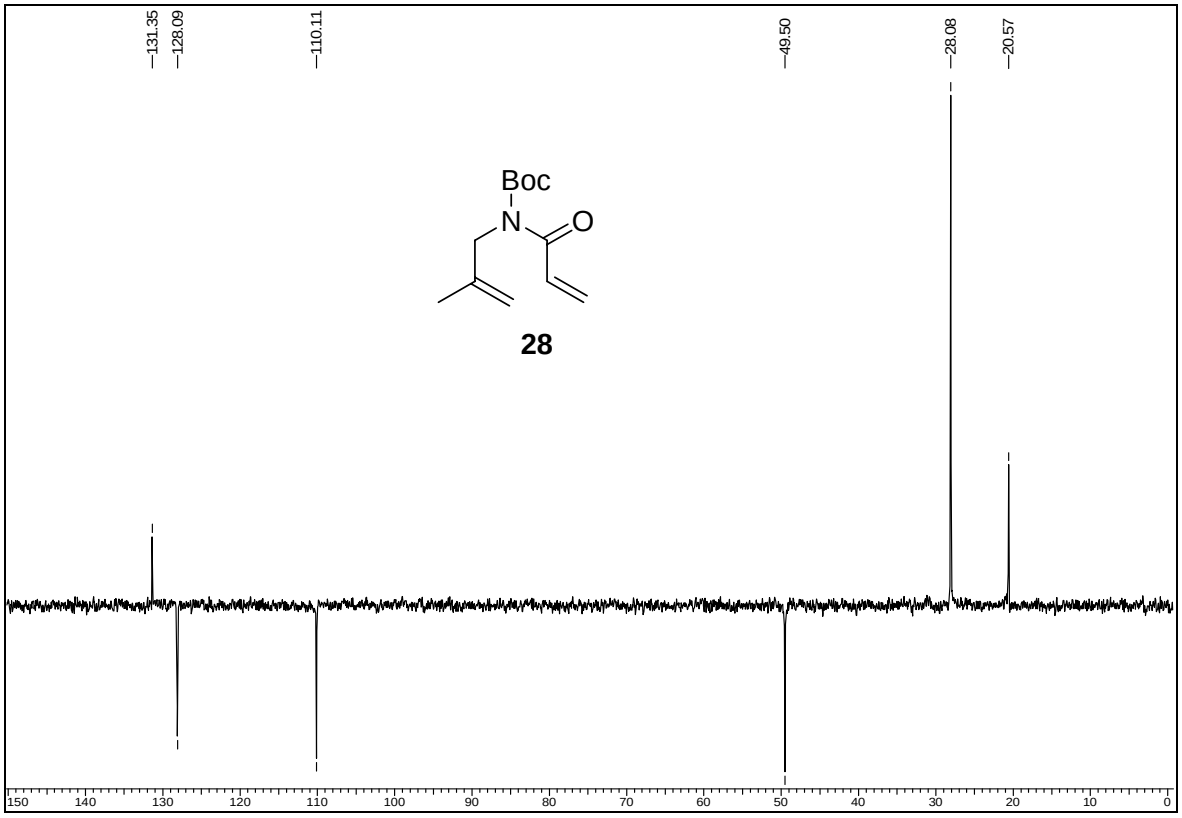
DEPT spectrum of compound 29 ($CDCl_3$ + CCl_4, 50 MHz)



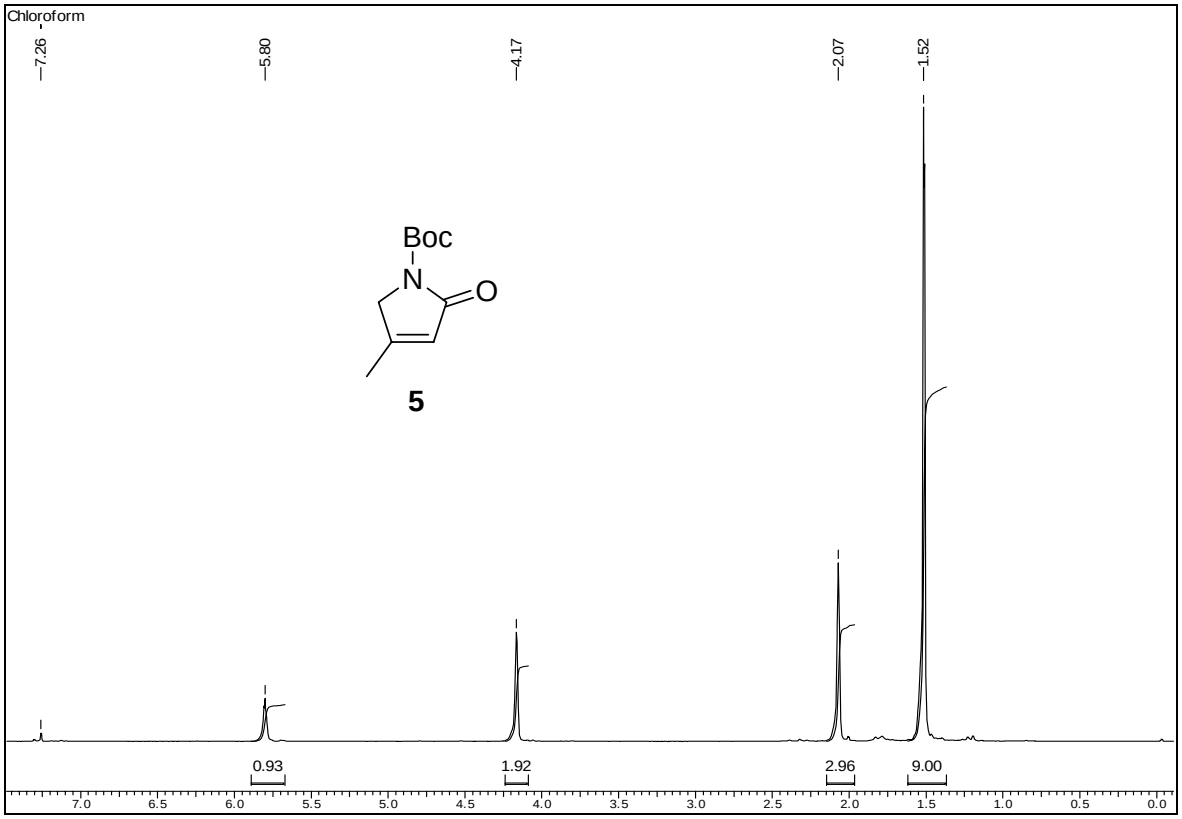
^{1}H NMR spectrum of compound 28 ($CDCl_3$ + CCl_4, 200 MHz)



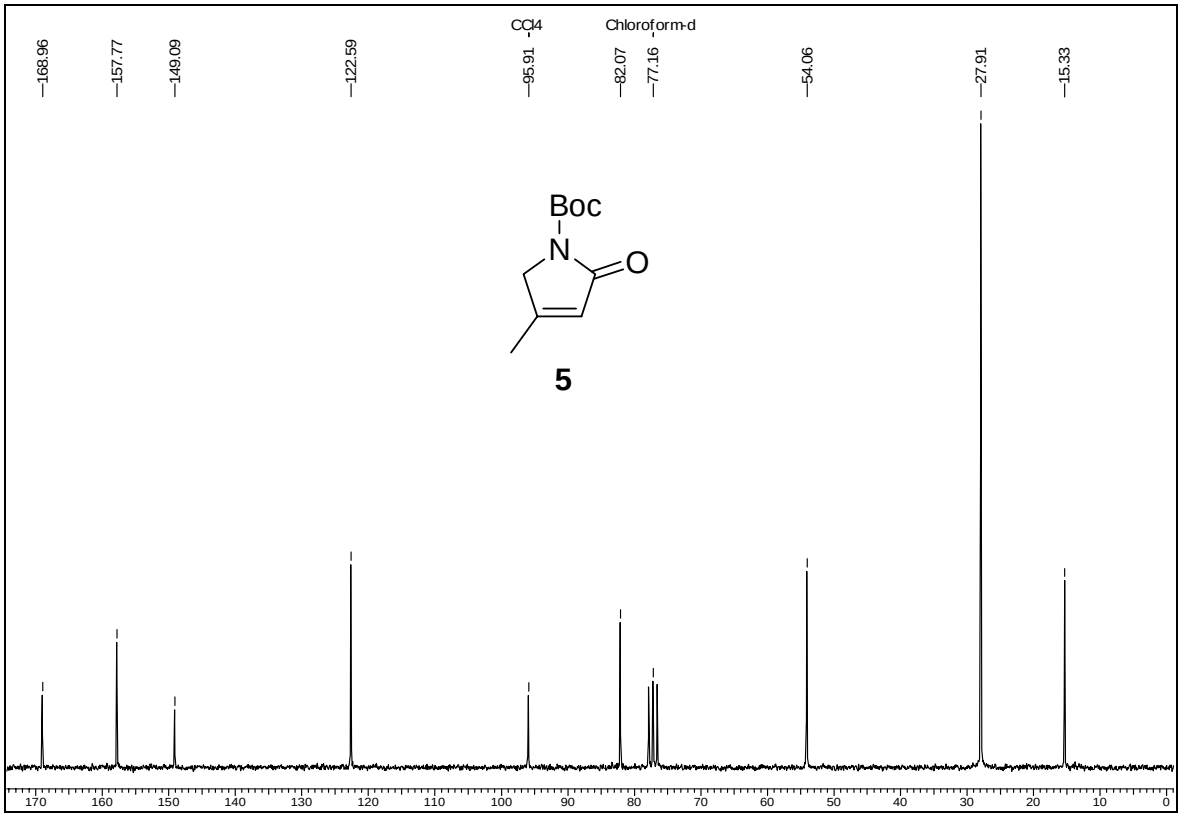
^{13}C NMR spectrum of compound 28 ($CDCl_3$ + CCl_4, 50 MHz)



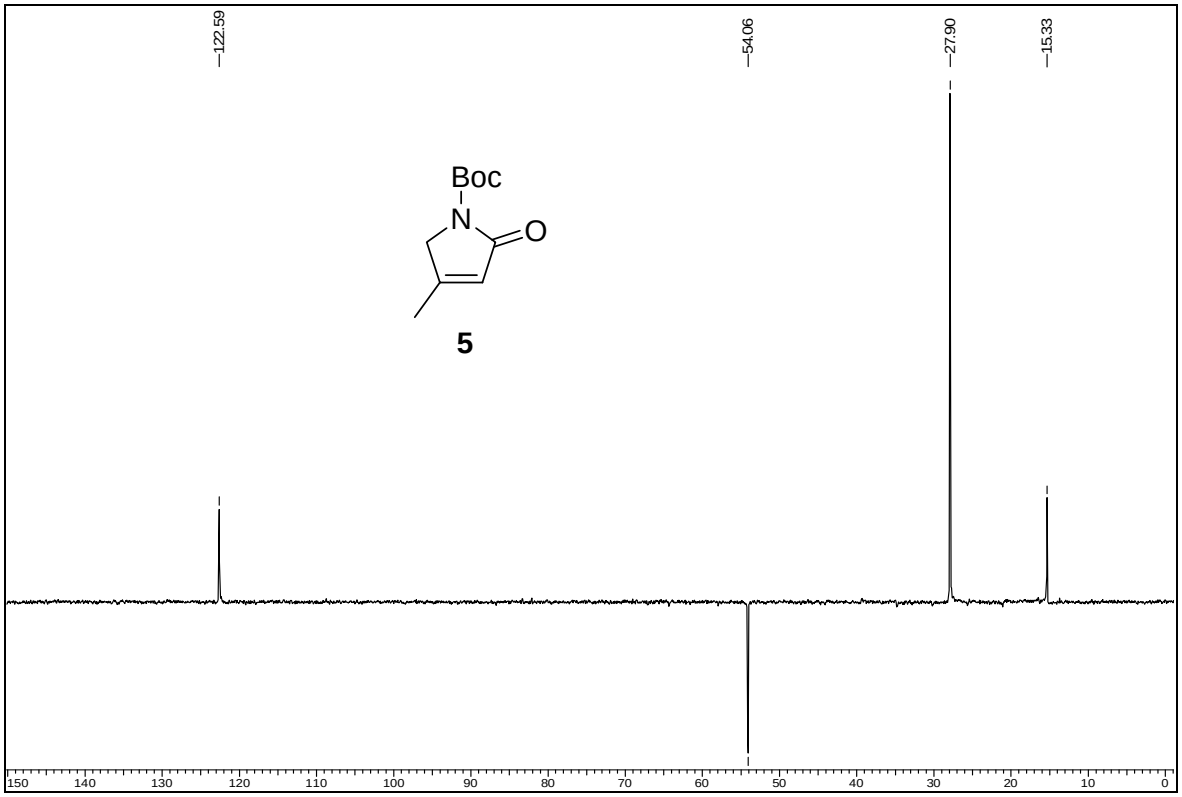
DEPT spectrum of compound 28 ($CDCl_3$ + CCl_4, 50 MHz)



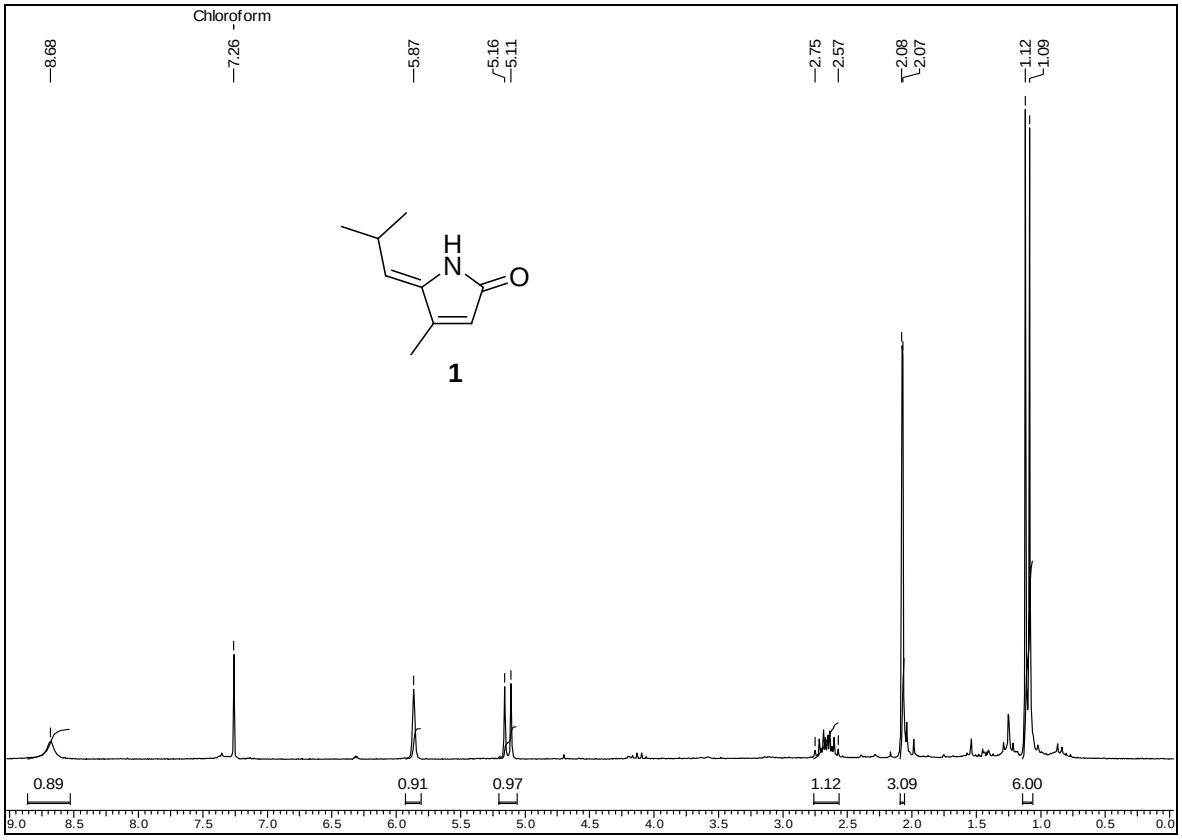
^{1}H NMR spectrum of compound 5 ($CDCl_3$ + CCl_4, 200 MHz)



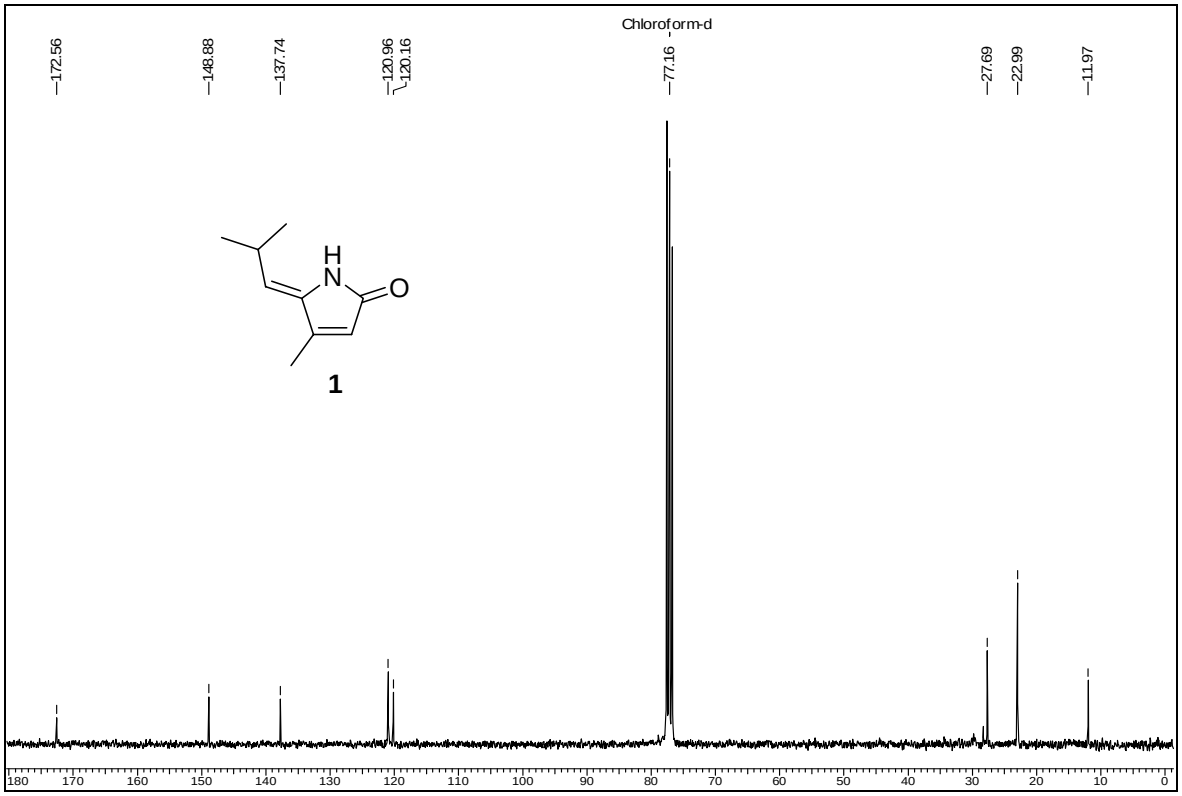
^{13}C NMR spectrum of compound 5 ($CDCl_3$ + CCl_4, 50 MHz)



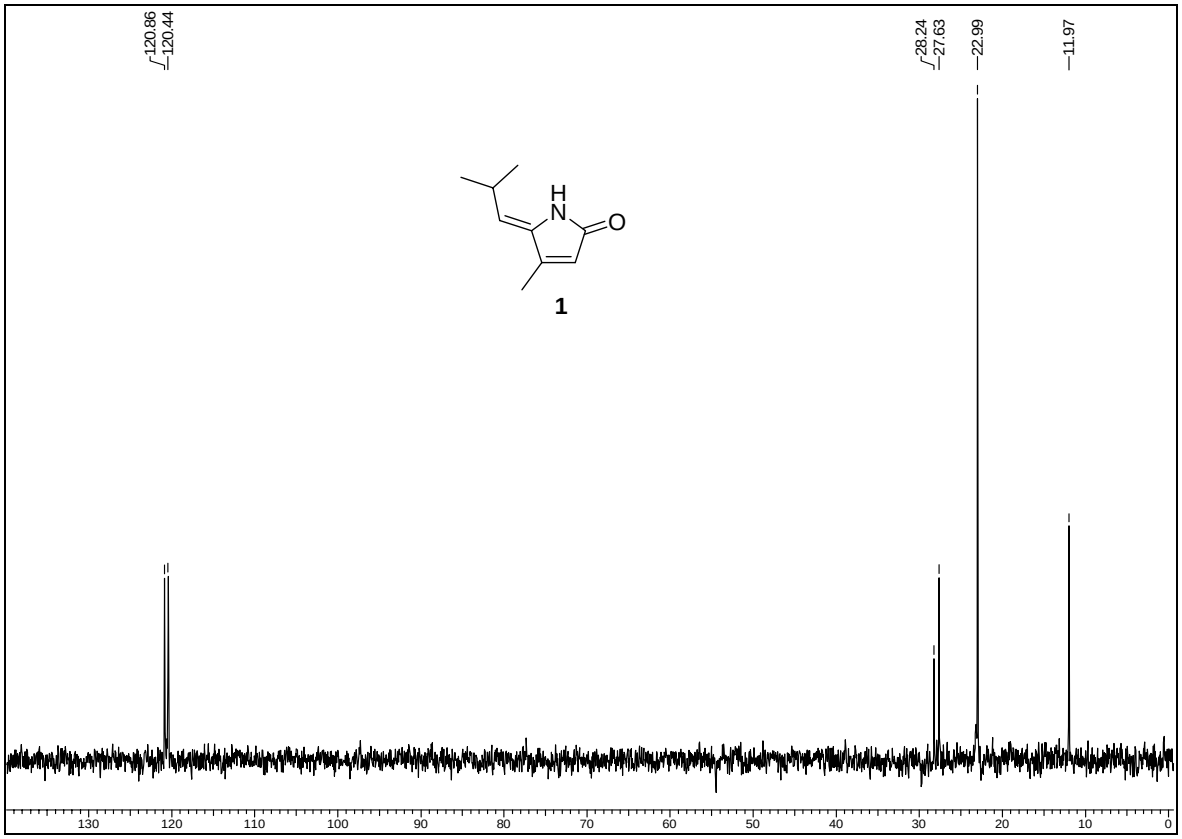
DEPT spectrum of compound 5 ($CDCl_3$ + CCl_4, 50 MHz)



^{1}H NMR spectrum of compound 1 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound 1 ($CDCl_3$, 75 MHz)



DEPT spectrum of compound 1 ($CDCl_3$, 75 MHz)

3.2.8 References:

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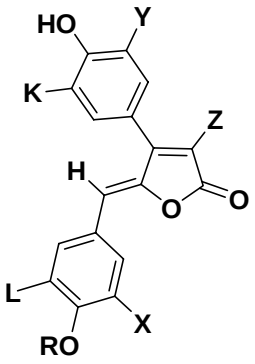
Chapter 3, Section III

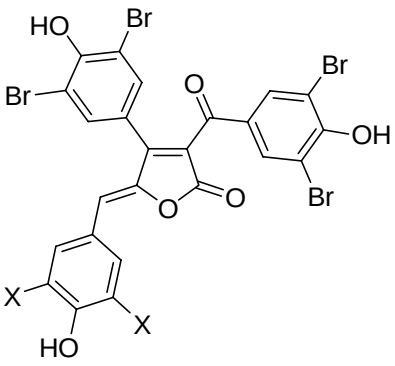
Total synthesis of rubrolide E

3.3.1 Introduction:

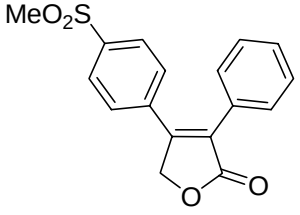
Rubrolides (**1, A-F, I-N**) are the biologically active marine tunicate metabolites which have been isolated in1991 by Andersen from tunicate *Ritterella rubra*[1] and in 2000 by Salva and his co-workers from tunicate *Synoicum blochmanni.*[2] Structurally, rubrolides contain butenolide frameworks with two *para*- hydroxyphenyl moieties with or without halogen atoms. These rubrolides show potent in-vitro antibiotic activity, cytotoxicity against cancer cell lines and moderate but selective inhibition of protein phosphatases.[3] Cardiolide A **2a** & cardiolide B **2b**[4] and other structurally related drugs viz. Rofecoxib **3** exhibit antitumor activity[5] while Benfurodil hemisuccinate **4** shows activity against heart failure.[6]



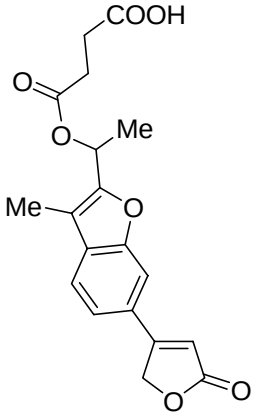
Rubrolide A (1a) R = Z = H; K = L = X = Y = Br
Rubrolide B (1b) R = H; K = L = X = Y = Br; Z = Cl
Rubrolide C (1c) R = K = Y = Z = H; L = X = Br
Rubrolide D (1d) R = L = X = Z = H; K = Y = Br
Rubrolide E (1e) R = L = K = X = Y = Z = H
Rubrolide F (1f) R = Me; L = K = X = Y = Z = H
Rubrolide I (1i) R = K = H; L = X = Y = Br; Z = Cl
Rubrolide J (1j) R = K = Z = H; L = X = y = Br
Rubrolide K (1k) R = K = L = H; X = Y = Br; Z = Cl
Rubrolide L (1l) R = K = Y = H; L = X =Br; Z = Cl
Rubrolide M (1m) R = K = L = Y = H; X = Br; Z = Cl
Rubrolide N (1n) R = K = L = H; Y = Cl; X = Z = Br



Cadiolide A (2a) X = H
Cadiolide B (2b) X = Br



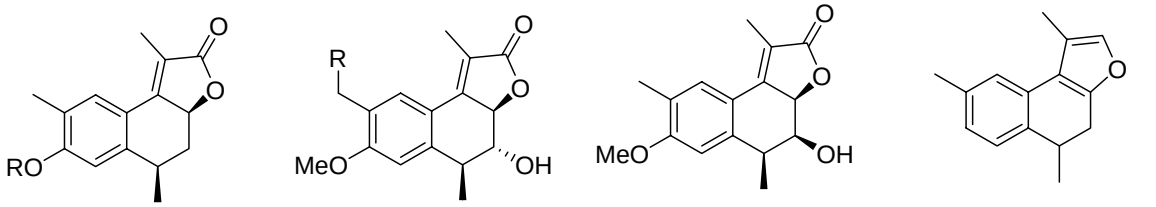
3 Rofecoxib



4 Benfurodil hemisuccinate

Figure 1.

The molecules Heritol **5a**, Heritonin **5b**, Heritianin **6a**, Vallapin **6b**, Vallapianin **7** and (±)-Laevigatin **8**[5-9] described in fig. 2 also show some structural similarity of possessing 3 aryl butenolide as the common framework and exihibit itchthiotoxicity.



5a Heritol, R = H
5b Heritonin, R = Me

6a Heritianin, R = H
6b Vallapin, R = OH

7 Vallapianin, R = OH

8 (±) Laevigatin

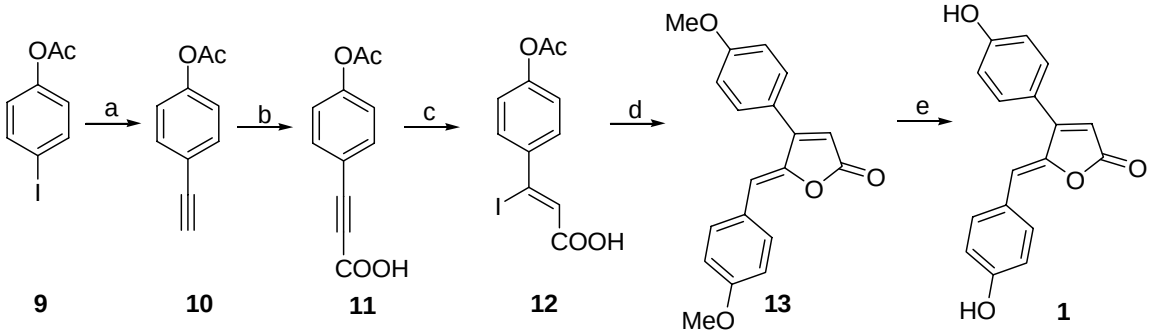
Figure 2.

3.3.2 Literature survey:

The literature investigation shows that the numerous short and elegant syntheses of rubrolide E have been devised by chemists utilizing novel chemistry. These are described below.

Negeshi's approach[10] (*Synthesis*, **1997**, 121)

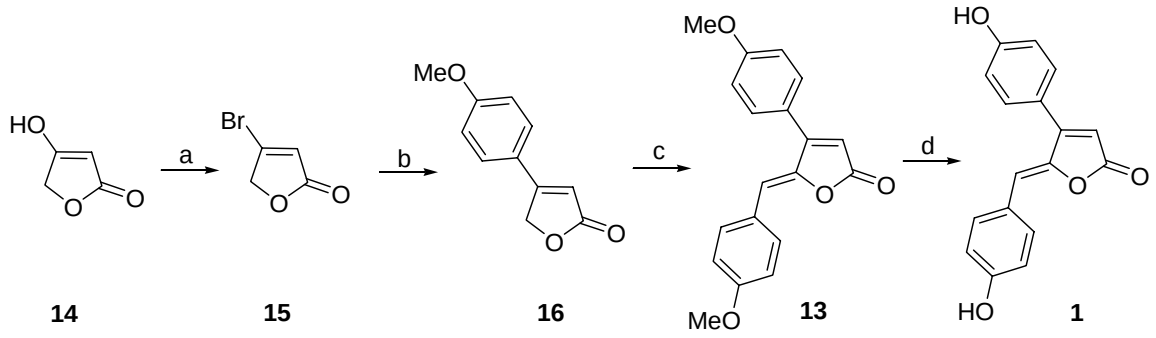
Negeshi and co-workers devised elegant synthesis of **1e** from *p*-iodo aromatic compound **9** which was treated with ethynylzinc bromide in presence of $Pd(PPh_3)_4$ to afford compound **10** in 73% yield. The acetylene **10** was reacted with BuLi and dry ice at -78 ^oC furnishing corresponding acid **11** in 94% yield. Compound **11** was treated with sodium iodide in acetic acid to give iodo compound **12** in 77% yield. The cross coupling-lactonization reaction of **10** with **12** was accomplished using $Pd(PPh_3)_4$, CuI and Et_3N as a base in CH_3CN at room temperature to give **13** in 50% yield. Lastly the demethylation of aromatic methoxy groups was accomplished using boron tribromide to furnish rubrolide E **1** in 98% yield. Thus synthesis was achieved in five-steps in 26% overall yield employing Pd-mediated cross coupling-lactonization sequence as key reaction.



Scheme 1. *Reagents and conditions: (a) Zinc, Pd $(PPh_3)_4$, 73% (b) BuLi, CO_2, -78 ^oC, 94%. (c) NaI, AcOH, 77%. (d)* ***10****, Pd $(PPh_3)_4$, CuI, Et_3N, CH_3CN, 24 h, rt, 50%. (e) BBr_3, -78 ^oC- rt, 24 h, 98%.*

Boukouvalas's approach[11] (*Tetrahedron Letters*. **1998**, *39*, 7665)

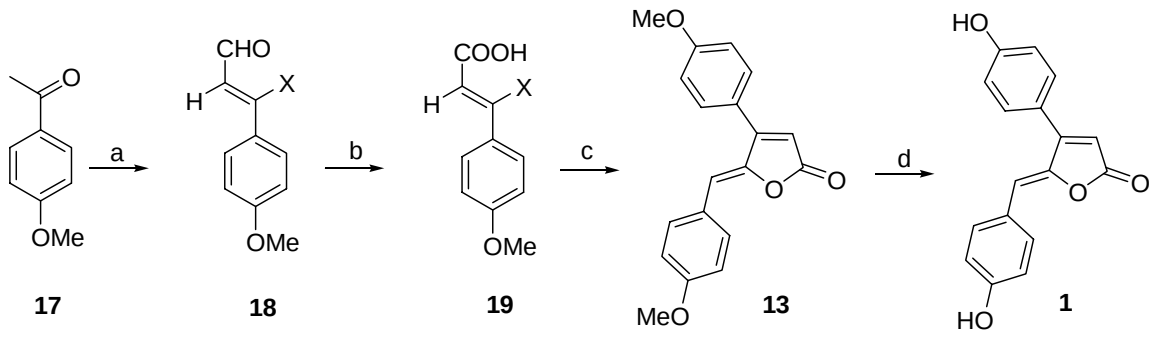
Boukouvalas *et al.* achieved a short and efficient synthesis of rubrolide E employing Suzuki coupling as the key step. The Vilsmeier bromination was carried out on commercially available β-tetronic acid **14** to furnish 4-bromo-2(5*H*)-furanone **15** in 86% yield. The bromo butenolide **15** underwent Suzuki coupling reaction with *p*-methoxyphenylboronic acid using $Pd(PPh_3)_4$ in aq. Na_2CO_3 to afford aryl furanone **16** in 79% yield. Treatment of **16** with anisaldehyde in presence of TBDMSOTf and diisopropylethylamine, followed by DBU mediated dehydration furnished corresponding *Z*-arylmethylenebutenolide **13** in 84% yield. Demethylation of **13** using boron tribromide in dry DCM at low temperature gave rubrolide E **1** in 98% yield. Thus the total synthesis was achieved in four-steps in 56% overall yield.



Scheme 2. *Reagents and conditions: (a) Vilsmeir bromination, 86%. (b) $ArB(OH)_2$, $Pd(PPh_3)_4$, aq. Na_2CO_3, C_6H_6/EtOH, 80 ^oC, 2.5 h, 79%.(c) TBDMSOTf (1.2 equiv), i-Pr_2NEt (3.0 equiv), CH_2Cl_2, rt, 1-2 h, DBU (2.0 equiv), rt, 3 h, 84% (d) BBr_3, -78 ^oC- rt, 24 h, 98%.*

Prim's approach[12] (*JCS Perkin Trans-2*, **1999**, 1175)

Prim *et al.* started their synthesis from *p*-methoxyacetophenone **17** employing Vilsmeier-Haack reaction and Negeshi coupling as the key steps. The treatment of **17** with DMF $POCl_3$ furnished β-aryl-β-haloacrolein **18** in 90% yield. The oxidation of carbaldehyde **14** using H_2O_2, NaH_2PO_4 and $NaClO_2$ in acetonitrile at room temperature gave corresponding cinnamic acid **19** in 82% yield. The acid **19** underwent smooth Negeshi coupling with aryl acetylene furnishing coupled product **13** in 74% yield and finally demethylation using BBr_3 at -78 ^oC – rt furnished rubrolide E **1** in 98% yield. Thus rubrolide **1** was synthesized in four-steps in 54% overall yield.

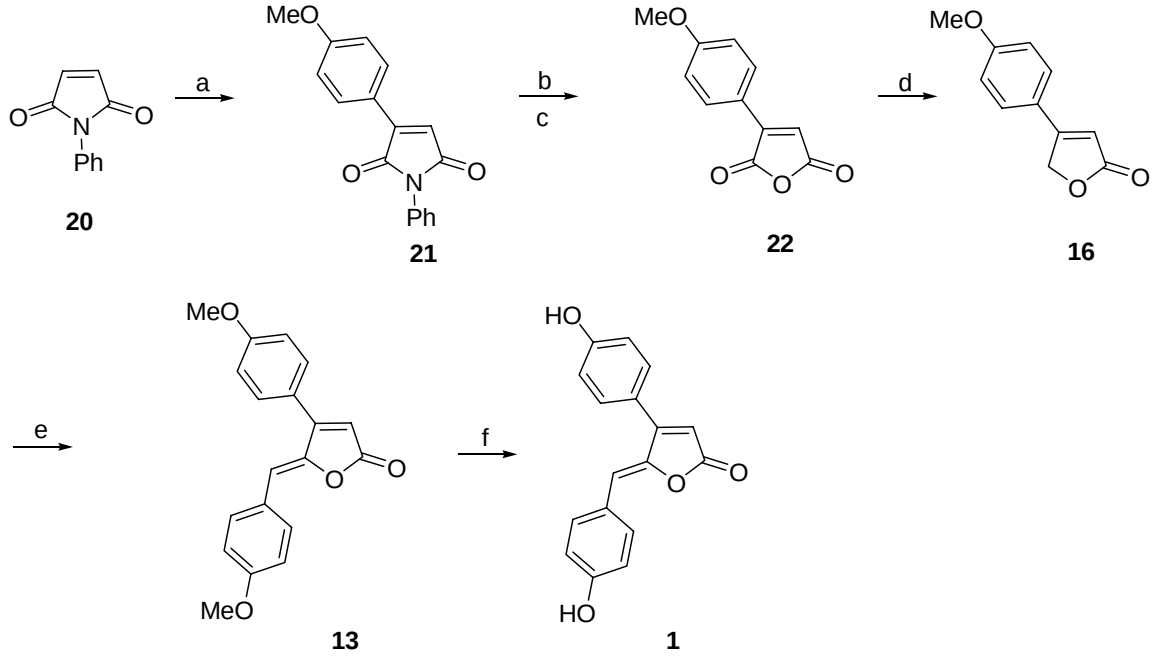


17 **18** **19** **13** **1**

Scheme 3. *Reagents and conditions: (a) DMF, $POCl_3$, 90% (b) H_2O_2, H_2O, NaH_2PO_4, $NaClO_2$, CH_3CN, rt, 82%. (c) $Pd(PPh_3)_4$, CuI, Et_3N, R_3PhCCH, CH_3CN, rt, 74% (d) BBr_3, -78 ^oC- rt, 24 h, 98%.*

Argade's approach[13] (*Synthesis*, **2005**, 2284)

Argade *et al.* synthesized rubrolide E from commercially available *N*-phenylmaleimide **20** which was coupled with *p*-anisyldiazonium chloride employing Meerwein coupling using $CuCl_2$ in aq. acetone at pH 3 at 0 to 35 ^oC to furnish arylmaleimide **21** in 65% yield.



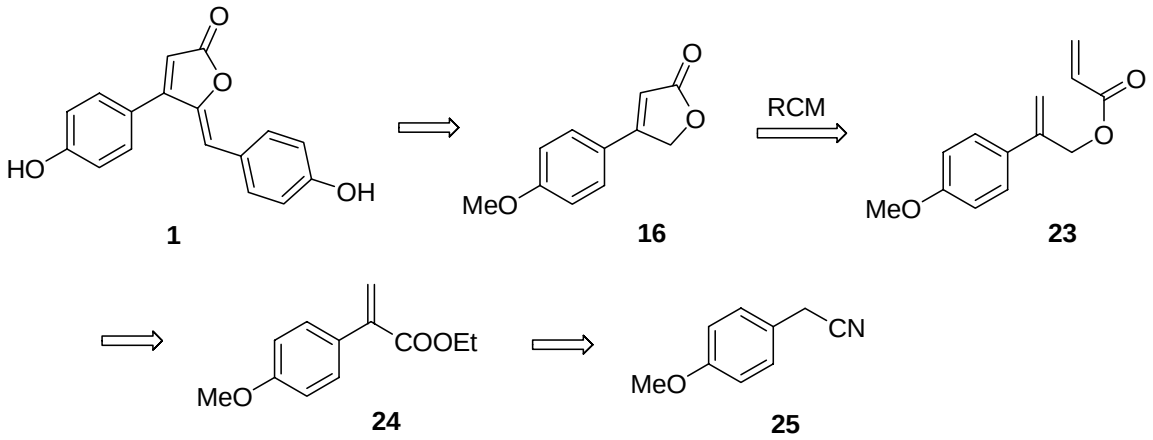
20 **21** **22** **16** **13** **1**

Scheme 4. *Reagents and conditions: (a) p-anisyldiazonium chloride, $CuCl_2$, pH 3, aq. Acetone, 0-35 ^oC, 24 h, 65% (b) (i) 20% aq. KOH, MeOH, reflux, 4 h (ii) H^+/HCl (c) Ac_2O, reflux, 3 h, 100% for b & c (d) $NaBH_4$, THF, 0 ^oC, 2 h, 62% (e) piperidine, p-anisaldehyde, MeOH, rt, 15 h, 78%. (f) BBr_3, CH_2Cl_2, -78 ^oC- rt, 24 h, 95%.*

The basic hydrolysis of **21** followed by treatment with acetic anhydride induced dehydrative-closure furnished *p*-anisylmaleic anhydride **22** in quantitative yield. The regioselective reduction of **22** using sodium borohydride in THF to yielded the corresponding butyrolactone **16** in 62% yield. Butyrolactone **16** was condensed with *p*-anisaldehyde employing Knoevenagel condensation using piperidine as a base in methanol at room temperature to afford required (*Z*) butenolide **13** in 78% yield. The demthylation of **13** using BBr_3 at lower temperature furnished target molecule rubrolide E **1** in 95% yield. Thus the total synthesis was completed in six-steps in 30% overall yield employing Meerwein coupling as a key reaction.

3.3.3 Present work:

As a part of ongoing programme on the synthesis of biologically active natural products coupled with the limited availability of rubrolide E from natural sources and the impressive bioactivity exhibited by it against different diseases it was decided to undertake the synthesis of rubrolide E **1**. Practical routes of different compounds employing various strategies have been developed earlier from this group. This section describes different protocols like RCM, intramolecular Knoevenagel condensation and Reformatsky reaction for the synthesis of rubrolide E.



Scheme 5. *Retrosynthetic plan 1.*

According to retrosynthetic analysis (scheme 5), the key precursor butenolide **16** could be elaborated to the target molecule **1** by intermolecular Knoevenagel condensation followed by demethylation. The butenolide **16** can be realized by ring-closing metathesis of

appropriate compound **23**. Compound **23** could be obtained from compound **24** by treatment with acryloyl chloride and compound **24** can be readily accessed from readily available 4-methoxyphenylacetonitrile **25** by alcoholysis followed by exomethylene introduction.

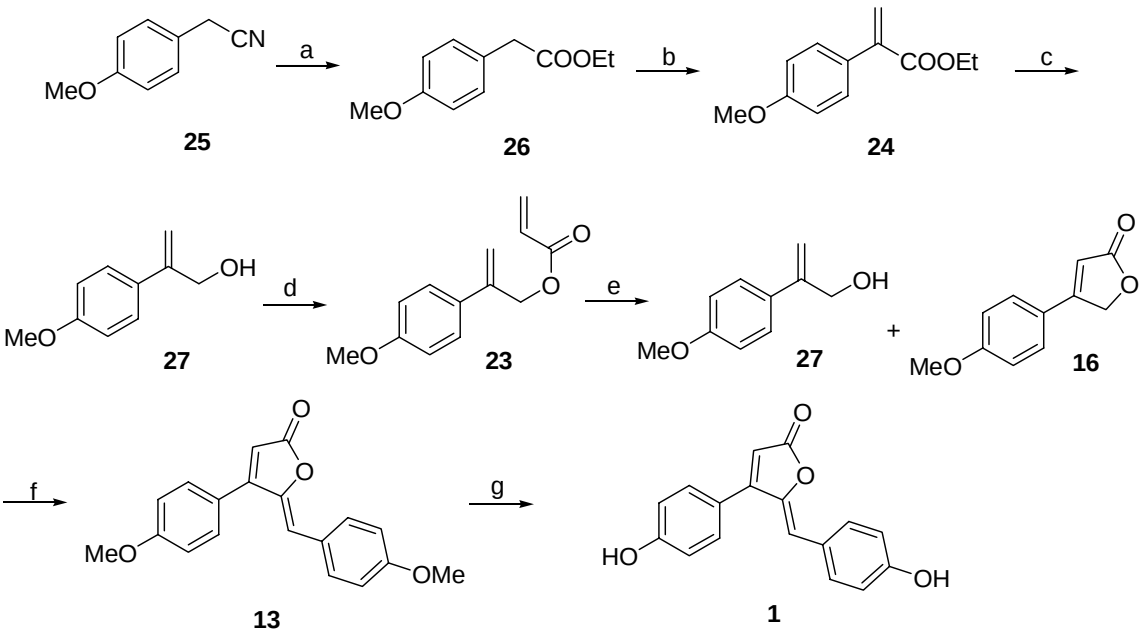
3.3.4 Results and discussion:

Accordingly the ester **26** was prepared in 96% yield by alcoholysis of nitriles from commercially available 4-methoxyphenylacetonitrile **25** by literature method.[14] Treatment of the ester **26** with paraformaldehyde using potassium carbonate as the base and $TBAHSO_4$ as a phase transfer catalyst gave α,β-unsaturated ester **24** in 89% yield.[15] The formation of **24** was ascertained by spectral analysis. ^{1}H NMR spectrum of **24** displayed a triplet at δ 1.33 integrating for three protons and was ascribed to ($OCOCH_2C\underline{H_3}$), singlet at δ 3.81 integrating for three protons was assigned to ($ArOC\underline{H_3}$), quartet at δ 4.28 integrated for two protons was attributed to ($OCOC\underline{H_2}CH_3$), two singlets at δ 5.82 and δ 6.25 integrating for one proton each which were assigned to olefinic protons and aromatic protons resonated as two doublets at δ 6.88 and δ 7.37 (J = 9.0 Hz). ^{13}C NMR spectrum of **24** showed the presence of ten signals. DEPT spectrum of **24** displayed two methylene carbons at δ 61.0 and 124.8 and finally the structure of **24** was confirmed by mass spectral and elemental analysis. The mass spectrum of **24** showed the *m/z* peak at 207 $(M + H)^+$. In an elemental analysis the experimental values were found to be in good agreement with its theoretical values.

The ester **24** was reduced to alcohol using DIBAL-H at –78 ^oC to furnish the corresponding allyl alcohol **27** in 97% yield, the formation of alcohol **27** was confirmed by spectral studies. IR spectrum of **27** displayed the absence of absorption band corresponding to ester functionality while the presence of a broad absorption band at 3443 cm^{-1} clearly indicating the transformation of ester to alcohol. ^{1}H NMR spectrum of **27** showed absence of signals corresponding to ester functionality while presence of singlet that appeared at δ 4.52 for two protons was attributed to the methylene protons of the allyl alcohol. The *m/z* peaks at 216 $(M)^+$ was observed in mass spectrum of **27** which confirmed the structure of alcohol **27**. Finally the structure of **27** was ascertained by its elemental analysis also, which was found to be in good agreement with the calculated values.

The treatment of alcohol **27** with acryloyl chloride using triethyl amine as the base in anhydrous dichloromethane at 0 ^oC to furnish acrylate **23** in excellent yield (92%). The

structure of **23** was elucidated by spectral data. IR spectrum of **23** showed the disappearance of broad absorption band corresponding to OH group while appearance a strong absorption band at 1721 cm^{-1} suggested the transformation of alcohol to acrylate. ^{1}H NMR spectrum of **23** revealed the doublet of doublet at δ 5.83 (*J* =10.0, 2.0 Hz) integrated for one proton, doublet of doublet at δ 6.14 (*J* = 18.0, 10.0 Hz) integrated for one proton, doublet of doublet at δ 6.43 (*J* = 10.0, 2.0 Hz) integrated for one proton indicated the presence of α,β-unsaturated olefin present in compound **23**. ^{13} C NMR along with DEPT spectra of **23** revealed eleven signals and the presence of three methylene carbons in compound **23**. The mass spectrum of **23** displayed the molecular ion peak at *m/z* 218 $(M)^{+}$ which confirmed the structure of **23**. Finally the structure of **23** was further confirmed by its elemental analysis as well.



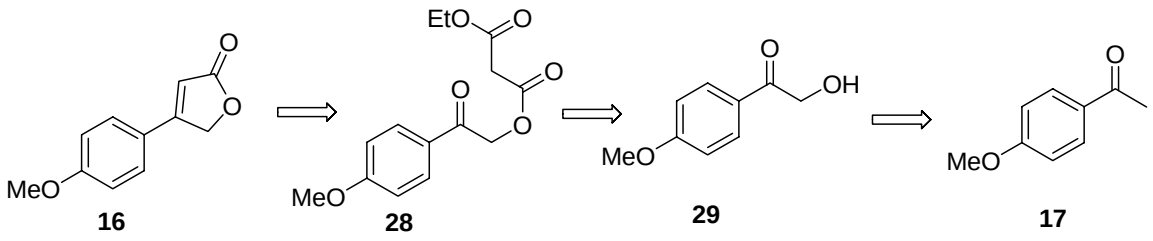
Scheme 6. *Reagents and conditions: (a) H_2SO_4 (2.0 eq.), EtOH, reflux, 3h, 96%. (b) $(CH_2O)_n$ (1.5 eq.), K_2CO_3 (1.5 eq.), $TBAHSO_4$ (0.1 eq.), toluene, 80 ^{o}C, 6h, 89%. (c) DIBAL-H (2.1 eq.), dry DCM, -78 ^{o}C, 3h, 97%. (d) Et_3N (1.5 eq.), acryloyl chloride (1.2 eq.), dry DCM, 0 ^{o}C, 1h, 92%. (e) Grubbs' catalyst (2nd generation, 10 mol %), titanium isopropoxide (1.2 eq.), dry DCM, reflux, 12h, 83%. (f) Piperidine (0.7 eq.), anisaldehyde (1.0 eq.), MeOH, rt, 15h, 81%. (g) BBr_3 (3.0 eq.), dry DCM, -78 ^{o}C, 30 min, rt, 24h, 94%.*

After obtaining the compound **23** it was subjected to ring-closing metathesis (RCM) reaction using Grubbs' second generation catalyst (10 mol %). The catalyst was used under a variety of reaction conditions including various solvents, concentrations, mode of additions, all without success but after the addition of additives like titanium isopropoxide as a Lewis acid and performing RCM in refluxing dichloromethane for 12 h, butenolide **16** was obtained in 83% yield along with hydrolyzed compound **27** in 15% due to cleavage of allylic ester.[16]

The butenolide **16** is the common intermediate in literature for the synthesis.[11] The spectral data of **16** was in complete agreement with the literature data. After successfully obtaining the aryl butenolide **16,** it was condensed with *p*-anisaldehyde to furnish exclusively (*Z*) butenolide **13** in 81% yield. The formation of **13** was confirmed by spectroscopic methods and also matched with reported data.[11] Finally the demethylation of both an aromatic methoxy groups gave target molecule rubrolide E **1** in 94% yields. The structure elucidation of **1** was confirmed by spectral analysis and the data exactly matched with reported literature data.[11]

Having a synthesis of rubrolide E **1** in hand by RCM approach, an alternative practical route which is outlined in scheme 7 was envisioned.

The key intermediate butenolide **16** could be accessed from ester **28** employing intramolecular Knoevenagel condensation followed by decarboxylation as a key step and the ester **28** can be obtained form alcohol **29** by esterification and the alcohol **29** could be readily obtained form commercially available 4-methoxyacetophenone **17** by Rubottom oxidation.

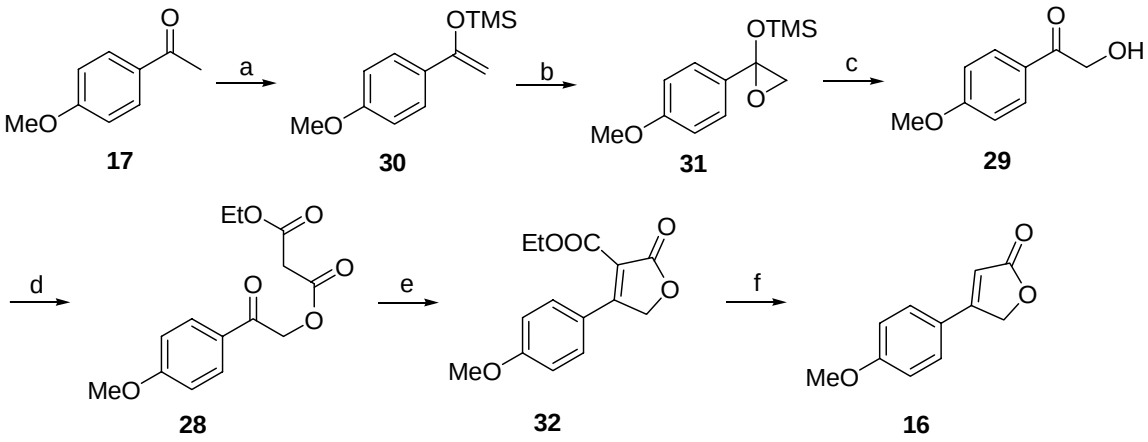


Scheme 7. *Retrosynthetic plan 2***.**

According to retrosynthetic analysis (scheme 7) the synthesis commenced from cheap and commercially available 4-methoxyacetophenone **17**. Treatment of **17** with TMSCl using trimethyl amine as the base in dry acetonitrile at reflux temperature afforded the silyl enol

ether **30**, which was further converted to epoxide **31** utilizing m-CPBA and sodium bicarbonate in dichloromethane and the generated epoxide **31** was transformed in to desired alcohol **29** in 87% yield (in three steps) by treatment of 10% HCl.[17]

The formation of alcohol **29** was confirmed by spectral study. IR spectrum of **29** displayed broad absorption bands at 3467 cm^{-1} characteristic of hydroxyl group and 1677 cm^{-1} due to ketone attached to electron donating aromatic moiety. ^{1}H NMR spectrum of **29** presented triplet at δ 3.58 (J = 3.9 Hz) integrated for one proton and which was assigned to (-O<u>H</u>), singlet at δ 3.88 integrated for three protons was attributed to (Ar-OC<u>H_3</u>), doublet that appeared at δ 4.81 (J = 3.9 Hz) integrated for two protons was ascribed to methylene protons, while four aromatic protons appeared as two doublets at δ 6.96 and δ 7.89 (J = 9.0 Hz). ^{13}C NMR spectrum of **29** displayed seven signals clearly suggested the assigned structure. DEPT spectrum of **29** showed only one methylene carbon attached to the hydroxy functionality at δ 65.0 and finally the structure of **29** was confirmed by mass spectrum and elemental analysis. The mass spectrum of **29** displayed molecular ion peak at *m/z* 166 $(M)^{+}$ corresponding to its molecular weight. The elemental analysis of **29** showed the experimental values were found to be in good agreement with the theoretical values.



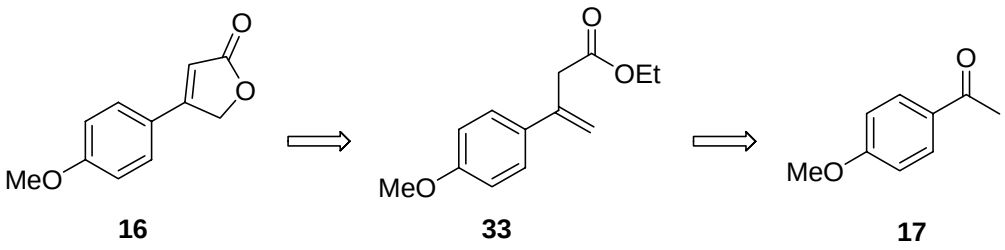
Scheme 8. *Reagents and conditions: (a) Et_3N (1.5 eq.), TMSCl (1.5 eq.), dry acetonitrile, reflux, 6h. (b) MCPBA (1.5 eq.), 10% $NaHCO_3$ (2.0 eq.), DCM, 0 ^{o}C-rt, 4-5h. (c) 10% HCl (1.5 eq.), rt, overnight, 87% over three steps (d) Et_3N (1.2 eq.), ethyl malonyl chloride (1.2 eq.), dry DCM, 0 ^{o}C-rt, 3-4h, 93%. (e) NaH (1.2 eq.), dry THF, 0 ^{o}C, 1h, 97%. (f) NaCl (4.0 eq.), wet DMSO, 120-130 ^{o}C, 6h, 91%.*

Alcohol **29** was subjected to the treatment with ethyl malonyl chloride using triethyl amine as a base in dry dichloromethane, gave ester **28** in excellent yield (93%). The structure elucidation of ester **28** was confirmed by spectral data. IR spectrum of **28** displayed the absence of absorption band corresponding to hydroxy group while presence of strong absorption bands at 1759 and 1737 cm^{-1} clearly indicated the incorporation of ester moieties. ^{1}H NMR spectrum of **28** exhibited disappearance of triplet corresponding to hydroxyl proton while a triplet appeared at δ 1.29 integrating for three protons of the ester group, singlet at δ 3.56 integrated for two protons due to active methylene and a quartet at δ 4.23 integrated for two protons was ascribed to the methylene protons of ester moiety attached to oxygen atom (J = 7.1 Hz), it clearly suggested the insertions of ethyl malonyl group. ^{13}C NMR spectrum of **28** showed five signals at δ 14.2, 41.35, 61.8, 166.3 and 166.4 also supported the assigned structure including DEPT spectrum of **28** which revealed the presence of three methylene carbons at δ 41.3, 61.8 and 66.6. The presence of molecular ion peak at *m/z* 280 $(M)^{+}$ in the mass spectrum of **28** and finally the structure of **28** was ascertained by its elemental analysis also.

The intramolecular Knoevenagel condensation was achieved employing sodium hydride as a base in anhydrous tetrahydrofuran at 0 ^{o}C for 1 h yielded five-membered α,β-unsaturated lactone **32** in excellent yield (97%).[18] The compound **32** was ascertained by spectral analysis. ^{1}H NMR spectrum of **32** displayed the disappearance of the singlet corresponding to two methylene protons flanked between two ester groups. ^{13}C NMR spectrum of **32** showed the disappearance of the signals corresponding to methylene carbon flanked between two ester groups and ketonic carbonyl carbon while new signals appeared at δ 117.0 and 170.1. The DEPT spectrum of **32** possesses two methylene carbons that resonated at δ 61.9 and 70.3 supported the structure elucidation. Finally the structure of **32** was confirmed by mass spectrum and elemental analysis. The mass spectrum of **32** showed *m/z* peak at 263 $(M + H)^{+}$ and 285 $(M + Na)^{+}$. In an elemental analysis the experimental values were found to be in good agreement with the theoretical values.

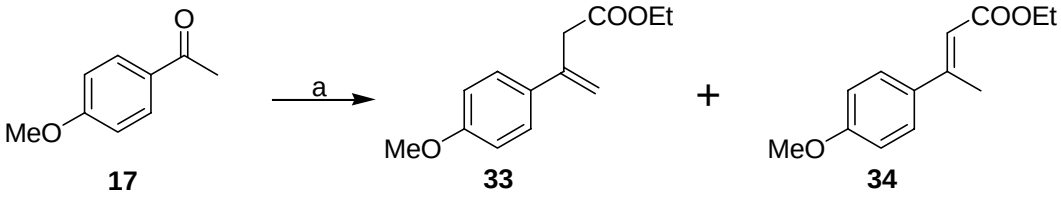
The compound **32** was decarboxylated under Krapcho's condition using sodium chloride in a mixture of dimethyl sulfoxide and water (3:1) as a solvent at 120-130 ^{o}C for 6 h resulted in the formation of butenolide **16** in excellent yield (91%).[19] This is the same common intermediate in scheme 6 for the synthesis of rubrolide.

Having two syntheses of Rubrolide E **1** in hand by two different approaches, another simple and mild strategy employing Reformatsky reaction described in scheme 11 was envisaged. Here it was surmised that the butenolide **16** could by obtained from compound **33** employing dehydroxylation followed by dehydration and lactonization, and compound **33** in turn could be synthesized from readily available 4-methoxyacetophenone **17** employing Reformatsky reaction followed by dehydration.



Scheme 9. *Retrosynthetic plan 3.*

According to retrosynthetic plan 3 (scheme 9), the 4-methoxyacetophenone **17** was subjected to Reformatsky reaction using ethyl bromoacetate and zinc in (Et_2O-C_6H_6, 1:1) at reflux temperature for 6 h[20] to give the alcohol and during reaction the generated alcohol was converted into the thermodynamically stable α,β-unsaturated ester **34** exclusively, instead of the anticipated desired β,γ-unsaturated ester **33**.

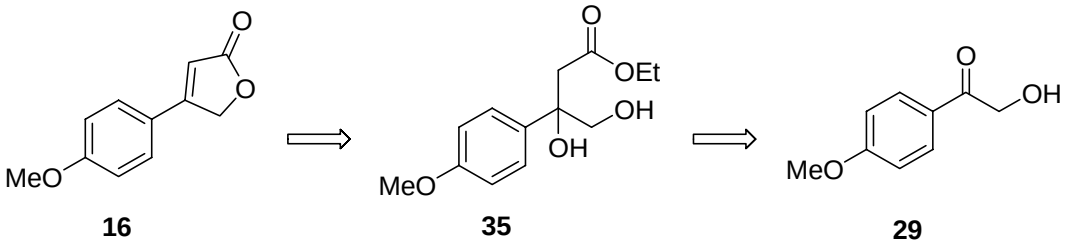


Scheme 10. *Reagents and conditions: (a) Activated Zinc (3.0 equiv), ethyl bromoacetate (1.5 equiv), C_6H_6-Et_2O (1:1), reflux, 6 h.*

The formation of **34** was confirmed by spectral data. IR spectrum of **34** showed the disappearance of absorption band due to conjugated ketone functionality while strong absorption band was observed at 1722 $cm.^{-1}$ This clearly indicated the formation of α,β-unsaturated ester instead of β,γ-unsaturated ester. ^{1}H NMR spectrum of **34** revealed the

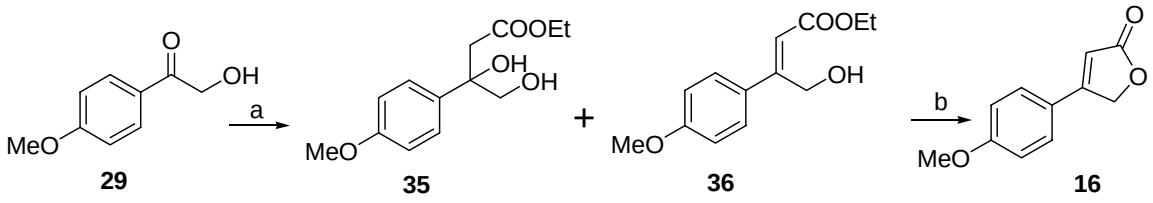
appearance of signal pattern as follows: triplet and quartet at δ 1.31 and 4.20 (J = 7.1 Hz) corresponding to ethyl ester functionality, singlet at δ 2.56 integrated for two protons which were assigned to allylic methylene group. Singlet at δ 6.1 integrating for one proton that was assigned to the α-proton of α,β-unsaturated ester. Finally the structure of **34** was confirmed by mass spectrum it revealed the *m/z* peaks at 221 $(M + H)^+$, 243 $(M + Na)^+$.

After the failure in selective installment of terminal olefin in scheme 10, it was proposed to access the butenolide **16** from alcohol **29** employing the same reaction strategy (Reformatsky reaction) as outlined in scheme 11.



Scheme 11. *Retrosynthetic plan 4.*

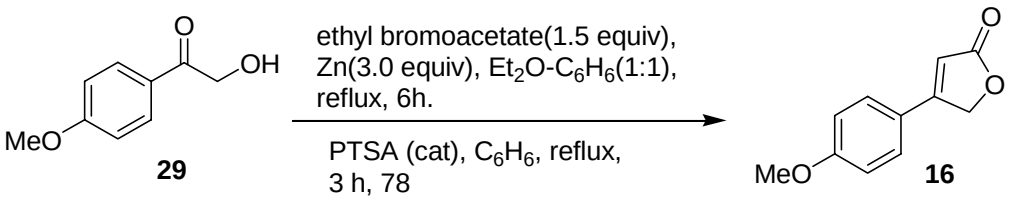
Accordingly the alcohol **29** was subjected to the treatment with 1.5 equivalent of ethyl bromoacetate and 3.0 equivalent activated zinc powder in diethyl ether-benzene (1:1) at reflux temperature for 6 h to form the mixture of diol **35** and dehydrated compound **36** (TLC), and the resultant crude mixture was further treated with catalytic amount of PTSA in refluxing benzene for 3 h furnished the desired butenolide **16** in very good yield (87%).



Scheme 12. *Reagents and conditions: (a) Zn (3.0 eq.), $BrCH_2COOEt$ (1.5 eq.), C_6H_6-Et_2O (1:1) reflux 6h. (b) PTSA (cat.), C_6H_6, reflux, 3h, 87%.*

After the successful Reformatsky reaction on alcohol **29**, it was decided to perform this reaction in one-pot. Accordingly the Reformatsky reaction was carried out under similar

reaction conditions as shown in scheme 13, and after the disappearance of starting material (TLC), a catalytic amount of PTSA was added and the reaction mixture was refluxed for additional 3-4 h. It was indeed gratifying to note that the anticipated butenolide **16** was obtained in 78% yield.



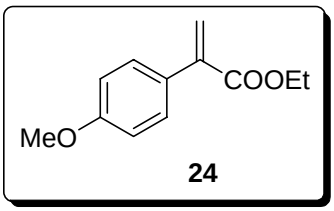
Scheme 13.

3.3.5 Conclusion:

The total synthesis of Rubrolide E has been achieved by three different protocols *viz*. (i) ring-closing metathesis in seven-steps in 50% overall yield, (ii) intramolecular Knoevenagel condensation in eight-steps in 56% overall yield and (iii) Reformatsky reaction in six-steps in 52% overall yield. The Reformatsky reaction, dehydration and lactonization steps were carried out in one-pot in third protocol and a practical formal synthesis of Rubrolide C has been achieved.

3.3.6 Experimental:

Ethyl 2-(4-methoxyphenyl) acrylate (24)



24

A mixture of ethyl 2- (4-methoxyphenyl) acetate **26** (5.0 g, 25 mmol), K_2CO_3 (5.37 g, 37 mmol), $TBAHSO_4$ (0.875 g, 2.5 mmol) and $(CH_2O)_n$ (1.125 g, 37 mmol) in anhydrous toluene (50 mL) was heated at 80 ^oC for 12 h. After completion of the reaction (TLC), H_2O (25 mL) was added and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) using 2% ethyl acetate-petroleum ether as eluent gave compound **24** as a colourless oil (5.3 g, 89% yield).

MF: $C_{12}H_{14}O_3$, **MW**: 206

IR ($CHCl_3$) ν_{max}: 3424, 1716, 1610, 1513, 1251, 1216, 1177, 836 cm^{-1}

^{1}H NMR (CDCl3, 200 MHz) δ: 1.33 (t, *J* = 7.1 Hz, 3H), 3.81 (s, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 5.82 (d, *J* = 1.3 Hz, 1H), 6.25 (d, *J* = 1.3 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.37 ppm (d, *J* = 9.0 Hz, 2H).

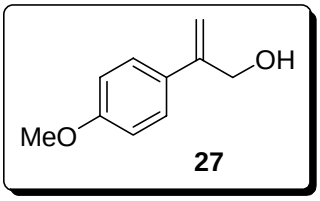
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.2, 55.2, 61.0, 113.5, 124.8, 129.2, 129.4, 140.9, 159.6, 167.0 ppm.

MS (ESI) *m/z*: 207 $(M + H)^+$.

Elemental analysis Calculated: C, 69.88; H, 6.84%.

Found: C, 69.74; H, 7.02%.

2-(4-methoxyphenyl) prop-2-en-1-ol (27)



27

To the stirred solution of ethyl 2-(4-methoxyphenyl) acrylate **24** (3.0 g, 14.5 mmol) in anhydrous CH_2Cl_2 (20 mL), 2 M DIBAL-H (4.34 g, 15.3 mL, 30.5 mmol) was added dropwise at -78 ^oC, stirred for 1 h and gradually warmed up to room temperature and further stirred for 2 h. The progress of reaction was monitored by TLC and then reaction was quenched with addition of methanol. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and solvent was removed on rotary evaporator under reduced pressure. The

resulted residue was purified by flash column chromatography (SiO_2) with ethyl acetate-petroleum ether (2:3) as eluent, afforded compound **27** as a white solid (2.31 g, 97% yield).

MF: $C_{10}H_{12}O_2$. **MW**: 215

M.P.: 80-83 ^oC

IR ($CHCl_3$) ν_{max}: 3443, 1609, 1513, 1249, 1216, 1034 cm^{-1}

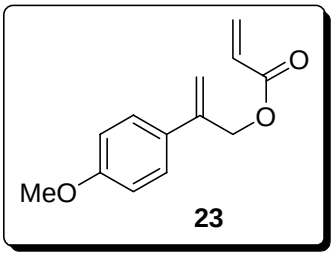
^{1}HNMR ($CDCl_3$, 200 MHz) δ: 3.82 (s, 3H), 4.52 (s, 2H), 5.25 (s, 1H), 5.39 (s, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 7.40 ppm (d, *J* = 9.0 Hz, 2H).

MS (ESI) *m/z*: 216 $(M)^+$.

Elemental analysis Calculated: C, 73.14; H, 7.36%.

Found: C, 72.91; H, 7.07%.

2- (4-methoxyphenyl) allyl acrylate (23)



23

To a stirred solution of alcohol **27** (2.0 g, 12.19 mmol) in anhydrous CH_2Cl_2 (25 mL), Et_3N (1.85 g, 2.54 mL, 18.28 mmol) was added at 0 ^oC. The reaction mixture was allowed to stir for 15 minutes and then acryloyl chloride (1.32 g, 1.18 mL, 14.6 mmol) was added dropwise over 10 minutes and the reaction mixture was allowed to stir for further 1 h at 0 ^oC. After the completion of reaction (TLC), H_2O (20 mL) was added and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue obtained was purified by flash column chromatography with mixture of ethyl acetate-petroleum ether (1:4) as eluent gave ester **23** as a viscous colourless liquid (2.44 g, 92% yield).

MF: $C_{13}H_{14}O_3$. **MW**: 218

IR ($CHCl_3$) ν_{max}: 1721, 1608, 1514, 1215, 758 cm^{-1}

^{1}HNMR ($CDCl_3$, 200 MHz) δ: 3.82 (s, 3H), 5.04 (d, *J* = 1.1 Hz, 2H), 5.30 (d, *J* = 1.1 Hz, 1H), 5.49 (s, 1H), 5.83 (dd, *J* = 10.2, 1.65 Hz, 1H), 6.14 (dd, *J* = 17.2, 10.2 Hz, 1H), 6.43 (dd, *J* = 17.2, 1.65 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.39 ppm (d, *J* = 9.0 Hz, 2H).

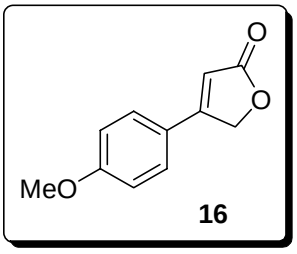
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.3, 65.9, 113.7, 113.9, 127.2, 128.3, 130.5, 131.1, 141.75, 159.6, 165.9 ppm.

MS (ESI) *m/z*: 218 $(M)^+$.

Elemental analysis Calculated: C, 71.54; H, 6.47%.

Found: C, 71.48; H, 6.42%.

4- (4-methoxyphenyl) furan - 2- (*5H*) – one (16)



16

(a) To a solution of allyl acrylate **23** (0.2 g, 0.91 mmol) in anhydrous CH_2Cl_2 (50 mL), titanium isopropoxide (0.312 g, 0.323 mL, 1.10 mmol) and Grubbs' 2nd generation catalyst (0.077 g, 0.091 mmol) was added and the reaction mixture was degassed under argon atmosphere and refluxed for 12 h. After the disappearance of starting material (TLC), the solvent was removed on rotary evaporator under diminished pressure. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-pet ether (30:70) as eluent yielded the butenolide **16** as a pale yellow solid (0.144 g, 83% yield).

(b) To a solution of ester **32** (0.5 g, 1.9 mmol) in DMSO-H_2O (3:1) (20 mL) was added NaCl (0.442 g, 7.6 mmol) and the resultant reaction mixture was heated at 120-130 ^oC for 6 h. After the disappearance of starting material (TLC), H_2O (20 mL) was added and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* and the residue obtained was purified by flash column chromatography using ethyl acetate-pet ether (30:70) as eluent afforded the butenolide **16** as a pale yellow solid (0.329 g, 91% yield).

(c) A mixture of compound **29** (0.5 g, 3.0 mmol), Zinc power (0.587 g, 9.0 mmol), ethylbromoacetate (0.75 g, 0.5 mL, 4.5 mmol) and I_2 (cat.) in C_6H_6-Et_2O (1:1) (20 mL) was refluxed for 3-4 h and the progress of reaction was monitored by (TLC). After the disappearance of starting material (TLC), catalytic amount of *p*-TSA was added and it was further refluxed for additional 3 h, and monitored by TLC. The reaction mixture was quenched with addition of 10% HCl and extracted with Et_2O (3 x 10 mL). The organic phase was washed with saturated $NaHCO_3$ solution, brine, dried over anhydrous sodium sulphate, filtered and concentrated under diminished pressure. The residue was purified by flash column chromatography eluting with ethyl acetate-petroleum ether (3:7) furnished butenolide **16** as a pale yellow solid (0.446 g, 78%) yield.

MF: $C_{11}H_{10}O_3$, **MW**: 190

M.P.: 138 ^oC

IR ($CHCl_3$) ν_{max}: 1745, 1620, 1609, 1514, 1215 cm $^{-1}$

^{1}HNMR ($CDCl_3$, 200 MHz) δ: 3.86 (s, 3H), 5.19 (d, *J* = 1.6 Hz, 2H), 6.23 (t, *J* = 1.6 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.45 ppm (d, *J* = 9.0 Hz, 2H).

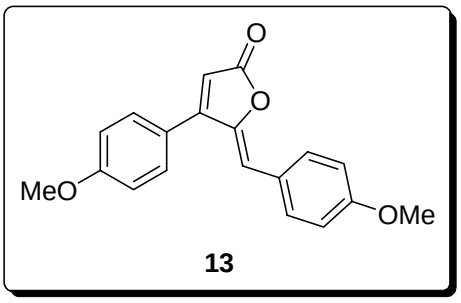
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.6, 71.0, 110.65, 114.8, 122.35, 128.3, 162.5, 163.7, 174.4 ppm.

MS (ESI) *m/z*: 191 $(M + H)^+$, 213 $(M + Na)^+$.

Elemental analysis Calculated: C, 69.46; H, 5.30%.

Found: 69.38; H, 5.16%.

(Z)- 5- (4-methoxybenzylidene) –4- (4-methoxyphenyl) furan-2 (*5H*) – one (13).



13

To a stirred solution of lactone **16** (1.90 g, 10 mmol) in MeOH were added piperidine (0.595 g, 0.69 mL, 7 mmol) and *para*-anisaldehyde (1.36 g, 1.21 mL, 10 mmol) at room temperature and the mixture was stirred for 15 h. Removal of solvent *in vacuo* followed by flash column chromatographic purification of the residue using ethyl acetate-petroleum ether (1:9) as eluent furnished *Z*-butenolide **13** as a yellow solid (2.4 g, 78% yield).

MF: $C_{19}H_{16}O_4$, **MW**: 307

M.P.: 136–140 °C

IR ($CHCl_3$) ν_{max}: 1754, 1604, 1511, 1256, 1176, 1032 cm^{-1}

^{1}HNMR ($CDCl_3$, 200 MHz) δ**:** 3.84 (s, 3H), 3.88 (s, 3H), 6.09 (s, 1H), 6.16 (s, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.77 ppm (d, *J* = 8.8 Hz, 2H).

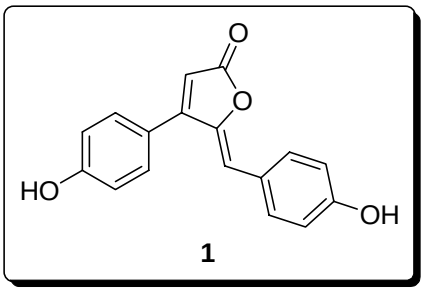
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.4, 55.5, 112.3, 113.7, 114.4, 114.6, 123.0, 126.0, 130.1, 132.6, 146.7, 158.4, 160.5, 161.45, 169.4 ppm.

MS (ESI) *m/z*: 308 $(M + H)^+$.

Elemental analysis Calculated: C, 74.01; H, 5.23%.

Found: C, 73.87; H, 5.12%.

Rubrolide E (1):



1

To a stirred solution of **13** (1.54 g, 5 mmol) in anhydrous CH_2Cl_2 (25 mL) at –78 °C, was added a 1 M solution of BBr_3 in CH_2Cl_2 (15 mL, 15 mmol) over a period of 15 minutes. The mixture was then allowed to warm up to room temperature and stirred for further 24 h. After the completion of reaction (TLC), reaction was

quenched with addition of H_2O (25 mL), organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue thus obtained was purified by flash silica gel column chromatography using ethyl acetate-petroleum ether (2:3) as eluent furnished Rubrolide E **1** as a yellow solid (1.33 g, 95% yield).

MF: $C_{17}H_{12}O_4$. **MW**: 280

M.P.: 278–281°C (Lit. 282-283 ^oC)

IR ($CHCl_3$) ν_{max}: 3276, 2854, 1683, 1597, 1461, 1376, 1279, 1170 cm^{-1}

^{1}HNMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ: 6.40 (s, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 10.43 (bs, 1H), 10.48 ppm (bs, 1H).

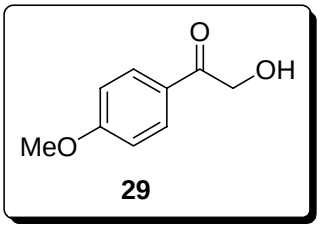
^{13}C NMR ($CDCl_3$ + DMSO-d_6, 50 MHz) δ: 111.2, 114.2, 116.6, 121.35, 124.8, 130.9, 133.2, 145.9, 158.7, 159.15, 160.1, 169.6 ppm.

MS (ESI) *m/z*: 280 $(M)^+$.

Elemental analysis Calculated: C, 72.85; H, 4.32%.

Found: 72.73; 4.25%.

2-hydroxy-1- (4-methoxyphenyl) ethanone (29)



29

(a) To a well stirred mixture of 4-methoxyacetophenone **17** (1.0 g, 6.6 mmol) and Et_3N (1.34 g, 1.84 mL, 13.2 mmol) in anhydrous CH_3CN (20 mL) was dropwise added TMSCl (1.07 g, 1.25 mL, 9.9 mmol) at room temperature and refluxed for 12 h. The progress of reaction was monitored by TLC, the reaction was quenched by the addition of saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and solvent was evaporated under reduced pressure to furnish enol ether **30**.

(b) To a stirred solution of crude enol ether **30** (1.48 g, 6.6 mmol) in CH_2Cl_2 (20 mL), 5% $NaHCO_3$ (1.11 g, 13.2 mmol) and MCPBA (1.38 g, 7.92 mmol), the reaction mixture was stirred at room temperature for 3 h. After the disappearance of starting material (TLC), the organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL).

The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* afforded epoxide **31**.

(c) To a stirred solution of crude epoxide **31** (1.58 g, 6.6 mmol) in CH_2Cl_2 (10 mL), 10% HCl solution (0.36 g, 3.6 ml, 9.9 mmol) was added and the reaction mixture was allowed to stir at room temperature for 12 h. The progress of reaction was monitored by TLC, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and the resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (3:7) as eluent furnished alcohol compound **29** (0.96 g, 87% yield) as a white solid.

MF: $C_9H_{10}O_3$. **MW**: 165

M.P.: 103-106 ^oC

IR ($CHCl_3$) ν_{max}: 3467, 1677, 1602, 1264, 1215, 759, 669 cm^{-1}

^{1}HNMR ($CDCl_3$, 200 MHz) δ: 3.58 (t, *J* = 3.9 Hz, 1H), 3.88 (s, 3H), 4.81 (d, *J* = 3.9 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.89 ppm (d, *J* = 9.0 Hz, 2H).

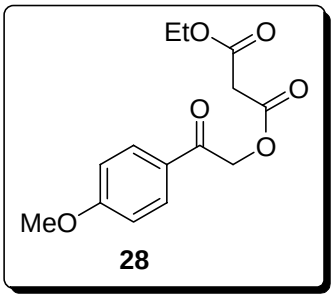
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.6, 65.0, 114.2, 126.4, 130.0, 164.4, 196.8 ppm.

MS (ESI) *m/z*: 166 $(M + H)^+$.

Elemental analysis Calculated: C, 65.05; H, 06.06%.

Found: C, 65.19; H, 05.90%.

Ethyl 2- (4-methoxyphenyl) –2-Oxoethyl malonate (28)



28

To a stirred solution of compound **29** (0.5 g, 3.0 mmol), Et_3N (0.608 g, 6.0 mmol) in CH_2Cl_2 (25 mL) the solution was cooled to 0 ^oC and ethyl malonyl chloride (0.54 g, 0.45 mL, 3.6 mmol) was added drop wise at 0 ^oC and stirred for 1 h. After the completion of reaction (TLC), H_2O (50 mL) was added, organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). Combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* and residue thus obtained was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:3) as eluent provided ester **28** as a thick yellow liquid (0.815 g, 97% yield).

MF: $C_{14}H_{16}O_6$. **MW**: 280

IR ($CHCl_3$) ν_{max}: 3022, 1758, 1736, 1695, 1602, 1264, 1242, 756, 667 cm^{-1}

^{1}HNMR ($CDCl_3$, 200MHz) δ: 1.29 (t, *J* = 7.1 Hz, 3H), 3.56 (s, 2H), 3.87 (s, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 5.36 (s, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 7.88 ppm (d, *J* = 9.0 Hz, 2H).

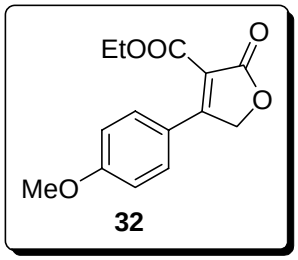
^{13}C NMR (CDCl3, 50 MHz) δ: 14.2, 41.35, 55.7, 61.8, 66.6, 114.2, 127.2, 130.2, 164.3, 166.3, , 189.9 ppm.

MS (ESI) *m/z*: 280 $(M)^+$.

Elemental analysis Calculated: C, 59.99; H, 5.75%.

Found: C, 60.11; H, 5.67%.

Ethyl 4- (4-methoxyphenyl) –2-oxo- 2, 5 dihydrofuran –3- carboxylate (32)



32

To a 60 % NaH (0.102 g, 2.57 mmol) prewashed with anhydrous petroleum ether (3 x 10 mL) was added anhydrous THF (10 mL), and cooled to 0 ^oC and then compound **28** (0.6 g, 2.14 mmol) in anhydrous THF (10 mL) was added dropwise at 0 ^oC and the resultant reaction mixture was stirred for 1 h at 0 ^oC. After the completion of reaction (TLC), the reaction mixture was quenched by addition of saturated ammonium chloride solution, organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and solvent was removed on rotary evaporator under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:2) as eluent yielded compound **32** as a pale yellow solid (0.533 g, 95% yield).

MF: $C_{14}H_{14}O_5$. **MW**: 262.

M.P.: 133 ^oC

IR ($CHCl_3$) ν_{max}: 3020, 1763, 1722, 1606, 1516, 1216, 1038, 758, 668 cm^{-1}

^{1}HNMR ($CDCl_3$, 200 MHz) δ: 1.35 (t, *J* = 7.1 Hz, 3H), 3.87 (s, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 5.16 (s, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.54 ppm (d, *J* = 9.0 Hz, 2H).

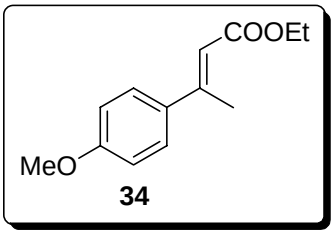
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.1, 55.6, 61.9, 70.3, 114.6, 117.0, 121.5, 130.0, 162.9, 163.0, 163.5, 170.1 ppm.

MS (ESI) *m/z*: 263 $(M + H)^+$, 285 $(M + Na)^+$.

Elemental analysis Calculated: C, 64.11; H, 5.38%.

Found: C, 64.19; H, 5.11%.

(E)-Ethyl 3-(4-methoxyphenyl) but-2-enoate (34)



34

To a well stirred mixture of **17** (1.0 g, 6.6 mmol), Zn (1.3 g, 20.0 mmol), I_2 (cat) in anhydrous diethyl ether-benzene (20 mL) was dropwise added ethyl bromoacetate (1.67 g, 10.0 mmol) and the resultant reaction mixture was heated at 80 ^oC for 6-8 h. After the completion of reaction (TLC), the reaction mixture was cooled to room temperature and quenched with addition of 10% HCl and extracted with the ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (SiO_2) using ethyl acetate-petroleum ether (1:9) as eluent furnished the exclusively α,β-unsaturated ester **34** in 1.21 g, 83% yield.

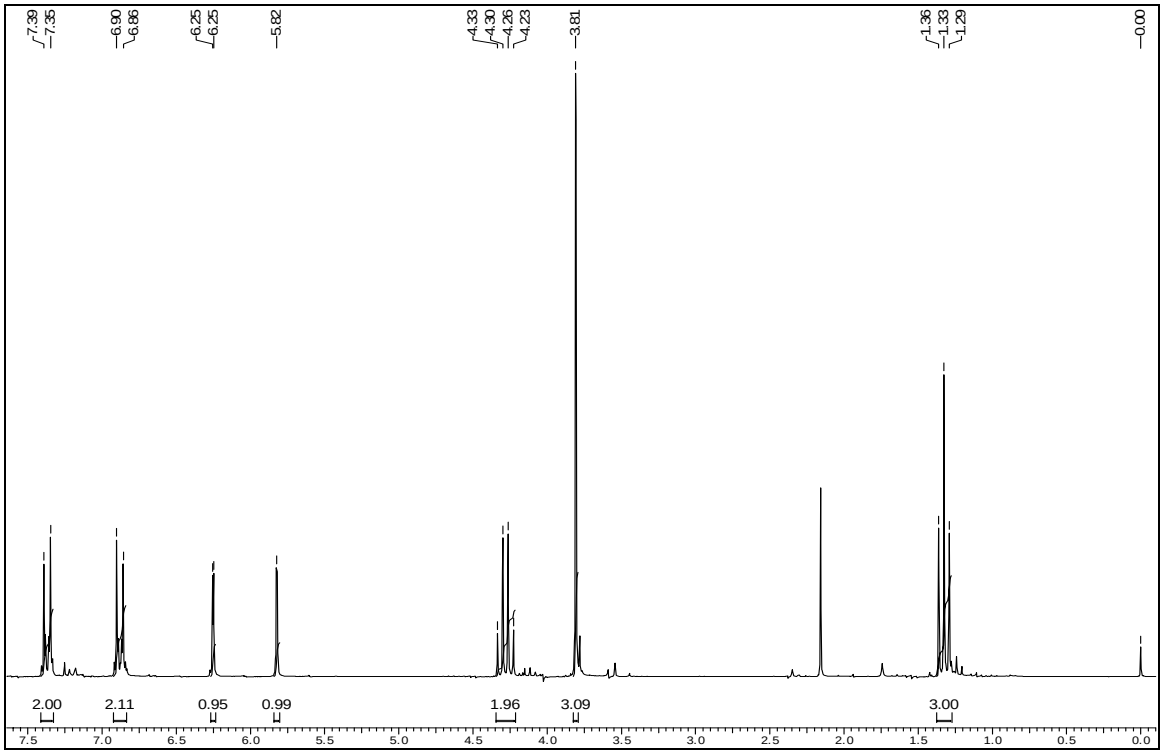
MF: $C_{13}H_{16}O_3$. **MW**: 262

IR ($CHCl_3$) ν_{max}: 1722, 1606, 1516, 1216, 1038, 758, 668 cm^{-1}

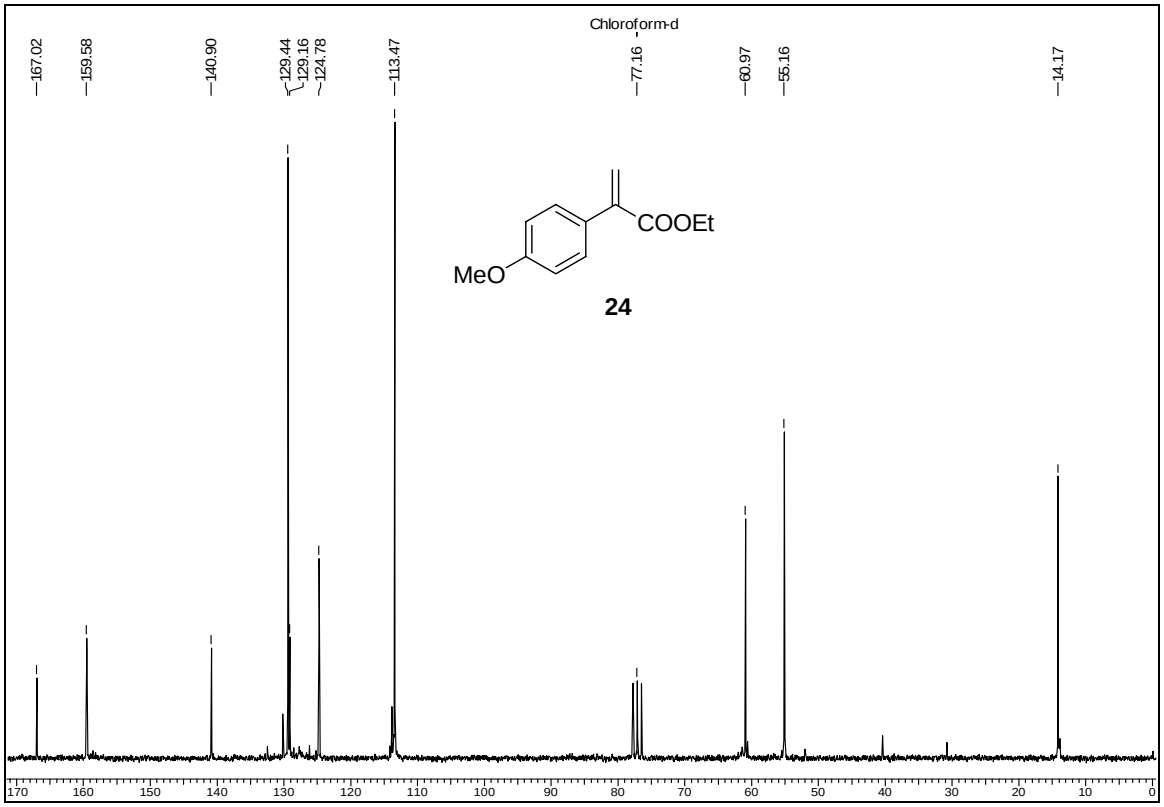
^{1}HNMR ($CDCl_3$, 200 MHz) δ: 1.31 (t, *J* = 7.1 Hz, 3H), 2.56 (s, 3H), 3.83 (s, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 6.10 (s, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 7.45 ppm (d, *J* = 9.0 Hz, 2H).

MS (**ESI)** *m/z*: 263 $(M + H)^+$, 285 $(M + Na)^+$.

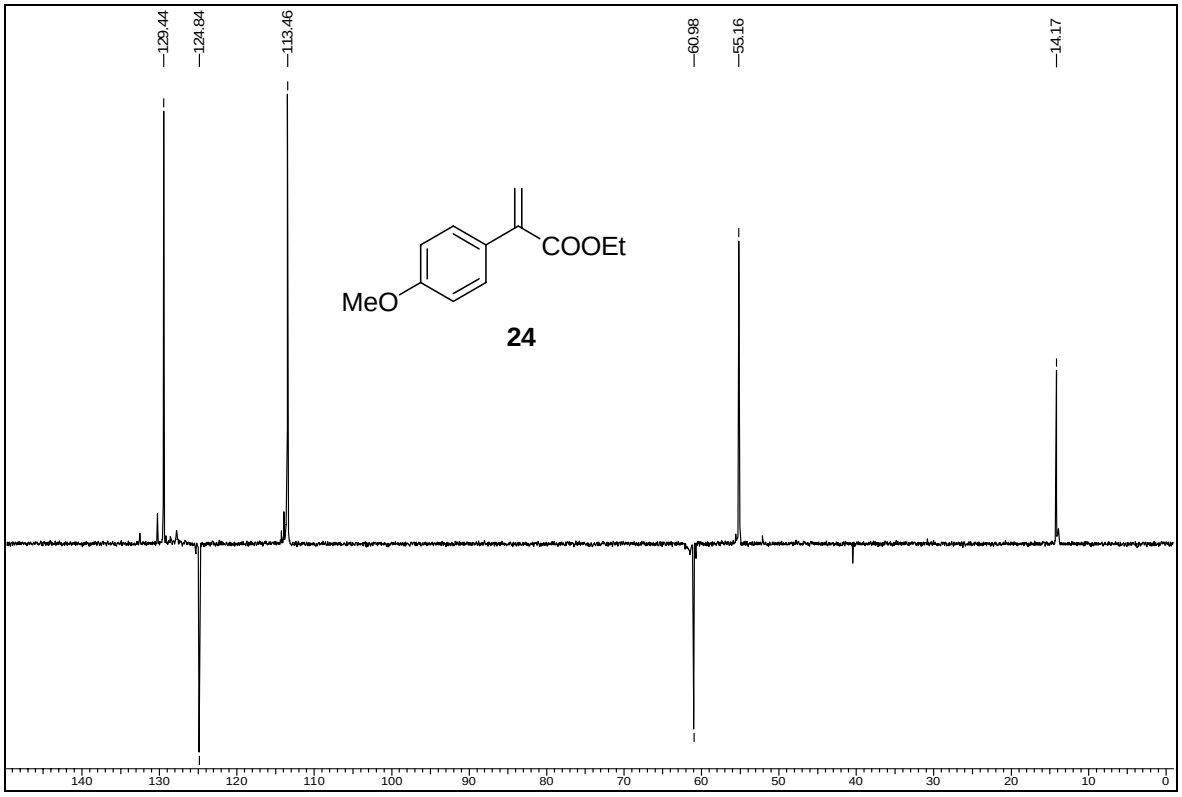
3.3.7 Spectra:



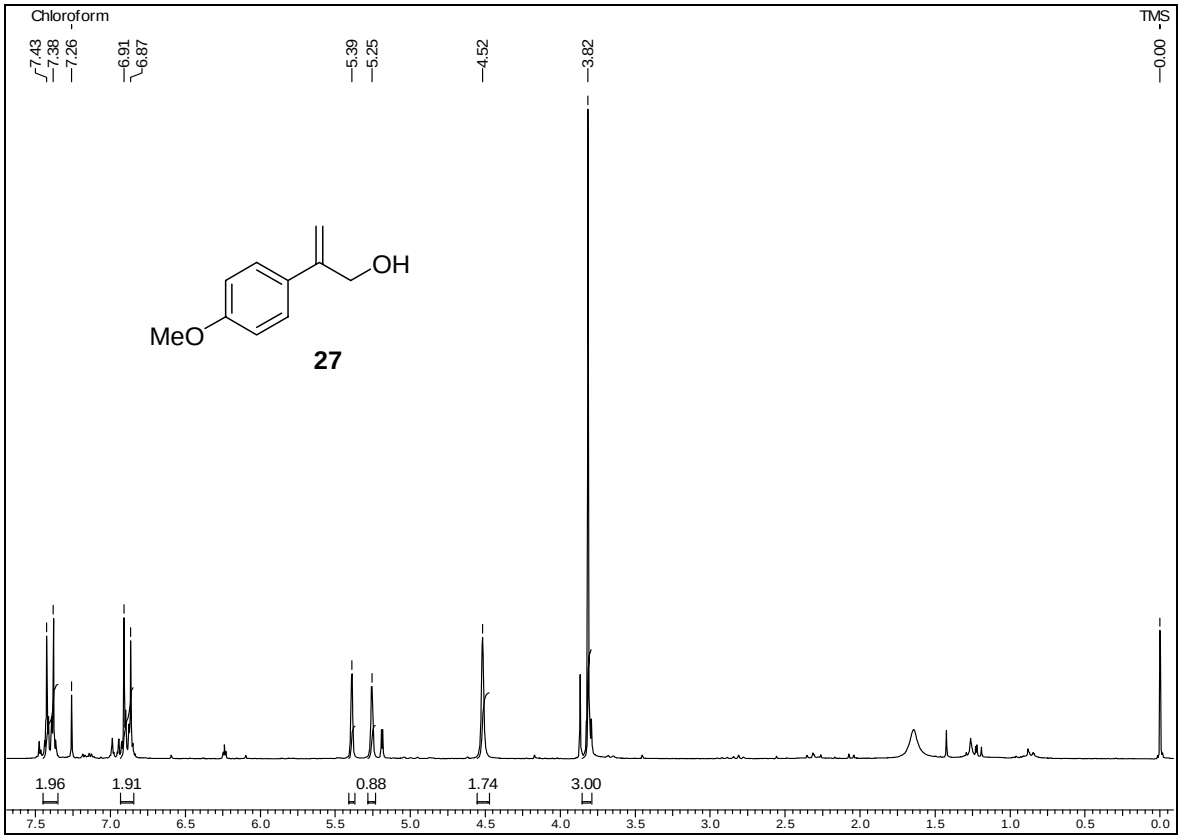
^{1}H NMR spectrum of compound 24 ($CDCl_3$, 200 MHz)



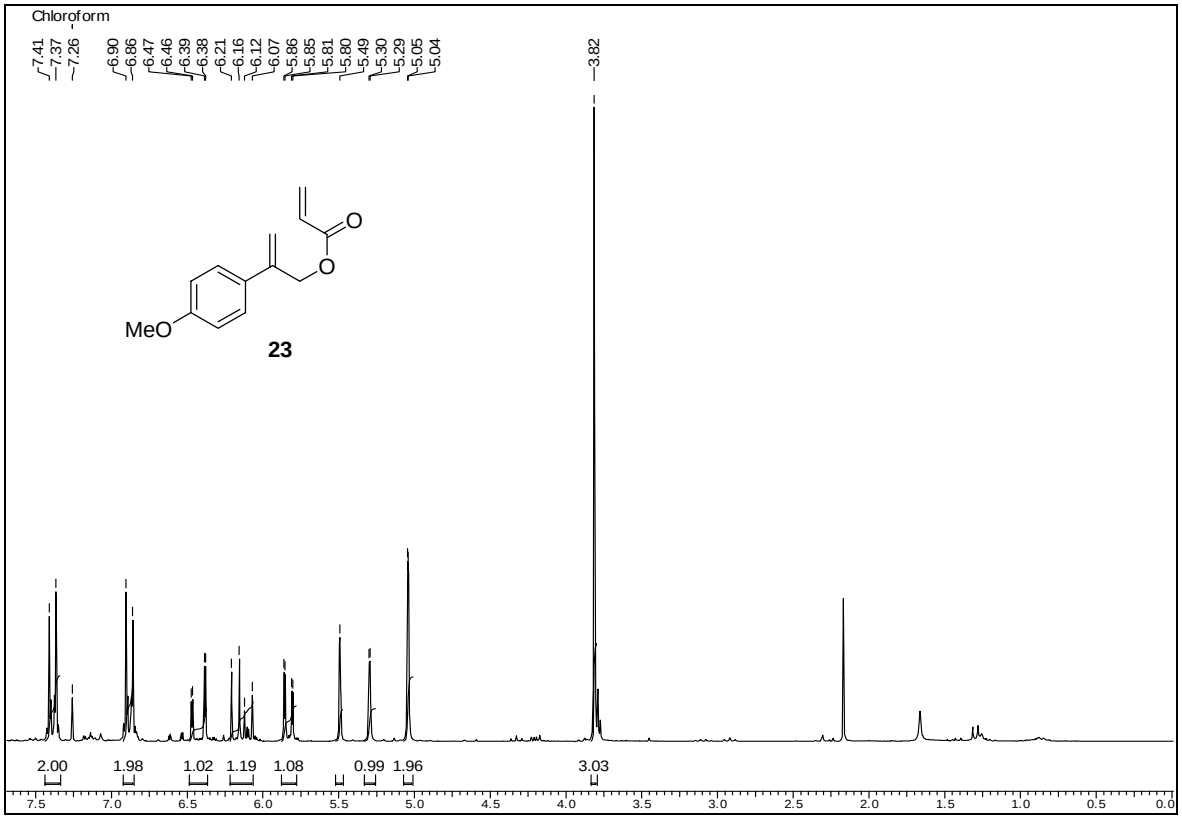
^{13}C NMR spectrum of compound 24 ($CDCl_3$, 50 MHz)



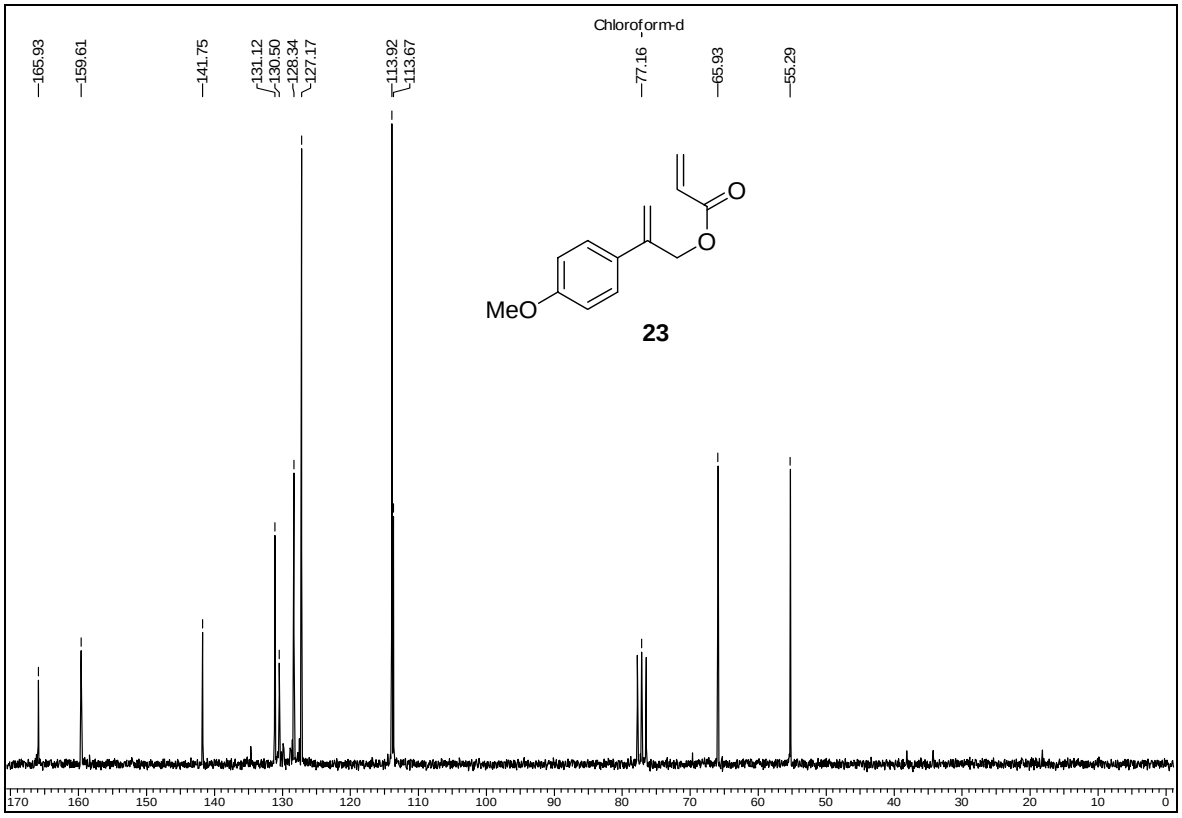
DEPT spectrum of compound 24 ($CDCl_3$, 50 MHz)



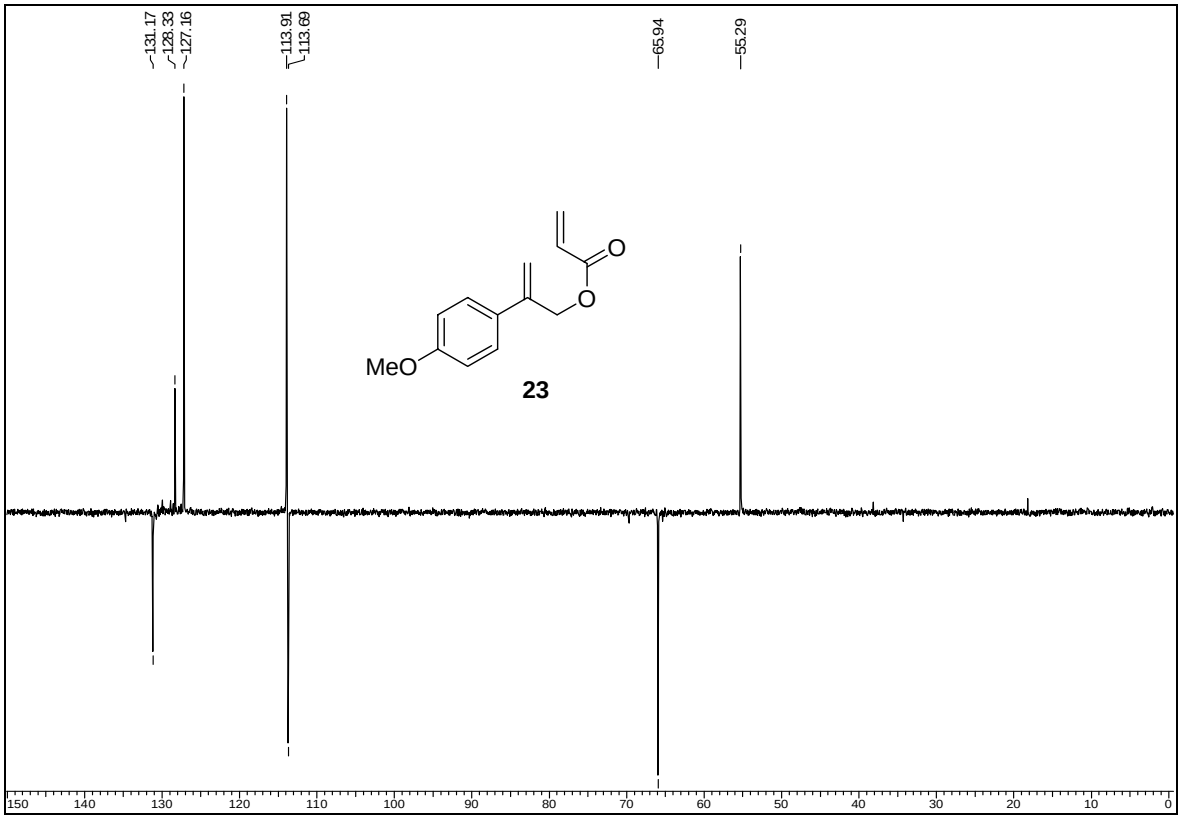
^{1}H NMR spectrum of compound 27 ($CDCl_3$, 200 MHz)



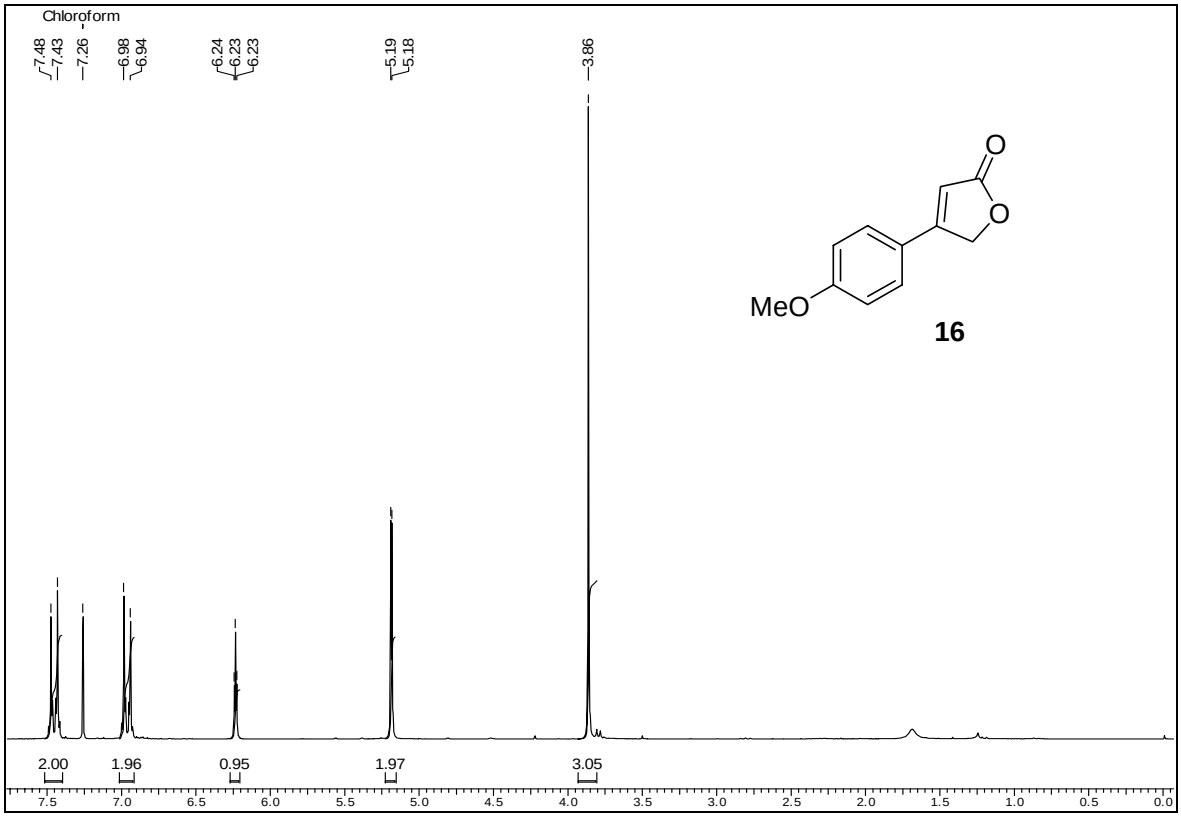
^{1}H NMR spectrum of compound 23 ($CDCl_3$, 200 MHz)



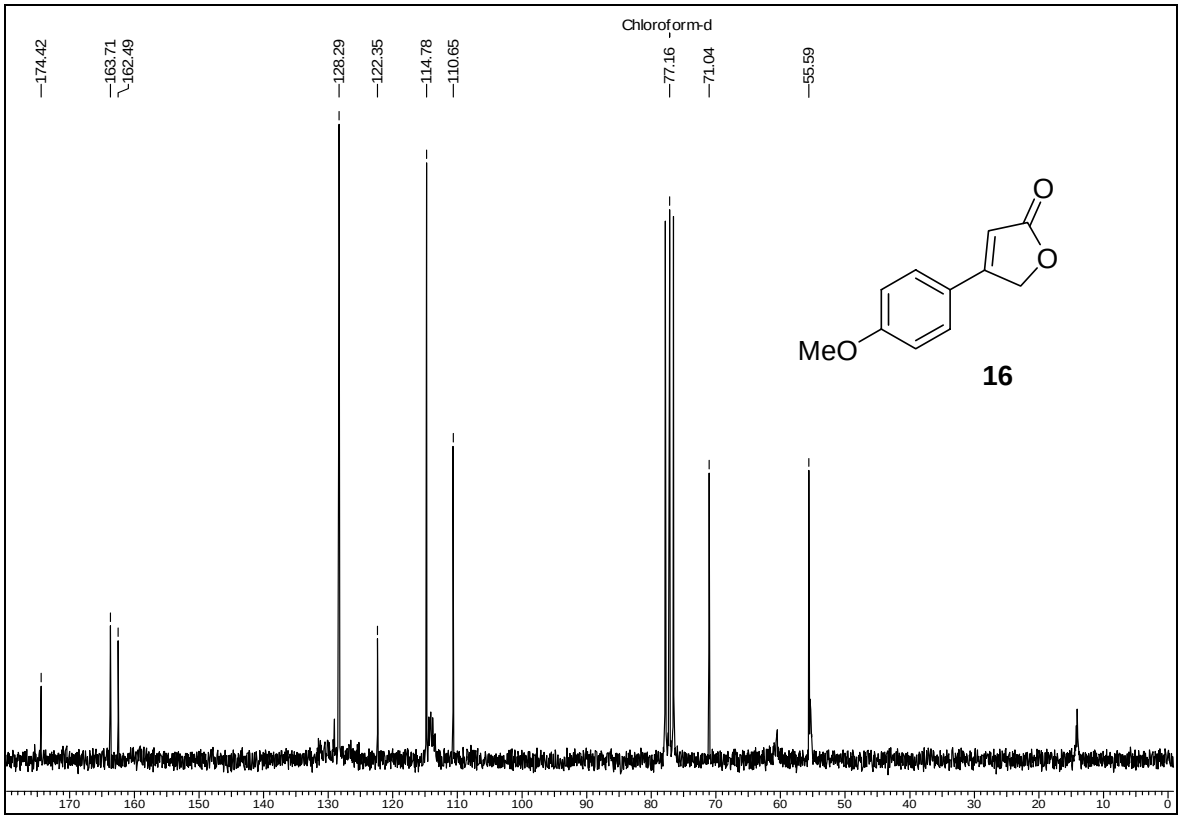
^{13}C NMR spectrum of compound 23 ($CDCl_3$, 50 MHz)



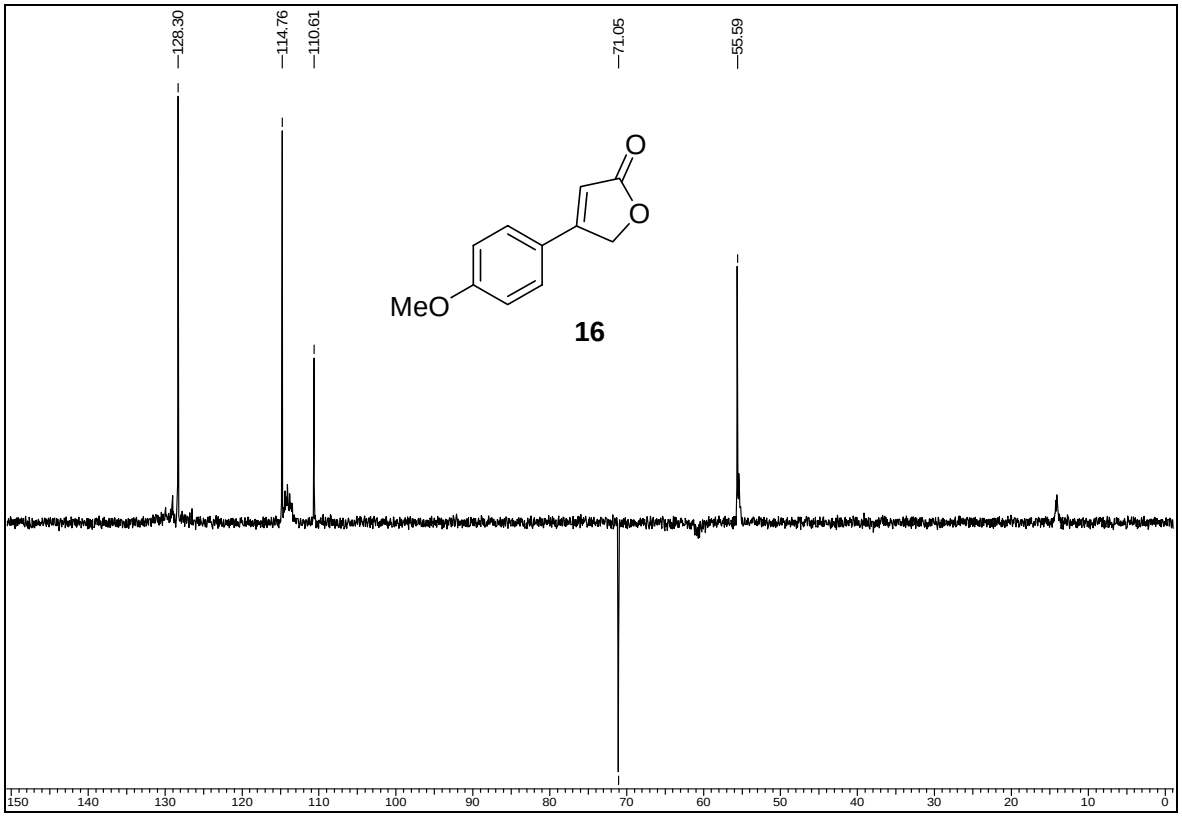
DEPT spectrum of compound 23 ($CDCl_3$, 50 MHz)



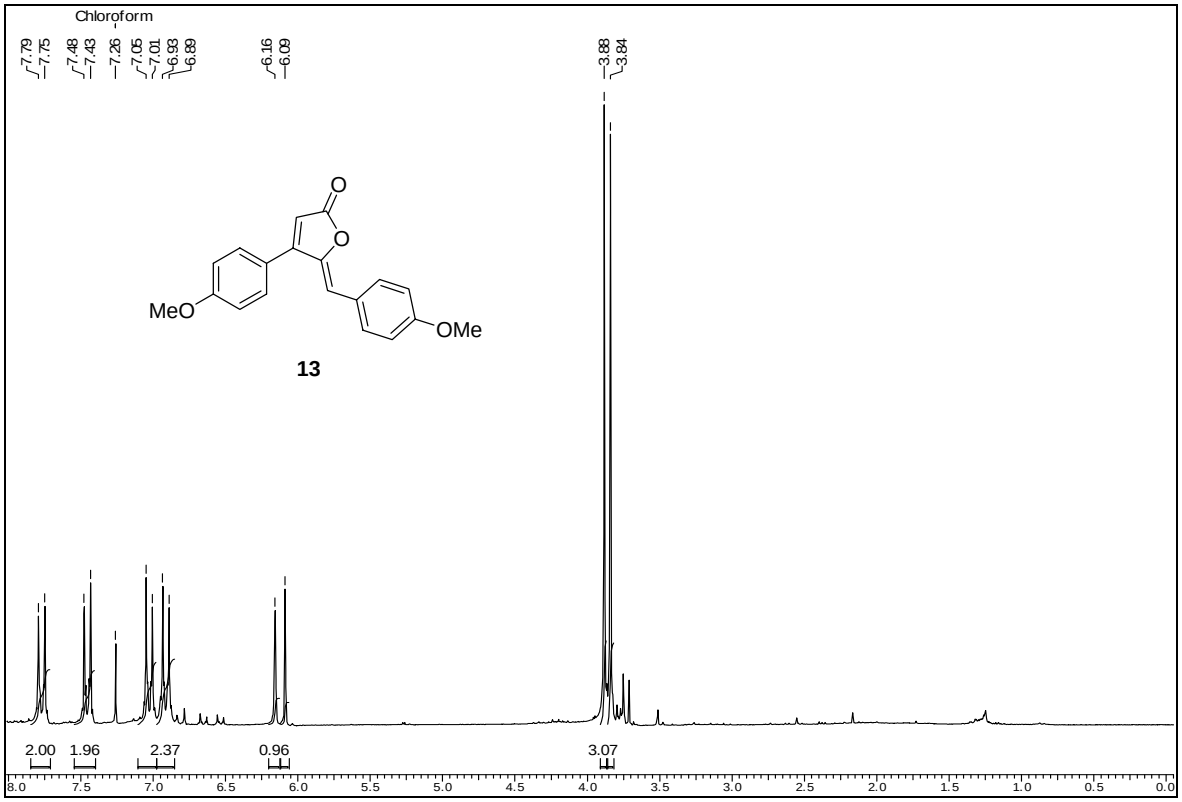
^{1}H NMR spectrum of compound 16 ($CDCl_3$, 200 MHz)



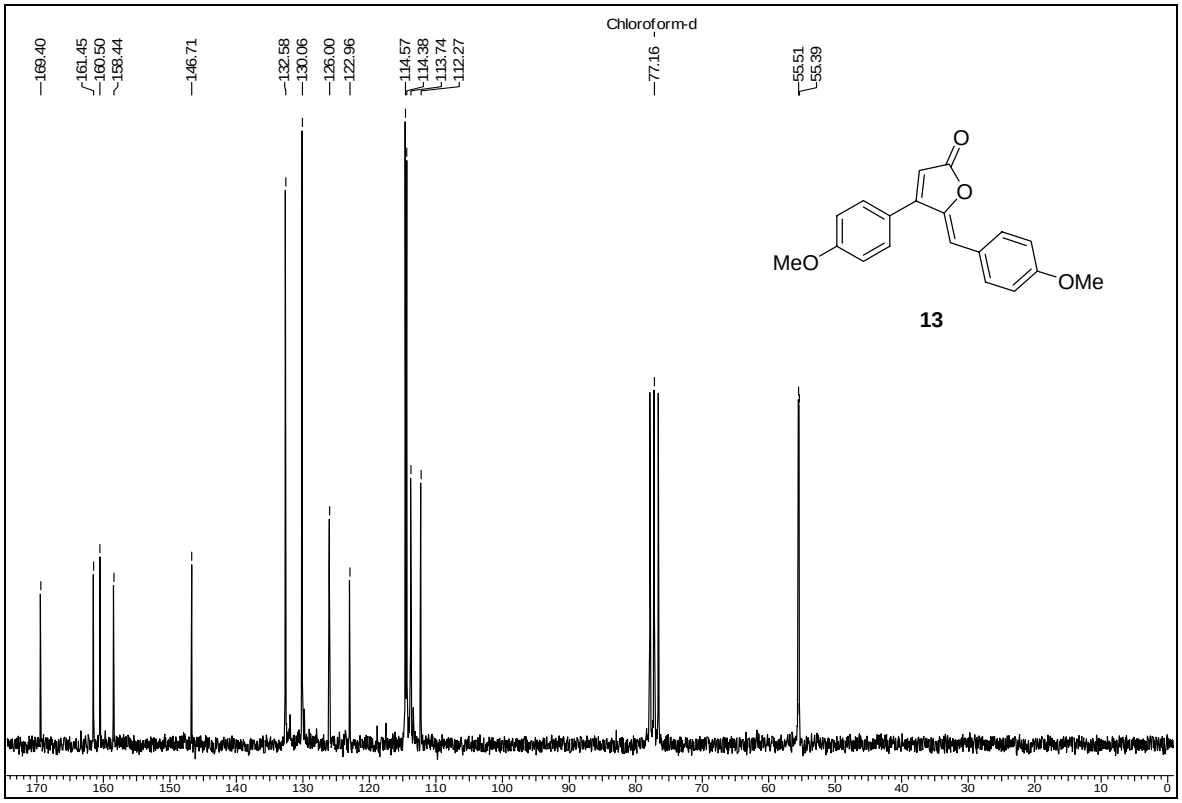
^{13}C NMR spectrum of compound 16 ($CDCl_3$, 50 MHz)



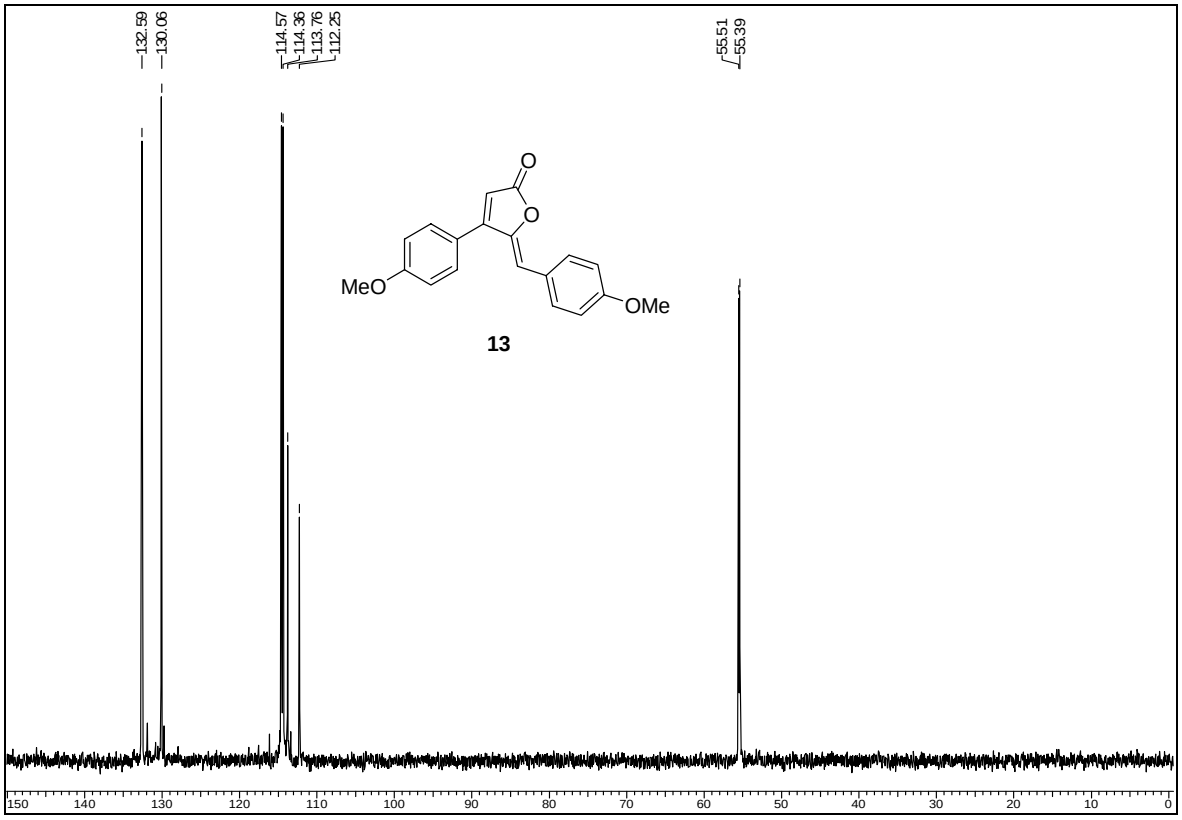
DEPT spectrum of compound 16 ($CDCl_3$, 50 MHz)



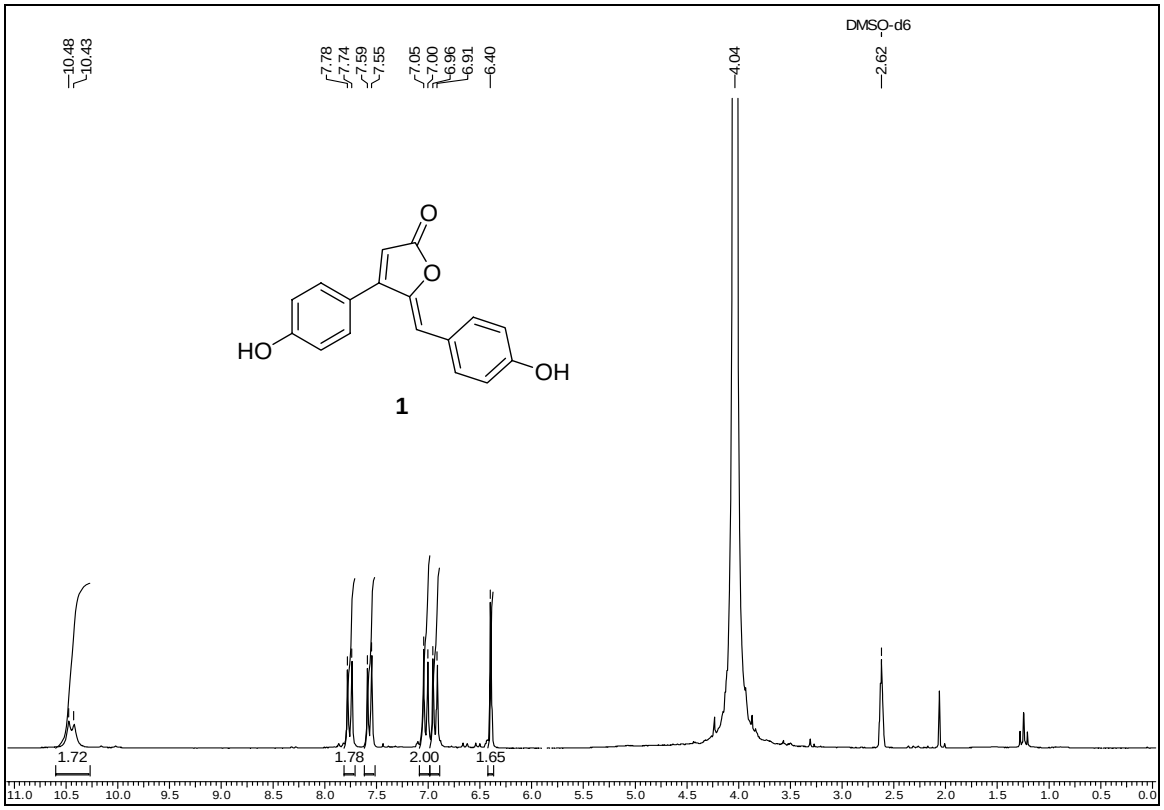
^{1}H NMR spectrum of compound 13 ($CDCl_3$, 200 MHz)



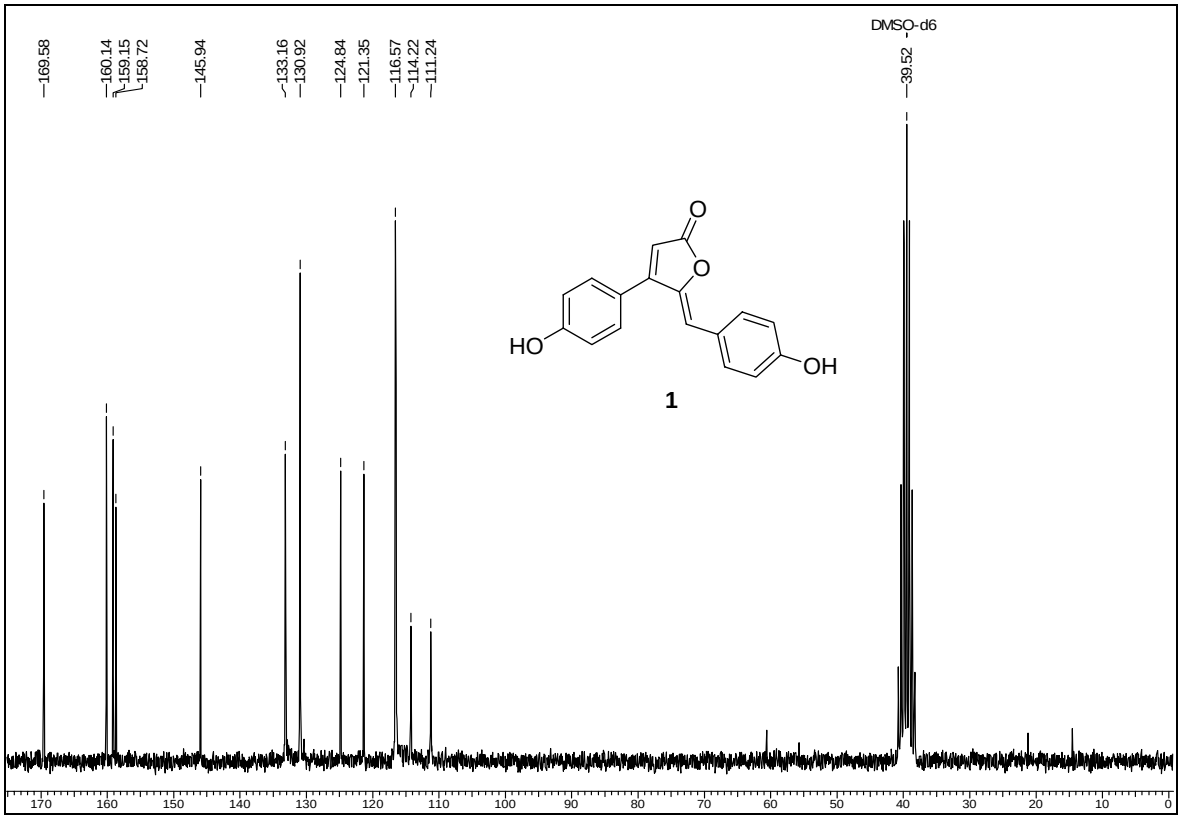
^{13}C NMR spectrum of compound 13 ($CDCl_3$, 50 MHz)



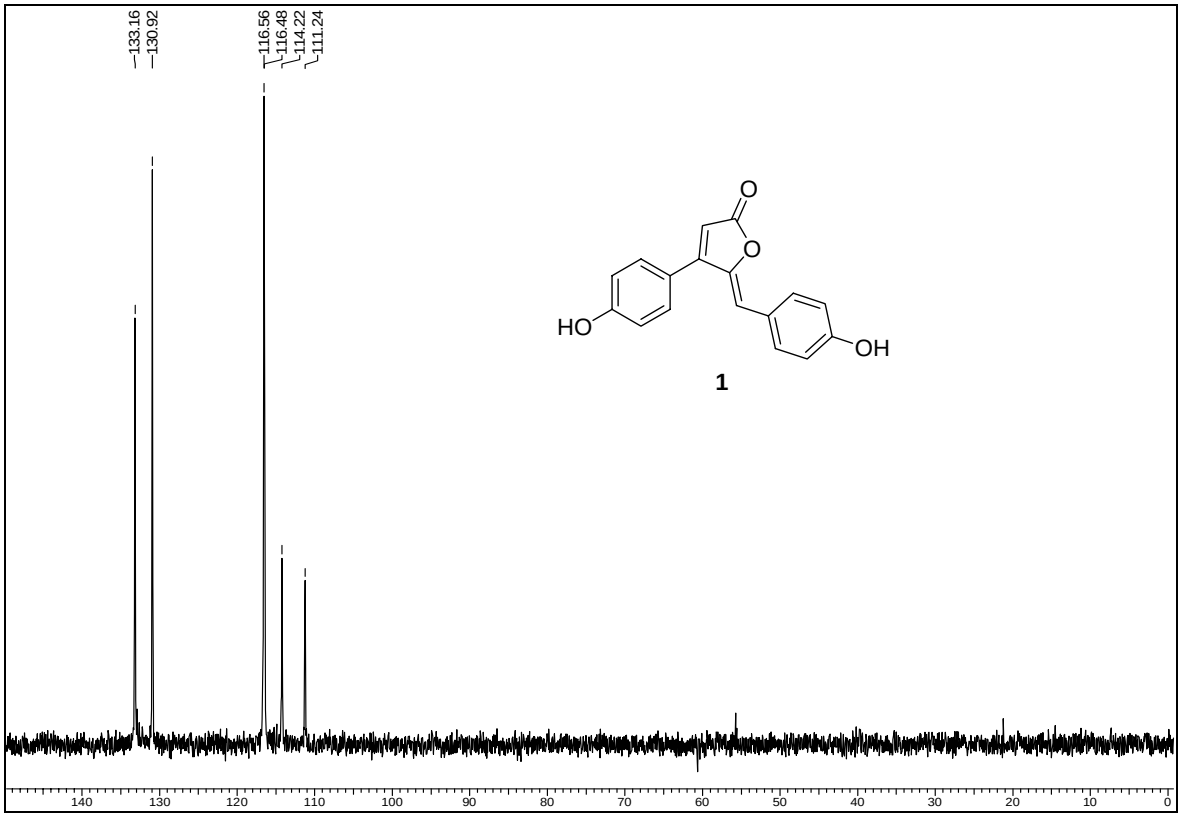
DEPT spectrum of compound 13 ($CDCl_3$, 50 MHz)



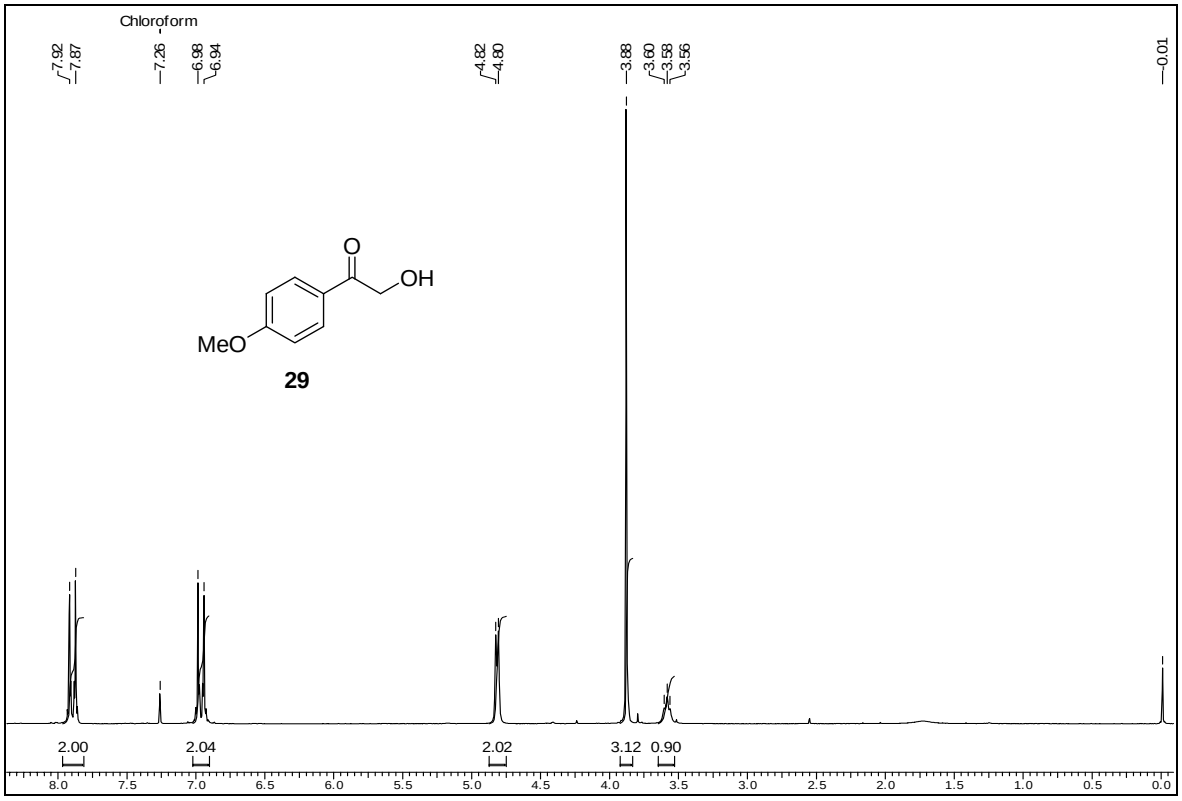
^{1}H NMR spectrum of compound 1 ($CDCl_3$ + DMSO-d_6, 200 MHz)



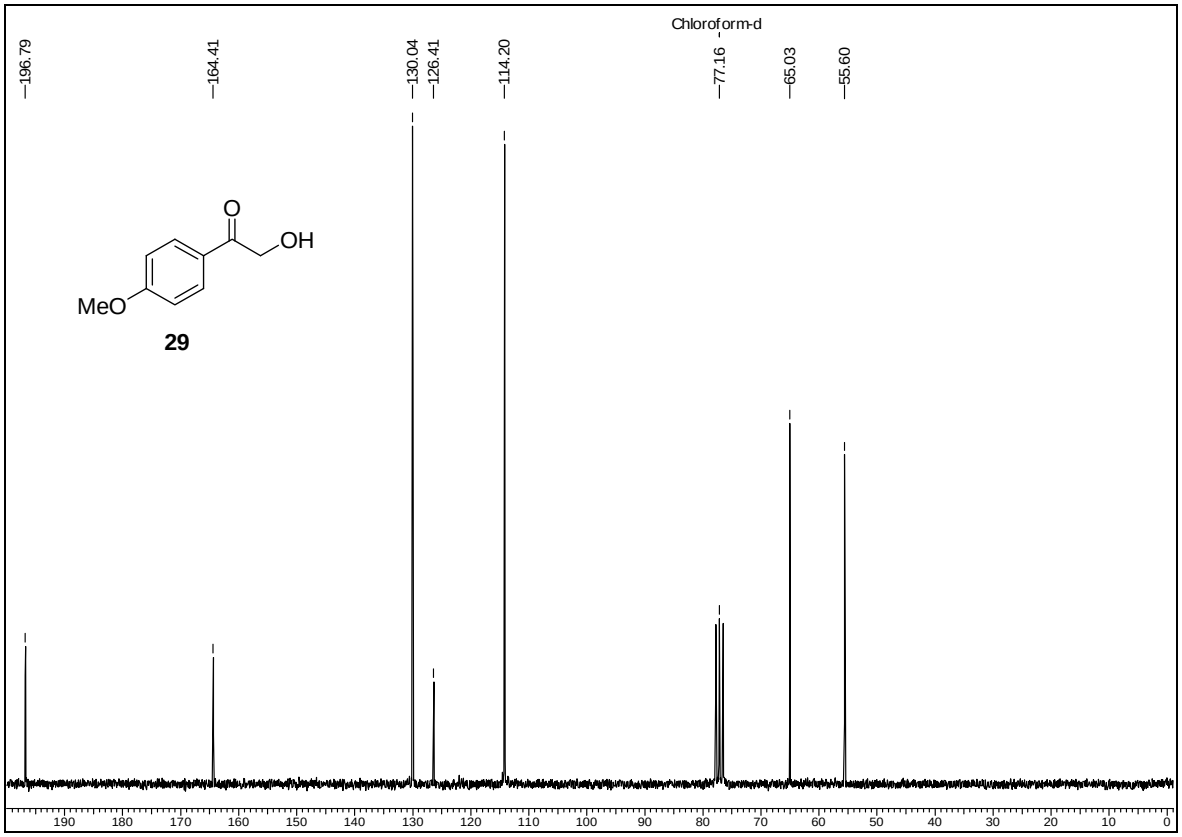
^{13}C NMR spectrum of compound 1 ($CDCl_3$ + DMSO-d_6, 50 MHz)



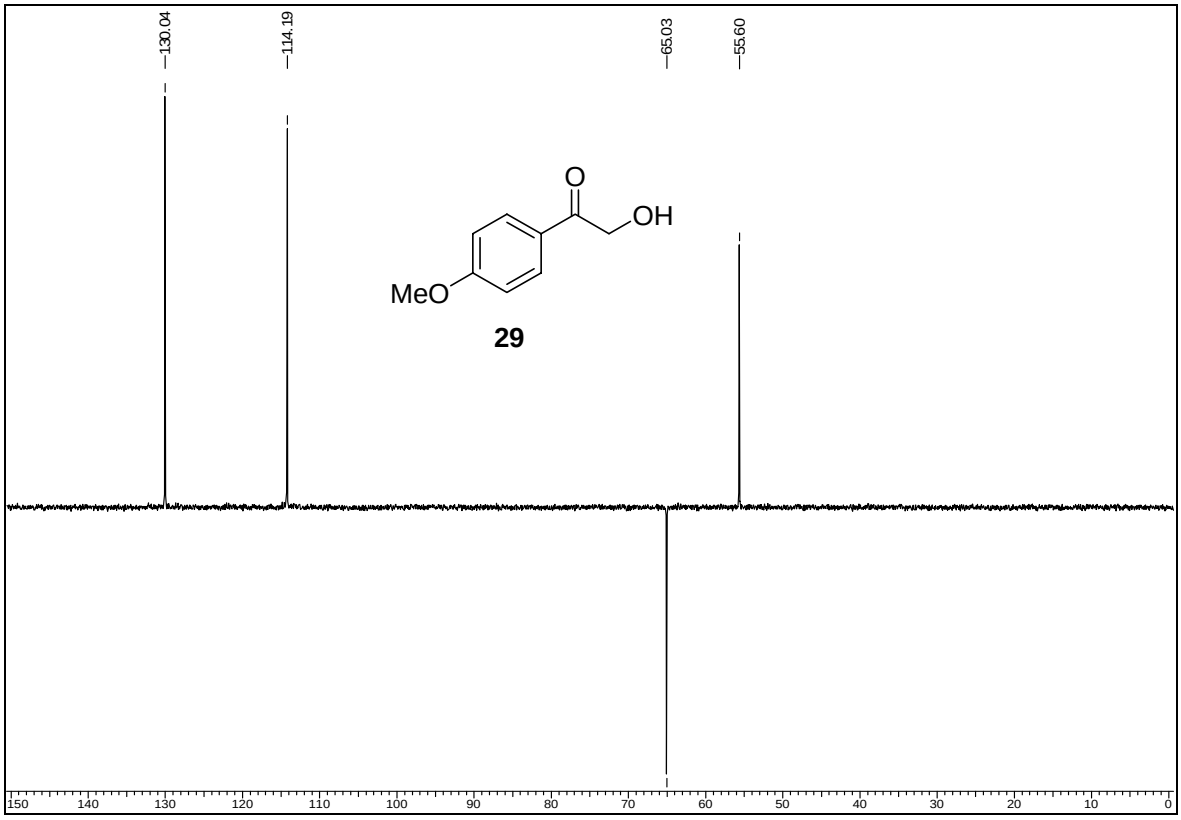
DEPT spectrum of compound 1 ($CDCl_3$ + DMSO-d_6, 50 MHz)



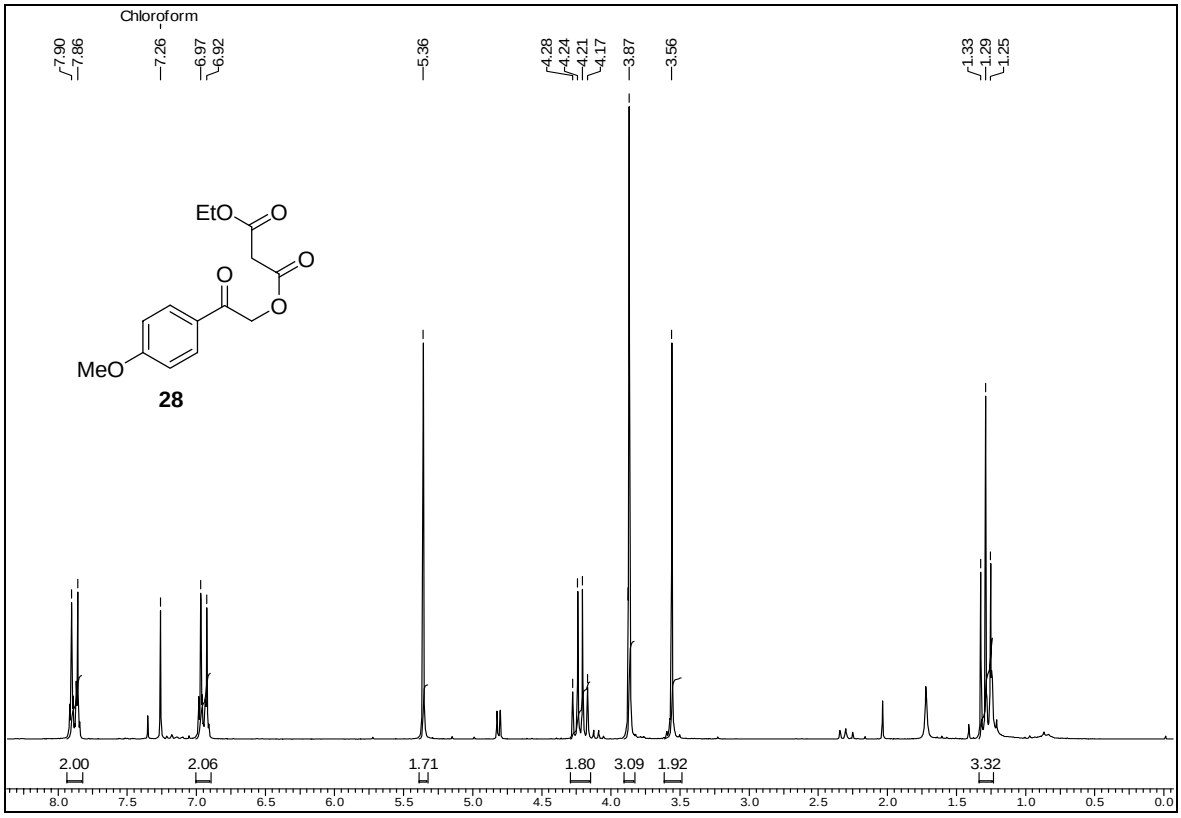
^{1}H NMR spectrum of compound 29 ($CDCl_3$ + CCl_4, 200 MHz)



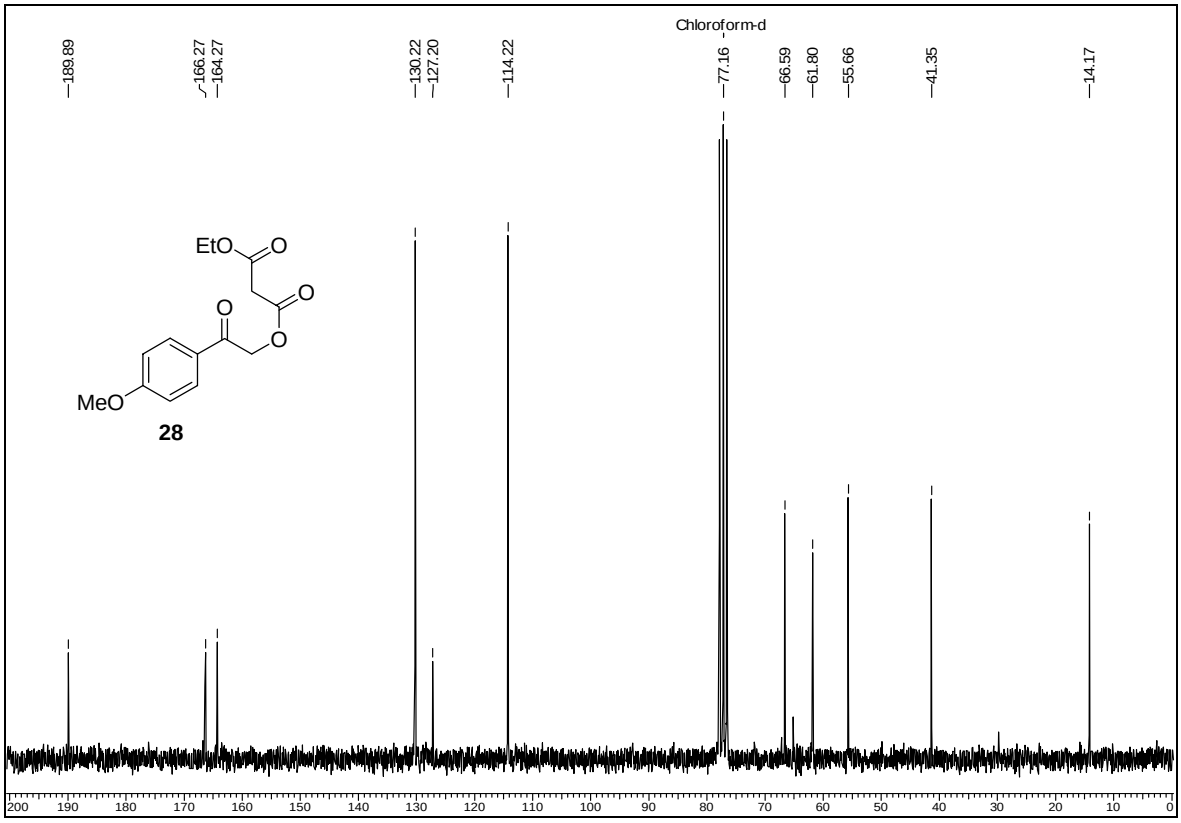
^{13}C NMR spectrum of compound 29 ($CDCl_3$, 50 MHz)



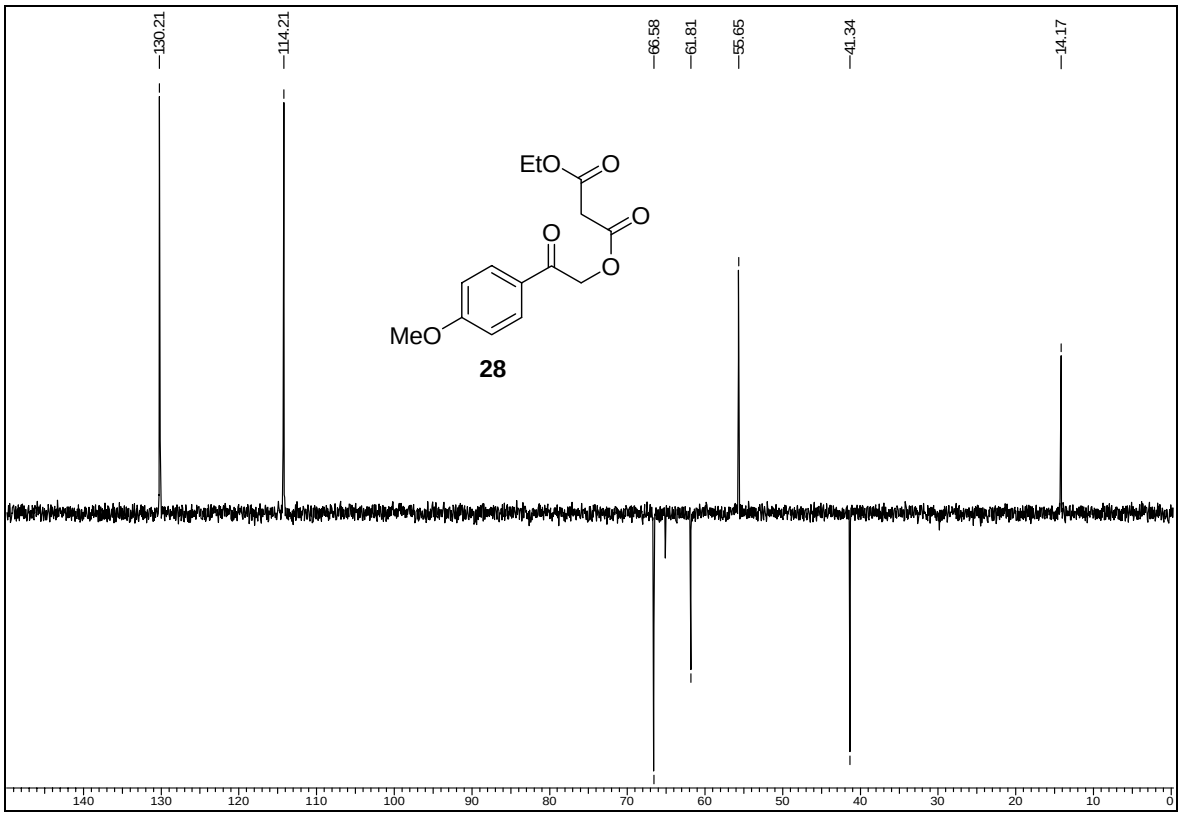
DEPT spectrum of compound 29 ($CDCl_3$, 50 MHz)



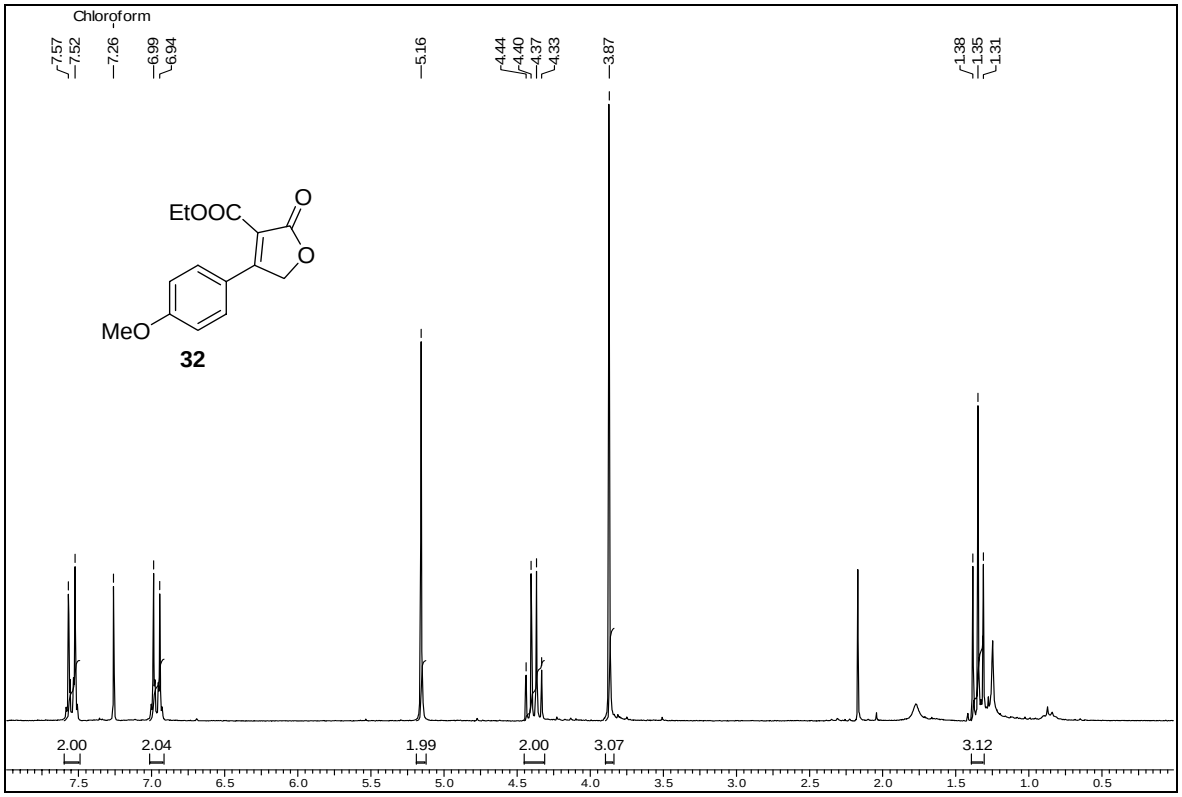
^{1}H NMR spectrum of compound 28 ($CDCl_3$, 200 MHz)



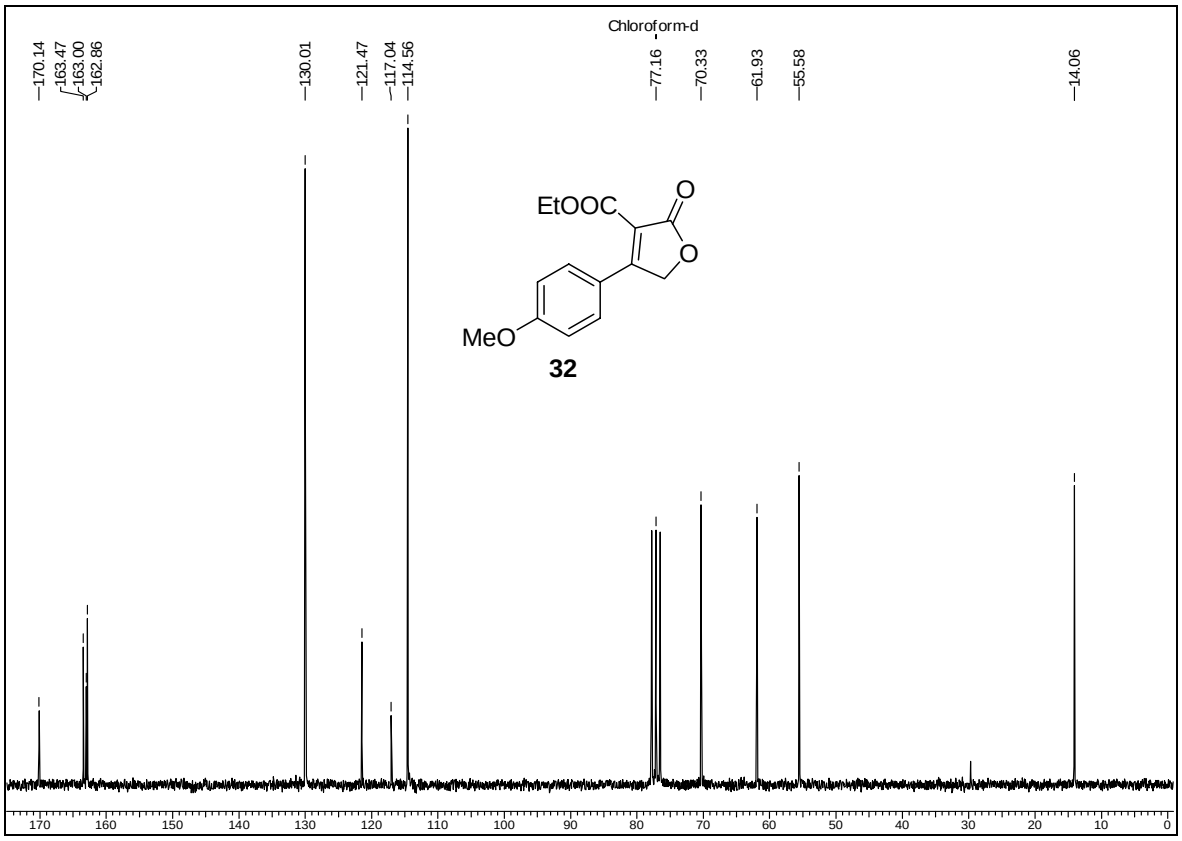
^{13}C NMR spectrum of compound 28 ($CDCl_3$, 50 MHz)



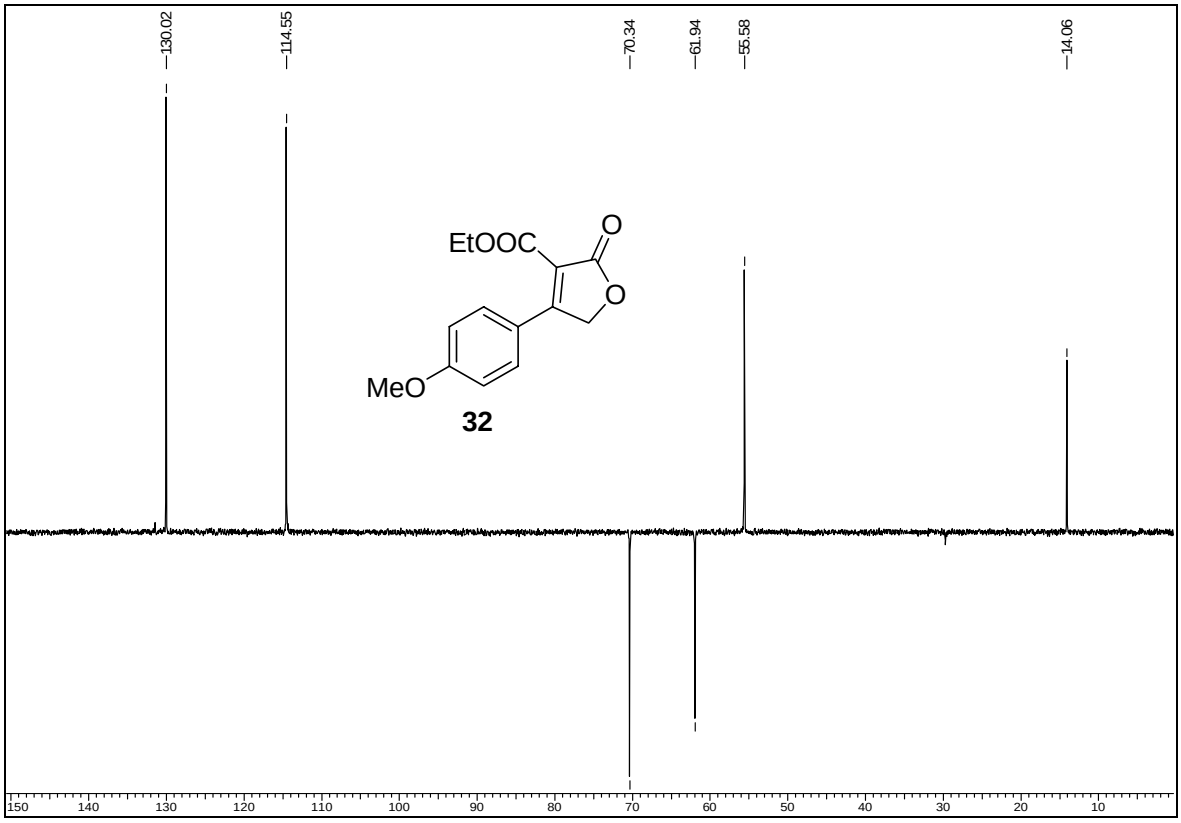
DEPT spectrum of compound 28 ($CDCl_3$, 50 MHz)



^{1}H NMR spectrum of compound 32 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound 32 ($CDCl_3$, 50 MHz)



DEPT spectrum of compound 32 ($CDCl_3$, 50 MHz)

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