SYNTHETIC STUDIES TOWARDS CAMPTOTHECIN AND OTHER BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

TO

UNIVERSITY OF PUNE

BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Synthetic Studies towards Camptothecin and Other Biologically Active Compounds"** submitted by Mr. Abasaheb N. Dhawane 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.

August, 2010
Division of Organic Chemistry
National Chemical Laboratory
Pune 411 008

Subhash P. Chavan
(Research Supervisor)

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled **"Synthetic Studies towards Camptothecin 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.

August, 2010

Abasaheb N. Dhawane

Division of Organic Chemistry

National Chemical Laboratory

Pune 411 008, India.

Dedicated To

…….My Father and Inspirational
Memories of Dilip Anna

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Chapter 2 **Tandem one-pot reaction approaches towards the synthesis of camptothecin**

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Abasaheb

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 refer 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 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
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
n-Bu	normal butyl
s-Bu	secondary butyl
t-Bu	tertiary butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
Cat.	Catalytic
Cbz	Carbobenzyloxy
^{o}C	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
ee	Enantiomeric excess
EDC	Ethylene dichloride
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
MeOH	Methanol
mL	millilitre/s
mmol	millimole
MOM	methoxymethyl
m.p.	Melting point
MS	Mass spectroscopy or Molecular sieves
MW	Molecular weight
NaH	Sodium hydride
$NaIO_4$	Sodium metaperiodate
NCS	*N*-Chlorosuccinimide
NMO	*N*-Methyl morpholine *N*-oxide
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PEG	Polyethylene glycol

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
TBAI	Tetrabutyl ammonium iodide
TBAF	Tetra-*n*-butylammonium fluoride
$TBAHSO_4$	Tetrabutyl ammonium hydrogen sulphate
TBDMSOTf	*tert*-Butyldimethylsilyl triflate
TBSCl	*tert*-butyldimethylsilyl chloride
TBTH	tributyltin hydride
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethyl silane
TMSCl	Trimethyl silyl chloride
TMSI	Trimethyl silyl iodide
TPP	Triphenyl phosphine
Ts	Tosyl
UV	Ultraviolet

Abstract

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

Chapter 1 deals with a brief review on the camptothecin and the present synthetic studies towards camptothecin and is divided into two sections.

Chapter 2 constitutes of the formal synthesis of camptothecin in both racemic as well as asymmetric fashion and is divided into three sections.

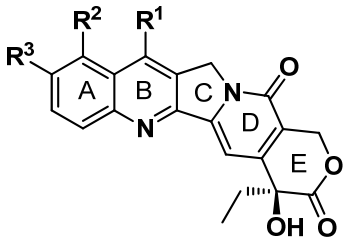
Chapter 3 deals with a brief review on cuparenone and its total synthesis *via* two routes and is divided into three sections.

Chapter 1: Synthetic study towards camptothecin

Section 1: Camptothecin: A family of alkaloids-A brief review

Camptothecin **1** was isolated from the Chinese plant *Camptotheca acuminata* by Wall and Wani in 1966. Camptothecin **1** elicited extensive interest due to its potent antitumor activity. The initial excitement quickly waned however, because of problems associated with its insolubility and toxicity. Liu and coworkers in 1985 reported that camptothecin had an unique mechanism of action that concerned selective inhibition of DNA topoisomerase I. This disclosure served to regenerate interest in camptothecinoids and has led to the development of its analogues *viz* topotecan **2** and irinotecan **3** which are marketed as anticancer drugs.

The present section elucidates the general introduction of camptothecin **1** along with brief account of its isolation, biosynthesis, mechanism of action and structure activity relationship studies. Also this section deals with a review on synthesis of camptothecin, emphasizing mainly the synthetic approaches which have appeared since 2006.



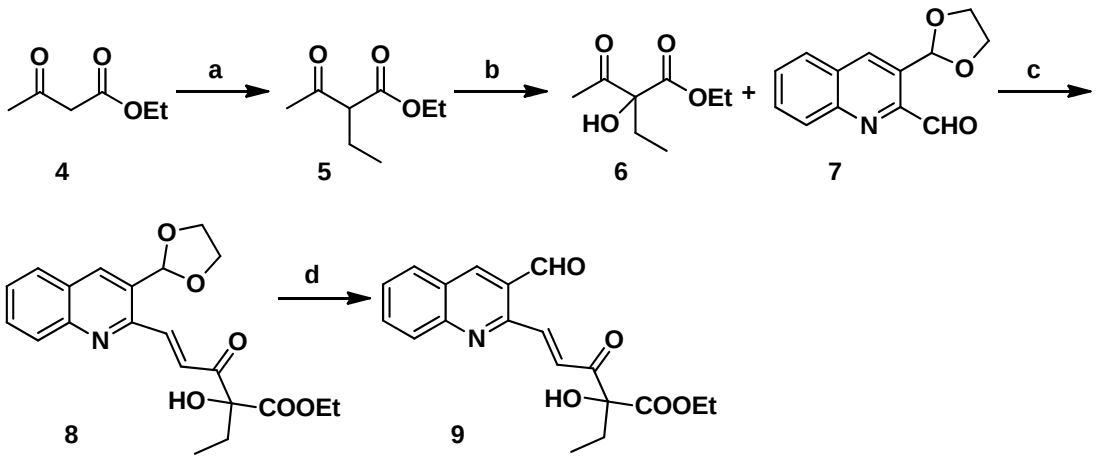
1. Camptothecin R^1, R^2, R^3 = H
2. Topotecan R^1=H, R^2=CH_2NMe_2,HCl, R^3=OH
3. Irinotecan R^1=Et, R^2=H, R^3=OCOPipPip,HCl $3H_2O$

Figure 1

Section 2: Attempted synthesis of camptothecin employing reductive amination as a key step

The present section describes the synthesis of four advanced intermediates for the synthesis of camptothecin **1**, employing aldol reaction and Reformatsky reactions as the key step.

Thus synthesis started from ethyl acetoacetate **4**. Ethyl acetoacetate **4** was monoalkylated followed by hydroxylation using cobalt chloride, isopropanol under oxygen atmosphere to afford hydroxy compound **6**. Aldehyde **7** was prepared from commercially available acetanilide following literature procedure. Having both fragments in hand, they were subjected to condensation using LDA in THF at -78 ^{o}C to afford **8**. Acetal deprotection of **8** was carried out using 2N HCl to afford required aldehyde **9**. Unfortunately yield of aldol condensation product was poor (Scheme 1).

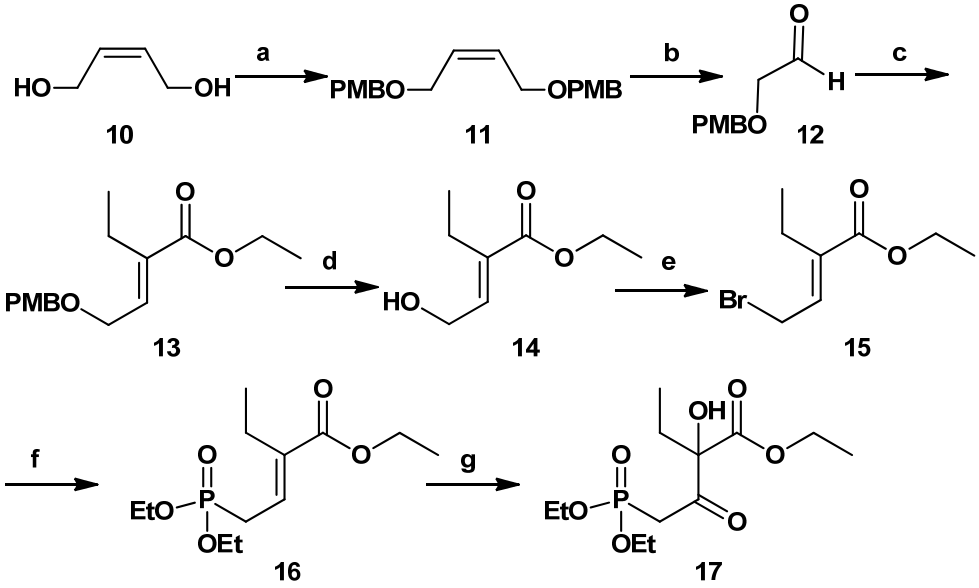


Scheme 1: Reagents and conditions: *a) K_2CO_3, acetone, ethyl iodide, reflux, 4 h, 70%; b) $CoCl_2$, CH_3CN, isopropanol, O_2, 24 h, 65%; c) LDA, THF, -78 ^{o}C, 2 h, 20%; d) 2N HCl, ether:water, 1 h, 85%.*

So the retrosynthetic plan to synthesize the required aldehyde **9** was changed. It was presumed that it can be obtained by Wittig-Horner reaction between aldehyde **7** and phosphonate ester **17**. This can be synthesized from commercially available *cis*-2-butene-1,4-diol **10** (Scheme 2).

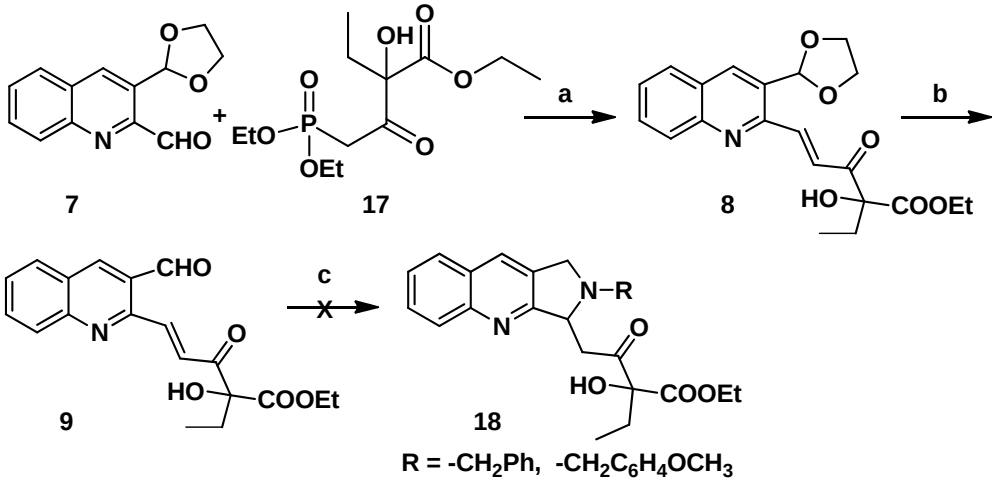
Accordingly, *cis*-2-butene-1,4-diol **10** was protected as di-*PMB* **11**. Ether **11** was then subjected to oxidative cleavage of olefin to afford **12**. The aldehyde **12** was subjected to Wittig reaction to provide the *α, β*-unsaturated ester **13**. Removal of *p*-methoxybenzyl ether in **13** afforded the allyl alcohol **14**. Conversion of alcohol **14** to the corresponding

bromo derivative **15** was carried out using PBr_3, followed by Michaelis-Arbuzov reaction of the resulting bromo intermediate **15** to afford phosphonate **16**. Phosphonate **16** on $KMnO_4$ oxidation furnished required fragment **17** (Scheme 2).



Scheme 2: **Reagents and Conditions:** *a) NaH, PMB-chloride, DMF, rt, 4 h, quant.; b) OsO_4, $NaIO_4$, acetone-water (4:1) 3 h, 95%; c) $CH_3CH_2CPPh_3COOEt$, DCM, rt, 12 h, 73%; d) DDQ, DCM-water (9:1) 3 h, 94%; e) PBr_3, diethyl ether 2 h, 96%; f) Triethyl phosphite, 100 ^oC, 12 h, quant.; g) $KMnO_4$, acetone-water (9:1), 1 h, 90%.*

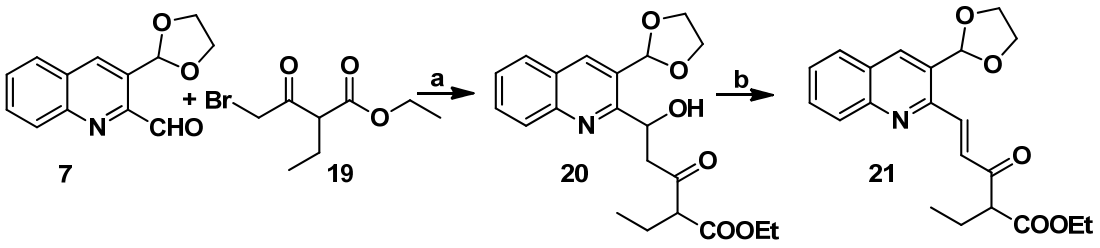
Having phosphonate ester **17** in hand, aldehyde **7** was subjected to Wittig-Horner olefination using triethyl amine in DCM solvent to furnish the enone **8** in 80% yield. Acetal deprotection was carried out using 2N HCl in THF to afford the aldehyde **9** in 85% yield (Scheme 3).



Scheme 3: <u>Reagents and conditions</u>: *a) Triethylamine, dry dichloromethane, rt, 6 h, 80%; b) 2N HCl, THF, rt, 2 h, 85%; c) i) $PhCH_2NH_2$ or $CH_3OC_6H_4CH_2NH_2$, methanol, then $NaBH_4CN$; ii) $Ti(O^iPr)_4$, $PhCH_2NH_2$ or $CH_3OC_6H_4CH_2NH_2$, MeOH, then $NaBH_4CN$.*

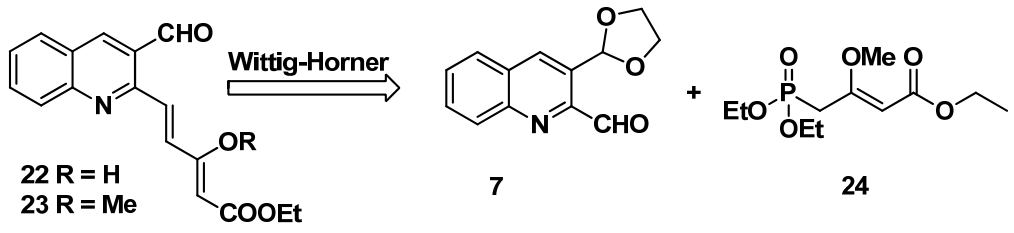
Having the required hydroxy aldehyde **9** in hand, attention was focused on the synthesis of tricyclic skeleton of camptothecin by reductive amination under different conditions, but unfortunately the reaction led to a complex reaction mixture from which the desired tricyclic compound could not be obtained (Scheme 3).

Thus, it was thought that the problem may be due to the tertiary hydroxyl group. Hence it was decided to synthesise the dehydroxy compound **21**. Accordingly, Reformatsky reaction on aldehyde **7** using bromo compound **19** in presence of zinc and catalytic iodine furnished alcohol **20**. To get the required olefin **21**, reaction was attempted using PTSA as well as using dil HCl but these efforts failed to furnish the desired compound **21**. The alcohol **20** was then treated with triethyl amine and mesyl chloride in DCM to afford the compound **21** in low yields (Scheme 4).



Scheme 4: <u>Reagent and conditions:</u> *a) Zn, iodine (cat), benzene-ether (1:1), reflux, 7 h, 30%; b) Triethyl amine, mesyl chloride, DCM, 0 ^oC, 3 h, 35%.*

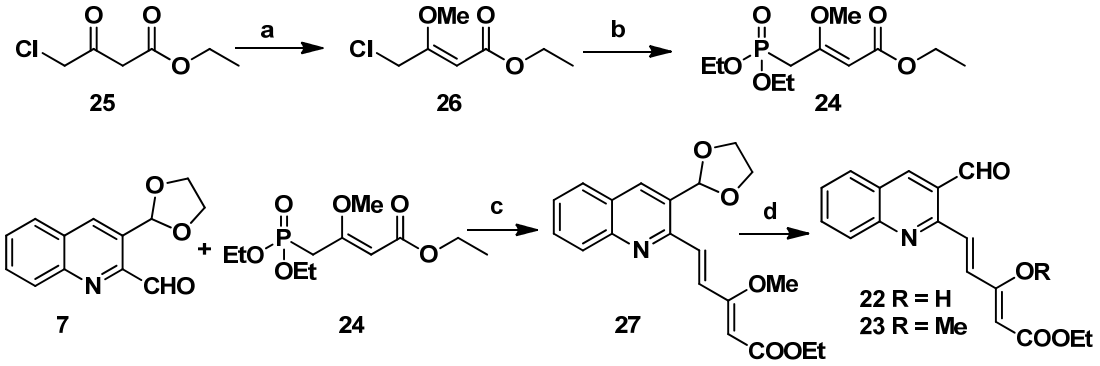
Though success was achieved in formation of carbon-carbon bond, the yields were very disappointing. So it was thought to prepare another substrate utilizing Wittig-Horner reaction (Scheme 5).



Scheme 5

Accordingly, the phosphonate ester **24** was prepared from 4-chloro-ethylacetoacetate **25**, which on treatment with thionyl chloride, methanol and

methanesulfonic acid afforded the enol ether **26**. Enol ether **26** was heated at 120 ^{o}C with triethylphosphite to afford a phosphonate ester **24** (Scheme 6).



Scheme 6: **Reagents and conditions:** *a) i) $SOCl_2$, MeOH, methanesulphonic acid, rt, 4 h, 90%; b) Triethyl phosphite, 120 ^{o}C, 12 h, 84%; c) NaH, THF, -5 to -20 ^{o}C, 1 h, 82%; d) 2N HCl, diethyl ether, rt, 2 h, 85%; d) 6N HCl, diethyl ether, rt, 3 h, 80%.*

Having aldehyde **7** and phosphonate ester **24** in hand they were subjected to Wittig-Horner olefination by using NaH in THF as the solvent, to afford the condensed product **27** in 82% yield. Acetal deprotection was carried out using 2N HCl in diethyl ether to afford the aldehyde **23** in 85% yield while on treatment with 6N HCl in ether, **22** was obtained (Scheme 6). Both the compounds **22** and **23** were separately subjected to reductive amination under various conditions but all the reactions ended up as intractable complex mixtures.

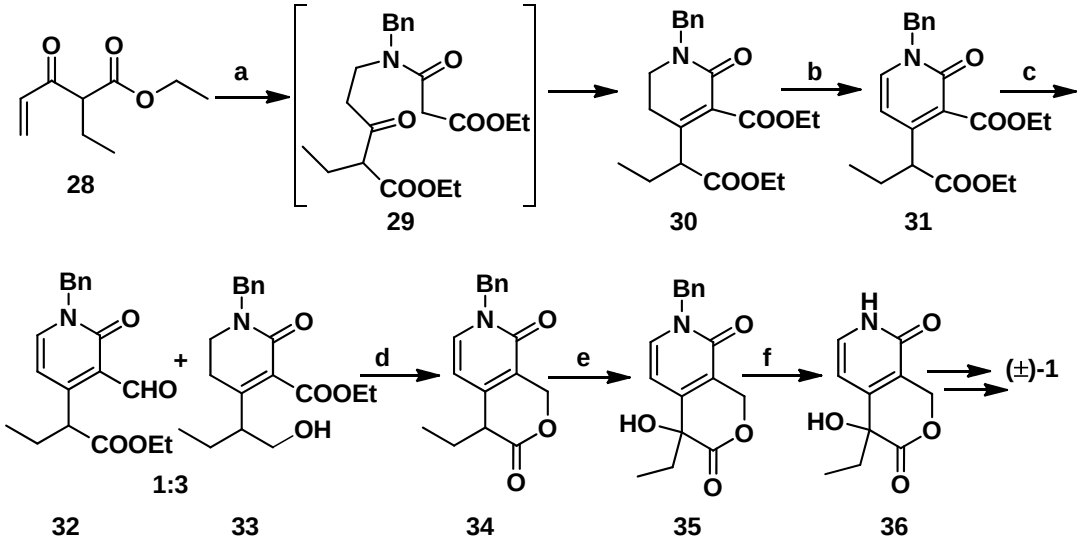
Chapter 2 : Tandem one-pot reaction approaches towards the synthesis of camptothecin

Section 1: Formal synthesis of (+)-camptothecin *via* DE-ring synthon employing tandem aza-Michael-condensation-Knoevenagel cyclization reaction.

Having failed in the synthesis of camptothecin **1** in linear manner, it was envisaged to synthesise camptothecin by adopting convergent strategy. Synthetic approaches for camptothecin **1** and its analogues have typically involved synthesis of suitably functionalized CDE-rings or DE-rings or precursors thereof, which were then coupled with appropriate counterparts. Keeping this concept in mind, it was proposed to synthesize

the DE synthon, which can be synthesized from commercially available benzyl amine and α, β–unsaturated compound **28**.

Thus the α, β-unsaturated ketone **28** was subjected to one pot Michael addition, condensation and Knoevenagel cyclization with benzyl amine and after 30 minutes addition of 4 eq. K_2CO_3 followed by the addition of ethyl malonyl chloride at 0 ^oC to obtain dihydropyridone **30** in 70% yield *via* the intermediate **29**. The dihydropyridone **30** was subjected to DDQ oxidation to afford pyridone **31** in 91% yield (Scheme 7).

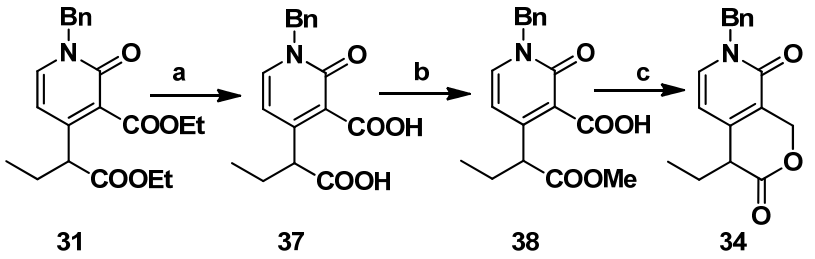


Scheme 7: <u>Reagents and conditions</u>: *a) Benzyl amine, DCM, ½ h, K_2CO_3, DCM, ethyl malonyl chloride, 8 h, 70%; b) DDQ, dioxane, reflux, 24 h, 91%.; c) DIBAL-H, THF, -60 ^oC, 80%; d) $NaBH_4$, THF-H_2O, 93%.; e) $CuCl_2$, Me_2NH, O_2, DMF, rt, 24 h, 92%; f) $Pd(OH)_2$, H_2, EtOH, 50 ^oC, 5 h, 72%.*

Having pyridone **31** in hand, next goal was to build the lactone ring by selective reduction of aromatic ester. Accordingly the pyridone **31** was subjected to reduction using 3 eq. of DIBAL-H at -60 ^oC in THF to furnish the required aldehyde **32,** along with over reduced product *viz* alcohol **33** in 1:3 ratio. Aldehyde **32** on reduction with $NaBH_4$ resulted in the formation of lactone **34** in 93% yield (Scheme 7).

Alternatively, lactone **34** was obtained from pyridone **31**. Pyridone **31** on treatment with excess of lithium hydroxide in ethanol afforded diacid **37** in 84% yield. The selective esterification of aliphatic acid was accomplished using nickel chloride to deliver compound **38** in 76% yield. Compound **38** was treated with methyl chloroformate in THF

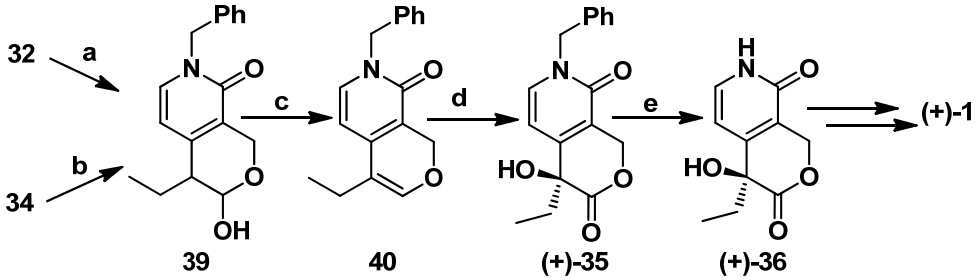
at 0 ^{o}C and subsequently reduced to alcohol *via* mixed anhydride intermediate followed by lactonization using $NaBH_4$ to result in formation of lactone **34** in 84% yield (Scheme 8).



Scheme 8: **Reagents and conditions:** *a) LiOH, EtOH, rt, 24 h, 84%; b) $NiCl_2$, MeOH, reflux, 12 h, 76%; c) i) Et_3N, methyl chloroformate, anhydrous THF, 0 ^{o}C, 1 h; ii) $NaBH_4$, -78 ^{o}C, 3 h, 10% HCl, rt, 12 h, 84%.*

The hydroxylation was carried out using $CuCl_2$ and catalytic amount of dimethyl amine under oxygen atmosphere to furnish α-hydroxy lactone **35** in 92% yield. Finally, *N*-debenzylation using catalytic amount of palladium hydroxide in ethanol at 50 ^{o}C furnished the desired DE-ring synthon (±)-**36** in 72% 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.

Being successful in the synthesis of (±)-DE synthon it was decided to perform enantioselective synthesis of (*S*)-DE synthon, which is essential for biological activity.

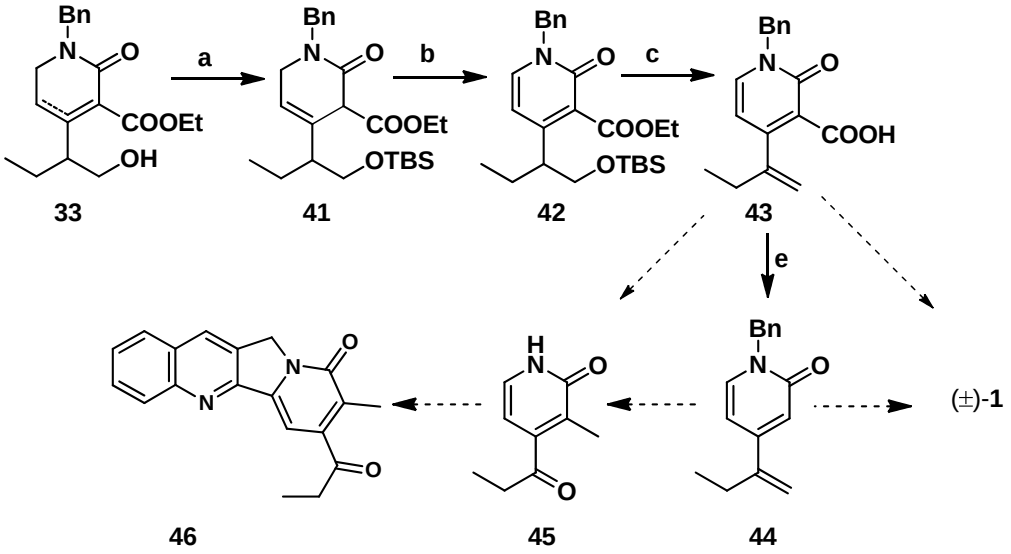


Scheme 9: **Reagents and conditions:** *a) $NaBH_4$, THF-H_2O, 0 ^{o}C-rt, 30 min, 90%. b) $NaBH_4$, THF-H_2O, 0 ^{o}C-rt, 15 min, 90%. c) MsCl, Et_3N, anhydrous THF, rt, 24 h, 95%; d) i) $(DHQD)_2$-PYR (cat.), OsO_4 (cat.), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $CH_3SO_2NH_2$ (1.0 equiv), t-BuOH-H_2O (1:1), 0 ^{o}C; ii) I_2 (10 equiv), $CaCO_3$ (10 equiv), CH_3OH-H_2O (10:1), rt, 24 h, 90% over two steps. e) $Pd(OH)_2$, H_2, EtOH, 50 ^{o}C, 5 h, 72%.*

Accordingly, lactol **39** was synthesized from aldehyde **32** and lactone **34** by treatment with $NaBH_4$. The lactol **39** was transformed into enol ether **40** in 95% yield *via*

O-mesylation followed by elimination. Sharpless asymmetric dihydroxylation on **40** followed by oxidation afforded **35** (90% yield, 95% *ee*). Finally, *N*-debenzylation of **35** furnished (+)-DE synthon **36** (72% yield, 95% ee) of camptothecin **1** (Scheme 9).

In the DIBAL-H reduction of pyridone **31**, an unusual formation of over-reduced alcohol **33** was observed. It was thought to utilize alcohol **33** for the synthesis of camptothecin and its analogues. Accordingly, alcohol **33** was protected as its TBS ether **41**, followed by DDQ oxidation which resulted in the desired pyridone **42** in 98% yield. TBS deprotection was carried out using TBAF in THF to afford unusual rearranged acid **43** in 60% yield, which on decarboxylation using naphthalene and Cu powder afforded pyridine **44** which can be converted into advanced intermediate **45** by alkylation and debenzylation, which is precursor for the synthesis of mappicine. It can also be further manipulated into camptothecin **1** (Scheme 10).



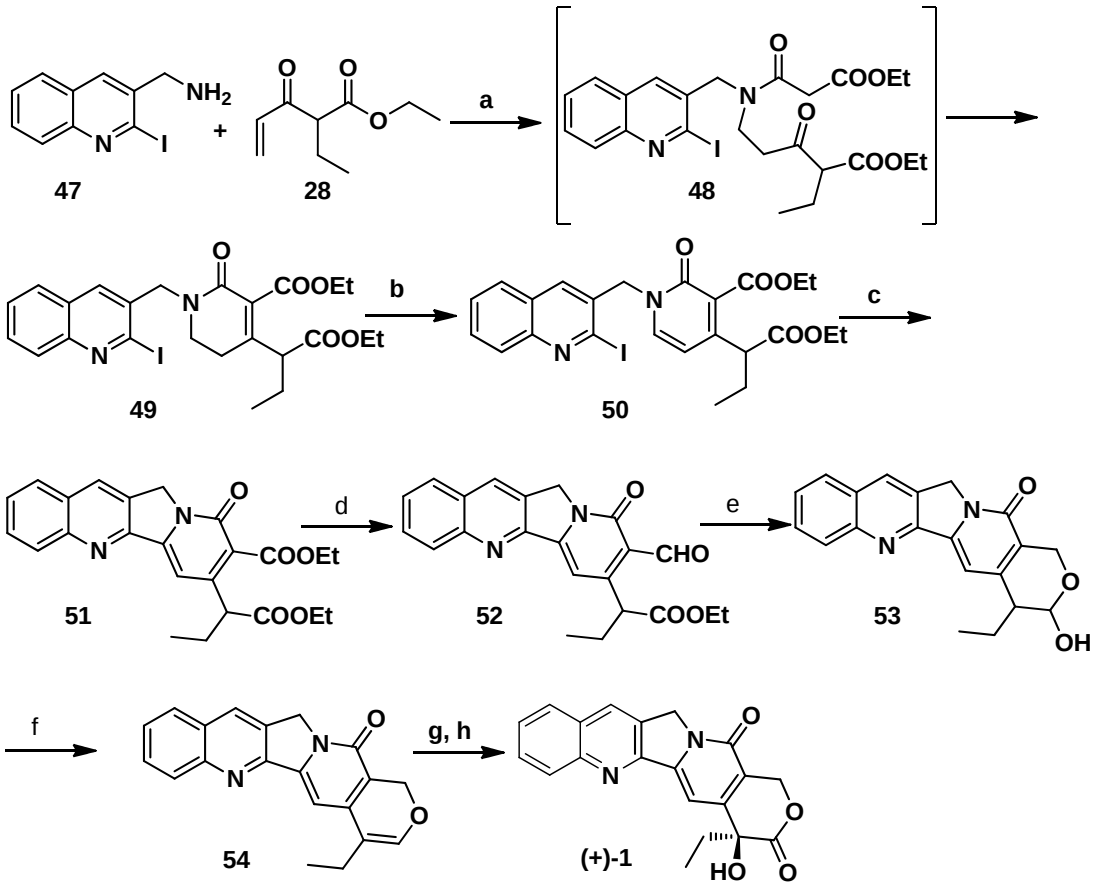
Scheme 10: **<u>Reagents and conditions:</u>** *a) Imidazole, TBS-Cl, DCM, 0 °C-rt, 1 h, 95%; b) DDQ, dioxane, reflux, 5 h, 98%; c) TBAF, THF, rt, 1 h, 60%; e) Naphthalene, Cu powder, reflux, 3 h, 94%.*

In summary, the formal total synthesis of (+)-camptothecin employing tandem one-pot three steps transformations involving aza-Michael reaction, condensation with ethyl malonyl chloride followed by intramolecular “Knoevenagel” reaction to furnish dihydropyridone has been accomplished.

Section 2 : Formal synthesis of (+)-camptothecin

After achieving the formal synthesis of camptothecin **1** *via* (*S*)-DE synthon employing tandem one-pot three-steps transformations, in this section the idea of one pot reaction towards formal total synthesis of camptothecin **1** by using the quinoline amine **47** on same α, β unsaturated compound **28** was explored (Scheme 11).

Iodo quinoline amine **47** was subjected to one-pot Michael addition, condensation and Knoevenagel cyclization with α, β-unsaturated ketone **28** and after 30 minutes 4 eq. K_2CO_3 followed by ethyl malonyl chloride were added at 0 ^oC and stirred at rt for 8 h to afford dihydropyridone **49** in 70% yield *via* the intermediate **48**. The product thus obtained was subjected to DDQ oxidation in 1,4-dioxane at reflux temperature to result in the desired pyridone **50** in 91% yield.



Scheme 11: **Reagents and conditions:** *a) K_2CO_3, DCM, ethyl malonyl chloride, 8 h, 70%.; b) DDQ, 1,4-dioxane, reflux, 24 h, 91%; c) PEG-2000, Et_3N, $Pd(OAc)_2$, 90 ^oC, 10 h, 84%.; d) DIBAL-H (3.0 equiv.), dry THF, -60 ^oC, 2 h, 83%; e) $NaBH_4$, THF-H_2O*

(9:1), 0 ^{o}C, 0.5 h, 90%; f) MsCl, Et_3N, 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 ^{o}C; h) I_2 (12.5 equiv), $CaCO_3$ (12.5 equiv), CH_3OH-H_2O (10:1), rt, 24 h.

The compound **50** under Heck coupling conditions using PEG-2000, triethylamine and $Pd(OAc)_2$ afforded pyridone **51** in 84% yield**.** The selective reduction of aromatic ester **51** to aldehyde **52** in 83% yield was achieved using DIBAL-H. The aldehyde **52** was further reduced to lactol **53** in 90% yield using $NaBH_4$. The lactol **53** was transformed into enol ether **54** in 92% yield *via O*-mesylation followed by elimination. Sharpless asymmetric dihydroxylation on **54** followed by oxidation provided (+)-camptothecin **1** (Scheme 11).

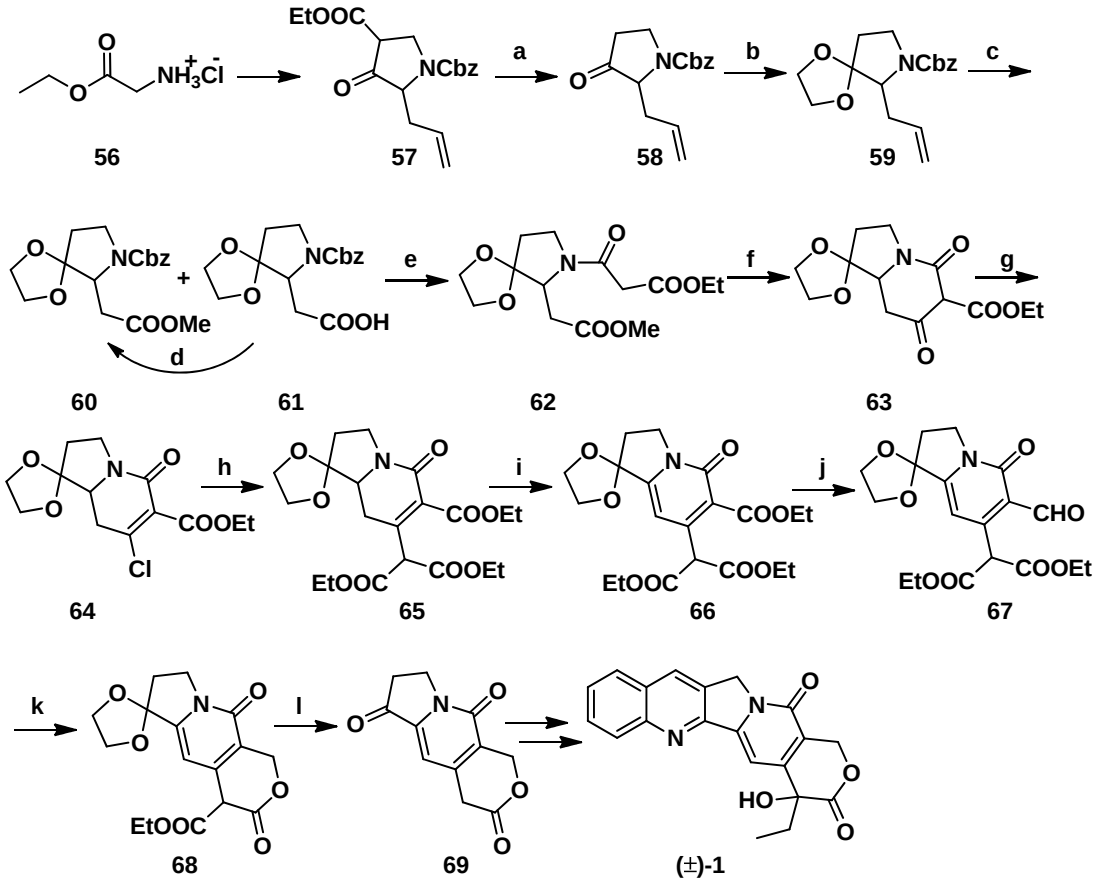
In conclusion, asymmetric synthesis of camptothecin was realized strating from quinoline amine employing tandem one-pot three-step transformations involving aza-Michael reaction, condensation with ethyl malonyl chloride followed by intramolecular "Knoevenagel " reaction and PEG mediated Heck cyclization.

Section 3. Formal total synthesis of camptothecin *via* tricyclic lactone

The clinical use of camptothecin has been limited owing to its insolubility and toxicity, but extensive structure-activity relationship studies have identified its various analogues having better solubility and with equal or better antitumor activity. This 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 were then coupled with appropriate counterparts.

Accordingly, synthesis started from β-keto ester **57** as the starting material, which was prepared according to the literature procedure from glycinate salt **56**. Keto ester **57** was subjected to hydrolysis-decarboxylation under Krapcho conditions to afford the keto compound **58**, which was protected as acetal using ethylene glycol to afford urethane **59** in 90% yield. Urethane **59** was subjected to oxidative cleavage by using catalytic osmium tetroxide followed by $NaIO_4$ to afford the crude aldehyde which on treatment with oxone in methanol/ethanol at room temperature afforded corresponding ester urethane **60** in 60% yield along with acid **61** in 25% yield. Acid **61** was converted into required ester on treatment with diazomethane. To synthesize D ring, ester **60** was subjected to cbz deprotection by using Pd/C at 60 psi pressure followed by condensation with ethyl malonyl chloride to afford the amide **62** in 88% yield over two steps**.** Amide **62** was

treated with sodium hydride in ethanol at 0 ^{o}C to yield the cyclised compound in 98% yield which existed as the diketo ester **63**. Without further purification, the keto compound **63** was treated with $POCl_3$ in anhydrous dichloromethane at reflux condition, afforded chloro compound **64**.



Scheme 12: **Reagents and conditions**: *a) NaCl (4.0 equiv), DMSO-H_2O (3:1), 120-130 ^{o}C, 3 h, 78%; b) 1, 2-Ethane diol, PTSA, benzene, reflux, 8 h, 90%; c) i) OsO_4, acetone-water (3:1), $NaIO_4$, 3 h; ii) Oxone, methanol, rt, 16 h; d) Diazomethane, Et_2O, 0 ^{o}C-rt, 12 h, 95%; e) i) Pd/C, ethanol, 60 psi, 2 h; ii) K_2CO_3, DCM, ethyl malonyl chloride, 0 ^{o}C, rt, 88%; f) NaH, ethanol, rt, 3 h, 98%; g) $POCl_3$, DCM, reflux, 4 h; h) NaH, diethyl malonate, dry benzene, rt, overnight, 65%; i) DDQ, 1,4-dioxane, reflux, 48 h, 96 %; j) DIBAL-H, THF, -60 ^{o}C, 2 h, 82%; k) $NaBH_4$, THF-H_2O (9:1), 0 ^{o}C, 5 min, 90%; l) 10% HCl, 90-100 ^{o}C, 6 h, 82%.*

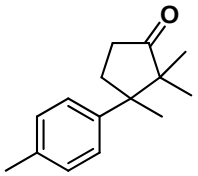
The resulting chloro compound **64** being unstable was immediately taken for addition-elimination reaction with diethyl malonate using sodium hydride in anhydrous benzene to afford the desired compound **65** in 65% yield. Aromatization of **65** was

achieved employing DDQ to furnish pyridone **66** in 96% yield. Pyridone **66** was subjected to selective reduction of aromatic ester using 3 eq. of DIBAL-H in THF at -60 ^{o}C to afford aromatic aldehyde **67** in 82% yield. Aldehyde **67** on further treatment with sodium borohydride in THF-H_2O (9:1) at 0 ^{o}C furnished the lactone **68** in 90% yield. Acetal deprotection, ester hydrolysis and decarboxylation was carried out in one pot by refluxing lactone **68** with 10% HCl for 6 h to afford the tricyclic lactone **69** in 82% yield (Scheme 12). This is the common intermediate in Shamma's synthesis which could be converted to (±)-camptothecin **1** by a three-step sequence *i.e.* Friedlander condensation with 2-amino benzaldehyde followed by alkylation and hydroxylation.

Chapter 3: Synthetic Studies towards α-Cuparenone

Section 1 : Cuparenone: A family of sesquiterpene-A brief review

This section elucidates the general introduction of α-cuparenone **70**, which was isolated from *Thuja orientalis* (Mayurpankhi) by Sukh Dev and Chatty in 1964. This compound poses a synthetic challenge to organic chemists due to the presence of two contiguous quaternary centers in a cyclopentane ring.



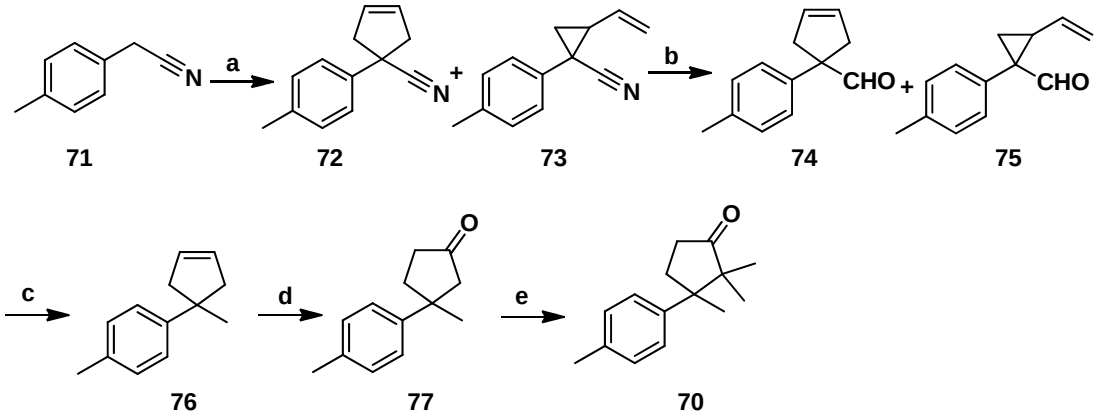
α-Cuparenne 70

Also in this section a concise review on synthesis of α-cuparenone is presented. Synthesis of racemic and optically pure α-cuparenone reported only after 1997 and some representative syntheses have been described in the present section.

Section 2 : Synthesis of (±)-α-cuparenone employing one pot cyclopentannulation

As described in section 1, the synthesis of α-cuparenone **70** is a good synthetic challenge for organic chemist. Interest of the group in synthesis of cyclopentanoid natural products led to application of simple cyclopentannulation approach towards the synthesis of α–cuparenone. Synthetic sequence as depicted in Scheme 13 starts from commercially available 4-methylbenzyl cyanide **71**. Dialkylation of **71** was carried out using sodium hydride and *cis*-1,4-dichlorobutene in THF to afford cyclopentene **72** along with

cyclopropyl side product **73** in 2:1 ratio as an inseparable mixture. So the mixture was subjected to further reactions with the hope that it could be separated at hydroboration oxidation step. Thus the mixture of **72** and **73** was subjected to reduction with DIBAL-H to furnish aldehydes **74** and **75** which were further reduced under Huang-Minlon reaction conditions without further purification to furnish required olefin intermediate **76** having one of the quaternary center. Formation of a single product at Huang-Minlon reduction was initially surprising but it was thought that the cyclopropane product may undergo vinyl-cyclopropane rearrangement.



Scheme 13: <u>Reagents and conditions</u>: *a) NaH, cis 1,4-dichlorobutene, THF, rt, 8 h, 80%; ii) DIBAL-H , DCM, -78 ^{o}C, 1 h; c) $NH_2NH_2.H_2O$, NaOH, diethylene glycol, 180 ^{o}C, 8 h, 60%; d) i) $BH_3.SMe_2$, THF, H_2O_2, 3N NaOH; ii) IBX, DMSO, 12 h, 85%; e) LiHMDS, MeI, DME, HMPA, 3 h, 70%.*

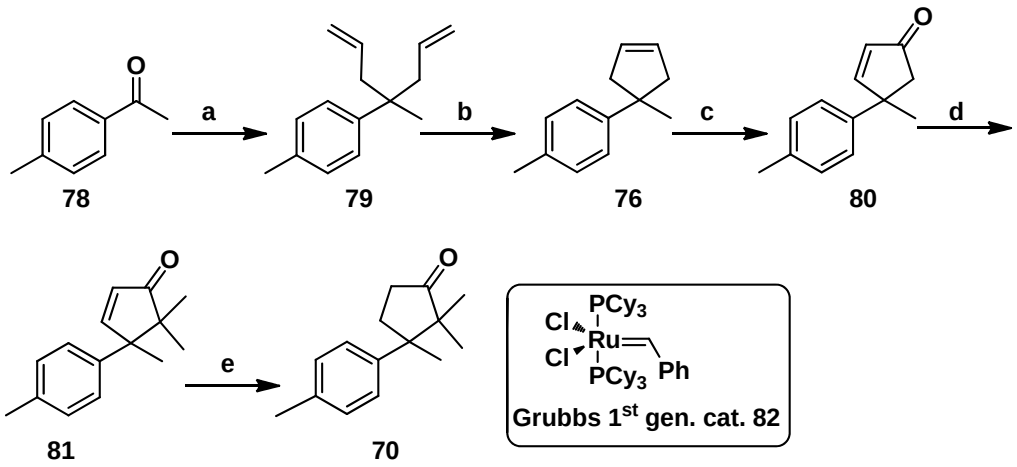
The olefin **76** was subjected to hydroboration, oxidation sequence using $BH_3.Me_2S$, H_2O_2-NaOH, IBX to give cyclopentanone **77** in 85% yield. Finally ketone **77** on selective dialkylation using LiHMDS, methyliodide furnished α- cuparenone **70** (Scheme 13).

In conclusion, one of the short and efficient synthesis of the α-cuparenone has been achieved in five steps in 28 % overall yield.

Section 3 : Synthesis of (±)-α-cuparenone employing gem-diallylation and RCM

The strategy involved a new and efficient approach for the synthesis of (±)-α-cuparenone **70**. The key intermediate **76** was synthesized utilizing gem-diallylation followed by intramolecular ring closing metathesis reaction.

Accordingly, synthesis started from commercially available starting material 4-methyl acetophenone **78**. Diallylation was carried out by using $InCl_3$, allyl trimethylsilane and TMS-Cl in ethylene dichloride at room temperature to afford diallyl compound **79** in 30% yield.



Scheme 27: <u>Reagents and conditions:</u> *a) $InCl_3$, Me_3SiCl, allyltrimethylsilane, EDC, 8 h, 30%. b) Grubbs cat. Ist generation, DCM, 85%; c) PDC, pyridine, 100 ^{o}C, 60%; d) NaH, DMF, CH_3I, 67%; e) H_2-Pd/C, EtOH, piperidine, 98%.*

The diallyl compound **79** was subjected to ring closing metathesis by using 1st generation Grubbs catalyst to give the cyclopentene compound **76**. Treatment of **76** with PDC in pyridine at 100 ^{o}C afforded the rearranged α, β-unsaturated ketone **80**. Dialkylation was carried out by using sodium hydride and methyl iodide in THF to afford dialkylated compound **81**. Finally hydrogenation of **81** using Pd/C in ethanol and catalytic piperidine gave target molecule **70** in quantitative yield.

In conclusion, the synthesis of α-cuparenone has been accomplished in concise and efficient fashion in five steps employing simple reaction conditions and from commercially available starting materials.

Chapter 1. Synthetic study towards camptothecin

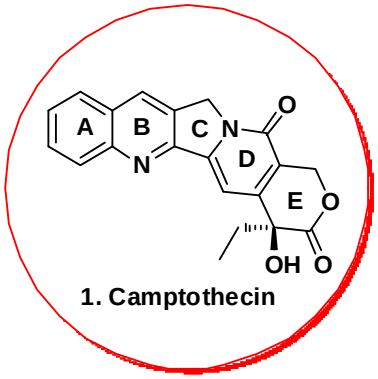
Section 1

Camptothecin: A family of alkaloids-A brief review

1.1.1 Introduction

Camptothecin **1** is a quinoline alkaloid isolated by Wall and Wani[1] in 1966 from the bark and stem of Chinese plant *Camptotheca acuminata* at Research Triangle Institute. *Camptotheca* is known by many names in China including "happy tree", "dragon tree" and "fine tree". It has been used as traditional medicine for psoriasis, leukemia and diseases of liver, gallbladder, spleen and stomach.

This invention became milestone in the area of chemical and medicinal science. Camptothecin and its analogues, collectively called as camptothecins or camptothecinoids have been isolated from various plants. Camptothecin **1** elicited extensive interest from both the academic community and the pharmaceutical industry due to its potent antitumor activity. The initial excitement quickly waned however, because of problems associated with its insolubility and toxicity (myelosupression, severe and unpredictable hemorrhagic cystitis and diarrhoea). Later studies pointed to the insolubility of camptothecin, which required the drug to be formulated as the ring-opened seco acid salt, as a key aspect in its clinical failure.

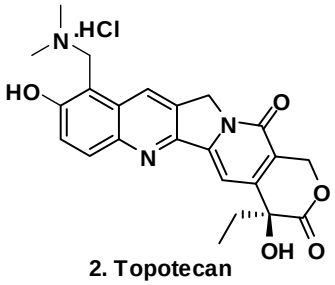


1. Camptothecin

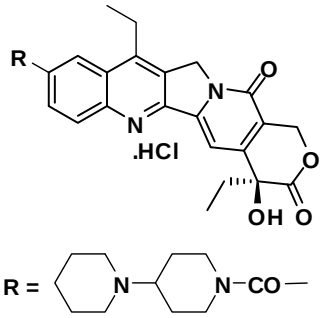
Camptotheca acuminata

Manroe Wall (left) and Mansukh Wani (right) observe a beaker of camptothecin dissolved in chloroform and methanol as it fluoresces in UV light.

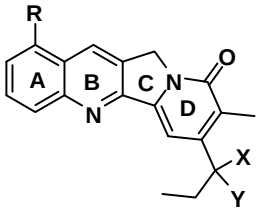
Liu and coworkers[2] in 1985 reported that camptothecin had a unique mechanism of action that concerned selective inhibition of DNA topoisomerase I. Topoisomerase I is an enzyme essential for relaxation of DNA during important cellular processes and triggers a cascade of events leading to apoptosis and programmed cell death. This disclosure served to regenerate interest in camptothecinoids and has led to the development of its analogues *viz* topotecan **2**[3] and irinotecan **3**[4] which are marketed as anticancer drugs.



2. Topotecan



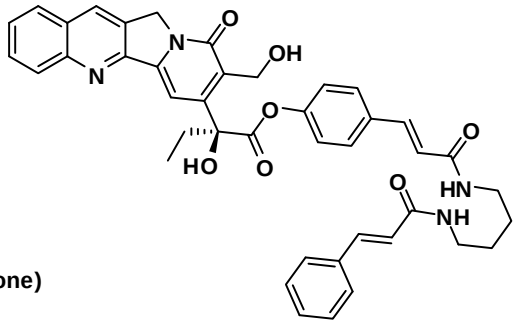
3. Irinotecan



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



7. Foetidine

Figure 1

Nothapodytine B **5** (mappicine ketone), has been recently isolated from *Nothapodytine foetida*[5] which is an oxidized form of mappicine **6** and E-ring decarboxylative analogue of camptothecin **1**, exhibited potent antiviral activities against HSV-1, HSV–2 and HCMV. One of its analogues, foetidine **7**, exhibits anti-HIV activity[6] while others are in different stages of clinical trials.

1.1.2 Structural elucidation of camptothecin

Structure of camptothecin was determined by a combination of spectral methods, chemical properties and by X-ray analysis. The compound was a high melting substance, with molecular weight of 348.11 related to the formula $C_{20}H_{16}N_2O_4$ and was optically active with $[\alpha]_D^{25}$ 31.3°. Based on the spectral and chemical properties, structure of

camptothecin was deduced to be (**1**). Later it was confirmed by formation of monoacetate **1a** on treatment with acetic anhydride, chloroacetate **1b** with chloroacetic anhydride and chloro-camptothecin **1c** on treatment with thionyl chloride and pyridine, suggesting the presence of hydroxyl group. Presence of lactone ring was confirmed by saponification to give sodium salt and its regeneration on acidification and lactol formation with $NaBH_4$.

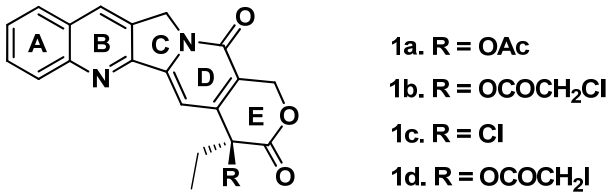


Figure 2

The X-ray crystallography of iodoacetate **1d**, prepared from chloroacetate by treatment with NaI in acetone and crystallized in orthorhombic crystals, undeniably confirmed the structure to be *S*-4-ethyl-4-hydroxy-1*H* pyrano [3', 4'; 6, 7] indolizino [1,2-*b*] quinoline-3, 14 (4*H*, 12*H*)-dione and revealed that the rings ABCD and the amide carbonyl are coplanar. The ring-E exists in a boat form and the C-20 and lactone oxygen deviate from the planarity. The absolute configuration was determined by Bijvoet's method.

Contrasting other alkaloids, camptothecin does not form a stable salt with mineral acids and shows negative tests with Dradgendroff and Meyer reagents. This indicates the neutral nature of the camptothecin. The hydroxyl group imparts electrophilic character to the lactone carbonyl, thus making it highly reactive towards nucleophilic attack by amines, aq. alkali and $NaBH_4$.

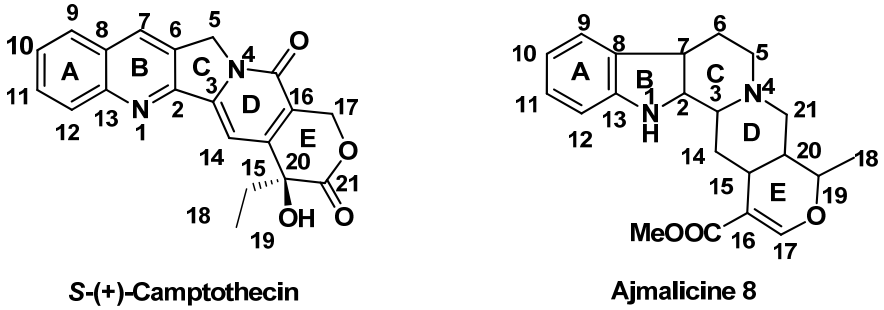


Figure 3

Le Men-Taylor[7] numbering system had been employed for camptothecin based on the close biogenetic relationship with the indole alkaloid ajmalicine **8** (Figure 3).

1.1.3 Naturally occurring camptothecins

The isolation of the novel pyrrolo-3,4-quinoline alkaloid camptothecin **1** from *Camptothica acuminata* Deane (Nyssaceae) was first reported in 1966 as part of an antitumor screening program carried out under the auspices of the National Cancer Institute of the National Institutes of Health. Due to the excellent biological activity of camptothecin several analogues**,** collectively called as camptothecins or camptothecinoids,[8] have been isolated from a variety of botanical species. Some of them hold powerful antitumor and anti-HIV properties, often more active than the parent molecule which indicates the combinatorial approach adapted by the nature for lead optimization. In light of the ongoing active development on the efforts to find new analogues of camptothecin, it is suitable to mention about some of them.

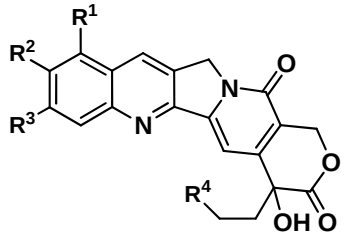


Figure 4

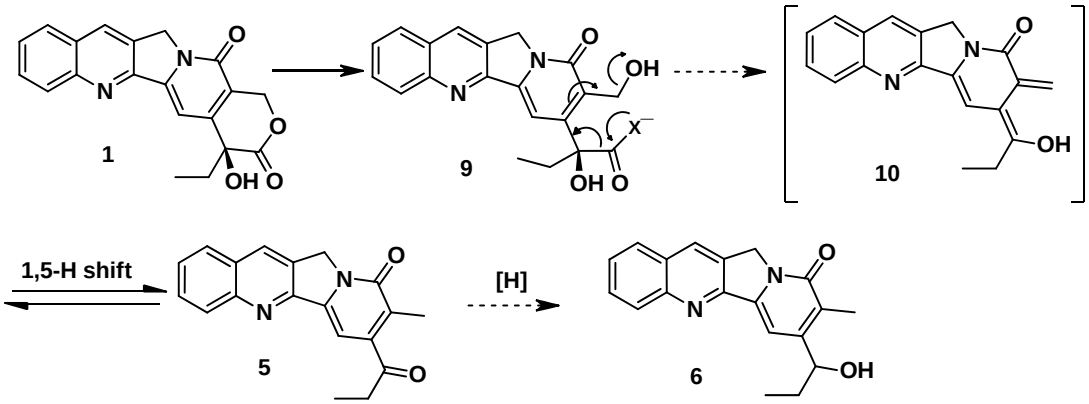
Table 1

Structure	Name	*Source*
$R^1 = R^2 = R^3 = R^4 = H$	Camptothecin (**1**)	*Camptothcea acuminata Decene*[8a] *Nothapodytes foetida*[8b] *Ophiorizamungos*[8c] *Ervatimiaheyneana*[8d] *Merrillidendronmegacarpum*[8e] *Mostucabrunonis*[8f] *Ophiorizapumila*[8g]
$R^1 = R^3 = R^4 = H$, $R^2 = OH$	10-Hydroxycamptothecin (**1e**)	*Camptotheca acuminata Decene*[8h] *Nothapodytes foetida*[8b]
$R^1 = R^3 = R^4 = R^5 = H$, $R^2 =$ OMe	10-Methoxycamptothecin (**1f)**	*Camptotheca acuminata*[8h] *Ophioriza mungos*[8c]

R^1 = OMe, R^2 = R^3 = R^4 = H	9-Methoxycamptothecin (**1g**)	*Camptotheca acuminata*[8h] *Nothapodytes foetida* *Ervatimia heyneana*[8h]
R^1 = R^2 = R^4 = H, R^3 = OH	11-Hydroxylcamptothecin (**1h**)	*Camptotheca acuminata*[8e]
R^1 = R^3 = H, R^2 = OMe, R^4 = $(COCH_2)_4Me$	20-Hexanoyl-10-methoxy camptothecin **(1i)**	*Camptotheca acuminata*[8g]
R^1 =R^2 = R^3 = H, R^4 = OH	18-Hydroxycamptothecin(**1j**)	*Camptotheca acuminata*[8j]
R^1 = OMe, R^2 = β-D-gl, R^3 = R^4 = H	Chaboside **(1k**)	*Ophioriza pumila champ*[8g]
R1 = β D-Glu, R^2 = R^3 = R^4 = R^5 = H	9-β-Glucosylcamptothecin (**1l**)	*Ophioriza pumila*[8f]

Nothapodytine A (4), Nothapodytine B (5) and Mappicine (6) : These compounds also contain A, B, C, D rings like camptothecin **1**. These were isolated by Govindachari[8b] in 1971 from Indian plant *Nothapodytes foetida* (formerly known as *Mapia foetida Miers*). Occurrence of Campothecin, Mappicine, Nothapodytine B (Mappicine ketone) and Nothapodytine A in *Nothapodytes foetida*[5] suggests that these alkaloids have a common biosynthetic precursor or it is quite possible that **1** is the precursor of **5** and **6** as shown in mechanism (Scheme 1).

Recently Nothapodytine B (**5)** has been identified as an antiviral lead compound with selective activity against HSV-1, HSV-2 and human cytomegalovirus (HCMV) with PR_{50} of 2.9, 0.5 and 13.2 μM respectively. The antiviral mechanism of Nothapodytine B (**5)** is distinct from that of acyclovir (ACV) as demonstrated by the observation that ACV-resistant HSV-1 and HSV-2 are inhibited by MPK and that MPK resistant mutants remain sensitive to ACV, which permits them to be used in a complimentary fashion to each other.



Scheme 1

Foetidine 7: It has A, B, C, D rings in common with camptothecin and differs in its E-ring having a side chain through a phenolic ester bond. It showed antitumor activity against ovarian cells A2780 WT (IC_{50}=3.4x10^{-7}) and antiviral activity against HIV viruses (IC_{50}=0.6 μg cm^3).

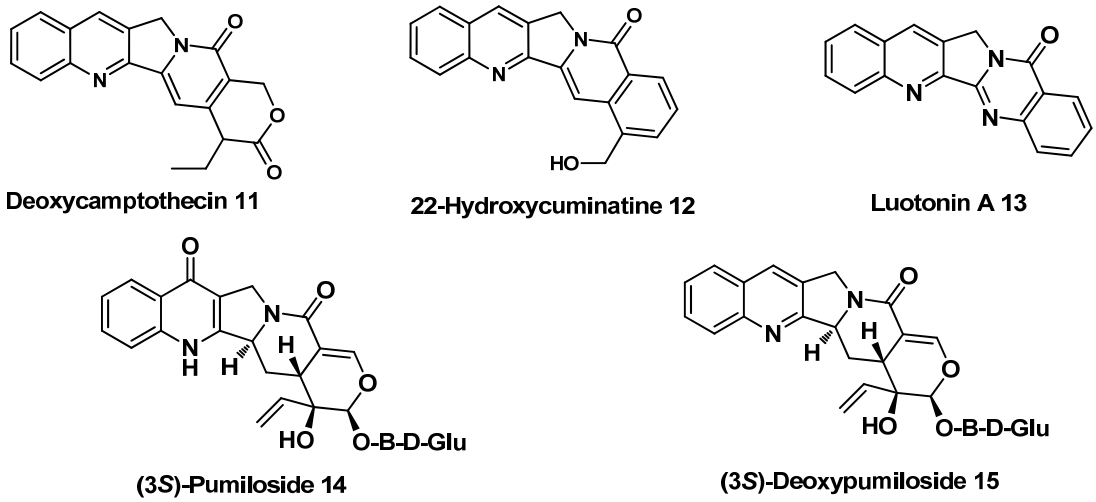


Figure 5

Deoxycamptothecin 11: Showed insignificant activity, presumably due to the lack of hydroxy group.

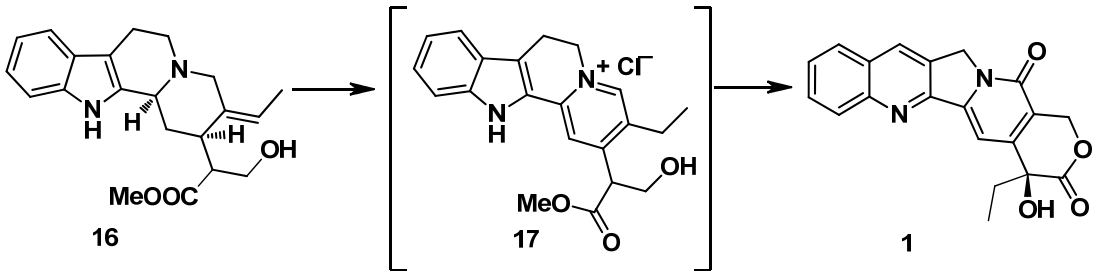
22-Hydroxycuminatine 12: It is a biogenetically novel alkaloid as A-D rings are similar to those of camptothecin. It showed cytotoxic activity against P388 and KB test systems *in vitro* with Ed50 values of 1.32 and 0.61μg /ml respectively.

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

Pumiloside 14 and Deoxypumiloside 15: Pumiloside was postulated as the post strictosamide intermediate of camptothecin biosynthesis.

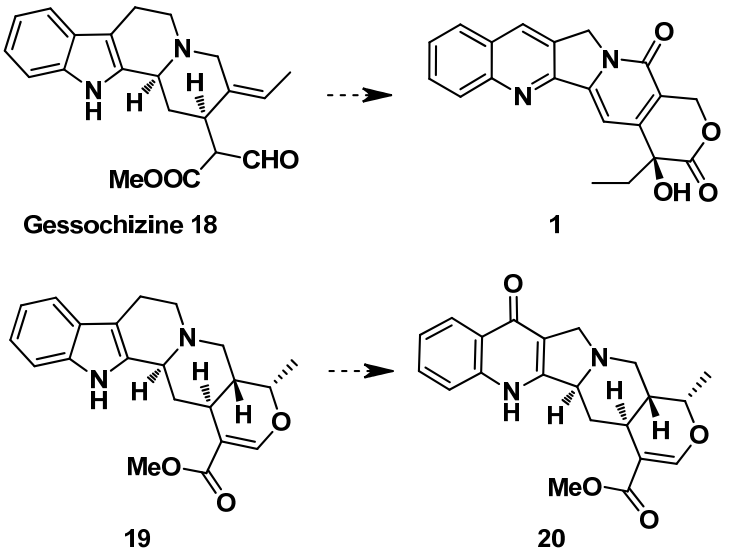
1.1.4 Biogenesis

Wenkert *et al.*[9] speculated camptothecin to be a monoterpenoid alkaloid, a masked indole alkaloid of Corynantheidine type. The plausible chemical sequences from isositstrikine **16** to camptothecin would include oxidation to **17**, D-ring unraveling, reclosing and adjustment in the final oxidation states of the carbons (Scheme 2).



Scheme 2

Winterfield *et al.*[10] proposed gessiochizine **18** as a more likely intermediate based on his findings of indole alkaloid **19** oxidation to quinoline **20** (Scheme 3).

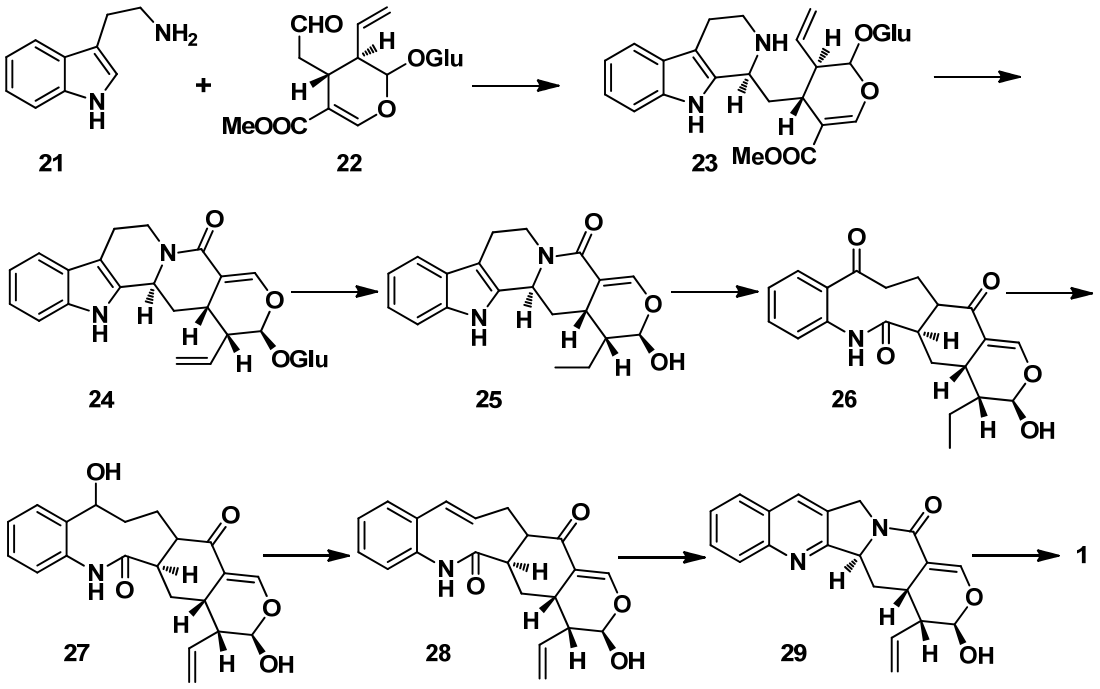


Scheme 3

Initially *in vivo* results in which the incorporation of radioactive tryptamine **21**,[11a] mevalonic acid,[11a] geraniol/nerol isomeric mixture,[11b] secologanin[11a] **22** and strictosidine[11c] **23** delivered radioactive camptothecin in apical cuttings of young seedlings of *Camptotheca acuminata* established that camptothecin was a monoterpene indole alkaloid.

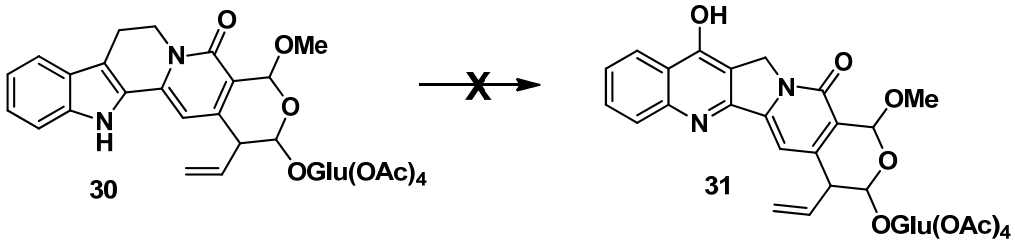
Heckendrof *et al.* fed the isotopically labeled precursors and confirmed strictosidine **23** as the specific precursor and eliminated epimeric (H-3-beta) vincoside.[11d]

Radiochemically labeled strictosomide **24** was also tested and efficient incorporation was observed in camptothecin. An easy conversion of strictosidine **23** into strictosomide **24** under basic condition and its structural similarity to camptothecin also indicated strictosomide **24** as main biosynthetic precursor of camptothecin[12] (Scheme 4).



Scheme 4

Hence, mevalonate is converted into secologanin **22** *via* geraniol and loganin, which combines with the tryptamine **21** to give strictosidine **23** which in turn is transformed into strictosomide **24**. The formation of camptothecin from **24** 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[13] wherein they found that the removal of the glucose unit occurred after the formation of strictosamide **24**. This possibility depends on the biosynthetic fate of strictosidine **23** in other plants.[14]



Scheme 5

Actually the conversion of pyridone **30** to quinoline **31** would not realize (Scheme 5), suggested that prior to D-ring oxidation BC rearrangement takes place. The mechanism of rearrangement is not still understood. It is assumed that indole moiety gets opened by oxidative cleavage into the ketolactam **26**, which in turn is reduced to alcohol **27**, followed by dehydration and subsequent ring closure *via* stepwise ionic or concerted electrocyclic process that results in formation of **1** (Scheme 4).

1.1.5 Pharmacology

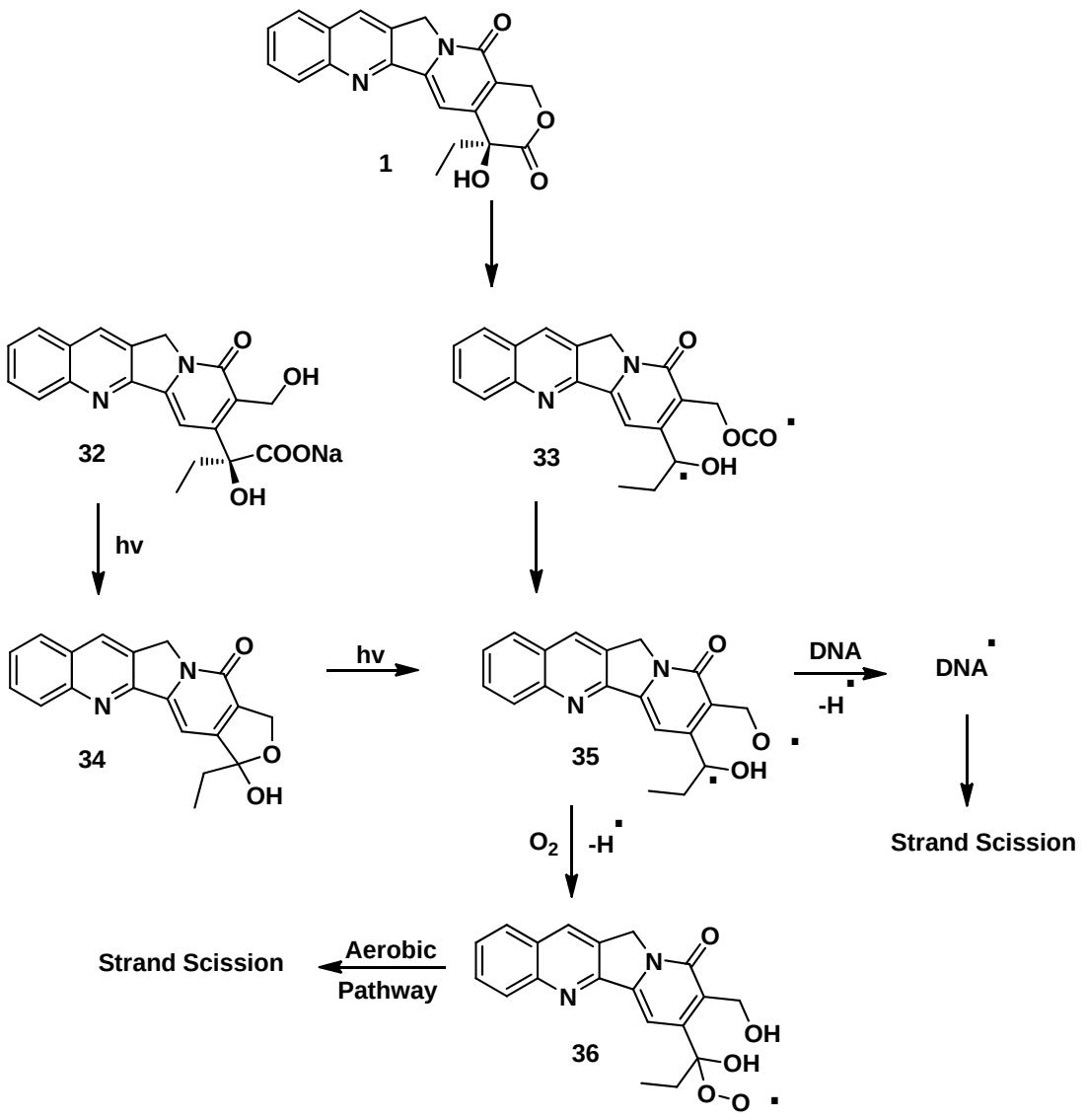
Camptothecins, topoisomerase I inhibitors, are proving useful against a range of refractory tumors, most prominently against some colon and ovarian cancers.[15] Two of the camptothecins, topotecan and irrinotecan have received Food and Drug Administration approval and several others are in clinical trials. Camptothecin is active against MDRI-tumors, hence it has broad spectrum of antitumor activity.[16] Camptothecin inhibits replication of both SV40[17] virus and adenoviruses.[18] Camptothecin inhibits retroviruses such as the HIV and the equine infectious anaemia virus.[6] The anti-HIV activity is due to the inhibition of TaT-mediated transcription from the viral promoter.

Camptothecin and its analogues also have significant activity against *Trypanosoma brucei*, the causative parasite of African trypanosomiasis.[19] Camptothecin possesses activity against the malarial parasite[20] as well. Leishmaniasis, a spectrum of disease caused by the Leishmania parasite, is treated by antimony-based drugs which are normally considered to operate by topo-I inhibition which led to the hope that camptothecin would be better lead to be tested as antileishmenial agents and trials are on in this direction. Camptothecin is also used in China for the treatment of psoriasis, a skin disease.

1.1.6 Mode and mechanism of action

The impressive activity of camptothecin has led to intensive investigation into its mode of action. Camptothecin was shown to inhibit both DNA and RNA syntheses. Inhibition of DNA synthesis appears to be irreversible while inhibition of RNA synthesis is highly reversible. Another striking effect of camptothecin is its rapid fragmentation of chromosomal DNA. All the cellular effects of camptothecin remained unexplained until the identification of topoisomerase I 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.[21] During this time, Liu and coworkers, 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, catalyzes the topoisomerisation reactions of DNA *viz.* relaxation/supercoiling, knotting/unknotting and catenation/decatenation *via* transient enzyme linked single strand break. Generally the cancer cells are more prone to topoisomerase I inhibition compared to the normal cells because they contain a higher concentration of the enzyme.



Scheme 6

Topoisomerase I is responsible for the fast growth and reproduction of cancer cells therefore, the affinity of camptothecin for topoisomerase I translates 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 regenerates 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 cell death. The cleavable ternary complex structure is very important for elucidation of the mechanism of action and development of new topoisomerase inhibitors.[2, 22] Lewn *et al.*[23] proposed a free radical mechanism as shown in scheme 6.

1.1.7. Structure-activity relationship study of camptothecin

Initially it was reported that the entire planar pentacyclic ring structure (A-E rings) of camptothecins having one chiral center at C20 position is essential for the antitumor activity. Succeeding to the identification of cellular target as Topoisomerase I and mechanism of action, camptothecin became a valuable lead for cancer treatment. Recent structure-activity studies led to identification of number of analogues with improved antitumor activity on modification at different positions. In this section detailed study of SAR is discussed.

The stereochemistry at C-20: The stereochemistry at C-20 is very important for its activity as 20(*S*) hydroxy camptothecin is active while 20(*R*) hydroxy camptothecin is inactive.[24] Cushman and coworkers[25] demonstrated that the preferred conformation of camptothecins has the 20-Et pseudo axial while the 20-OH is pseudo equatorial based on quantum mechanical study.

Modification in A and B rings: In general analogues with substitution on rings A and B especially at C7, C9, C10 and to some extent C11 showed good biological activity with improved physical and pharmacological properties, while analogues with substituent at position C12 were completely inactive.[26] This is due to the possibility that camptothecin may bind to an enzyme or enzyme-DNA complex on the face proximal to the C11 and particularly to the C12 region. Hence groups substituted at this position may cause unfavorable steric and stereoelectronic interaction. Substitutents at position C9 and C10 are more distant from this region and hence substitution at this location is favorable. However, a 10, 11-methylenedioxy or ethylenedioxy 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.

Topotecan **2** and Irinotecan **3** have passed through clinical trials and are now being used for the treatment of solid tumors after the approval of FDA. The camptothecin *N*-oxide **37** showed decreased activity indicating the importance of quinoline nitrogen for biological activity.[27] Rubitecan **38** serves as a metabolic precursor to 9-amino camptothecin **39** and currently it is in phase III clinical trials for the pancreatic cancer.[28] Lurtotecan **40** and exatecan mesylate **41** are the most successful derivatives of camptothecin **1** and presently they are in clinical trials for breast, colorectal and small cell

lung cancers.[29] Hexacyclic camptothecin analogues like **42** exhibited antitumor activity superior to those of pentacyclic ring system, probably due to the increased planarity exerted by an additional ring.[30] 7-Ethyl-10-amino camptothecin[31] **43** shows comparable activity to that of camptothecin (Figure 5).

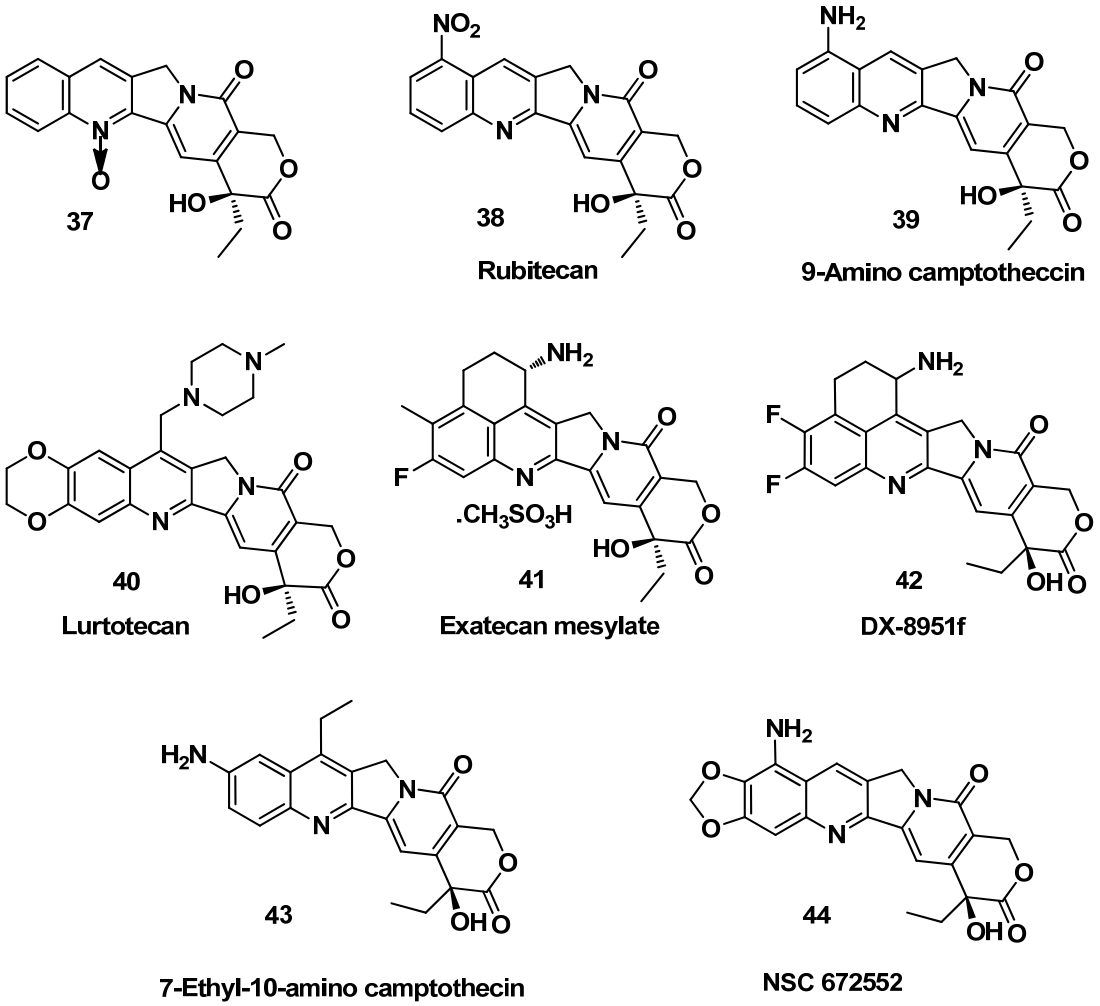


Figure 5

The heteroatomic analogues **45**[26a] and tetrahydrocamptothecin **46**[32] show less activity than parent camptothecin. This suggests that the quinoline moiety is essential for biological activity. The DE-310 **47** is a prodrug which is especially conjugate and polymer bound camptothecin, 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[33] (Figure 6).

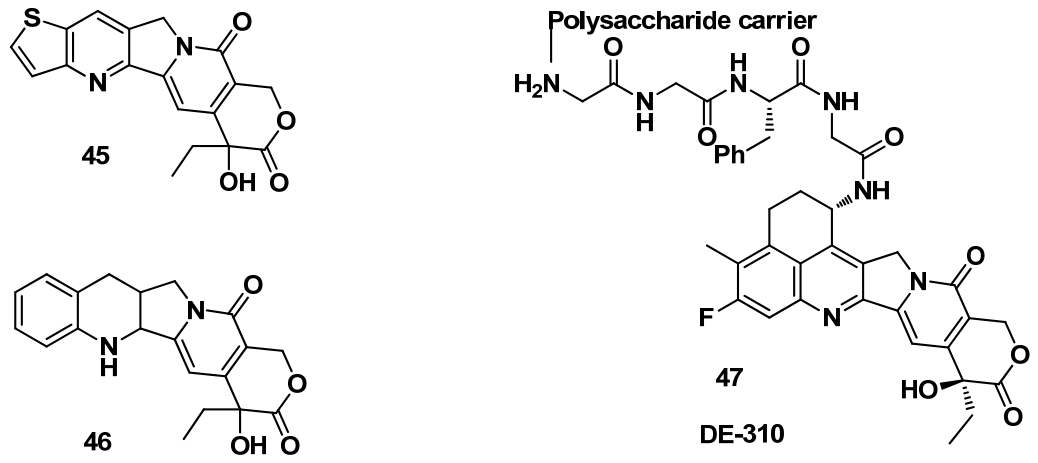


Figure 6

Modification in C and D rings: Modification at C and D ring has not shown much success. The C-nor-4, 6-secocamptothecin **48**[34] and compounds **49** and **50** with the modifications at C-5 have been reported to result in less or loss of activity,[35] it might be due to loss of planarity which is essential for enzyme-DNA-camptothecin ternary complex stabilization. The azacamptothecin **51** is the hybrid of Luotonin A **13** and camptothecin **1**. It showed promising cytotoxicity due to its shape and planarity.[36] Reduction of 17-carbonyl in **52** leads to loss of its activity. This evidence indicates that the pyridine carbonyl and pyridone ring is essential for receptor binding[37] (Figure 7).

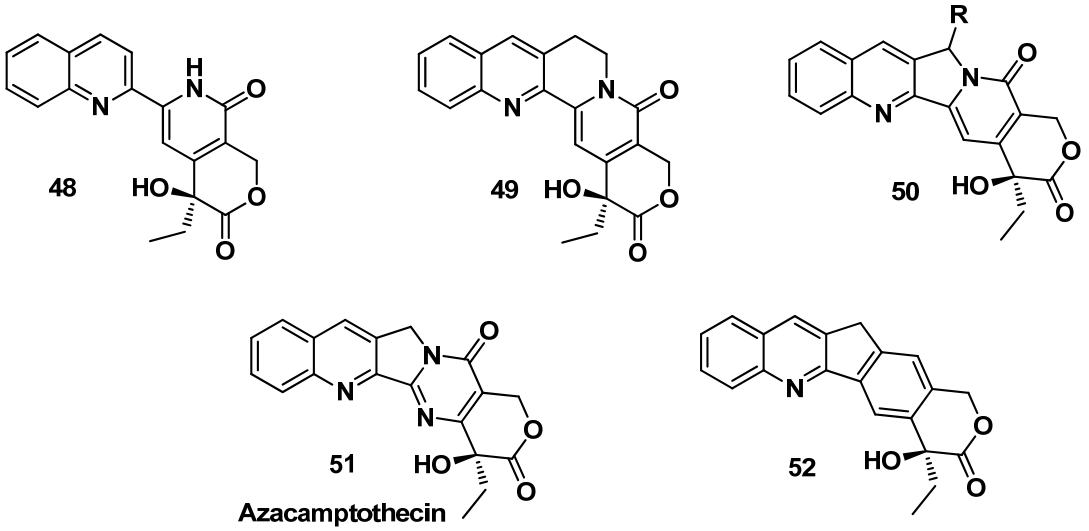


Figure 7

Modification in E ring: Structure-activity relationship studies (SARs) pointed out that the ring opened carboxylate form of several camptothecin derivatives have been shown to be significantly less active.[38] The camptothecin lactone ring undergoes facile hydrolysis and equilibrates with its ring-opened form even at the physiological conditions (Figure 8).[39] The sodium salt of the carboxylate **53** form of camptothecin was only one tenth active than that of **1** when administered intravenously (Figure 8).

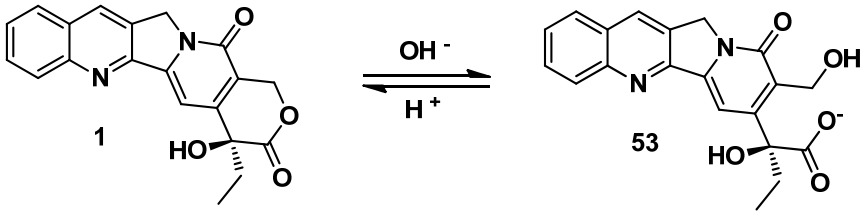
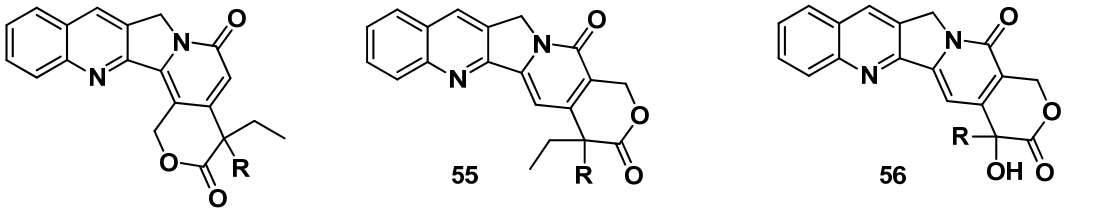


Figure 8

Isocamptothecin **54a**[26a] showed slight activity while isohomocamptothecin **54b**[40] exhibited no activity, replacement of C-20 'OH' group in camptothecin by N_3, NH_2, Cl, H, ethyl, hydroxymethyl and allyl moieties **55**[41,26a] showed no activity. Replacement of C-20 ethyl group of camptothecin **56** by allyl, propargyl, benzyl and methoxyethyl shows no marked change in activity while replacement by benzoyl group showed reduced activity suggests that ethyl group in **1** can be replaced by an appropriate functionality (Figure 9).[41a]



54a R = OH
54b R = CH_2OH

R = N_3, NH_2, Cl, H, Et, CH_2OH, allyl

R = allyl, propargyl, benzyl, methoxyethyl, benzoyl

Figure 9

The lactol **57**,[27] lactam **58**[37] and aminal **59**[38b] (Figure 10) showed no antitumor activity. This indicated that intact lactone ring might be essential for camptothecin's activity. Sugasawa reported that ester **60** showed activity comparable to racemic camptothecin.[41a] The thiolactone **61** has also been reported with activity,[38] the phosphate monoester compound **62** was very toxic, though it was less powerful than camptothecin[40b] (Figure 10).

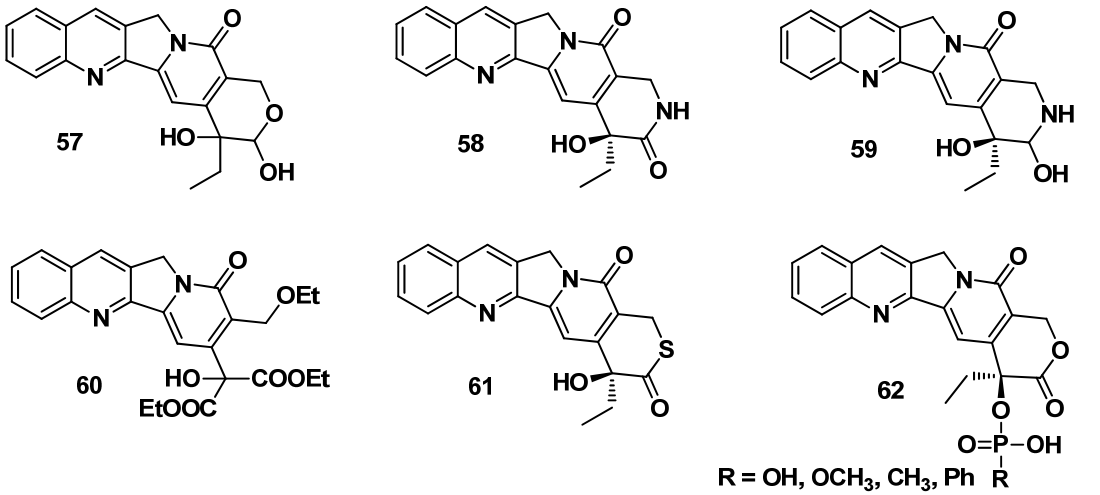


Figure 10

Apart from lactone and lactam E-ring, series of cyclopentyl E-ring analogues like **63, 64** and **65** have been synthesized and evaluated (Figure 11).[42]

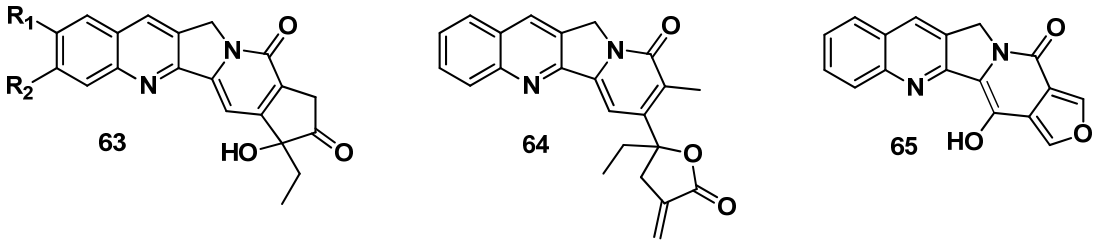


Figure 11

<u>Homocamptothecin:</u> Lavergne *et al.*[43] in 1997 reported new analogues with an expanded *β*-hydroxy lactone ring called homocamptothecin **66** (Figure 12). The lactone ring of camptothecin opens rapidly and reversibly while lactone ring of homocamptothecin opens very slowly and irreversibly. Therefore homocamptothecin molecules exhibit high plasma stability in the biological system and most importantly they are much more cytotoxic than camptothecin.

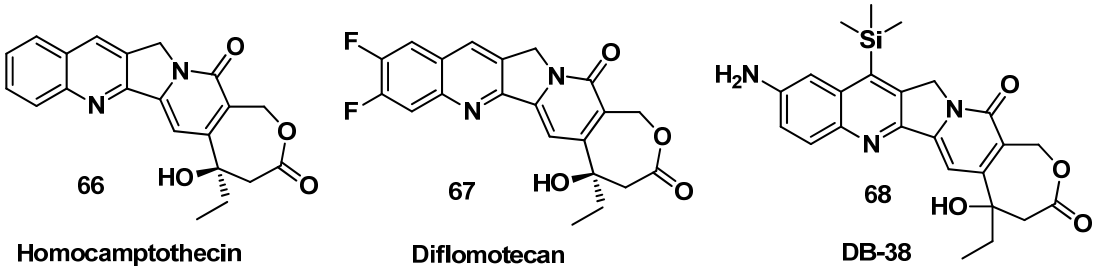


Figure 12

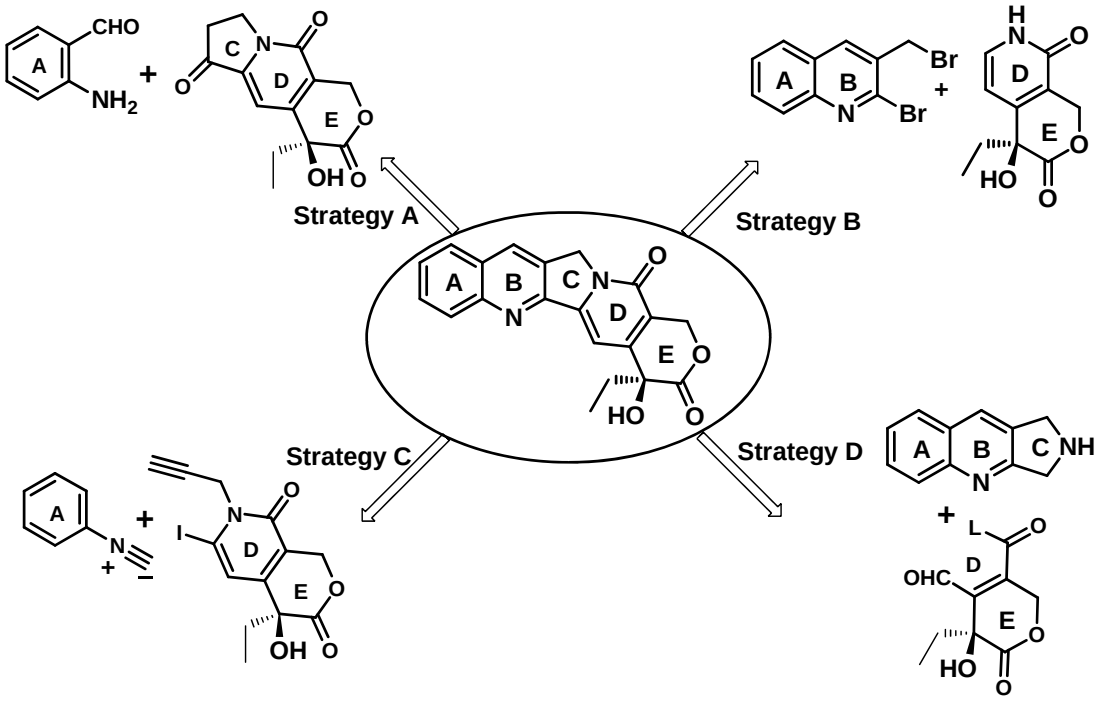
Novel analogues of homocamptothecin such as fluorinated homocamptothecin **67** and silylated homocamptothecin **68** are much more potent than parent homocamptothecin **66**.[44]

Thus research of camptothecins exemplifies drug development, which within a few years progressed from a laboratory interest to clinical application. Despite enormous efforts in this area, however, many aspects of the cytotoxycity and antitumor activity of camptothecins remain unclear and demand further continuation of the quest for the identification of the better lead.

1.1.8 Synthesis of Camptothecin: A Literature Survey

Attributable to excellent biological activity and challenging pentacyclic ring structure of camptothecin including a pyrrole (3,4β) quinoline moiety and having one chiral centre within the α-hydroxy lactone ring with 20(*S*)-configuration (ring-E), many research groups are attracted towards the synthesis of camptothecin[45] and its analogues. As a result, variety of total syntheses involving inventive adaptations of classical reactions as well as new chemistry inspired by the camptothecin as a target were accomplished and based on their strategic similarities, they are categorized under four groups (Scheme 7).

Major synthetic approaches are roughly classified as A) Broadly applied Friedlander condensation approach. B) C-ring construction approach. C) The cascade radical cyclization approach. D) Various Michael addition approaches and various Diels–Alder reaction approaches. Each of these synthetic routes represents either a highly efficient and practical synthesis of camptothecin, a pioneering development of new synthetic methodology, or a unique synthetic approach.



Scheme 7

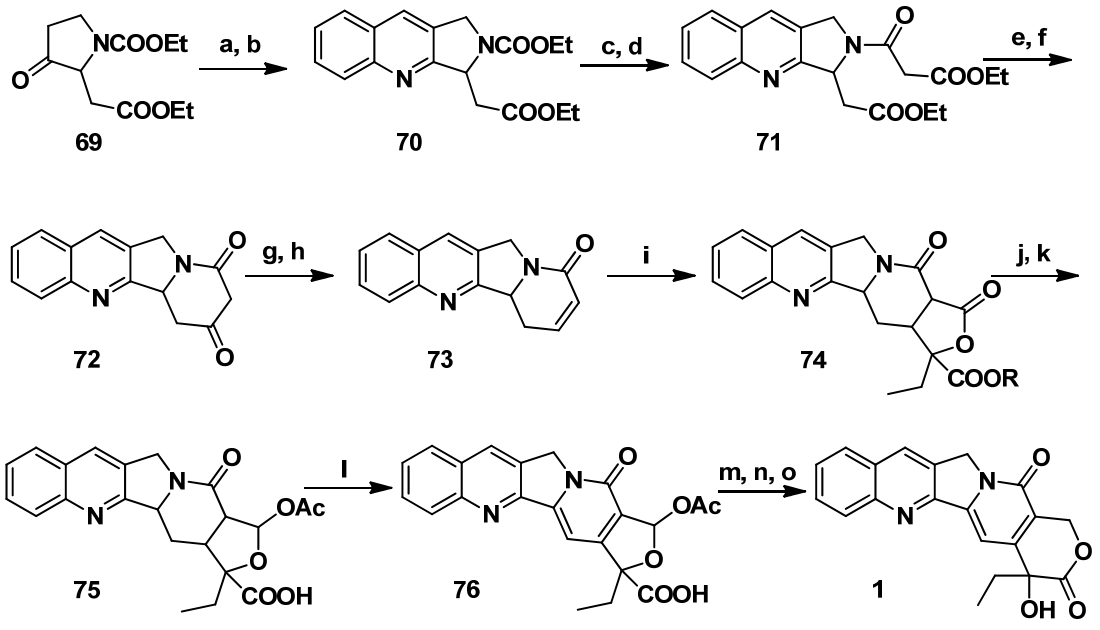
Among these four strategies, strategies A and B emerged during the "classical era of Camptothecin" while strategies C and D are contemporary and reflect recent advances in synthetic technology.

Since review on synthesis of all categories up to 2007 has been covered by Venkat,[46a] Sivappa,[46b] Pasupathy[46c] and Pathak[46d] from this group, synthesis of racemic and optically pure camptothecin reported after 2006 and representative synthesis of each strategy has been described in this present section.

Stork's Approach

Five years after the isolation of camptothecin, Stork and coworkers[47] reported the first racemic synthesis of camptothecin.

Scheme 8: Stork *et al*. *J. Am. Chem. Soc*. **1971**, *93*, 4074.



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, ethyl 2-((ethoxycarbonyl)oxy)butanoate, -78 ºC; j) i) Con. HCl; ii) $NaBH_4$, rt, 20 h; k) Ac_2O, pyridine; l) DDQ, 1,4- dioxane; m) 0.1N NaOH; n) $NaBH_4$; o) dil HCl.*

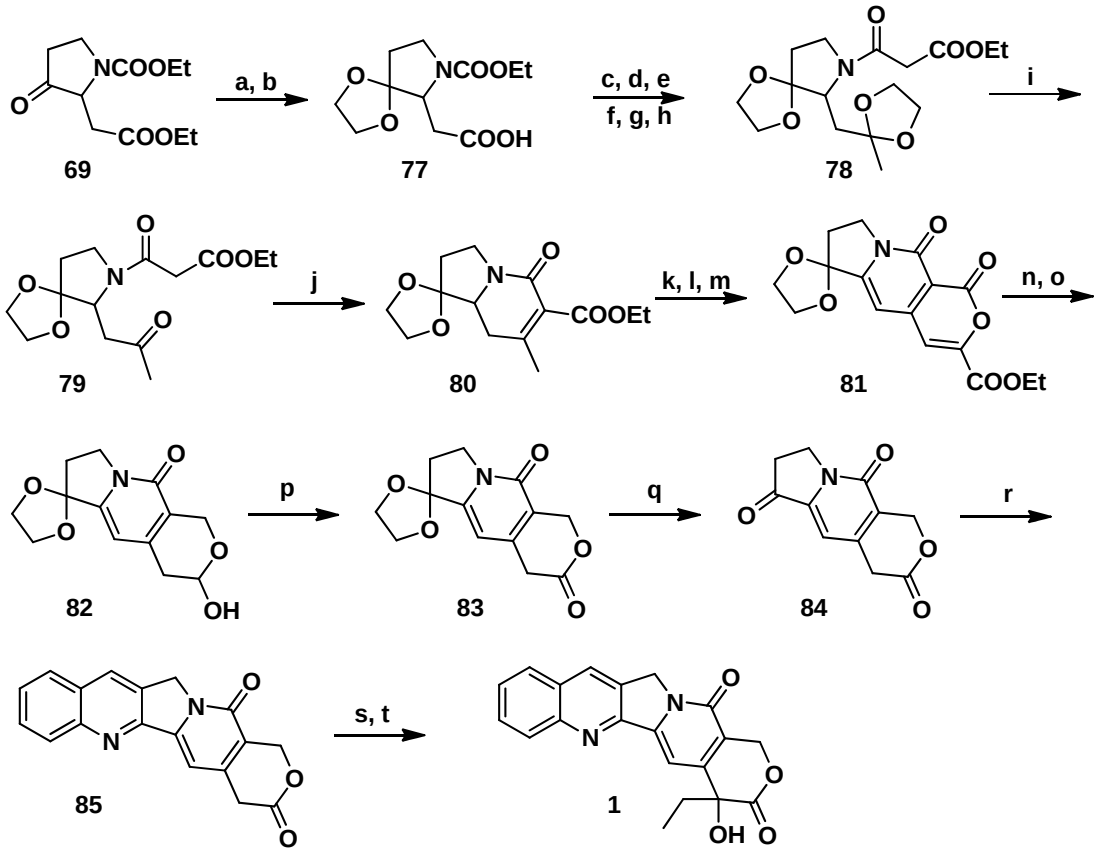
Thus the base catalyzed Friedlander condensation of pyrrolidine **69** with 2-amino benzaldehyde afforded the tricyclic quinoline ester **70**. The amino-ester resulting from the hydrolysis of **70** followed by protection with ethyl malonyl chloride furnished the diester

amide **71**. The tetracyclic *β*-keto ester obtained by the intramolecular Dieckmann condensation of **71**, was subjected to decarboxylation, reduction and elimination to give the desired dihydropyridone **73**. The unsaturated lactam underwent smooth intermolecular Michael addition efficiently at low temperature to afford the crucial pentacyclic lactone **74**. Finally, hydrolysis of the ethyl ester of **74** followed by reduction and protection gave the lactol **75**, which upon oxidation with DDQ gave pyridone **76**. Hydrolysis, reduction followed by lactonization gave the (±)-camptothecin **1**. The synthesis was achieved in 15 steps with an overall yield 1-2% employing 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 as key steps.

Shamma's Approach

Shamma *et al.*[48] reported the synthesis of camptothecin *via* tricyclic lactone **84**. An intramolecular aldol condensation has been employed for the construction of pyridone ring.

Scheme 9: Shamma *et al. Tetrahedron,* **1973**, *29*, 1949.



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 ^{o}C; j) NaOEt, 0 ^{o}C; 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.

The pyrrolidinone **69** was protected as its ethylene glycol acetal. Hydrolysis of ester gave the corresponding acid **77** in 91% yield. 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 **78** in 91% yield. Deprotection to methylketone **79** was effected using acetic acid at 60 ^{o}C. Aldol condensation using sodium ethoxide furnished dihydropyridone **80** in 83% yields. Oxidation to pyridone using DDQ followed by condensation with diethylmalonate and esterification furnished pyridone **81** in 65% yield. Sodium borohydride reduction followed by periodate oxidation provided lactol **82**. Oxidation to lactol **82** using Pt/O_2 and deprotection of acetal using oxalic acid gave ketone **84** in 57% yield. Friedlander condensation with *o*-amino benzaldehyde gave lactone **85** which on ethylation and oxidation furnished (±)-**1**.

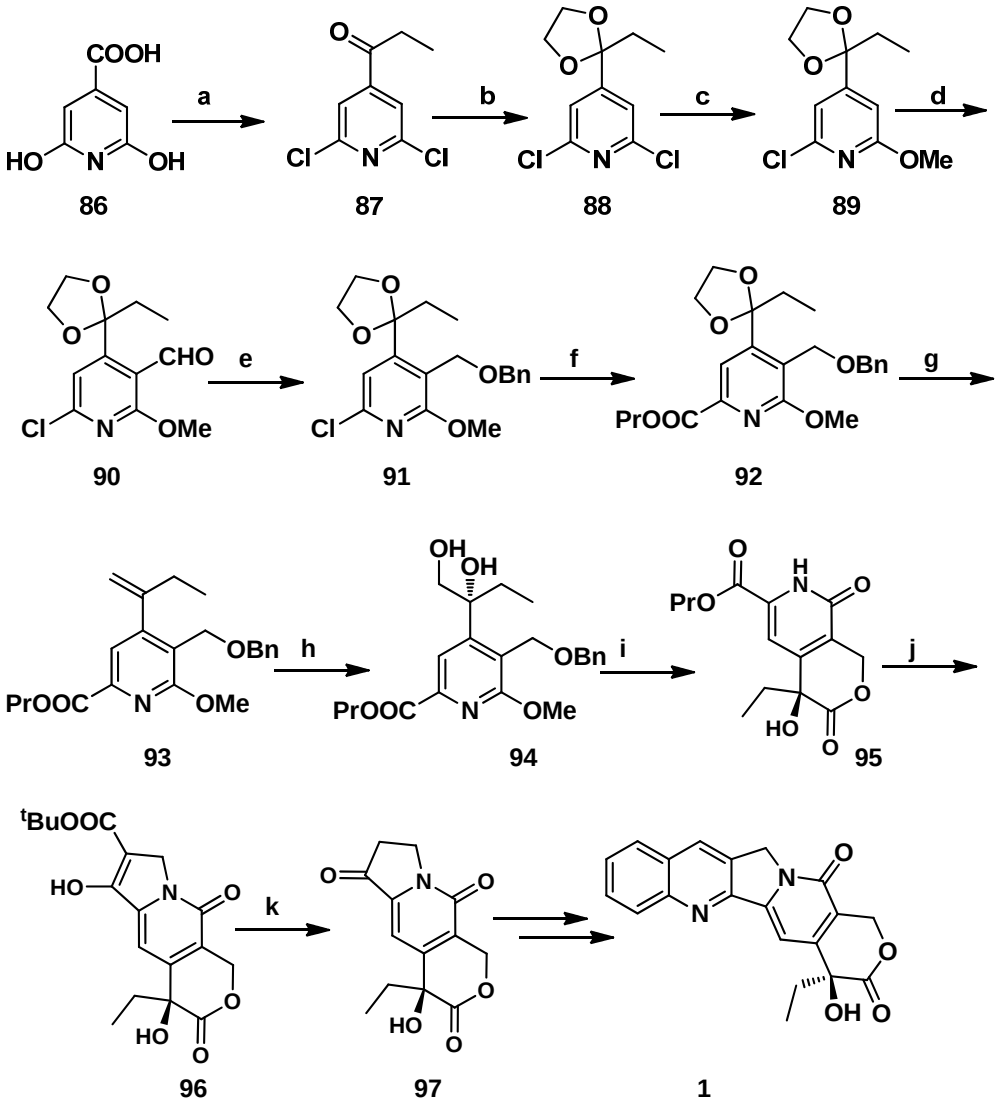
Henegar's Approach

Heneger and coworkers[49] developed a practical synthesis of camptothecin *via* tricyclic synthon **97** starting from readily available citrazinic acid **86**.

Synthesis started from citrazinic acid **86** which was converted to dichlorocitrazinic acid by treatment with $POCl_3$, which was in turn reacted with ethyl magnesium bromide to obtain ethylketone **87.** Keto protection of **87** with ethylene glycol to afford **88**, followed by dissymetrization of the acetal using NaOMe afforded **89**. Ortholithiation, followed by treatment with DMF afforded aldehyde **90**. Reduction of aldehyde **90** with $NaBH_4$ and the protection of thus formed alcohol with benzyl bromide afforded benzyl ether **91**. Benzyl ether **91** was carbonylated by reaction with CO, $Pd(OAc)_2$, DPPPA, 1-propanol and potassium acetate in DMF to afford **92**. Compound **92** was deprotected to ketone using TFA and olefinated with phosphorane to afford olefin **93.** Dihydroxylation of olefin **93** gave racemic diol, which was resolved by acetylation with isopropenyl acetate/amino PS-309 lipase immobilized on celite to afford **94**. *S*-Diol **94** thus obtained in 99% *ee* was converted to compound **95** in four high yielding steps. 1) Oxidation of primary -OH to

aldehyde with NaOCl/TEMPO, 2) hydrogenolysis of benzyl ether to lactol with Pd/C, 3) TEMPO oxidation of lactol to lactone, 4) Deprotection of *O*-methoxy group of methoxy lactone with TMSI.

Scheme 10: Henegars *et al. J. Org. Chem.* **1997**, *62*, 6588.



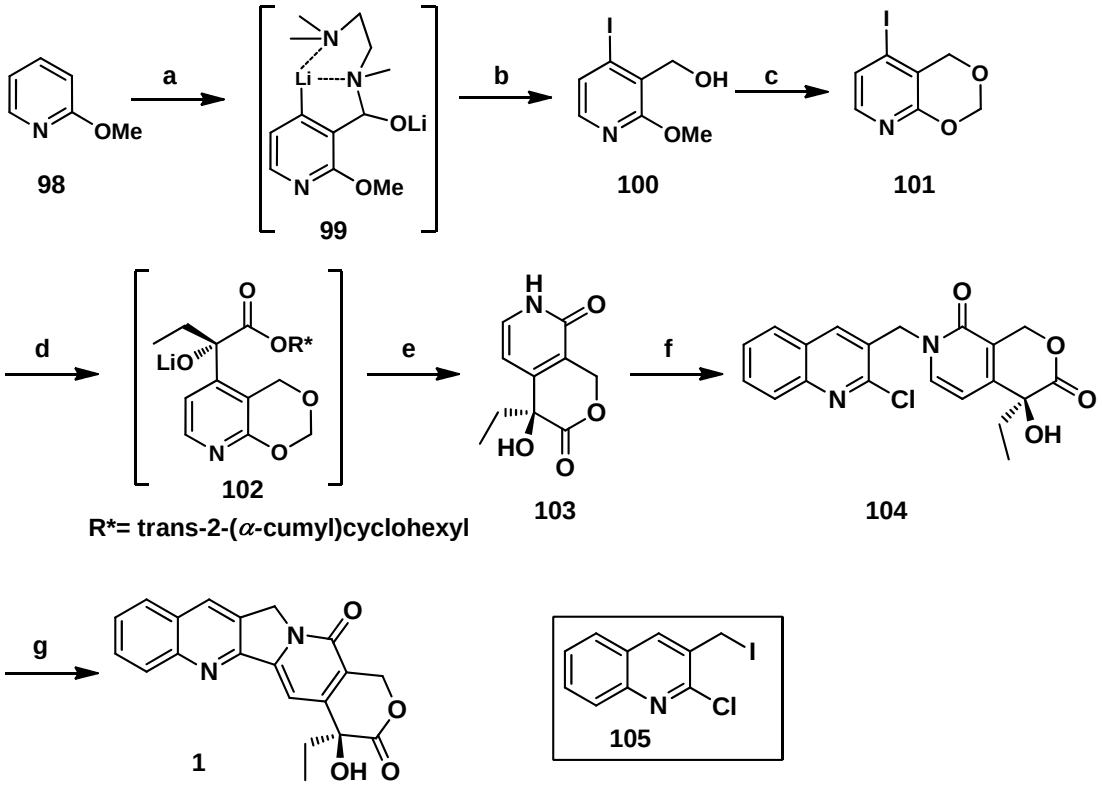
Reagents and conditions: *a) i) $POCl_3$, Me_4NCl, 78%; ii) EtMgBr, 84%; b) 1,2-Ethanediol, TMSCl, 99%; c) CH_3ONa, 65 ^oC, 89%; d) i) RLi; ii) DMF; e) i) $NaBH_4$, 99%; ii) BnBr, t-BuOK, 99%; f) CO, $Pd(OAc)_2$, DPPP, DMF, KOAc, n-PrOH, DMF, 90 ^oC, 89%; g) i) 50% TFA, 99%; ii) Ph_3PCH_3Br, KHMDS, DMF, 92%; h) i) OsO_4, $Me_3NO.2H_2O$, t-BuOH, 45 ^oC, 92%; ii) PS-30 catalyst, isopropenyl acetate, MTBE, 38%; i) i) NaOCl, TEMPO, 95%; ii) H_2, Pd/C, 92%; iii) NaOCl, TEMPO, 95%: iv) TMSCl, NaI, 85%; j) t-Butyl acrylate, Cs_2CO_3, DMSO, 75%; k) TFA, toluene, 95%.*

Annulation of cyclopentanone ring was done using *t*-butyl acrylate and cesium carbonate to afford **96** and decarboxylation of **96** with TFA afforded **97**, tricyclic synthon in 99.6% *ee* (18 steps from **86** and 6.4% overall yield).

Comins Approach

Comins and coworkers[50] reported a short (six steps) synthesis of (*S*)-camptothecin starting from two commercially available heterocycles.

Scheme 11: Comins *et al. Org. Lett*. **2001**, *3*, 4255.



Reagents and conditions: *a) i) MesLi; ii) N*-Formyl-*N,N',N'*-trimethylethylenediamine*; iii) n-BuLi; b) i) I_2; ii) $NaBH_4.CeCl_3$, (one pot), 46%; c) TMSCl/NaI, $(CH_2O)n$, CH_3CN, 87%; d) n-BuLi, $CH_3CH_2COCOOR^*$; e) HCl, i-PrOH, 60%; f) t-BuOK,* ***105****, DME, Δ, 81%; g) $(Ph_3P)_2Pd(OAc)_2$, KOAc, CH_3CN, 64%.*

Thus, commercially available 2-methoxypyridine **98** was lithiated at C-3 with mesityllithium and treated with *N*-formyl-*N,N',N'*-trimethylethylenediamine to afford α-amino alkoxide. Addition of *n*-BuLi effected α-amino alkoxide directed lithiation[51] at C-4 to give the dianion **99**, which was treated with iodine and worked up with $NaBH_4/CeCl_3$ to obtain alcohol **100** in one pot process. Alcohol **100** was converted directly to dioxane

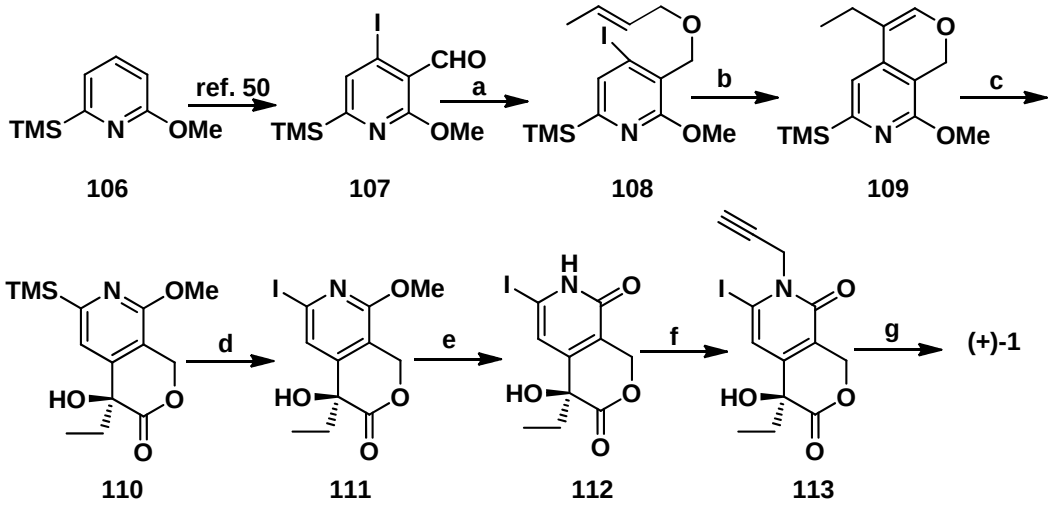
101 on treatment with NaI/TMSCl/paraformaldehyde, which upon successive treatment with *n*-BuLi followed by the addition of ketoester gave alkoxide **102** *in situ.* Addition of HCl /i-PrOH effected protonation, acetal hydrolysis and lactonization to afford the desired DE ring intermediate **103**. Commercially available 2-chloroquinoline carboxaldehyde was converted to iodide **105**.[52] The two fragments **103** and **105** were joined by treatment with *t*-BuOK in DME to provide compound **104** and the final C-ring was closed using modified Heck reaction conditions *i. e*. $Pd(PPh_3)_2(OAc)_2$ (15%), and KOAc in acetonitrile.

Authors have achieved the shortest asymmetric synthesis of camptothecin to date, involving a commercially available material which makes it a practical and amenable to the large-scale synthesis.

Curran's Approach

Curran *et al.*[53] reported the total synthesis of camptothecin employing novel 4+1 radical methodology for construction of quinoline part of camptothecin.

Scheme 12: Curran *et al. Angew. Chem. Int. Ed.* **1996**, *34*, 2683.



Reagents and conditions: *a) (E)-But-2-en-1-ol, Et_3SiH, TFA; b) $Pd(OAc)_2$, K_2CO_3, Bu_4NBr; c) i) OsO_4, $(DHQD)_2$.Pyr; ii) I_2, $CaCO_3$, 85%; d) ICl, 47%; e) aq. HI, 72%; f) Propargyl bromide, NaH, LiBr, DMF, 88%; g) Phenyl isonitrile, hexamethyldistannane, benzene, 80 ^oC, hv, 99% ee.*

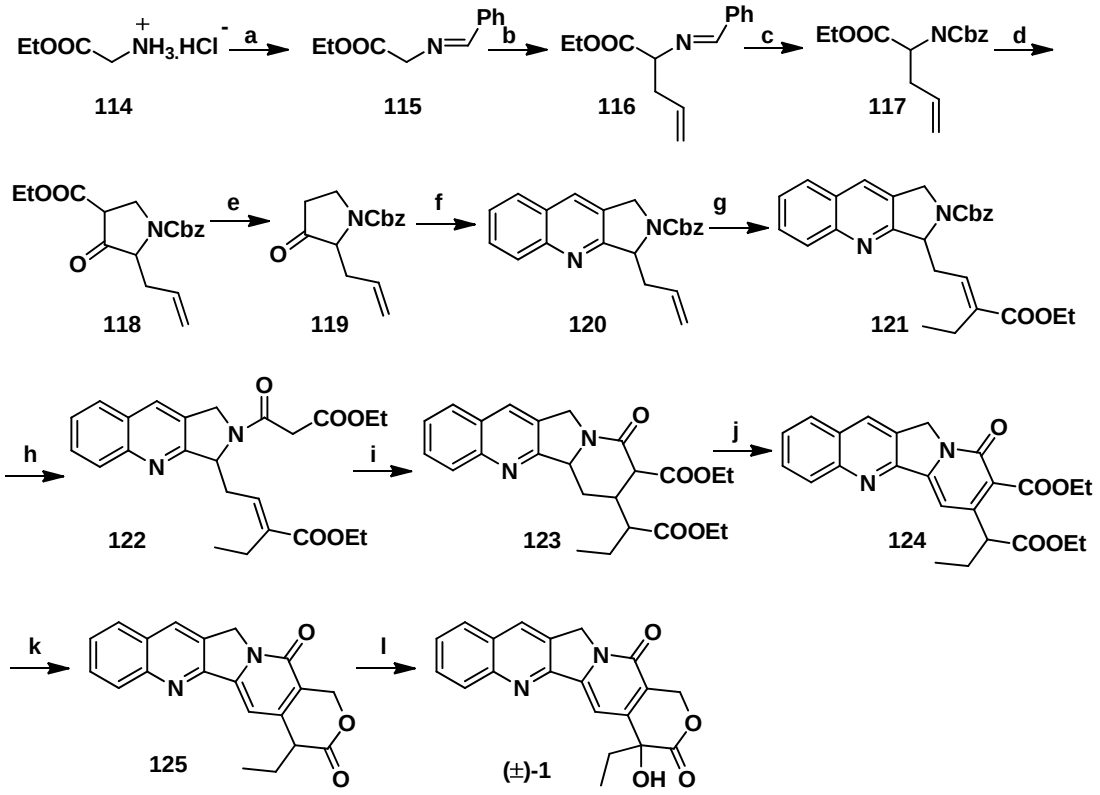
Synthesis started from pyridine **106** which was converted to iodo aldehyde **107** by using Comins conditions.[51] Triethyl silyl hydride reduction of **107** in presence of crotyl alcohol gave the crotyl ether **108** in 63% yield. Intramolecular Heck reaction of **108** using $Pd(OAc)_2/K_2CO_3$ afforded enol ether **109** in 69% yield. Asymmetric dihydroxylation

under Sharpless conditions followed by oxidation using I_2/calcium carbonate provided lactone **110** in 85% yield. Treatment with ICl converted **110** into the iodo compound **111**. Conversion to pyridone **112** was effected using either TMSI or aq. HI. *N*-Propargylation of **112** gave pyridone **113**. Radical annulations using phenyl isocyanide and bistrimethyl tin gave camptothecin **1** in optically pure form.

Chavan's 1st Approach

Chavan *et al.*[54] reported a practical and efficient synthesis of (±)-camptothecin from glycine *via* an intramolecular Michael addition for the construction of D-ring.

Scheme 13: Chavan *et al. Tetrahedron Lett*. **1998**, *39*, 6745.



Reagents and conditions: *a) Benzaldehyde, Et_3N, molecular sieves, DCM, 1 h, 98%; b) Allyl bromide, NaOH, $TBAHSO_4$, DCM, rt, 0.5 h, 97%; c) i) HCl, rt, 0.5 h, 94%; ii) CbzCl, K_2CO_3, DCM, rt, 3 h, 96%; d) i) NaH, C_6H_6, ethyl acrylate, reflux, 3 h, 65%; e) 10% HCl, reflux, 4 h; f) N-(o-Amino benzylidine)p-toluidine, PTSA, toluene, reflux, 6 h, 72%; g) i) OsO_4, $NaIO_4$, dioxane, H_2O, 4 h; ii) $PPh_3C(Et)CO_2Et$, DCM, rt, 5 h, 83%; h) i) TMSCl/NaI, CH_3CN, 1 h; ii) Ethyl malonyl chloride, K_2CO_3, DCM, 0 ºC to rt, 3 h, 66%; i)*

NaH, THF, rt, 0.5 h, 92%; j) DDQ, dioxane, reflux, 1 h, 78%; k) i) DIBAL-H, THF, -60 ºC, 83%; ii) $NaBH_4$, THF, H_2O, 0 ºC, 1 h; l) $CuCl_2$, dimethyl amine, O_2, 20 h.

Synthesis began from hydrochloride salt of ethyl ester of glycine **114**. This was converted into its Schiff's base **115** and it was alkylated with allyl bromide under PTC condition to give **116**. The imine **116** was hydrolysed and protection of the resulting amine with CbzCl yielded the urethane **117** in high yield. A tandem Michael-Dieckmann condensation furnished β-keto ester **118** which on subsequent decarboxylation gave the pyrrolidinone **119**. The pyrrolidinone **119** underwent modified Friedlander condensation with Schiff's base to furnish the tricyclic carbamate **120**. Oxidative cleavage of the double bond in **120** furnished aldehyde which was subjected to Wittig olefination with phosphonium salt to furnish the *α,β*-unsaturated ester **121**. Deprotection of carbamate of **121** was carried out employing Olah's protocol. The resulted free amine was reacted with ethyl malonyl chloride to afford the key amide **122**. The intramolecular Michael addition was carried on **122** using NaH to deliver tetrahydropyridone **123.** The tetrahydropyridone **123** was oxidized using DDQ to provide pyridone **124**. The regioselective reduction of the aromatic ester in **124** using DIBAL-H furnished the aldehyde, which on reduction using $NaBH_4$ underwent lactonization to give 20-deoxycamptothecin **125**. The hydroxylation of **125** was done employing Danishefsky's protocol,[55] utilizing oxygen as oxidant to give (±)-**1**.

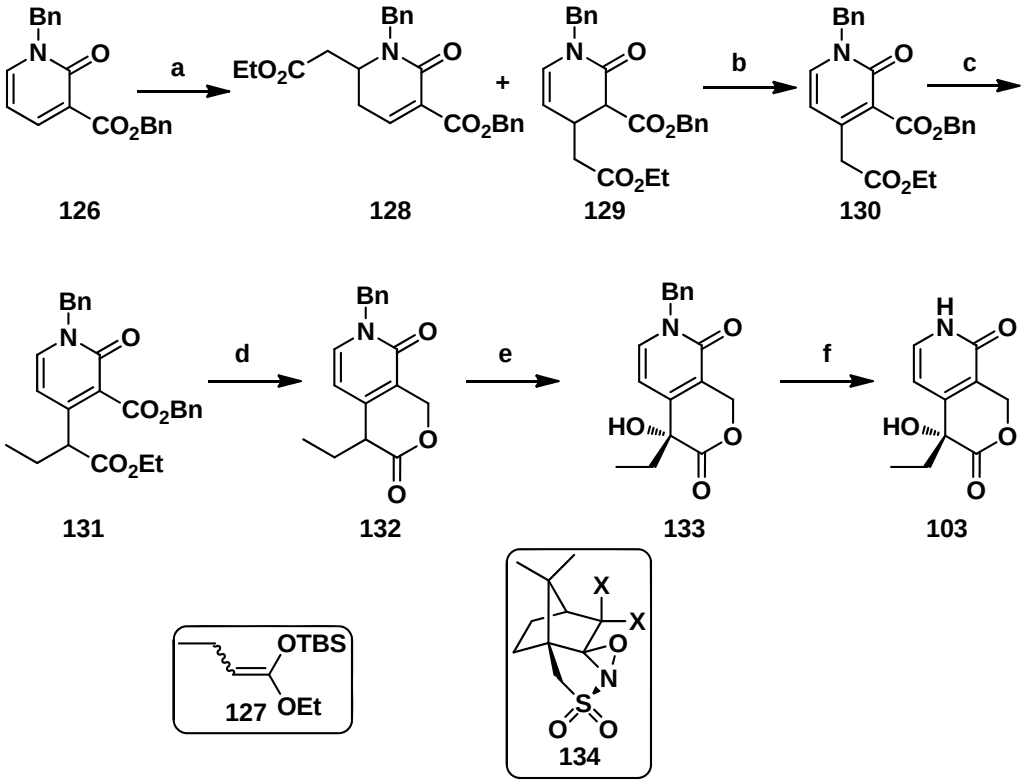
Hiroya's Approach

Hiroya *et al.*[56] reported the synthesis of DE ring system of (20*S*)-camptothecin from commercially available nicotinic acid in six steps utilizing the nucleophilic addition reaction of the silyl ketene acetal to the pyridinone ring as a key step.

The synthesis started from pyridone **126** wherein the reaction between **126** and silyl ketene acetal **127** resulted in two products, **128** and desired compound **129**. Treatment of **129** with NaH and $CuBr_2$ resulted in formation of pyridone **130.** Ethylation was carried out using LiHMDS as the base to give alkylated product **131** in 71% yield. The reduction of aromatic benzyloxy carbonyl group to alcohol and *in situ* lactonization was accomplished using $NaBH_4/CeCl_3.7H_2O$ to afford lactone **132**. Asymmetric hydroxylation of **132** was achieved using KHMDS as a base and *N*-sulfonyloxaziridine **134** as the reagent to furnish hydroxy compound **133** in 84% yield. Finally the

debenzylation was successfully carried out by hydrogenation using $Pd(OH)_2/C$ to provide (+)-**103** in 77% yield and 95% *ee*.

Scheme 14: Hiroya *et al. Synlett* **2006**, *16*, 2636.



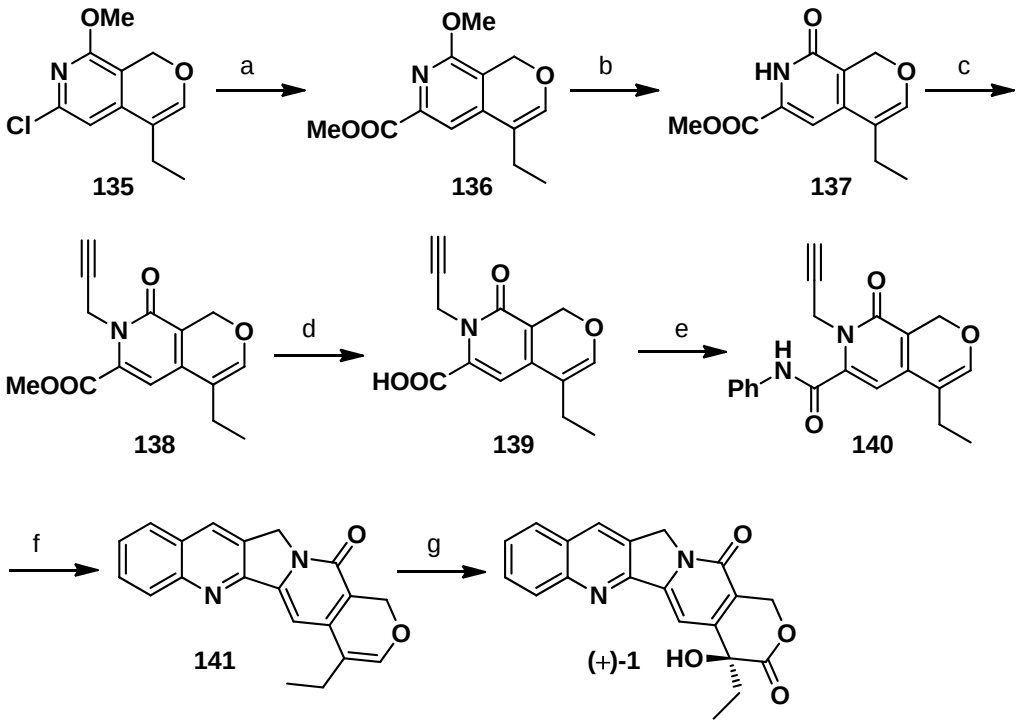
Reagents and conditions: *a) Enol ether* ***127****, Et_2AlCl, -40 ^oC, 5 h, (****128****+****129****) 80%; b) NaH, $CuBr_2$, DMF-DMSO (1:1), 0-50 ^oC, 28 h, 56%; c) LiHMDS, EtI, THF, -78 ^oC to rt, 11 h, 71%; d) $NaBH_4$, $CeCl_3.7H_2O$, EtOH, 0 ^oC, 1.5 h, then 1N HCl, rt, 8 h, 57%; e) KHMDS, N-sulfonyloxaziridines, THF, -78 ^oC, 5 h, 84%; f) H_2, $Pd(OH)_2/C$, EtOH, 50 ^oC, 3 h, 77%.*

Thus starting from commercially available pyridone, synthesis of optically active DE synthon was accomplished in six steps but the problem of regioselective addition of the ketene silyl acetal remained unresolved.

Yao's approach

Yao and coworkers[57] disclosed short and elegant synthesis of camptothecin utilizing domino reaction and Sharpless dihydroxylation in eight steps starting from known chloropyridine derivative **135**.

Scheme 15: Yao *et al. Org. Lett*. **2007**, *9*, 2003.



Reagents and conditions: *a) $PdCl_2(CH_2Cl_2)$dppf (2 mol%), CO (120 psi), Et_3N, MeOH, 97%; b) TMSCl, NaI, CH_3CN, H_2O (cat.), 5 h, 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.*

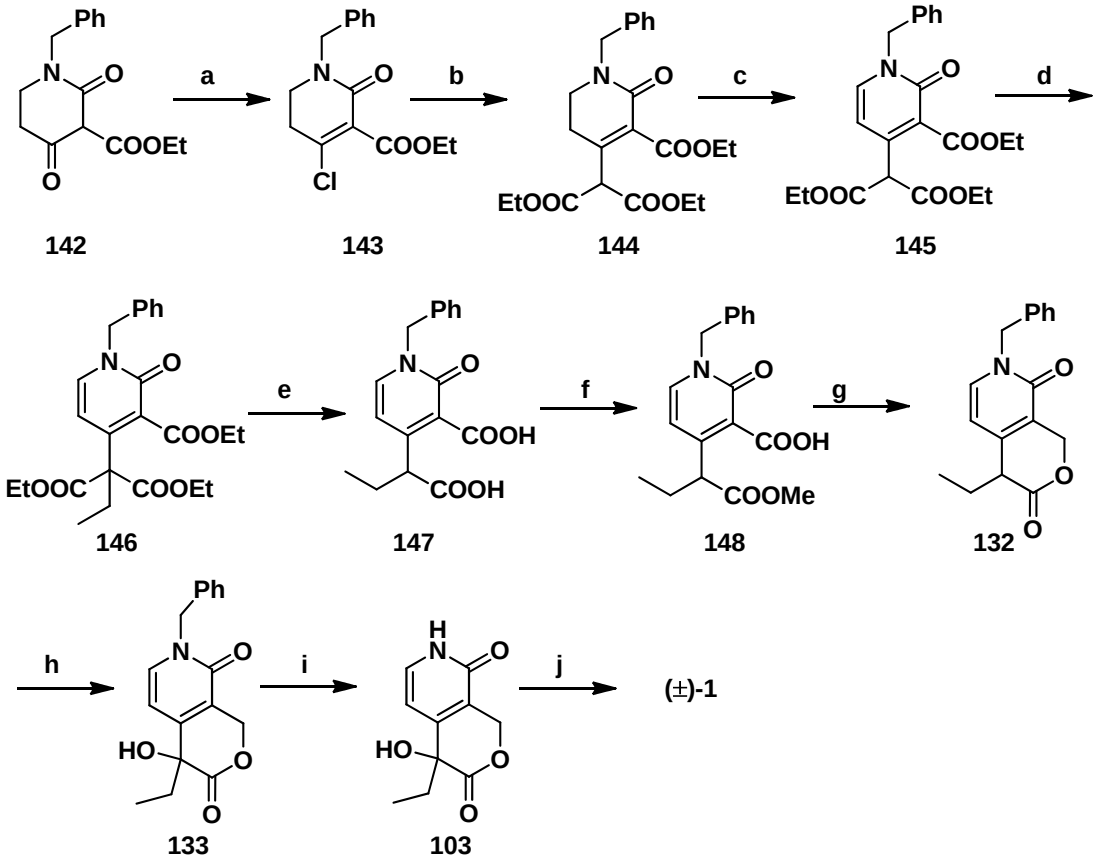
The carbonylation on **135** was accomplished employing $PdCl_2(CH_2Cl_2)$dppf and Et_3N in methanol under the CO atmosphere at 90 ^oC to furnish methyl ester **136** in excellent yield. Selective *O*-demethylation of **136** using TMSI in CH_3CN afforded pyridone **137** in 96% yield. *N*-Propargylation of **137** was accomplished with propargyl bromide and K_2CO_3 using PTC and LiBr in toluene to result in the formation of *N*-alkylated pyridone **138** in 70% yield. The basic hydrolysis of ester **138** afforded corresponding acid **139** and subsequently the resulting acid was converted into its amide **140** in 90% yield *via* acid chloride. The intramolecular hetero-Diels-Alder reaction was successfully carried out by treating with bis(triphenyl)oxodiphosponium trifluromethanesulfonate at room temperature to result in the formation of known[58] quinoline enol ether **141** in excellent yield. Finally the Sharpless asymmetric

dihydroxylation followed by oxidation was accomplished to furnish (+)-**1** in 83% yield and 95% *ee*.

Chavan's 4th approach

Chavan *et al.*[59] reported their fourth approach to camptothecin *via* DE ring of camptothecin employing an addition elimination reaction and selective esterification of an aliphatic carboxylic acid as key steps.

Scheme 16: Chavan *et al*. *Tetrahedron Lett*. **2007**, *46*, 6561.



Reagents and conditions **:** *a) $POCl_3$ (1.2 equiv), CH_2Cl_2, reflux, 3 h, 97%; b) NaH (1.2 equiv), diethyl malonate (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), methyl chloroformate (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, 24 h, 92%; i) $Pd(OH)_2$, H_2, EtOH, 50 ^oC, 5 h, 62%; j) Ref. 50.*

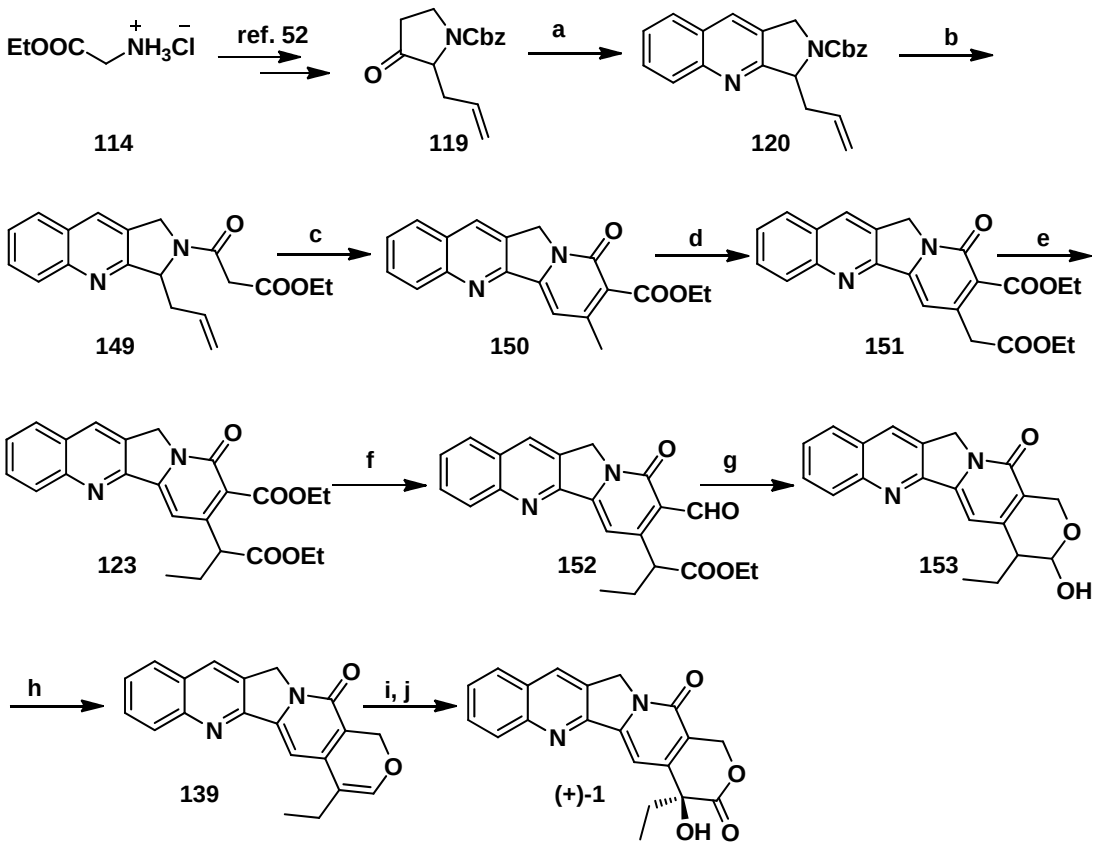
Accordingly, the β-ketoester **142** was prepared as per literature procedure[60] and treatment of **142** with $POCl_3$ in DCM furnished 4-chloro dihydropyridone **143**. Addition-elimination reaction of diethyl malonate was accomplished on **143** using NaH in benzene to furnish triester dihydropyridone **144**. The aromatization of dihydropyridone **144** using DDQ in refluxing 1,4-dioxane furnished pyridone **145** in 96% yield. The triester **145** was treated with ethyl iodide in the presence of K_2CO_3 to afford alkylated product **146** in 91% yield. The global hydrolysis of esters followed by monodecarboxylation of aliphatic acid was achieved in one pot using excess lithium hydroxide at room temperature to furnish diacid **147** 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 **148** in good yield. Compound **148** was subjected to the treatment with methyl chloroformate in THF at 0 ^oC to furnish mixed anhydride intermediate whose subsequent reduction to alcohol using $NaBH_4$ resulted in lactonization to furnish lactone **132** 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 **133** in 92% yield. Finally the *N*-debenzylation was successfully carried out employing catalytic amount of palladium hydroxide in ethanol at 50 ^oC to furnish desired DE-ring synthon **103** 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.

Chavan's 5th approach

Chavan *et al.*[61] reported their fifth approach towards camptothecin employing novel cascade intramolecular Pd-catalyzed cyclization followed by aromatization for the construction of D ring of (+)-camptothecin as key steps.

Thus the pyrrolidinone **119** was synthesised from glycinate salt **114**. The pyrrolidinone **119** underwent modified Friedlander condensation with Schiff base to furnish the tricyclic carbamate **120**. Deprotection of carbamate of **120** was carried out employing Olah's protocol. The resultant free amine was reacted with ethyl malonyl chloride to afford the key amide **149**. The compound **149** was treated with catalytic amounts of $PdCl_2$ and 2.1 equivalent $CuCl_2.2H_2O$ in DMF-H_2O (3:1) at 95 ^oC to furnish the compound **150** in 54% yield.

Scheme 17: Chavan *et al. Synlett* **2007**, *17*, 3635.



Reagents and conditions*: a) N-(o-Aminobenzylidine)-p-toluidine (1.2 equiv), PTSA (cat.), anhydrous toluene, azeotropic distillation, 4 h, 75%; b) i) KOH (14.0 equiv), EtOH, reflux, 8 h; ii) K_2CO_3 (1.2 equiv), ethyl malonyl chloride (1.2 equiv), anhyd CH_2Cl_2, 0 °C, 1 h, 71% over two steps; c) $PdCl_2$ (0.1 equiv), $CuCl_2$ (2.1 equiv), DMF-H_2O (3:1), 95 °C, 6 h, 54 %; d) LDA (1.1 equiv), diethyl carbonate (1.0 equiv), THF, -78 °C, 3-4 h, 70%; e) NaH (1.1 equiv), EtI (1.1 equiv), anhydrous DME, 0 °C- rt, 3-4 h, 64%; f) DIBAL-H (3.0 equiv), dry THF, -60 °C, 2 h, 83%; g) $NaBH_4$ (2.0 equiv), THF-H_2O (5:1), 0 °C, 0.5 h, 90%; h) MsCl (4.0 equiv), Et_3N (8.0 equiv), anhydrous THF, rt, 24 h, 92%; i) $(DHQD)_2$-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 °C, 7 h; j) I_2 (12.5 equiv), $CaCO_3$ (12.5 equiv), CH_3OH-H_2O (10:1), rt, 24 h, 33% over two steps.*

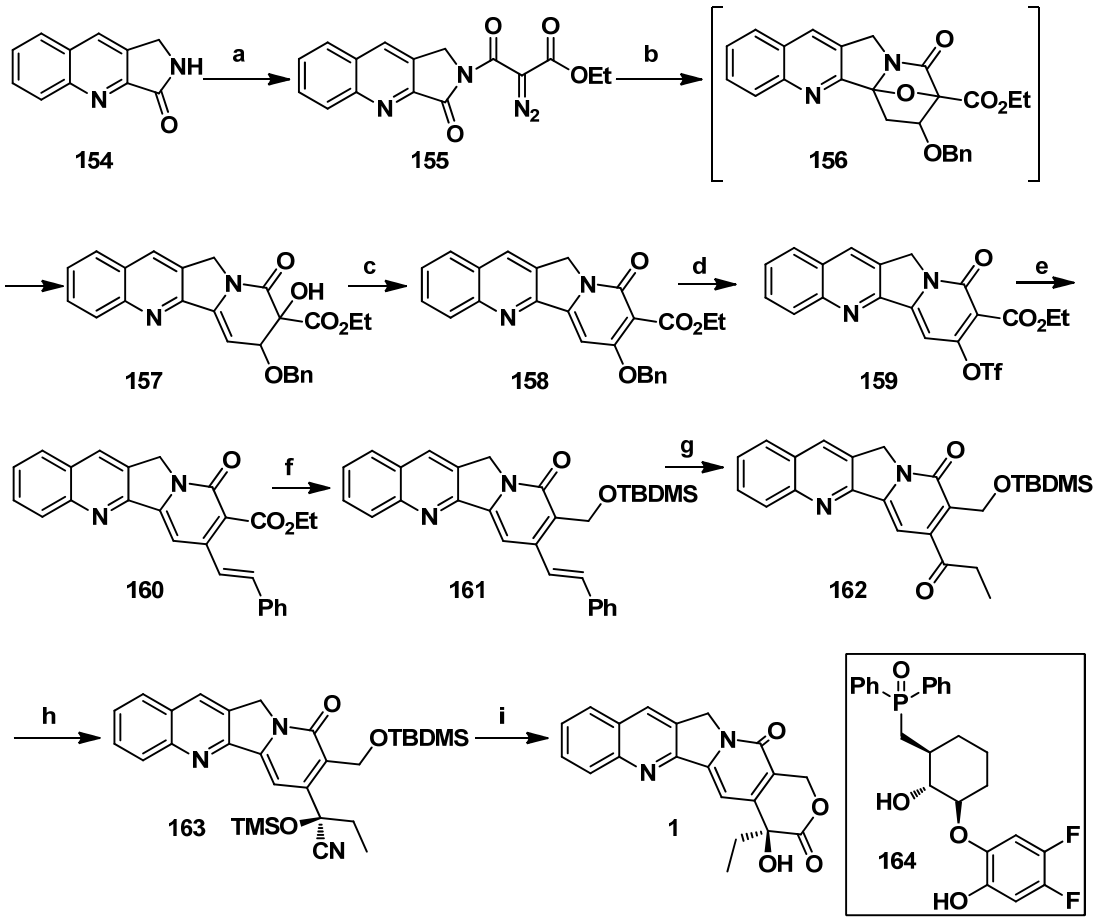
The compound **150** was treated with diethyl carbonate using LDA in THF at -78 °C to afford the compound **151** in 70% yield. The treatment of compound **151** with ethyl iodide using NaH in THF furnished diester **123** in 64% yield. The selective reduction of aromatic ester **123** to aldehyde **152** in 83% yield was achieved using DIBAL-H. The

aldehyde **152** was further reduced to lactol **153** in 90% yield. The lactol **153** was transformed into enol ether **139** *via O*-mesylation followed by elimination. Sharpless asymmetric dihydroxylation on **139** followed by oxidation furnished (+)-camptothecin **1**.

Kanazawa's Approach

Kanazawa and coworkers[62] reported novel approach for synthesis of camptothecin employing [3+2] cycloaddition of an isomünchnone intermediate to construct the D and E rings of camptothecin.

Scheme 18: Kanazawa *et al*. *Synlett*, **2008**, 15, 2275.



Reagents and conditions: *a) LiHMDS, THF, then ethyl diazomalonyl chloride, 68%; b) $[Rh(OAc)_2]_2$, benzyl vinyl ether, benzene, 91%; c) DBU, CH_2Cl_2, 94%; d) i) H_2, Pd/C, EtOH 88%; ii) Tf_2O, pyridine, $CHCl_3$, 96%; e) $PhCH=CHB(OH)_2$, $Pd(PPh_3)_4$, aq. Na_2CO_3, toluene 89%; f) i) DIBAL-H, CH_2Cl_2, then $NaBH_4$, MeOH; ii) TBDMSCl, imidazole, DMF, 89; g) i) OsO_4 (cat.), $NaIO_4$, t-BuOH, THF–H_2O, 99%; ii) $MeCHN_2$, Et_2O–$CHCl_3$; h) $Gd(Oi\text{-}Pr)_3$ (10 mol%),* ***164*** *(20 mol%), TMSCN (3 equiv), CH_2Cl_2, –20*

*°C, 60 h, 66%; i) Chiral HPLC separation, then for (–)-**158** [→ (+)-**1**]: 2 M HCl in Et_2O, EtOH (92%); for (+)-**158** (→ **157**): TBAF (1 equiv), THF, –80 °C (92%).*

Thus they started their synthesis from lactam **154**. Acylation of lactam **154** with ethyl 2- diazomalonyl chloride using LHMDS in THF afforded diazoester **155** in 68% yield. Exposure of the diazoester **155** to excess benzyl vinyl ether in the presence of a catalytic amount of rhodium acetate in refluxing benzene afforded the bridged ether **156** *via* [3+2]-cycloaddition, which suffered ring opening to generate **157**. Tetracycle **157** underwent base mediated dehydration to afford pyridone **158**. Pyridone **158** was debenzylated by hydrogenolysis and the derived hydroxy pyridone was transformed into its triflate **159**. Suzuki coupling of **159** with phenylvinylboronic acid in the presence of tetrakis(triphenylphosphine) palladium and sodium carbonate furnished the styrene derivative **160** in 89% yield. The ester functionality of **160** was selectively reduced to produce the corresponding hydroxymethyl derivative, which was protected as the *TBS*-ether **161**. Oxidative cleavage of the styryl group afforded aldehyde, which was efficiently transformed into ethyl ketone **162** by treatment with diazoethane. Introduction of the 20(*S*) stereocenter was addressed through Shibasaki's methodology.[63] Thus, ketone **162** was subjected to *S*-enantioselective cyanosilylation with TMSCN in the presence of the Gd complex generated from glucose-derived **164**, which gave a 2:1 mixture of (–)-**163** and (+)-**163** in 66% yield. The major enantiomer (–)-**163** was converted into natural camptothecin by an intramolecular Pinner reaction on treatment with HCl in hot ethanol.

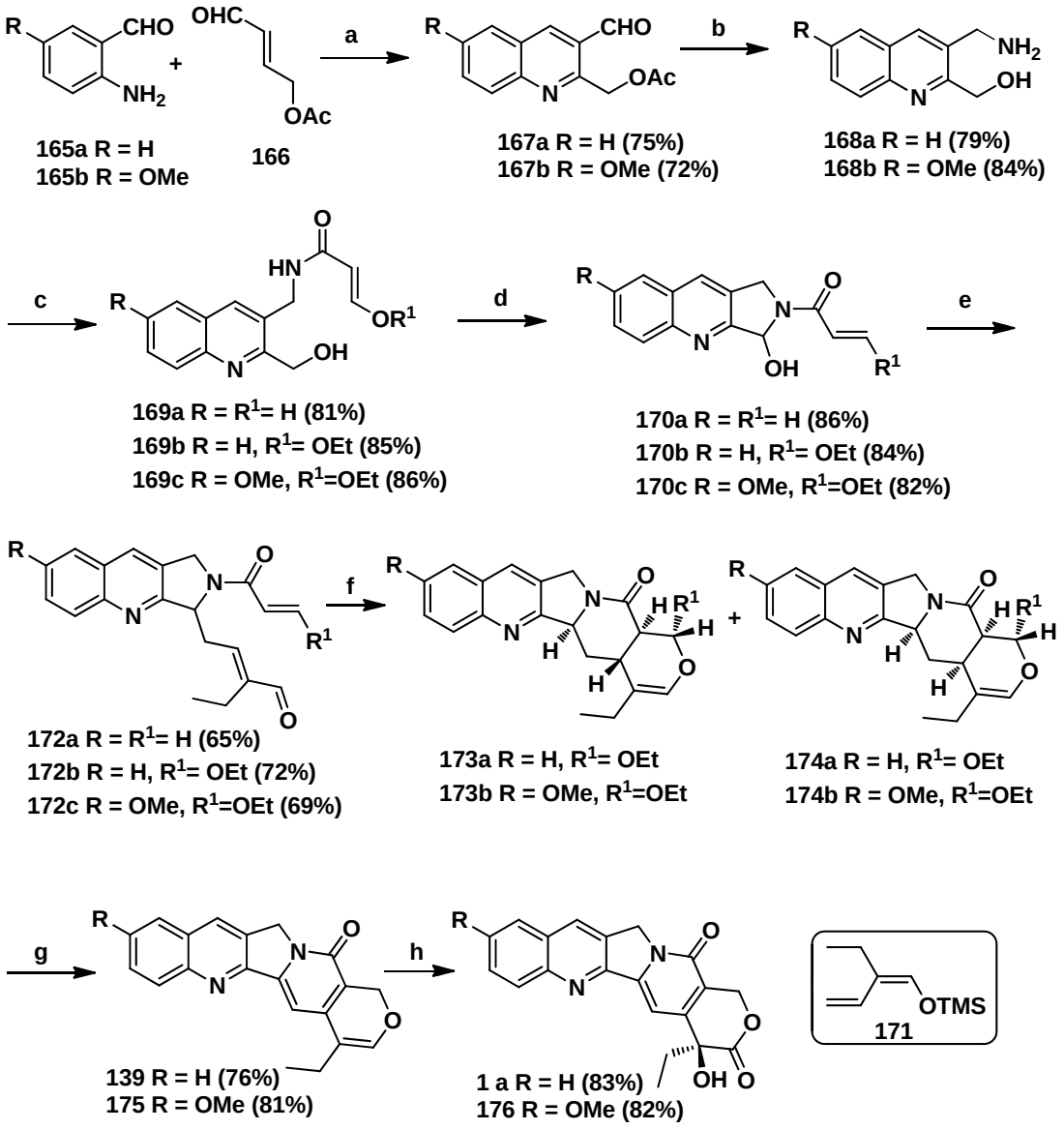
Yao's Approach

Very recently, Yao and coworkers[64] disclosed expeditious total synthesis of camptothecin utilizing cascade reaction consisting pyrrolidine-catalysed Michael addition and an intramolecular aldol condensation cascade reaction for construction of A/B ring of camptothecin **1**.

Thus they started synthesis from 2-aminobenzaldehydes **165** which in the presence of catalytic amounts of pyrrolidine and benzoic acid reacted with aldehyde **166** to afford two inseparable products. Mixture was treated with the MnO_2 to afford quinoline **167.** Oximation of the aldehydes **167** with NH_2OH, removal of the acetate with K_2CO_3 in methanol followed by hydrogenation of oxime in methanol with 10% Pd-C provided the corresponding benzylamines **168**. Parallel acylation of amines **168** with acryloyl chloride or 3-ethoxyacryloyl chloride in DMF yielded the corresponding acrylamide **169**. MnO_2-based oxidation of quinolin-2-ylmethanols **169** was mildly carried out in dichloromethane

to afford aminal derivatives **170**. Acetylation of aminals **170** followed by treatment with enol silyl ether **171** in the presence of $BF_3 \cdot Et_2O$ at -78 °C furnished the substrates **172.**

Scheme 19: Yao *et al. Org. Lett*. **2008**, *9*, 5393.



Reagents and conditions: *a) i) Pyrrolidine (cat), benzoic acid, DCM, silica gel, rt.; ii) MnO_2, DCM, 75%; b) i) H_2NOH, HCl, EtOH; ii) K_2CO_3, MeOH; iii) 10% Pd-C, MeOH, 79%, (over three steps); c) 3-Ethoxyacryloyl chloride, DMF, 85%; d) MnO_2, DCM, 86%; e) i) Ac_2O, Et_3N, DMAP, DCM; ii) Silyl ether* ***171****, $BF_3.Et_2O$, DCM, -78 ^oC, 72%; f) Mesitylene, 160 ^oC, sealed tube, 83%; g) i) DDQ, cat. AcOH, 1,4-dioxane; ii) Et_3SiH, $BF_3.Et_2O$, DCM, 76%; h) i) $K_2OsO_2(OH)_4$ (cat.), $(DHQD)_2$-PYR (cat.), $K_3Fe(CN)_6$,*

K_2CO_3, $CH_3SO_2NH_2$, t-BuOH-H_2O (1:1), 0 ^oC; ii) I_2, $CaCO_3$, CH_3OH-H_2O (2:1), 40 ^oC, 83% (two steps), 99% ee.

Thermal cycloaddition[65] of the modified substrate **172** proceeded smoothly, providing two separable diastereomers (**173** and **174**, 3:1) in an excellent yield. The mixture of **173** and **174** was treated with DDQ and a catalytic amount of CH_3COOH in 1,4-dioxane followed by reductive removal of the ethoxy group to afford camptothecin precursor **139** in 76% yield. Further oxidative transformation with Sharpless asymmemetric dihydroxylation followed by $I_2/CaCO_3$ based hemiacetal oxidation successfully converted the cylic enol-ethers **139** to (+)-camptothecin **1**.

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Chapter 1. Synthetic study towards camptothecin

Section 2

Attempted synthesis of camptothecin employing reductive-amination as key step

1.2.1 Summary

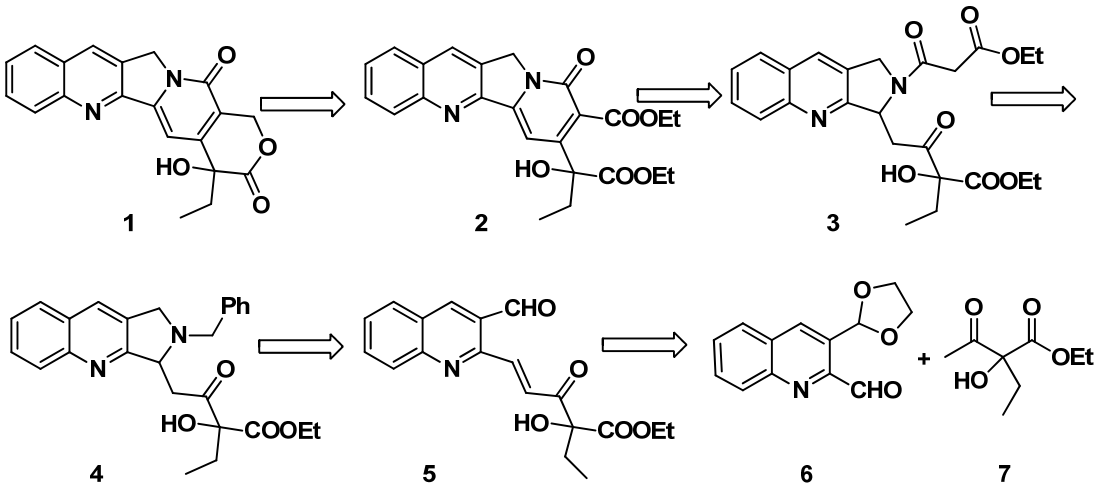
The present section deals with the attempted synthesis of camptothecin employing intramolecular tandem reductive amination and cyclization as key steps. Four advanced intermediates for synthesis of camptothecin were prepared.

1.2.2 Introduction

In light of the remarkable biological activity and intriguing mode of action reported for camptothecin[1] **1**, this group is involved in the synthesis of camptothecin and its analogues[2] by using different synthetic routes particularly for the construction of pyridone (D-ring) of camptothecin. Considering the pharmaceutical importance of camptothecin and low availability from natural sources, till date numerous imaginative syntheses[3,4] have been disclosed by different research groups. This section describes attempted syntheses towards camptothecin **1**. Different intermediates for elaboration towards camptothecin were synthesized employing "aldol" reaction and Wittig-Horner olefination as the key steps in the synthesis.

1.2.3 Present work

Retrosynthetic analysis of camptothecin **1**, shown in Scheme 1, revealed that, camptothecin **1** can be obtained from hydroxypyridone **2**. Pyridone **2**, in turn could be obtained from α-hydroxy-β-ketoester **3** by employing intramolecular Knoevenagel condensation. α-Hydroxy-β-ketoester **3** could be realized from compound **4** *via N*-debenzylation followed by condensation.

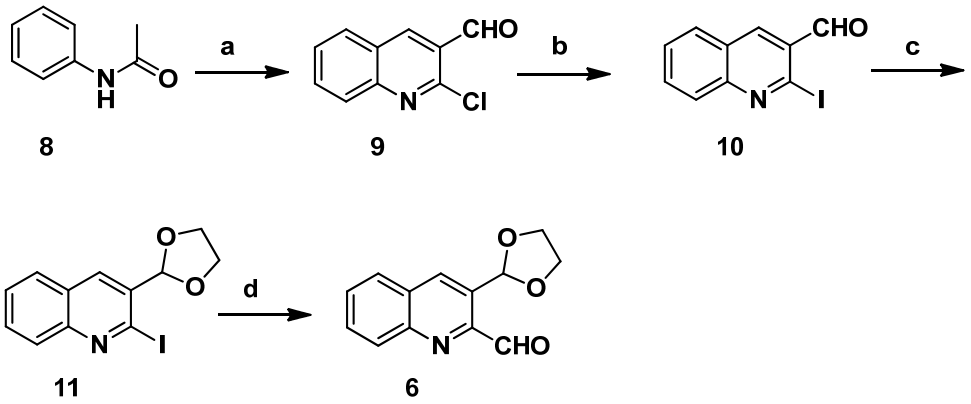


Scheme 1

Compound **4** could be achieved from aldehyde **5** by employing tandem reductive amination and cyclisation. The key intermediate **5** could be obtained from aldehyde **6** and hydroxy compound **7** by employing "aldol" condensation (Scheme 1).

1.2.4 Results and discussion

Accordingly, required quinoline aldehyde **6** was prepared from commercially available acetanilide **8** using literature[5] procedure (Scheme 2). Acetanilide **8** on Vilsmeier-Haack reaction gave the 2-chloro-3-formyl quinoline **9**. Chlorine atom was replaced with iodine using sodium iodide and HCl (cat.) in acetonitrile at reflux temperature for 5 h to furnish iodoquinoline **10**. To avoid further functional group complications, the formyl group of the iodoaldehyde **10** was protected as its cyclic acetal **11** by treating with ethylene glycol in presence of *p-T*SA (cat.) with azeotropic removal of water. Formylation of **11** was carried out by treating it with *n*-BuLi to furnish lithio derivative which was quenched with DMF to afford 2-formyl quinoline **6** in 58% yield. The aldehyde **6** was used for the "aldol" and Wittig-Horner reaction. All the compounds from **9** to **6** were characterized by spectroscopic methods. Spectroscopic data was in good agreement with the one reported in literature[5] (Scheme 2).

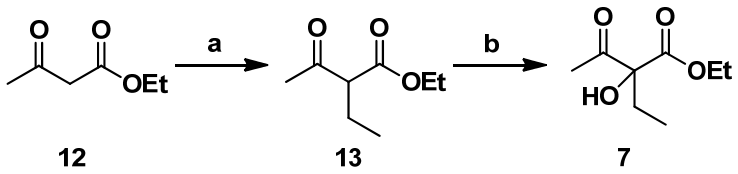


Scheme 2: ***Reagents and conditions:*** *a) $POCl_3$, DMF, 75 ^oC, 16 h, 65%; b) NaI, HCl (cat), acetonitrile, reflux, 6 h, 95%; c) Ethylene glycol, benzene, p-TSA, reflux, 7 h, 90%; d) n-BuLi, DMF, dry Et_2O, -70 ^oC, 1 h, 58%.*

^{1}H NMR spectrum of **6** showed a singlet at δ 10.37 integrating for one proton which was attributed to aldehydic proton. The singlet that appeared at δ 6.73 integrating for one proton and singlet at δ 4.16 integrating for four protons were assigned

to acetal protons. ^{13}C NMR spectrum of **6** showed peak at δ 194.1 confirming the presence of aldehyde. The rest of proton and carbon peaks resonated at expected positions. Finally the mass spectrum of **6** showed the *m/z* peak at 230 $(M + H)^+$ and elemental analysis was also found to be in good agreement with the calculated values.

Having aldehyde **6** in hand, next task was to synthesise coupling partner **7**. The compound **7** was synthesized from commercially available ethyl acetoacetate **12**. Ethyl acetoacetate on monoalkylation using ethyl iodide, K_2CO_3 in acetone afforded alkylated compound **13** in 70% yield. Compound **13** on hydroxylation[6] using cobalt chloride and isopropanol in acetonitrile under oxygen atmosphere afforded hydroxy compound **7** in 65% yield (Scheme 3).

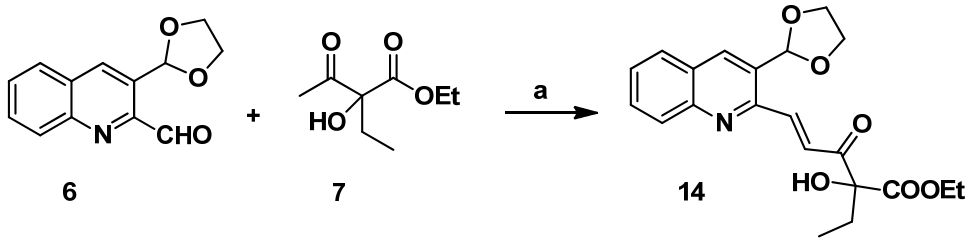


Scheme 3: ***Reagents and conditions:*** *a) K_2CO_3, ethyl iodide, acetone, reflux, 4 h, 70%; b) $CoCl_2$, CH_3CN, isopropanol, O_2, 24 h, 65%.*

IR spectrum of **7** showed strong absorptions at 3450, 1740 and 1715 cm^{-1} signifying the presence of hydroxy, ester and keto functionalities respectively. ^1H NMR spectrum of **7** showed disappearance of triplet due to proton α to both carbonyl groups. The two triplets that appeared at δ 0.88 ($-CH_2\underline{CH_3}$) and 1.33 ($-COCH_2\underline{CH_3}$) integrating for three protons each were assigned to methyl group protons. The multiplet at δ 1.60-1.82 ($-\underline{CH_2}CH_3$) and quartet at δ 4.11 ($-CO\underline{CH_2}CH_3$) integrating for two protons each were assigned to methylene group protons. The singlet at δ 2.00 integrating for three protons was assigned to methyl ($\underline{CH_3}CO-$) protons. Finally, the mass spectrum of **7** showed the *m/z* peak at 175 $(M + H)^+$ thus confirming the structure **7**.

Having the hydroxy compound **7** in hand, it was subjected to "aldol" condensation with aldehyde **6** using excess of LDA in anhydrous THF at -78 ^oC to furnish the aldol product **14** in 20% yield (Scheme 4). IR spectrum of **14** showed absorptions at 3390, 1737 and 1705 cm^{-1} signifying the presence of hydroxy, ester and keto functionalities respectively. ^1H NMR spectrum of **14** showed disappearance of peak due to aldehydic proton and appearance of the new peaks at δ 8.03 and 8.36 as doublets integrating for one proton each having coupling constant 15.1 Hz thus confirming the condensation. The two

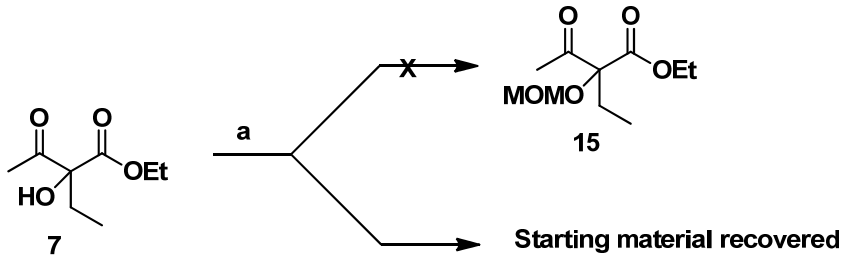
triplets that appeared at δ 0.95 and 1.32 integrating for three protons each were assigned to methyl protons. The two multiplets at δ 2.10-2.35 (-$\underline{CH_2}CH_3$) and δ 4.10-4.25 (-OCH_2-CH_2O-) integrating for two and four protons were assigned to methylene protons next to chiral center and acetal methylene protons respectively. The quartet at δ 4.29 integrating for two protons was assigned to ester methylene protons. The singlet that appeared at δ 6.19 integrating for one proton was assigned to acetal proton, while the aromatic protons resonated at expected positions. Finally the mass spectrum of **14** showed the *m/z* peak at 408 $(M + Na)^+$.



Scheme 4: ***Reagents and conditions:*** *a) LDA, THF, -78 °C, 2 h, 20%.*

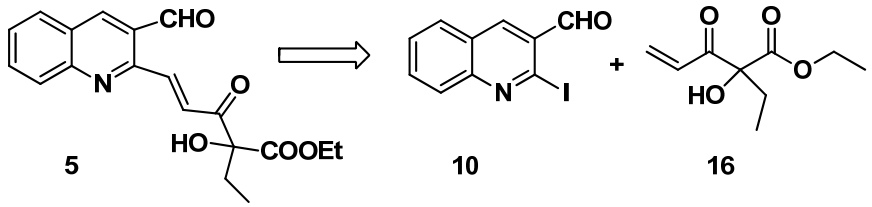
Though intermediate **14** was synthesized in short sequence, the yield of reaction was poor. Low yield of reaction can be attributed to the free hydroxy group. Attempts were made to protect hydroxy group however the desired transformation could not be achieved.

An attempt for the protection of alcohol **7** to the corresponding benzyl derivative with NaH and benzyl bromide in THF as well as DMF resulted in the formation of unidentified products. Also, when hydroxy compound **7** was treated with diisopropyl ethylamine and MOM chloride in anhydrous THF, instead of the required compound **15**, starting material was recovered (Scheme 5).



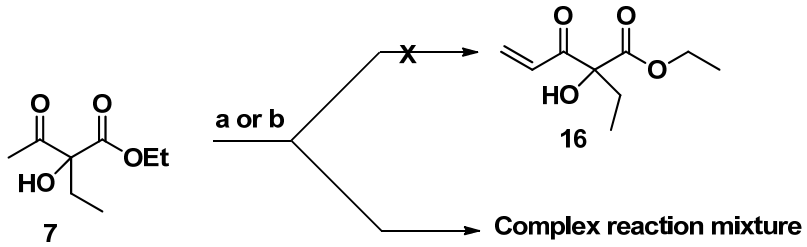
Scheme 5: ***Reagents and conditions:*** *a) Diisopropyl ethylamine, THF, MOMCl, 0 °C-rt.*

Having failed to improve the yield of aldol reaction by several trials, retrosynthetic plan to synthesize the required aldehyde **5** was changed. It was presumed that the compound **5** can be obtained by Heck reaction[7] (Scheme 6) between iodoaldehyde **10** and α, β-unsaturated compound **16**.



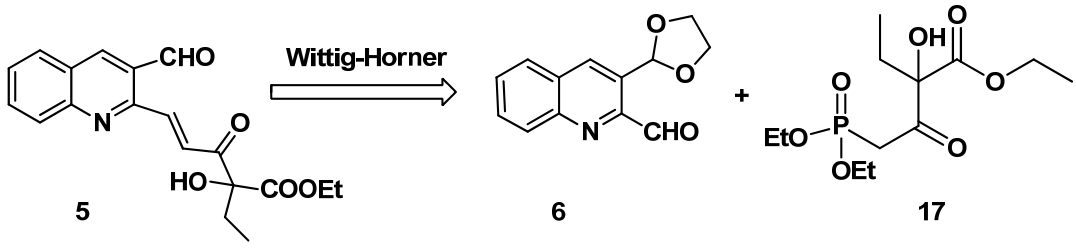
Scheme 6

Having this idea in mind, it was thought to synthesize α, β-unsaturated compound **16** from hydroxy compound **7**. Accordingly, attempt was made by reacting hydroxy compound **7** with formaldehyde using different bases but none of the reactions led to expected product **16** (Scheme 7).



Scheme 7: ***Reagents and conditions:*** *a) NaH, formaldehyde, THF, rt-reflux; b) Formaldehyde, diethylamine hydrochloride, hydroquinone, water, 120 ^{o}C.*

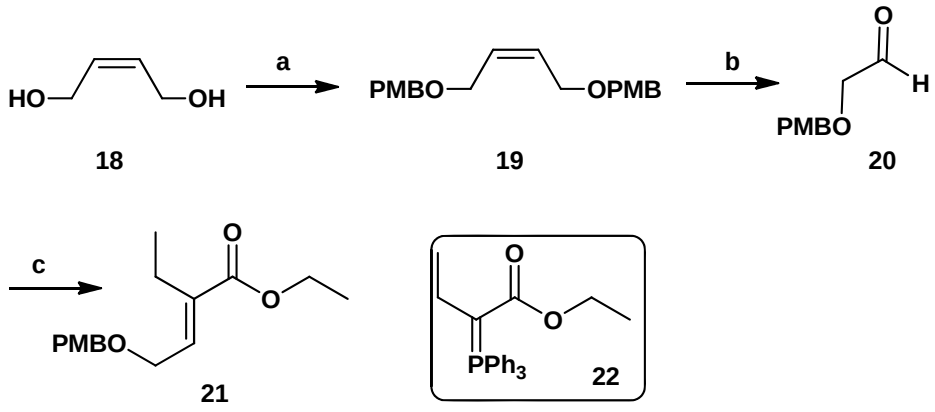
Having failed in synthesis of aldehyde **5** and α, β-unsaturated compound **16**, it was thought to utilize Wittig-Horner reaction for the synthesis of required aldehyde **5** (Scheme 8).



Scheme 8

With this idea in mind, the next synthetic target was to synthesize phosphonate derivative **17**, for which commercially available *cis*-2-butene-1,4-diol **18** was identified as the starting material. Accordingly *cis*-2-butene-1,4-diol **18** was protected as its di-*PMB* ether **19** using PMB chloride and NaH in DMF at room temperature in quantitative yield. Di-PMB ether **19** was subjected to oxidative cleavage of olefin with OsO_4 in presence of sodium metaperiodate in acetone/H_2O (3:1) to afford aldehyde **20** in 95% yield (Scheme 9). Aldehyde **20** was characterized by using spectroscopic techniques. IR spectrum of **20** showed strong absorption bands at 2730 and 1702 cm^{-1} which indicated the presence of aldehyde. The ^1H NMR spectrum of **20** displayed the absence of peaks corresponding to olefinic protons and a new singlet appeared at δ 9.70 integrating for one proton and was assigned to aldehydic proton. The singlet at δ 3.82 integrating for three protons was assigned to methoxy group protons. The singlets at δ 4.08 and 4.57 integrating for two protons each were assigned to benzyl and methylene protons α to carbonyl group. The two doublets that appeared at δ 6.90 and 7.30 integrating for two protons each having coupling constant 8.2 Hz were assigned to aromatic protons. ^{13}C NMR along with DEPT spectra of **20** revealed the presence of aldehyde carbonyl carbon by resonance at δ 200.4, while rest of carbons associated with structure resonated at expected positions. The mass spectrum of compound **20** displayed the *m/z* peaks at 181 $(M + H)^+$ and 203 $(M + Na)^+$.

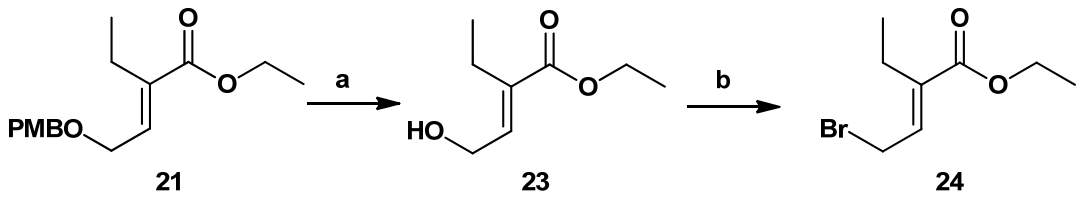
Aldehyde **20** was subjected to four-carbon homologation by Wittig olefination[8] with the stable ylide **22** in CH_2Cl_2 at room temperature to provide the *α, β*- unsaturated ester **21** in satisfactory yield (Scheme 9). IR spectrum of **21** showed a strong absorption band at 1731 cm^{-1} indicating the presence of ester carbonyl.



Scheme 9: ***Reagents and conditions:*** *a) NaH, PMB-chloride, DMF, rt, 4 h, quant.; b) OsO_4, $NaIO_4$, acetone-water (3:1), 3 h, 95%; c)* ***22****, DCM, rt, 12 h, 73%.*

The ^{1}H NMR spectrum of **21** displayed the absence of peak corresponding to aldehydic proton. Triplets that appeared at δ 1.00 and 1.30 integrating for three protons each were assigned to (-$CH_2\underline{CH_3}$) and (-$COCH_2\underline{CH_3}$) methyl group protons. The quartet at δ 2.28 integrating for two protons was assigned to (-$\underline{CH_2}CH_3$) methylene protons. The triplet that appeared at δ 6.83 integrating for one proton was assigned to olefinic proton, while rest of protons resonated at expected positions. ^{13}C NMR along with DEPT spectra of **21** revealed the presence of three methyl group carbons and four methylene carbons. The mass spectrum of compound **21** displayed the *m/z* peaks at 279 $(M + H)^+$ and 301 $(M + Na)^+$ and its elemental analysis was also found to be in good agreement with the calculated values.

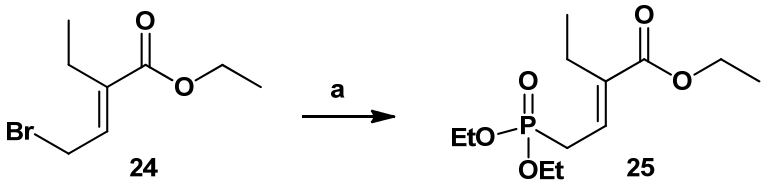
Removal of *p*-methoxybenzyl ether in **21** was effected with DDQ in CH_2Cl_2/H_2O (9:1) at 0 ^{o}C to afford the allyl alcohol **23** in 94% yield (Scheme 10). IR spectrum of **23** showed a strong absorption band at 3350 cm^{-1} indicating the presence of alcohol functionality. The ^{1}H NMR spectrum of **23** showed disappearance of signals due to the methyl ether and related aromatic peaks of −*PMB* ether clearly indicating the occurrence of the transformation. The doublet that appeared at δ 4.36 (*J* = 6.2 Hz, 2H) was attributed to methylene protons adjacent to hydroxy group. The two triplets at δ 1.01 and 1.30 and two quartets at δ 2.29 and 4.20 integrating for three and two protons each were assigned to ethyl group. The signal that appeared at δ 6.78 as a triplet integrating for one proton was assigned to olefinic proton. ^{13}C NMR along with DEPT spectra of **23** revealed disappearance of signal due to the methyl ether and related aromatic peaks of −*PMB* ether and presence of two methyl group carbons and three methylene carbons. The mass spectrum of compound **23** displayed the *m/z* peaks at 159 $(M + H)^+$ and 181 $(M + Na)^+$ and its elemental analysis was also found to be in good agreement with calculated values.



Scheme 10: ***Reagents and conditions:*** *a) DDQ, DCM-H_2O (9:1), 3 h, 94%; b) PBr_3, diethyl ether, 2 h, 96%.*

Having hydroxy compound **23** in hand, next task was to replace hydroxy with bromide. An attempt for the conversion of alcohol **23** to the corresponding bromo derivative **24** with TPP/CBr_4[9] resulted in the formation of unidentified products. However, the conversion was smoothly achieved using PBr_3[10] in diethyl ether at 0 ^oC (Scheme 10). The compound thus obtained showed characteristic change in ^1H and ^{13}C NMR spectral pattern. The methylene protons ($BrCH_2CH$-) were shielded and resonated upfield at δ 4.03 (d, J = 8.5 Hz, 2H) thereby confirming the transformation, while rest of the protons and all carbons resonated at expected positions. Finally, the mass spectrum of compound **24** displayed the *m/z* peaks at 222 and 224 (1:1) $(M + H)^+$ and its elemental analysis was also found to be in good agreement with calculated values.

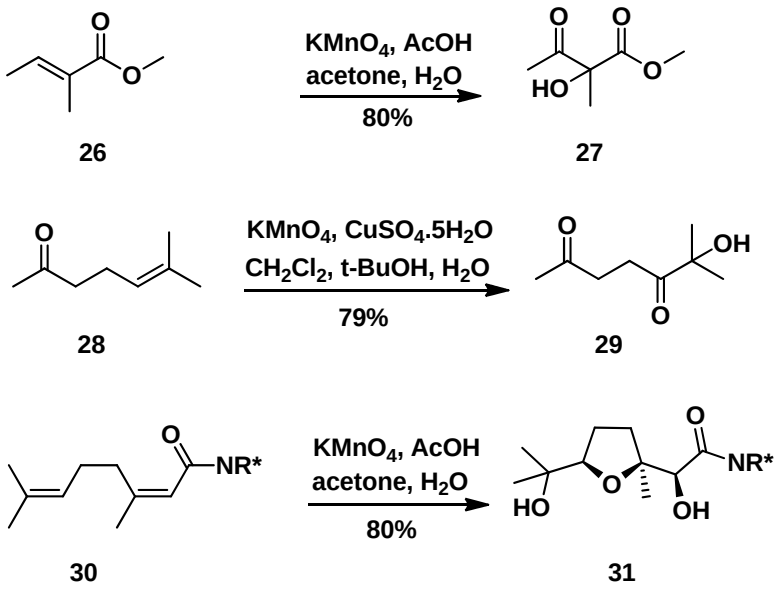
Michaelis-Arbuzov[11] reaction of the resultant bromo compound **24** with $P(OEt)_3$ at 120 ^oC afforded the phosphonate **25** (Scheme 11)**,** whose structure was confirmed by spectroscopic techniques.



Scheme 11: ***Reagents and conditions:*** *a) Triethyl phosphite, 100 ^oC, 12 h, quant.*

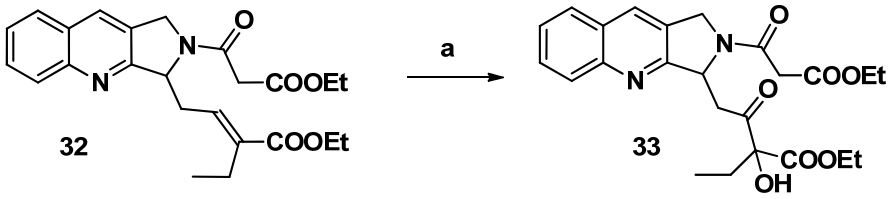
^1H NMR spectrum of **25** showed the active methylene protons which appeared as a doublet of doublet at δ 2.74 (J = 8.2 and 23.5 Hz, 2H). The methylene protons of the $P(OEt)_2$ and ester group appeared as a multiplets in the region of δ 4.04-4.26 integrating for six protons, while the methyl protons appeared between δ 1.25-1.35 integrating for nine protons as a multiplet. The triplet at δ 1.02 integrating for three protons was assigned to methyl protons of ethyl group. All other resonances were in good agreement with the assigned structure. ^{13}C NMR along with DEPT spectra of **25** revealed the presence of four methyl group carbons and five methylene carbons. The mass spectrum of compound **25** displayed the *m/z* peaks at 279 $(M + H)^+$ and 301 $(M + Na)^+$ and its elemental analysis was also found to be in good agreement with calculated values.

Having the olefin phosphonate ester **25** in hand, next goal was to introduce keto-hydroxy moiety by oxidation of olefin. Literature precedents are there wherein the tri-substituted olefins have been converted into corresponding keto-hydroxy compounds by exposing to $KMnO_4$ involving a 4e- oxidation[12] (Scheme 12).

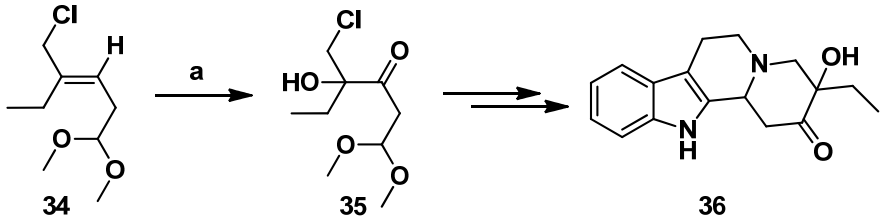


Scheme 12

This strategy has earlier been utilized by this group for the functionalization of substituted alkenes and that was a key step in the synthesis of camptothecin,[2d] a quinoline alkaloid (Scheme 13) as well as in the synthesis of mitralactonine, an indole alkaloid[13] (Scheme 14).

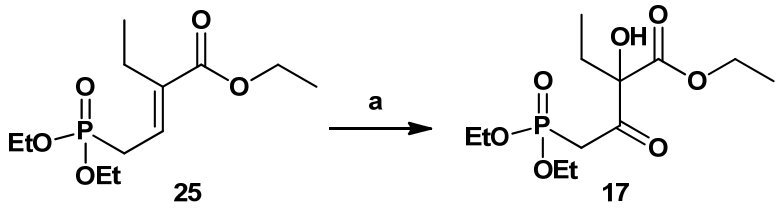


Scheme 13: ***Reagents and conditions:*** *a) $KMnO_4$, AcOH, acetone-H_2O, -10 ^oC, 0.5 h, 90%.*



Scheme 14: ***Reagents and conditions:*** *a) $KMnO_4$, AcOH, acetone-H_2O, -10 ^oC, 0.5 h, 84%.*

Encouraged by this possibility to obtain the ketol **17** in a single step, the olefin compound **25** was subjected to react with $KMnO_4$ under acidic conditions in acetone-water (9:1) solvent system at -10 ^oC. As expected the oxidation reaction furnished the ketol compound **17** in 90 % yield (Scheme 15).

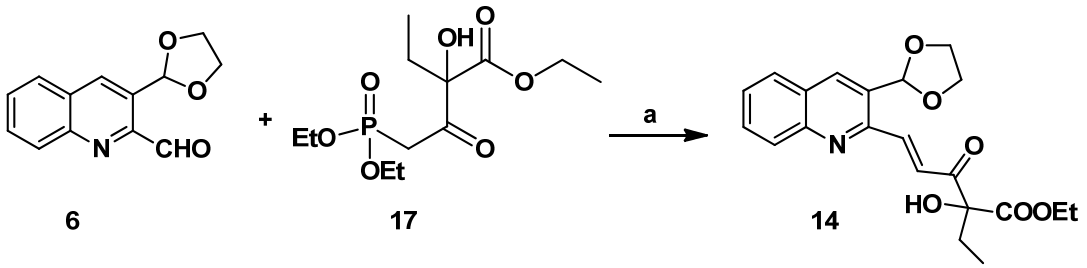


Scheme 15: ***Reagents and conditions:*** *a) $KMnO_4$, AcOH, acetone-H_2O (9:1), -10 ^oC, 0.5 h, 90%.*

The IR spectrum of **17** showed strong absorptions at 3449 and 1715 cm^{-1} typical of hydroxy ketone functionality and 1734 cm^{-1} corresponding to ester functionality. The ^1H NMR spectrum of **17** displayed the absence of peak corresponding to olefinic proton, thereby confirming oxidation. The two signals that appeared as doublet of doublet at δ 3.22 and 3.47 integrating for one proton each having coupling constants 13.8 and 22.3 Hz were assigned to active methylene (-PO$\underline{CH_2}$CO-) protons. The methylene protons next to chiral center appeared as two multiplets at δ 1.84-1.93 and 2.00-2.09 integrating for one proton each. The methylene protons of the $P(OEt)_2$ and ester group appeared as a multiplet in the region of δ 1.22-1.32 integrating for nine protons, while the methyl protons of the $P(OEt)_2$ and ester group appeared between δ 4.07-4.15 and 4.18-4.28 as multiplets integrating for four and two protons respectively. ^{13}C NMR spectrum of **17** showed the peaks at δ 170.0 and 200.2 which were assigned to the ester and carbonyl carbons, while rest of the carbons associated with the compound resonated at expected positions. The mass spectrum of compound **17** displayed the *m/z* peaks at 311 $(M + H)^+$ and 333 $(M + Na)^+$ and its elemental analysis was also found to be in good agreement with calculated values.

Having synthesized the required phosphonate ester **17**, next task was to condense it with aldehyde **6** by utilizing Wittig-Horner reaction. Condensation attempted by using different bases was not very successful. Finally, the base triethylamine worked well for this transformation. Thus, aldehyde **6** was subjected to Wittig-Horner olefination with

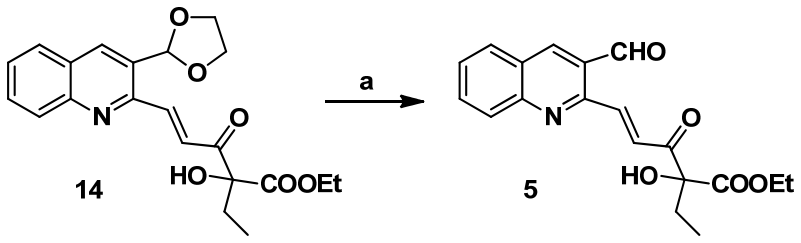
phosphonate ester **17** using triethyl amine in DCM for 6 h to furnish the condensed compound **14** in 80% yield (Scheme 16).



Scheme 16: ***Reagents and conditions:*** *a) Triethylamine, dry dichloromethane, rt, 6 h, 80%.*

The IR spectrum of **14** showed strong absorptions at 3390, 1705 and 1737 cm^{-1} corresponding to hydroxy, ketone and ester functionalities respectively. ^1H NMR spectrum of **14** showed disappearance of peak due to aldehydic proton and appearance of the new peaks as doublets at δ 8.03 and 8.36 integrating for one proton each having coupling constant 15.1 Hz confirming the condensation. The two triplets that appeared at δ 0.95 and 1.32 integrating for three protons each were assigned to methyl protons. The two multiplets at δ 2.10-2.35 (-$\underline{CH_2}CH_3$) and δ 4.10-4.25 integrating for two and four protons were assigned to methylene protons next to chiral center and acetal methylene protons respectively. The quartet at δ 4.29 integrating for two protons was assigned to ester methylene protons. The singlet at δ 6.19 integrating for one proton was assigned to acetal proton while rests of aromatic protons resonated at expected positions. Finally the mass spectrum of **14** showed the *m/z* peak at 408 $(M + Na)^+$.

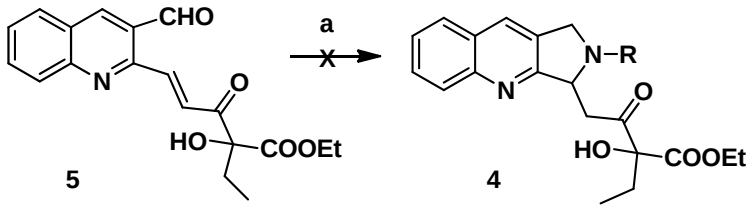
Having synthesised the condensed compound **14** in good yield, next goal was to get required aldehyde **5** by simple acetal deprotection. Compound **14** was subjected to treatment with 2N HCl in THF to afford the required aldehyde **5** in 85% yield (Scheme 17).



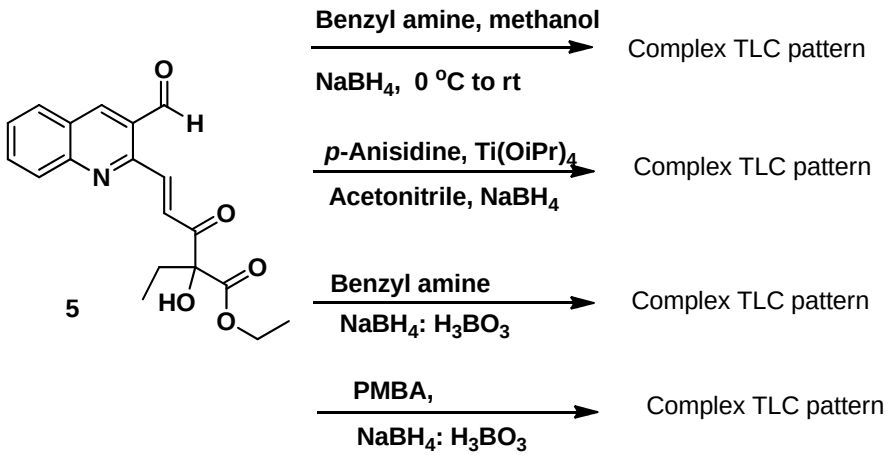
Scheme 17: ***Reagents and conditions:*** *a) HCl, THF, rt, 2 h, 85%.*

The IR spectrum of **5** showed strong absorption at 2730 cm^{-1} corresponding to aldehydic CH stretch, 3390 and 1705 cm^{-1} corresponding to hydroxy and ketone functionalities and 1736 cm^{-1} corresponding to ester functionality. The ^1H NMR spectrum of **5** showed disappearance of signals due to the acetal group protons and new signal that appeared at δ 10.44 integrating for one proton was assigned to aldehydic proton clearly indicating the accomplishment of desired transformation, while rest of the protons resonated at expected positions. The mass spectrum of compound **5** displayed the *m/z* peaks at 342 $(M + H)^+$ and 364 $(M + Na)^+$.

Thus with the required aldehyde **5** in hand, next aim was to construct the C ring camptothecin **1** *i. e.* synthesis of tricyclic compound **4** *via* reductive amination. Unfortunately attempts to cyclization *via* reductive amination[14,15] failed by using different conditions (Scheme 18). Some of the conditions tried led to complex reaction mixture (Scheme 19).

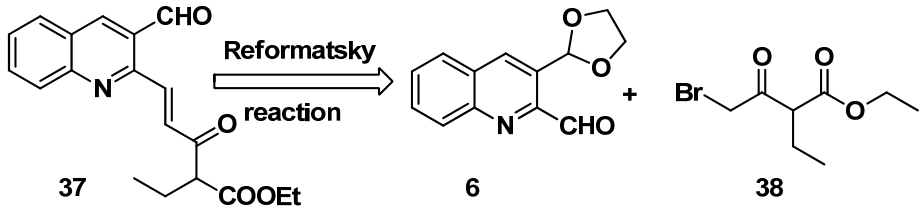


Scheme 18: ***Reagents and conditions:*** *a) i) $PhCH_2NH_2$ or $CH_3OC_6H_4CH_2NH_2$, methanol, then $NaBH_4CN$; ii) $Ti(O^iPr)_4$, $PhCH_2NH_2$ or $CH_3OC_6H_4CH_2NH_2$, MeOH, then $NaBH_4CN$.*



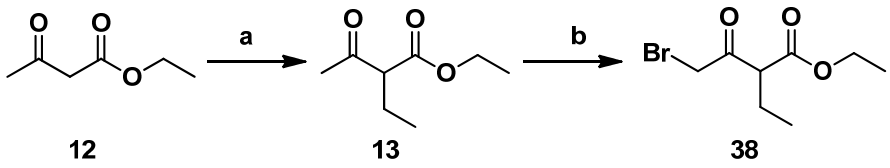
Scheme 19

It was thought that the problem may be due to the free tertiary hydroxy group and hence attempts were made to protect the tertiary hydroxy group but all the efforts to protect hydroxy group failed to give desired product. Hence it was decided to change retrosynthetic plan and it was decided that instead of preparing hydroxy compound **7** synthesis of dehydroxy compound **37** should be undertaken. The dehydroxy compound **37** could be obtained by performing Reformatsky reaction on aldehyde **6** with bromo compound **38** (Scheme 20).



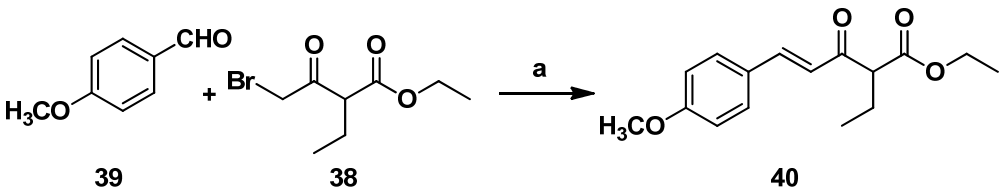
Scheme 20

The bromo compound **38** was synthesized from commercially available ethyl acetoacetate by following the literature[16] procedure. Thus, ethyl acetoacetate on monoalkylation using ethyl iodide and K_2CO_3 in acetone afforded alkylated compound **13** in 70% yield. Selective bromination was carried out using chloroform and bromine[16a] at room temperature for 10 h to afford the bromo compound **38** in 82% yield. Both the compounds **13** and **38** were characterized by spectroscopic methods. Spectroscopic data of compound **13** and **38** was in complete agreement with the values reported in literature[16b] (Scheme 21).



Scheme 21: ***Reagents and conditions:*** *a) K_2CO_3, ethyl iodide, acetone, reflux, 4 h, 70%; b) Bromine, chloroform, rt, 10 h, 82%.*

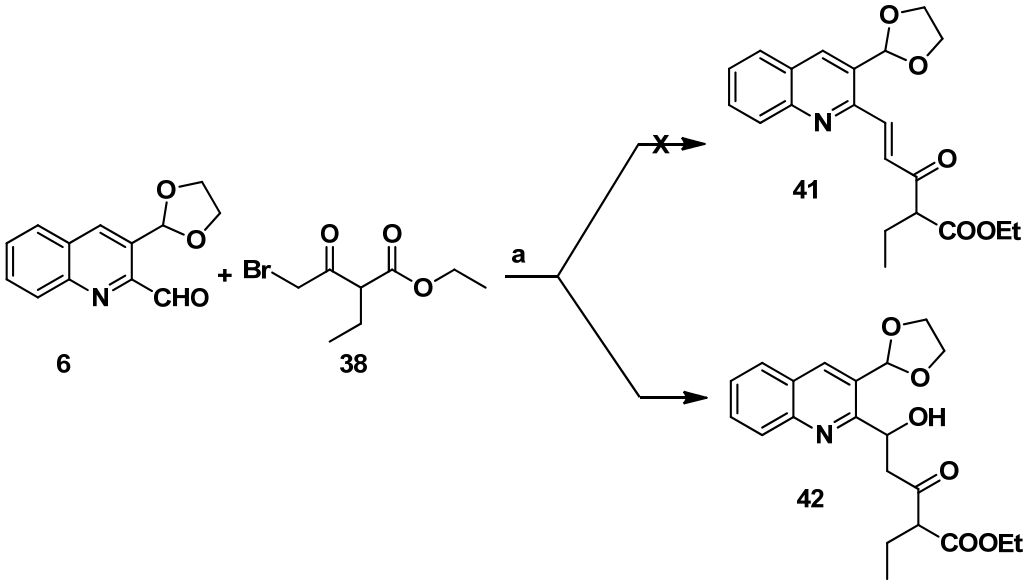
Having bromo compound **38** in hand, it was decided to perform a model Reformatsky reaction on anisaldehyde **39** using bromo compound **38**. Accordingly when the Reformatsky reaction was performed in the presence of activated zinc and catalytic iodine it was observed that reaction gave expected eliminated compound **40** in 87% yield (Scheme 22).



39 38 40

Scheme 22: ***Reagents and conditions:*** *a) Zn, iodine (cat), benzene-ether (1:1), reflux, 5 h, 87%.*

Encouraged by this possibility to obtain the required compound **41** in a single step, the bromo compound **38** was subjected to Reformatsky reaction with quinoline aldehyde **6** in presence of activated zinc and catalytic iodine in benzene-ether solvent system, but in this case instead of the formation of olefin **41**, alcohol **42** was obtained as diastereomeric mixture in 30% yield (Scheme 23).



6 38 41 42

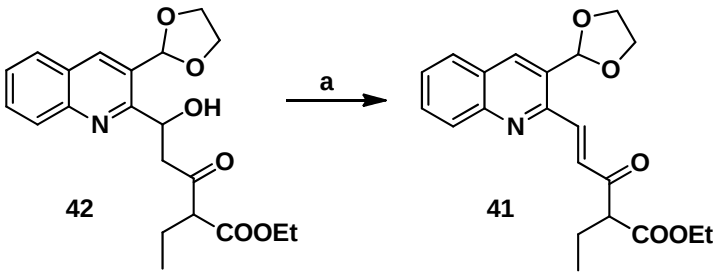
Scheme 23: ***Reagents and conditions:*** *a) Zn, iodine (cat), benzene-ether (1:1), reflux, 7 h, 30%.*

Formation of alcohol **42** was confirmed by its ^{1}H, ^{13}C NMR and mass spectral analysis. The ^{1}H NMR spectrum of **42** showed disappearance of signal due to the aldehydic proton. The signal that appeared at δ 5.67-5.74 as multiplet integrating for one proton was assigned to proton adjacent to hydroxy group (-CHOHCH$_2$-). The two triplets at δ 0.97 and 0.98 integrating for three protons and a multiplet at δ 1.22-1.33 integrating for three protons due to diastereomeric mixture were assigned to methyl group protons.

The three multiplets at δ 1.83-2.08, 2.97-3.31 and 3.49-3.58 integrating for two, two and one proton were assigned to ($CH_3\underline{CH_2}CH$-), (-$\underline{CH_2}COCH$-) and ($CH_3CH_2\underline{CH}$-) protons respectively. Acetal protons and ester methylene protons showed multiplet at δ 4.06-4.26 integrating for six protons. ^{13}C NMR and DEPT spectra of **42** clearly showed it to be a mixture of diastereomer by showing doubling of peaks *viz* 169.4, 169.6 and 203.5, 203.7 corresponding to ester and ketone carbonyls respectively, while rest of the carbons associated with structure resonated at expected positions.

Efforts to directly get eliminated product **41** failed. It was decided to isolate the alcohol **42** and then subject it to mesylation and elimination. Accordingly, alcohol **42** was treated with triethyl amine and mesyl chloride in DCM to afford the eliminated compound **41** in low yield (Scheme 24).

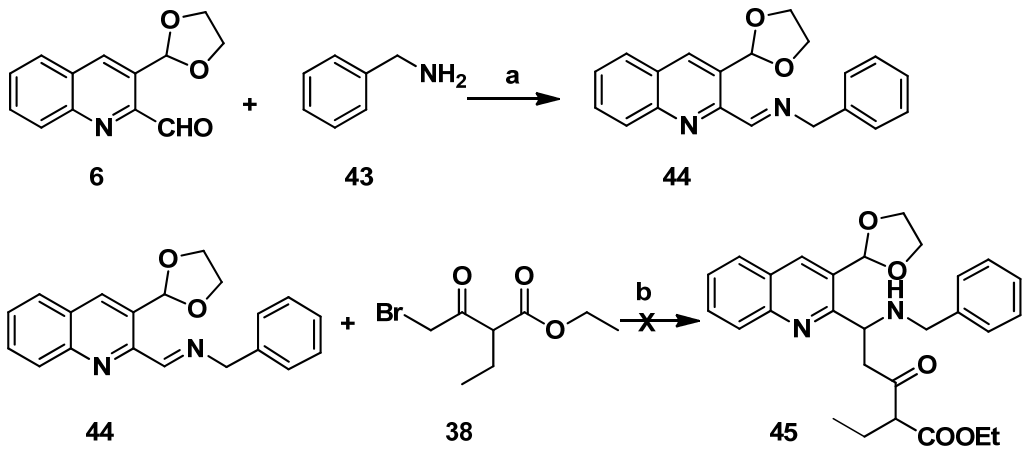
Thus though it was possible to form carbon-carbon bond using Reformatsky reaction, the yield was very disappointing even after changing quality and quantity of zinc as well as by changing the solvent from benzene/ether to THF.



Scheme 24: ***Reagents and conditions:*** *a) Triethylamine, mesyl chloride, 0 ^oC-rt, 30%.*

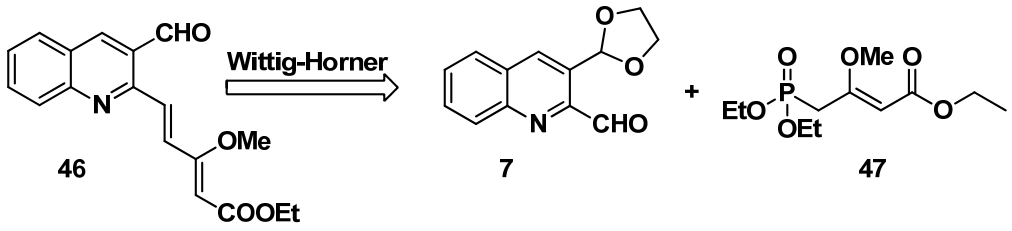
Having failed to improve the yield of Reformatsky reaction with repeated trials, attention was shifted to utilization of Reformatsky reaction on imine **44**, based on the literature precedence.[17]

The imine **44** was prepared by using quinoline aldehyde **6** and benzyl amine **43** in methanol at 0 ^oC and without characterization of imine **44**, it was treated with bromo compound **38** in presence of activated zinc and catalytic amount of iodine in THF at room temperature to reflux but it resulted in complex reaction mixture (Scheme 25).



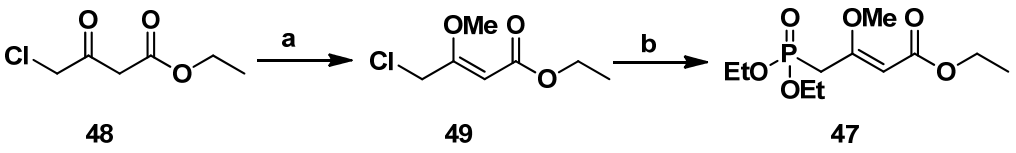
Scheme 25: ***Reagents and conditions:*** *a) Methanol, 0 °C to rt, 1 h; b) Zn, iodine, THF, rt-reflux.*

Though success was achieved in synthesis of enone **41**, the yields were very disappointing. So it was thought to prepare aldehyde **46** by utilizing Wittig-Horner reaction (Scheme 26) to get tricyclic frame of camptothecin **1** *via* reductive amination.



Scheme 26

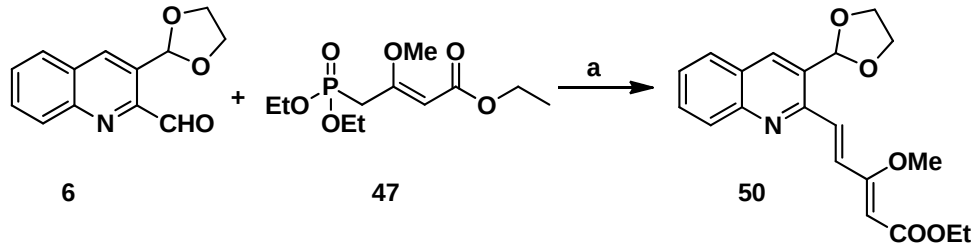
The phosphonate ester **47** was synthesized from commercially available ethyl 4-chloroacetoacetate **48** by following the literature procedure.[18] Thus ethyl 4-chloroacetoacetate **48** was treated with thionyl chloride and methanol at -5-0 °C and reaction was stirred at room temperature for 30 min. Then catalytic amount of methanesulfonic acid was added to the reaction mixture and it was heated for 3 h to afford the enol ether **49**. Enol ether **49** was heated at 120 °C with triethylphosphite to afford the phosphonate ester **47** (Scheme 27). Compounds **49** and **47** were characterized by spectroscopic techniques. Spectroscopic data was in good agreement with reported data.[18]



48 **49** **47**

Scheme 27: ***Reagents and conditions:*** *a) $SOCl_2$, MeOH, methanesulphonic acid (cat), rt-heat, 4 h, 90%; b) Triethylphosphite, 120 ^oC, 12 h, 84%.*

Having synthesized the required phosphonate ester **47**, next task was to condense with aldehyde **6** by utilizing Wittig-Horner reaction. Thus, aldehyde **6** was subjected to Wittig-Horner olefination using NaH in THF for 1 h to furnish the condensed compound **50** in 82% yield as a mixture of *E* and *Z* isomers (Scheme 28). The IR spectrum of **50** showed strong absorption at 1731 cm^{-1} corresponding to ester functionality. ^1H NMR spectrum of **50** showed two triplets that appeared at δ 1.35 and 1.36 integrating for three protons and two singlets at δ 3.77 and 3.82 integrating for three protons due to the presence of *E/Z* isomers and were assigned to ester methyl and methoxy group protons. The two singlets at δ 5.23 and 5.26 integrating for one proton were assigned to proton α to ester group. The multiplet that appeared at δ 4.10-4.29 integrating for six protons was assigned to acetal methylene and ester methylene protons. ^{13}C NMR and DEPT spectra clearly showed that the compound **50** existed as the mixture of E/Z isomers by showing doubling of peaks. The mass spectrum of compound **50** displayed the *m/z* peaks at 356 $(M + H)^+$ and 378 $(M + Na)^+$ and its elemental analysis was also found to be in good agreement with calculated values.

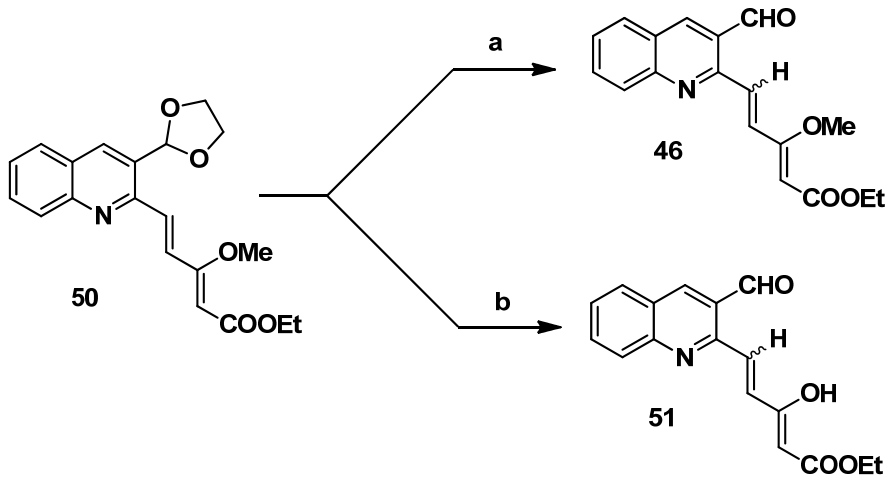


6 **47** **50**

Scheme 28: ***Reagents and conditions:*** *a) NaH, THF, 0 ^oC to rt, 1 h, 82%.*

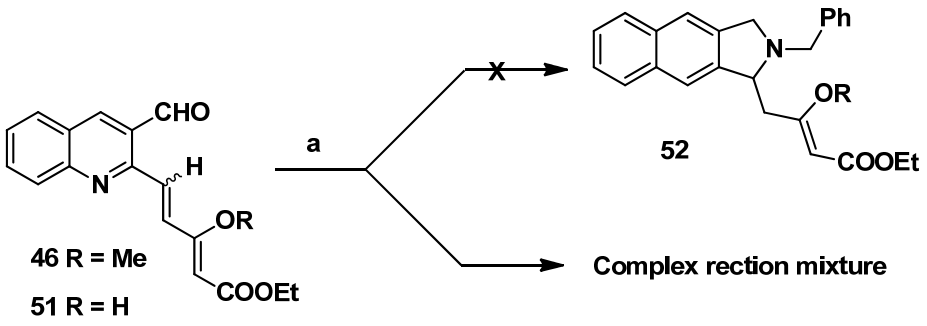
With condensed compound **50** in hand, next goal was to get aldehyde **46** to perform reductive amination. Thus, acetal deprotection was carried out using 2N HCl in diethyl ether to afford the aldehyde **46** in 85% yield while compound **50** on treatment with 6N HCl in diethyl ether afforded aldehyde **51** in 80% yield (Scheme 29). Both the

compounds **46** and **51** were characterized by using spectroscopic methods. The IR spectrum of **46** showed strong absorptions at 2720, 1700 and 1730 cm^{-1} corresponding to aldehydic CH stretch, carbonyl and ester functionalities respectively. ^{1}H NMR spectrum of **46** showed disappearance of peak due to acetal protons and appearance of new peaks at δ 10.40 and 10.45 (due to *E*/*Z* isomer) integrating for one proton which was assigned to aldehydic proton. The signal that appeared at δ 3.83 as singlet integrating for three protons was assigned to methoxy protons thus confirming the transformation. ^{13}C NMR along with DEPT spectra of **46** revealed the presence of two methyl group carbons and signal that appeared at δ 190.8 was assigned to aldehydic carbon. The rest of protons and carbons associated with the structure resonated at expected positions. The mass spectrum of compound **46** displayed the *m/z* peaks at 312 $(M + H)^+$ and 334 $(M + Na)^+$ and its elemental analysis was also found to be in good agreement with calculated values.



Scheme 29: ***Reagents and conditions:*** *a) 2N HCl, diethyl ether, rt, 2 h, 85%; b) 6 N HCl, diethyl ether, rt, 3 h. 80%.*

The IR spectrum of **51** showed strong absorptions at 3250 and 1702 cm^{-1} corresponding to enol hydroxy and aldehyde carbonyl functionality and at 1730 cm^{-1} corresponding to ester functionality. ^{1}H NMR spectrum of **51** showed disappearance of peak due to acetal protons and methoxy protons and appearance of new peaks at δ 10.40 and 11.90 integrating for one proton each which were assigned to aldehydic and enolic proton and thus confirmed the desired transformation, while rest of protons associated with compound resonated at expected positions. The mass spectrum of compound **51** displayed the *m/z* peaks at 298 $(M + H)^+$ and 320 $(M + Na)^+$.



Scheme 30: ***Reagents and conditions:*** *a) $PhCH_2NH_2$, methanol, then $NaBH_4$.*

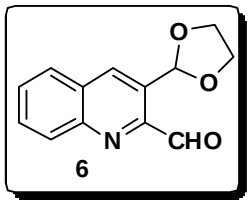
Having aldehydes **46** and **51** in hand, next task was to construct the tricyclic ring by utilizing reductive amination. Accordingly both the aldehydes **46** and **51** were separately subjected to reductive amination by using benzyl amine in methanol at 0 ^oC followed by reduction of imine by addition of $NaBH_4$ but unfortunately both the reactions led to complex reaction mixture (Scheme 30).

1.2.5 Conclusion

In conclusion, four advanced intermediates **14, 41, 46** and **51** for synthesis of camptothecin were prepared and out of these three were studied for cyclisation to build C ring of camptothecin by using reductive amination. Although due to paucity of time, these could not be converted to tricyclic framework under the conditions tried, by proper choice of reagents and conditions these would serve as important substrates to access tricyclic quinoline.

1.2.6 Experimental

3-(1, 3-Dioxolan-2-yl) quinoline-2-carbaldehyde (6)



6

3-[1,3] Dioxolan-2-yl-2-iodo-quinoline **11** (1.0 g, 3.05 mmol) in dry diethyl ether (50 mL) at -70 ^{o}C under N_2 atmosphere was treated with *n*-BuLi (1.67 mL, 2M solution in toluene, 3.35 mmol) with stirring and after few minutes dry DMF was added. After reaching ambient temperature, the solution was treated with water and extracted with $CHCl_3$ (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude aldehyde, which was purified by flash column chromatography over silica gel using ethyl acetate/pet ether (3:7) as eluent to give pure **6** (0.4 g, 58%) as yellow solid.

Mol. Formula **:** $C_{13}H_{11}NO_3$ (MW: 229.23).

Melting Point **:** 145 ^{o}C.

IR ($CHCl_3$) **:** 1685, 1617, 1560, 1145, 910 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 4.16 (s, 4H), 6.73 (s, 1H), 7.57 (t, *J* = 8.3 Hz, 1H), 7.61 (t, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 8.60 (s, 1H), 10.37 (s, 1H).

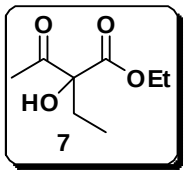
^{13}C NMR ($CDCl_3$, 50 MHz): δ 65.2 (2C), 98.8, 127.9, 128.5, 129.3, 129.8, 130.5, 130.6, 135.0, 147.2, 150.0, 194.1.

Mass (ESI) m/z **:** 230 $(M + H)^+$.

Elemental analysis **:** Calculated**:** C, 68.11; H, 4.84; N, 6.11%

: Found**:** C, 68.11; H, 4.84; N, 6.14%

Ethyl 2-ethyl-2-hydroxy-3-oxobutanoate (7)



7

To the anhydrous cobalt (II) chloride (0.038 g, 0.316 mmol) heated at 60 ^{o}C in acetonitrile, was addded isopropanol (1 mL) under oxygen atmosphere. The *β*-keto ester **13**[16b] (1 g, 6.32 mmol) was then added to the reaction mixture in acetonitrile (5 mL). After completion of reaction (24 h, TLC), the solvent was evaporated in *vacuo* and the residue was purified by flash column chromatography using ethyl acetate/pet ether (3:7) as eluent to afford hydroxy compound **7** as oil (0.94 g, 65%).

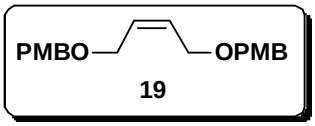
Mol. Formula **:** $C_8H_{14}O_4$ (MW: 174.19).

IR ($CHCl_3$) **:** 3450, 1740, 1715 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.60-1.82 (m, 2H), 2.00 (s, 3H), 4.11 (q, *J* = 7.0 Hz, 2H).

Mass (ESI) m/z **:** 175 $(M + H)^+$.

(*Z*)-1, 4-Bis(4-methoxybenzyloxy)but-2-ene (19)



To the suspension of NaH (50% dispersion in oil, 5.99 g, 124.84 mmol) in DMF (80 mL), the solution of *cis*-butene-1,4-diol **18** (5.0 g, 56.74 mmol) in dry DMF (20 mL) was added. After 30 min, PMBCl (16.9 mL, 124.84 mmol) was introduced and stirred for additional 4 h at room temperature. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was done by flash column chromatography (SiO_2) using ethyl acetate/pet ether (2:8) as an eluent to afford PMB ether **19** (18.6 g) as a yellow liquid in quantitative yield.

Mol. Formula **:** $C_{20}H_{24}O_4$ (MW: 328.40).

IR (Neat) **:** 3008, 2931, 1684, 1035, 759 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.84 (s, 6H), 4.07 (d, *J* = 4.8 Hz, 4H), 4.46 (s, 4H), 5.81 (t, *J* = 4.8 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 4H), 7.29 (d, *J* = 8.7 Hz, 4H).

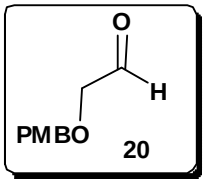
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.0 (2C), 65.3 (2C), 71.7 (2C), 113.6 (4C), 129.2 (4C), 129.3 (2C), 130.1 (2C), 159.0 (2C).

Mass (ESI) m/z **:** 329 $(M + H)^+$, 351 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 73.15; H, 7.37; O, 19.49%

: Found: C, 73.05; H, 7.32; O, 19.45%

2-(4-Methoxybenzyloxy) acetaldehyde (20)



To a stirred solution of **19** (10.0 g, 30.45 mmol) in acetone-H_2O (3:1, 100 mL) at room temperature, was added OsO_4 (0.33 mL, 0.61 mmol, 2M solution in toluene). The reaction mixture was stirred for 30 min and $NaIO_4$ (16.28 g, 76.12 mmol) was added to the reaction mixture.

The mixture was stirred at room temperature for 12 h and then quenched with aqueous Na_2SO_4 and extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2) using ethyl acetate/pet ether (3:7) as eluent to afford aldehyde **20** (11.4 g, 95%) as colourless liquid.

Mol. Formula **:** $C_{10}H_{12}O_3$ (MW: 180.20).

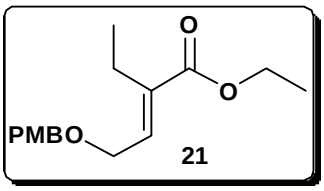
IR (Neat) **:** 3010, 2730, 1702, 1684, 763 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.82 (s, 3H), 4.08 (s, 2H), 4.57 (s, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 9.71 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 55.1, 73.1, 74.8, 113.8 (2C), 128.7, 129.6 (2C), 159.4, 200.4.

Mass (ESI) m/z **:** 181 $(M + H)^+$.

(*E*)-Ethyl 2-ethyl-4-((4-methoxybenzyl)oxy)but-2-enoate (21)



21

To a solution of aldehyde **20** (5.0 g, 27.70 mmol) in dichloromethane (100 mL), Ph_3P=C(Et)COOEt **22** (15.8 g, 41.6 mmol) was added at room temperature and the reaction mixture was stirred for 12 h at the same temperature. Removal of the solvent under reduced pressure gave crude compound **21**. The residue was purified by flash column chromatography (SiO_2) using ethyl acetate/pet ether (1:9) as eluent to afford compound **21** (5.6 g, 73 %) as colorless oil.

Mol. Formula **:** $C_{16}H_{22}O_4$ (MW: 278.34).

IR (Neat) **:** 2936, 1731, 1612, 1367, 1173, 757 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.00 (t, *J* = 7.5 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 2.28 (q, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.15-4.26 (m, 4H), 4.48 (s, 2H), 6.83 (t, *J* = 6.1 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H).

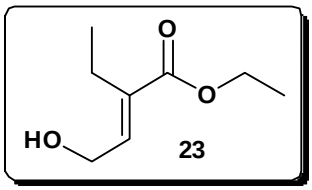
^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.6, 14.1, 20.4, 55.1, 60.4, 66.0, 72.3, 113.7 (2C), 129.3, 129.7 (2C), 135.5, 137.4, 159.2, 167.0.

Mass (ESI) m/z **:** 279 $(M + H)^+$, 301 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 69.04; H, 7.97%

: Found: C, 69.01; H, 7.91%

(*E*)-Ethyl 2-ethyl-4-hydroxybut-2-enoate (23)



To a solution of PMB ether **21** (4.0 g, 14.32 mmol) in DCM:H_2O (9:1) at 0 °C was added DDQ (3.5 g, 15.80 mmol). The reaction mixture was stirred for 3 h at the room temperature and diluted with dichloromethane and saturated sodium bicarbonate. The organic layer was washed with sodium bicarbonate, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified using flash column chromatography (SiO_2) eluting with ethyl acetate/pet ether (3:7) to afford alcohol **23** (2.1 g, 94%) as a colorless oil.

Mol. Formula **:** $C_8H_{14}O_3$ (MW: 158.19).

IR (Neat) **:** 3350, 1731, 1600, 1137 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 2.29 (q, *J* = 7.5 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.36 (d, *J* = 6.2 Hz, 2H), 6.78 (t, *J* = 6.2 Hz, 1H).

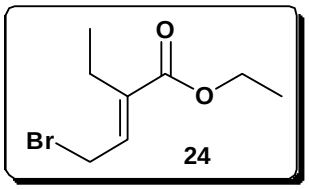
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.7, 14.0, 20.2, 58.9, 60.6, 134.5, 139.8, 167.4.

Mass (ESI) m/z **:** 159 $(M + H)^+$, 181 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 60.74; H, 8.92%

: Found: C, 60.69; H, 8.88%

(*E*)-Ethyl 4-bromo-2-ethylbut-2-enoate (24)



A solution of **23** (2.0 g, 12.64 mmol) and PBr_3 (1.2 mL, 6.32 mmol) in diethyl ether (60 mL) was stirred at 0 ^oC for 4 h. The reaction mixture was quenched by the addition of saturated aqueous solution of KBr and layers were separated. The aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford title compound **24** (2.68 g, 96%) as a yellowish oil, and was pure enough for further use.

Mol. Formula **:** $C_8H_{13}BrO_2$ (MW: 221.09).

IR (Neat) **:** 1730, 1630, 1245 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.08 (t, *J* = 7.5 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 2.40 (q, *J* = 7.5 Hz, 2H), 4.03 (d, *J* = 8.5 Hz, 2H), 4.22 (d, *J* = 7.2 Hz, 2H), 6.86 (t, *J* = 8.5 Hz, 1H).

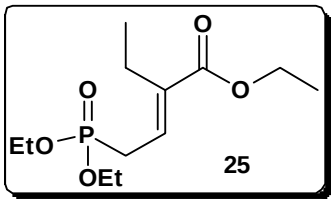
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.6, 14.0, 19.8, 25.7, 60.7, 134.2, 137.9, 166.7.

Mass (ESI) m/z **:** 222 and 224 (1:1) $(M + H)^+$.

Elemental analysis **:** Calculated: C, 43.46; H, 5.93%

: Found: C, 43.42; H, 5.89%

(*E*)-Ethyl 4-(diethoxyphosphoryl)-2-ethylbut-2-enoate (25)



25

The bromo compound **24** (2.5 g, 11.30 mmol) and triethylphosphite (2.2 mL, 12.4 mmol) were heated at 120 ^oC for 12 h. Excess of triethylphosphite was removed under high vacuum to furnish **25** (3.11 g) as colorless oil and was pure enough for further use.

Mol. Formula **:** $C_{12}H_{23}O_5P$ (MW: 278.28).

IR (Neat) **:** 2934, 1730, 1446, 1392, 1167 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.02 (t, *J* = 7.5 Hz, 3H), 1.25-1.35 (m, 9H), 2.27-2.40 (m, 2H), 2.74 (dd, *J* = 8.2 and 23.5 Hz, 2H), 4.04-4.26 (m, 6H), 6.63-6.75 (m, 1H).

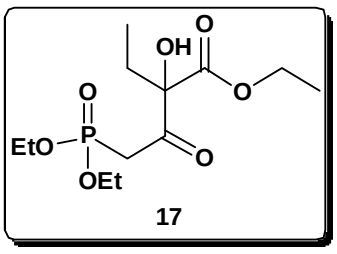
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.3 (d), 14.0, 16.2 (d, 2C), 19.9 (d), 27.0 (d), 60.4, 62.0 (d, 2C), 129.3 (d), 137.6 (d), 166.7 (d).

Mass (ESI) m/z **:** 279 $(M + H)^+$, 301 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 51.79; H, 8.33%

: Found: C, 51.75; H, 8.29%

Ethyl 4-(diethoxyphosphoryl)-2-ethyl-2-hydroxy-3-oxobutanoate (17)



17

To a well-stirred solution of olefin **25** (2 g, 7.18 mmol) and AcOH (2.2 mL, 35.9 mmol) in aqueous acetone (40 mL, 9:1) maintained at –10 ^oC, was added $KMnO_4$ (2.27 g, 14.3 mmol) in portions such that the reaction temperature remained below –10 ^oC. After stirring for 0.5 h at –10 ^oC, the black precipitate of MnO_2 was filtered off through a celite pad and the filtrate was

evaporated at reduced pressure to remove acetone and the aqueous layer was extracted with DCM (3 x 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish crude ketol. The ketol was purified by flash column chromatography (SiO_2) using ethyl acetate/pet ether (5:5) as eluent to afford product **17** (2.0 g, 84%).

Mol. Formula **:** $C_{12}H_{23}O_7P$ (MW: 310.28).

IR (Neat) **:** 3449, 2934, 1734, 1715, 1352, 1145 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.22-1.32 (m, 9H), 1.84-1.93 (m, 1H), 2.00-2.09 (m, 1H), 3.22 (dd, *J* = 22.3 and 13.8 Hz, 1H), 3.47 (dd, *J* = 13.8 and 22.3 Hz, 1H), 4.07-4.15 (m, 4H), 4.18-4.28 (m, 2H).

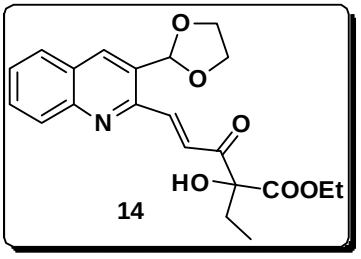
^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.3, 13.9, 16.1, 16.2, 28.9, 37.2 (d), 62.6, 67.7 (d), 62.8 (d), 84.8 (d), 170.0, 200.2 (d).

Mass (ESI) m/z **:** 311 $(M + H)^+$, 333 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 46.45; H, 7.47%

: Found: C, 46.41; H, 7.42**%**

(*E*)-Ethyl 5-(3-(1,3-dioxolan-2-yl)quinolin-2-yl)-2-ethyl-2-hydroxy-3-oxopent-4-enoate (14)



14

To the stirred solution of aldehyde **6** (1 g, 4.36 mmol) in dry DCM (20 mL) at room temperature was added Et_3N (1.1 mL, 10.9 mmol). Reaction mixture was stirred for 15 min and then phosphonate ester **17** (1.48 g, 4.79 mmol) in DCM (10 mL) was added dropwise. After completion of reaction (TLC, 5 h), the reaction mixture was quenched by water and the organic phase was separated and aqueous phase was extracted with DCM (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 was purified by flash column chromatography (SiO_2) using ethyl acetate/pet ether (3:7) as an eluent to afford condensed compound **14** as a pale yellow thick liquid (1.3 g, 82%).

Mol. Formula **:** $C_{21}H_{23}NO_6$ (MW: 385.41).

IR (Neat) **:** 3390, 1737, 1705, 1610, 1444, 1256, 1143, 865, 763 cm^{-1}.

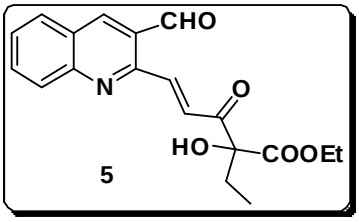
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H), 2.10-2.35 (m, 2H), 4.10-4.25 (m, 4H), 4.29 (q, *J* = 7.0 Hz, 2H), 6.19 (s, 1H), 7.59 (t, *J* = 6.8 Hz, 1H), 7.73-7.88 (m, 2H), 8.03 (d, *J* = 15.1 Hz, 1H), 8.20-8.24 (m, 2H), 8.36 (d, *J* = 15.1 Hz, 1H).

Mass (ESI) m/z **:** 408 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 65.44; H, 6.02; N, 3.63%

: Found: C, 65.40; H, 6.04; N, 3.59%

(*E*)-Ethyl 2-ethyl-5-(3-formylquinolin-2-yl)-2-hydroxy-3-oxopent-4-enoate (5)



5

To the acetal **14** (0.075 g, 2.59 mmol) dissolved in THF (10 mL) was added 10% HCl (2 mL) and stirred for 2 h. After removing the THF under reduced pressure, the residue was diluted with DCM. The organic layer was washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The generated residue was purified by flash column chromatography (SiO_2) eluting with 25% ethyl acetate/pet ether to afford aldehyde **5** (0.075 g, 85%) as yellow thick oil.

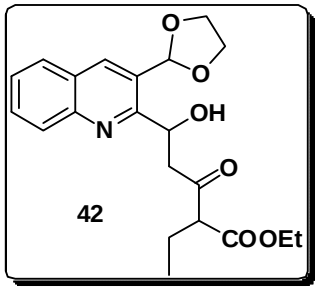
Mol. Formula **:** $C_{19}H_{19}NO_5$ (MW: 341.36).

IR (Neat) **:** 3390, 2730, 1736, 1705, 1600, 1560, 1445, 1154, 856 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.96 (t, *J* = 7.4 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 2.08-2.35 (m, 2H), 4.30 (q, *J* = 7.0 Hz, 2H), 7.63-7.71 (m, 1H), 7.87-8.05 (m, 3H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.66 (s, 1H), 8.77 (d, *J* = 15.5 Hz, 1H), 10.44 (s, 1H).

Mass (ESI) m/z **:** 342 $(M + H)^+$, 364 $(M + Na)^+$.

Ethyl 5-(3-(1, 3-dioxolan-2-yl) quinolin-2-yl)-2-ethyl-5-hydroxy-3-oxopentanoate (42)



To the stirred suspension of activated zinc (0.255 g, 3.92 mmol) in anhydrous benzene-ether (10 mL, 1:1), was added quinoline aldehyde **6** (0.3 g, 1.30 mmol) followed by solution of bromo compound **38** (0.339 g, 1.42 mmol) in anhydrous benzene-ether (5 mL, 1:1) followed by catalytic amount of iodine at room temperature. Reaction mixture was heated at reflux for 7 h. After completion, the reaction mixture was cooled and diluted with ethyl acetate (10 mL), water was added, resulting mixture was filtered through sintered funnel and residue was washed with ethyl acetate (20 mL) and the filtrate was extracted with ethyl acetate (3 x 30 mL). Organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure and residue was purified by flash column chromatography (SiO_2) eluting with ethyl acetate/pet ether (4:6) to furnish desired compound **42** (0.153 g, 30%).

Mol. Formula **:** $C_{21}H_{25}NO_6$ (MW: 387.43).

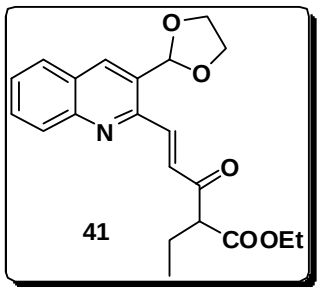
IR (Neat) **:** 3400, 1738, 1715, 1610, 1535, 1145, 863, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.97 and 0.98 (2t, *J* = 7.4 Hz, 3H), 1.22-1.33 (m, 3H), 1.83-2.08 (m, 2H), 2.97-3.31 (m, 2H), 3.49-3.58 (m, 1H), 4.06-4.26 (m, 6H), 5.67-5.74 (m, 1H), 6.12 (d, *J* = 5.0 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.76 (t, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.38 (s, 1H).

^{13}C NMR ($CDCl_3$), 50 MHz): δ 11.9, 12.0, 14.1, 14.2, 21.3, 21.4, 49.2, 49.5, 61.0, 61.11, 61.18, 61.6, 65.3, 66.9, 67.4, 101.0, 101.2, 127.0, 127.1, 127.7, 127.8, 127.9, 128.3, 128.4, 130.4, 130.5, 135.9, 136.1, 146.23, 146.28, 159.4, 159.5, 169.4, 169.6, 203.5, 203.7 (mixture of diastereomers).

Mass (ESI) m/z **:** 410 $(M + Na)^+$.

(*E*)-Ethyl 5-(3-(1, 3-dioxolan-2-yl) quinolin-2-yl)-2-ethyl-3-oxopent-4-enoate (41)



To the stirred solution of alcohol **42** (0.1 g, 0.259 mmol) in anhydrous DCM (10 mL), was added triethyl amine (0.06 mL, 0.516 mmol) followed by mesyl chloride (0.03 mL, 0.387 mmol) at 0 ^{o}C. The reaction mixture was stirred at 50 ^{o}C for 4 h, cooled and water was added. The aqueous phase was extracted with DCM (3 x 20 mL). Combined organic layer was washed with aqueous solution of $NaHCO_3$ and then brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with the mixture of ethyl acetate/petroleum ether (3:7) as eluent to afford the compound **41** (0.028 g, 30%).

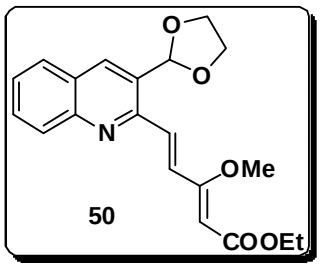
Mol. Formula **:** $C_{21}H_{23}NO_5$ (MW: 369.41).

IR (Neat) **:** 1733, 1716, 1610, 1450, 1535, 1145, 863, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.02 and 1.16 (t, *J* = 7.0 Hz, 3H), 1.29 and 1.37 (t, *J* = 7.4 Hz, 3H), 2.04 (q, *J* = 7.0, 14.6 Hz, 1H), 2.64 (q, *J* = 7.0, 14.6 Hz, 1H), 3.72 (t, *J* = 7.0 Hz, 1H), 4.11-4.36 (m, 6H), 6.20 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 6.9 Hz, 1H), 7.67 (d, *J* = 15.2 Hz, 1H), 7.75-7.88 (m, 2H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 15.2 Hz, 1H), 8.37 (s, 1H).

Mass (ESI) m/z **:** 370 $(M + 1)^+$, 392 $(M + Na)^+$.

(2*Z*,4*E*)-Ethyl 5-(3-(1,3-dioxolan-2-yl)quinolin-2-yl)-3-methoxypenta-2,4-dienoate (50)



To the suspension of 50% NaH (0.156 g, 3.27 mmol) (washed with dry petroleum ether 2-3 times) in dry THF (10 mL), was added **47** (0.73 g, 2.61 mmol) in dry THF (10 mL) at 0 ^{o}C, and stirred for 5 min. Then aldehyde **6** (0.5 g, 2.18 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h. On completion of the reaction, it was quenched by the addition of saturated ammonium chloride solution, extracted with ethyl acetate (3 x 20 mL) and washed with brine. The

combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by flash column chromatography using ethyl acetate/petroleum ether (3:7) as eluent to afford compound **50** (0.635, 82%) as yellowish thick oil.

Mol. Formula **:** $C_{20}H_{21}NO_5$ (MW: 355.38).

IR (Neat) **:** 2900, 1731, 1620, 1560, 1395, 1305, 856 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.35 and 1.36 (t, *J* = 7.4 Hz, 3H), 3.77 and 3.82 (s, 3H), 4.10-4.29 (m, 6H), 5.23 and 5.26 (s, 1H), 6.21 and 6.25 (2s, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.67-7.82 (m, 3H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.34 (s, 1H), 8.76 (d, *J* = 15.4 Hz, 1H).

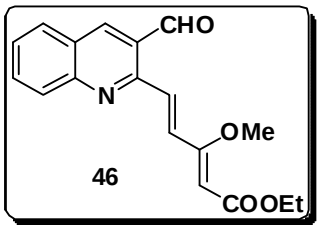
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.2, 14.4, 50.9, 51.0, 55.3, 65.2, 94.1, 100.9, 101.4, 126.6, 126.7, 126.8, 127.0, 127.6, 129.4, 129.7, 129.8, 130.4, 130.6, 133.7, 147.9, 152.5, 165.8, 166.0, 166.6, 167.0.

Mass (ESI) m/z **:** 356 $(M + H)^+$, 378 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 67.59; H, 5.96; N, 3.94%

: Found: C, 67.62; H, 5.92; N, 3.94%

(2*Z*, 4*E*)-Ethyl 5-(3-formylquinolin-2-yl)-3-methoxypenta-2,4-dienoate (46)



To the acetal **50** (0.5 g, 1.40 mmol) dissolved in THF (15 mL) was added 2N HCl solution (2 mL) and stirred for 2 h. After removing the THF under reduced pressure, the residue was diluted with DCM (25 mL). The organic layer was washed with saturated sodium bicarbonate solution. The organic layer was 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/pet ether (3:7) as eluent to provide the title compound **46** (0.372 g, 82%) as yellow thick oil.

Mol. Formula **:** $C_{18}H_{17}NO_4$ (MW: 311.33).

IR (Neat) **:** 2910, 2720, 1730, 1700, 1610, 1445, 1150, 855 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.34 and 1.36 (t, *J* = 7.0 Hz, 3H), 3.83 (s, 3H), 4.22 and 4.25 (2q, *J* = 7.0 Hz, 2H), 5.31 (s, 1H), 7.60 (t, *J* = 7.7 Hz,

1H), 7.81-7.95 (m, 2H), 8.20 (d, *J* = 8.6 Hz, 1H), 8.31 (d, *J* = 15.5 Hz, 1H), 8.62 (s, 1H), 8.80 (m, 1H), 10.4 and 10.45 (s, 1H).

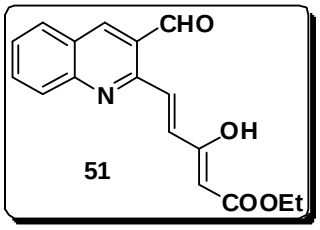
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.2, 14.3, 51.05, 51.08, 55.5, 59.7, 65.3, 94.1, 95.1, 126.5, 127.3, 127.4, 128.5, 128.7, 129.9, 130.0, 132.6, 142.6, 149.3, 153.1, 153.2, 165.6, 165.8, 166.6, 167.0, 190.8.

Mass (ESI) m/z **:** 312 $(M + H)^+$, 334 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 69.44; H, 5.50; N, 4.50%

: Found: C, 69.41; H, 5.47; N, 4.52%

(2*Z*,4*E*)-Ethyl 5-(3-formylquinolin-2-yl)-3-hydroxypenta-2,4-dienoate (51)



51

To the acetal **50** (0.2 g, 0.562 mmol) dissolved in THF (10 mL) was added 6N HCl solution (2 mL) and stirred for 2 h. After removing the THF under reduced pressure, the residue was diluted with DCM. The organic layer was washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (SiO_2) using ethyl acetate/pet ether (4:6) as eluent to provide of the title compound **51** (0.133 g, 80%) as brown thick oil.

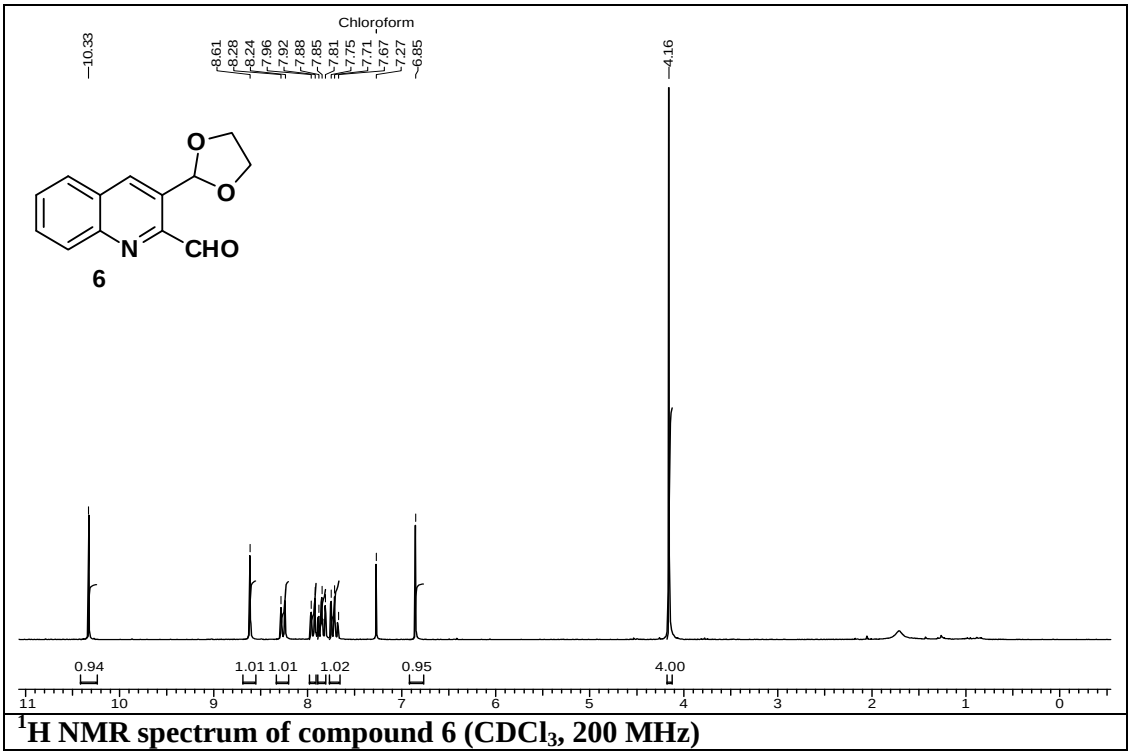
Mol. Formula **:** $C_{17}H_{15}NO_4$ (MW: 297.31).

IR (Neat) **:** 3250, 2900, 2710, 1730, 1702, 1590, 1145, 856 cm^{-1}.

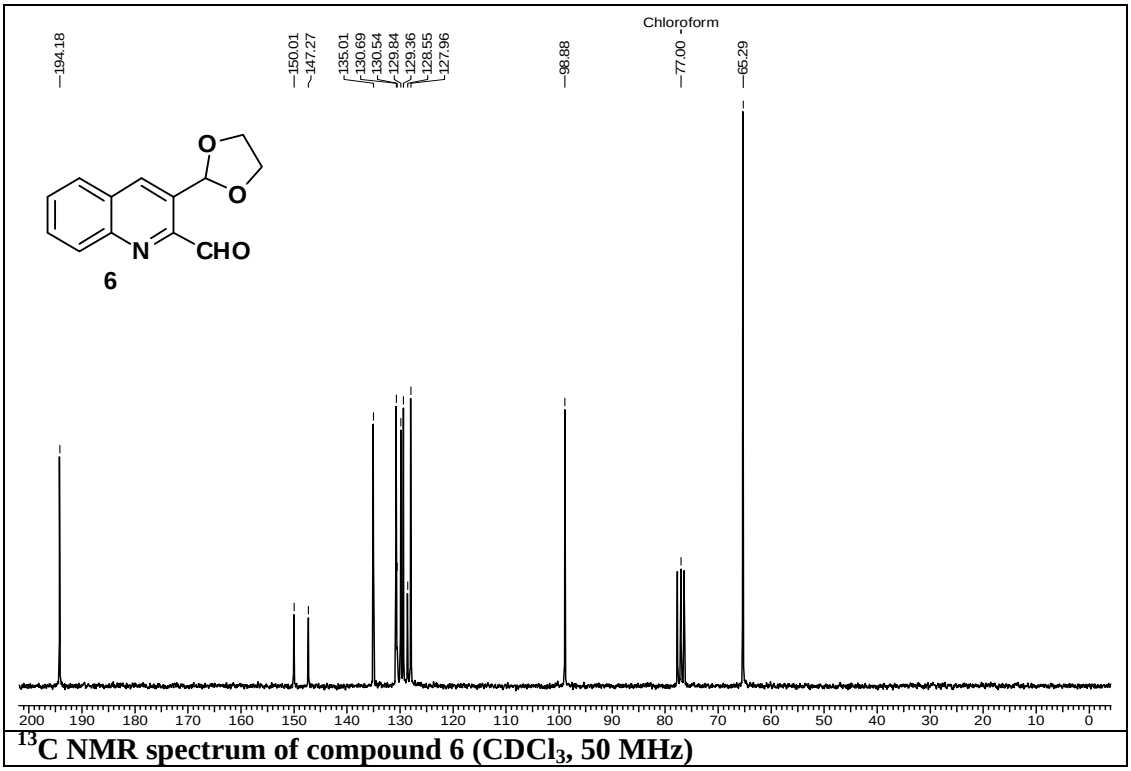
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.36 (t, *J* = 7.0 Hz, 3H), 4.28 (q, *J* = 7.0 Hz, 2H), 5.39 (s, 1H), 7.43 (dd, *J* = 13.5 and 15.1 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.83-7.92 (m, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.46 (d, *J* = 15.1 Hz, 1H), 8.65 (s, 1H), 10.40 (s, 1H), 11.90 (s, 1H).

Mass (ESI) m/z **:** 298 $(M + H)^+$, 320 $(M + Na)^+$.

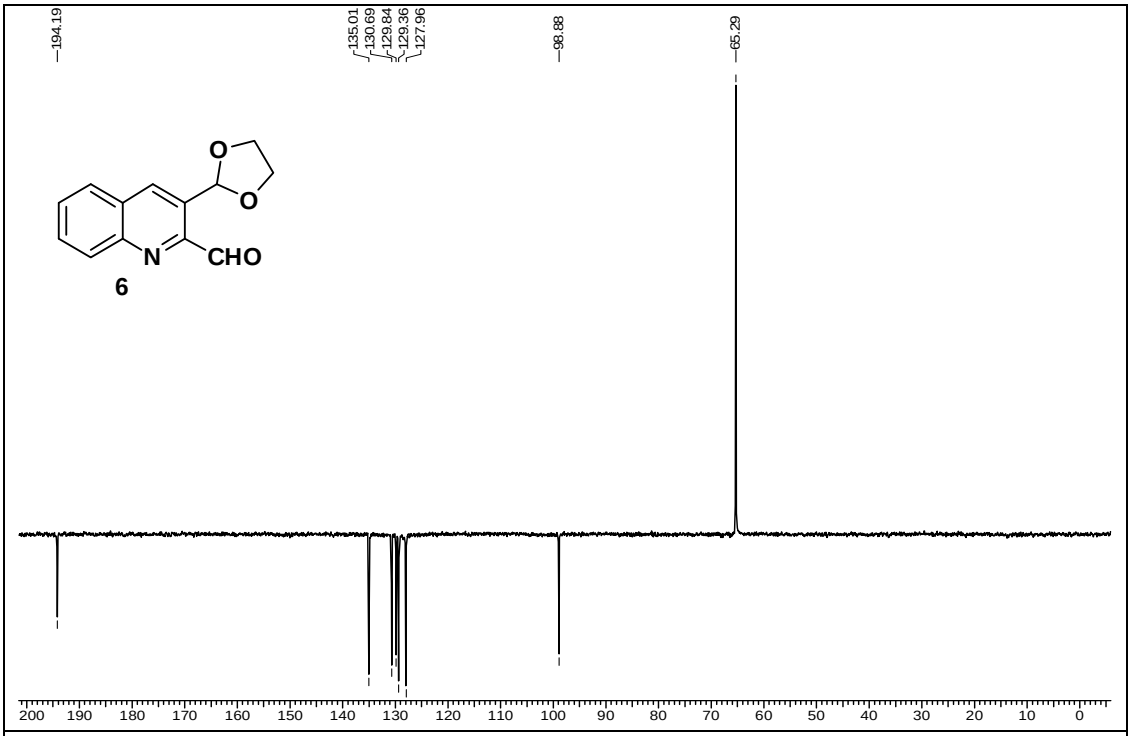
1.2.7 Spectra



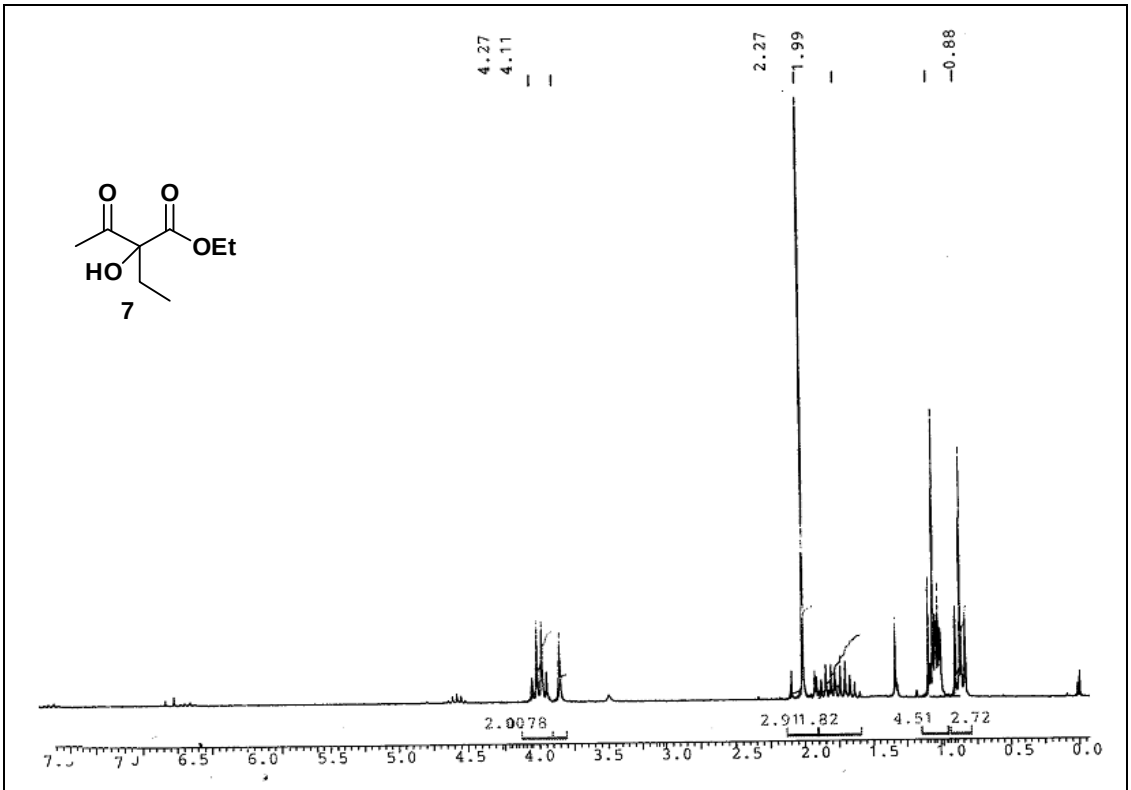
^{1}H NMR spectrum of compound 6 ($CDCl_3$, 200 MHz)



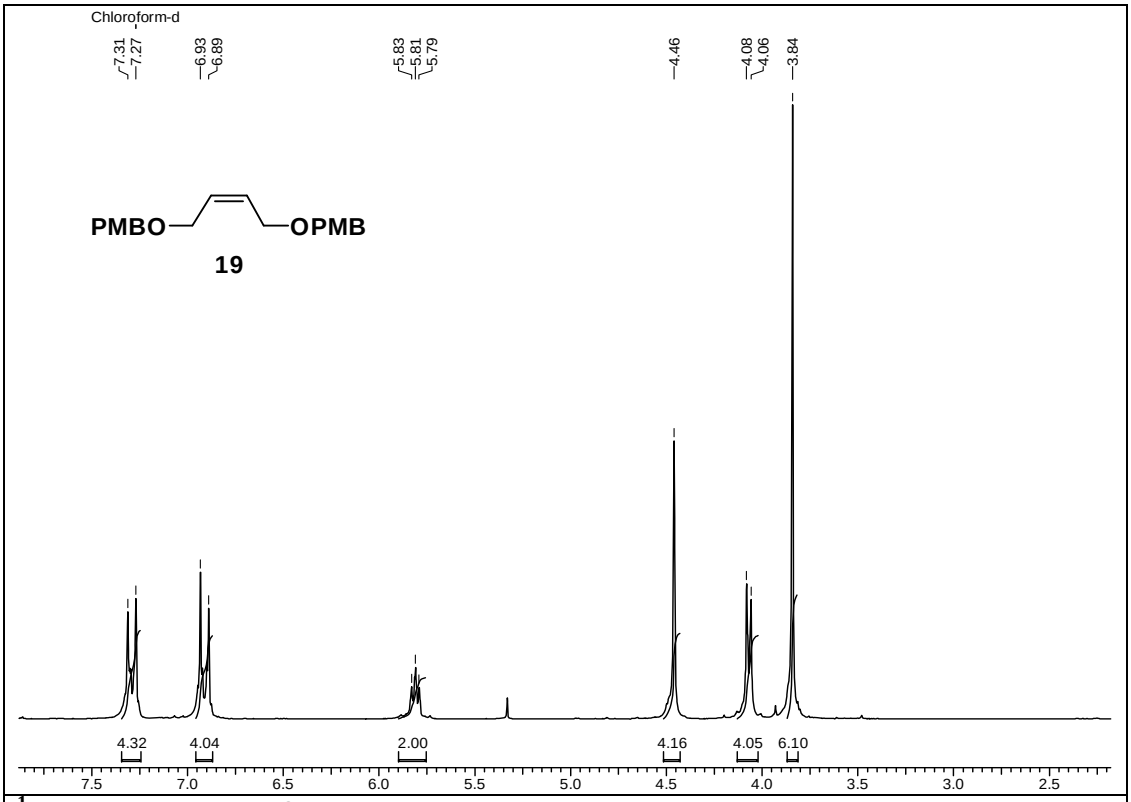
^{13}C NMR spectrum of compound 6 ($CDCl_3$, 50 MHz)



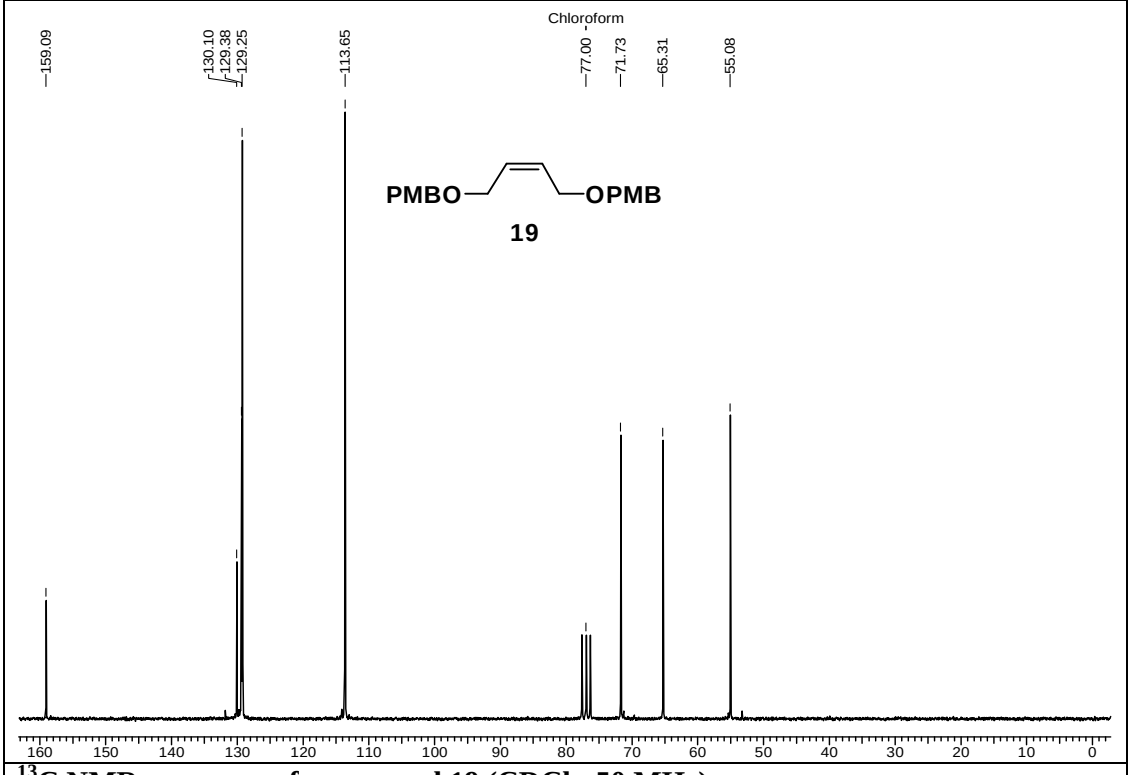
DEPT spectrum of compound 6 ($CDCl_3$, 50 MHz)



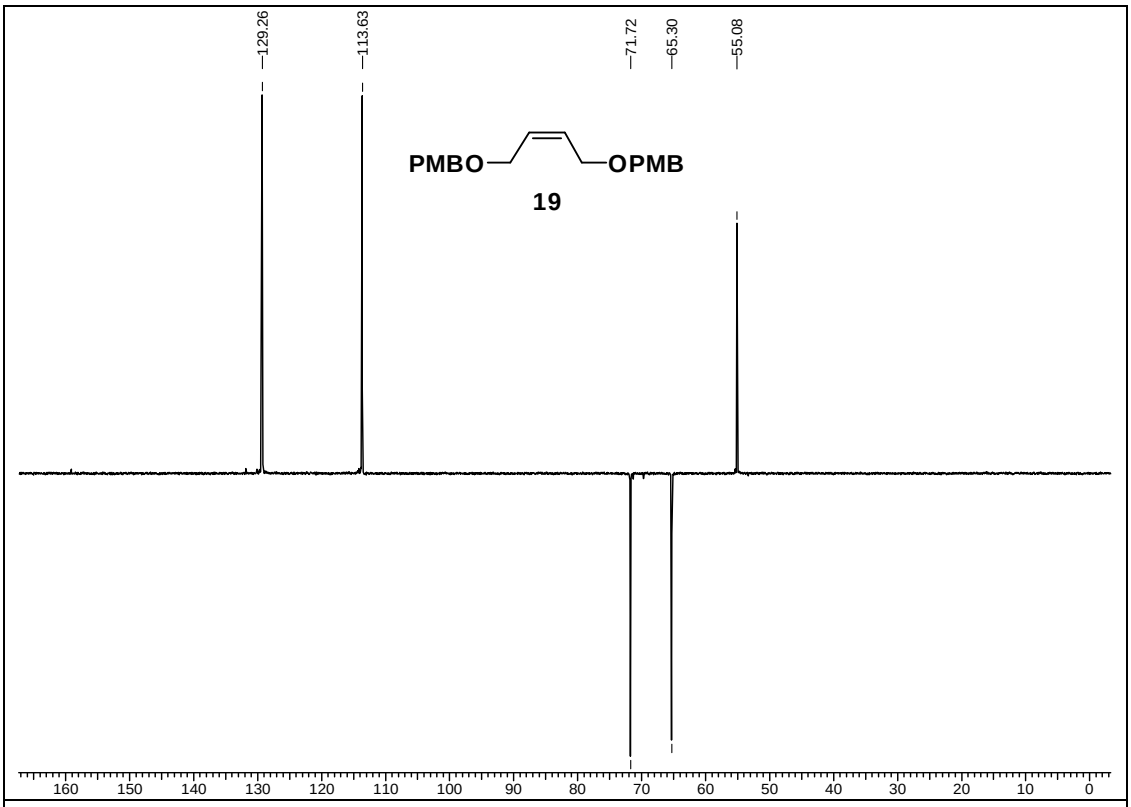
^{1}H NMR spectrum of compound 7 ($CDCl_3$, 200 MHz)



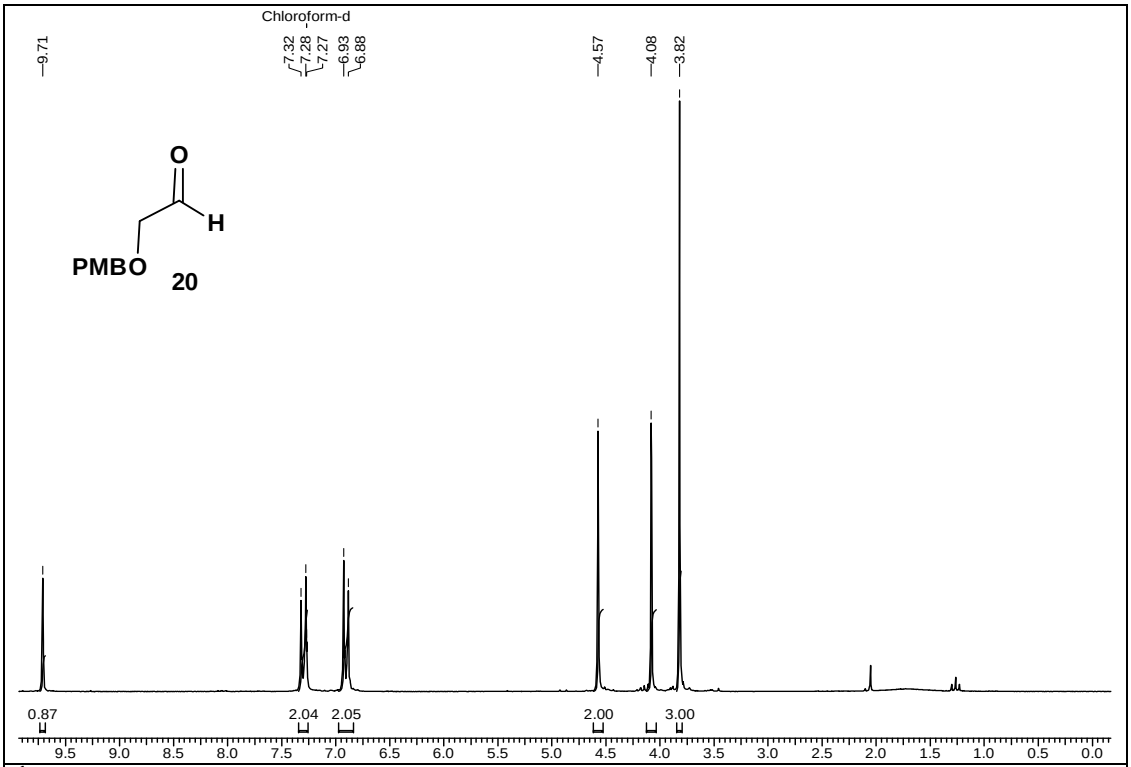
^{1}H NMR spectrum of compound 19 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound 19 ($CDCl_3$, 50 MHz)



DEPT spectrum of compound 19 ($CDCl_3$, 50 MHz)



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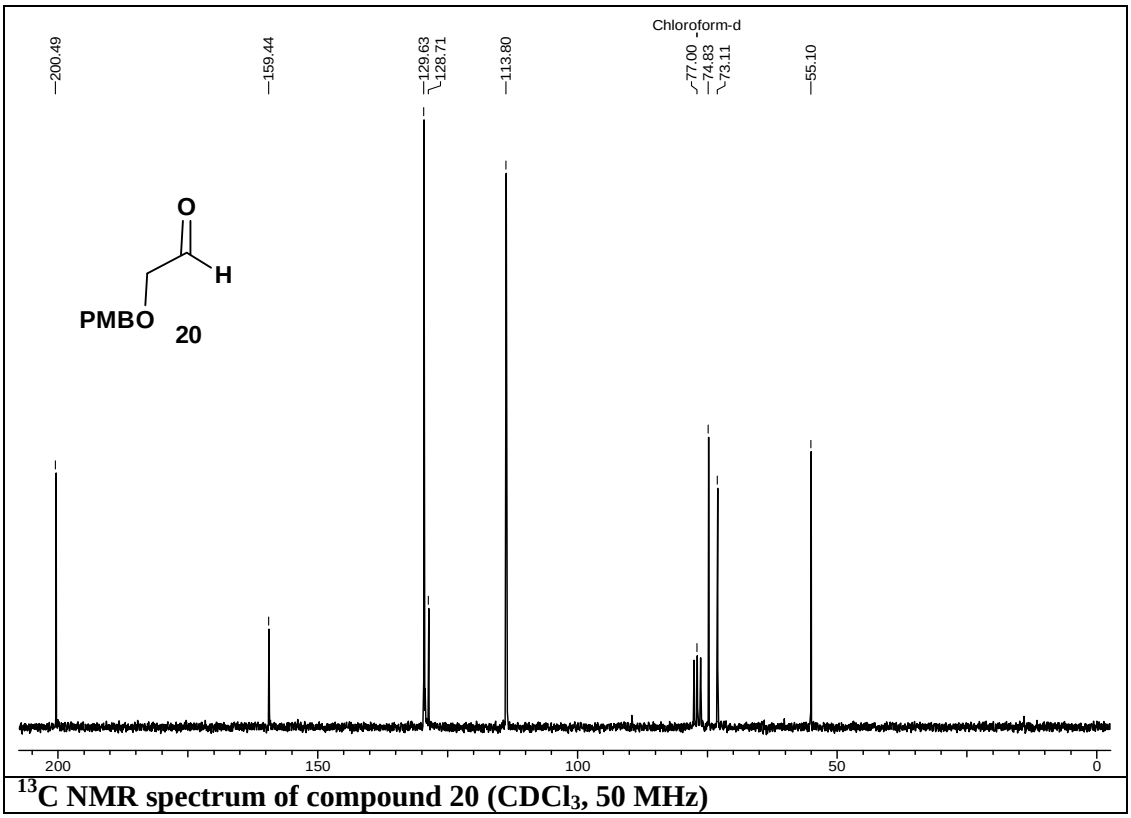
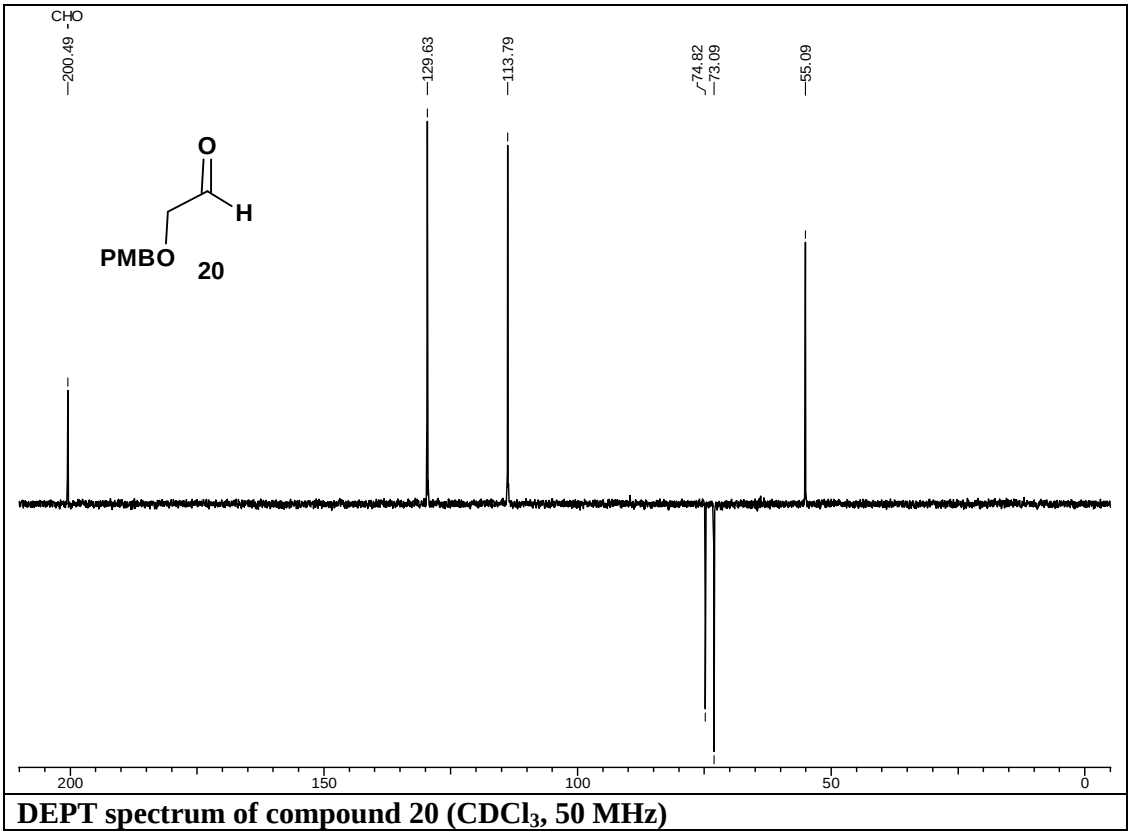
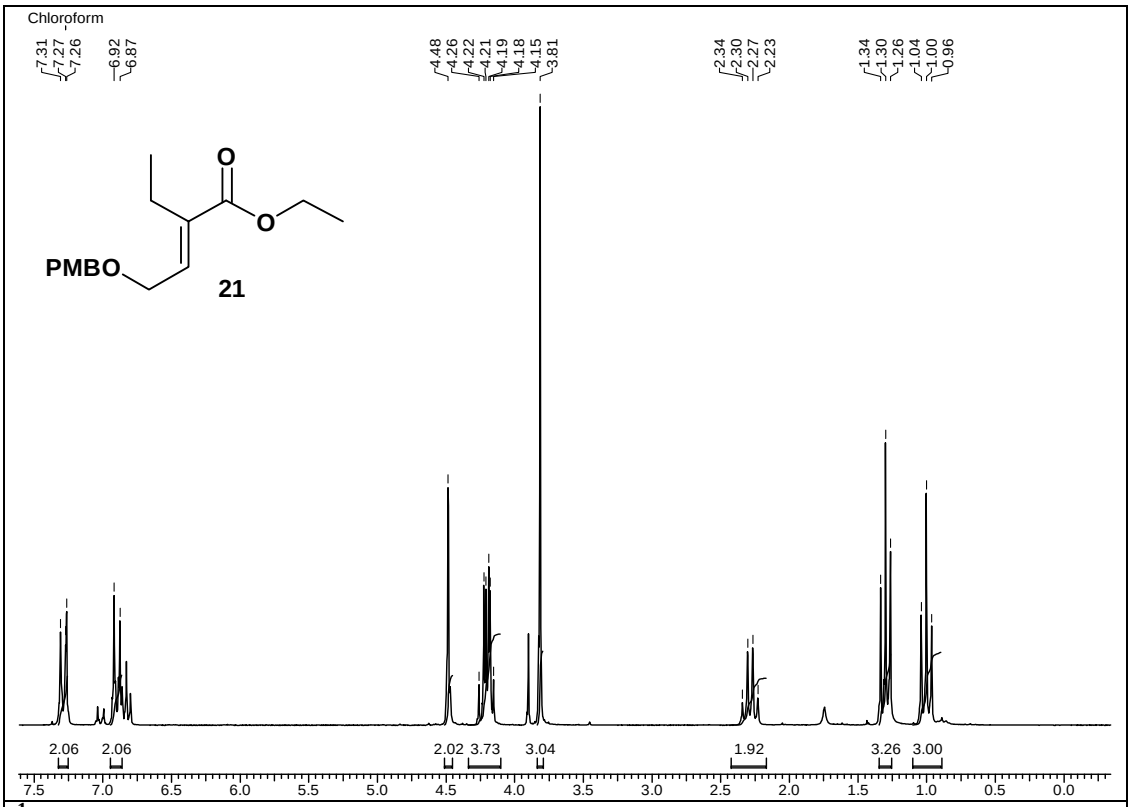


^{13}C NMR spectrum of compound 20 ($CDCl_3$, 50 MHz)



DEPT spectrum of compound 20 ($CDCl_3$, 50 MHz)



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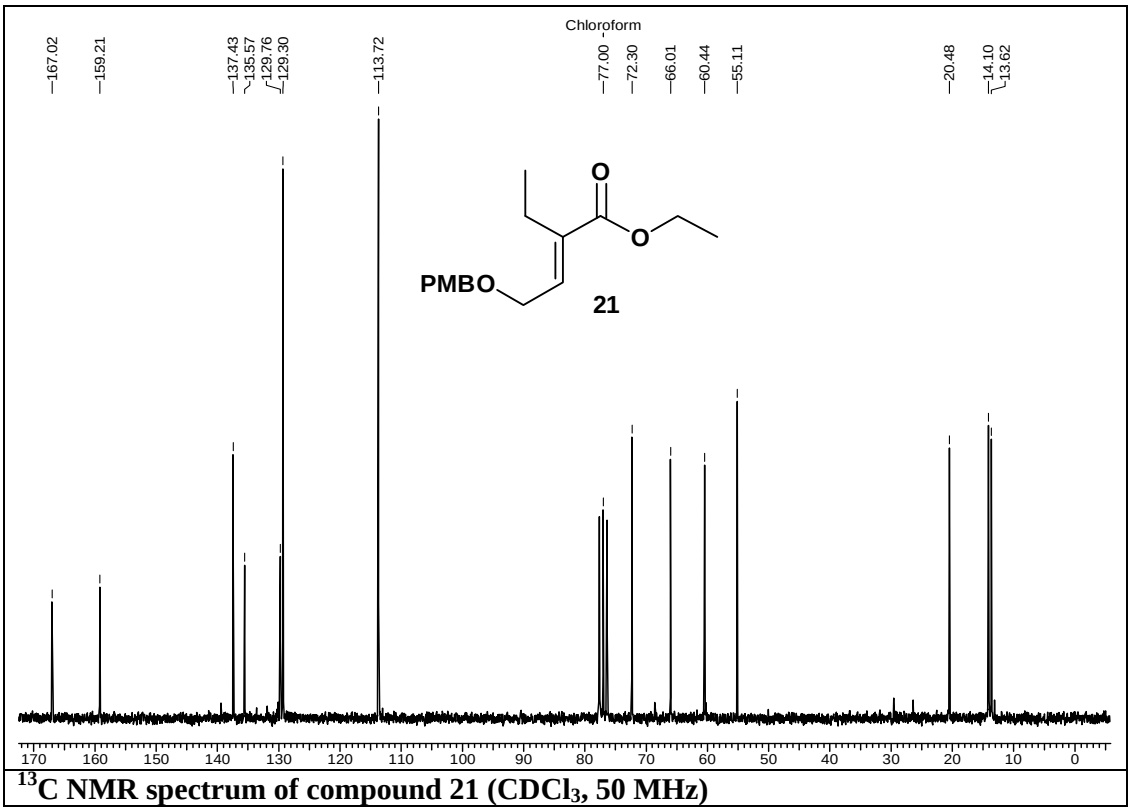
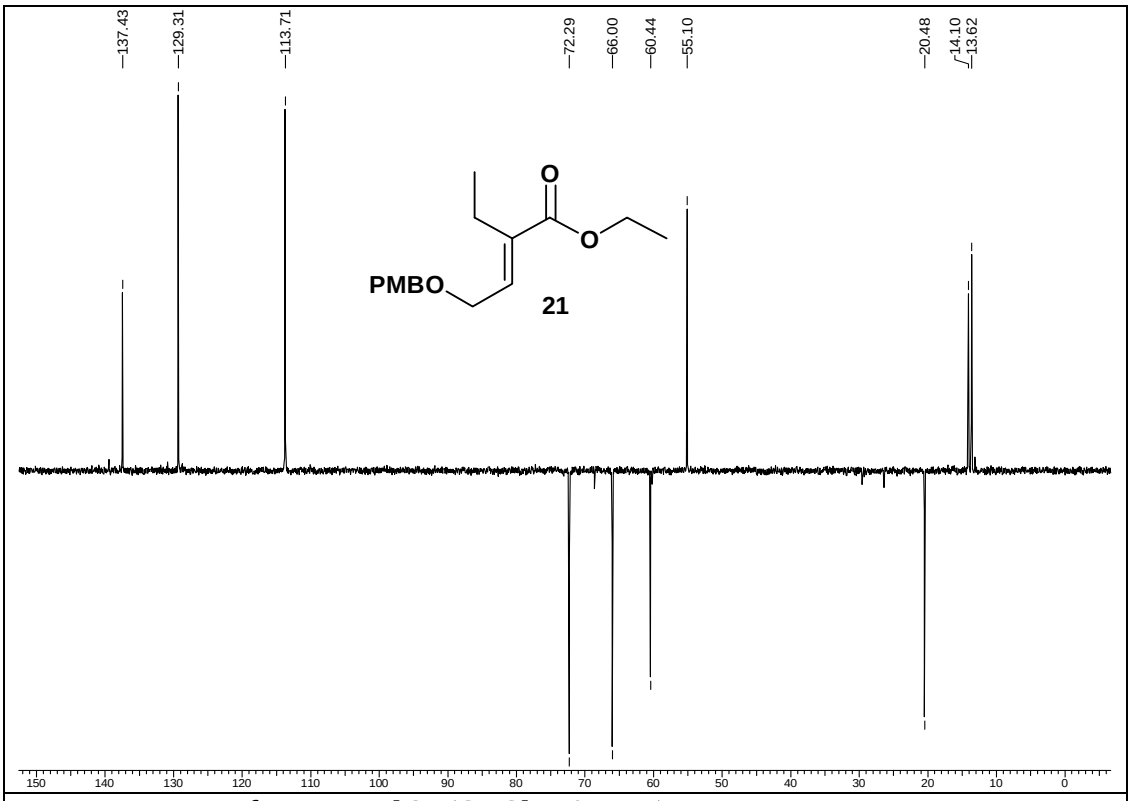
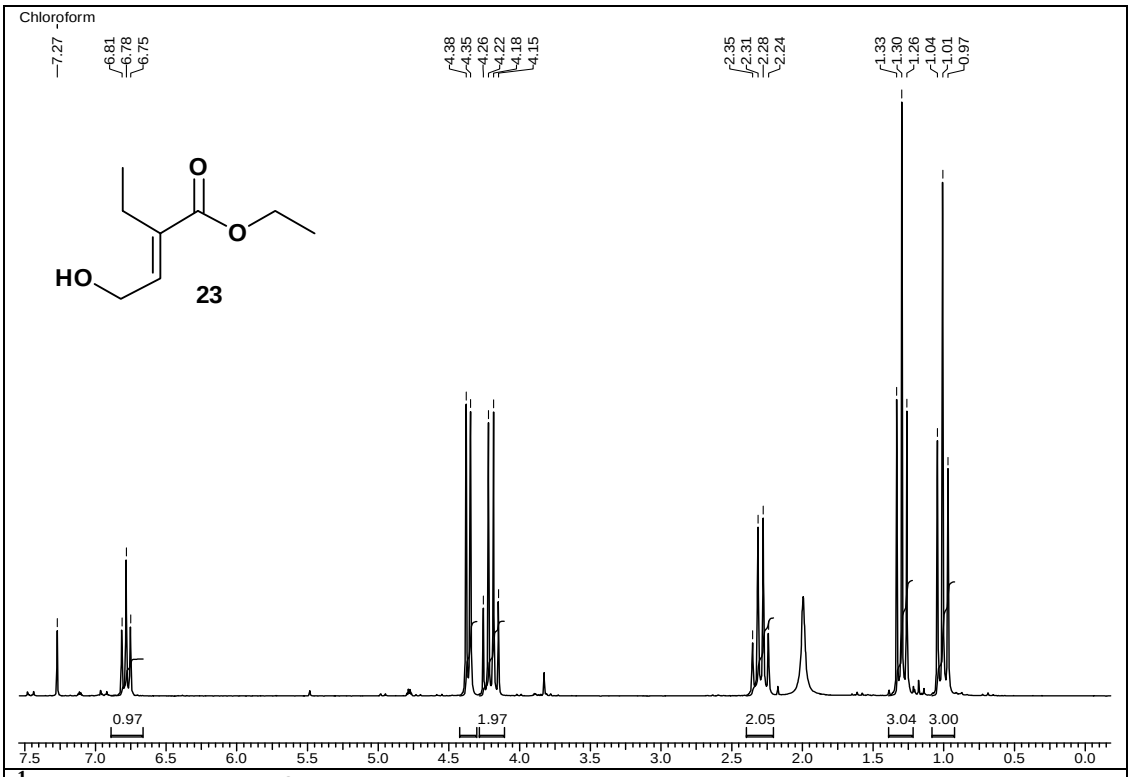


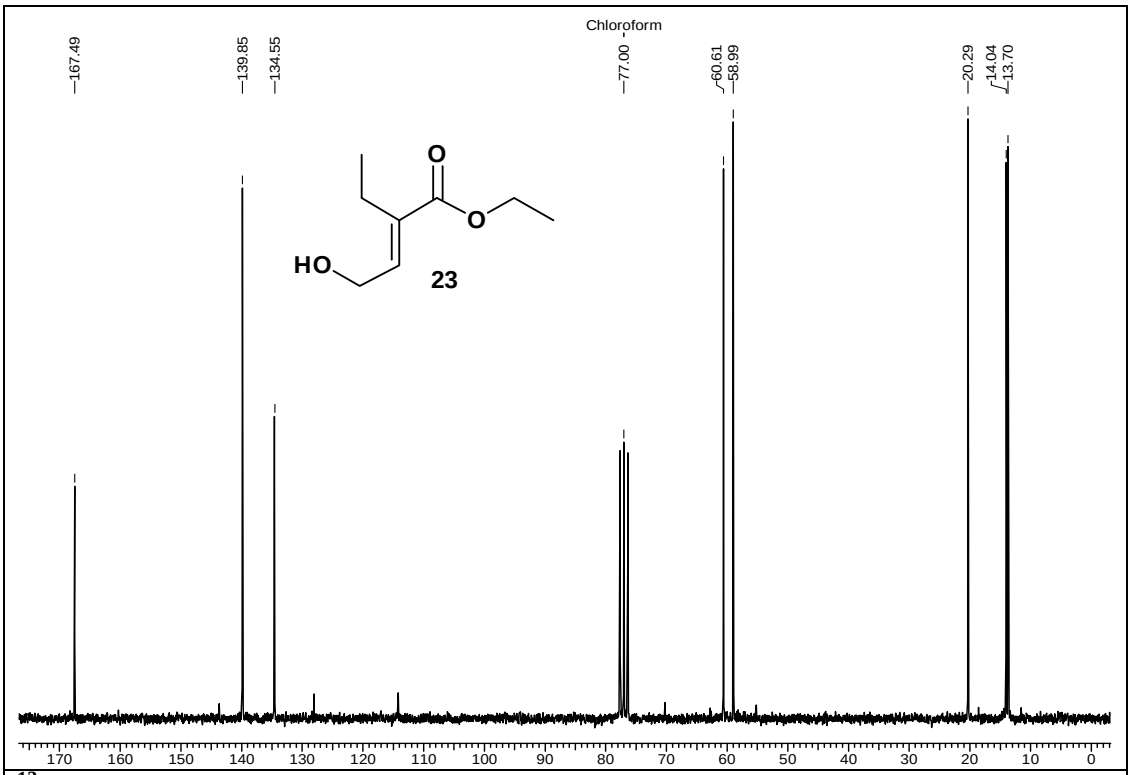
^{13}C NMR spectrum of compound 21 ($CDCl_3$, 50 MHz)



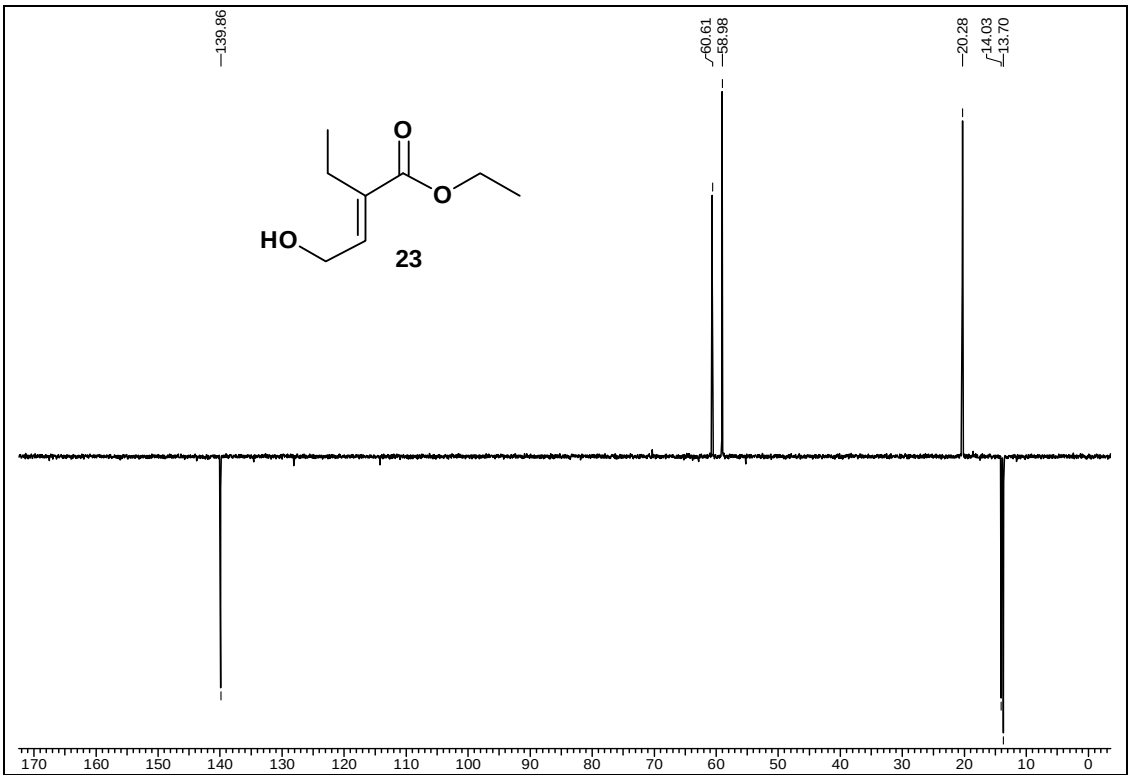
DEPT spectrum of compound 21 ($CDCl_3$, 50 MHz)



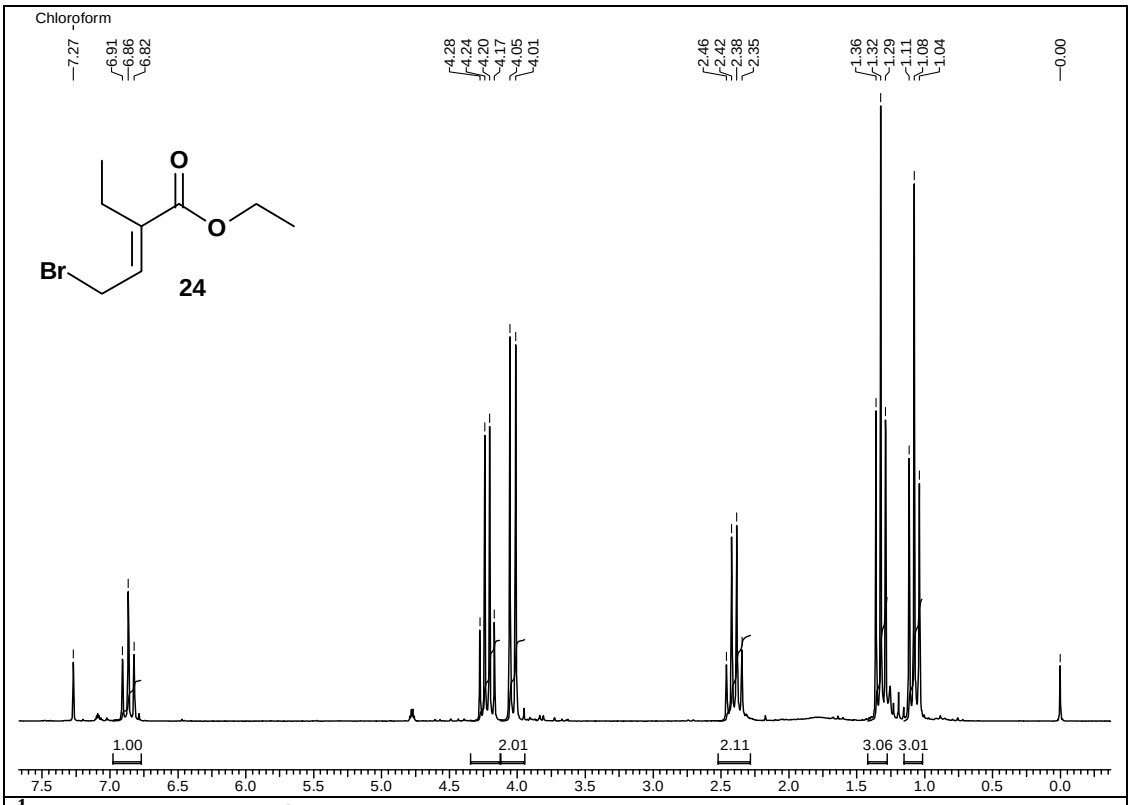
^{1}H NMR spectrum of compound 23 ($CDCl_3$, 200 MHz)



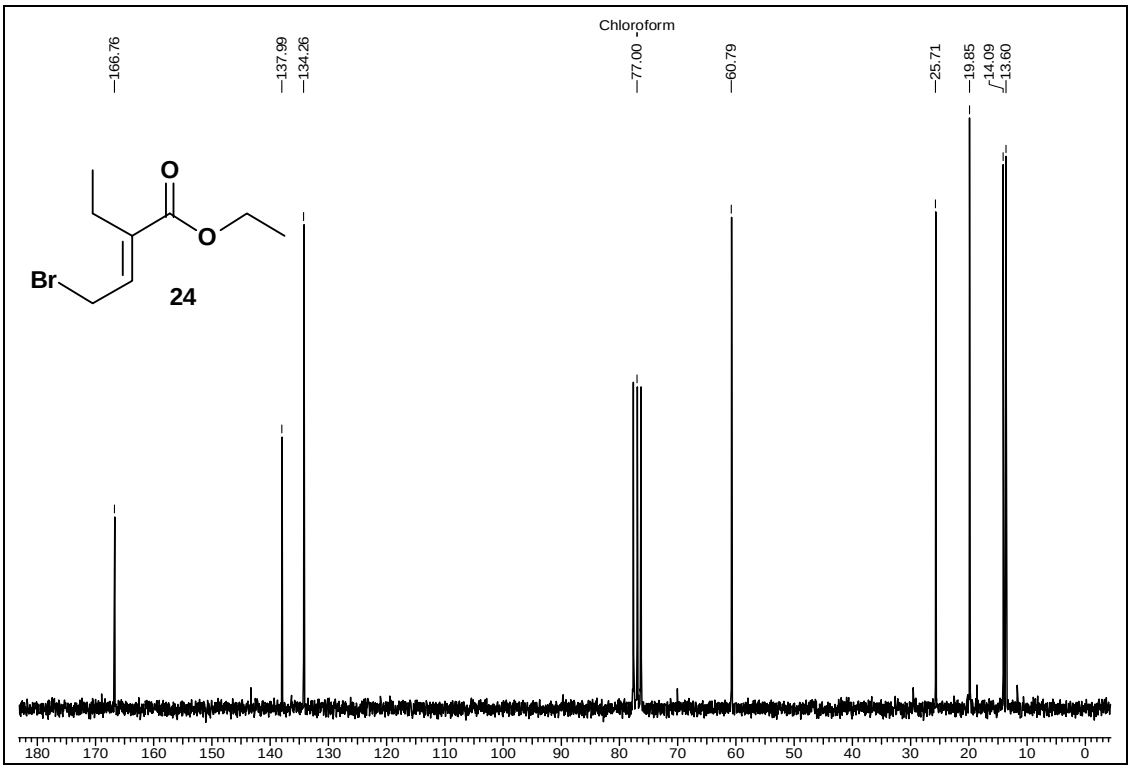
^{13}C NMR spectrum of compound 23 ($CDCl_3$, 50 MHz)



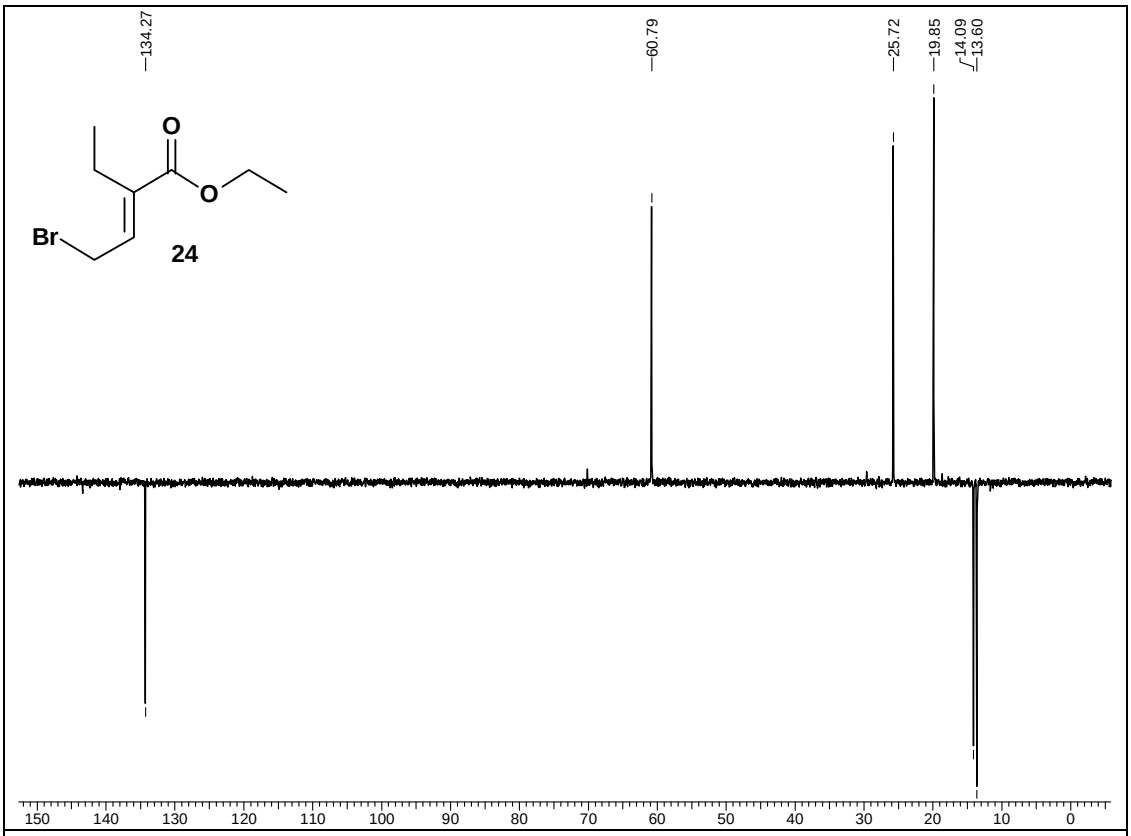
DEPT spectrum of compound 23 ($CDCl_3$, 50 MHz)



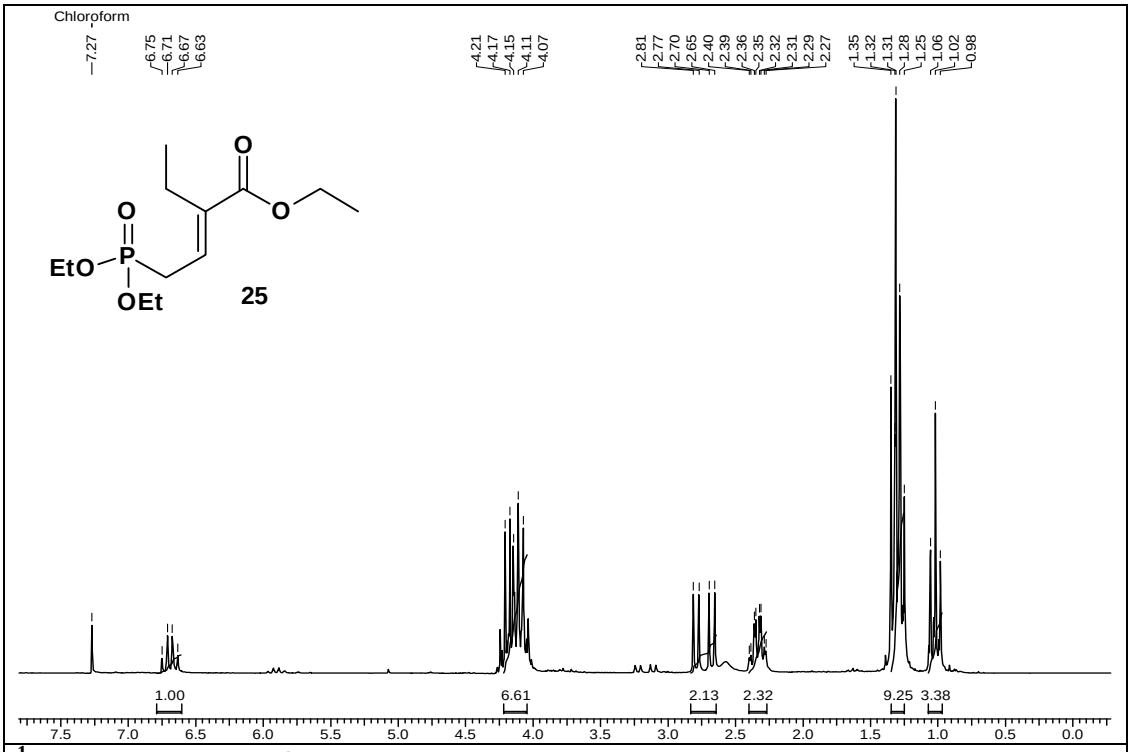
^{1}H NMR spectrum of compound 24 ($CDCl_3$, 200 MHz)



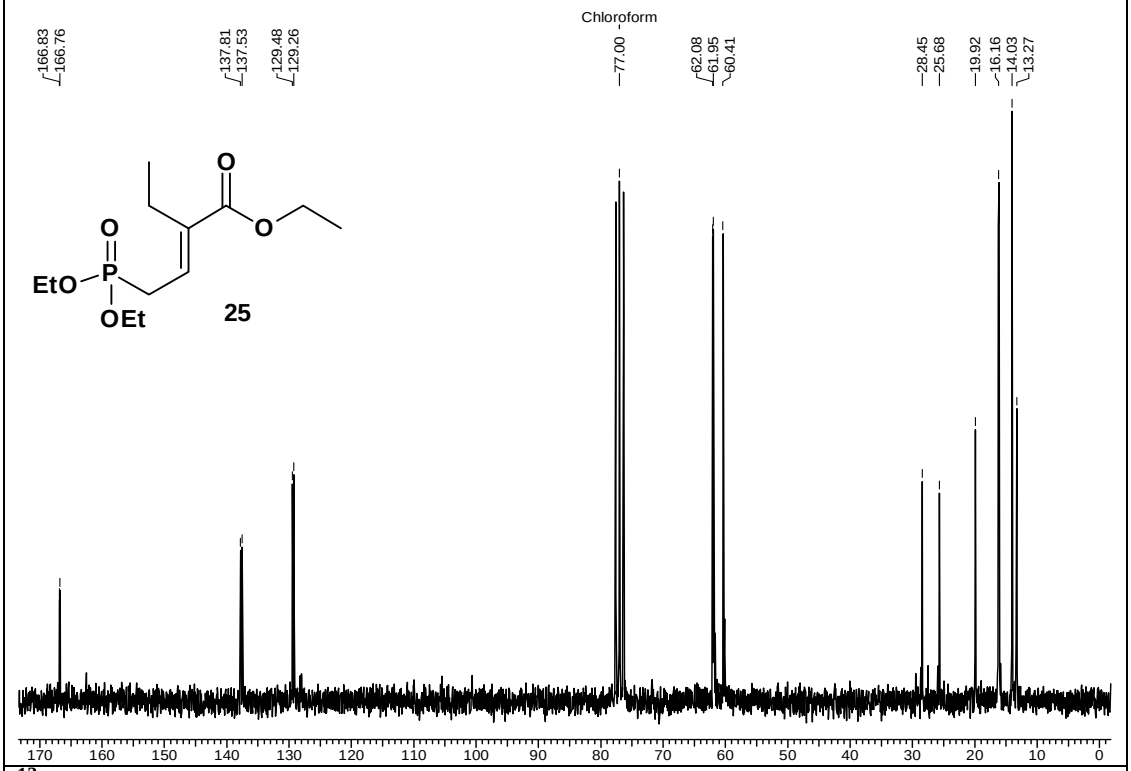
^{13}C NMR spectrum of compound 24 ($CDCl_3$, 50 MHz)



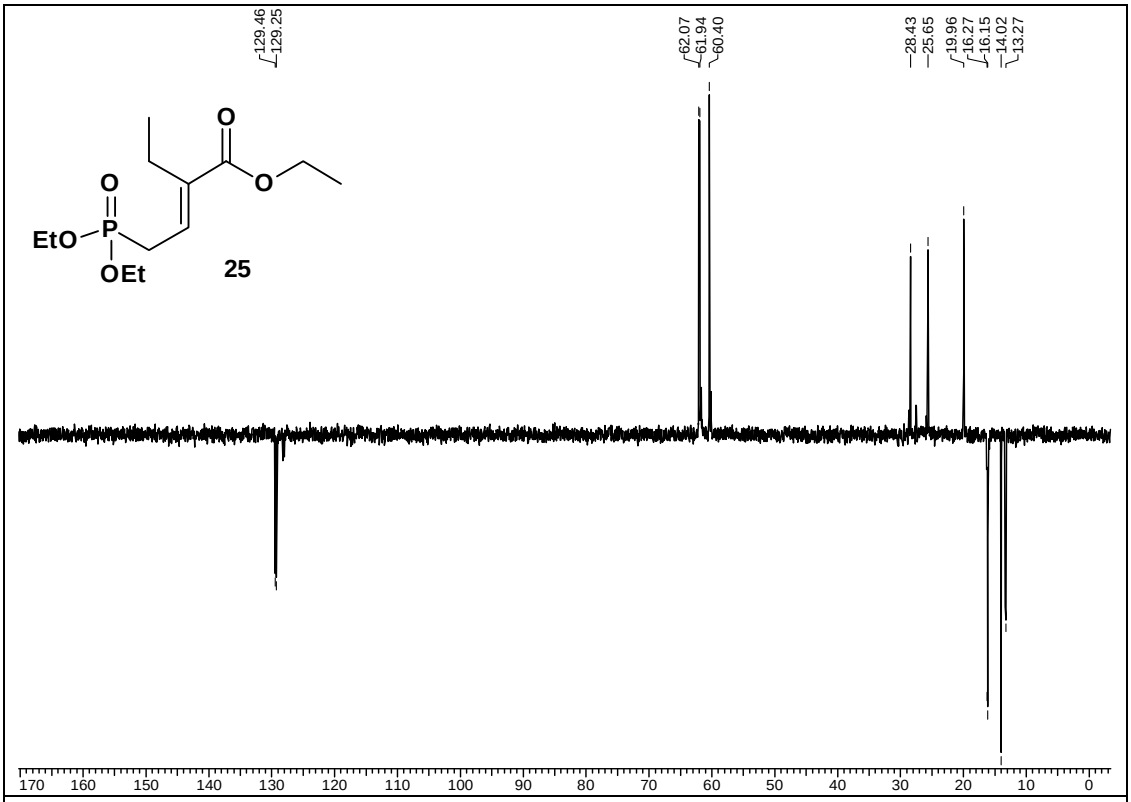
DEPT spectrum of compound 24 ($CDCl_3$, 50 MHz)



^{1}H NMR spectrum of compound 25 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound 25 ($CDCl_3$, 50 MHz)



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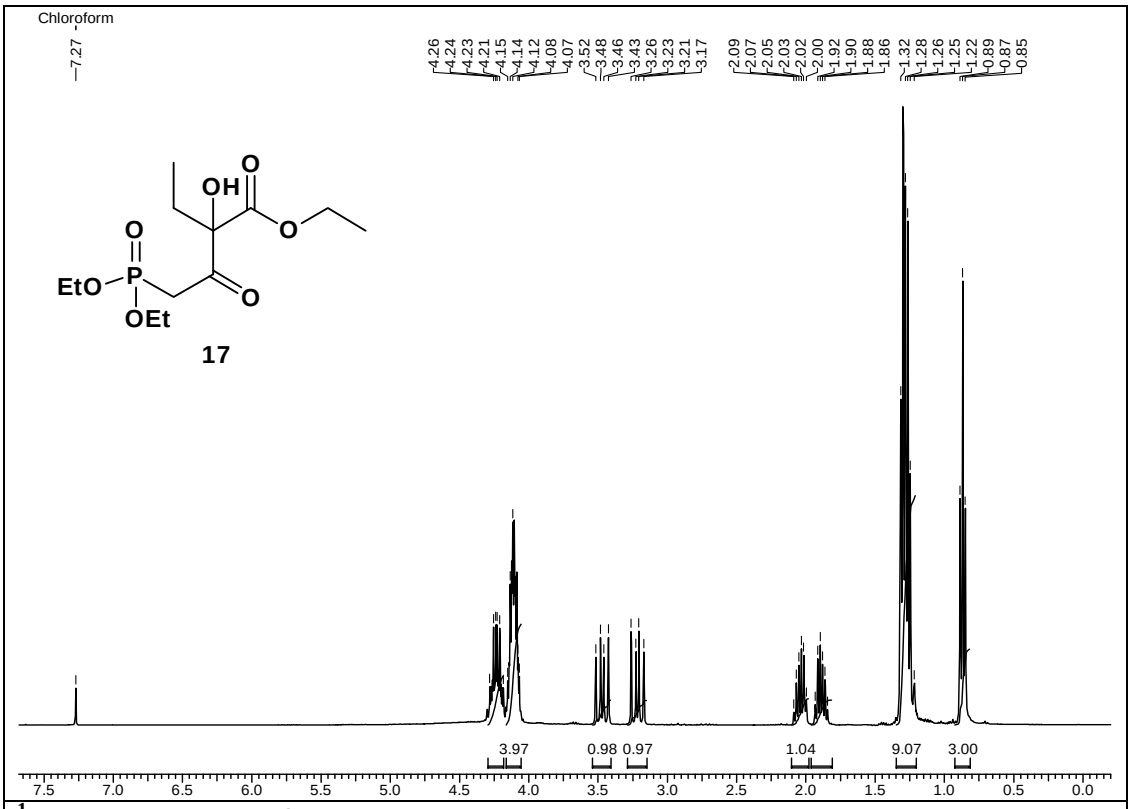
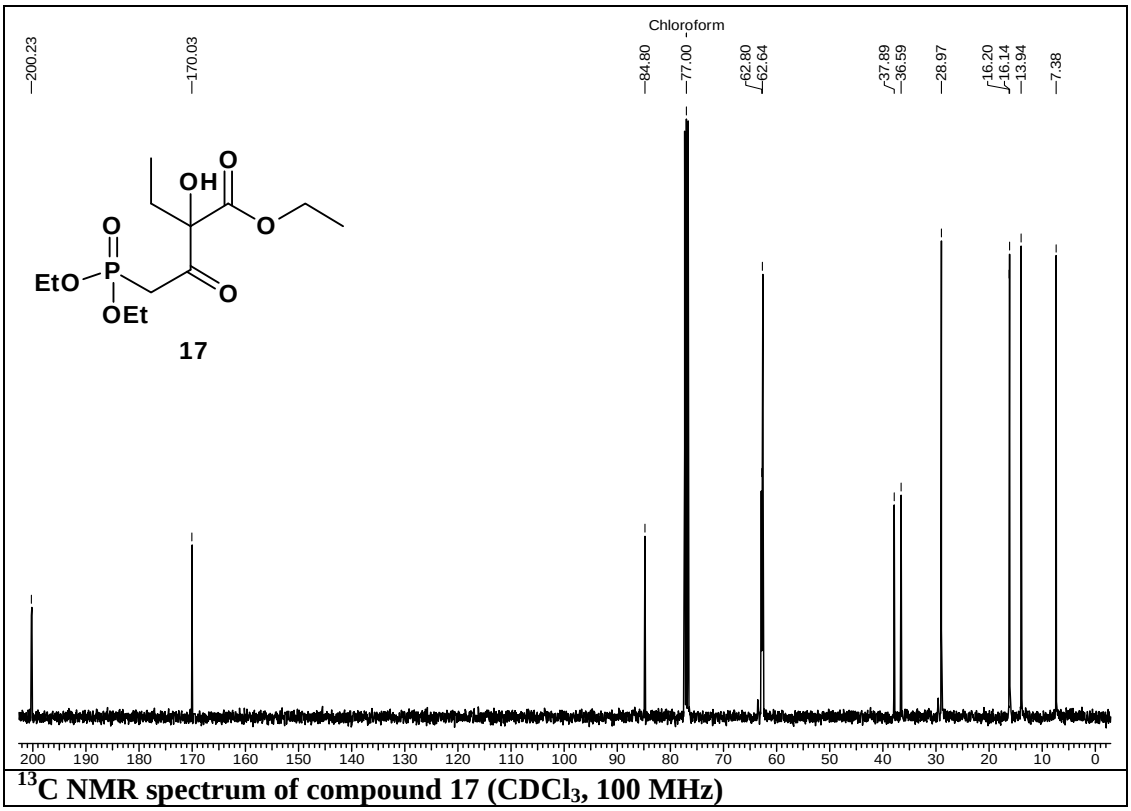
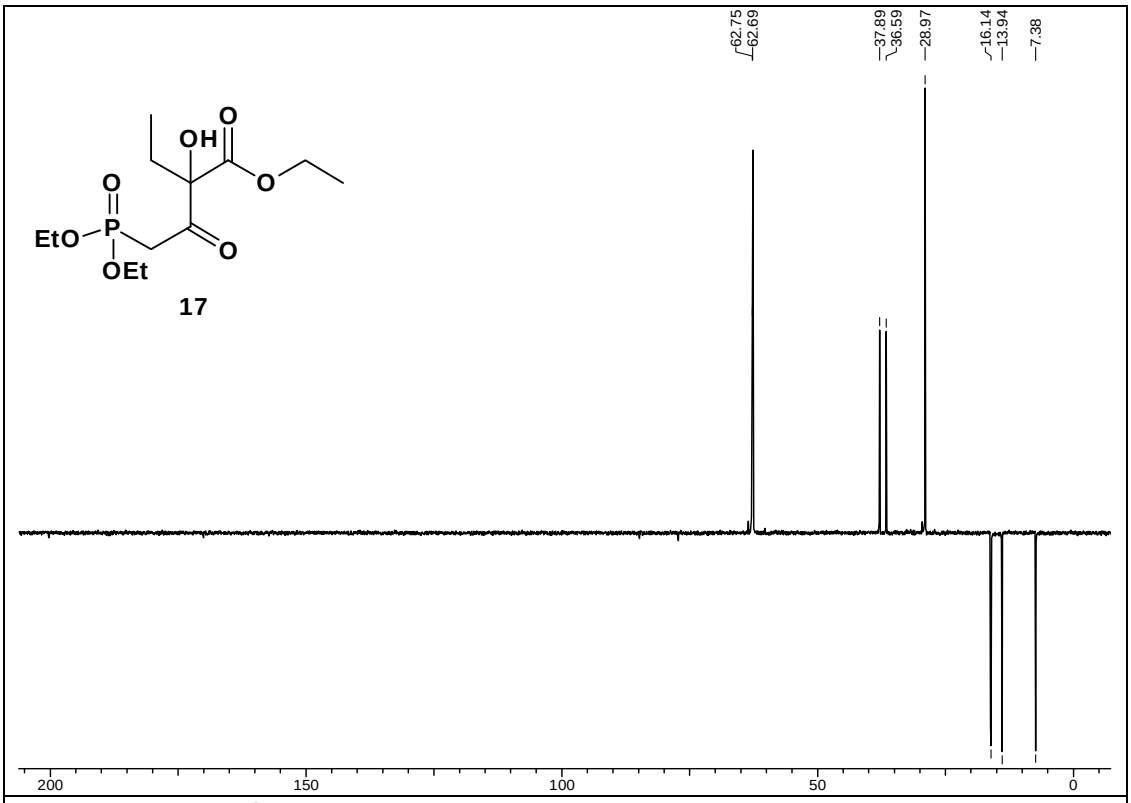


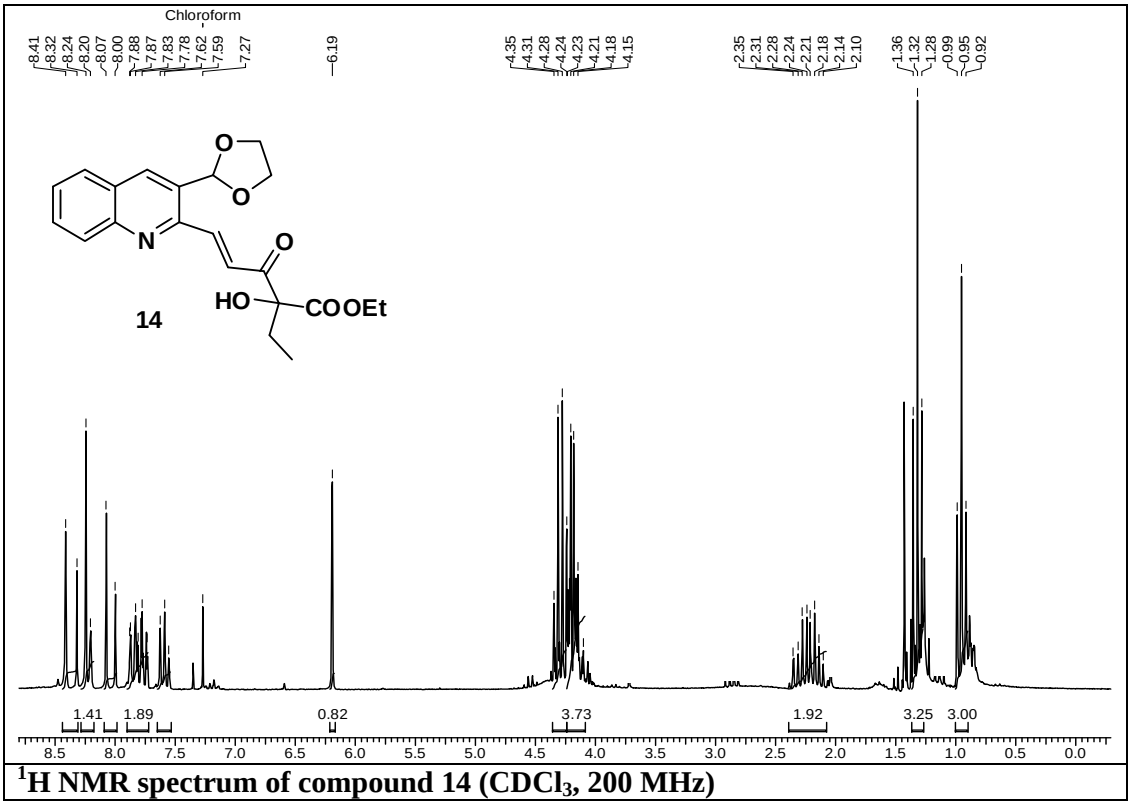
^{1}H NMR spectrum of compound 17 ($CDCl_3$, 400 MHz)



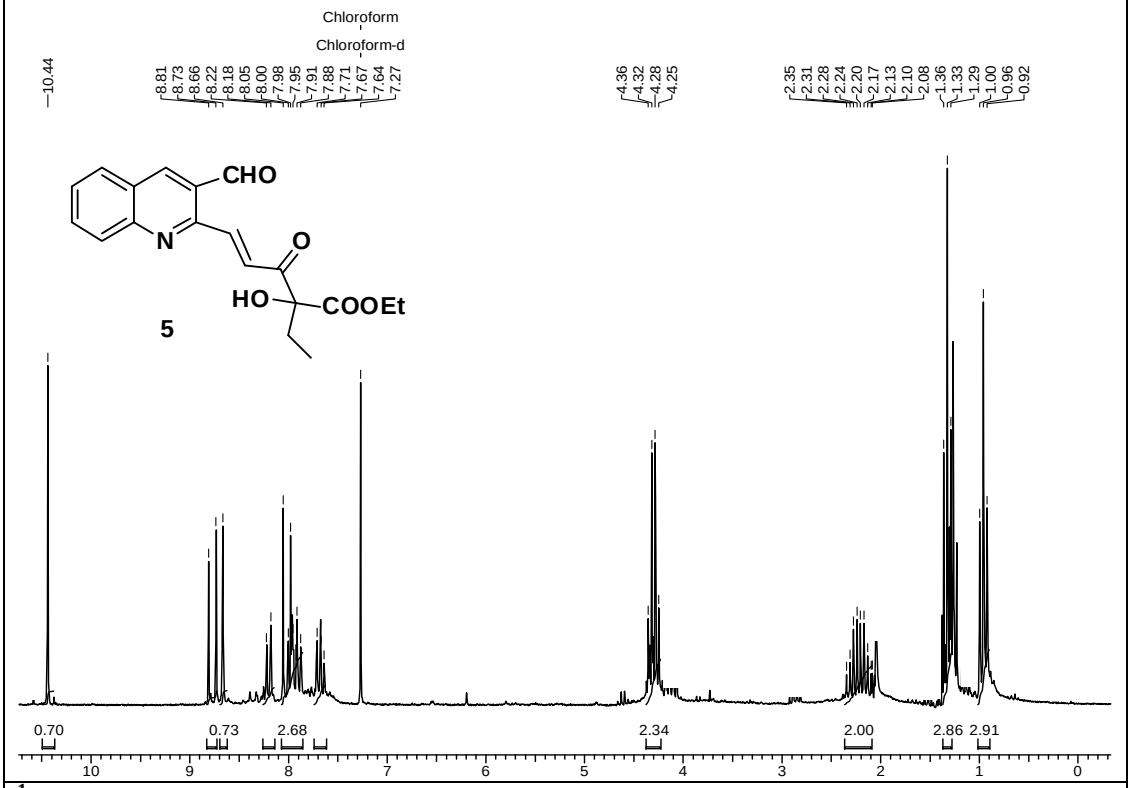
^{13}C NMR spectrum of compound 17 ($CDCl_3$, 100 MHz)



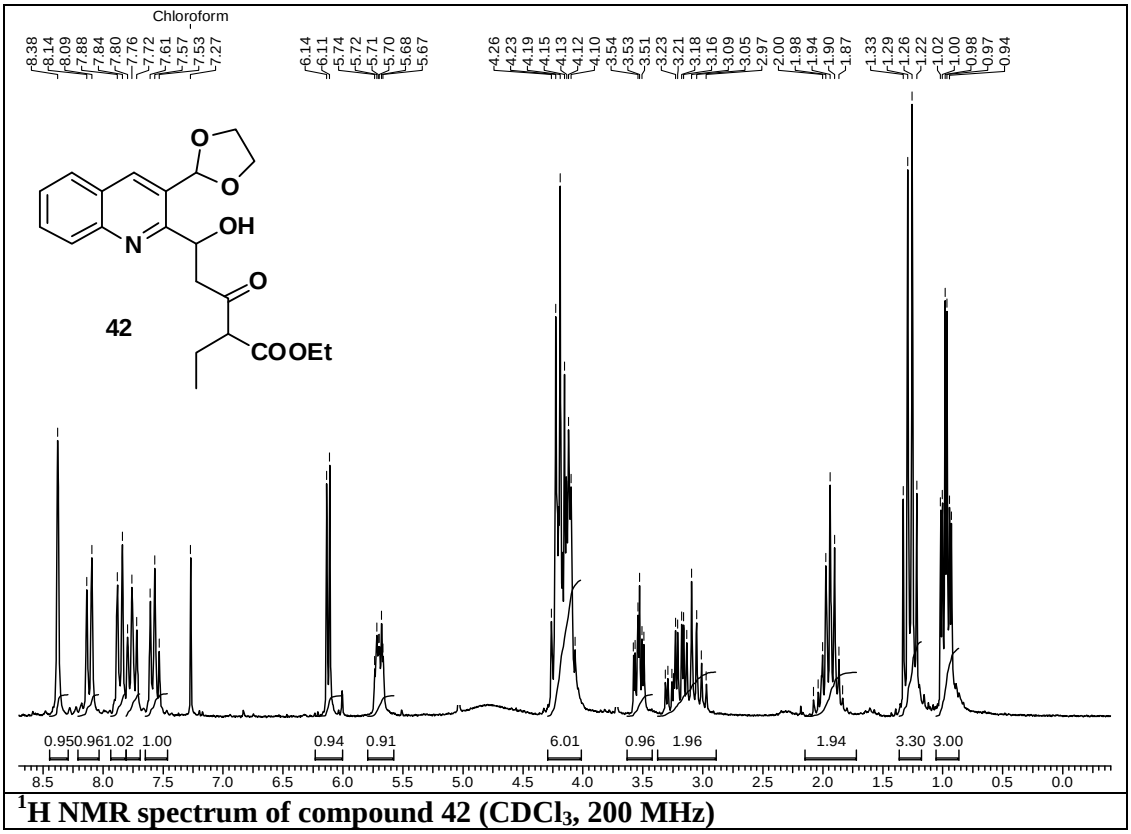
DEPT spectrum of compound 17 ($CDCl_3$, 100 MHz)



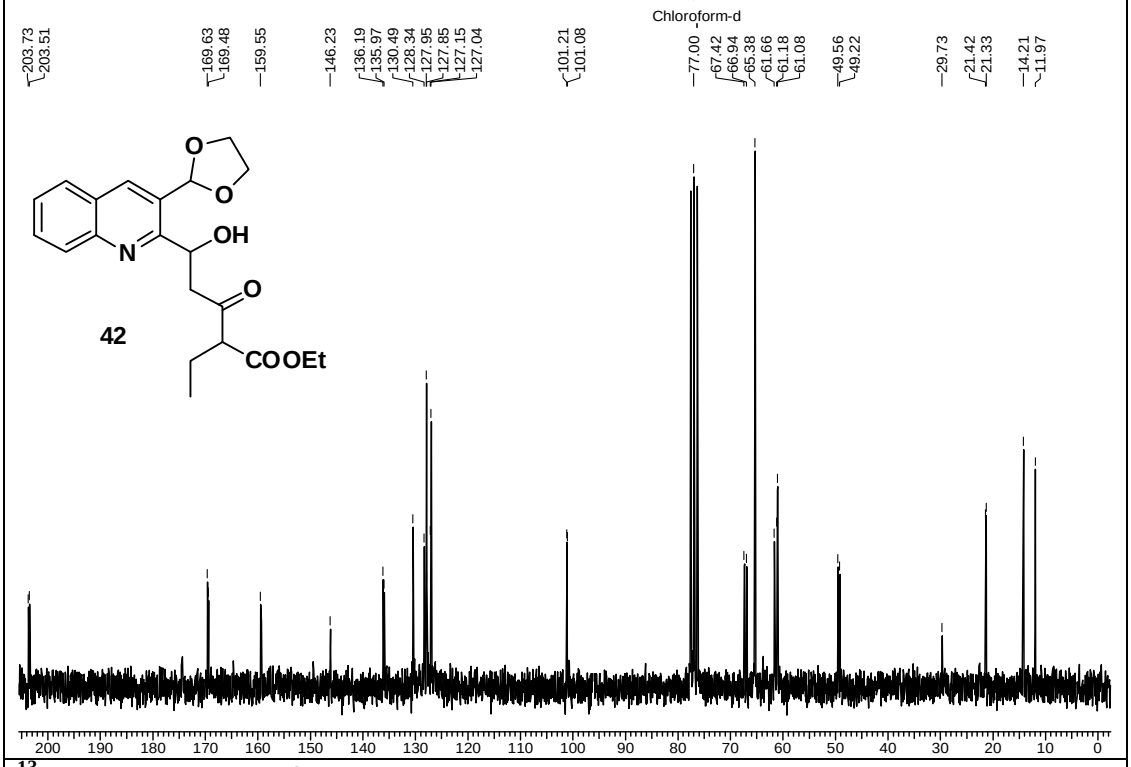
^{1}H NMR spectrum of compound 14 ($CDCl_3$, 200 MHz)



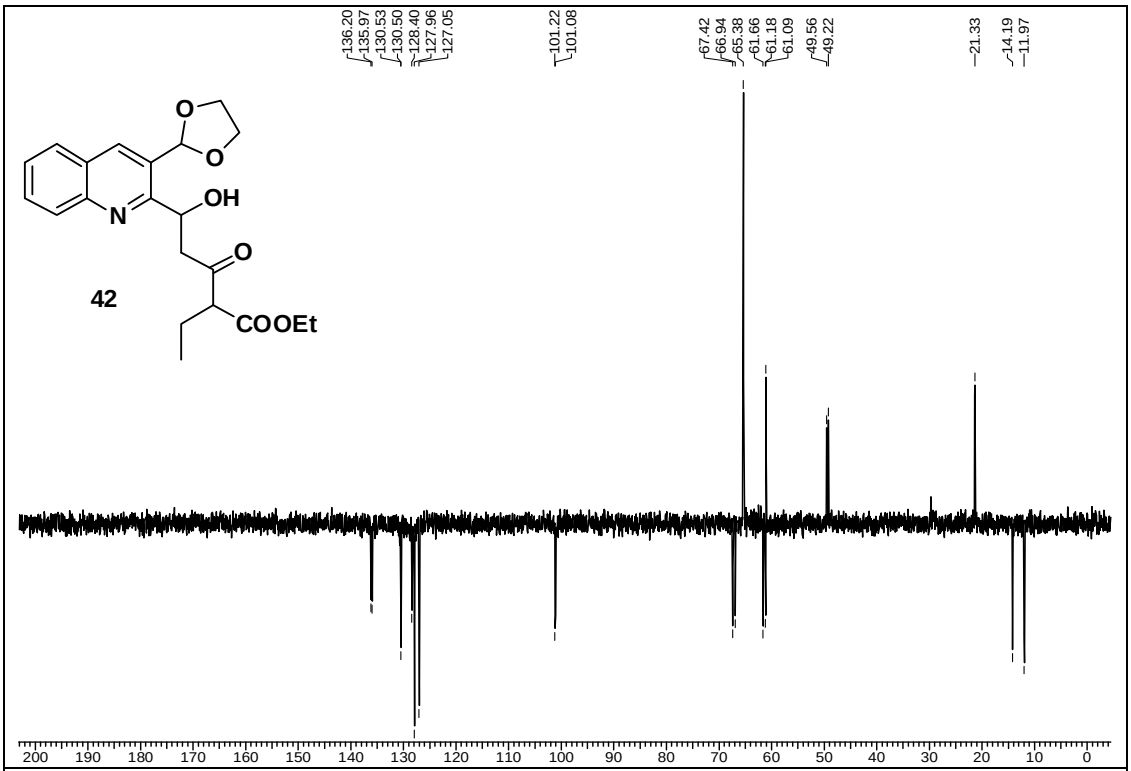
^{1}H NMR spectrum of compound 5 ($CDCl_3$, 200 MHz)



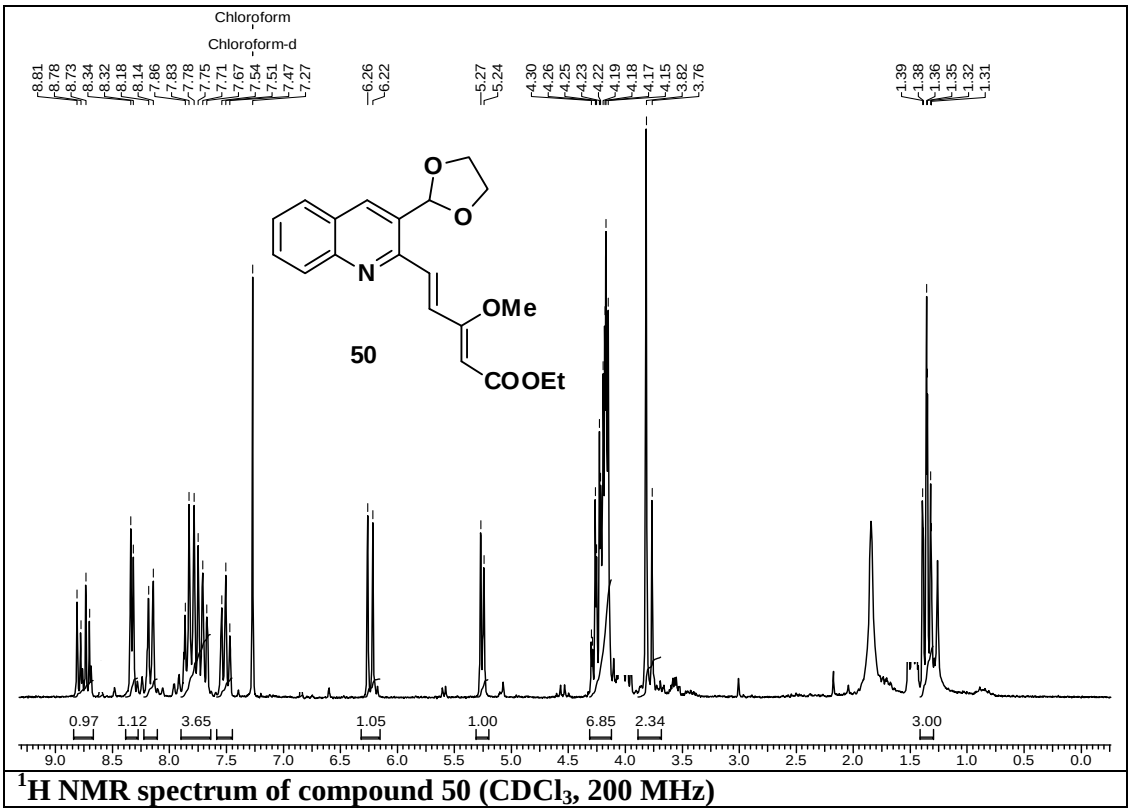
^{1}H NMR spectrum of compound 42 ($CDCl_3$, 200 MHz)



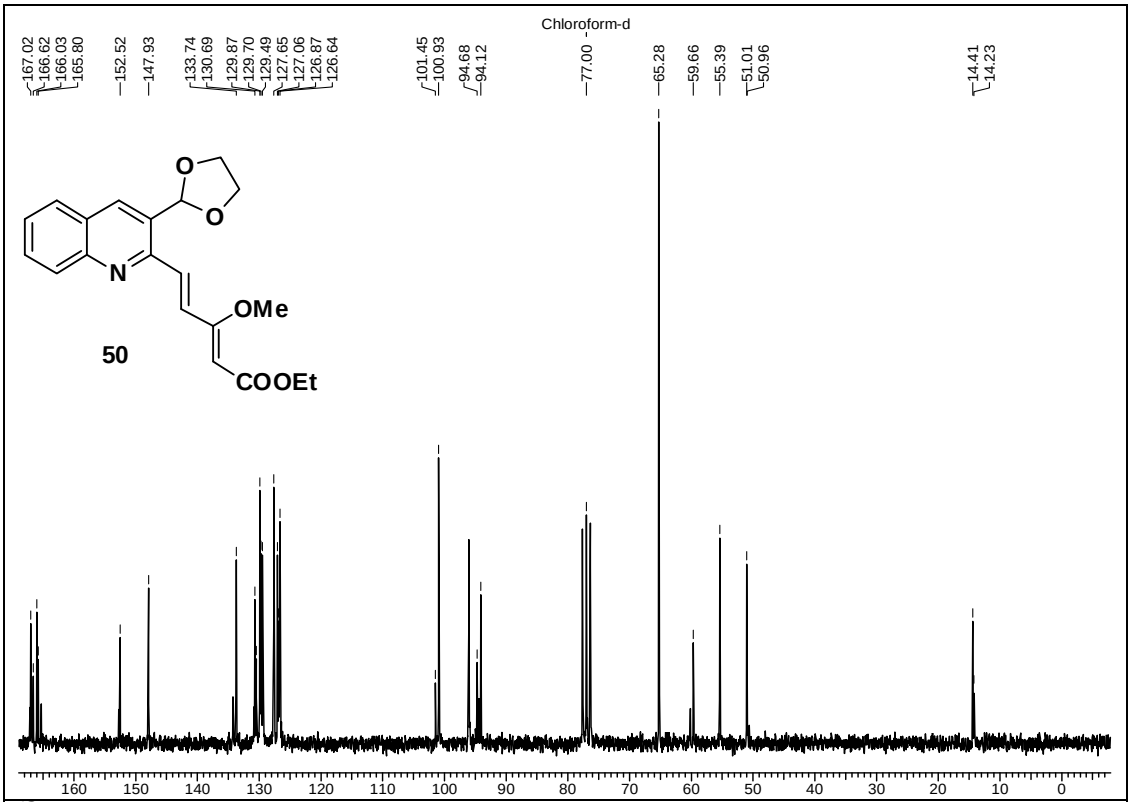
^{13}C NMR spectrum of compound 42 ($CDCl_3$, 50 MHz)



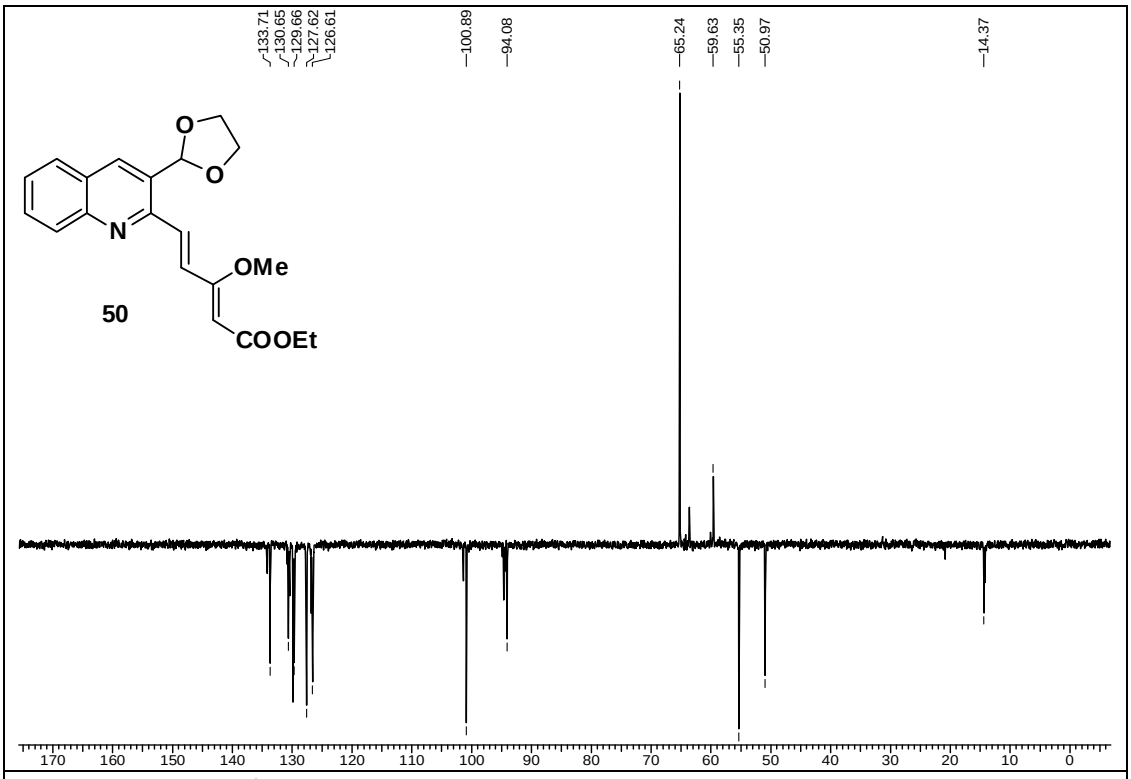
DEPT spectrum of compound 42 ($CDCl_3$, 50 MHz)



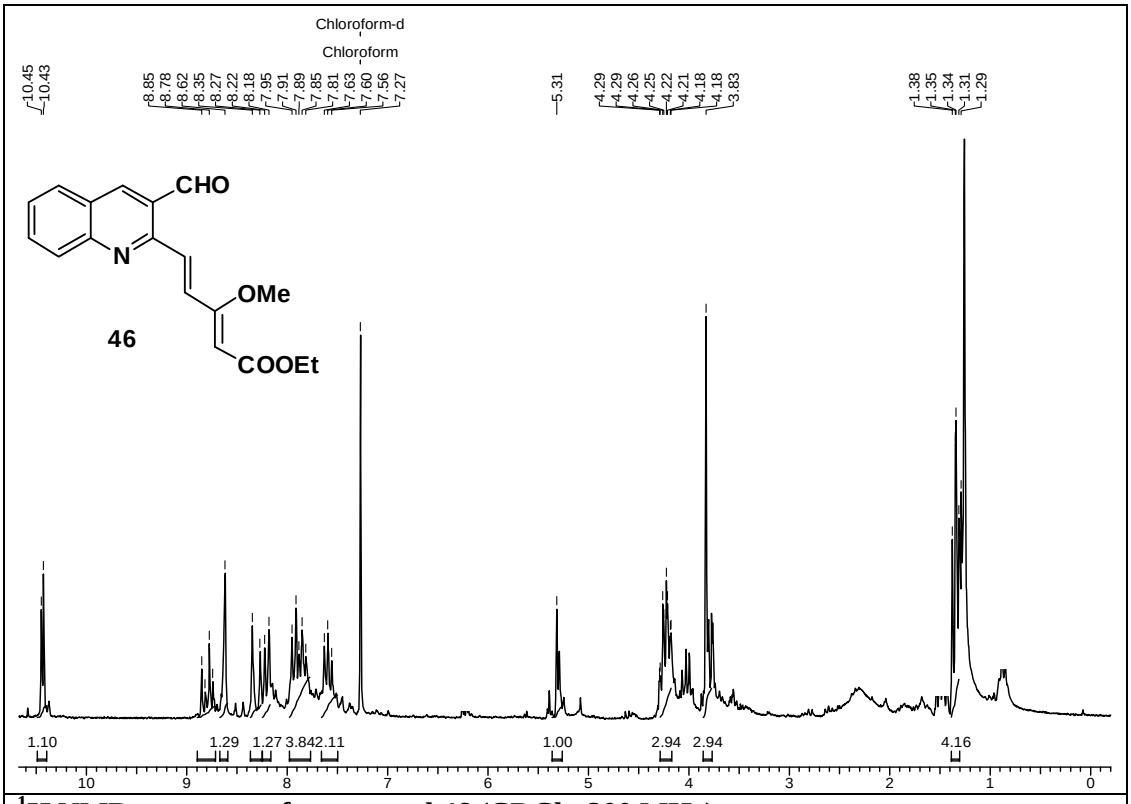
^{1}H NMR spectrum of compound 50 ($CDCl_3$, 200 MHz)



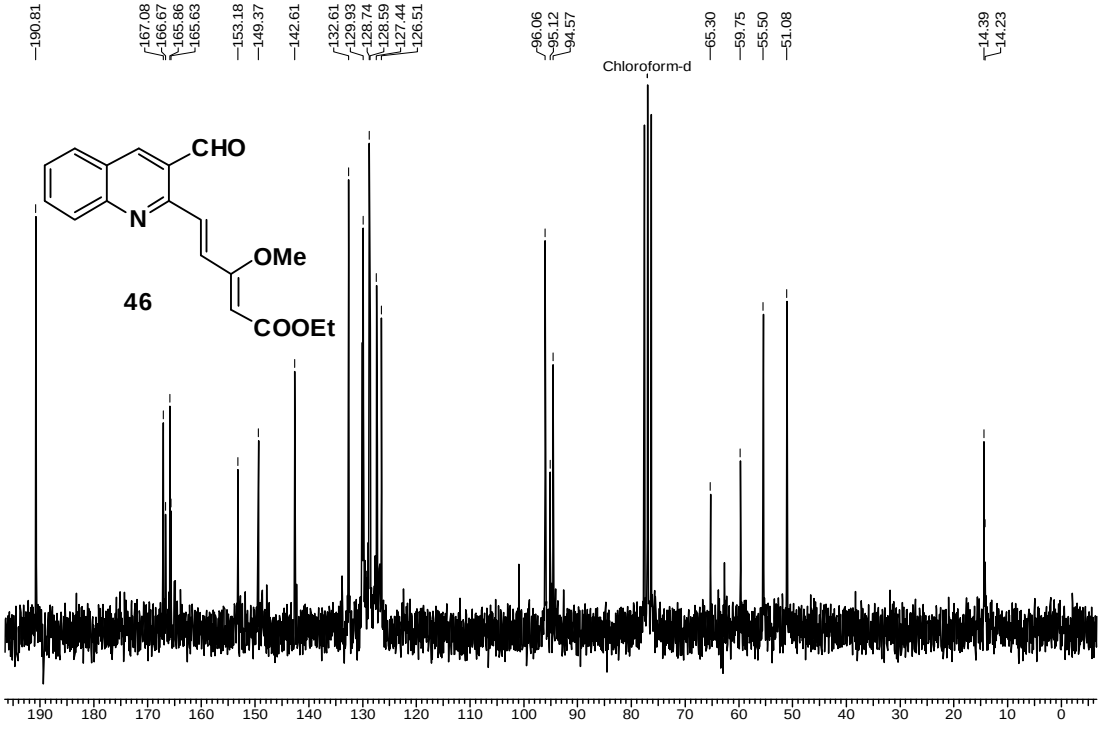
^{13}C NMR spectrum of compound 50 ($CDCl_3$, 50 MHz)



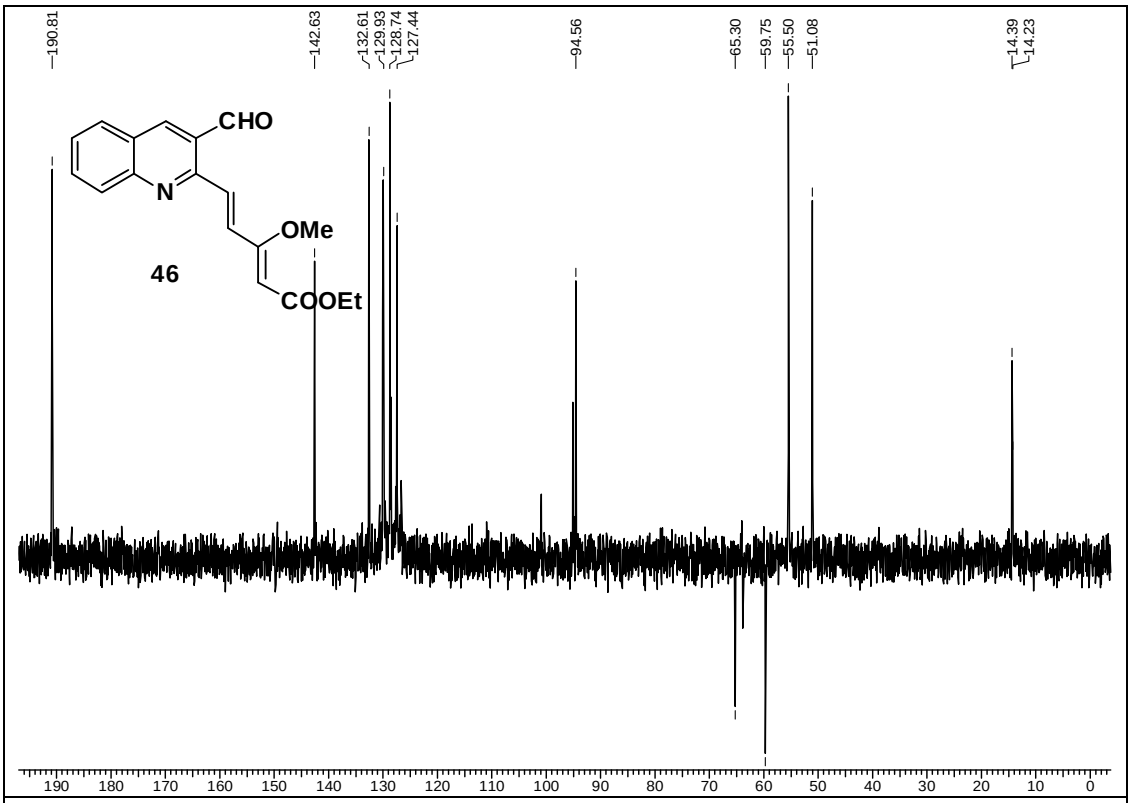
DEPT spectrum of compound 50 ($CDCl_3$, 50 MHz)



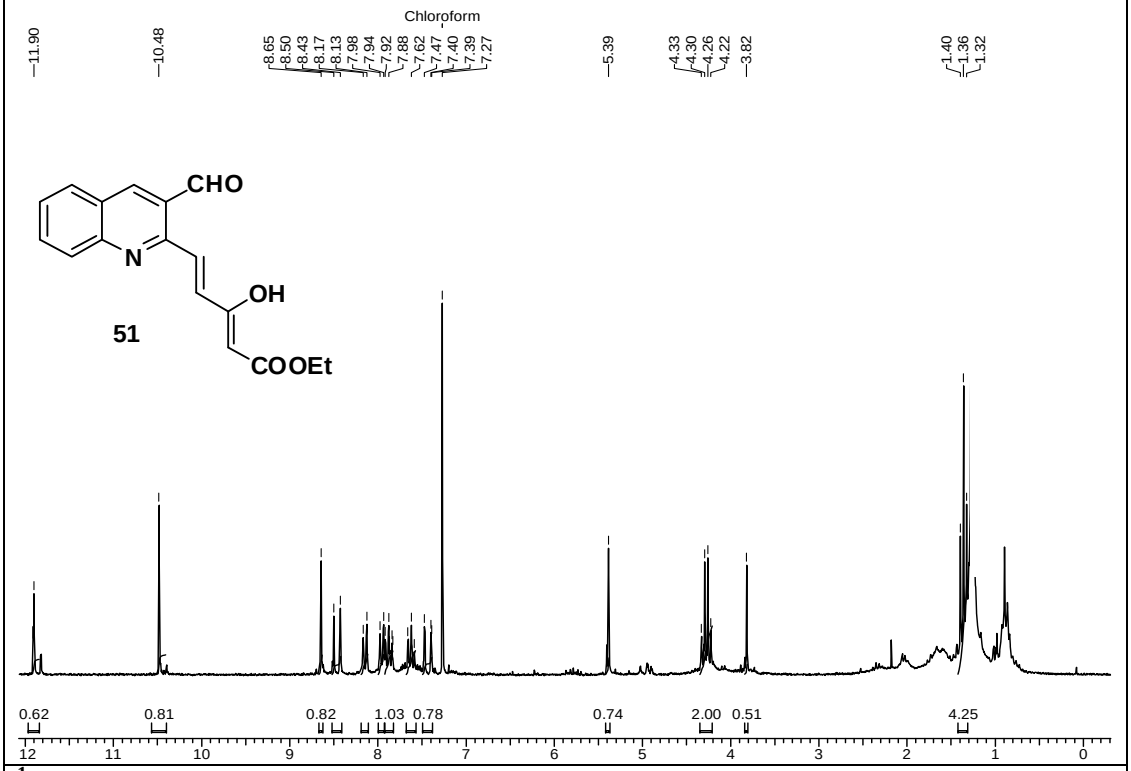
^{1}H NMR spectrum of compound 46 ($CDCl_3$, 200 MHz)



13C NMR spectrum of compound 47 (CDCl3, 50 MHz)



DEPT spectrum of compound 46 ($CDCl_3$, 50 MHz)



^{1}H NMR spectrum of compound 51 ($CDCl_3$, 200 MHz)

1.2.8 References

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Chapter 2. Tandem one-pot reaction approaches towards the synthesis of camptothecin

Section 1

Formal synthesis of (+)-camptothecin via DE-ring synthon employing tandem aza-Michael-condensation-Knoevenagel cyclization reaction

2.1.1 Summary

The present section deals with the introduction of tandem reaction and formal synthesis of racemic and enantioselective synthesis of camptothecin *via* DE-ring synthon employing tandem aza-Michael-condensation-Knoevenagel cyclization reactions.

2.1.2 Synthesis of (±)-DE synthon

2.1.2.1 Introduction

The tandem reaction has recently been of interest for organic synthesis because it offers a convenient and economical method to prepare desired organic molecules.[1] The Michael addition and the Knoevenagel reaction are acknowledged as useful tools for constructing complex organic molecules, and combining the two reactions in one pot has attracted much attention in organic synthesis.[2]

Sequential transformations, which are known to every chemist under the all-embracing term “one-pot reactions”, can be divided into two groups.

1. Domino Reactions

2. Consecutive Reactions

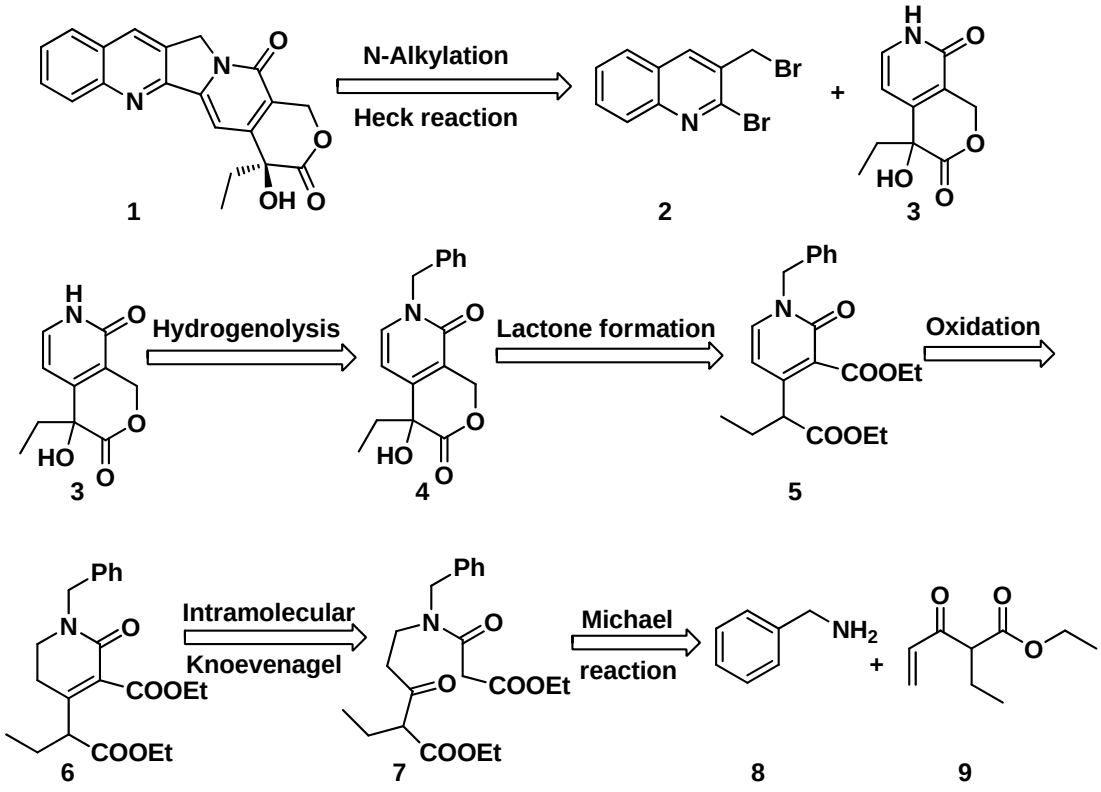
Domino reaction,[3] frequently described as tandem or cascade reaction, is a process involving two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step. The preliminary formation of a reactive intermediate such as a carbocation or a carbanion is not counted here as a reaction step. On the other hand, the formation of a diene by a retro-Diels-Alder reaction with a subsequent cycloaddition would be considered as a domino reaction.

Consecutive reaction is a reaction in which another reagent, mediator, or catalyst is added after the first transformation without isolation of the first formed product; the subsequent reaction steps then lead to the final product. Strictly, sequences in which the individual steps are carried out at different temperatures should also be included in this group. Finally, the term iterative process is also found in the literature. This can also be carried out as domino, consecutive, or individual reactions.

2.1.2.2 Present work

Having failed in the synthesis of camptothecin **1** in linear manner, efforts were continued towards the synthesis of naturally occurring alkaloids namely camptothecin[4] and its analogues, which exhibited impressive anticancer activity. This led to the synthesis of camptothecin by adopting convergent strategy employing tandem one-pot reaction to synthesise the pyridone which could later be elaborated to DE synthon **3** of camptothecin **1**.

The retrosynthetic analysis for camptothecin **1** is delineated in Scheme 1, which reveals that camptothecin **1** can be synthesized from DE synthon **3** by *N*-alkylation with **2** followed by cyclization *via* Heck coupling or radical cyclization.



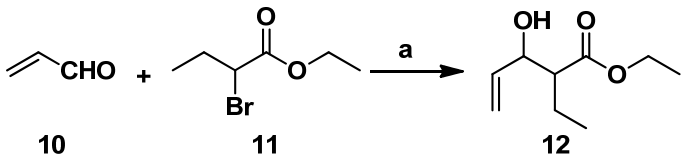
Scheme 1

The DE ring synthon **3** can be synthesized from lactone **4** by *N*-debenzylation. The lactone **4** could be obtained from compound **5** by selective reduction of ester and lactonization. Pyridone **5** could be obtained from dihydropyridone **6**. The key synthon **6** can be obtained from diester **7**, which in turn could be obtained from commercially

available benzyl amine **8** and α, β–unsaturated ketone **9** *via* Michael addition followed by condensation.

2.1.2.3 Results and discussion

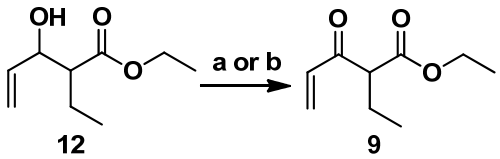
According to retrosynthesis, the initial concern was to obtain the α, β–unsaturated ketone **9.** α, β–Unsaturated ketone **9** can be prepared by performing Reformatsky reaction. Thus acrolein **10** and ethyl 2-bromobutyrate **11** were refluxed in THF in the presence of zinc and catalytic amount of iodine for 8 h to afford β-hydroxy ester **12** in 67% yield.



Scheme 2: ***Reagents and conditions:*** *a) Zn, iodine (cat), THF, reflux, 8 h, 67%.*

Formation of **12** was confirmed by using spectroscopic methods. IR spectrum showed strong absorption bands at 1736 and 3484 cm^{-1} indicating the presence of ester and alcohol functionality respectively. ^{1}H-NMR spectrum showed two triplets that appeared at δ 0.95 ($\underline{CH_3}CH_2CH$-) and 1.28 ($\underline{CH_3}CH_2CO$-) integrating for three protons each assigned to methyl group protons. The multiplets which appeared in the region at δ 5.27-5.35 ($\underline{CH_2}$=CH-) integrating for two protons and δ 5.79-5.91 (CH_2=$\underline{CH}$-) integrating for one proton confirmed the presence of olefinic protons. ^{13}C NMR and DEPT spectra showed doubling of signals for carbonyl and olefinic carbons revealing it to be a mixture of diastereomers. Finally the structure of **12** was confirmed by mass spectral and elemental analysis. The mass spectrum showed the *m/z* peak at 173 $(M + 1)^{+}$. Elemental analysis was also found to be in good agreement with the calculated values.

Having hydroxy compound **12** in hand, next task was the oxidation of secondary alcohol to get required fragment **9**. It was thought to perform oxidation by using mild and green conditions and with this idea in mind, compound **12** was subjected to oxidation using different conditions (Table 1, Scheme 3). Only five of the various conditions tried gave the required compound **9** of which Jones oxidation and IBX oxidation gave excellent yields, while others gave poor to moderate yield.



Scheme 3: ***<u>Reagents and conditions:</u>*** *a) Jones reagent, acetone, 0 ^{o}C to rt, 85%; b) IBX, ethyl acetate, reflux, 4 h, 90%.*

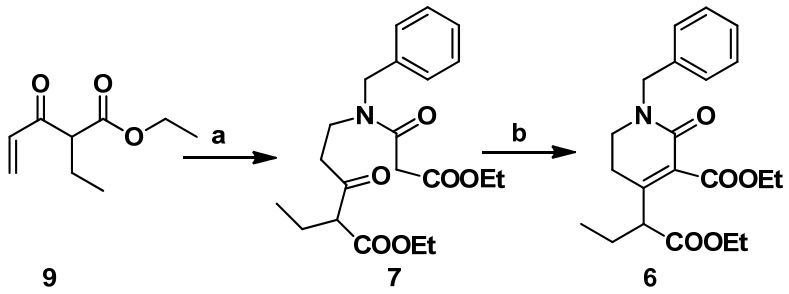
Table 1.

Sr. No	Reagents and conditions	Observation/yield
1	MCPBA, TBAB, TEMPO, DCM, 0 ^{o}C -rt	30%
2	TEMPO, TBAB, Oxone	Complex TLC
3	TBHP, $CuCl_2$, TBAB, DCM, rt	Starting material recovered
4	H_2O_2, HBr, acetonitrile, rt	Intractable reaction mixture
5	K_2CO_3, KI, I_2, water	Intractable reaction mixture
6	TEMPO, I_2, aq. $NaHCO_3$, toluene, 20 ^{o}C	Complex TLC
7	$KMnO_4$+MnO_2, DCM, rt	65%
8	MnO_2, DCM, rt	60%
9	IBX, ethyl acetate, reflux, 4h	90%
10	Jones reagent	85%

Formation of α,β-unsaturated ketone **9** was confirmed by using spectroscopic methods. Absorption at 1710 and 1736 cm^{-1} in the IR spectrum of **9** indicated the presence of two carbonyls which were attributed to ketone and ester carbonyl respectively. ^{1}H NMR spectrum showed triplets at δ 0.95 (J = 7.4 Hz) and 1.26 (J = 7.2 Hz) integrating for three protons each, a multiplet at δ 1.84-2.03 integrating for two protons and a quartet at δ 4.18 (J = 7.4 Hz) integrating for two protons which was assigned to two ethyl group protons. The signals that appeared at δ 5.86 (dd, J = 1.7 and 9.8 Hz), 6.33 (dd, J = 1.7 and 17.4 Hz) and 6.49 (dd, J = 9.8 and 17.4 Hz) integrating for one proton each were attributed to olefinic protons. ^{13}C NMR spectrum of **9** revealed signals that appeared at δ 11.8, 14.0, 21.6 and 61.2 which were assigned to two ethyl group carbons and the signals that appeared at δ 129.5 and 134.6 were assigned to olefinic carbons, while the signals that appeared at δ 169.6 and 194.8 were attributed to ester and ketone carbonyl carbons

respectively. Finally the structure of **9** was confirmed by mass spectral and elemental analysis. The mass spectrum of **9** showed the $(M + H)^+$ and $(M + Na)^+$ peaks at *m/z* 171 and 193 respectively and its elemental analysis was also found to be in good agreement with theoretical values.

Having obtained the desired α, β-unsaturated compound **9**, attention was focused on one-pot Michael addition and condensation with appropriate counterpart. Thus the α, β-unsaturated ketone **9** was subjected to Michael addition with benzyl amine **8** at room temperature for 30 minutes followed by addition of dichloromethane, 1 equivalent K_2CO_3 and ethyl malonyl chloride at 0 ^oC and stirring at room temperature to afford condensed product **7** in 70% yield (Scheme 4).



Scheme 4: ***Reagents and conditions:*** *a) Benzyl amine, rt, ½h; DCM, 1 eq. K_2CO_3, ethyl malonyl chloride, 0 ^oC, 1 h, 70%; b) K_2CO_3, DCM, rt, 5 h, 95%.*

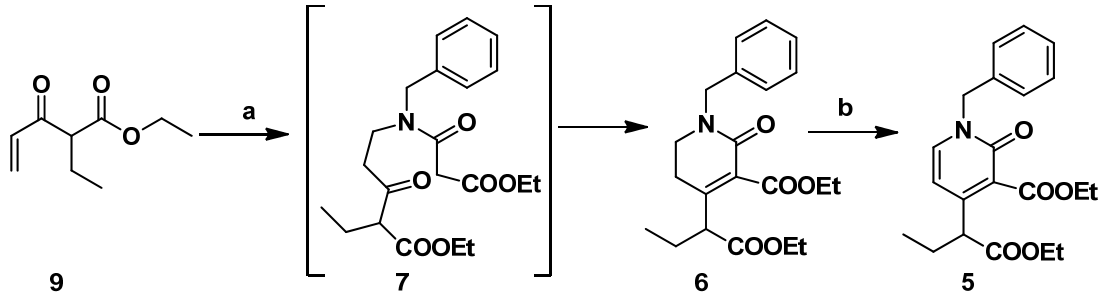
The formation of compound **7** was confirmed by spectral techniques. Absorption at 1735, 1710 and 1681 cm^{-1} in the IR spectrum of **7** indicated the presence of ester, ketone and amide carbonyls respectively. ^1H NMR spectrum of **7** showed a multiplet at δ 7.16-7.26 integrating for five protons and was attributed to aromatic protons thereby confirming Michael addition reaction and peaks that appeared at δ 3.40 and 3.61 as singlets integrating for two protons due to mixture of rotamers were attributed to methylene protons (-CO$\underline{CH_2}$CO-) confirmed the condensation reaction. The triplet that appeared at δ 0.91 integrating for three protons was assigned to methyl group which belonged to Michael acceptor while a triplet at δ 1.27 (J = 7.1 Hz) integrating for six protons and signals at δ 4.16 (q, J = 7.2, 2H) and 4.17 (q, J = 7.1, 2H) were assigned to ethyl ester protons and singlet that resonated at δ 4.59 integrating for two protons was assigned to benzyl protons thereby confirming Michael addition and condensation. ^{13}C NMR along with DEPT spectra of **7** revealed that it existed as the mixture of rotamers showing double

peaks *viz.* 166.3, 166.6, 167.3, 167.6, 169.2, 169.4, 203.0, 204.2 that were assigned to four carbonyl carbons, while rest of the protons and carbon peaks appeared at expected positions and finally the structure of **7** was confirmed by mass spectral and elemental analysis. The *m/z* peaks at 392 and 414 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively were observed in mass spectrum and in elemental analysis the experimental values were in good agreement with the theoretical values.

Having synthesized the required condensed compound **7** in one pot, the stage was now set for evaluating the construction of D-ring of camptothecin *via* intramolecular Knoevenagel condensation. In this direction, substrate was subjected to cyclization using different bases. It was found that reaction went smoothly using K_2CO_3 as a base in anhydrous DCM as a solvent to furnish excellent yields of dihydropyridone **6**. Formation of dihydropyridone **6** was confirmed by using spectroscopic methods. IR spectrum showed no peak corresponding to the ketone carbonyl while other carbonyls appeared at expected positions (1735 and 1657 cm^{-1} for ester and amide carbonyls respectively) thereby confirming Knoevenagel cyclization. ^1H NMR spectrum of **6** showed disappearance of methylene (-CO$\underline{CH_2}$CO-) protons thus confirming the cyclization. Three triplets that appeared at δ 0.92 (t, *J* = 7.4 Hz), 1.25 (t, *J* = 7.2 Hz) and 1.36 (t, *J* = 7.3 Hz) integrating for three protons each and two quartets at δ 4.15 (q, *J* = 7.2 Hz) and 4.36 (q, *J* = 7.3 Hz) integrating for two protons each were attributed to ethyl ester protons. Multiplets at δ 2.22-2.52 (m, 2H) and 3.17-3.44 (m, 2H) were attributed to methylene protons in pyridone ring, while aromatic and benzylic protons resonated at expected positions. ^{13}C NMR along with DEPT spectra of **6** showed presence of three methyl and six methylene carbons along with peaks at δ 161.5, 165.5 and 171.3 corresponding to three carbonyls present in the dihydropyridone **6**. Finally the structure was further confirmed by mass spectral analysis which revealed signals at *m/z* 374 $(M + H)^+$ and 396 $(M + Na)^+$ thus confirming the structure of **6** and the experimental values of elemental analysis were in good agreement with the theoretical values.

Having successfully synthesised the dihydropyridone **6** in two steps it was thought to perform this transformation in one pot as in both the transformations K_2CO_3 is the base and DCM as the solvent. For the execution of this hypothesis, the α,β-unsaturated ketone **9** was subjected to Michael addition with benzyl amine **8** and after 30 minutes dichloromethane, 4 eq. of K_2CO_3 and ethyl malonyl chloride were added at 0 ^oC and the

reaction mixture was stirred at room temperature for 8 h to achieve the condensation and Knoevenagel cyclization to delightfully afford dihydropyridone **6** in 70% yield *via* the intermediate **7** (Scheme 5). Spectral data for the isolated product matched perfectly with that of the product **6** synthesized by the two-step sequence described above.

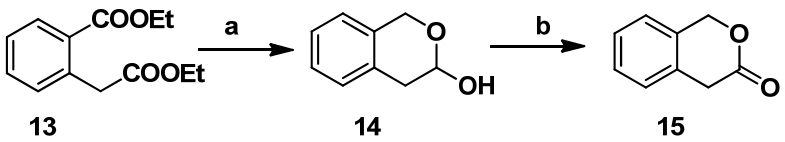


Scheme 5: ***Reagents and conditions:*** *a) Benzyl amine, DCM, ½ h; K_2CO_3, DCM, ethyl malonyl chloride, 8 h, 70%; b) DDQ, 1, 4-dioxane, reflux, 24 h, 91%.*

Having been successful in synthesis of dihydropyridone **6**, employing tandem one pot aza-Michael addition, condensation with ethyl malonyl chloride and Knoevenagel condensation, the next task was to oxidize compound **6**. Thus dihydropyridone **6** was subjected to DDQ oxidation in 1,4-dioxane as the solvent at reflux for 24 h to afford the pyridone **5** in 91% yield. The structure of pyridone **5** was confirmed by spectral data. IR spectrum showed absorptions at 1735, 1718 and 1681 cm^{-1} signifying the presence of aromatic ester, aliphatic ester and amide carbonyl functionality respectively. ^{1}H NMR spectrum of **5** showed appearance of signals at δ 6.28 (d, *J* = 7.2 Hz, 1H) and 7.24 (d, *J* = 7.2 Hz, 1H) which were attributed to pyridone ring protons adjacent to each other thereby confirming oxidation. The triplet that appeared at δ 3.50 integrating for one proton was assigned to proton α to ethyl ester ($CH_3CH_2\underline{CH}COOEt$). Three signals that appeared as triplets at δ 0.92, 1.24 and 1.40 integrating for three protons each, two quartets at δ 4.13 and 4.42 integrating for two protons each and two multiplets at δ 1.70-1.81 and 1.93-2.04 for diastereotopic protons adjacent to chiral center were atributed to three ethyl group protons. The benzylic protons appeared as two doublets at δ 5.05 and 5.13 integrating for one proton each having the geminal coupling constant *J* =14.4 Hz and aromatic protons appeared as multiplet at δ 7.29-7.35 integrating for five protons. ^{13}C NMR spectrum of **5** showed 19 peaks corresponding to 21 carbons. A DEPT spectrum revealed presence of three methyl and four methylene carbons. Finally the mass spectrum of **5** showed the *m/z*

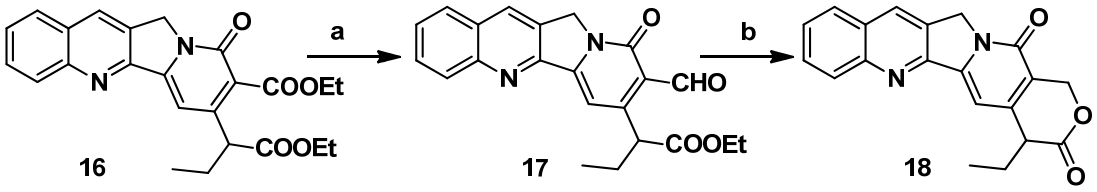
peaks at 372 $(M + H)^+$ and 394 $(M + Na)^+$ and elemental analysis was also found to be in good agreement with the calculated values.

Having synthesized the required pyridone **5** in a short sequence, next objective was to build a lactone ring (E ring of camptothecin **1**) by selective reduction of aromatic ester in presence of aliphatic ester. Kraiss[5] reported selective reduction of aromatic ester to lactol (Scheme 6). The heartening fact was the single isomer obtained during the reduction step with aromatic ester reducing faster than aliphatic one. A variety of conditions were available for the oxidation of lactol to the desired lactone.



Scheme 6: ***Reagents and conditions:*** *a) DIBAL-H (3 equiv.), THF, -60 ^oC, 80%; b) Oxidation.*

Same reaction conditions were applied earlier by this group for the synthesis of pentacyclic lactone.[6] Thus, treatment of diester **16** with 3 equivalents of DIBAL-H at -60 ^oC in dry THF for 2 h furnished aldehyde **17** in 81% yields. No trace of the aliphatic aldehyde or lactol was obtained. And finally, aldehyde on reduction with $NaBH_4$ gave the desired lactone **18** (Scheme 7).

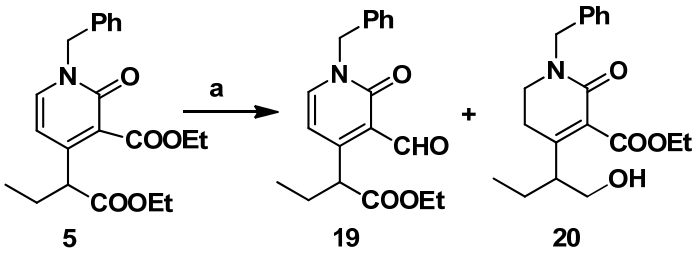


Scheme 7: ***Reagents and conditions:*** *a) DIBAL-H (3 equiv.), THF, -60 ^oC, 81%. b) $NaBH_4$, THF-H_2O, 92%.*

Based on this success of selective reduction of heteroaromatic ester it was planned to apply the same conditions for the synthesis of DE synthon of camptothecin **1**. Thus, ester **5** was subjected to reduction using DIBAL-H under the reaction conditions previously described. Surprisingly, treatment of **5** with 3 eq. DIBAL-H at -60 ^oC in THF furnished the required aldehyde **19,** along with overreduced product *viz* alcohol **20** in 1:3 ratio which were separated by column chromatography (Scheme 8). Formation of alcohol

20 was unexpected based on the propensity of DIBAL-H to selectively reduce the heteroaromatic ester over the aliphatic ester.

The aldehyde **19** and alcohol **20** were characterized by spectral methods. IR spectrum of the aldehyde **19** indicated the presence of ester, aldehyde and amide carbonyl group by revealing absorptions at 1734, 1705 and 1680 cm^{-1} respectively. ^{1}H NMR spectrum of **19** revealed absence of peaks corresponding to aromatic ester and the presence of new singlet that appeared at δ 10.52 integrating for one proton and was assigned to aldehydic proton. The triplet at δ 4.95 integrating for one proton was attributed to proton α to ester ($CH_3CH_2\underline{CH}COOEt$). Signals that appeared at δ 6.30 (d, J = 7.2 Hz, 1H) and 7.46 (d, J = 7.2 Hz, 1H) were attributed to pyridone ring protons adjacent to each other. ^{13}C NMR spectrum of **19** showed absence of peak corresponding to aromatic ester while a new signal at δ 192.7 was assigned to aldehyde carbonyl. Finally, the mass spectrum of **19** showed the *m/z* peaks at 328 $(M + H)^+$ and 350 $(M + Na)^+$ and elemental analyses were also found to be in good agreement with the calculated values.

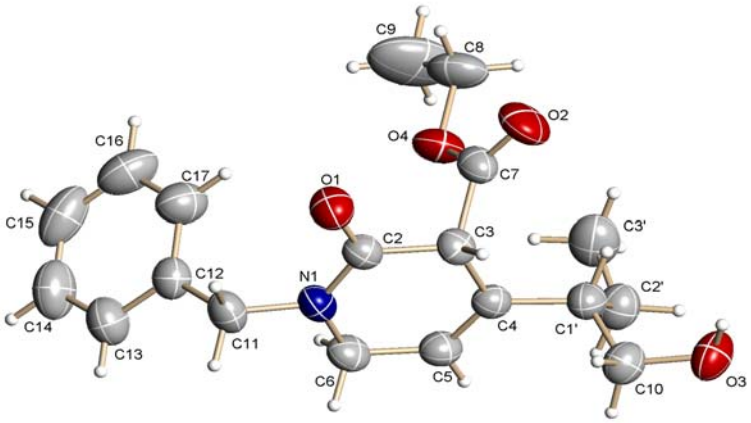


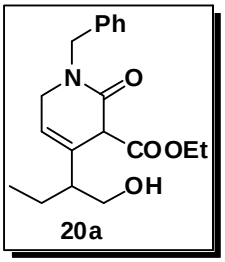
5 19 20

Scheme 8: ***Reagents and conditions:*** *a) DIBAL-H (3 equiv.), THF, -60* ^{o}C.

Structure of **20** was also confirmed by using spectroscopic techniques. IR spectrum of **20** showed the appearance of strong absorption at 3421 cm^{-1} which was assigned to hydroxy functionality. ^{1}H NMR spectrum of alcohol **20** displayed the absence of peaks corresponding to aliphatic ester and aromatic pyridone protons. It showed new signals appearing at δ 2.36-2.47 (m, 1H), 2.52-2.64 (m, 1H) and 3.26-3.40 (m, 2H) corresponding to ring protons which confirmed overreduction and signal that appeared at δ 2.22-2.32 as a multiplet integrating for one proton was assigned to quaternary proton ($CH_3CH_2\underline{CH}CH_2OH$). ^{13}C NMR spectrum of **20** revealed absence of peak corresponding to aliphatic ester and aromatic carbons in pyridone ring but it showed the presence of new signals that appeared at δ 43.2, 49.5 and 67.3 corresponding to methylene carbons which were formed by reduction of pyridone ring and aliphatic ester. DEPT spectrum of **20**

revealed the presence of two methyl and six methylene carbons. The mass spectrum of **20** showed the *m/z* peaks at 332 $(M + H)^+$ and 354 $(M + Na)^+$ and elemental analysis was also found to be in good agreement with the calculated values. Finally, to confirm the structure it was subjected to crystallisation using ethyl acetate/pet ether solvent system. Surprisingly, the ORTEP diagram obtained from the crystal data showed that the compound **20** isomerised during crystallisation to afford the deconjugated isomer **20a**. Formation of **20a** on heating is surprising as it leads to deconjugated ester. This isomerization was explained by using spectroscopic techniques.



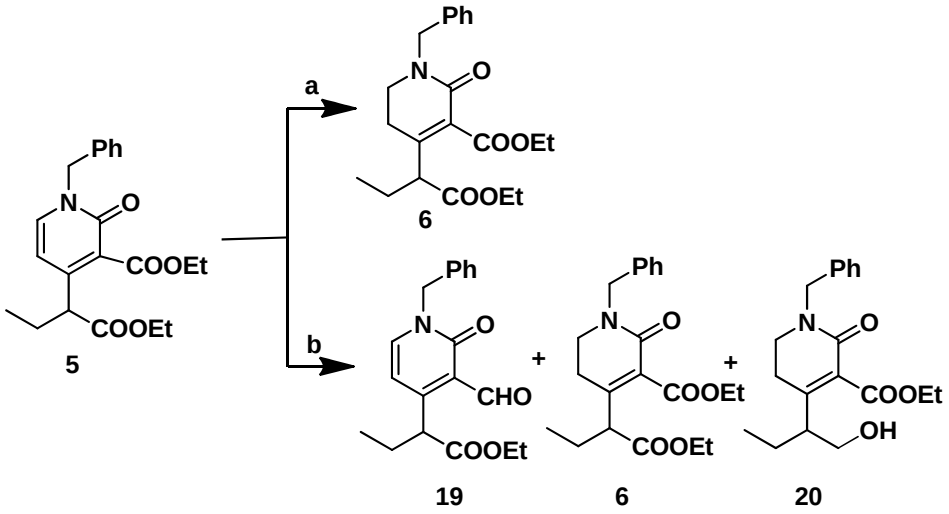


ORTEP Diagram of 20a

The ^1H and ^{13}C NMR data of the crystals obtained were different than the original compound. ^1H NMR of compound **20a** showed a multiplet at δ 5.76-5.80 integrating for one proton and was attributed to olefinic proton in **20a** thereby confirming the isomerization. ^{13}C NMR showed five $–CH_2$ and six –CH carbons instead of six $–CH_2$ and four –CH carbon peaks. The rest of the protons and carbons resonated at expected positions.

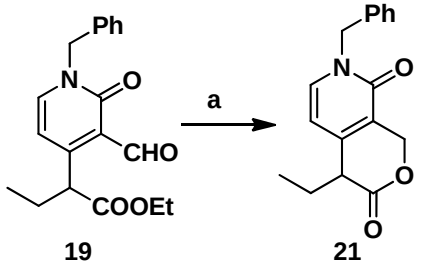
In order to get aldehyde **19** exclusively, it was thought to vary the stoichiometry of DIBAL-H. Accordingly, the ester **5** was subjected to the treatment with 1 equivalent of DIBAL-H but surprisingly it led to the formation of **6**, where one of the double bond of pyridone was selectively reduced, in 80% yield. Use of 2 equivalents of DIBAL-H at -60 ^oC led to the formation of a mixture of products. Compounds **19** and **6** have same R_f value

and were not separable by column chromatography, while alcohol **20** has low R_f (formation of mixture of product was evident from the ^{1}H NMR) (scheme 9).



Scheme 9: ***Reagents and conditions:*** *a) DIBAL-H (1 equiv.), THF, -60 ^{o}C, 80%; b) DIBAL-H (2 equiv.), THF, -60* ^{o}C.

In spite of failing to get the desired aldehyde **19** as the sole product, it was decided to go ahead with the available aldehyde **19**. Aldehyde **19** was subjected to reduction by using $NaBH_4$ in THF/H_2O solvent system to afford required lactone **21** in 93% yield (Scheme 10).

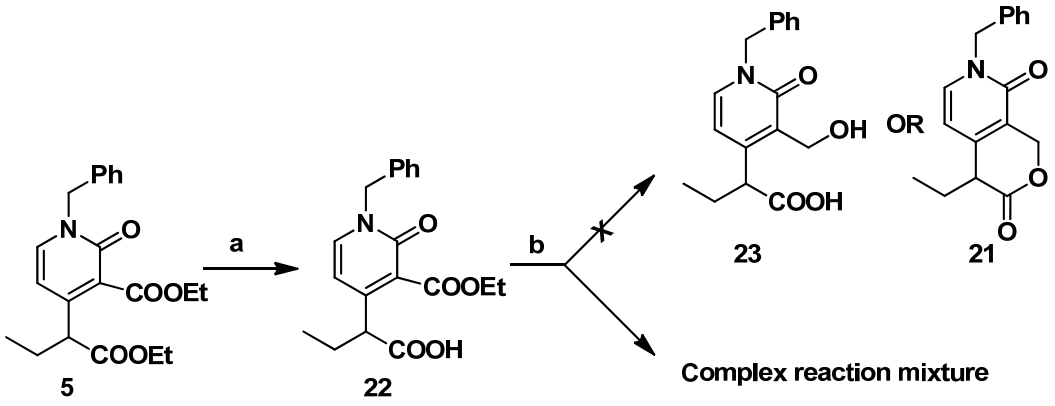


Scheme 10: ***Reagents and conditions:*** *a) $NaBH_4$, THF-H_2O, 30 min, 93%.*

The structure of lactone **21** was confirmed by spectral study. IR spectrum of **21** showed the absorption bands at 1720 and 1651 cm^{-1} corresponding to six-membered lactone and amide functionality respectively. ^{1}H NMR spectrum of **21** showed the presence of two doublets that appeared at δ 5.08 and 5.18 (J = 14.4 Hz) which were attributed to lactone methylene protons. ^{13}C NMR spectrum of **21** displayed the presence

of a signal at δ 51.9 which was assigned to the lactone methylene carbon and rest of the carbon peaks associated with the compound were observed at expected positions. Mass spectrum of **21** showed peaks at *m/z* 284 and 306 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively. Finally, the structure of **21** was confirmed by elemental analysis. The experimental values were in good agreement with its calculated values. All the spectral data of the lactone **21** were in good agreement with literature reported values.[7]

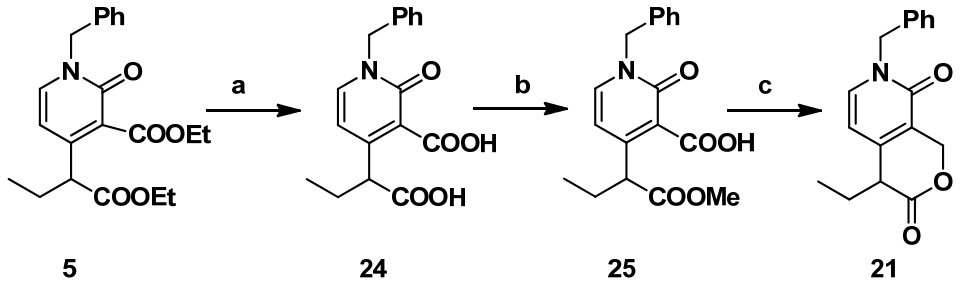
Having fruitfully synthesized the required lactone, albeit in low yield (for aldehyde formation) and failed in selective reduction of aromatic ester, attention was shifted to selective hydrolysis of ester **5** to acid. According to the plan, the selective hydrolysis of the aliphatic ester in presence of the aromatic ester was accomplished by treatment of the diester **5** with 1 equivalent of lithium hydroxide in ethanol/water solvent system at room temperature and it furnished the aliphatic acid **22** in 80% yield (Scheme 11). The structure of monoacid **22** was confirmed by spectral analysis. IR spectrum of **22** showed a very broad absorption band at 2500-3300 cm^{-1} which is characteristic of carboxylic acid.



Scheme 11: ***Reagents and conditions:*** *a) LiOH (1 equiv), EtOH/H_2O, rt, 2 h, 80%; b) $LiBH_4$, THF.*

The ^1H NMR spectrum of **22** displayed the absence of peaks corresponding to aliphatic ester. ^{13}C NMR spectrum of **22** also showed no peak corresponding to aliphatic ester while predictable peaks of protons and carbons associated with the compound resonated at expected positions. The acid **22** on treatment with lithium borohydride[8] at 0 ^oC to room temperature unfortunately instead of forming required product, ended up with complex reaction mixture (Scheme 11).

After the unsuccessful reduction of **22** to alcohol **23**, it was decided to hydrolyze both aliphatic and aromatic esters to diacid. Ester **5** on treatment with excess of lithium hydroxide in ethanol afforded diacid **24** in 84% yield (Scheme 12).



Scheme 12: ***Reagents and conditions:*** *a) LiOH, EtOH, rt, 24 h, 84%; b) $NiCl_2$, MeOH, reflux, 12 h, 76%; c) i) Et_3N, methyl chloroformate, anhydrous THF, 0 ^oC, 1 h; ii) $NaBH_4$ -78 ^oC, 3 h, 10% HCl, rt, 12 h, 84%.*

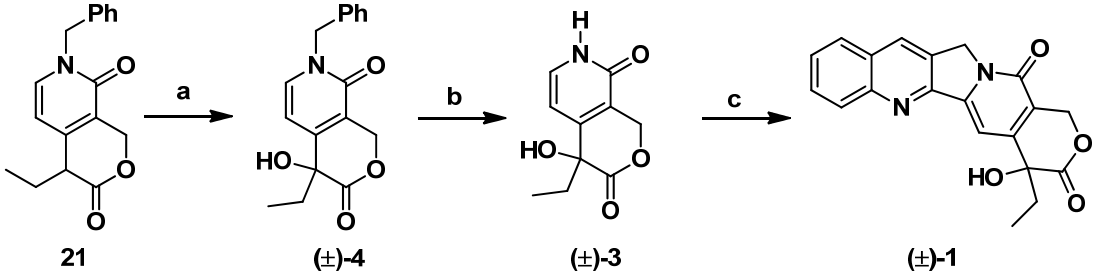
The diacid **24** was characterized by spectral methods. IR spectrum of **24** showed the disappearance of absorption band corresponding to ester functionality. The ^1H NMR spectrum of **24** displayed the absence of the signals corresponding to ester groups. ^{13}C NMR along with DEPT spectra of **24** revealed only two methylene carbons which was indicative of the hydrolysis of both esters, while other peaks associated with compound **24** were seen at expected positions. Finally the structure of compound **24** was confirmed by mass spectral and elemental analysis. The mass spectrum of diacid **24** showed the peaks at *m/z* 316 and 338 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively and in the elemental analysis of **24** the experimental values were in good agreement with calculated values.

The selective esterification of aliphatic acid in presence of heteroaromatic acid was accomplished using catalytic amount of $NiCl_2$[9] in anhydrous methanol at reflux temperature to yield monoester **25** in 76% yield (Scheme 12). The structure of compound **25** was ascertained by spectral study. IR spectrum of **25** displayed the strong absorption band at 1736 cm^{-1} indicating the presence of ester group. The ^1H NMR spectrum of **25** revealed a singlet at δ 3.68 integrating for three protons which was assigned to methyl ester group. ^{13}C NMR spectrum of **25** showed the appearance of signal at δ 172.7 corresponding to carbonyl of ester functionality (-$\underline{C}OCH_3$) and a signal at δ 52.0 corresponding to the methyl carbon of ester functionality (-CO$\underline{C}H_3$), while rest of the

carbon peaks associated the compound were present at expected positions. The mass spectrum of **25** showed the peaks at *m/z* 330 and 352 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively. Elemental analysis was in good agreement with calculated values.

Having compound **25** in hand, the attention was focused towards the E-ring construction. The acid **25** was reacted with methyl chloroformate using triethyl amine[10] as a base to afford the mixed anhydride. The generated mixed anhydride was immediately treated with sodium borohydride at -78 ^oC followed by addition of 10% HCl at room temperature and stirring for 12 h. It was satisfying to note that the desired lactone **21** was obtained in very good yields (Scheme 12). All the spectral data of the lactone **21** were in good agreement with literature reported values.[7]

Having accomplished the synthesis of the lactone **21** in satisfactory yield, next concern was the straightforward synthesis of DE synthon of camptothecin. The α-hydroxylation on lactone **21** 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 **4** in excellent yield.[11]

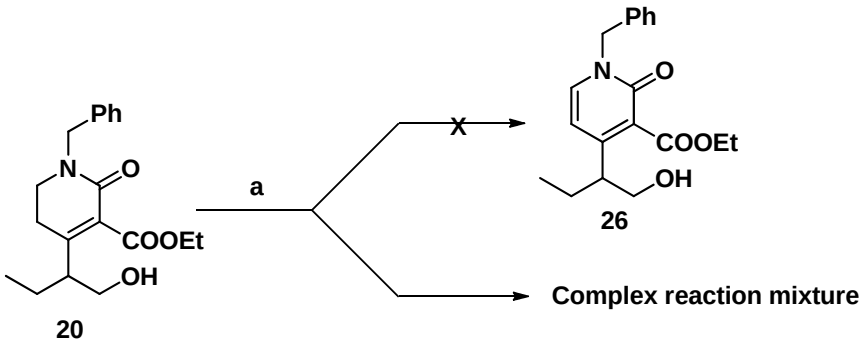


Scheme 13: ***Reagents and conditions:*** *a) $CuCl_2$, Me_2NH, O_2, DMF, rt, 24 h, 92%; b) $Pd(OH)_2$, H_2, EtOH, 50 ^oC, 5 h, 72%.; c) ref 13.*

Compound **4** was characterized by spectral techniques. IR spectrum of **4** showed a broad absorption band at 3350 cm^{-1} indicating the presence of hydrogen bonded hydroxyl functionality. The ^1H NMR spectrum of **4** displayed the absence of the triplet corresponding to methine proton. ^{13}C NMR spectrum along with DEPT spectrum of **4** showed the disappearance of the signal corresponding to methine carbon. The peaks at *m/z* 300 and 322 were observed in mass spectrum of **4** corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively. The elemental analysis of **4** revealed that the experimental values were in good agreement with its calculated values. Finally, *N*-debenzylation of **4** was

successfully carried out using catalytic amount of palladium hydroxide in ethanol under H_2 atmosphere at 50 ^oC for five hours to obtain the desired DE-ring synthon[12] **3** in satisfactory yield (Scheme 13). The structure of **3** was confirmed by spectral study wherein the spectral data of compound **3** was found to be in complete agreement with the literature data.[7,12] Compound **3** is a key intermediate in Comins synthesis.[13] The DE synthon **3** can be transformed into (±)-camptothecin **1** or its analogues by coupling with suitable AB-ring counterpart.

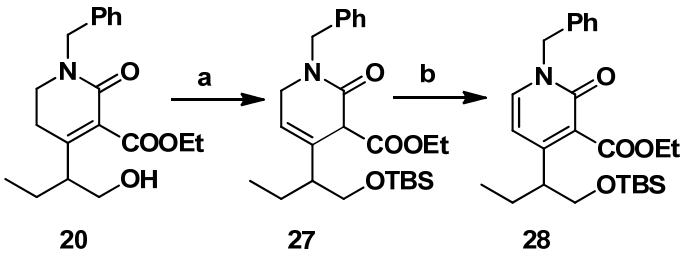
In the DIBAL-H reduction of pyridone **5,** formation of an unusual overreduced alcohol **20** was observed (Scheme 8). It was thought to utilize alcohol **20** for the synthesis of camptothecin and its analogues. Accordingly, alcohol **20** was subjected to DDQ oxidation in 1,4-dioxane at room temperature but under various tried conditions, the desired transformation could not be achieved. In all the attempts, the TLC showed complex pattern (Scheme 14). It was presumed that the free alcohol was interfering with the reagents under the conditions applied.



Scheme 14: ***Reagents and conditions:*** *a) DDQ, 1,4 dioxane, rt to reflux.*

So it was thought to protect alcohol first and then perform the aromatization. Accordingly, treatment of alcohol **20** with TBSCl and imidazole in anhydrous DCM at 0 ^oC-rt for 1 h smoothly delivered the TBS protected compound **27** with isomerization of double bond as diastereomeric mixture (Scheme 15). In the IR spectrum hydroxy absorption was absent indicating the conversion of -OH to its silyl derivative. In the ^1H NMR spectrum, signals corresponding to TBS group appeared at δ 0.01 (s, 3H), 0.02 (s, 3H) and 0.87 (s, 9H). The multiplet at 5.60-5.65 integrating for one proton was assigned for olefin proton. ^{13}C NMR spectrum along with DEPT spectrum of compound **27** showed doubling of peaks due to mixture diastereomers. The mass spectrum of **27** showed peaks

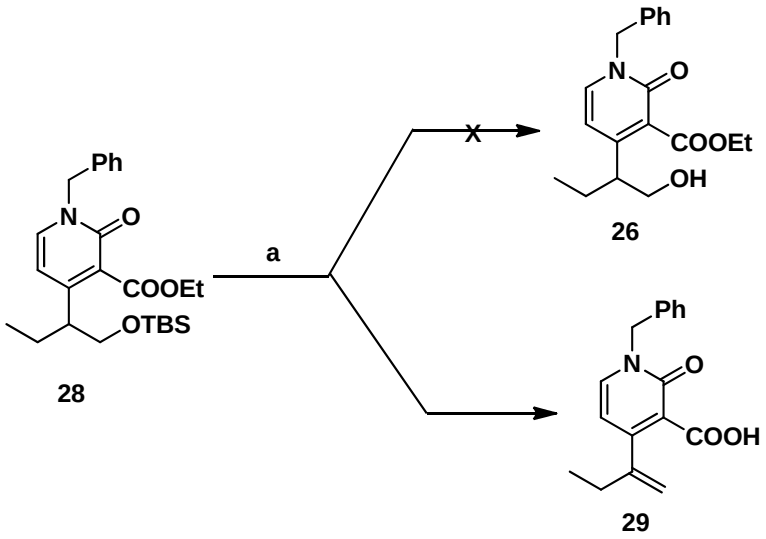
at *m/z* 446 and 468 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively and elemental analysis data was in good agreement with the proposed structure.



Scheme 15: ***Reagents and conditions:*** *a) Imidazole, TBSCl, DCM, 0 ^oC-rt, 1 h, 95%; b) DDQ, 1, 4-dioxane, reflux, 5 h, 98%.*

Having TBS protected compound **27** in hand, it was subjected to DDQ oxidation. Gratifyingly, aromatization occurred very smoothly in refluxing 1,4-dioxane as the solvent to afford excellent yield of compound **28** (Scheme 15). ^{1}H NMR spectrum showed signals corresponding to TBS group that appeared at δ -0.04 (s, 3H), -0.03 (s, 3H), and 0.83 (s, 9H). The two triplets at δ 0.85 ($\underline{CH_3}CH_2CH$-) and 1.36 (-$COOCH_2\underline{CH_3}$) were assigned to two methyl group protons. Signals that appeared at δ 6.17 (d, *J* = 7.2 Hz, 1H) and 7.22 (d, *J* = 7.2 Hz, 1H) were attributed to aromatic protons in pyridone ring which confirmed the oxidation. ^{13}C NMR spectrum along with DEPT spectrum of **28** showed signals at δ -5.7, -5.6 and 11.7 corresponding to TBS carbons, while rest of the carbon signals were seen at expected positions. Finally, mass spectrum of **28** showed the peaks at *m/z* 444 and 466 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively and elemental analysis data were in good agreement with the proposed structure.

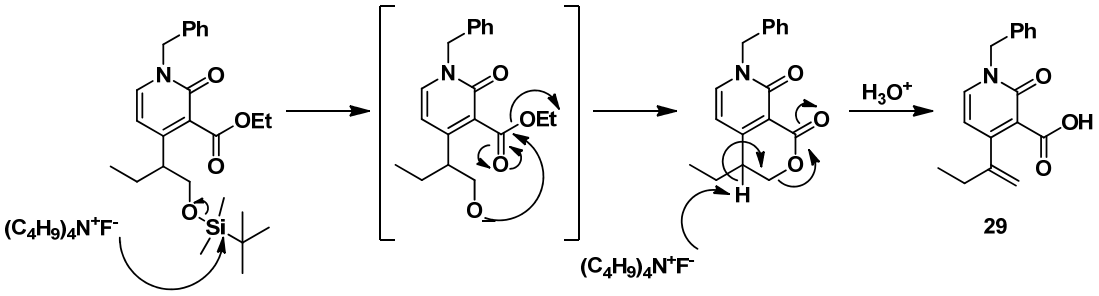
Having the compound **28** in hand, the next concern was to deprotect and eliminate the hydroxyl group to get exomethylene compound. Thus TBS deprotection was carried out using TBAF in THF but surprisingly instead of desired product **26**, formation of compound **29** was observed (Scheme 16). The formation of compound **29** was confirmed by spectral techniques. IR spectrum of **29** showed disappearance of absorption band corresponding to ester functionality and showed a very broad absorption band at 2500-3300 cm^{-1} which was characteristic of carboxylic acid. The ^{1}H NMR spectrum of **29** revealed the absence of peaks corresponding to aliphatic ester and TBS group. The signals at δ 1.08 (t, *J* = 7.4, 3H) and 2.39 (q, *J* = 7.4, 2H) were assigned to ethyl group protons, while exomethylene protons appeared as two singlets at δ 4.84 and 5.12.



Scheme 16: ***Reagents and conditions:*** *a) TBAF, THF, rt, 1 h, 60%*

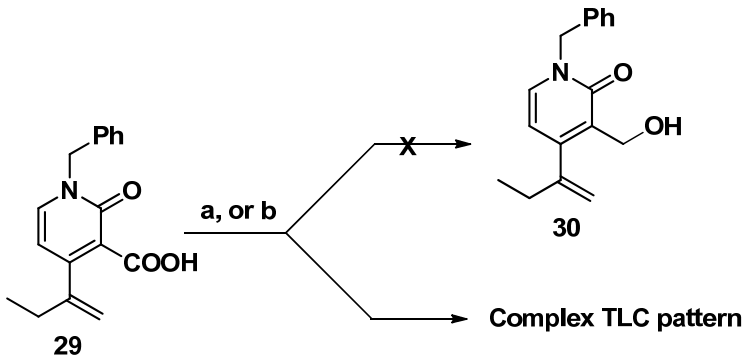
^{13}C NMR spectrum along with DEPT spectrum of **29** showed signal at δ 112.5 corresponding to exomethylene carbon. The structure of compound **29** was further supported by mass spectral and elemental analysis. The *m/z* peaks at 284 $(M + H)^+$ and 306 $(M + Na)^+$ were seen in the mass spectrum and elemental analysis values were in good agreement with the theoretical values.

The formation of compound **29** can be rationalized by the probable mechanism which is depicted in Scheme 17.



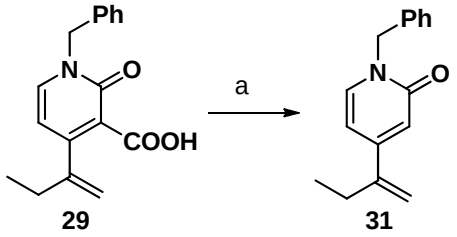
Scheme 17: Plausible mechanism

Having unusual rearranged product **29** in hand, it was thought to utilize this compound for the synthesis of camptothecin **1** and its analogues. The acid **29** was subjected to reduction under various conditions but unfortunately under the conditions tried, the desired transformation could not be achieved. In all the attempts, the TLC showed complex pattern (Scheme 18).



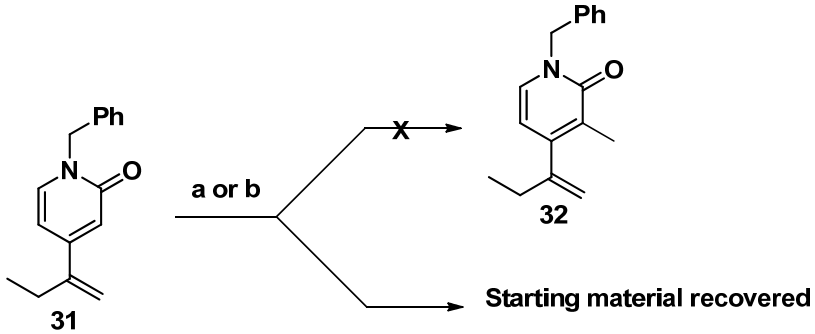
Scheme 18: ***Reagents and conditions:*** *a) i) Et_3N, methyl chloroformate, anhydrous THF, 0 ^oC, 1 h; ii) $NaBH_4$, -78-0 ^oC, 10% HCl, rt; b) $NaBH_4$, I_2, THF, 0 ^oC-rt.*

In spite of failing to reduce the acid **29** to corresponding alcohol, it was decided to decarboxylate the acid and then introduce the methyl group. Accordingly, decarboxylation was carried out using Cu and quinoline[14] at reflux condition to furnish desired compound **31** (Scheme 19).



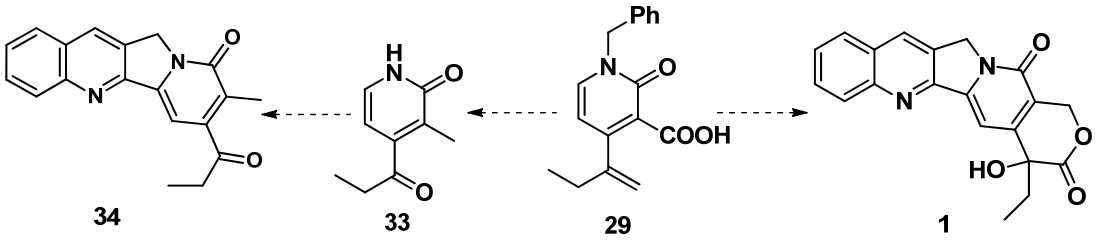
Scheme 19: ***Reagents and conditions:*** *a) Cu, quinoline, reflux, 3 h, 90 %.*

Having decarboxylated compound **31** in hand, it was subjected to introduction of methyl group using methyl iodide in presence of strong base like LDA or *n*-BuLi but unfortunately in both the cases starting material was recovered (Scheme 20).



Scheme 20: ***Reagents and conditions:*** *a) n-BuLi, MeI, THF, -78-0 ^oC; b) LDA, MeI, THF, -78-0 ^{o}C.*

Due to paucity of time these transformations could not be tried by other reagents and conditions which look straightforward. With proper choice of reagents and conditions, the compounds **29** and **31** would serve as versatile and important substrates to access advanced intermediate **33**,[15] which is a precursor for the synthesis of mappicine ketone **34**, as well as it can be further manipulated into camptothecin **1** (Scheme 21).



Scheme 21

2.1.3 Synthesis of (+)-DE synthon

2.1.3.1 Introduction

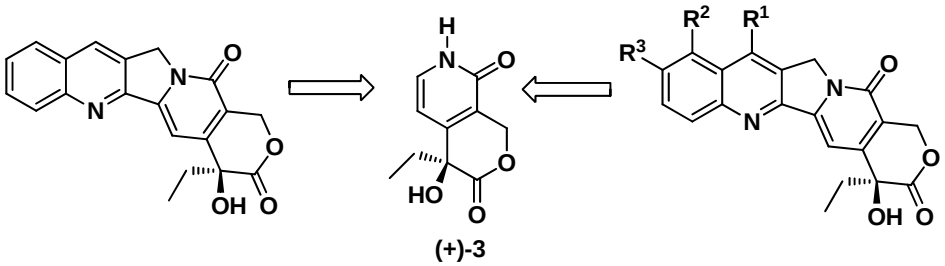
The earth is chiral and so most of the organic compounds. Chemists from pharmaceutical world, agro and cosmetic industries require access to enantiomerically pure compounds.

It is well known that all the biological receptors are chiral and as such can distinguish between two enantiomers of a ligand or substrate. Thus pharmacological compounds, which are chiral when screened for their activity, may behave differently in comparison to their enantiomers or racemate. Hence the quest to obtain enantiomerically pure compound has always been a challenge to the chemical world. An easy and straightforward solution is to isolate them from natural sources. Alternatively one can prepare the racemate and resolve it, plan a chiron approach for its synthesis or perform an asymmetric synthesis. The different objectives are restrained from factors such as amount of material required, the cost of starting material, length of synthetic plan *etc*. Resolution is restricted by the drawback that one of the enantiomers can be achieved in the maximum theoretical yield of 50% unless the unwanted enantiomer is recovered and recycled. The chiron approach utilises/consumes chiral natural starting material and at best can produce a single enantiomer from a given route.

Intrigued by the above mentioned facts and with the successful accomplishment of racemic synthesis of DE synthon **3** in short sequence, it was thought worthwhile to expand the chemistry towards the asymmetric accomplishment of the DE synthon **3**, which will give easy access to enantioselective synthesis of camptothecin and its analogues.

2.1.3.2 Present work

The present subsection deals with the study towards the asymmetric construction of the DE synthon **3**, which was efficiently synthesised in the previous section in racemic form. A careful inspection of **3** reveals that the only chiral center present therein and which is further carried over to the final molecule **1** (C20), can be fixed by Sharpless asymmetric dihyroxylation[16] of alkene **37**. The retrosynthetic approach described previously can be modified in light of asymmetric synthesis as delineated in Scheme 23.



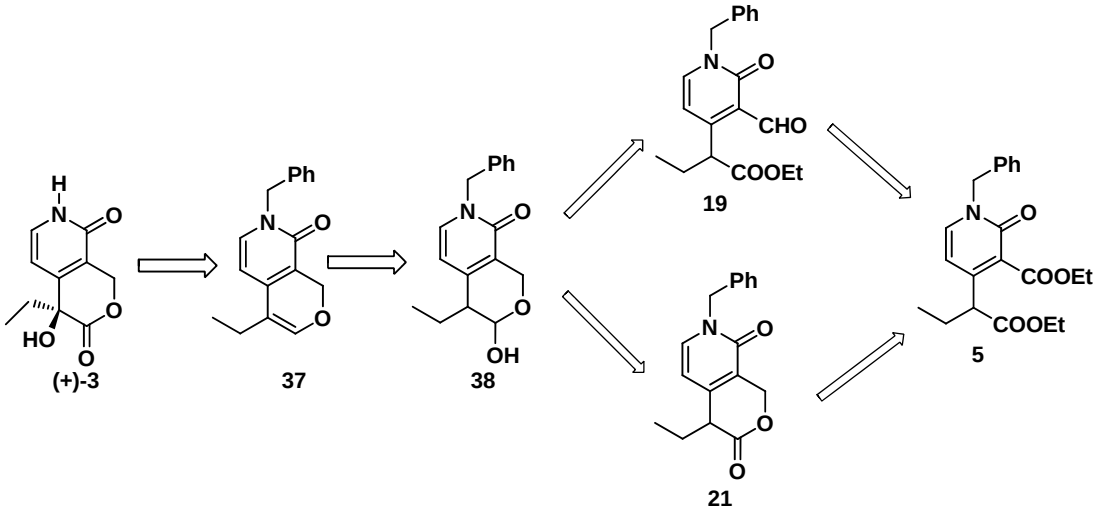
(+)-Camptothecin 1 **(+)-3**

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

36. Irinotecan R^1=Et, R^2=H, R^3=OCOPipPip.HCl.$3H_2O$

Scheme 22

Accordingly, (+)-**3** could be efficiently synthesised by selective dihydroxylation of alkene **37.** The alkene **37** could be realised by mesylation and elimination of hydroxy group of lactol **38**, which in turn could be efficiently synthesized by reduction of aldehyde **19** and lactone **21**. Both the aldehyde **19** and the lactone **21** can be accessed from ester **5** (Scheme 23).

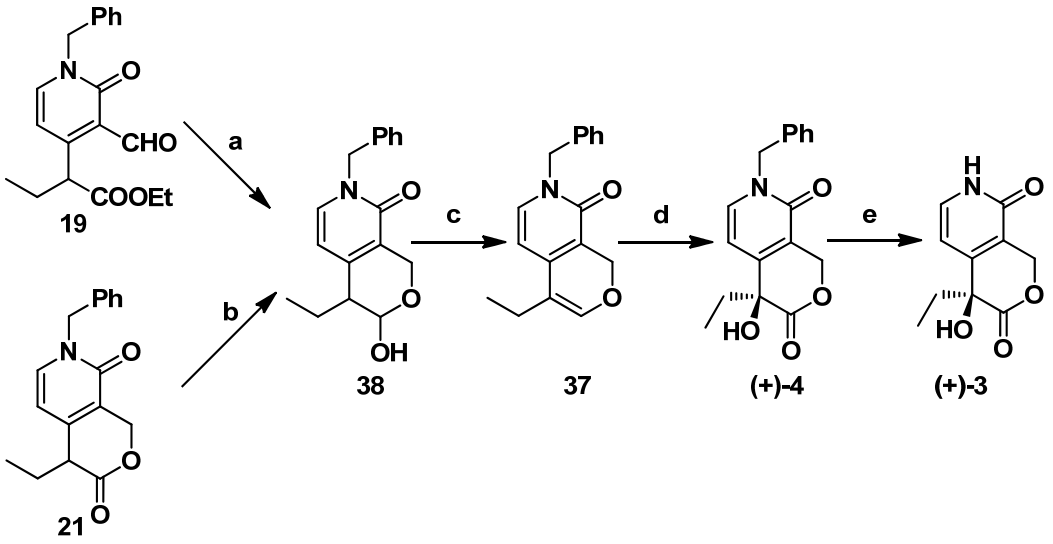


Scheme 23

2.1.3.3 Results and discussion

At the onset of the journey towards asymmetric synthesis, reduction was performed with $NaBH_4$ on already synthesized aldehyde **19** and lactone **21**, which in turn were synthesized from diester **5** as explained in previous subsection. The aldehyde **19** was converted into lactol **38** *via* the lactonization using two equivalents of $NaBH_4$ in THF/H_2O solvent system at 0 ^oC for 30 min. Formation of lactol **38** was confirmed by spectral techniques. IR spectrum of **38** showed a broad absorption band at 3400 cm^{-1} indicating the presence of hydroxy functionality. The ^1H NMR spectrum of **38** displayed the absence of signal corresponding to aldehyde proton and the presence of two doublets that appeared at δ 4.60 and 5.05 (J = 14.5 Hz) which were attributed to lactol methylene protons. A signal appearing at δ 0.99 as a quartet integrating for three protons and a multiplet at δ 1.57-1.74 integrating for two protons were assigned to ethyl group protons. Triplet at δ 2.39 integrating for one proton was assigned to proton α to ethyl group. Broad singlet at δ 3.92 integrating for one proton was assigned to lactol –OH proton. ^{13}C NMR spectrum of **38** showed the disappearance of the signal corresponding to aldehyde carbonyl. DEPT spectrum showed presence of one methyl and three methylene carbon while rest of the carbons associated with compound resonated at expected positions. Finally the mass spectrum showed the *m/z* peaks at 286 $(M + H)^+$ and 308 $(M + Na)^+$. Elemental analysis was also found to be in good agreement with calculated values. Lactol **38** was also obtained from lactone **21** (synthesized from diester **5** *via* mixed anhydride sequence of

reaction) by reduction using one equivalent of $NaBH_4$ in THF/H_2O solvent system at 0 ^oC for 15 min (Scheme 24).



Scheme 24: ***Reagents and conditions:*** *: a) $NaBH_4$ (2 eq.), $THF:H_2O$ (9:1), 0 ^{o}C-rt, 30 min, 90%. b) $NaBH_4$ (1 eq.), $THF: H_2O$ (9:1), 0 ^{o}C-rt, 15 min, 90%. c) MsCl, Et_3N, anhydrous THF, rt, 24 h, 95%; d) i) $(DHQD)_2$-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; ii) I_2 (10 equiv), $CaCO_3$ (10 equiv), CH_3OH-H_2O (10:1), rt, 24 h, 90% over two steps. e) $Pd(OH)_2$, H_2, EtOH, 50 ^oC, 5 h, 72%.*

With lactol **38** in hand, the elimination of hydroxy group was effected using 4 equivalents of mesyl chloride and eight equivalents of triethyl amine in THF at 50 ^{o}C for 24 h to afford enol ether **37** in 95% yield (Scheme 24). IR spectrum of enol ether **37** showed no peak corresponding to the -OH functionality. The ^{1}H NMR spectrum of **37** showed signal at δ 6.57 as a singlet integrating for one proton and was attributed to enol ether proton (-C=CH-O-) confirming elimination. The signals at δ 1.10 (t, J = 7.5 Hz, 3H) and 2.24 (q, J = 7.5 Hz, 2H) were attributed to ethyl group protons. ^{13}C NMR spectrum of **37** showed new peaks which appeared at δ 100.7 and 141.5 and were attributed to enol ether carbons (-C=CH-O-) while rest of the peaks were in good agreement with the proposed structure and finally the structure of **37** was confirmed by mass spectrum and elemental analysis. The mass spectrum showed the *m/z* peaks at 268 $(M + H)^+$ and 290 $(M + Na)^+$. Elemental analysis was also found to be in good agreement with calculated values.

Having the enol ether **37** in hand, the last and important task was to synthesize the enantiomerically pure α–hydroxy lactone **4**. Taking into account the well established enantioselective principle and mnemonic device for asymmetric dihydroxylation of trisubstitued alkene, it was concluded that $(DHQD)_2PYR$ would be the right ligand of choice to render the *S* enantiomer. Thus, when the substrate **37** was subjected to Sharpless dihydroxylation conditions,[16] employing $(DHQD)_2PYR$ as chiral ligand, potassium osmate as osmium source, methane sulphonamide, $K_3Fe(CN)_6$ and K_2CO_3 in *t*-BuOH:H_2O[17] (1:1), it furnished the diol as anomeric mixture which was subjected to oxidation using Corey's condition[18] *i. e.* $I_2/CaCO_3$ to afford optically pure **4** (90% yield, 95% ee), $[\alpha]_D^{25}$ = +112 (*c*=1, $CHCl_3$). The enantiopurity of the hydroxylactone was estimated to be in excess of 95% using chiral HPLC analysis (Chiralcel OD-H (250 x 4.6 mm), 80:20, IPA:*n*-hexane (12:88), 0.7 ml/min, 280 nm). The structure of **4** was confirmed by spectral study. The spectral data of compound **4** was in complete agreement with the literature data.[12]

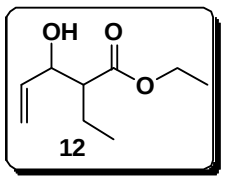
Finally *N*-debenzylation of **4** was successfully carried out using catalytic amount of palladium hydroxide in ethanol under H_2 atmosphere at 50 ^oC for five hours, to afford the desired DE-ring synthon (+)-**3** in satisfactory yield $[\alpha]_D^{25}$ = +120 (*c*=0.3, methanol) (Scheme 24). The spectral data of compound **3** was in complete agreement with the literature data.[19] The DE-ring can be transformed into (+)-camptothecin **1** or its analogues by coupling with suitable AB-ring counterpart.

2.1.4 Conclusion

In conclusion, the formal synthesis of (±)-camptothecin *via* DE ring synthon employing tandem one-pot, three-step transformations involving aza-Michael reaction, condensation with ethyl malonyl chloride followed by intramolecular "Knoevenagel" reaction to furnish dihydropyridone has been accomplished. Also, formal synthesis of (+)-camptothecin was achieved employing Sharpless dihydroxylation *via* DE synthon.

2.1.5 Experimental

Ethyl 2-ethyl-3-hydroxypent-4-enoate (12)



To the stirred suspension of zinc (34 g, 534 mmol) in anhydrous THF (150 mL), was added acrylaldehyde **10** (12.5 mL, 178 mmol) followed by solution of ethyl-2-bromobutyrate **11** (32 mL, 213 mmol) in anhydrous THF and catalytic amount of iodine at room temperature. Reaction mixture was heated at reflux temperature for 8 h. After completion of reaction, the reaction mixture was cooled and diluted with ethyl acetate, water was added, the resulting mixture was filtered through sintered funnel and residue was washed with ethyl acetate (250 mL). The resulting filtrate was extracted with ethyl acetate (3 x 50 mL). Organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2) eluting with ethyl acetate/pet ether (1:9) to furnish the desired compound **12** (20.5 g, 67%).

Mol. Formula **:** $C_9H_{16}O_3$ (MW: 172.22).

IR (Neat) **:** 3484, 1736, 1376, 1186 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.61-1.75 (m, 2H), 2.36-2.44 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.24-4.37 (m, 1H), 5.27-5.35 (m, 2H), 5.79-5.91 (m, 1H).

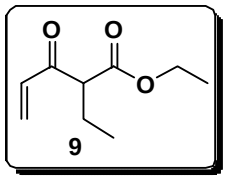
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.5, 11.9, 14.2, 20.5, 22.3, 52.5, 52.7, 60.4, 73.0, 73.2, 116.2, 116.3, 137.6, 138.5, 174.5, 175.0 (mixture of diastereomers).

Mass (ESI) m/z **:** 173 $(M + H)^+$.

Elemental analysis **:** Calculated: C, 62.77; H, 9.36%

: Found: C, 62.72; H, 9.33%

Ethyl 2-ethyl-3-oxopent-4-enoate (9)



Method A: To the stirred solution of alcohol **12** (10 g, 78.6 mmol) in acetone was added Jones reagent dropwise at 0 ^oC such that the reaction temperature remained around 0 ^oC. The initially formed green colored solution turned into reddish color indicating

completion of reaction. After completion of reaction (TLC), the reaction mixture was decanted. The residue was washed with 25% ethyl acetate/pet ether (50 mL) and combined layer was extracted using 25% ethyl acetate/pet ether and washed with water and dried over anhydrous Na_2SO_4. The combined organic layer was evaporated under reduced pressure to afford title compound **9** (8.3 gm, 85%). This was pure enough for further use.

Method B: To the stirred solution of alcohol **12** (5 g, 29.1 mmol) in anhydrous ethyl acetate was added IBX (9.7 g, 34.9 mmol) and the resultant solution was refluxed for 4 h. After completion of reaction (TLC), the reaction mixture was filtered through the celite pad. The residue was washed with ethyl acetate (25 mL) and combined layer was concentrated under reduced pressure to furnish the title compound **9** (8.9 g, 90%), which was pure enough for further use.

Mol. Formula **:** $C_9H_{14}O_3$ (MW: 170.21).

IR (Neat) **:** 1736, 1710, 1147 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.95, (t, *J* = 7.4 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.84-2.03 (m, 2H), 3.59 (t, *J* = 7.3, 1H), 4.18 (q, *J* = 7.4 Hz, 2H), 5.86 (dd, *J* = 1.7 and 9.8 Hz, 1H), 6.33 (dd, *J* = 1.7 and 17.4 Hz, 1H), 6.49 (dd, *J* = 9.8 and 17.4 Hz, 1H).

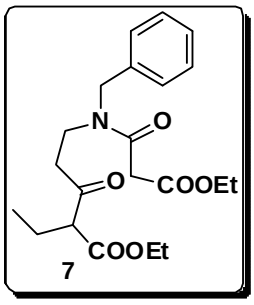
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.8, 14.0, 21.6, 58.0, 61.2, 58.0, 61.2, 129.5, 134.6, 169.6, 194.8.

Mass (ESI) m/z **:** 171 $(M + H)^+$, 193 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 63.51; H, 8.29%

: Found: C, 63.14; H, 8.25%

Ethyl 5-(*N*-benzyl-3-ethoxy-3-oxopropanamido)-2-ethyl-3-oxopentanoate (7)



7

To the keto compound **9** (5 g, 29.4 mmol), benzyl amine (3.21 mL, 29.4 mmol) was added dropwise at room temperature and allowed to stir for 30 min. After the completion of the reaction (TLC), dichloromethane (15 mL) and K_2CO_3 (4 g, 29.4 mmol) were added followed by drop wise addition of ethyl malonyl chloride (4.5 mL, 35.2 mmol) at 0 °C. The mixture was stirred at room temperature until completion (1 h, TLC), then it was filtered and the residue was washed with CH_2Cl_2

(3 × 30 mL). The organic layer was washed with H_2O, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2) using ethyl acetate/pet ether (3:7) as an eluent to afford the condensed product **7** as a colorless liquid (8.0 g, 70%).

Mol. Formula **:** $C_{21}H_{29}NO_6$. (MW: 391.46).

IR (Neat) **:** 1735, 1710, 1681, 1629, 1566, 1521, 1477, 1217, 769 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 6H), 1.74-1.92 (m, 2H), 2.67-2.93 (m, 2H), 3.17 and 3.32 (2t, *J* = 7.3 Hz, 1H), 3.40 and 3.61 (2s, 2H), 3.54-3.57 (2t, *J* = 7.3 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.59 (s, 2H), 7.16-7.39 (m, 5H). (Mixture of rotamers)

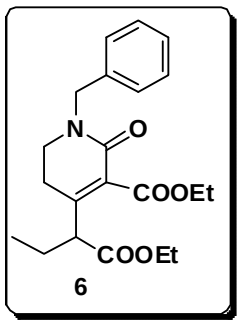
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.6, 11.7, 13.9, 21.2, 21.3, 39.8, 39.9, 40.9, 41.2, 42.1, 48.1, 52.8, 60.4, 60.6, 61.1, 61.3, 61.4, 126.3, 127.3, 127.7, 127.8, 128.5, 128.8, 136.1, 136.8, 166.3, 166.6, 167.3, 167.6, 169.2, 169.4, 203.0, 204.2. (Mixture of rotamers)

Mass (ESI) m/z **:** 392.42 $(M + H)^+$, 414 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 64.43; H, 7.47; N, 3.58%

: Found: C, 64.51; H, 7.45; N, 3.55%

Ethyl 1-benzyl-4-(1-ethoxy-1-oxobutan-2-yl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (6)



6

Method A : To a stirred solution of keto compound **9** (5 g, 29.4 mmol) in dry CH_2Cl_2, benzyl amine (3.21 mL, 29.4 mmol) was added dropwise at room temperature and allowed to stir for 30 min. After the completion of the reaction (TLC), K_2CO_3 (14.2 g, 102.9 mmol) was added followed by dropwise addition of ethyl malonyl chloride (4.89 mL, 38.2 mmol) at 0 °C. The mixture was stirred at room temperature until completion (8 h, TLC), and it was filtered and the residue was washed with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2) using ethyl

acetate/pet ether (3:7) as eluent to afford the dihydropyridone **6** (7.6 g, 70%) as colorless liquid.

Method B : To the stirred solution of diester compound **7** (5 g, 12.8 mmol) in dry dichloromethane was added potassium carbonate (4.4 g, 32 mmol) and allowed to stir for 5 h at room temperature. After the disappearance of starting material (TLC), the reaction was quenched by addition of saturated solution of ammonium chloride and extracted with CH_2Cl_2 (3 x 20 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) eluting with ethyl acetate/pet ether to yield dihydropyridone **6** (4.5 g, 95%) as colorless liquid.

Mol. Formula **:** $C_{21}H_{27}NO_5$ (MW: 373.44).

IR (Neat) **:** 1735, 1657, 1610, 1566, 1521, 1477, 1217, 769 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.3 Hz, 3H), 1.52-1.69 (m, 1H), 1.83-1.97 (m, 1H), 2.22-2.52 (m, 2H), 3.17-3.44 (m, 2H), 3.64-3.74 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.36 (q, *J* = 7.3 Hz, 2H), 4.49 (d, *J* = 14.7 Hz, 1H), 4.66 (d, *J* = 14.7 Hz, 1H), 7.23-7.30 (m, 5H).

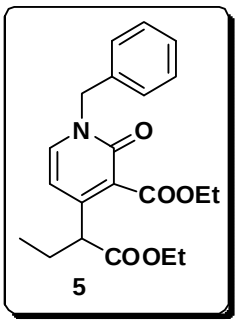
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.9, 14.1, 14.2, 22.9, 24.2, 43.7, 49.6, 50.4, 61.0, 61.3, 127.5, 127.9, 128.2 (2C), 128.6 (2C), 136.9, 147.6, 161.5, 165.5, 171.3.

Mass (ESI) m/z **:** 374 $(M + H)^+$, 396 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 67.54; H, 7.29; N, 3.97%

: Found: C, 67.51; H, 7.25; N, 3.95%

Ethyl 1-benzyl-4-(1-ethoxy-1-oxobutan-2-yl)-2-oxo-1,2-dihydropyridine-3-carboxylate (5)



5

To the stirred solution of dihydropyridone **6** (4 g, 10.8 mmol) in anhydrous 1, 4-dioxane (50 mL) was added DDQ (2.6 g, 11.8 mmol) and reaction mixture was refluxed till the completion of reaction (24 h, TLC). The reaction mixture was diluted with ethyl acetate, filtered using sintered funnel and filtrate was quenched by addition of 10% $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated

under reduced pressure. The generated residue was purified by flash column chromatography (SiO_2) eluting with 30% ethyl acetate/petroleum ether to yield pyridone **5** (3.6 g, 91%) as a pale yellow thick liquid.

Mol. Formula **:** $C_{21}H_{25}NO_5$ (MW: 371.43).

IR (Neat) **:** 1735, 1718, 1681, 1629, 1566, 1521, 1477, 1217, 769 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.70-1.81 (m, 1H), 1.93-2.04 (m, 1H), 3.50 (t, *J* = 7.4 Hz, 1H), 4.13 (q, *J* =7.2, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 5.05 (d, *J* = 14.4 Hz, 1H), 5.13 (d, *J* = 14.4 Hz, 1H), 6.28 (d, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.29-7.35 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 11.8, 13.9, 14.1, 25.6, 49.5, 51.9, 61.1, 61.5, 104.6, 125.7, 128.1, 128.5 (2C), 128.8 (2C), 135.4, 137.4, 148.7, 159.3, 165.9, 171.8.

Mass (ESI) m/z **:** 372 $(M + H)^+$, 394 $(M + Na)^+$.

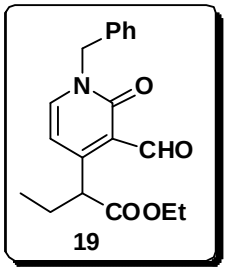
Elemental analysis **:** Calculated: C, 67.91; H, 6.78; N, 3.77%

: Found: C, 67.88; H, 6.73; N, 3.75%

Ethyl 2-(1-benzyl-3-formyl-2-oxo-1, 2-dihydropyridin-4-yl) butanoate (19) and ethyl-1-benzyl-4-(1-hydroxybutan-2-yl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (20)

The pyridone **5** (0.5 g, 1.40 mmol) was dissolved in dry THF (20 mL) under argon atmosphere and temperature lowered to –60 ^oC. DIBAL-H (2 M in toluene, 2.08 mL, 4.20 mmol) was added dropwise and left to stir at the same temperature till the completion of reaction (2 h, TLC). The reaction was quenched at –60 ^oC with the addition of methanol (2 mL) and water (1 mL) and then warmed to room temperature. The gelatinous precipitate was filtered through celite, washed thoroughly with THF and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting first with 25% ethyl acetate in pet ether as eluent to deliver the aldehyde **19** (0.088 g, 20%) as yellowish oil, and then with 50% ethyl acetate/pet ether as eluent to deliver the alcohol **20** (0.275 g, 60%) as a white solid in 1: 3 ratio.

Ethyl 2-(1-benzyl-3-formyl-2-oxo-1, 2-dihydropyridin-4-yl) butanoate (19)



19

Mol. Formula : $C_{19}H_{21}NO_4$ (MW: 327.37).

IR (Neat) : 2730, 1734, 1705, 1680, 1635, 1590, 1510, 765 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.62-1.73 (m, 1H), 1.98-2.08 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.95 (t, *J* = 7.5 Hz, 1H), 5.13 (s, 2H), 6.30 (d, *J* = 7.2 Hz, 1H), 7.33-7.39 (m, 5H), 7.46 (d, *J* = 7.2 Hz, 1H), 10.52 (s, 1H).

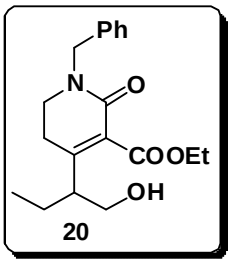
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.9, 14.0, 25.8, 46.3, 52.1, 61.0, 106.1, 122.2, 128.4, 128.5 (2C), 129.0 (2C), 135.1, 147.7, 156.5, 163.4, 172.3, 192.7.

Mass (ESI) m/z : 328.38 $(M + H)^+$, 350.35 $(M + Na)^+$.

Elemental analysis : Calculated: C, 69.71; H, 6.47; N, 4.28%

: Found: C, 67.9; H, 6.53; N, 4.25%

Ethyl 1-benzyl-4-(1-hydroxybutan-2-yl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (20)



20

Mol. Formula : $C_{19}H_{25}NO_4$ (MW: 331.41).

IR ($CHCl_3$) : 3421, 1734, 1641, 1496, 1176, 755 cm^{-1}.

Melting point : 79-81 ^oC.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.54-1.70 (m, 2H), 2.22-2.32 (m, 1H), 2.36-2.47 (m, 1H), 2.52-2.64 (m, 1H), 3.26-3.40 (m, 2H), 3.38 (q, *J* = 7.0 Hz, 2H), 4.24 (d, *J* = 10.7 Hz, 1H), 4.35 (d, *J* = 10.7 Hz, 1H), 4.52 (d, *J* = 14.8 Hz, 1H), 4.74 (d, *J* = 14.8 Hz, 1H), 7.29 (s, 5H).

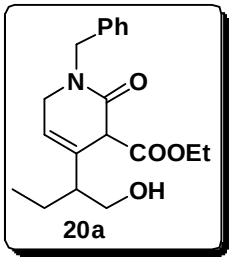
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.8, 18.1, 21.7, 27.4, 39.6, 43.2, 49.5, 58.1, 67.3, 120.5, 127.4, 128.0 (2C), 128.5 (2C), 136.9, 159.7, 160.1, 165.5.

Mass (ESI) m/z **:** 332 $(M + H)^+$, 354 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 68.86; H, 7.60; N, 4.23%

: Found: C, 68.83; H, 7.58; N, 4.21%

Ethyl 1-benzyl-4-(1-hydroxybutan-2-yl)-2-oxo-1,2,3,6-tetrahydropyridine-3-carboxylate (20a)



Mol. Formula **:** $C_{19}H_{25}NO_4$ (MW: 331.41).

IR ($CHCl_3$) **:** 3421, 1732, 1649, 1496, 759 cm^{-1}.

Melting point **:** 118-120 ^oC.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.36-1.44 (m, 1H), 1.47-1.54 (m, 1H), 2.27-2.34 (m, 1H), 3.40-3.45 (m, 1H), 3.54-3.58 (m, 1H), 3.63-3.74 (m, 1H), 4.02-4.06 (m, 2H), 4.19-4.26 (m, 2H), 4.48 (d, *J* = 14.8 Hz, 1H), 4.90 (d, *J* = 14.8 Hz, 1H), 5.76-5.80 (m, 1H), 7.25-7.35 (m, 5H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.7, 13.9, 21.5, 47.6, 49.2, 49.9, 52.0, 62.2, 64.0, 121.7, 127.5, 127.8 (2C), 128.6 (2C), 133.6, 136.1, 164.4, 169.4.

Mass (ESI) m/z **:** 332 $(M + H)^+$, 354 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 68.86; H, 7.60; N, 4.23%

: Found: C, 68.87; H, 7.57; N, 4.24%

Table 1. Crystal data and structure refinement for 20a

Empirical formula	: $C_{19}H_{25}NO_4$
Formula weight	: 331.40
Temperature	: 293(2) K
Wavelength	: 0.71073 A
Crystal system, space group	: Monoclinic, P21/c

Unit cell dimensions : a = 12.8414(7) A alpha = 90°.

b = 8.7972(5) A beta = 91.204(1)°.

c = 16.0038(9) A gamma = 90°.

Volume : 1807.52(17) A^3

Z, Calculated density : 4, 1.218 g/cc

Crystal size : 0.47 x 0.40 x 0.25 mm

Theta range for data collection : 1.59 to 25.00°.

Completeness to theta = 25.00 99.8 %

Refinement method Full-matrix least-squares on F^2

Final R indices [I>2sigma(I)] R1 = 0.0418, wR2 = 0.1083

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 20a.

U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	7558(1)	-496(1)	1612(1)	43(1)
C(2)	7125(1)	-451(2)	847(1)	41(1)
C(3)	6292(1)	743(2)	658(1)	42(1)
C(4)	6008(1)	1797(2)	1366(1)	41(1)
C(5)	6512(1)	1694(2)	2092(1)	46(1)
C(6)	7353(1)	580(2)	2285(1)	49(1)
C(7)	6612(1)	1655(2)	-97(1)	47(1)
C(8)	7850(2)	3412(2)	-589(1)	76(1)
C(9)	8788(2)	4178(4)	-279(2)	139(1)
C(10)	4104(1)	2135(2)	1509(1)	54(1)
C(11)	8336(1)	-1670(2)	1820(1)	52(1)
C(12)	9438(1)	-1064(2)	1867(1)	49(1)
C(13)	10064(1)	-1355(2)	2561(1)	63(1)
C(14)	11087(1)	-858(2)	2595(2)	76(1)

C(15)	11490(1)	-81(2)	1947(2)	79(1)
C(16)	10877(2)	241(3)	1251(1)	80(1)
C(17)	9853(1)	-247(2)	1216(1)	67(1)
O(1)	7367(1)	-1345(1)	286(1)	56(1)
O(2)	6133(1)	1724(2)	-748(1)	72(1)
O(3)	3184(1)	2870(1)	1205(1)	62(1)
O(4)	7488(1)	2407(1)	70(1)	59(1)
C(1')	5095(1)	2862(2)	1186(1)	46(1)
C(2')	5236(1)	4484(2)	1518(1)	59(1)
C(3')	6113(2)	5367(2)	1134(1)	75(1)

Table 3. Bond lengths [A] and angles [^{o}] for 20a.

N(1)-C(2)	1.3347(17)
N(1)-C(6)	1.4612(19)
N(1)-C(11)	1.4697(18)
C(2)-O(1)	1.2382(17)
C(2)-C(3)	1.5247(19)
C(3)-C(4)	1.5143(19)
C(3)-C(7)	1.515(2)
C(3)-H(3)	0.951(16)
C(4)-C(5)	1.3219(18)
C(4)-C(1')	1.5232(19)
C(5)-C(6)	1.486(2)
C(5)-H(5)	0.9300
C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700
C(7)-O(2)	1.1993(17)
C(7)-O(4)	1.3279(18)
C(8)-C(9)	1.457(3)

C(8)-O(4)	1.4599(19)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(9)-H(9A)	0.9600
C(9)-H(9B)	0.9600
C(9)-H(9C)	0.9600
C(10)-O(3)	1.4240(18)
C(10)-C(1')	1.523(2)
C(10)-H(10A)	0.9700
C(10)-H(10B)	0.9700
C(11)-C(12)	1.512(2)
C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700
C(12)-C(13)	1.381(2)
C(12)-C(17)	1.383(2)
C(13)-C(14)	1.384(3)
C(13)-H(13)	0.9300
C(14)-C(15)	1.354(3)
C(14)-H(14)	0.9300
C(15)-C(16)	1.379(3)
C(15)-H(15)	0.9300
C(16)-C(17)	1.384(3)
C(16)-H(16)	0.9300
C(17)-H(17)	0.9300
O(3)-H(3O)	0.8200
C(1')-C(2')	1.532(2)
C(1')-H(1')	0.9800
C(2')-C(3')	1.510(2)

C(2')-H(2'1)	0.9700
C(2')-H(2'2)	0.9700
C(3')-H(3'1)	0.9600
C(3')-H(3'2)	0.9600
C(3')-H(3'3)	0.9600
C(2)-N(1)-C(6)	125.29(12)
C(2)-N(1)-C(11)	119.81(12)
C(6)-N(1)-C(11)	114.87(11)
O(1)-C(2)-N(1)	122.69(13)
O(1)-C(2)-C(3)	118.61(12)
N(1)-C(2)-C(3)	118.70(12)
C(4)-C(3)-C(7)	110.22(12)
C(4)-C(3)-C(2)	116.89(11)
C(7)-C(3)-C(2)	108.83(11)
C(4)-C(3)-H(3)	110.7(9)
C(7)-C(3)-H(3)	105.0(9)
C(2)-C(3)-H(3)	104.3(9)
C(5)-C(4)-C(3)	119.63(13)
C(5)-C(4)-C(1')	124.64(13)
C(3)-C(4)-C(1')	115.63(11)
C(4)-C(5)-C(6)	124.61(13)
C(4)-C(5)-H(5)	117.7
C(6)-C(5)-H(5)	117.7
N(1)-C(6)-C(5)	114.60(11)
N(1)-C(6)-H(6A)	108.6
C(5)-C(6)-H(6A)	108.6
N(1)-C(6)-H(6B)	108.6
C(5)-C(6)-H(6B)	108.6

H(6A)-C(6)-H(6B)	107.6
O(2)-C(7)-O(4)	124.53(14)
O(2)-C(7)-C(3)	125.22(14)
O(4)-C(7)-C(3)	110.22(11)
C(9)-C(8)-O(4)	107.93(17)
C(9)-C(8)-H(8A)	110.1
O(4)-C(8)-H(8A)	110.1
C(9)-C(8)-H(8B)	110.1
O(4)-C(8)-H(8B)	110.1
H(8A)-C(8)-H(8B)	108.4
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
O(3)-C(10)-C(1')	112.73(13)
O(3)-C(10)-H(10A)	109.0
C(1')-C(10)-H(10A)	109.0
O(3)-C(10)-H(10B)	109.0
C(1')-C(10)-H(10B)	109.0
H(10A)-C(10)-H(10B)	107.8
N(1)-C(11)-C(12)	113.21(12)
N(1)-C(11)-H(11A)	108.9
C(12)-C(11)-H(11A)	108.9
N(1)-C(11)-H(11B)	108.9
C(12)-C(11)-H(11B)	108.9
H(11A)-C(11)-H(11B)	107.7

C(13)-C(12)-C(17)	118.38(15)
C(13)-C(12)-C(11)	120.20(15)
C(17)-C(12)-C(11)	121.40(14)
C(12)-C(13)-C(14)	120.61(18)
C(12)-C(13)-H(13)	119.7
C(14)-C(13)-H(13)	119.7
C(15)-C(14)-C(13)	120.44(18)
C(15)-C(14)-H(14)	119.8
C(13)-C(14)-H(14)	119.8
C(14)-C(15)-C(16)	120.10(17)
C(14)-C(15)-H(15)	119.9
C(16)-C(15)-H(15)	119.9
C(15)-C(16)-C(17)	119.7(2)
C(15)-C(16)-H(16)	120.2
C(17)-C(16)-H(16)	120.2
C(12)-C(17)-C(16)	120.75(18)
C(12)-C(17)-H(17)	119.6
C(16)-C(17)-H(17)	119.6
C(10)-O(3)-H(3O)	109.5
C(7)-O(4)-C(8)	115.93(13)
C(10)-C(1')-C(4)	108.86(12)
C(10)-C(1')-C(2')	111.53(13)
C(4)-C(1')-C(2')	114.98(12)
C(10)-C(1')-H(1')	107.0
C(4)-C(1')-H(1')	107.0
C(2')-C(1')-H(1')	107.0
C(3')-C(2')-C(1')	114.99(15)
C(3')-C(2')-H(2'1)	108.5

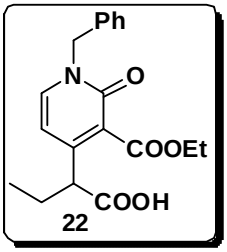
C(1')-C(2')-H(2'1)	108.5
C(3')-C(2')-H(2'2)	108.5
C(1')-C(2')-H(2'2)	108.5
H(2'1)-C(2')-H(2'2)	107.5
C(2')-C(3')-H(3'1)	109.5
C(2')-C(3')-H(3'2)	109.5
H(3'1)-C(3')-H(3'2)	109.5
C(2')-C(3')-H(3'3)	109.5
H(3'1)-C(3')-H(3'3)	109.5
H(3'2)-C(3')-H(3'3)	109.5

Table 6. Torsion angles [^{o}] for 20a

C(6)-N(1)-C(2)-O(1)	176.12(13)
C(11)-N(1)-C(2)-O(1)	-1.7(2)
C(6)-N(1)-C(2)-C(3)	-4.37(19)
C(11)-N(1)-C(2)-C(3)	177.81(12)
O(1)-C(2)-C(3)-C(4)	179.08(12)
N(1)-C(2)-C(3)-C(4)	-0.46(18)
O(1)-C(2)-C(3)-C(7)	-55.31(16)
N(1)-C(2)-C(3)-C(7)	125.16(13)
C(7)-C(3)-C(4)-C(5)	-121.94(14)
C(2)-C(3)-C(4)-C(5)	2.98(19)
C(7)-C(3)-C(4)-C(1')	61.40(15)
C(2)-C(3)-C(4)-C(1')	-173.68(11)
C(3)-C(4)-C(5)-C(6)	-0.9(2)
C(1')-C(4)-C(5)-C(6)	175.46(13)
C(2)-N(1)-C(6)-C(5)	6.3(2)
C(11)-N(1)-C(6)-C(5)	-175.77(12)
C(4)-C(5)-C(6)-N(1)	-3.5(2)

C(4)-C(3)-C(7)-O(2)	-112.33(16)
C(2)-C(3)-C(7)-O(2)	118.26(16)
C(4)-C(3)-C(7)-O(4)	65.97(14)
C(2)-C(3)-C(7)-O(4)	-63.43(15)
C(2)-N(1)-C(11)-C(12)	105.31(15)
C(6)-N(1)-C(11)-C(12)	-72.73(16)
N(1)-C(11)-C(12)-C(13)	128.57(16)
N(1)-C(11)-C(12)-C(17)	-53.1(2)
C(17)-C(12)-C(13)-C(14)	-1.0(3)
C(11)-C(12)-C(13)-C(14)	177.35(16)
C(12)-C(13)-C(14)-C(15)	-0.1(3)
C(13)-C(14)-C(15)-C(16)	0.9(3)
C(14)-C(15)-C(16)-C(17)	-0.6(3)
C(13)-C(12)-C(17)-C(16)	1.3(3)
C(11)-C(12)-C(17)-C(16)	-177.03(17)
C(15)-C(16)-C(17)-C(12)	-0.5(3)
O(2)-C(7)-O(4)-C(8)	2.1(2)
C(3)-C(7)-O(4)-C(8)	-176.21(13)
C(9)-C(8)-O(4)-C(7)	177.6(2)
O(3)-C(10)-C(1')-C(4)	-166.51(12)
O(3)-C(10)-C(1')-C(2')	65.58(17)
C(5)-C(4)-C(1')-C(10)	-81.58(17)
C(3)-C(4)-C(1')-C(10)	94.90(14)
C(5)-C(4)-C(1')-C(2')	44.36(19)
C(3)-C(4)-C(1')-C(2')	-139.16(13)
C(10)-C(1')-C(2')-C(3')	-171.72(14)
C(4)-C(1')-C(2')-C(3')	63.73(19)

2-(1-Benzyl-3-(ethoxycarbonyl)-2-oxo-1, 2-dihydropyridin-4-yl) butanoic acid (22)



The pyridone **5** (0.5 g, 1.34 mmol) in EtOH (10 mL) was treated with LiOH (0.064 g, 2.68 mmol) and the resultant reaction mixture was allowed to stir 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 with ethyl acetate (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to furnish mono acid **22** as a colorless syrup (0.413 g, 90%).

Mol. Formula **:** $C_{19}H_{21}NO_5$ (MW: 343.14).

IR (Neat) **:** 3020, 1718, 1681, 1629, 1566, 1521, 1477, 1217, 769 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.92 (t, *J* = 7.5 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.63-1.83 (m, 1H), 1.94-2.15 (m, 1H), 3.53 (t, *J* = 7.6 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 5.06 (d, *J* = 14.4 Hz, 1H), 5.14 (d, *J* = 14.4 Hz, 1H), 6.25 (d, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.32-7.36 (m, 5H).

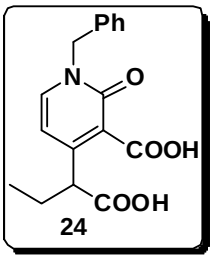
^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 11.9, 14.1, 25.2, 49.6, 52.1, 61.9, 105.0, 125.5, 128.3, 128.6 (2C), 129.0 (2C), 135.3, 137.7, 149.2, 159.4, 166.3, 174.8.

Mass (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 (24)



To the well stirred solution of pyridone **5** (2.0 g, 5.3 mmol) in ethanol (20 mL) was added LiOH (0.76 g, 21.8 mmol) and reaction mixture was stirred at room temperature for 24 h. After the completion of reaction (TLC), ethanol was evaporated *in vacuo* and the resultant residue was dissolved in water (10 mL) and washed with ethyl acetate (20 mL). The aqueous layer was acidified with 10% HCl to pH = 7 and extracted using ethyl acetate (3 x 40 mL). The combined organic layers were dried

over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **24** (1.19 g, 84%) as a white solid.

Mol. Formula **:** $C_{17}H_{17}NO_5$ (MW: 315.12).

Melting point **:** 130-132 ^oC.

IR (Neat) **:** 3018, 1718, 1681, 1629, 1566, 1521, 1477, 1217, 769 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.65 (t, *J* = 7.3 Hz, 3H), 1.35-1.49 (m, 1H), 1.69-1.82 (m, 1H), 4.95 (s, 2H), 6.31 (d, *J* = 7.0 Hz, 1H), 7.06 (s, 5H), 7.50 (d, *J* = 7.0 Hz, 1H).

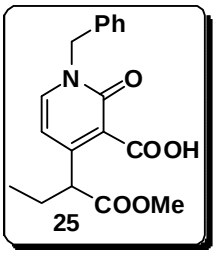
^{13}C NMR ($CDCl_3$, DMSO-d_6, 50 MHz): δ 11.6, 25.1, 47.9, 52.7, 109.2, 115.5, 127.8 (2C), 128.0, 128.4 (2C), 134.0, 139.3, 160.2, 164.0, 165.1, 173.0.

Mass (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 (25)



25

To a well stirred solution of dicarboxylic acid **24** (0.5 g, 1.58 mmol) in MeOH (10 mL) was added $NiCl_2{\cdot}6H_2O$ (0.037 g, 0.158 mmol) and reaction mixture was refluxed for 12 h. The progress of reaction was monitored by TLC and 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/pet ether (3:2) as an eluent to aford compound **25** as a gum (0.396 g, 76%).

Mol. Formula **:** $C_{18}H_{19}NO_5$ (MW: 329.13).

IR (Neat) **:** 3025, 1736, 1691, 1630, 1568, 1479, 1456, 1215, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.67-1.81 (m, 1H), 2.02-2.16 (m, 1H), 3.68 (s, 3H), 5.22 (s, 2H), 5.53 (t, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 7.0 Hz, 1H), 7.31-7.42 (m, 5H), 7.50 (d, *J* = 7.2 Hz, 1H).

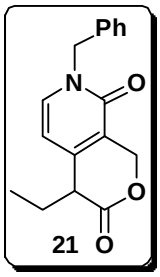
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.1, 26.0, 48.1, 52.0, 53.4, 109.6, 115.9, 128.6 (2C), 128.9, 129.2 (2C), 134.1, 139.2, 160.6, 164.8, 165.4, 172.7.

Mass (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%

7-Benzyl-4-ethyl-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (21)



Method A: To a well stirred mixture of **25** (0.2 g, 0.60 mmol) and Et_3N (0.060 g, 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 was 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 it was further stirred for additional 12 hours at room temperature. After the completion of reaction (TLC), the solvent was evaporated on rotary evaporator under diminished pressure and residue obtained was 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/pet ether (2:3) as an eluent to yield lactone **21** as a gum (0.144 g, 84% yield).

Method B: To a stirred solution of aldehyde **19** (0.1 g, 0.30 mmol) in THF-H_2O (6 mL, 9:1), was added $NaBH_4$ (0.005 g, 0.15 mmol) at 0 ^oC and the reaction mixture was allowed to stir at 0 °C for 15 min. 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* and the residue obtained was purified by flash column chromatography over silica gel using ethyl acetate/pet ether (2:3) as an eluent to furnish lactone **21** (0.08 g, 93%) as a colorless gum.

Mol. Formula **:** $C_{17}H_{17}NO_3$ (MW: 283.12).

IR (Neat) **:** 1720, 1651, 1567, 1523, 1477, 1215, 755 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.02 (t, *J* = 7.5 Hz, 3H), 1.85-2.17 (m, 2H), 3.37 (t, *J* = 6.4 Hz, 1H), 5.08 (d, *J* = 14.4 Hz, 1H), 5.18 (d, *J* = 14.4 Hz, 1H), 5.25 (d, *J* = 16.1 Hz, 1H), 5.43 (d, *J* = 16.1 Hz, 1H), 6.02 (d, *J* = 7.1 Hz, 1H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.29-7.36 (m, 5H).

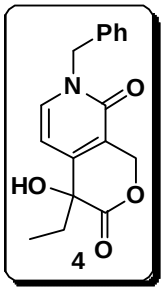
^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz) : δ 11.2, 25.1, 44.9, 51.9, 66.2, 105.0, 121.1, 128.3 (2C), 128.4, 129.0 (2C), 135.7, 136.7, 145.5, 158.8, 170.3.

Mass (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-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (±)-4



The mixture of lactone **21** (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) to obtain the hydroxyl compound **4** as white solid (0.103 g, 98%).

Mol. Formula **:** $C_{17}H_{17}NO_4$ (MW: 299.12).

Melting point **:** 139-141 ^oC (Lit.[12] 140 ^oC).

IR (Neat) **:** 3350, 1741, 1655, 1604, 1563, 1512, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200MHz) : δ 0.97 (t, *J* = 7.5 Hz, 3H), 1.80 (q, *J* = 7.5 Hz, 2H), 3.64 (bs, 1H), 5.12 (d, *J* = 14.5 Hz, 1H), 5.19 (d, *J* = 14.5 Hz, 1H), 5.19 (d, *J* = 16.3 Hz, 1H), 5.62 (d, *J* = 16.3 Hz, 1H), 6.51 (d, *J* = 7.0 Hz, 1H), 7.30-7.37 (m, 5H), 7.39 (d, *J* = 7.0 Hz, 1H).

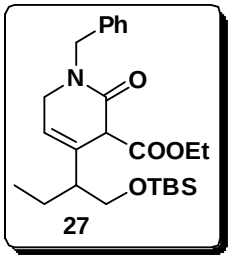
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 7.7, 31.5, 52.1, 66.5, 72.0, 103.0, 119.1, 128.2 (2C), 128.3, 129.0 (2C), 135.6, 137.3, 148.5, 158.6, 173.5.

Mass (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%

Ethyl 1-benzyl-4-(1-((tert-butyldimethylsilyl)oxy)butan-2-yl)-2-oxo-1,2,3,6-tetrahydropyridine-3-carboxylate (27)



27

To the stirred solution of alcohol **20** (0.7 g, 2.1 mmol) in DCM, was added imidazole (0.272 g, 4.0 mmol) followed by TBSCl (0.346 g, 2.3 mmol) at 0 ^oC and the reaction mixture was allowed to stir at room temperature for 1 h (TLC). After completion, water (10 mL) was added, organic layer was separated and aqueous layer was extracted with DCM. Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Residue was purified by flash column chromatography (SiO_2) using ethyl acetate/petroleum ether (1:9) as eluent to furnish compound **27** (0.89 g, 95%).

Mol. Formula **:** $C_{25}H_{39}NO_4Si$ (MW: 445.67).

IR (Neat) **:** 1734, 1655, 1565, 1158, 763 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.01 (s, 3H), 0.02 (s, 3H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.87 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.33-1.43 (m, 1H), 1.54-1.64 (m, 1H), 2.13-2.20 (m, 1H), 3.46-3.73 (m, 3H), 4.01-4.07 (m, 2H), 4.16-4.21 (m, 2H), 4.49-4.55 (m, 1H), 4.87-4.91 (m, 1H), 5.62-5.69 (m, 1H), 7.26-7.35 (m, 5H).

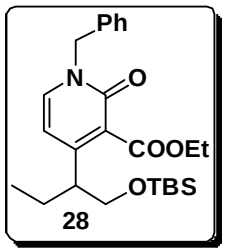
^{13}C NMR ($CDCl_3$, 50 MHz) : δ -5.5, 11.3, 11.5, 13.9, 14.0, 18.0, 18.1, 21.9, 22.9, 25.7, 25.8, 47.2, 47.6, 47.7, 47.9, 49.6, 49.7, 53.2, 54.2, 61.5, 61.6, 64.0, 65.9, 118.2, 119.5, 127.3, 127.7, 127.8, 128.5, 134.5, 134.6, 136.5, 164.8, 168.9, 169.2. (Mixture of diastereomers)

Mass (ESI) m/z **:** 446 $(M + H)^+$, 468 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 67.37; H, 8.82; N, 3.14%

: Found: C, 67.33; H, 8.58; N, 3.11%

Ethyl 1-benzyl-4-(1-((tert-butyldimethylsilyl)oxy)butan-2-yl-)-oxo-1,2-dihydropyridine-3-carboxylate (28)



28

To the stirred solution of dihydropyridone **27** (0.5 g, 1.12 mmol) in anhydrous 1, 4-dioxane (15 mL), was added DDQ (0.28 g, 1.23 mmol) and reaction mixture was refluxed till the completion of reaction (5 h, TLC). The reaction mixture was diluted with ethyl acetate, filtered using sintered funnel and filtrate was quenched by addition of 10% $NaHCO_3$ solution, the organic phase was separated and aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield pyridone **28** (0.487 g, 98%) as a pale yellow thick liquid which was pure enough for further use.

Mol. Formula **:** $C_{25}H_{37}NO_4Si$ (MW: 443.25).

IR (Neat) **:** 1725, 1647, 1450, 1163, 763 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ -0.04 (s, 3H), -0.03 (s, 3H), 0.83 (s, 9H), 0.85 (t, *J* = 7.5 Hz, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.47-1.56 (m, 1H), 1.74-1.81 (m, 1H), 2.60-2.65 (m, 1H), 3.64 (dd, 5.7 and 10.4 Hz, 1H), 3.71 (dd, *J* = 5.7 and 10.4 Hz, 1H), 4.34-4.39 (m, 2H), 5.05 (d, *J* = 14.5 Hz, 2H), 5.15 (d, *J* = 14.5 Hz, 2H), 6.17 (d, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.29-7.34 (m, 5H).

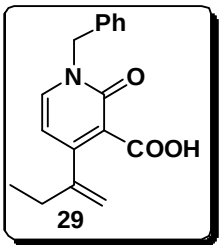
^{13}C NMR ($CDCl_3$, 100 MHz): δ -5.7, -5.6, 11.7, 14.1, 18.0, 23.3, 25.7, 46.6, 51.6, 61.3, 65.2, 105.2, 126.1, 128.0, 128.3 (2C), 128.7 (2C), 135.7, 136.5, 153.4, 159.5, 166.5.

Mass (ESI) m/z **:** 444 $(M + H)^+$, 466 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 67.68; H, 8.41; N, 3.16%

: Found: C, 67.63; H, 8.48; N, 3.18%

1-Benzyl-4-(but-1-en-2-yl)-2-oxo-1, 2-dihydropyridine-3-carboxylic acid (29)



29

To the stirred solution of compound **28** (0.3 g, 0.676 mmol) in anhydrous THF (10 mL), was added TBAF (1.35 mL, 1.35 mmol, 1M solution in THF) at room temperature. Reaction mixture was stirred for 1 h. After completion, water was added and the reaction mixture was extracted with ethyl acetate (3 x 10 mL). Combined

organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Residue was purified by flash column chromatography (SiO_2) using ethyl acetate/petroleum ether (4:6) as eluent to furnish compound **29** (0.11 g, 60%).

Mol. Formula **:** $C_{17}H_{17}NO_3$ (MW: 283.32).

IR (Neat) **:** 3300, 1653, 1535, 1137, 763 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.08 (t, *J* = 7.4 Hz, 3H), 2.39 (q, *J* = 7.4 Hz, 2H), 4.84 (s, 1H), 5.12 (s, 1H), 5.25 (s, 2H), 6.30 (d, *J* = 6.8 Hz, 1H), 7.34-7.44 (m, 5H), 7.51 (d, *J* = 6.8 Hz, 1H).

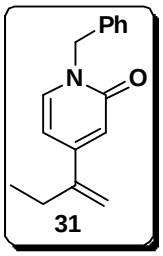
^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.3, 28.8, 53.3, 110.1, 112.5, 114.7, 128.5 (2C), 128.9 (2C), 129.2, 134.3, 139.1, 151.6, 163.7, 164.0, 164.7.

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

Elemental analysis **:** Calculated: C, 72.07; H, 6.05; N, 4.94%

: Found: C, 72.09; H, 6.06; N, 4.98%

1-Benzyl-4-(but-1-en-2-yl)pyridin-2(1*H*)-one (31)



31

The acid **29** (0.050 gm, 0.176 mmol) was added to copper powder (0.068 gm, 1.06 mmol) in quinoline (7 mL) and the resulting mixture was heated at 160 °C for 2 h. Upon cooling, ethyl acetate (25 mL) was added, and the copper was filtered off through Celite. The filtrate was washed with 10% hydrochloric acid. The organic layer was washed with water followed by brine, dried over Na_2SO_4 and concentrated under reduced pressure. Residue was purified by flash column chromatography (SiO_2) using ethyl acetate/petroleum ether (3:7) as eluent to furnish compound **31** (0.038 g, 90%).

Mol. Formula **:** $C_{16}H_{17}NO$ (MW: 239.31).

IR (Neat) **:** 1660, 1600, 1137, 763 cm^{-1}.

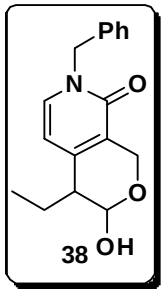
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.12 (t, *J* = 7.4 Hz, 3H), 2.41 (q, *J* = 7.4 Hz, 2H), 5.12 (s, 2H), 5.20 (s, 1H), 5.43 (s, 1H), 6.23 (d, *J* = 7.0 Hz, 1H), (m, 5H), 6.60 (s, 1H), 7.17 (d, *J* = 7.0 Hz, 1H) 7.31 (s, 5H).

Mass (ESI) m/z **:** 240 $(M + H)^+$, 262 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 80.30; H, 7.16; N, 5.85%

: Found: C, 80.25; H, 7.13; N, 5.81%

7-Benzyl-4-ethyl-3-hydroxy-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-8(7*H*)-one (38)



Method A: To the well stirred solution of aldehyde **19** (0.2 g, 0.61 mmol) in THF:$H_2$0 (9:1) was added $NaBH_4$ (0.02 g, 0.61 mmol) portionwise at 0 ^oC and the reaction mixture was stirred at room temp. After completion of reaction (30 min), it was quenched using 10% HCl. The pH was adjusted to 6.5 and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under diminished pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with ethyl acetate/petroleum ether (1:1) as a solvent system to deliver the hydroxyl compound **38** (0.155 g, 90 %).

Method B: To the well stirred solution of lactone **21** (0.1 g, 0.35 mmol) in THF:$H_2$0 (9:1) was added $NaBH_4$ (0.006 g, 0.17 mmol) portionwise at 0 ^oC and the reaction mixture was stirred for 15 min at room temp. After completion of reaction, it was quenched using 10% HCl. The pH was adjusted to 6.5 and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with ethyl acetate/petroleum ether (1:1) as a solvent system to deliver the hydroxyl compound **38** (0.09 g, 90%) as thick yellow oil.

Mol. Formula **:** $C_{17}H_{19}NO_3$ (MW: 285.14).

IR (Neat) **:** 3400, 1660, 1600, 1050, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.99 (t, *J* = 7.5 Hz, 3H), 1.57-1.74 (m, 2H), 2.39 (t, *J* = 6.6 Hz, 1H), 3.92 (bs, 1H), 4.60 (d, *J* = 17.0 Hz, 1H), 4.71 (d, *J* = 17.0 Hz, 1H), 5.05 (d, *J* = 14.5 Hz, 1H), 5.14 (d, *J* = 14.5 Hz, 1H), 5.70 (bs, 1H), 6.01 (d, *J* = 7.0 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 1H), 7.29-7.35 (m, 5H).

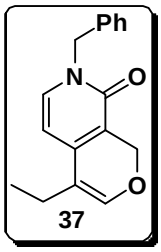
^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.5, 26.2, 43.4, 51.6, 58.3, 92.3, 107.9, 123.6, 127.9, 128.3 (2C), 128.8 (2C), 134.1, 136.2, 145.6, 159.7.

Mass (ESI) m/z **:** 286 $(M + H)^+$, 308 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 71.56; H, 6.71; N, 4.91%

: Found: C, 71.53; H, 6.69; N, 4.90%

7-Benzyl-4-ethyl-1*H*-pyrano[3,4-c]pyridin-8(7*H*)-one (37)



To the stirred solution of lactol **38** (0.09 g, 0.31 mmol) in anhydrous THF was added triethyl amine (0.35 mL, 2.5 mmol) followed by mesyl chloride (0.91 mL, 1.26 mmol) at 0 ^{o}C. The reaction mixture was stirred at 50 ^{o}C for 24 h. The reaction mixture was cooled and water was added and the aqueous phase was extracted with chloroform (3 x 20 mL). Combined organic layers were washed with $NaHCO_3$ followed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated under diminished pressure. The resultant residue was purified by flash column chromatography (SiO_2) eluting with ethyl acetate/pet ether (2:8) to deliver the olefin compound **37** (0.08 g, 95%) as colorless thick oil.

Mol. Formula **:** $C_{17}H_{17}NO_2$ (MW: 267.13).

IR (Neat) **:** 1660, 1620, 1540, 1020, 767 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.10 (t, *J* = 7.5 Hz, 3H), 2.24 (q, *J* = 7.5 Hz, 2H), 5.07 (s, 2H), 5.13 (s, 2H), 6.07 (d, *J* = 7.2 Hz, 1H), 6.57 (s, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.29-7.37 (m, 5H).

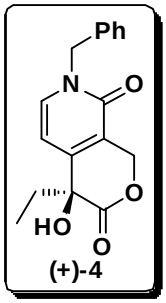
^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 20.3, 51.7, 63.3, 100.7, 113.9, 114.9, 127.9 (2C), 128.0, 128.8 (2C), 136.0, 136.4, 141.5, 146.6, 159.3.

Mass (ESI) m/z **:** 268 $(M + H)^+$, 290 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 76.38; H, 6.41; N, 5.24%

: Found: C, 76.36; H, 6.39; N, 5.21%

(*S*)-7-Benzyl-4-ethyl-4-hydroxy-1*H*-pyrano[3,4-*c*]pyridine-3,8(4*H*,7*H*)-dione (+)-4



A mixture of $(DHQD)_2$-PYR (0.003 g, 0.037 mmol), $K_3Fe(CN)_6$ (0.184 g, 0.561 mmol), K_2CO_3 (0.077 g, 0.561 mmol), $K_2OsO_2(OH)_4$ (0.0009 g, 0.037 mmol) and $CH_3SO_2NH_2$ (0.018 g, 0.187 mmol) in water and *tert*-butanol (5 mL, 1:1) was stirred at room temp until two phases were clear, and it was then cooled to 0 °C. Enol ether **37** (0.05 g, 0.0187 mmol) was added to the above mixture in one portion and the whole reaction mixture was stirred at 0 °C for 5 h. The reaction was quenched at the same temperature by adding sodium sulfite (0.05 g), and then warmed to room temperature and stirred for additional 30 min. CH_2Cl_2 (10 mL), CH_3OH (1 mL) and H_2O (10 mL) were

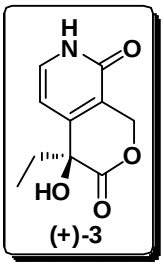
added and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to furnish crude diol.

To the crude diol in MeOH/H_2O (2:1) (7 mL), was added crystalline iodine (0.473 g, 1.87 mmol) followed by $CaCO_3$ (0.187 g, 1.87 mmol). The reaction was stirred at room temperature for 10 h and then quenched at room temperature by slowly adding Na_2SO_3 (0.2 g). The methanol was removed and CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by flash chromatography using ethyl acetate/pet ether (6:4) as eluent to afford (+)-**4** as a white solid (0.049 g, 90%) in 95% *ee*.

Mol. Formula	**:** $C_{17}H_{17}NO_4$ (MW: 299.12).
Specific Rotation	**:** $[\alpha]_D^{25}$ +112 (*c* = 1, $CHCl_3$) [Lit.[12] +107.2 (*c* = 1.01, $CHCl_3$) 91% ee]
ee	**:** 95 %
Melting point	**:** 139-141 ^oC (Lit.[12] 140 ^oC).
HPLC conditions	**:** Column: chiralcel OD-H (250 X 4.6mm)
	: Mobile phase: IPA:*n*-hexane (12:88)
	: Wavelength: 280 nm
	: Flow rate: 0.7mL/min
	: Sample concentration: 1 mg/2 mL

The other analytical data are identical with (*rac*)-**4**.

(*S*)-4-Ethyl-4-hydroxy-1*H*-pyrano[3,4-*c*]pyridine-3,8 (4*H*,7*H*)-dione (+)-3



(+)-3

To a well-stirred solution of compound **3** (0.05 g, 0.167 mmol) in EtOH (10 mL), was added 10% $Pd(OH)_2$ (2.3 mg, 0.016 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 ethyl acetate-petroleum ether (3:2) as eluent to furnish the desired DE-ring fragment **3** as a white solid (0.025 g, 72%).

Mol. Formula **:** $C_{10}H_{11}NO_4$ (MW: 209.07).

Melting point **:** 225 ^oC (Lit.[19] 227 ^oC).

Specific Rotation **:** $[\alpha]_D^{25}$+120 (*c* = 0.3, methanol [Lit.[19] +117.0 (*c* = 0.3, MeOH) 93% ee]

ee **:** 95 %

IR (Neat) **:** 3273, 1754, 1651, 1255, 837 cm^{-1}.

^{1}H NMR (CD_3OD, 400 MHz): δ 0.93 (t, *J* = 7.5 Hz, 3H), 1.85 (q, *J* = 7.5 Hz, 2H), 5.22 (d, *J* = 16.3 Hz, 1H), 5.41 (d, *J* = 16.3 Hz, 1H), 6.63 (d, *J* = 6.7 Hz, 1H), 7.47 (d, *J* = 6.7 Hz, 1H).

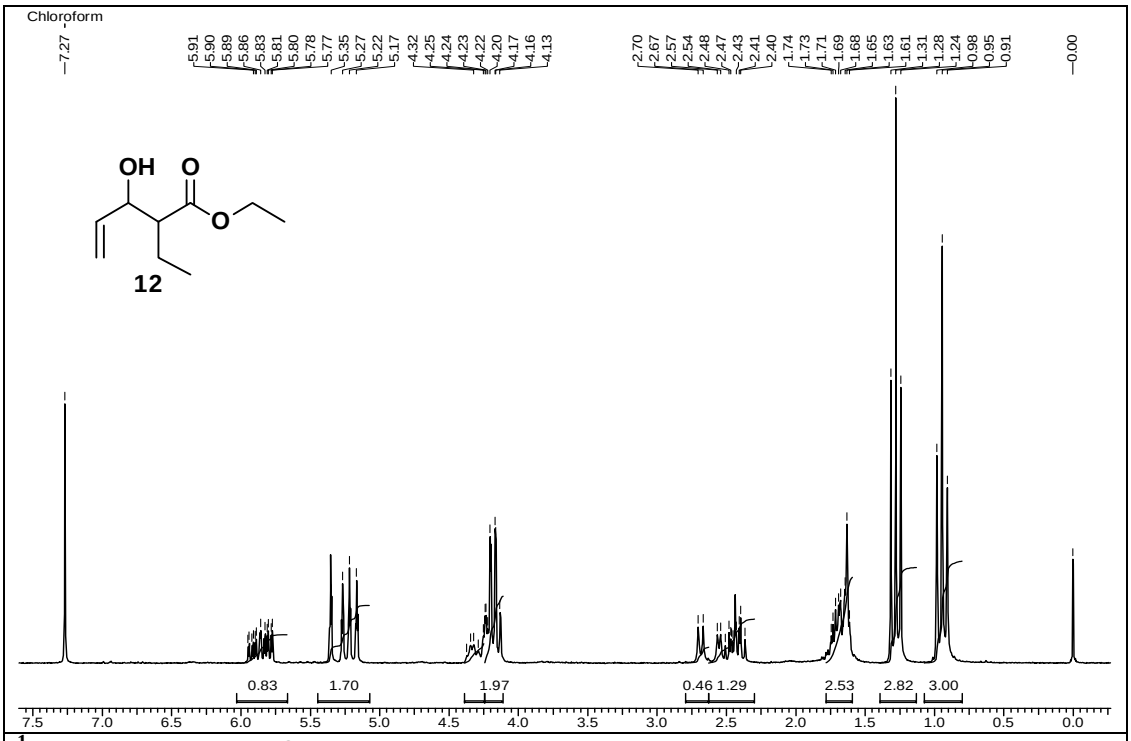
^{13}C NMR ($CDCl_3$+CCl_4+DMSO-d_6, 100 MHz): δ 7.6, 31.5, 65.7, 72.3, 104.4, 118.8, 134.4, 151.3, 160.4, 174.8.

Mass (ESI) m/z **:** 210 $(M + H)^+$, 232 $(M + Na)^+$.

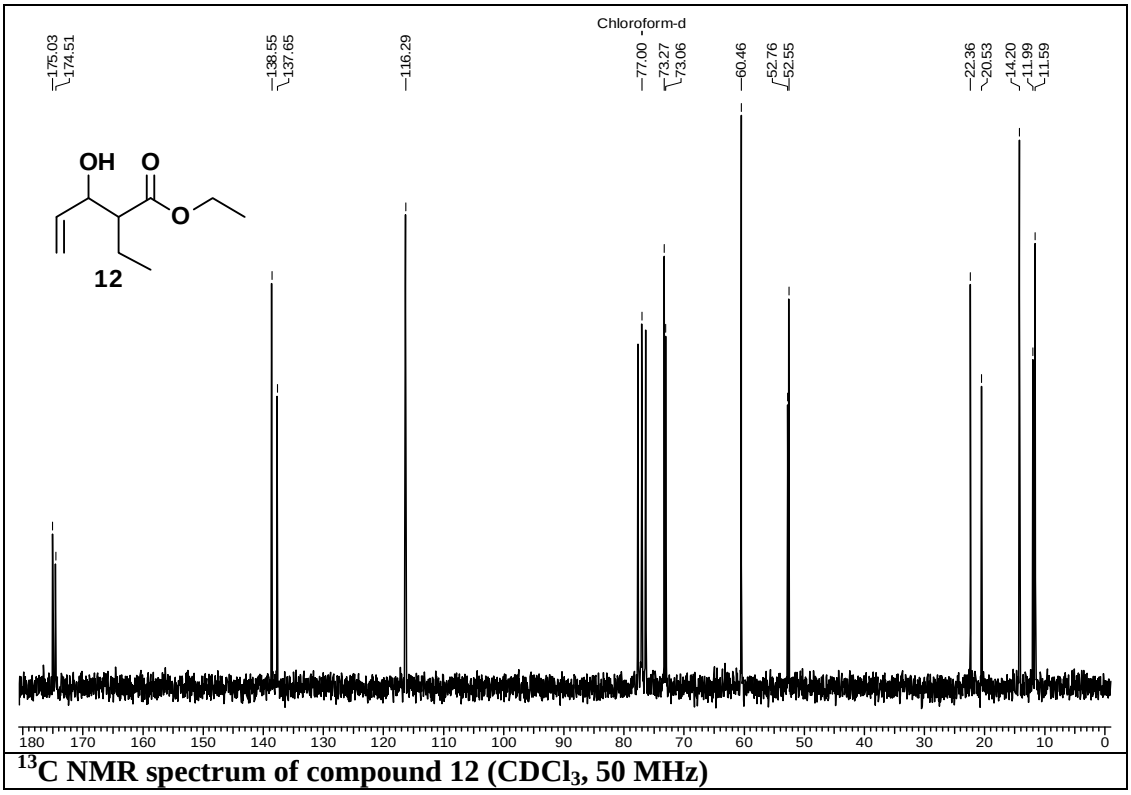
Elemental analysis **:** Calculated: C, 57.41; H, 5.30; N, 6.70%

: Found: C, 57.39; H, 5.34; N, 6.73%

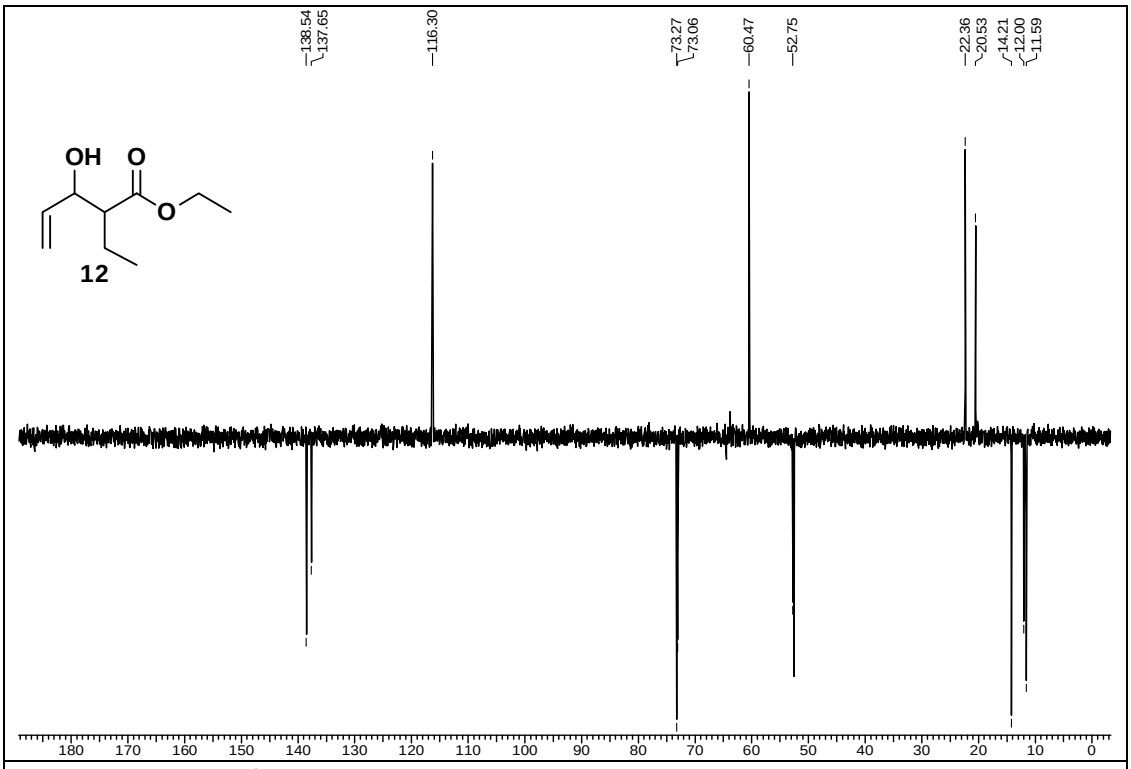
2.1.6 Spectra



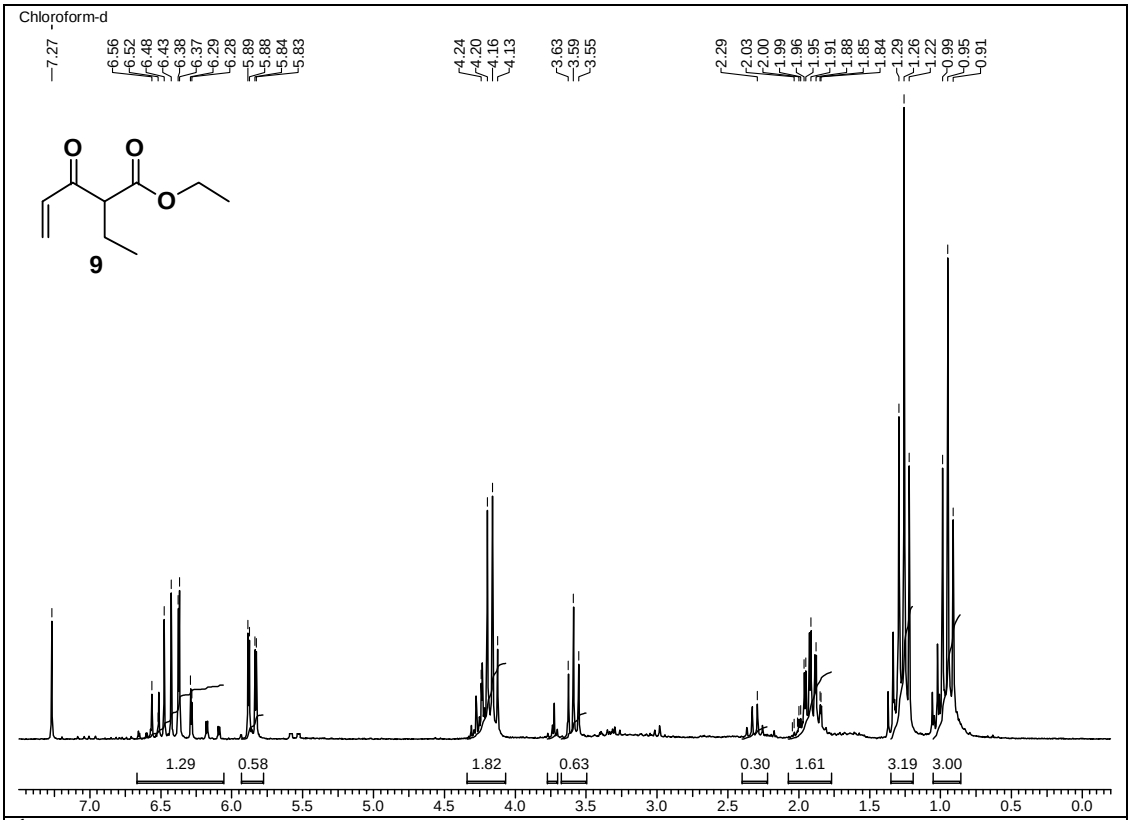
^{1}H NMR spectrum of compound 12 ($CDCl_3$, 200 MHz)



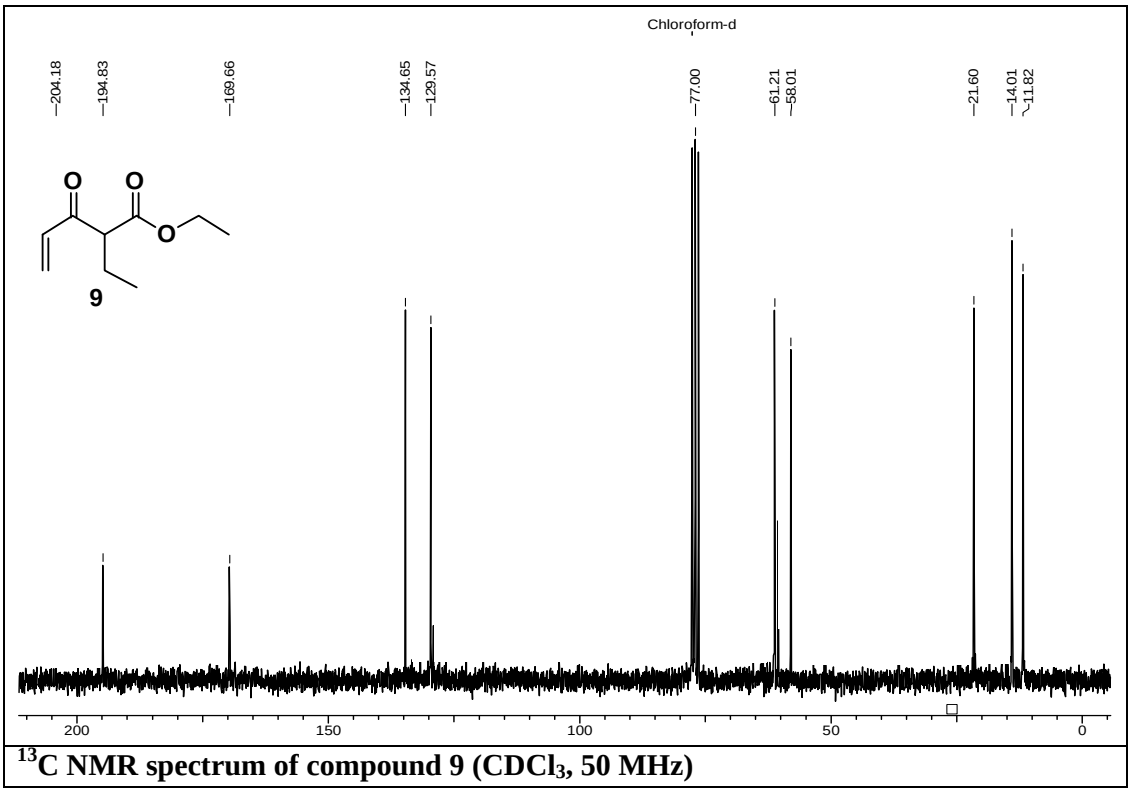
^{13}C NMR spectrum of compound 12 ($CDCl_3$, 50 MHz)



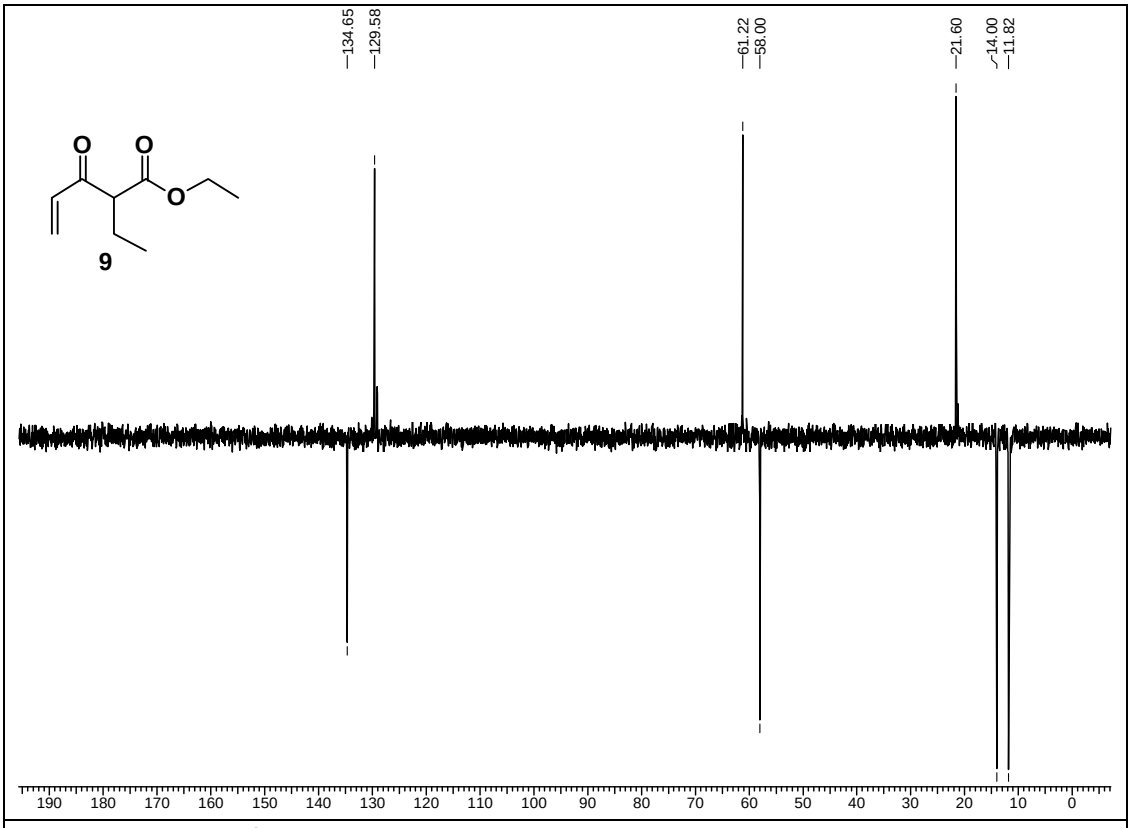
DEPT spectrum of compound 12 ($CDCl_3$, 50 MHz)



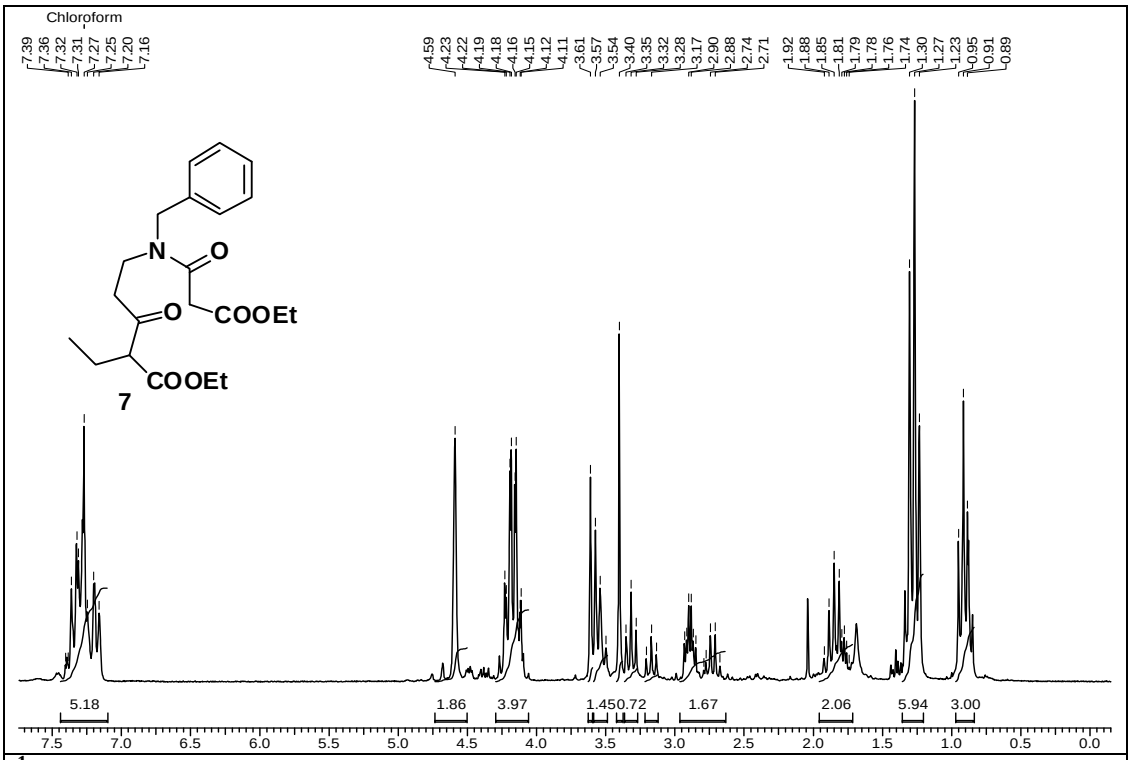
^{1}H NMR spectrum of compound 9 ($CDCl_3$, 200 MHz)



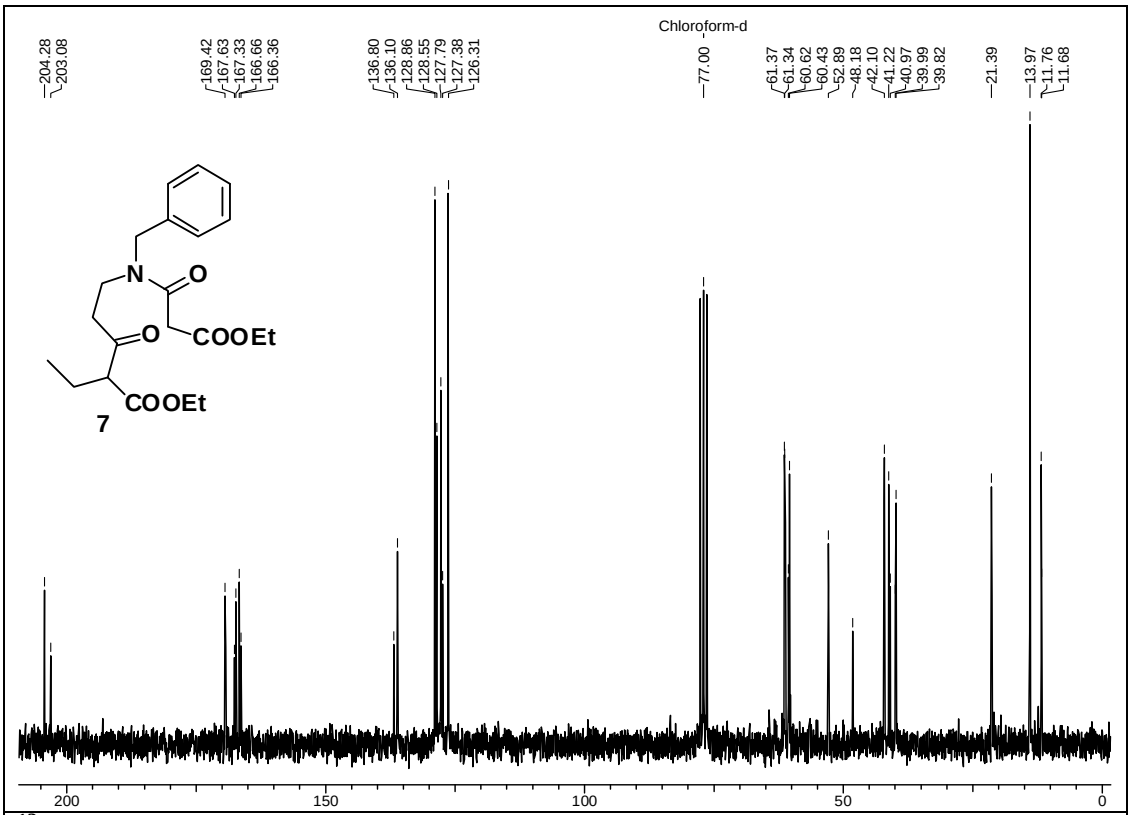
^{13}C NMR spectrum of compound 9 ($CDCl_3$, 50 MHz)



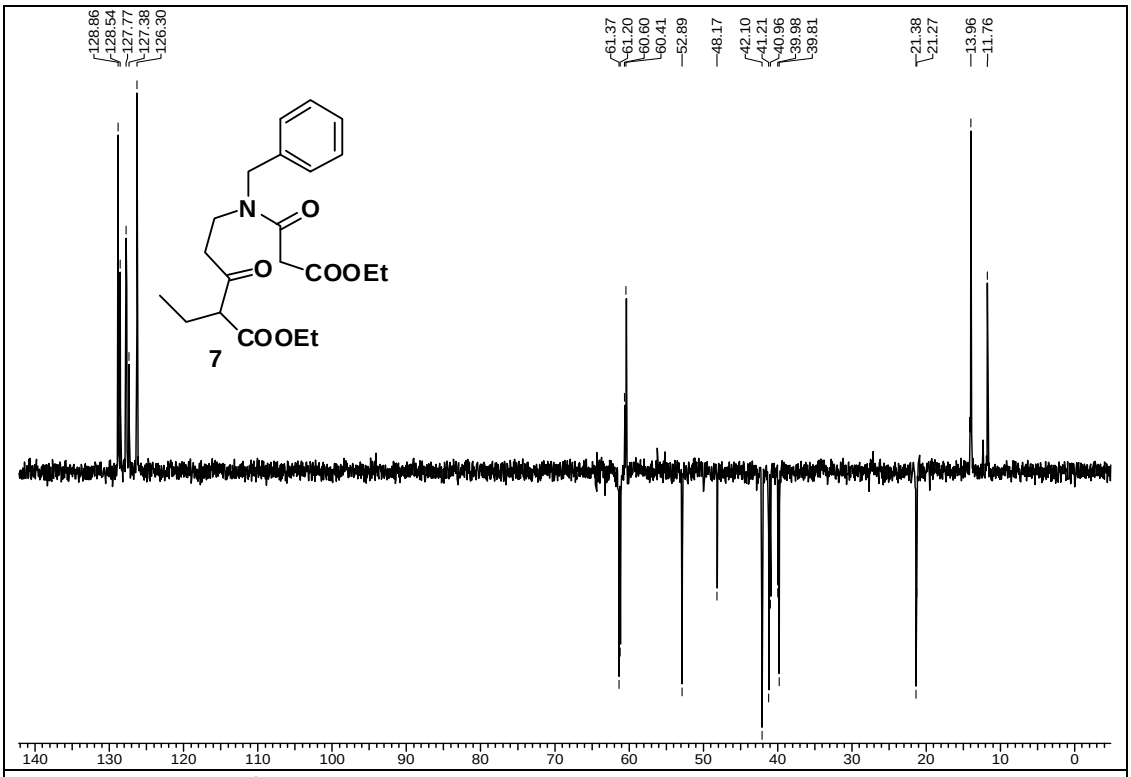
DEPT spectrum of compound 9 ($CDCl_3$, 50 MHz)



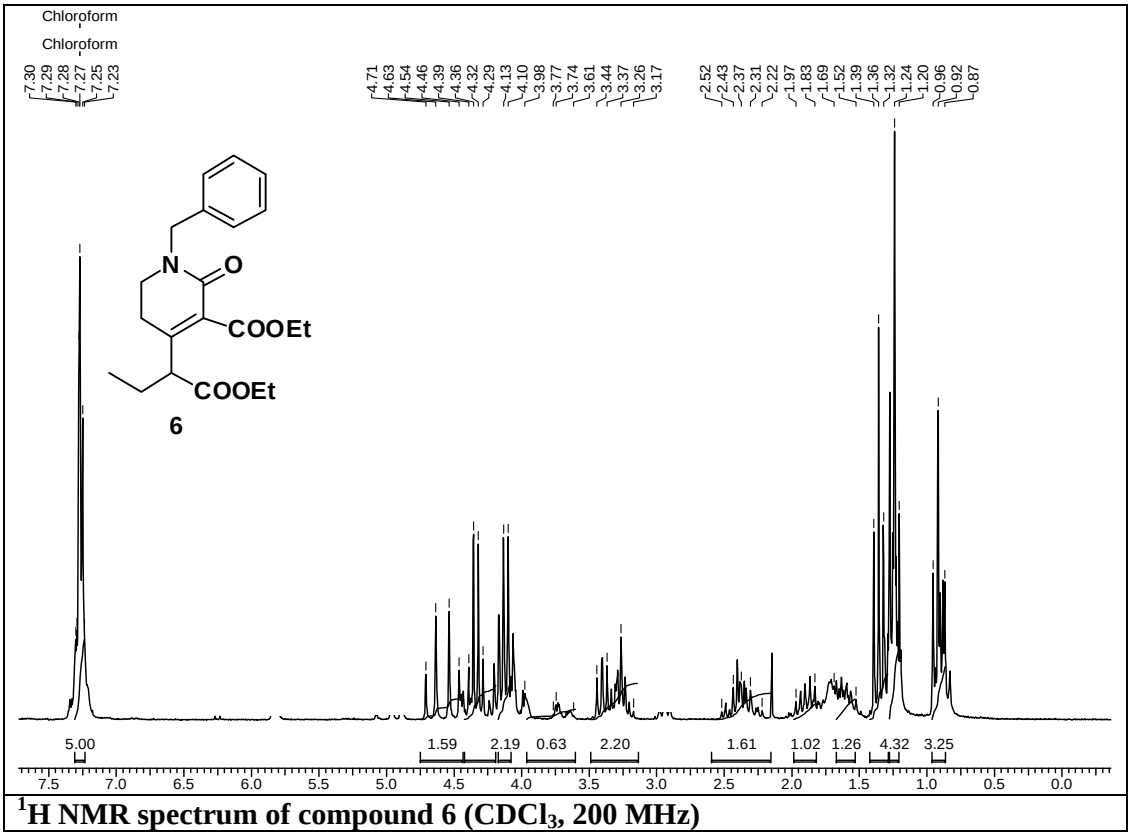
^{1}H NMR spectrum of compound 7 ($CDCl_3$, 200 MHz)



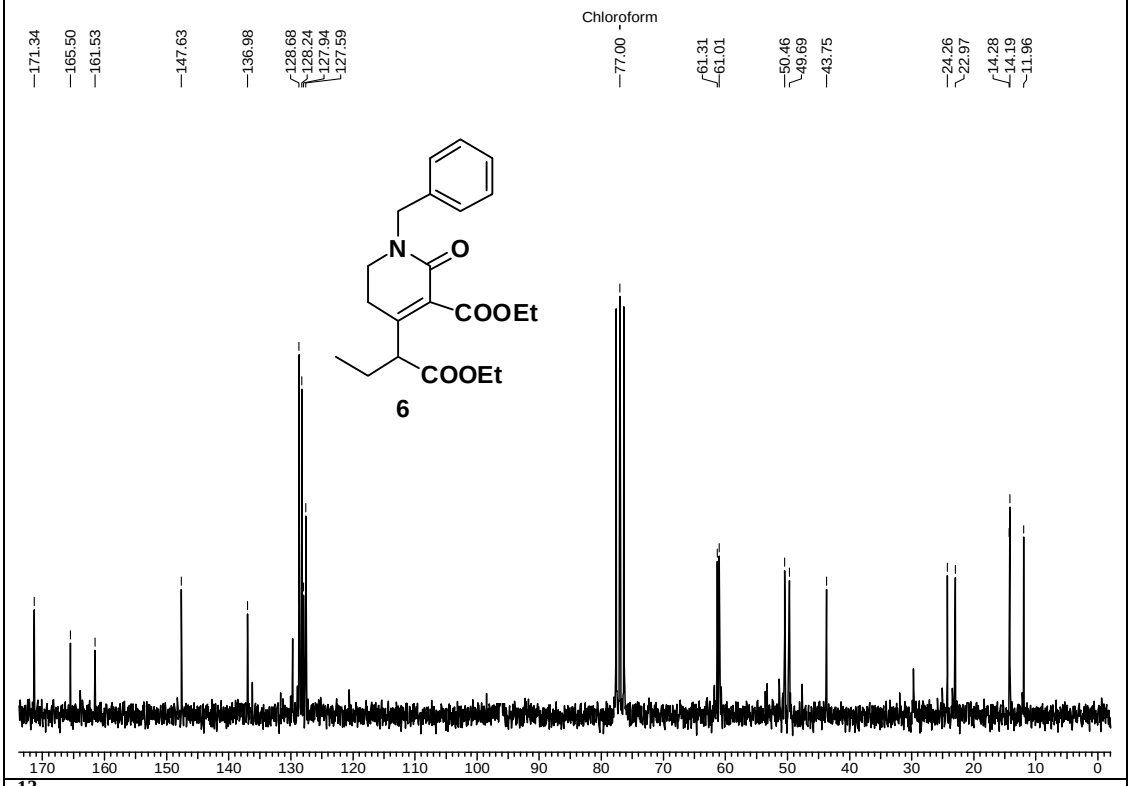
^{13}C NMR spectrum of compound 7 ($CDCl_3$, 50 MHz)



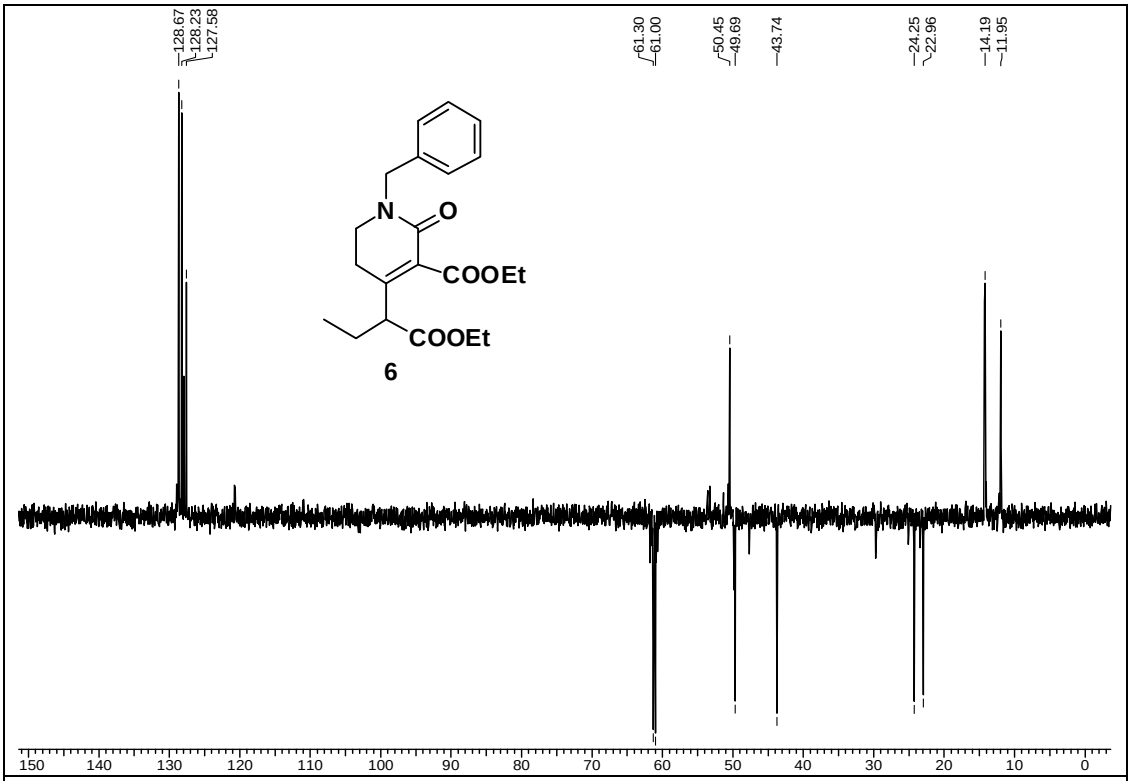
DEPT spectrum of compound 7 ($CDCl_3$, 50 MHz)



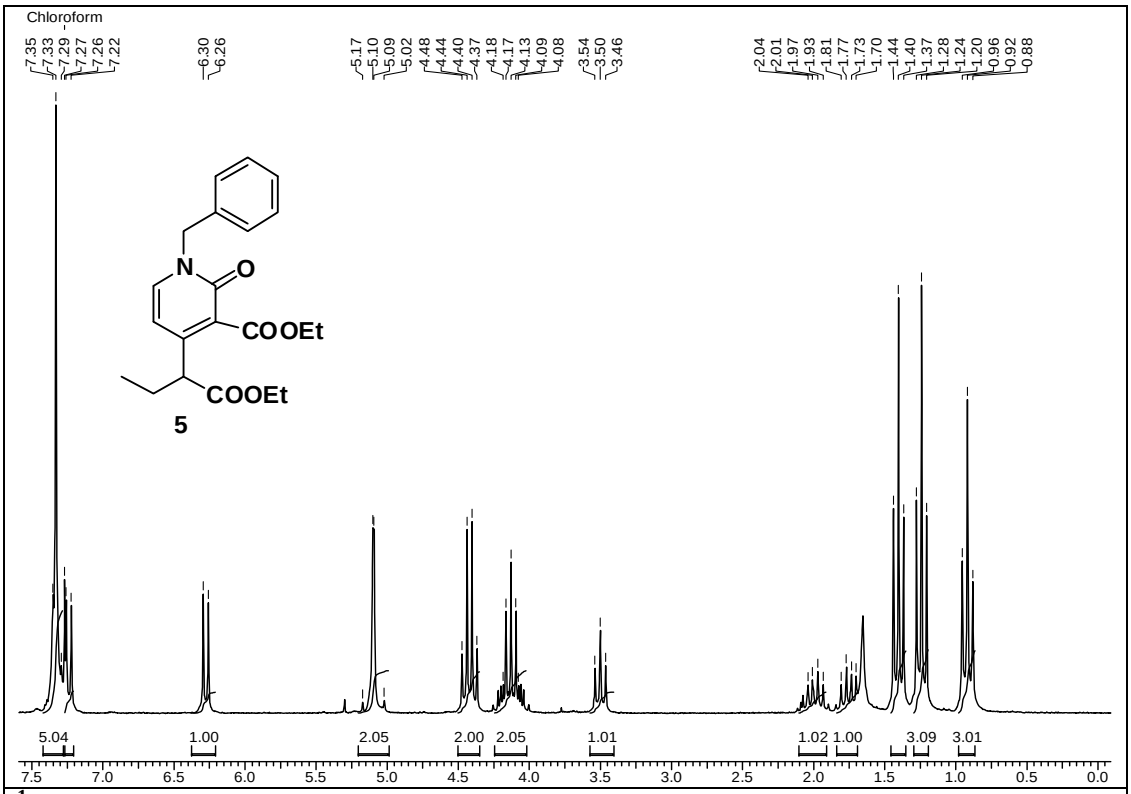
^{1}H NMR spectrum of compound 6 ($CDCl_3$, 200 MHz)



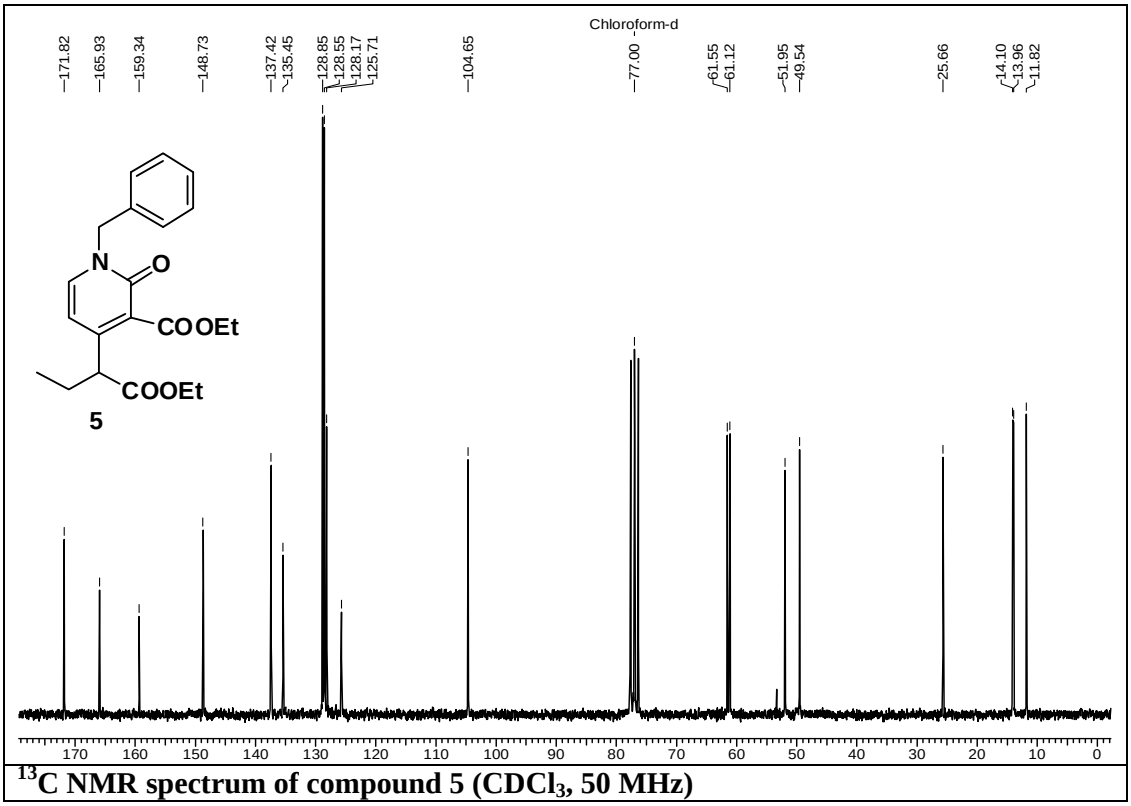
^{13}C NMR spectrum of compound 6 ($CDCl_3$, 50 MHz)



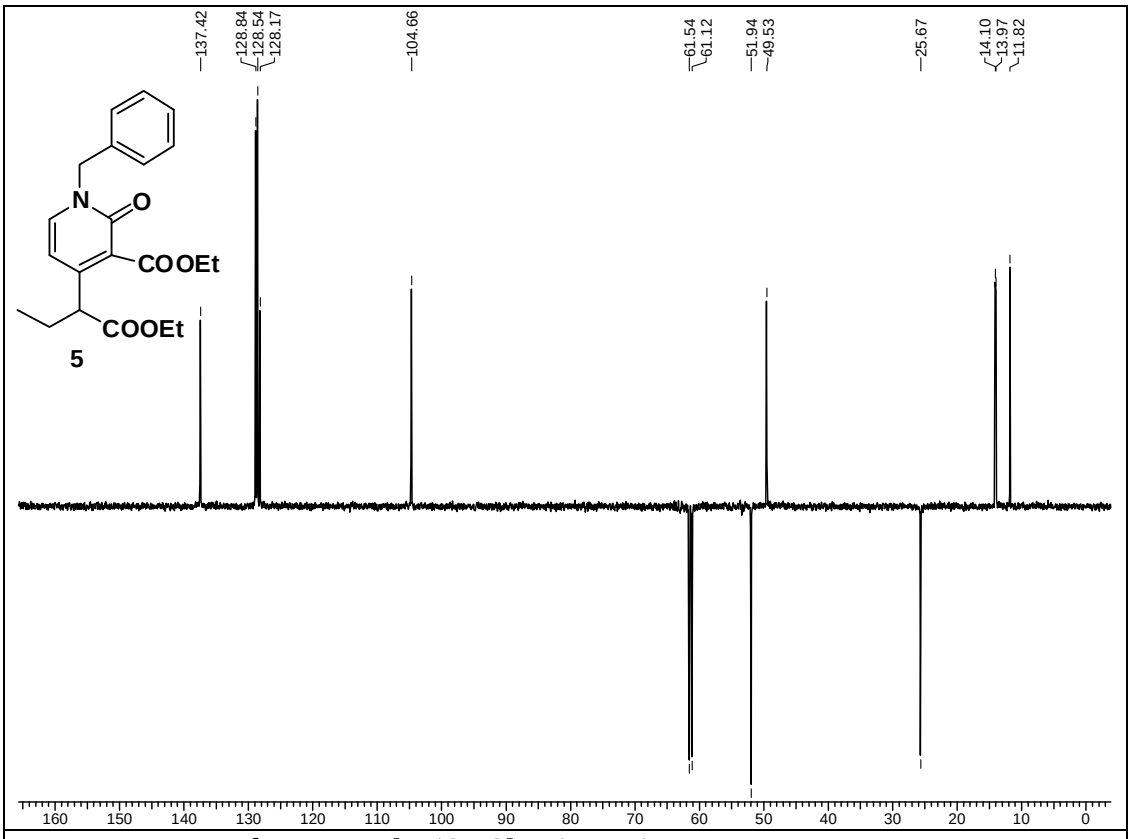
DEPT spectrum of compound 6 ($CDCl_3$, 50 MHz)



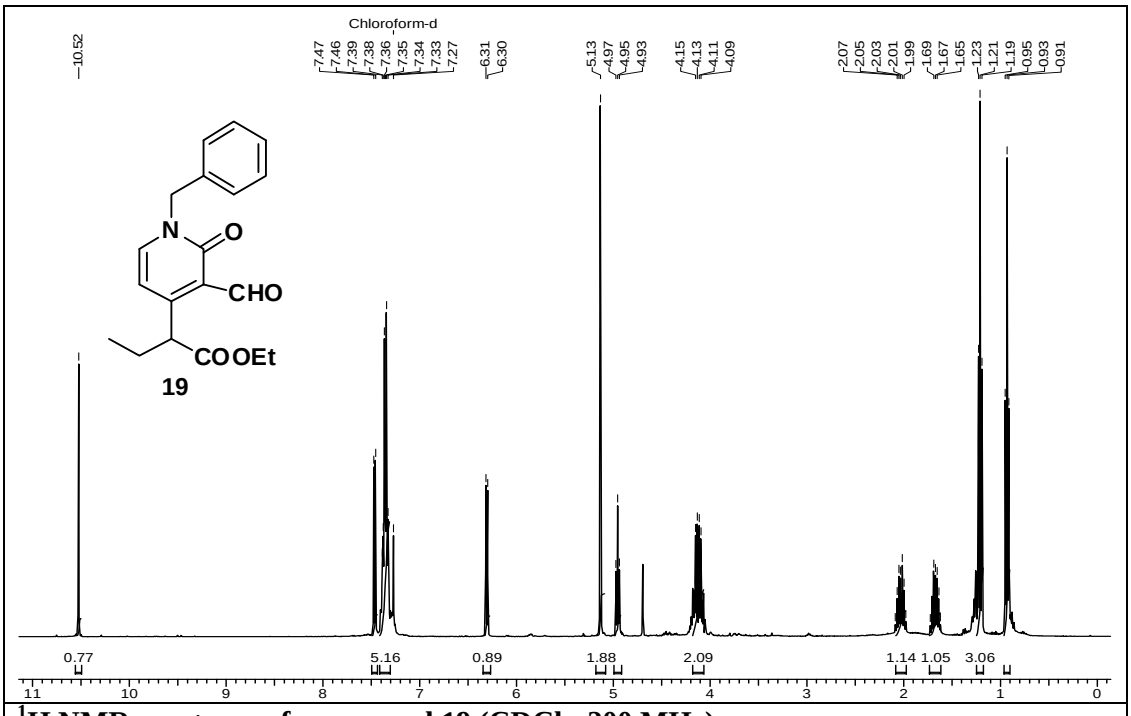
^{1}H NMR spectrum of compound 5 ($CDCl_3$, 200 MHz)



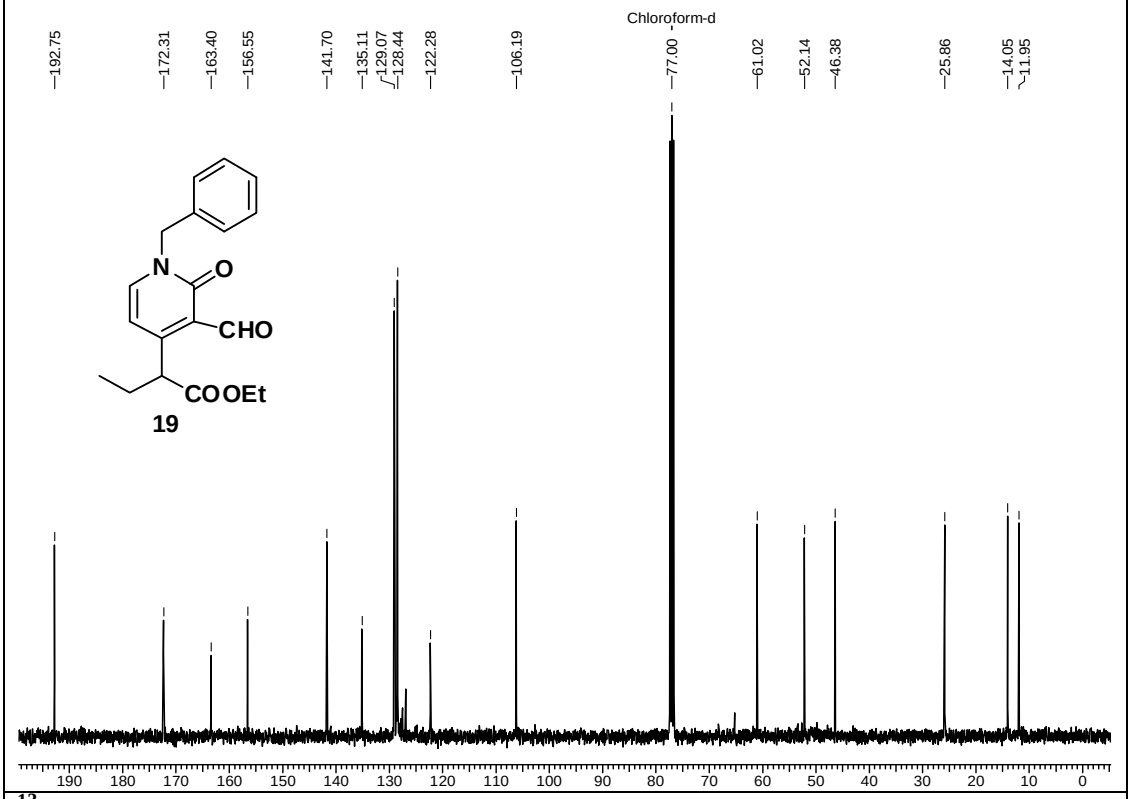
^{13}C NMR spectrum of compound 5 ($CDCl_3$, 50 MHz)



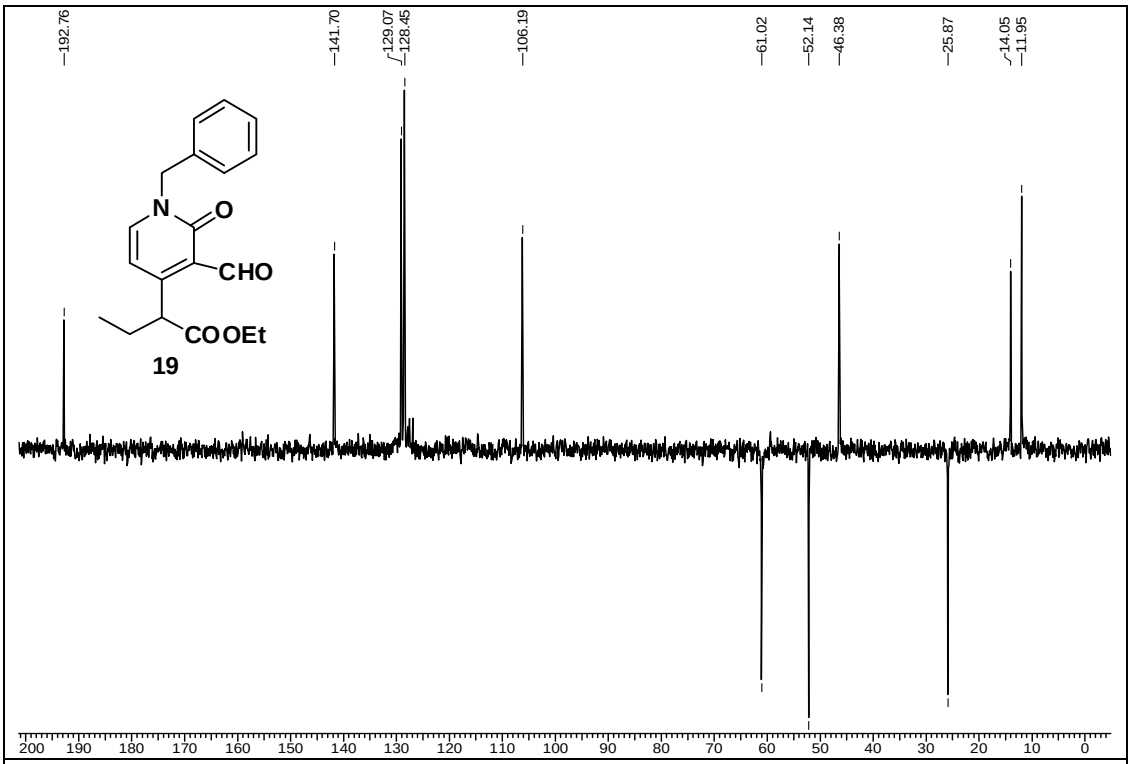
DEPT spectrum of compound 5 ($CDCl_3$, 50 MHz)



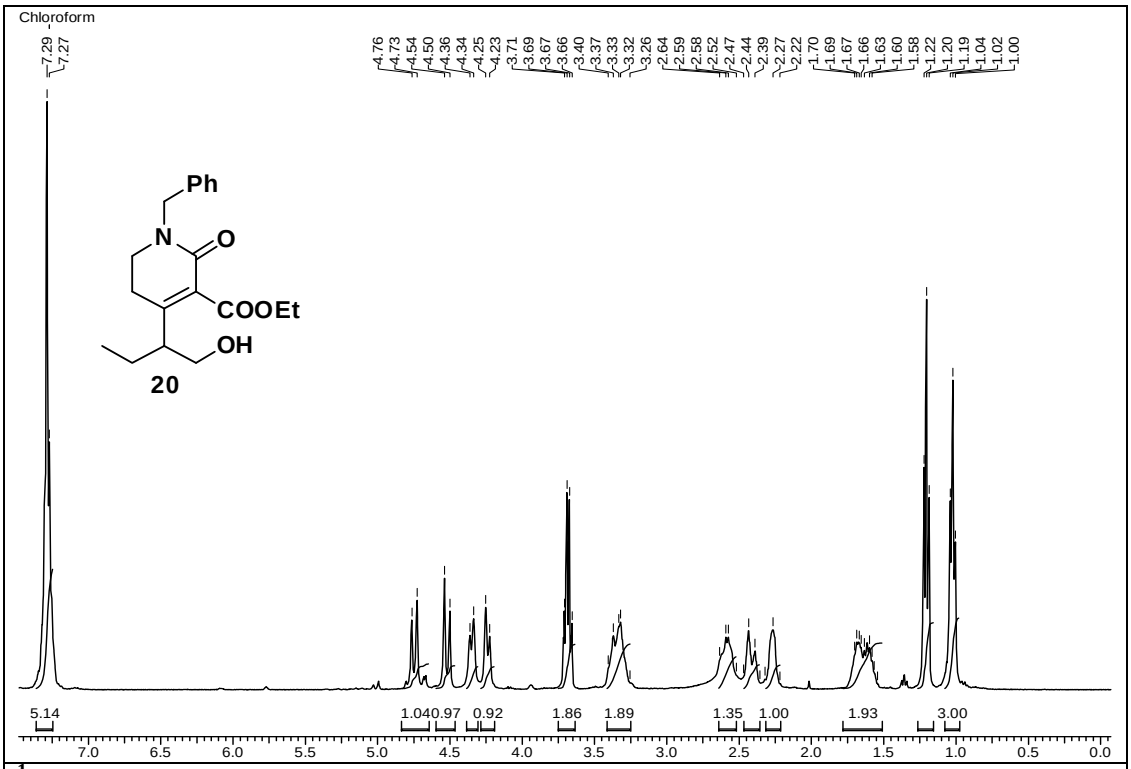
^{1}H NMR spectrum of compound 19 ($CDCl_3$, 200 MHz)



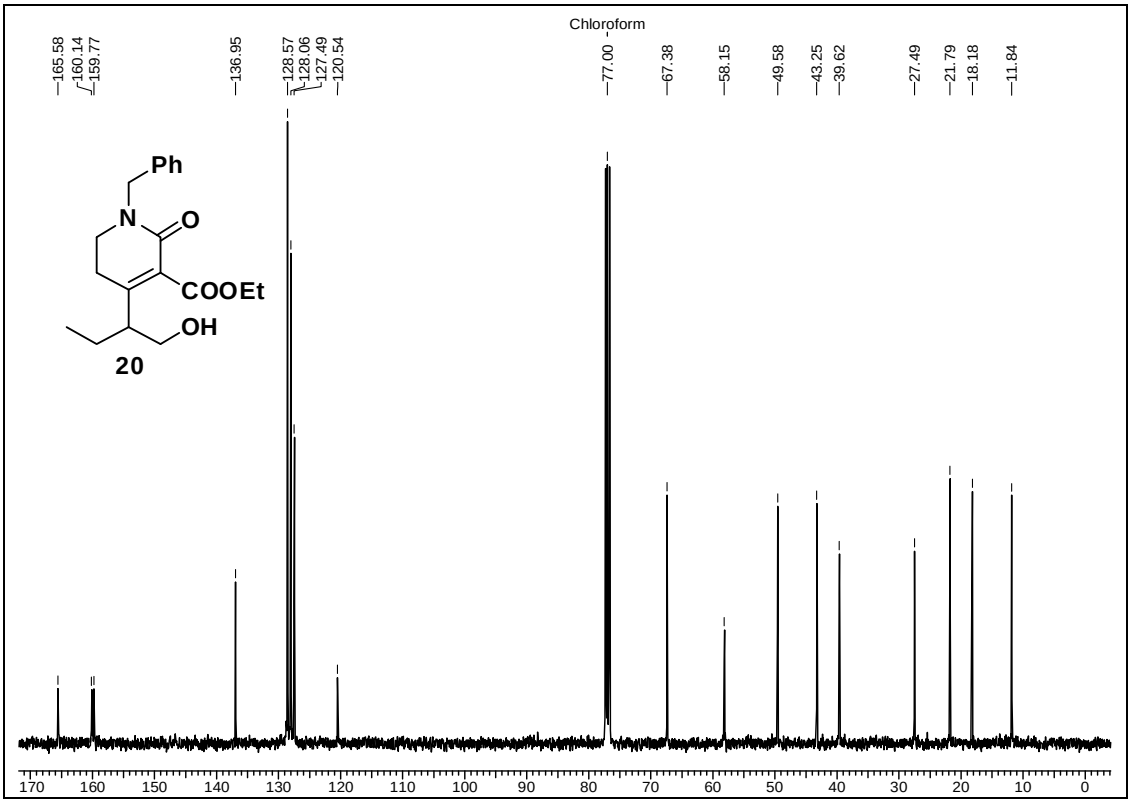
^{13}C NMR spectrum of compound 19 ($CDCl_3$, 50 MHz)



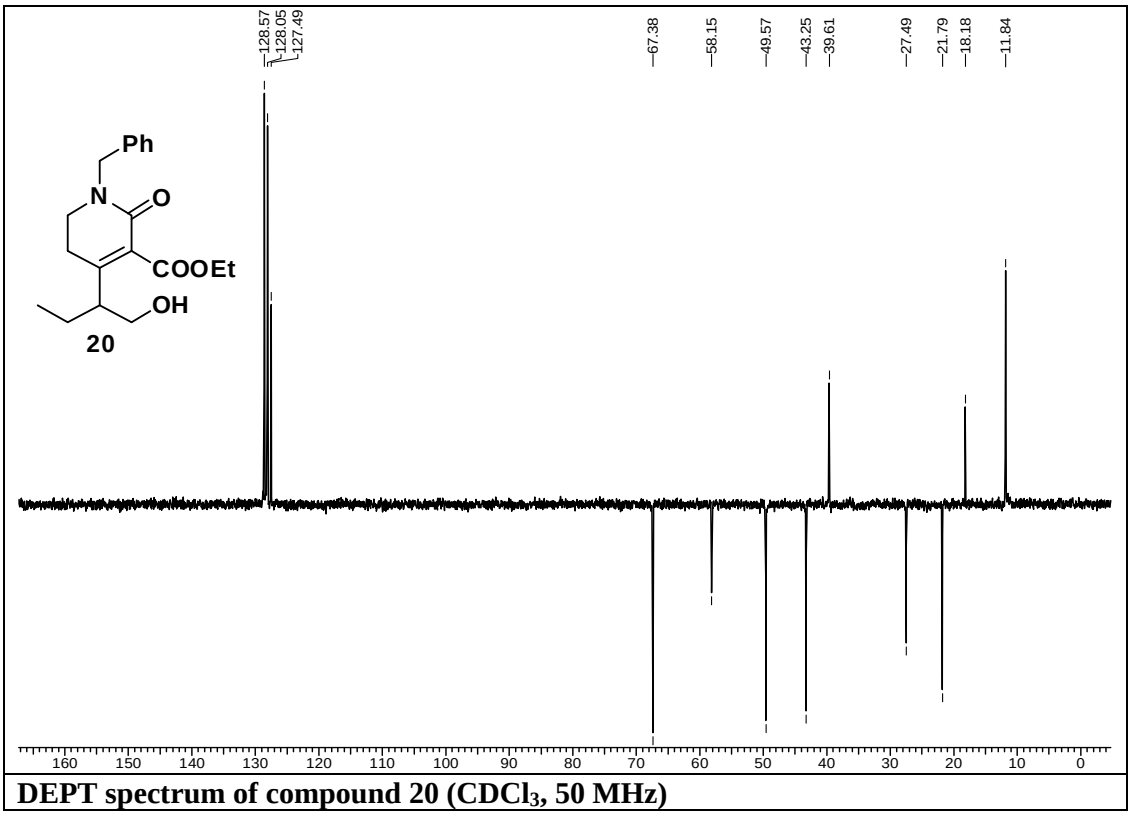
DEPT spectrum of compound 19 ($CDCl_3$, 50 MHz)



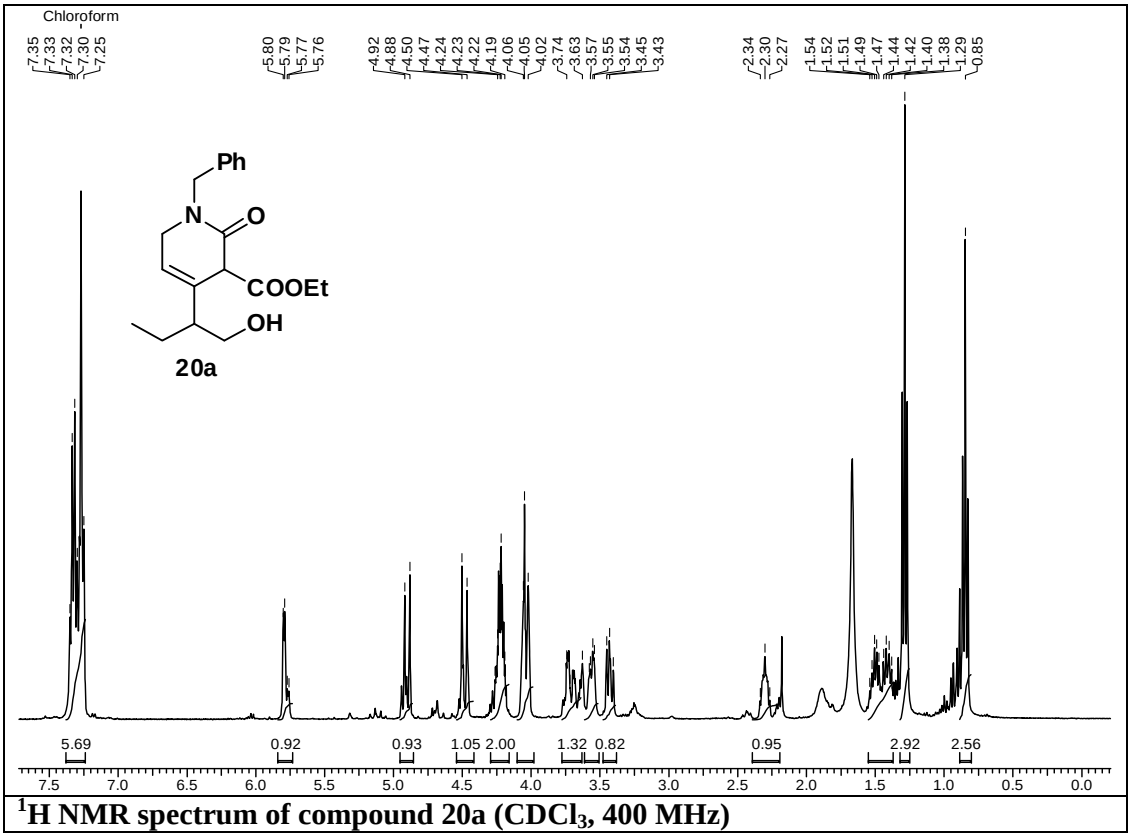
^{1}H NMR spectrum of compound 20 ($CDCl_3$, 200 MHz)



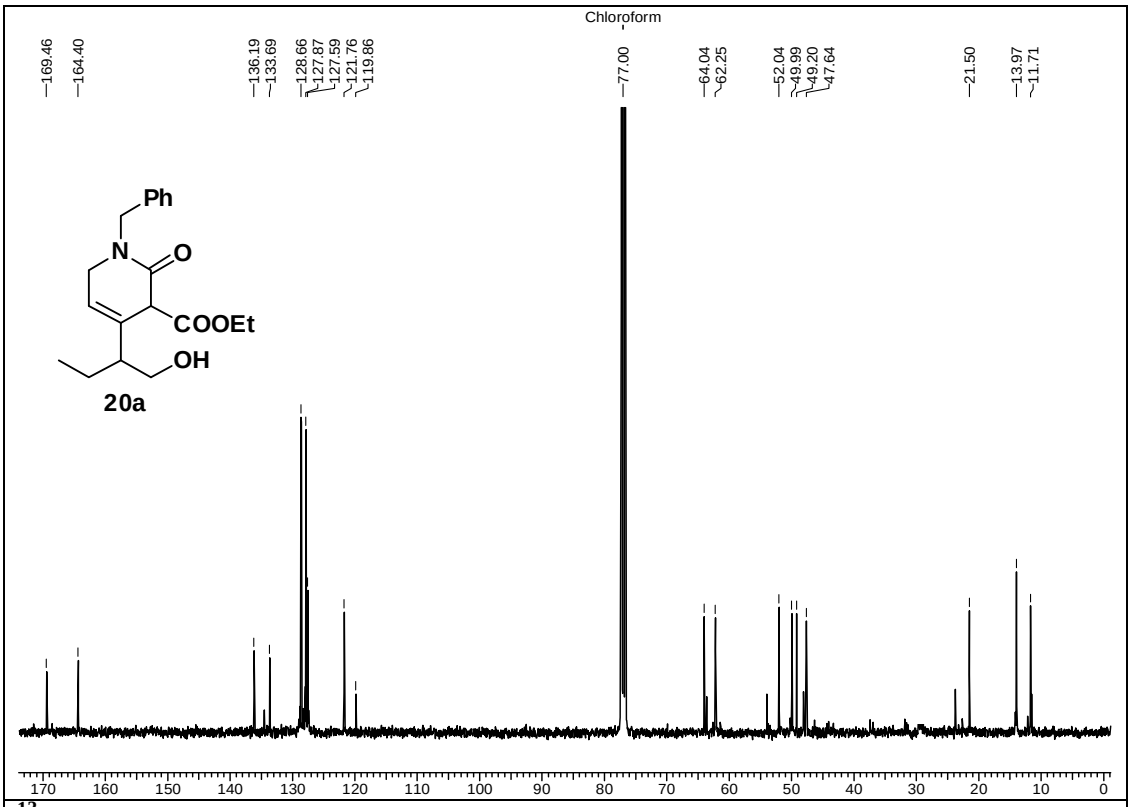
^{13}C NMR spectrum of compound 20 ($CDCl_3$, 50 MHz)



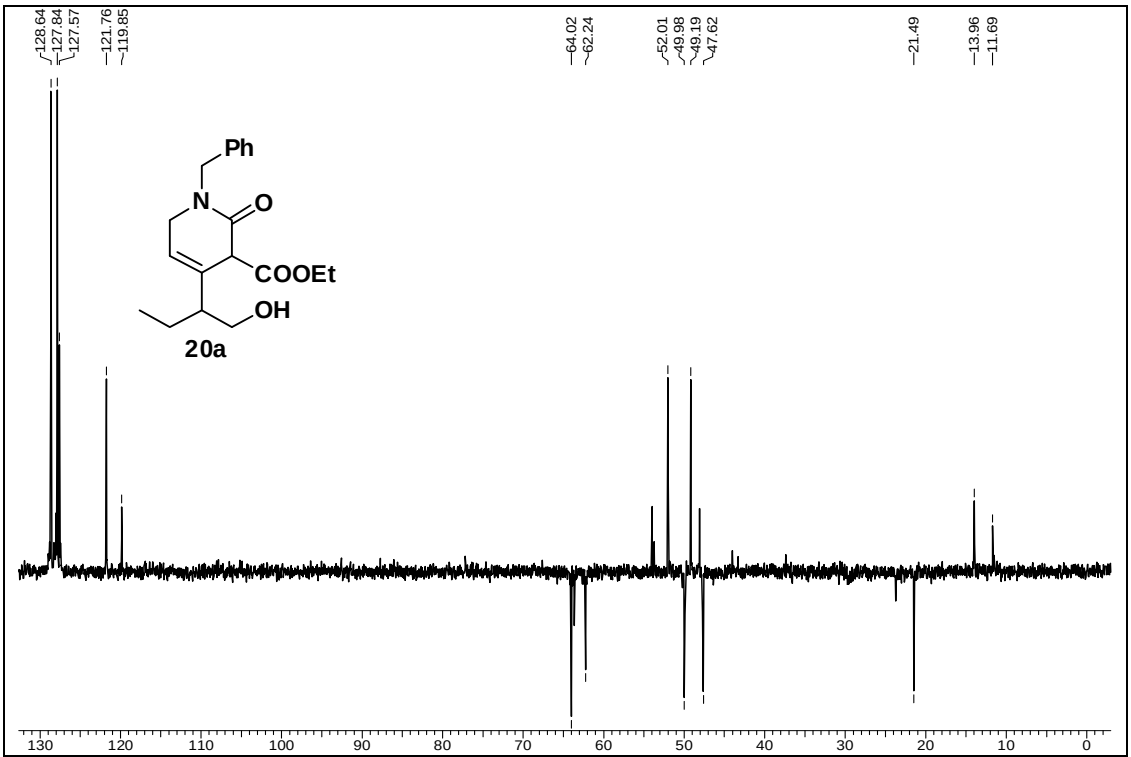
DEPT spectrum of compound 20 ($CDCl_3$, 50 MHz)



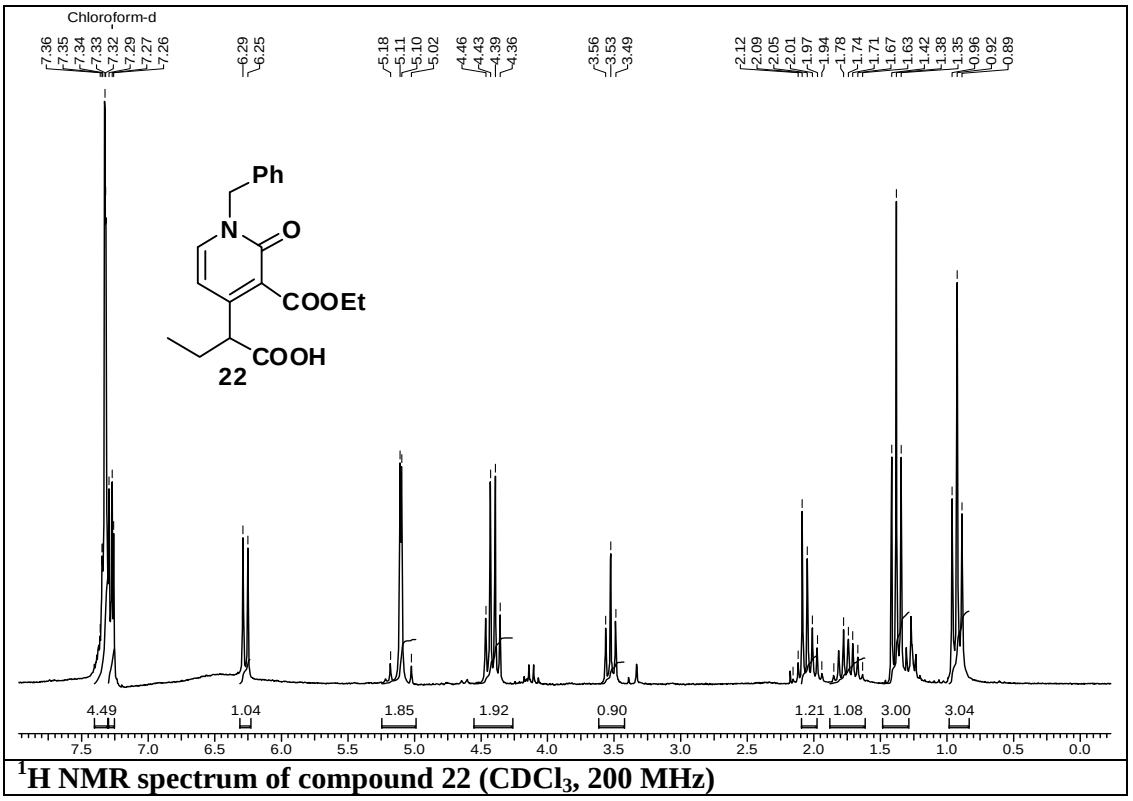
^{1}H NMR spectrum of compound 20a ($CDCl_3$, 400 MHz)



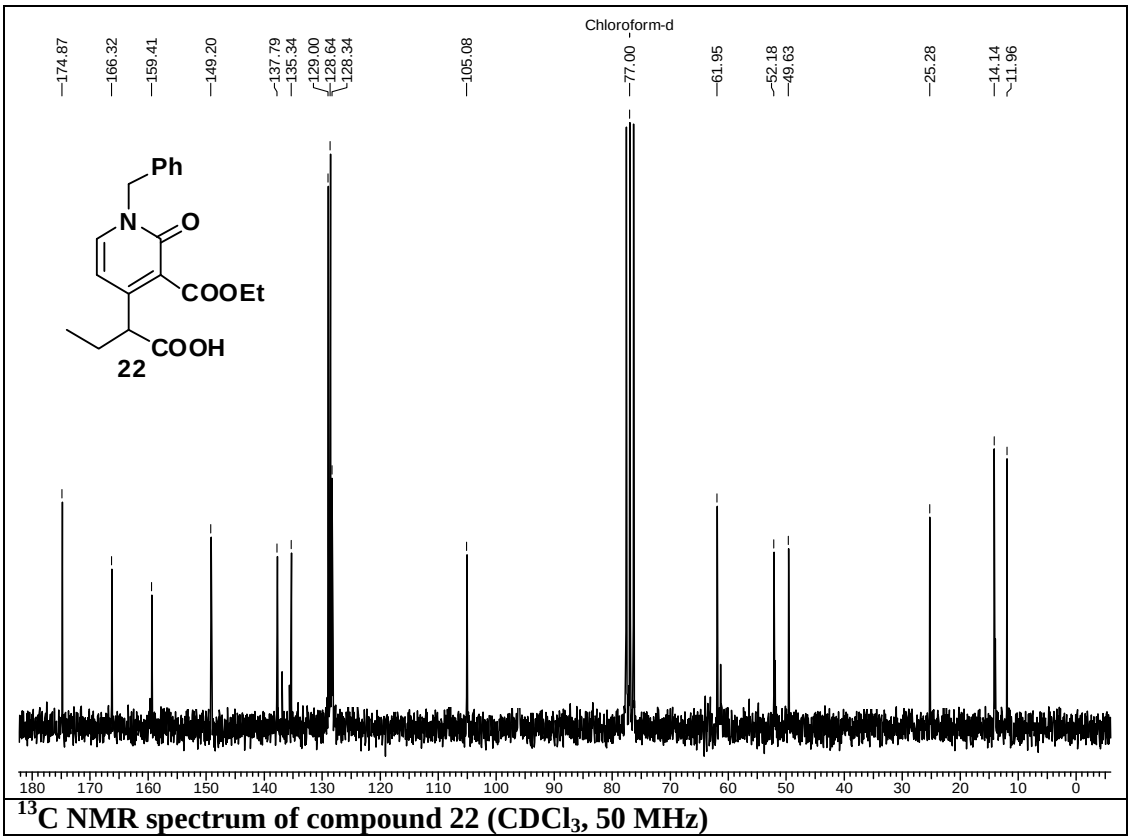
^{13}C NMR spectrum of compound 20a ($CDCl_3$, 100 MHz)



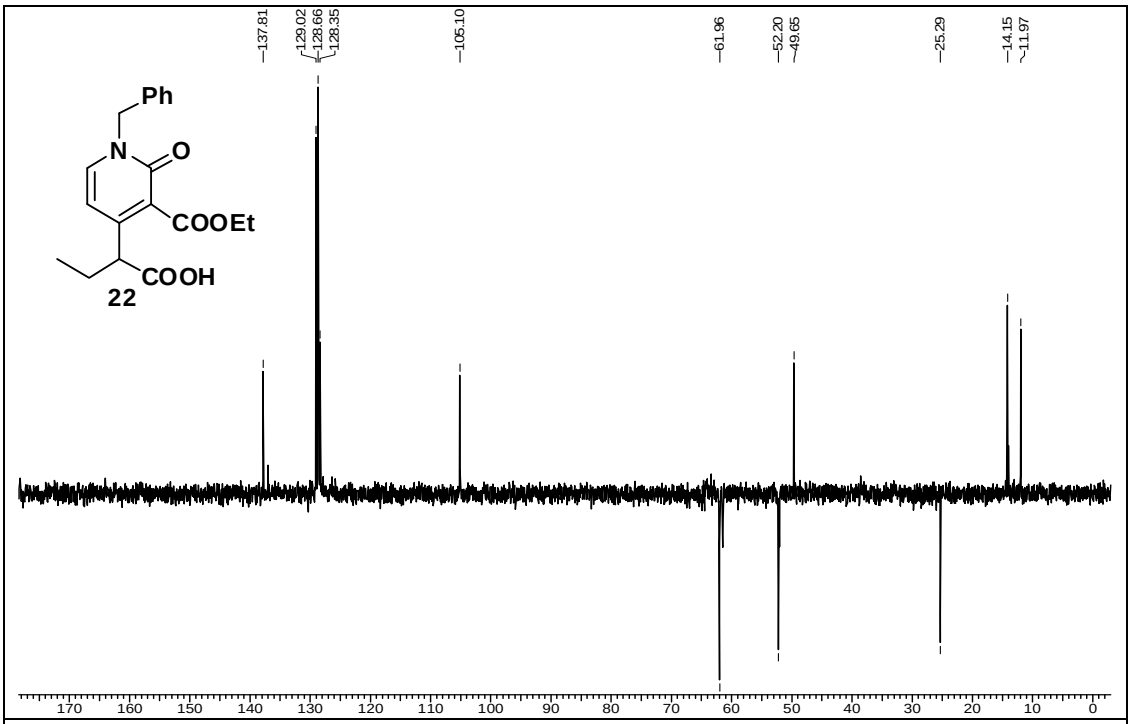
DEPT spectrum of compound 20a ($CDCl_3$, 100 MHz)



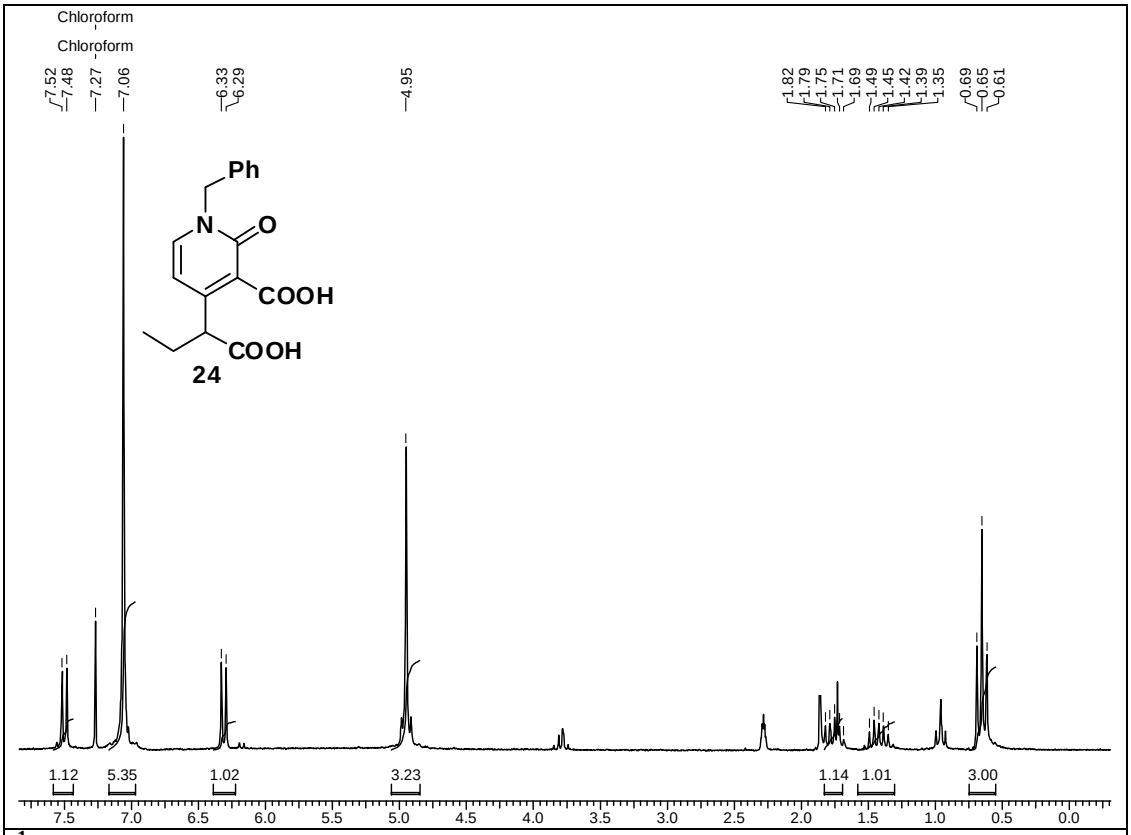
^{1}H NMR spectrum of compound 22 ($CDCl_3$, 200 MHz)



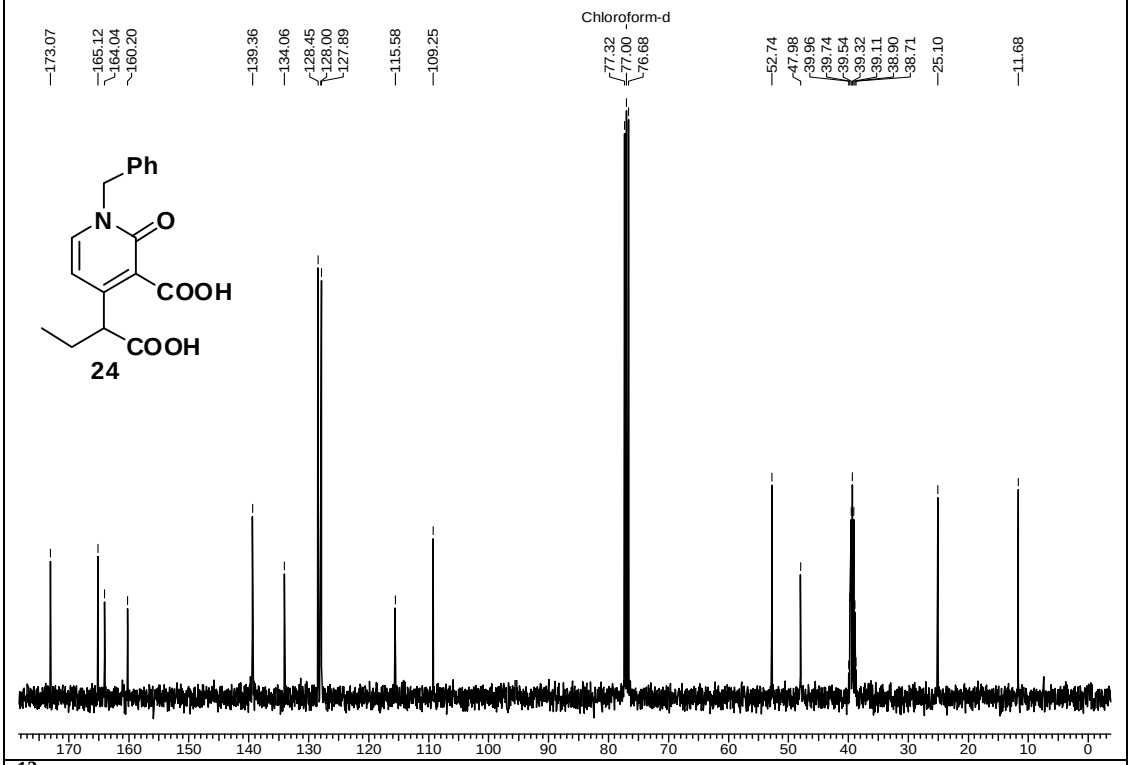
^{13}C NMR spectrum of compound 22 ($CDCl_3$, 50 MHz)



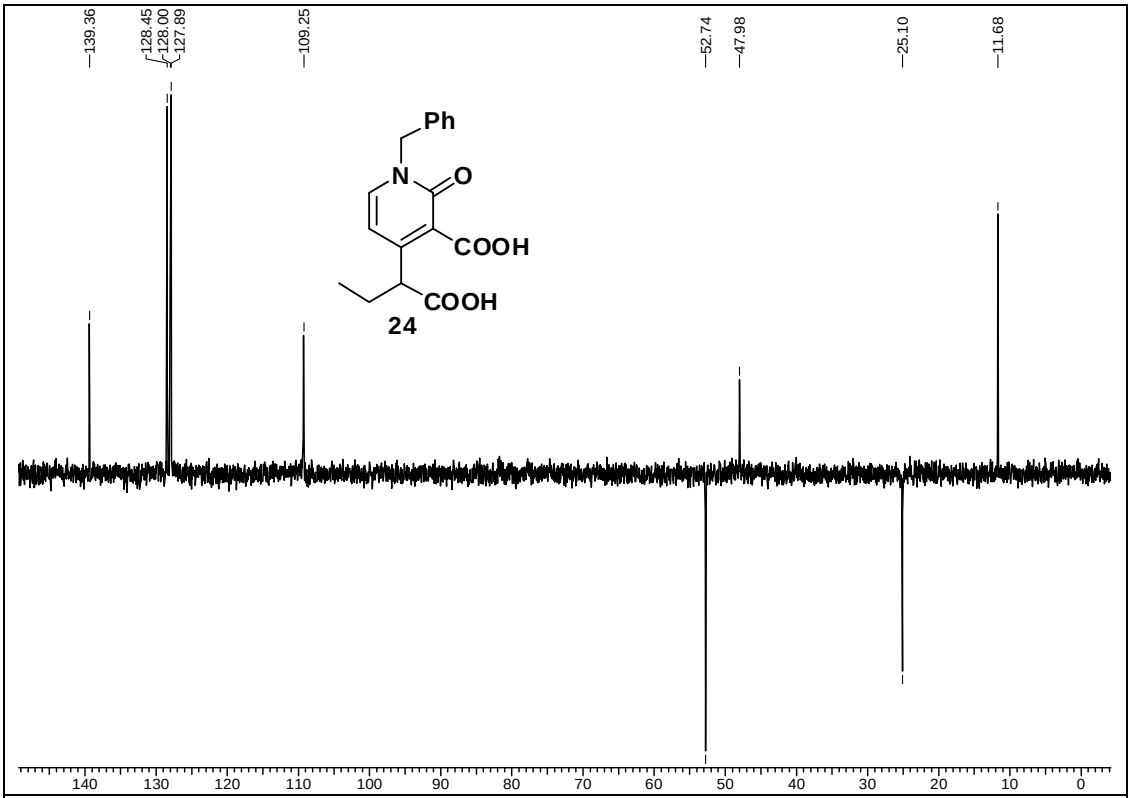
DEPT spectrum of compound 22 ($CDCl_3$, 50 MHz)



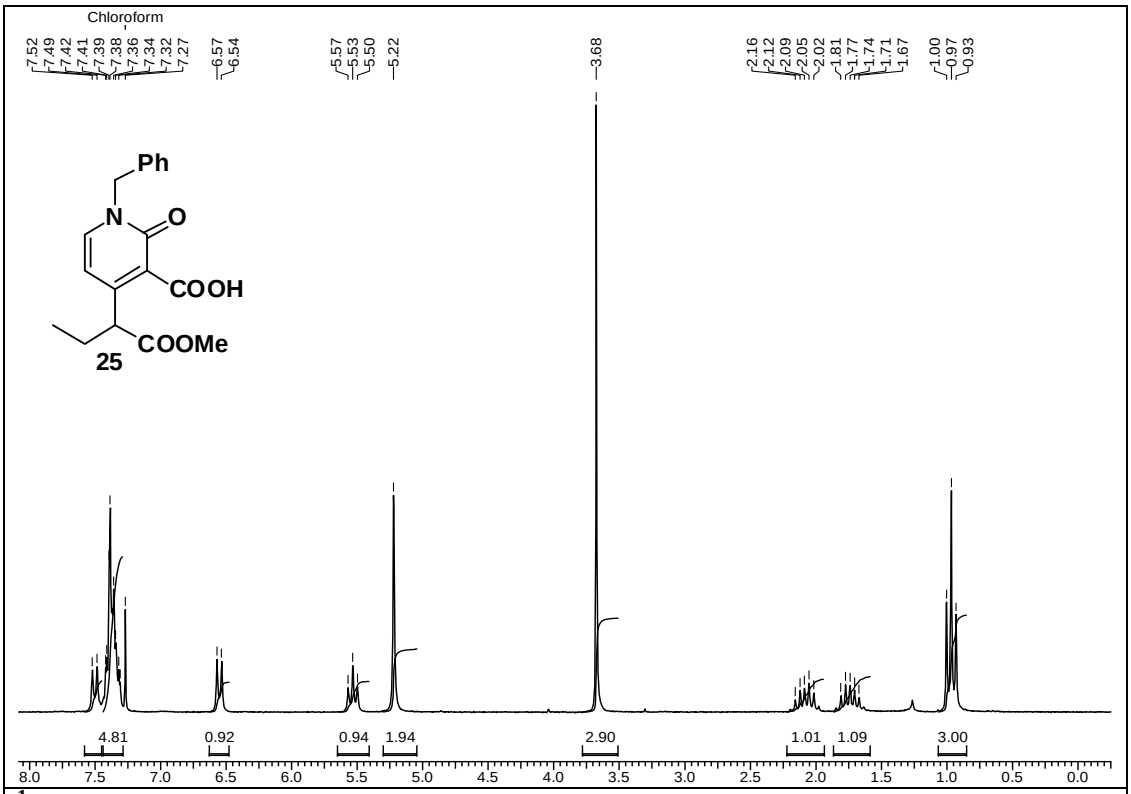
^{1}H NMR spectrum of compound 24 ($CDCl_3$ + DMSO-d_6, 200 MHz)



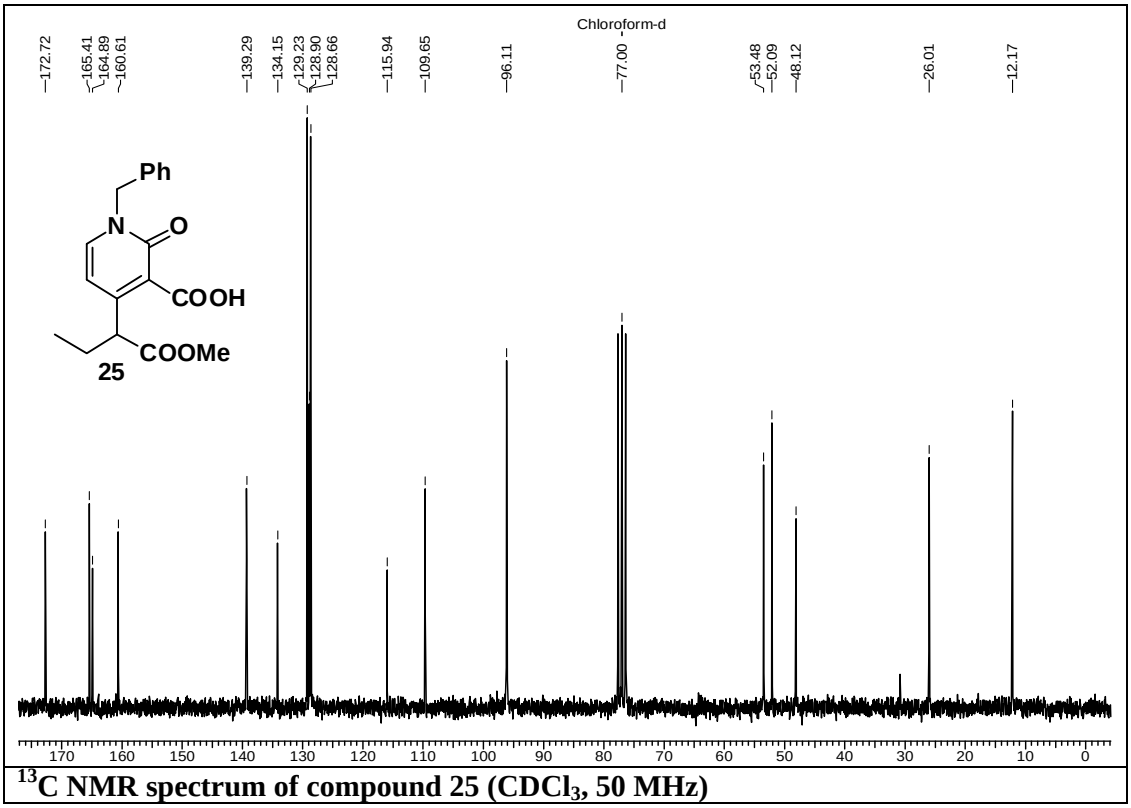
^{13}C NMR spectrum of compound 24 ($CDCl_3$ + DMSO-d_6 50 MHz)



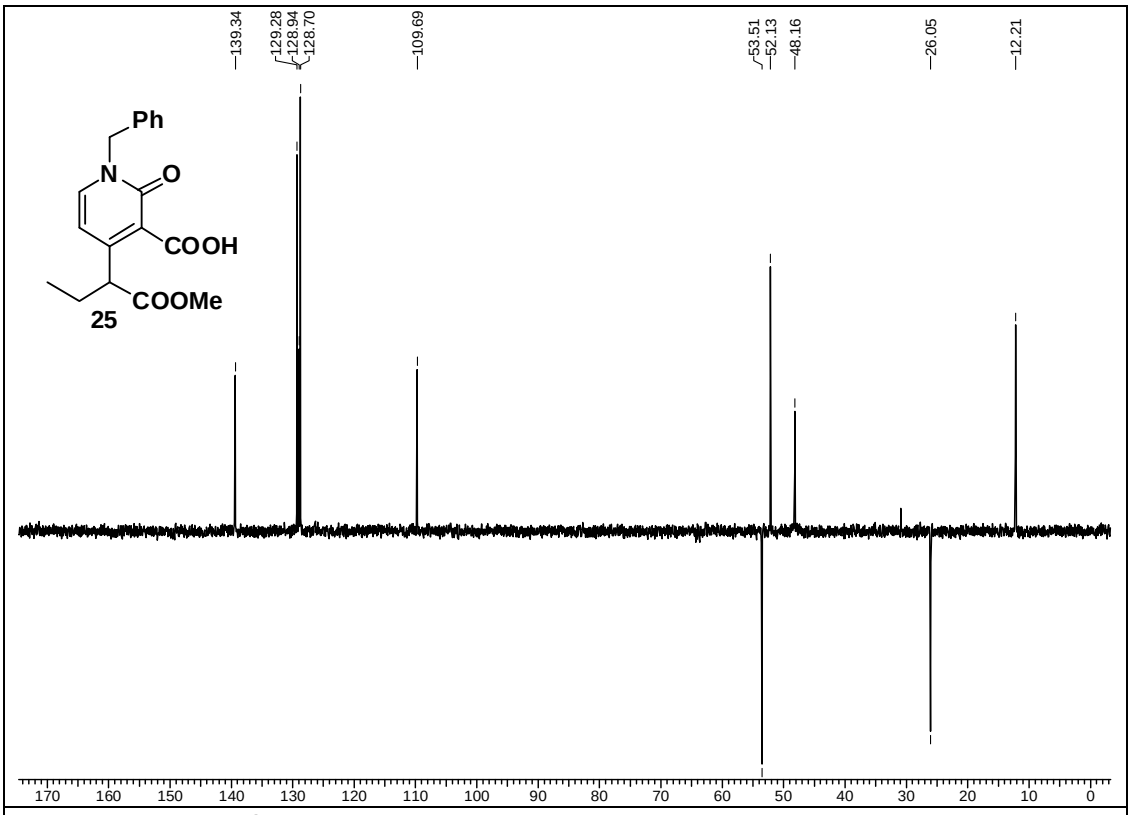
DEPT spectrum of compound 24 ($CDCl_3$ + DMSO-d_6, 50 MHz)



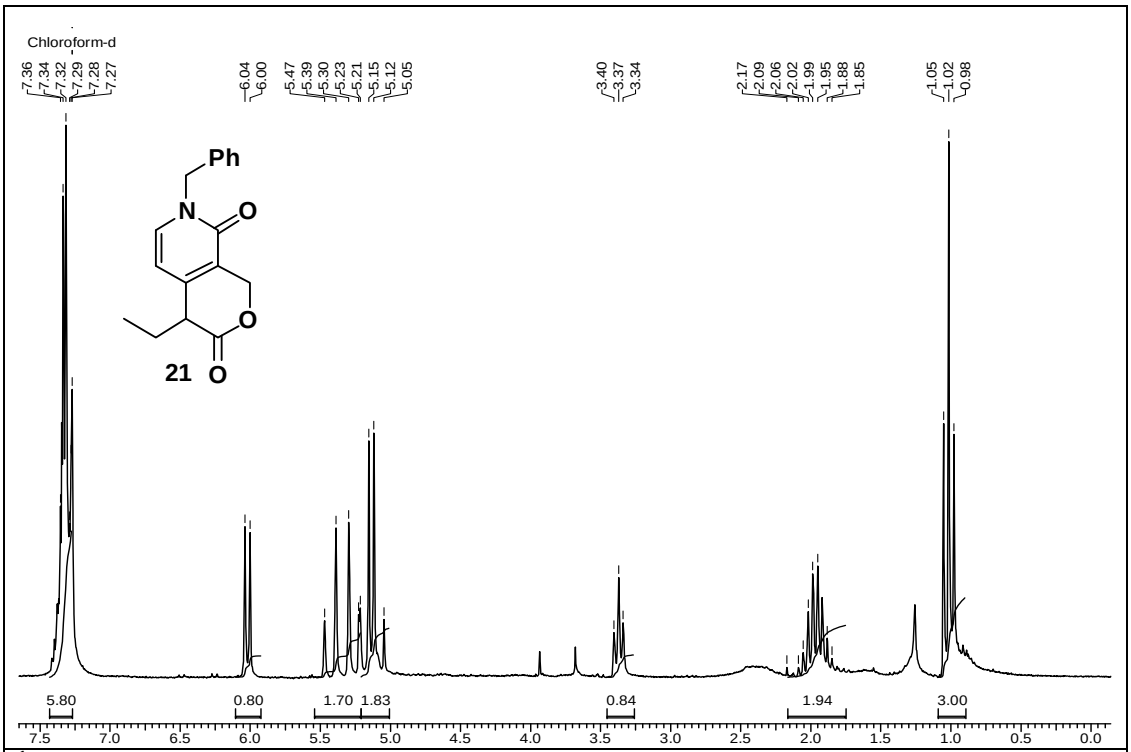
^{1}H NMR spectrum of compound 25 ($CDCl_3$, 200 MHz)



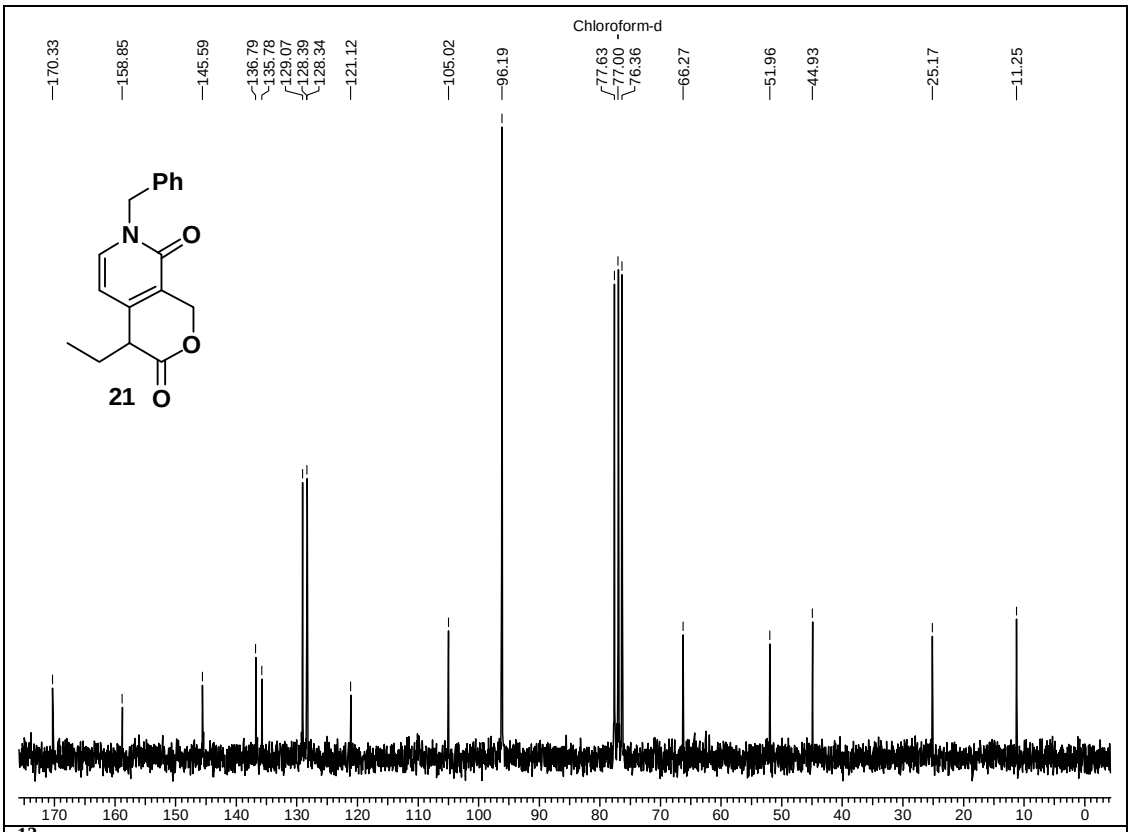
^{13}C NMR spectrum of compound 25 ($CDCl_3$, 50 MHz)



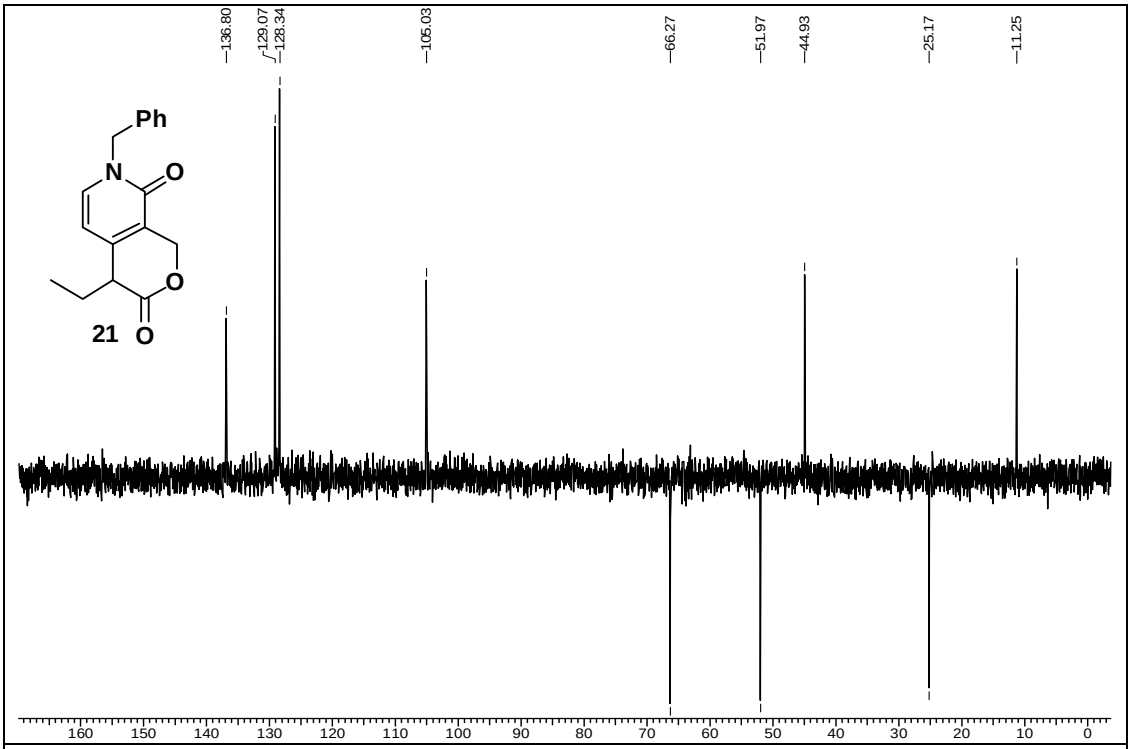
DEPT spectrum of compound 25 ($CDCl_3$, 50 MHz)



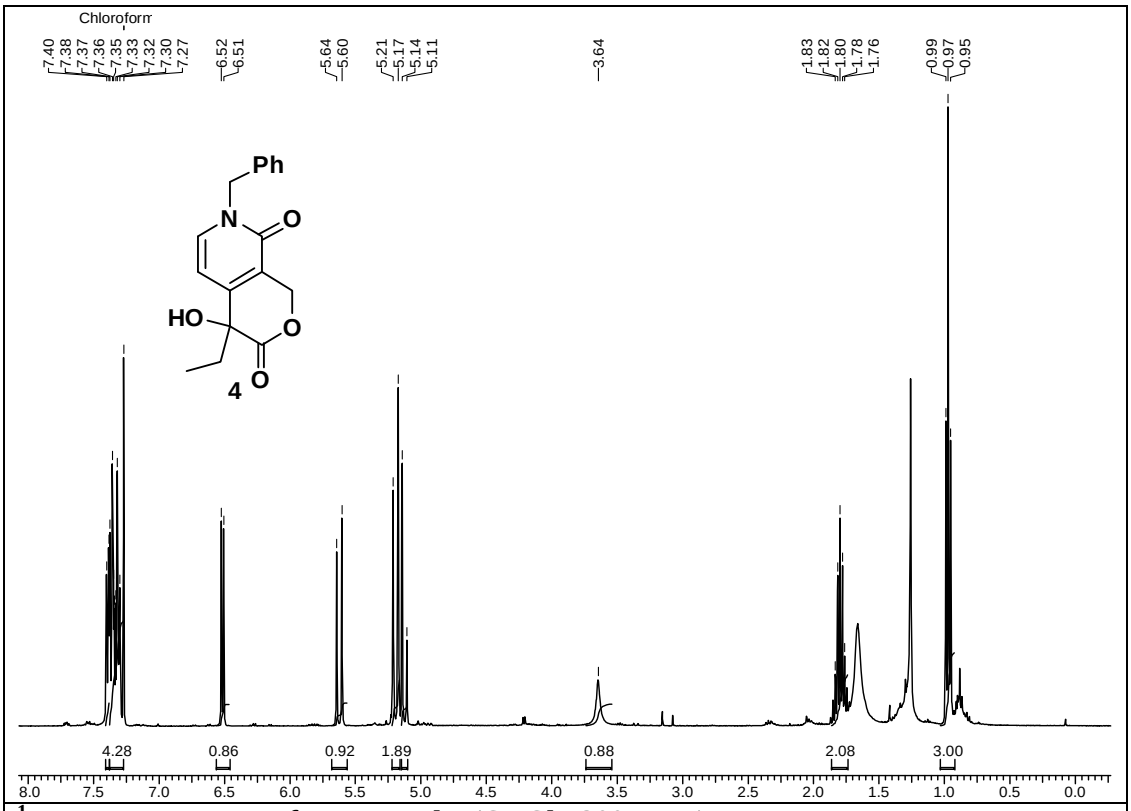
^{1}H NMR spectrum of compound 21 ($CDCl_3$, 200 MHz)



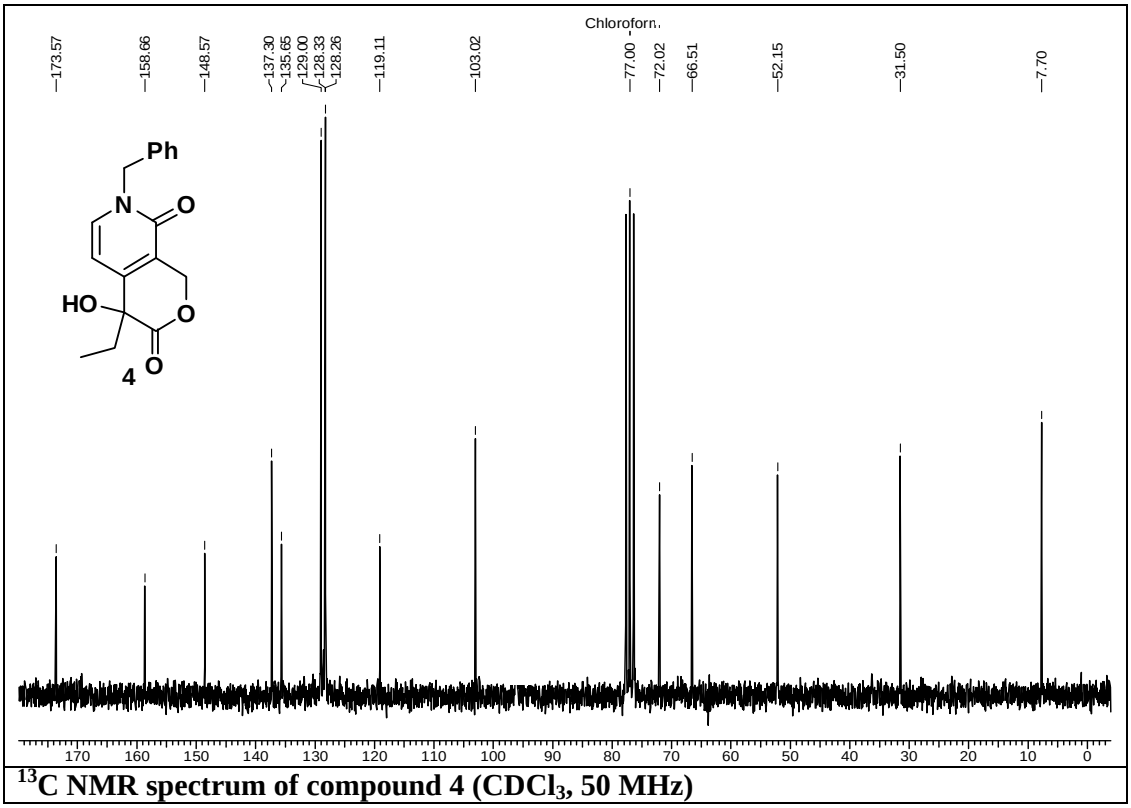
^{13}C NMR spectrum of compound 21 ($CDCl_3$ + CCl_4, 50 MHz)



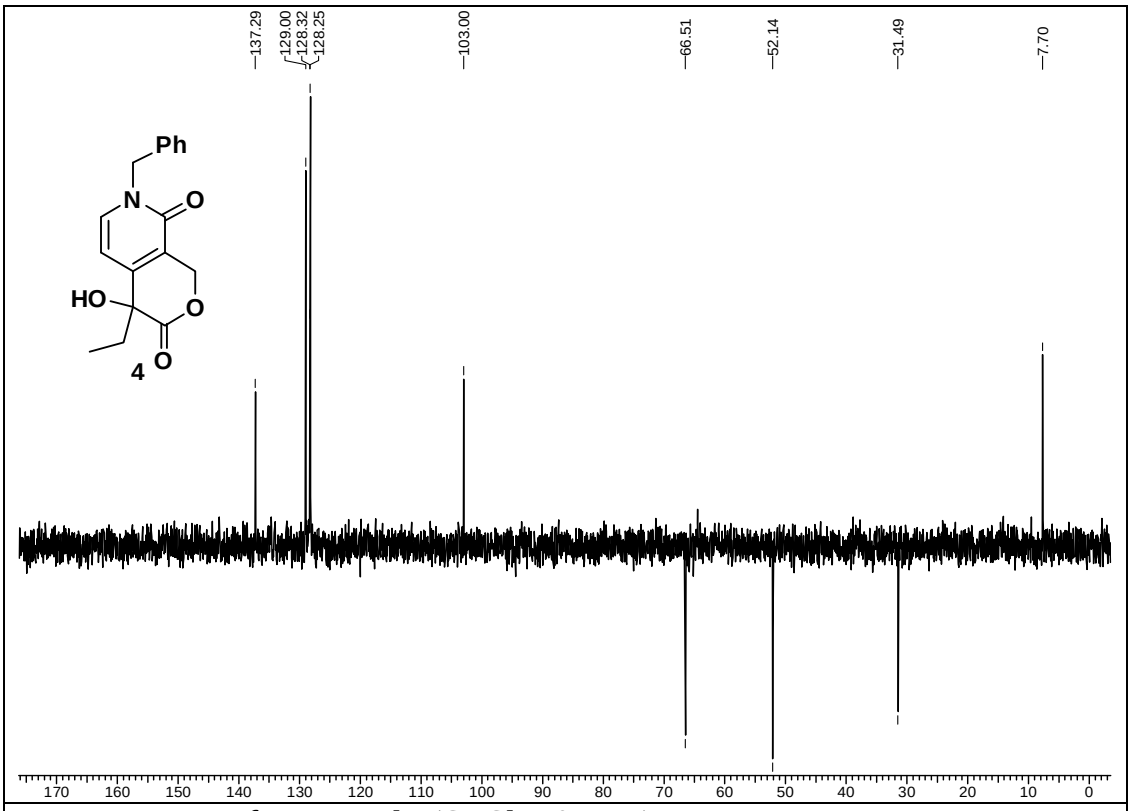
DEPT spectrum of compound 21 ($CDCl_3$+ CCl_4, 50 MHz)



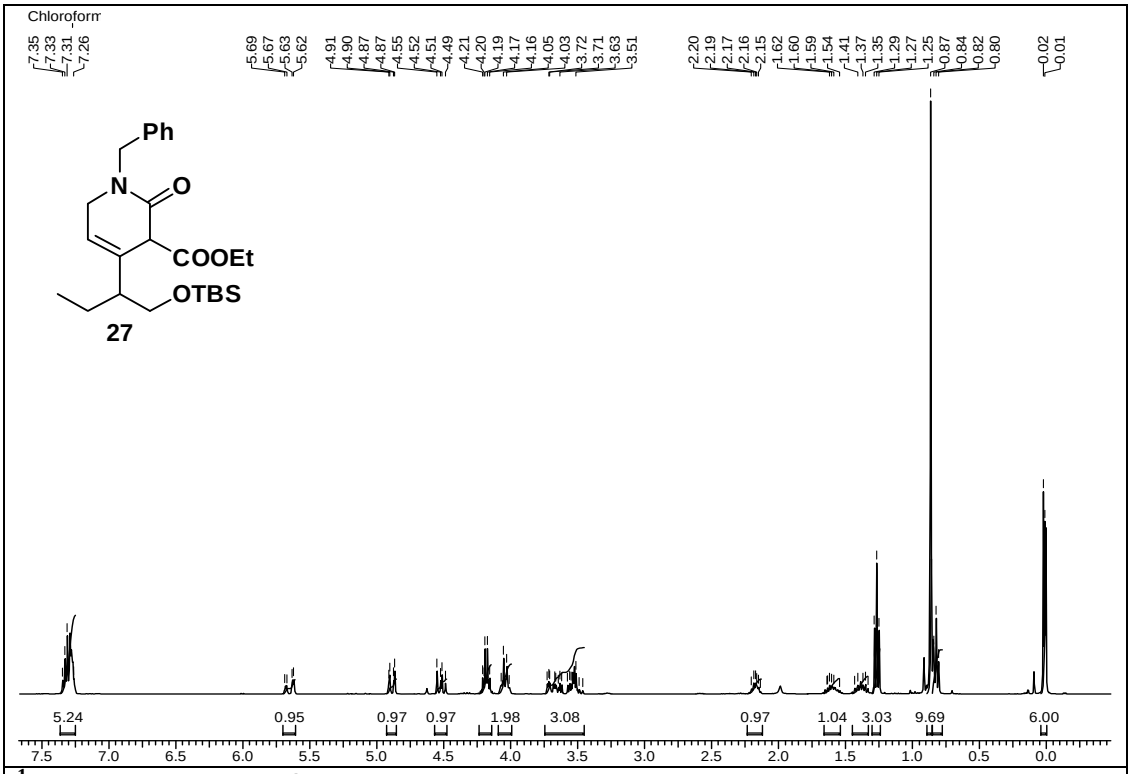
^{1}H NMR spectrum of compound 4 ($CDCl_3$, 200 MHz)



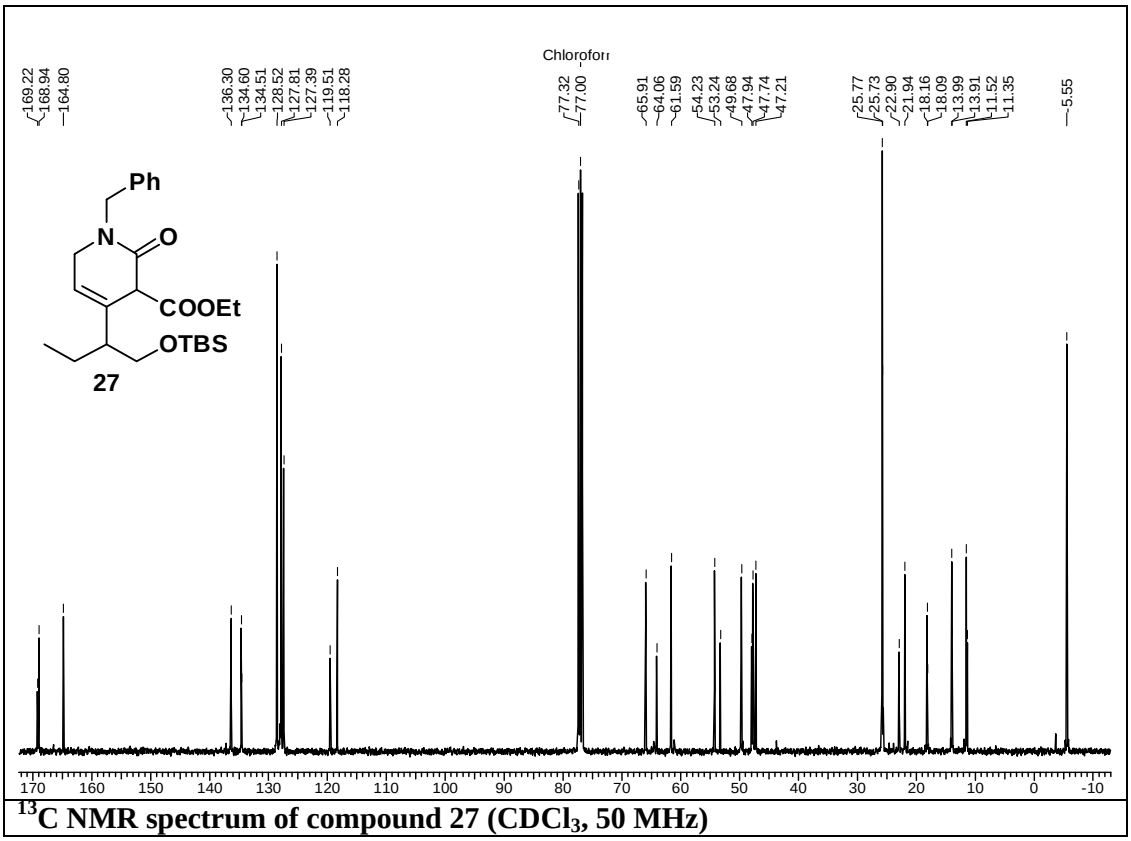
^{13}C NMR spectrum of compound 4 ($CDCl_3$, 50 MHz)



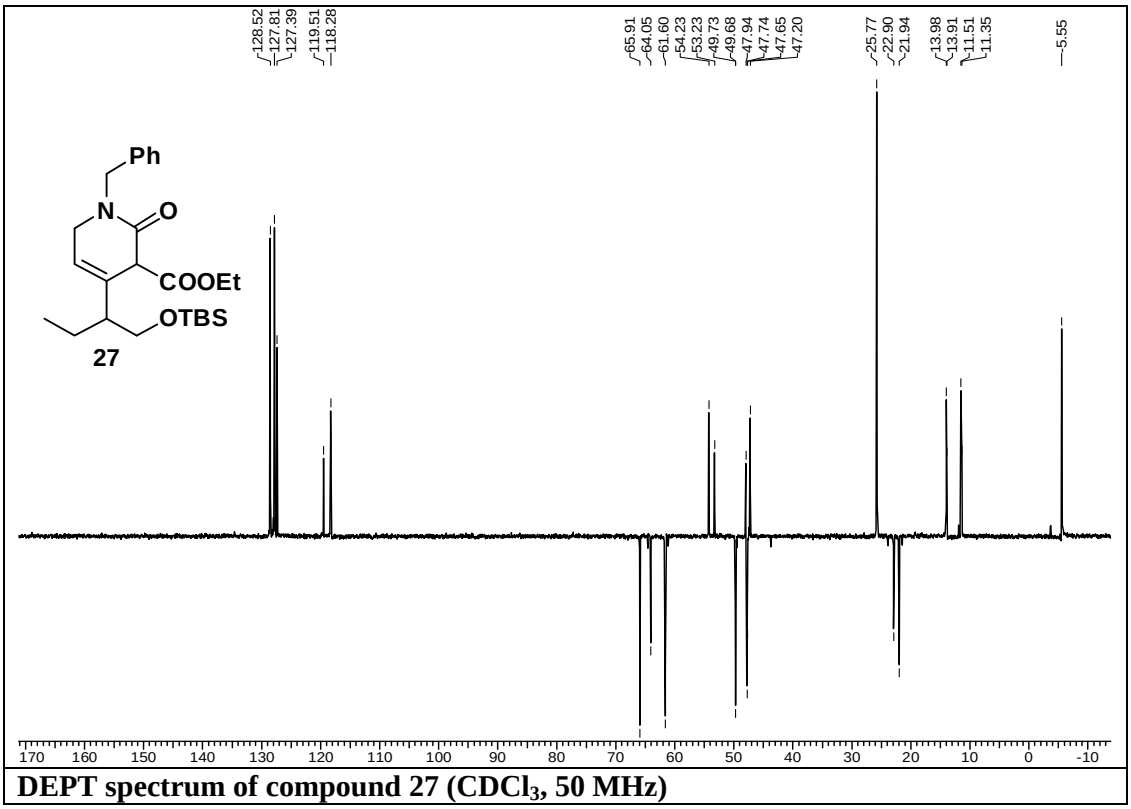
DEPT spectrum of compound 4 ($CDCl_3$, 50 MHz)



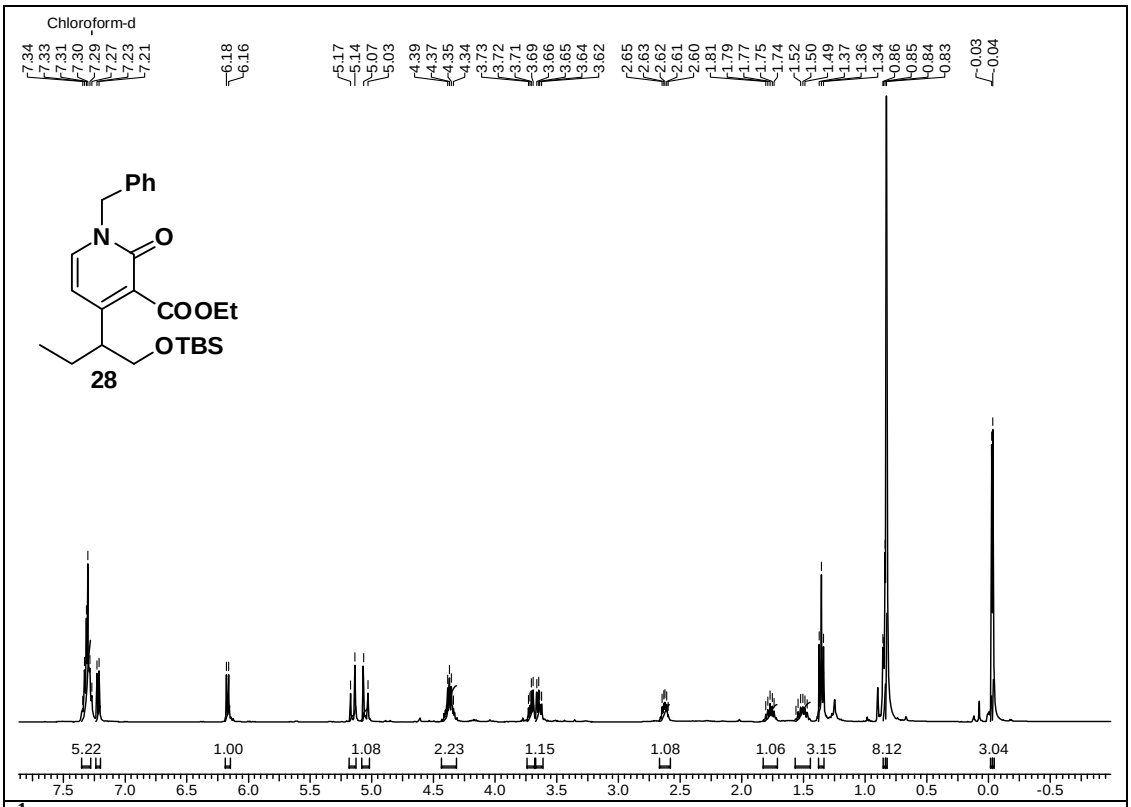
^{1}H NMR spectrum of compound 27 ($CDCl_3$, 200 MHz)



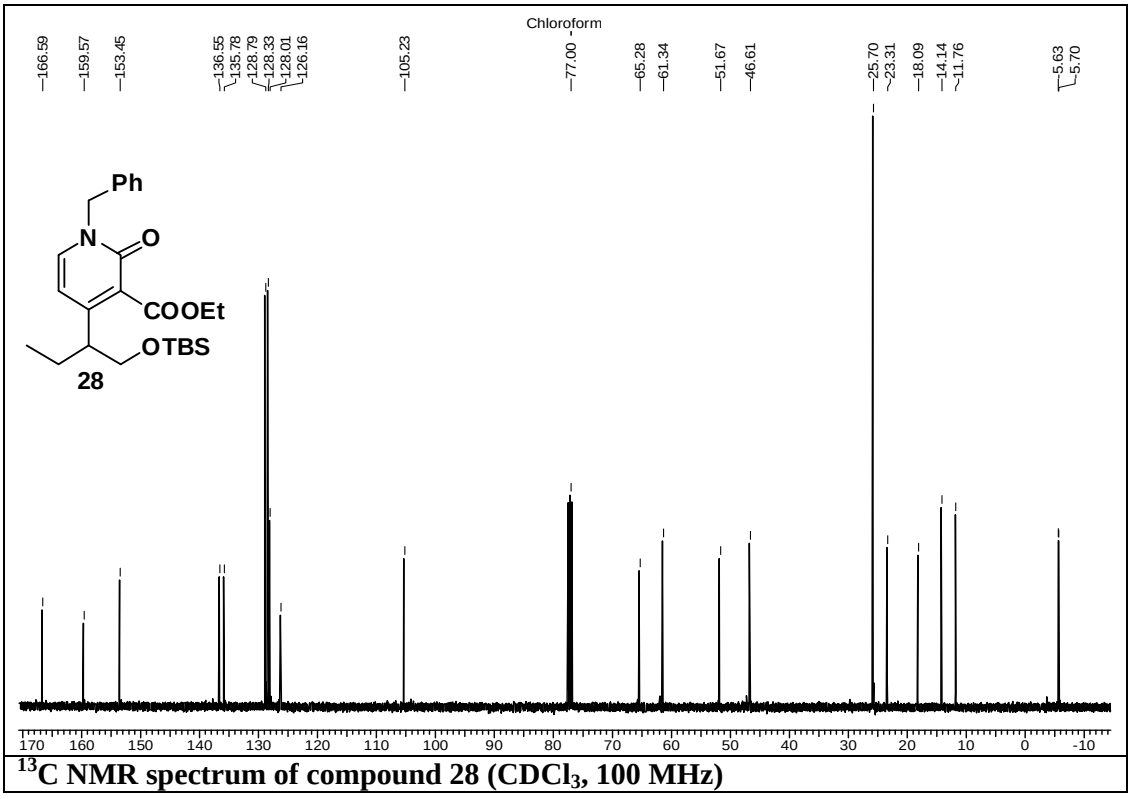
^{13}C NMR spectrum of compound 27 ($CDCl_3$, 50 MHz)



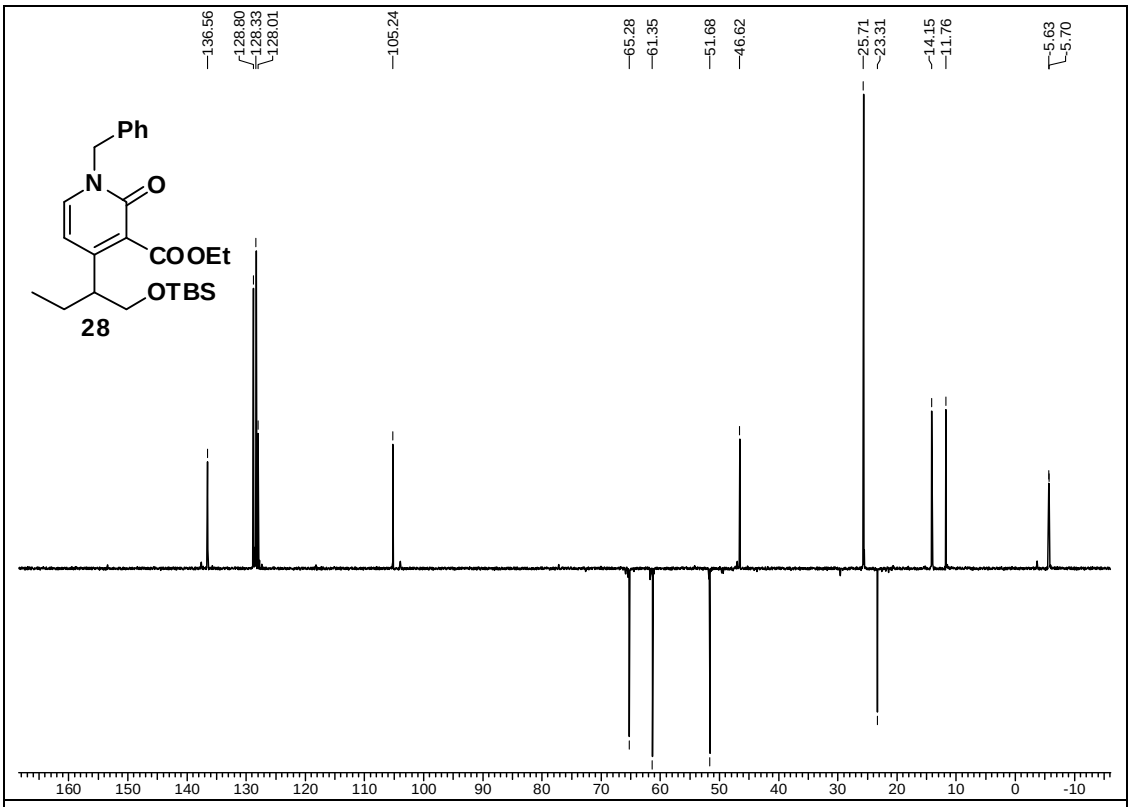
DEPT spectrum of compound 27 ($CDCl_3$, 50 MHz)



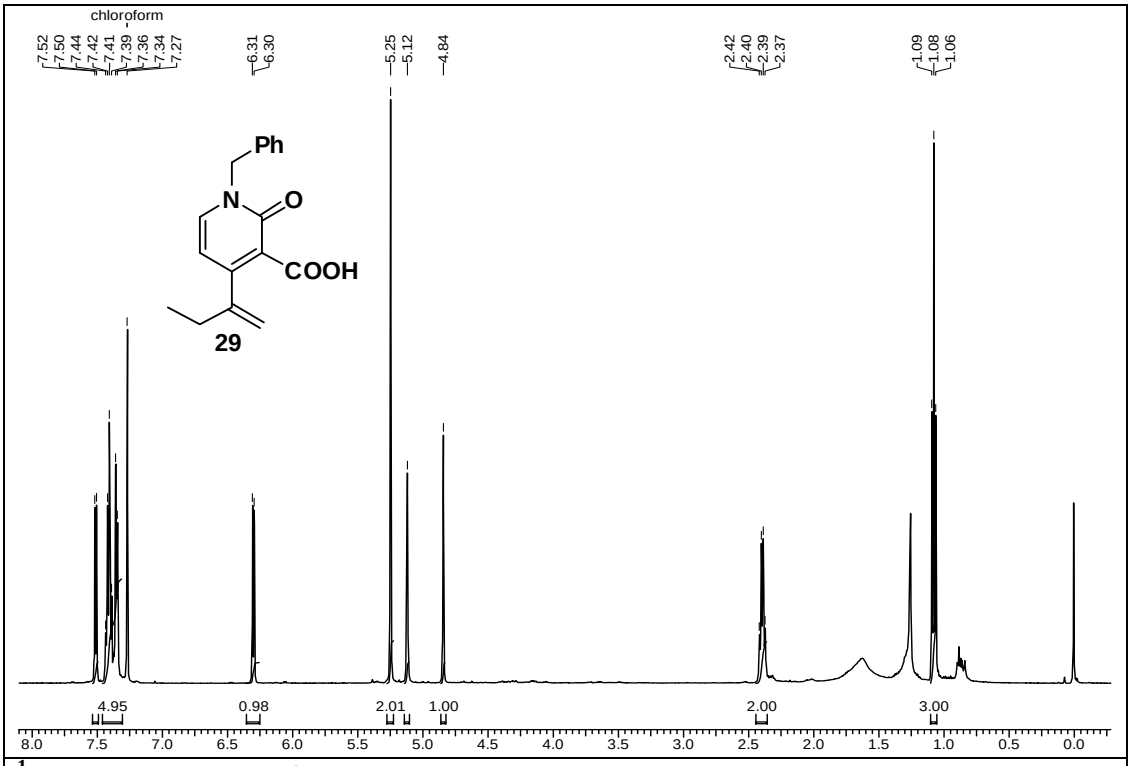
^{1}H NMR spectrum of compound 28 ($CDCl_3$, 400 MHz)



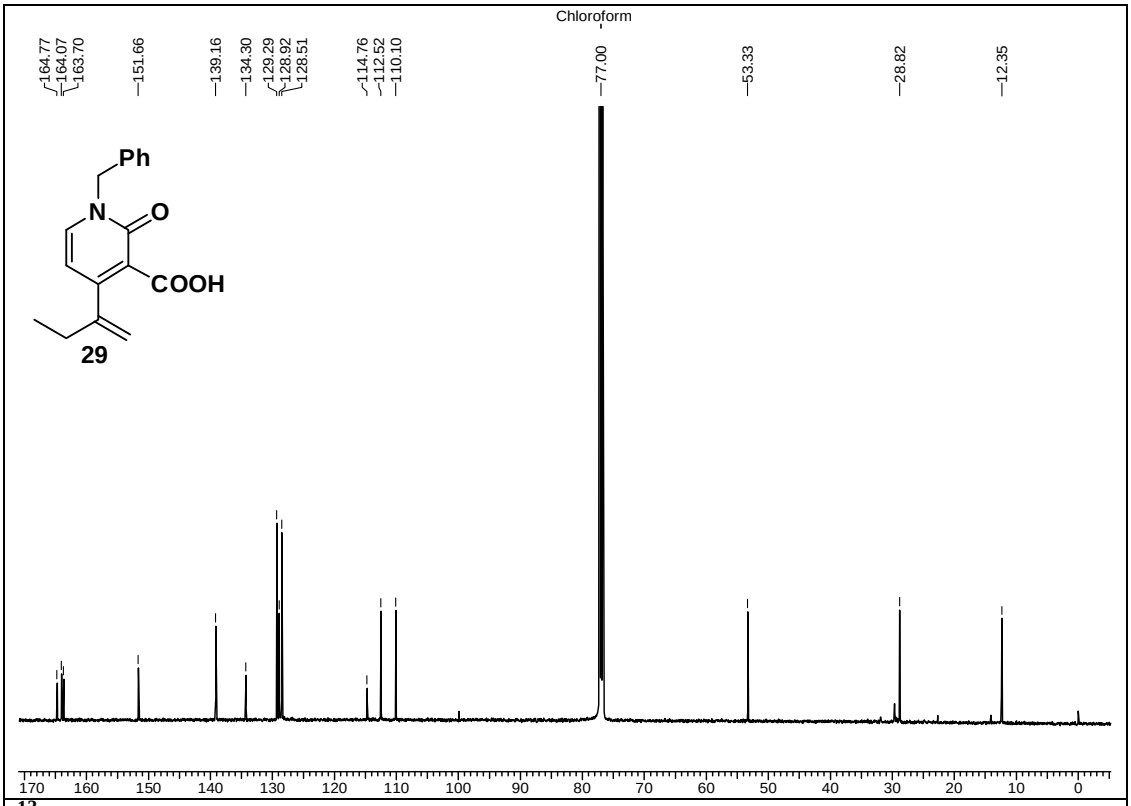
^{13}C NMR spectrum of compound 28 ($CDCl_3$, 100 MHz)



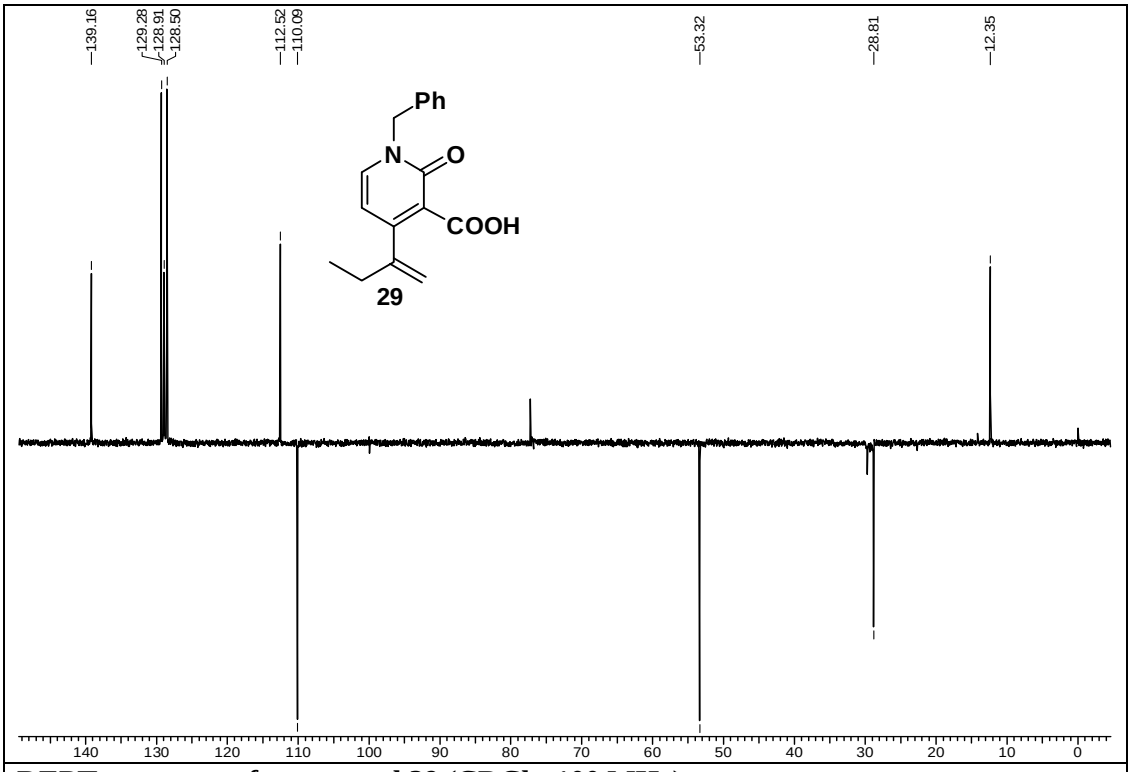
DEPT spectrum of compound 28 ($CDCl_3$, 100 MHz)



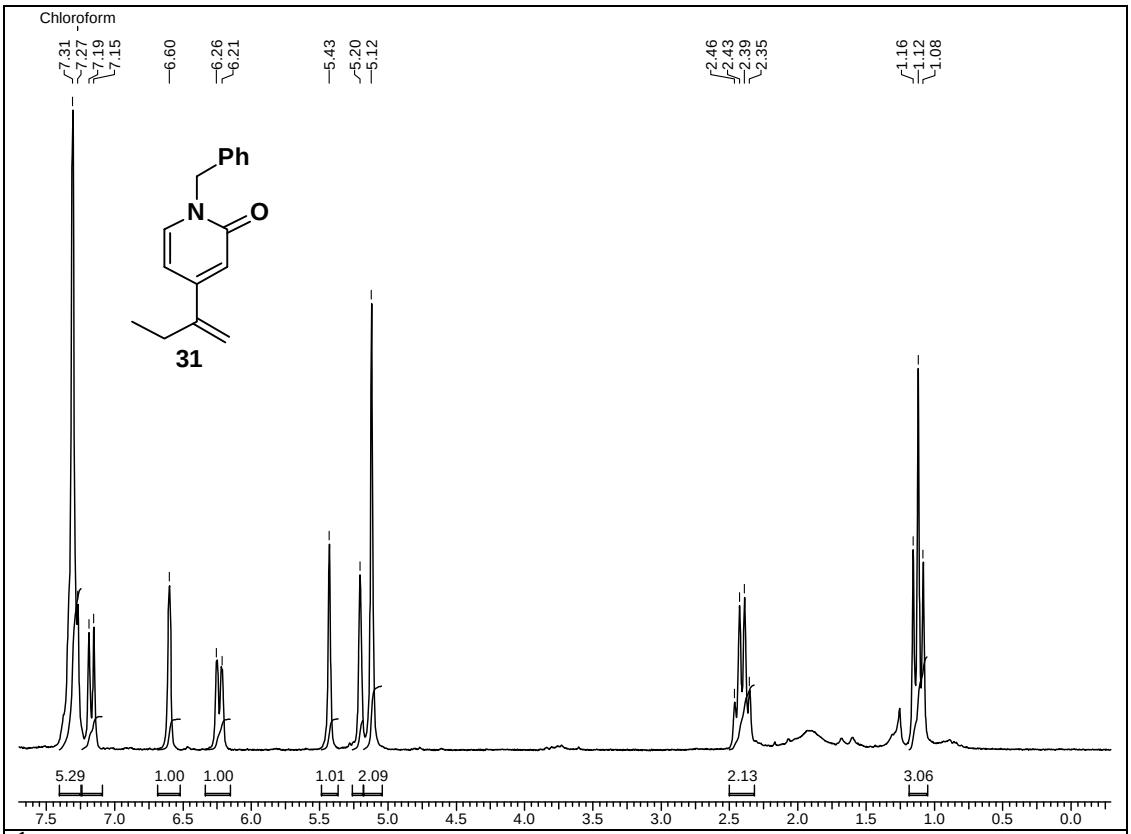
^{1}H NMR spectrum of compound 29 ($CDCl_3$, 400 MHz)



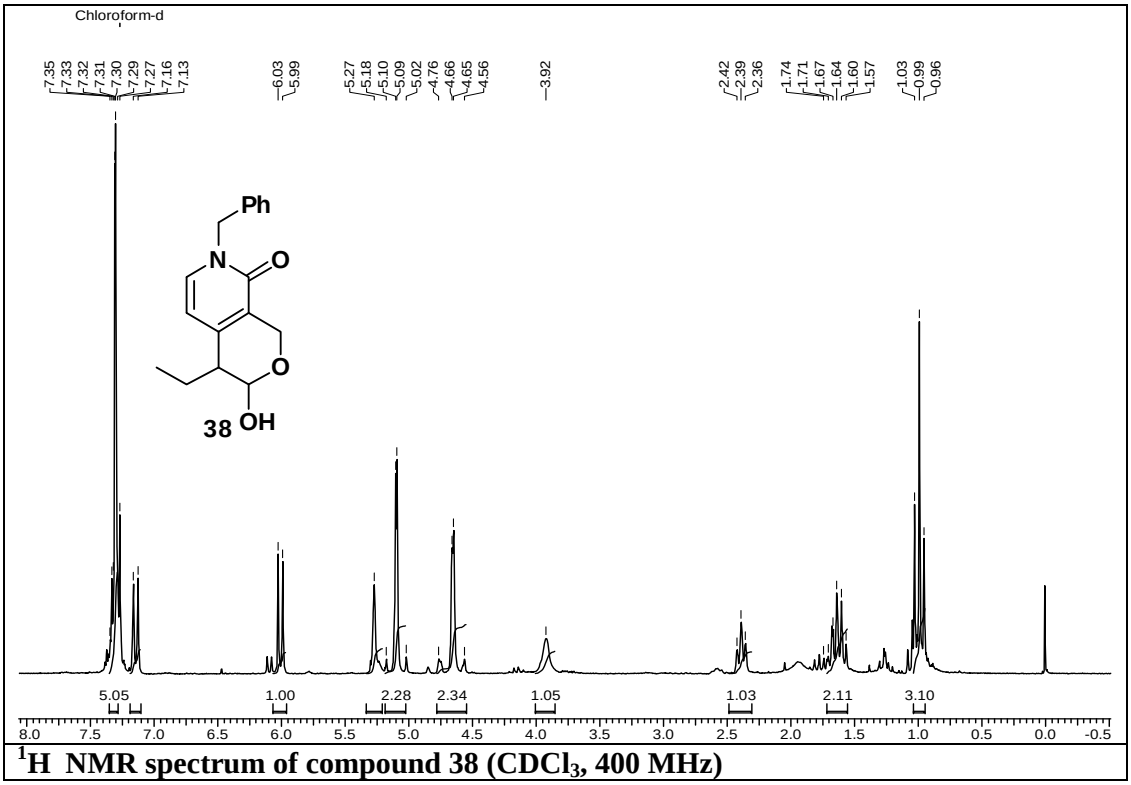
^{13}C NMR spectrum of compound 29 ($CDCl_3$, 100 MHz)



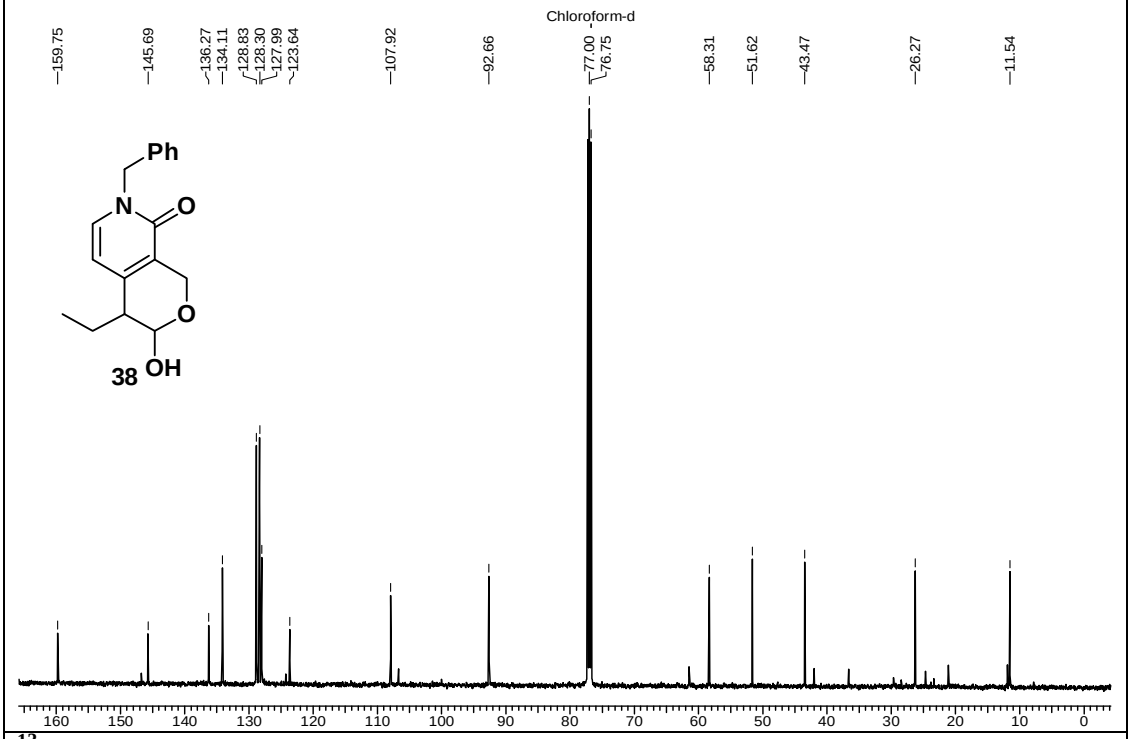
DEPT spectrum of compound 29 ($CDCl_3$, 100 MHz)



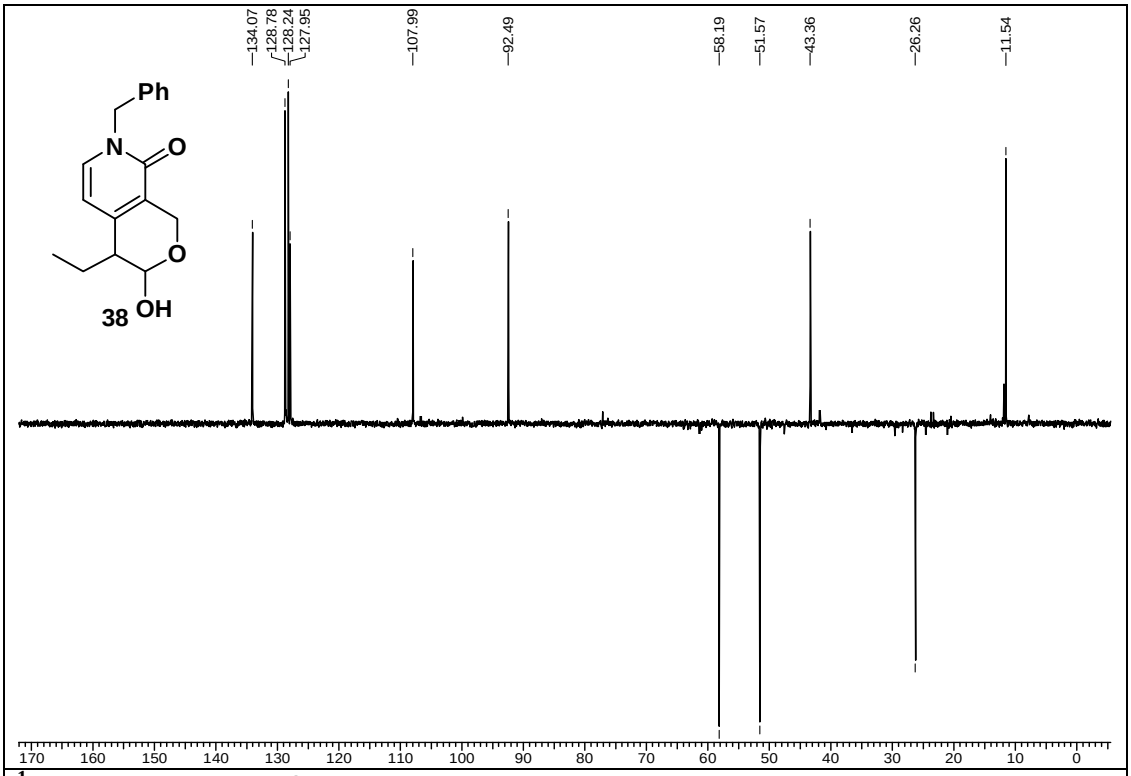
^{1}H NMR spectrum of compound 31 ($CDCl_3$, 400 MHz)



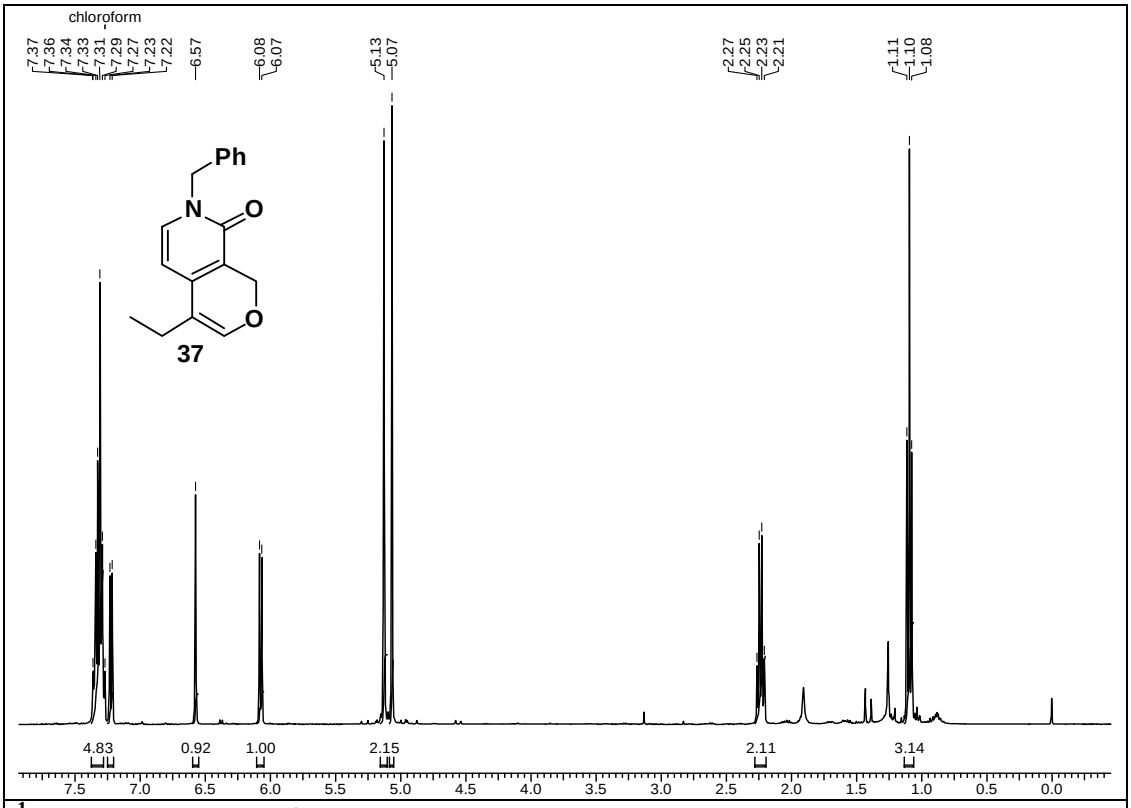
^{1}H NMR spectrum of compound 38 ($CDCl_3$, 400 MHz)



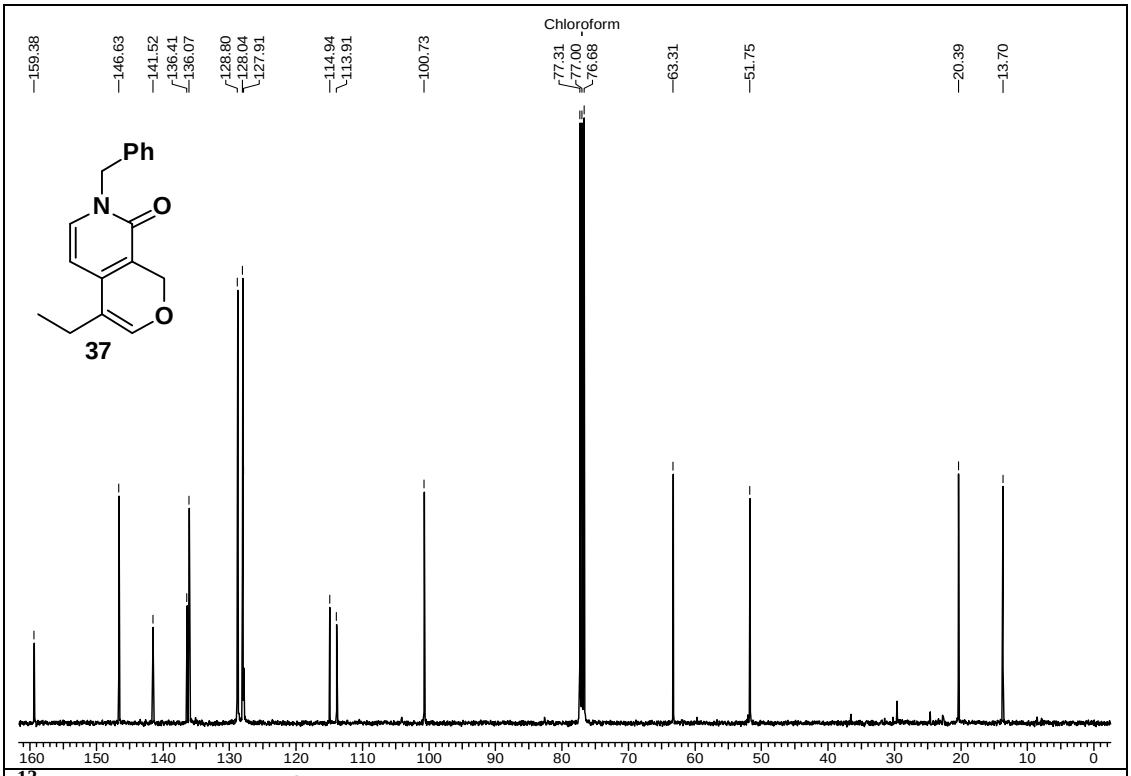
^{13}C NMR spectrum of compound 38 ($CDCl_3$, 100 MHz)



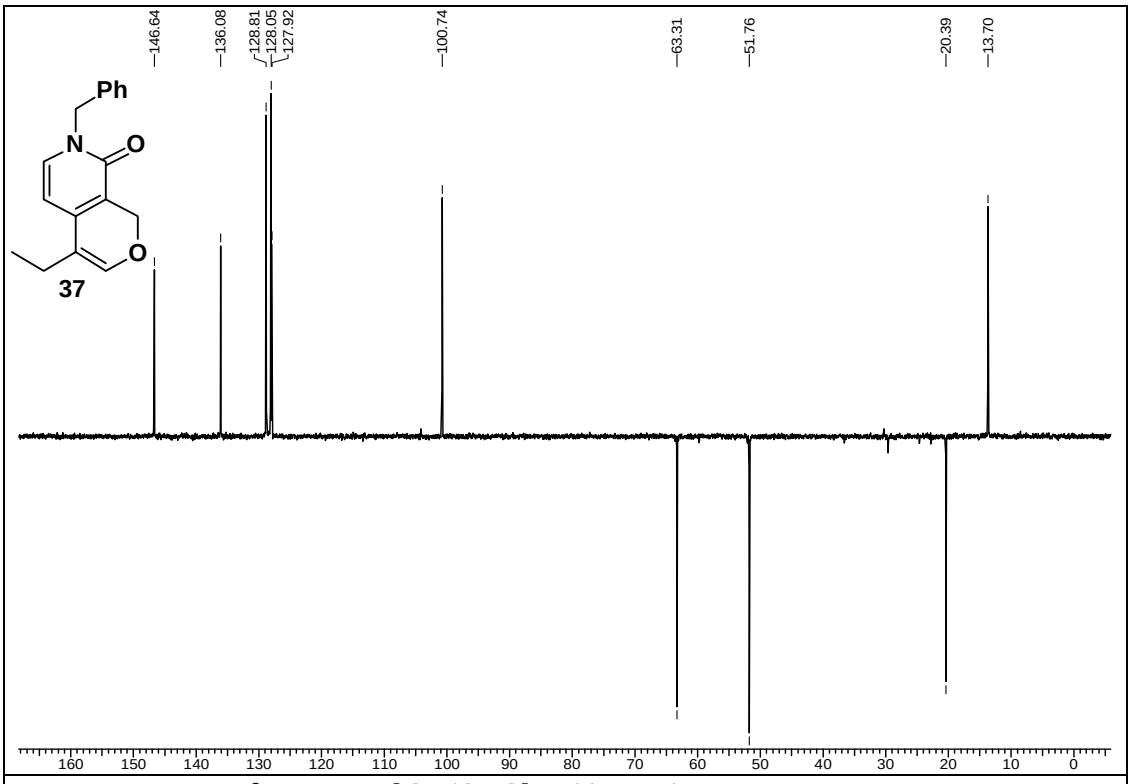
^{1}H NMR spectrum of compound 38 ($CDCl_3$, 100 MHz)



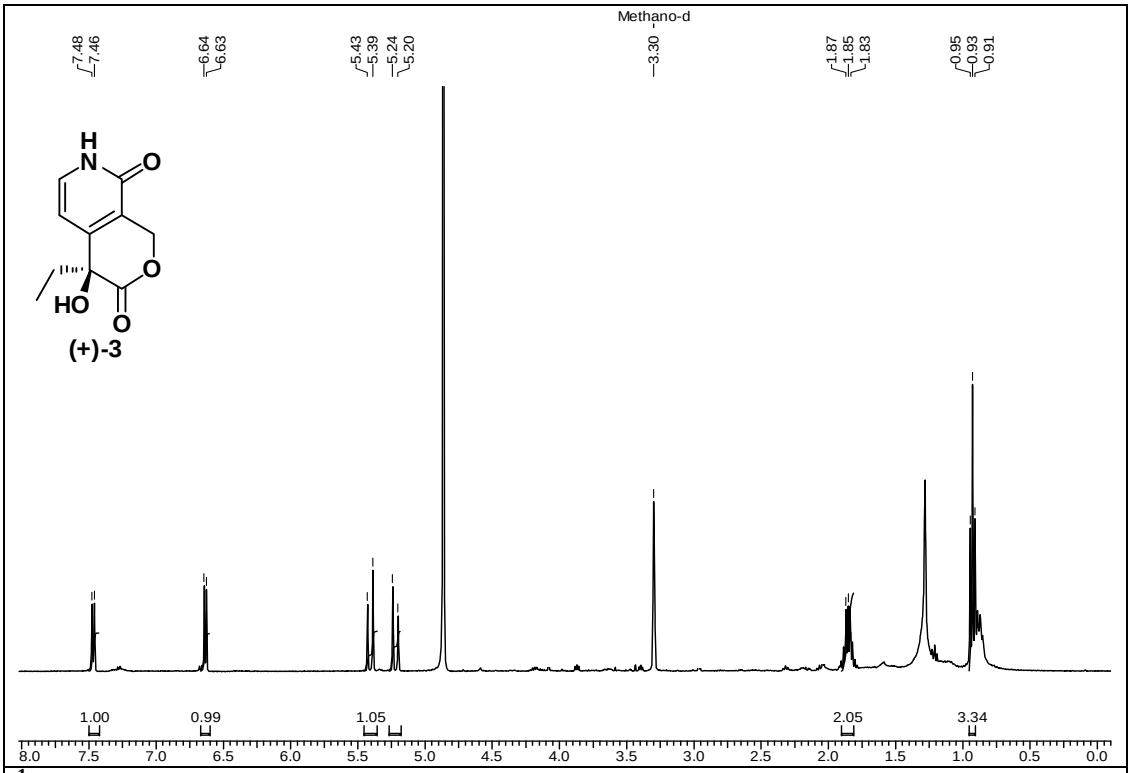
^{1}H NMR spectrum of compound 37 ($CDCl_3$, 400 MHz)



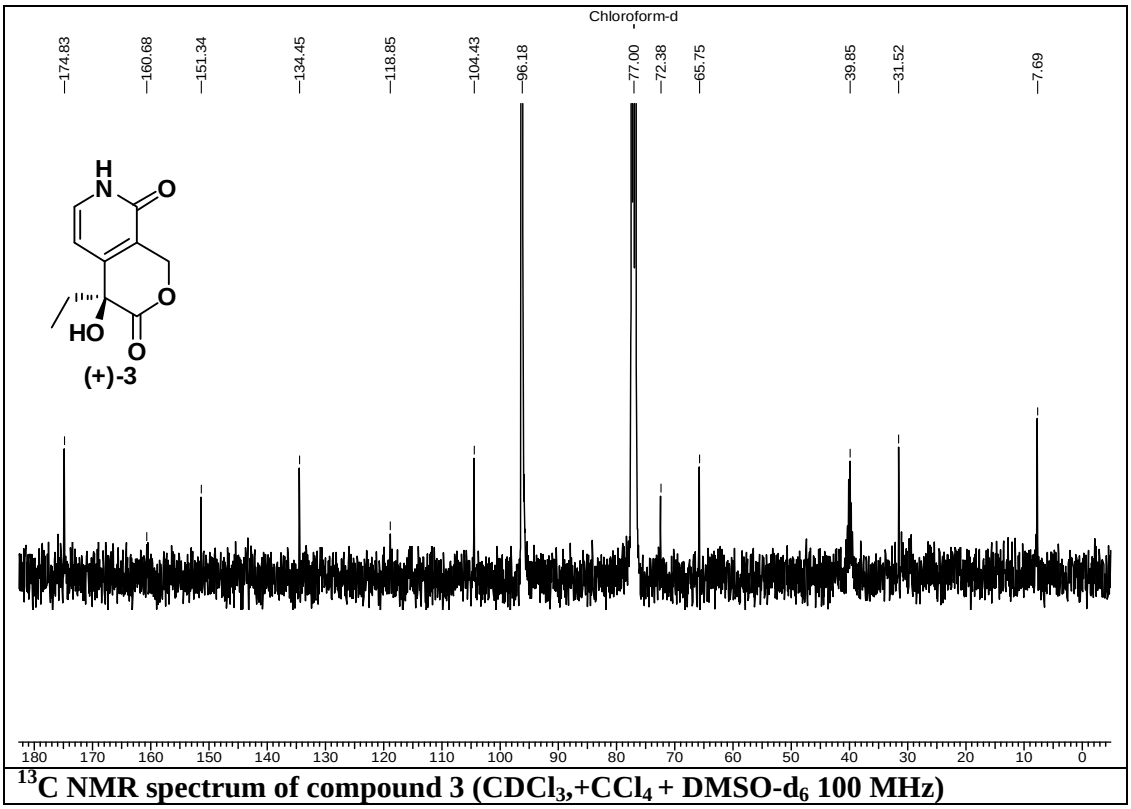
^{13}C NMR spectrum of compound 37 ($CDCl_3$, 100 MHz)



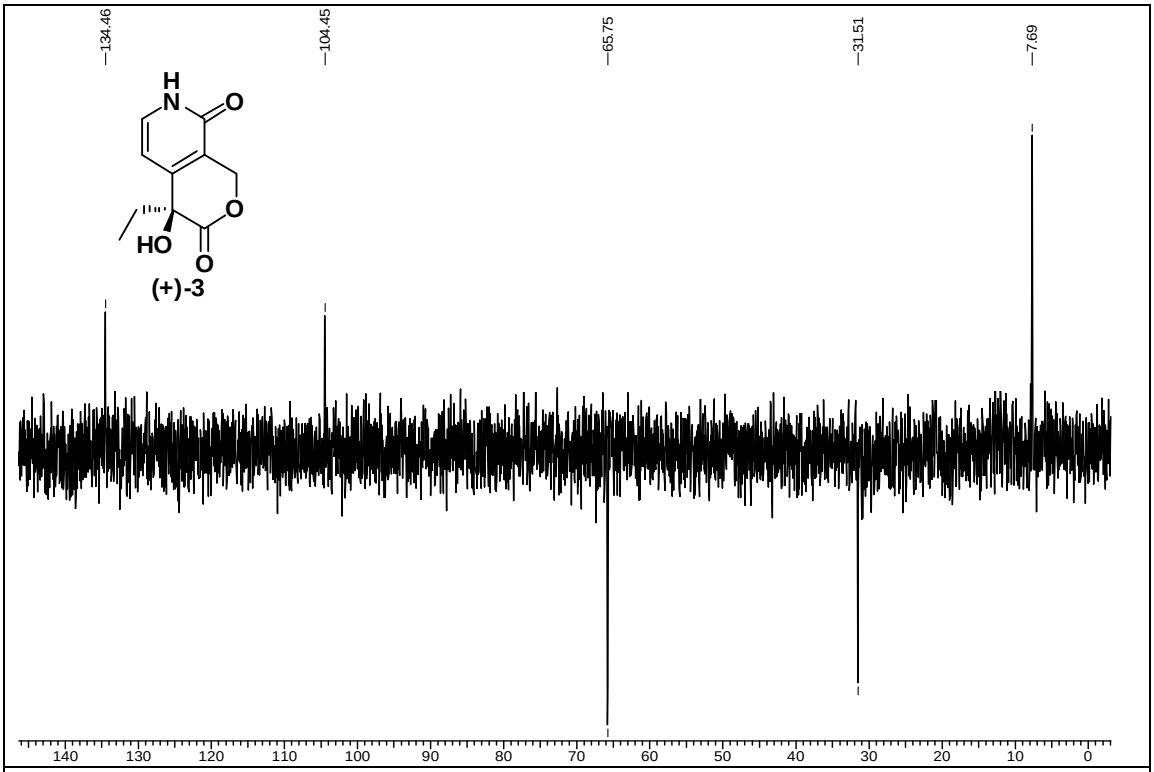
DEPT spectrum of compound 37 ($CDCl_3$, 100 MHz)



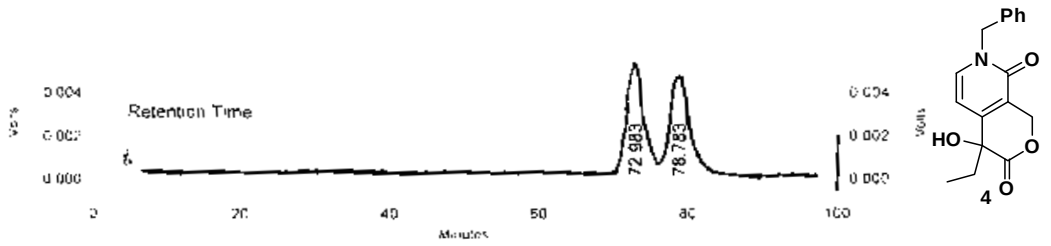
^{1}H NMR spectrum of compound 3 (CD_3OD, 400 MHz)



^{13}C NMR spectrum of compound 3 ($CDCl_3$,+CCl_4 + DMSO-d_6 100 MHz)



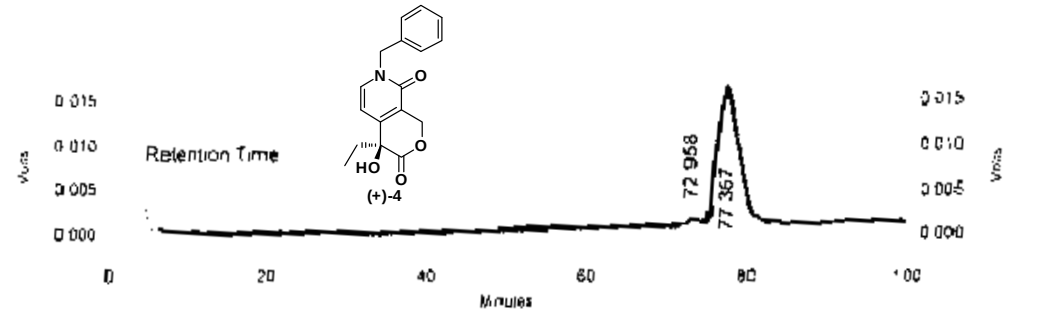
DEPT spectrum of compound 3 ($CDCl_3$,+CCl_4 + DMSO-d_6 100 MHz)



Detector A - 1
(280nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	72.983	741697	50.420	4794	53.64
2	78.783	729331	49.580	4144	46.36
Totals		1471028	100.000	8938	100.00

HPLC of (±)-4



–Detector A - 1
,280nm)

Pk #	Retention Time	Area	Area %	Heigh	Height Percent
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2	77.367	2687032	97.237	1411	96.65
Totals		2763374	100.000	1475	100.00

HPLC of (+)-4

2.1.7 References

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Chapter 2. Tandem one-pot reaction approaches towards the synthesis of camptothecin

Section 2

Formal synthesis of (+)-camptothecin

2.2.1 Summary

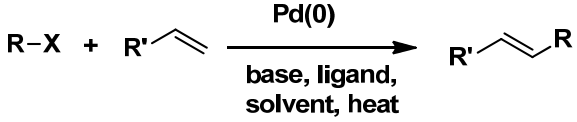
The present section deals with the formal synthesis of (+)-camptothecin **1**. A short and concise formal synthesis of **1** was achieved utilizing one-pot tandem reaction, Heck coupling for C ring formation.

2.2.2 Introduction

The palladium-catalyzed C-C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base is referred as the Heck reaction. It has received increasing attention because of its enormous synthetic potential for generating carbon–carbon bonds and its tolerance towards a wide range of functional groups.[1] Recent developments in the catalysts and reaction conditions have resulted in a much broader range of donors and acceptors being open to the Heck reaction. Unlike most catalytic organic reactions, the Heck reaction is not well defined and specific for particular reagents and catalysts with optimal conditions, solvents, ligands, *etc*. Instead, the scope of the reaction is changing, expanding, and being improved on frequently. Therefore, fine-tuning this reaction entails thousands of variations and involves learning about palladium catalysis as a whole.[2]

Heck reaction was first developed by Mizoroki[3] and Heck[4] in the early 1970's. Mizoroki and co-workers reported the reaction with aryl iodides and potassium acetate in methanol at 120 °C independently of Heck and co-workers. However, Heck and co-workers reported the reaction under more opportune laboratory conditions by reacting aryl halides with activated alkene compounds in the presence of a hindered amine base and catalytic palladium to form substituted olefins.

The Heck reaction is a general reaction in which aryl, benzyl and styryl halides react with activated olefins at high temperatures in the presence of an amine base and a catalytic amount of Pd(0) to form substituted olefins (Scheme 1).



Scheme 1

An important aspect of the Heck reaction is the generation of the active palladium species. The active palladium catalyst can be formed *in situ* from precatalysts such as $Pd(OAc)_2$ and $Pd(PPh_3)_4$. Usually the reaction is carried out with mono and bidentate ligands.[5] However, the reaction can work with or without phosphine ligands, but the

phosphine ligands stabilize the palladium in its zero oxidation state. The utilization of phosphine ligands is the common and well-established approach that gives optimal results in a majority of cases.[2]

It has also been found that the reaction rate depends on the degree of substitution of the olefinic compound. Generally, more substituted olefins undergo reaction at a slower rate than less substituted olefins. Also, the X group on the aryl or vinyl substituent has a large impact on the rate of the reaction. Typically the order of X from fastest to slowest rate is I > Br ~ OTf >> Cl. It is typically difficult in catalysis to execute a coupling reaction with an aryl or vinyl chloride and remains a challenge to have it work as well or better than other halides. The electronic nature of the substituents on the olefins has a limited influence on the reaction however, electron poor olefins tend to give higher yields.

The Heck reaction has been utilized in hundreds of works and still remains a mystery as to the exact scope of the reaction. Small variations such as substrate structure, nature of the base, ligands, temperature, *etc*. lead to mixed results. Sometimes more sophisticated ligands for more advanced organic transformations will be unsuccessful for the simplest cases of the Heck reaction.

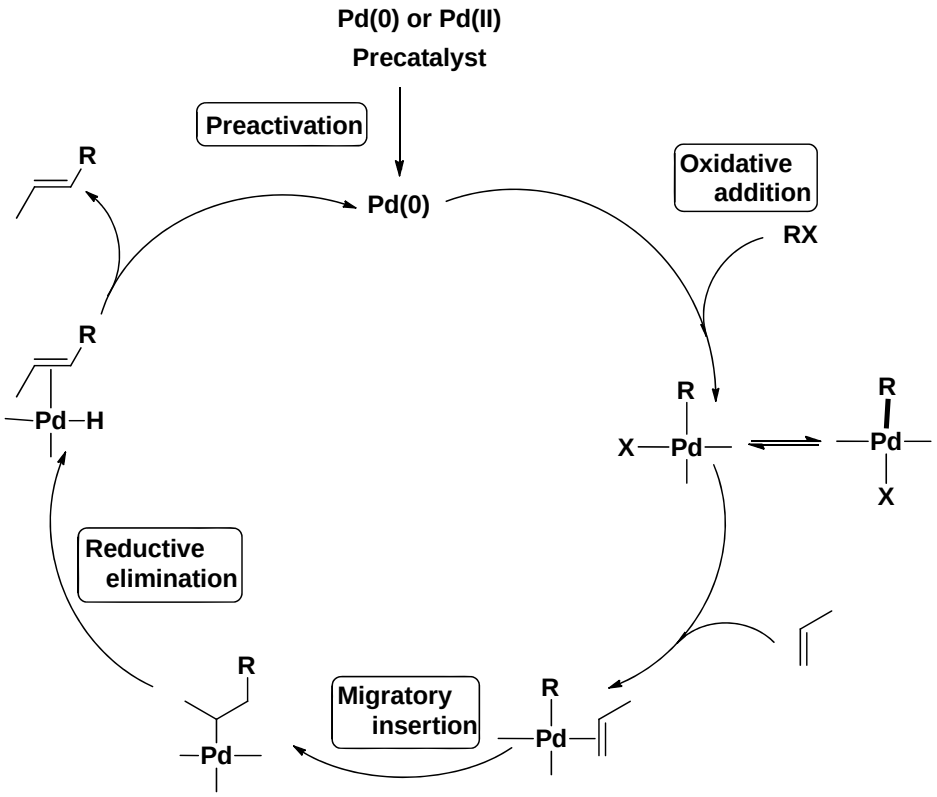
Mechanism

Heck reaction can proceed through a neutral mechanism or a cationic mechanism

1. Cationic mechanism[6,7]**:** The reaction undergoes a cationic mechanism when X is OTf, OAc, or when Ag^+, TI^+, quaternary ammonium and phosphonium salts are used to help displacement from halides. It is also a predominating pathway when chelating ligands are used for catalysis.
2. Neutral mechanism[8]**:** For the Heck reaction to undergo a neutral mechanism, X is usually a strong σ-donor such as Cl, Br or I.

Simplified scheme introducing major step of Heck cycle is shown in scheme 2. Broadly, mechanism of Heck reaction involves five steps.

1. Preactivation Step: The entry into the catalytic cycle includes the reduction of Pd(II) complexes to Pd(0) and the generation of active species through multiple ligand exchange equilibria. Usually the most common approach to obtain the active Pd(0) is to generate it *in situ* from $Pd(OAc)_2$ and PPh_3. The preactivation has been extensively studied by Amatore and Jutand[8,9] for phosphine-assisted reactions.



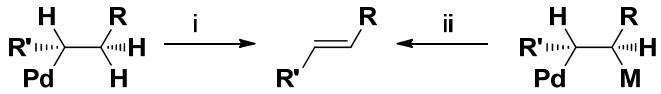
Scheme 2

2. Oxidative Addition: The oxidative addition of low-valent transition metal complex to C-X bond is usually the rate determining step and proceeds through a concerted type mechanism. The *cis*-geometry is formed first, but the *trans* geometry is preferred because phosphine ligands prefer to be opposite one another. The oxidative addition is much less sensitive to the substituents in the unsaturated system but much more sensitive to the nature of nucleofuge and the strength of C-X and M-X bonds. The order of reactivity is I > OTf > Br > Cl.[10]

3. Migratory Insertion: Migratory insertion is the product-forming step of the Heck cycle where the new C-C bond is formed. This step can explain regio- and stereoselectivity as well as substrate selectivity. For both mechanistic approaches (cationic and neutral), studies found that the reaction of the active intermediate is inhibited by excess phosphine, which establishes that a free coordination site is required for olefin coordination. Computational data has shown that by addition of a cationic carbene complex in the migratory insertion stage of the reaction, the degree of charge transfer from Pd to the olefin is negligible and there is no charge build-up in the transition state. This confirmed that the migratory insertion step takes place through a concerted process, not a SN_2 type

mechanism.[11] The stereochemistry of the product makes the Heck reaction an appealing reaction for organic synthesis. Generally, the Curtin-Hammet principle is the controlling factor for *E* and *Z* product ratio, where the *E* isomer is usually obtained unless R is very small.[2] However, steric and electronic factors play major role in controlling the outcome of the insertion process. Migratory insertion can place the aryl group on either carbon of the alkene. Electronic factors can control this placement. In the case of electron deficient alkenes and styrene derivatives, the aryl group is placed on the most electrophilic carbon β to the Ph or electron withdrawing group. With electron rich alkenes, the opposite regiochemistry is usually obtained with the aryl group α to the electron donating group, but with the aryl group still placed on the most electrophilic carbon. With neither electron rich nor electron deficient alkenes, a mixture of products can be produced with steric factors controlling the outcome.[12]

4. Termination: After the migratory insertion comes the step in which palladium (0) is released and launches the next turn of the Heck cycle. There are several possibilities briefly delineated below.



Scheme 3

a) Palladium hydride is eliminated to release the double bond (path i, Scheme 3). b) Elimination of Pd-M complex occurs with the same outcome (path ii Scheme 3). c) Palladotropic shift may occur giving a new intermediate with its own chemistry. d) PdH elimination cannot occur by stereochemical reasons or is slow. The termination occurs by nucleophilic attack at Pd, which either by nucleophilic substitution or by reductive elimination of coordinated nucleophile leads to the release of Pd(0). The product formed may be formally viewed as a *syn*-adduct of R-Nu to the starting olefin. e) As in d but the alkyl palladium intermediate goes into a subordinate catalytic process. *Cascade* of Pd catalyzed transformations is thus initiated realizing the atom economy principle.[13, 14]

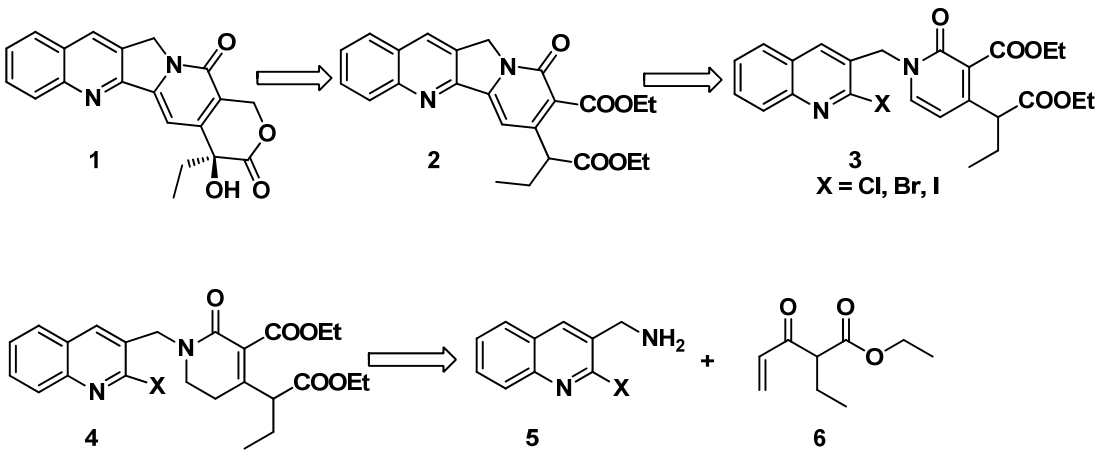
5. Palladium Hydride Elimination: Following migratory insertion, β-hydride elimination occurs. The elimination must occur through a *syn*-coplanar geometry between the Pd and the β hydrogen atom. The process is concerted and goes through a strong agostic interaction between the Pd and β–hydride. After the *syn*-elimination, the PdH is scavenged by base and Pd(0) is released back into the catalytic cycle.[11]

In conclusion, various catalytic asymmetric intramolecular Heck reactions are in progress for the synthesis of natural product. This has been done with a relatively small number of ligands, while current research is being done to find new ligands such as chiral

ones to be utilized in the asymmetric Heck reaction.[15] Due to the major problem of losing the palladium catalyst at the end of the reaction, extensive research has been done to solve this problem. Carmichael and co-workers[16] have found a number of low melting ionic liquids that the Heck reaction can be performed in. The high solubility of the Pd catalysts in ionic liquids and their low solubility in organic solvents allow the products of the reaction to be separated from the ionic liquid and catalyst by solvent extraction with an organic solvent or by fractional distillation. Due to the unpredictable, flexible character of the Heck reaction, research is continual, and advances are still being made. Its complexity and sometimes-surprising results lead many research groups try and facilitate to experiment and try to understand the reaction. However, such extensive and abundant research is done only because the Heck reaction is such a powerful carbon-carbon bond forming reaction with many uses for synthetic organic chemistry in the academic and industrial world.

2.2.3 Present work

The formal synthesis of camptothecin **1** was achieved *via* (*S*)-DE synthon employing tandem one-pot three-steps transformations involving aza-Michael reaction, condensation with ethyl malonyl chloride followed by intramolecular "Knoevenagel" reaction as described in section I of this chapter. In light of the impressive biological activity and intriguing mode of action reported for camptothecin **1**, it was decided to utilise the idea of one-pot reactions towards total synthesis of camptothecin **1**.

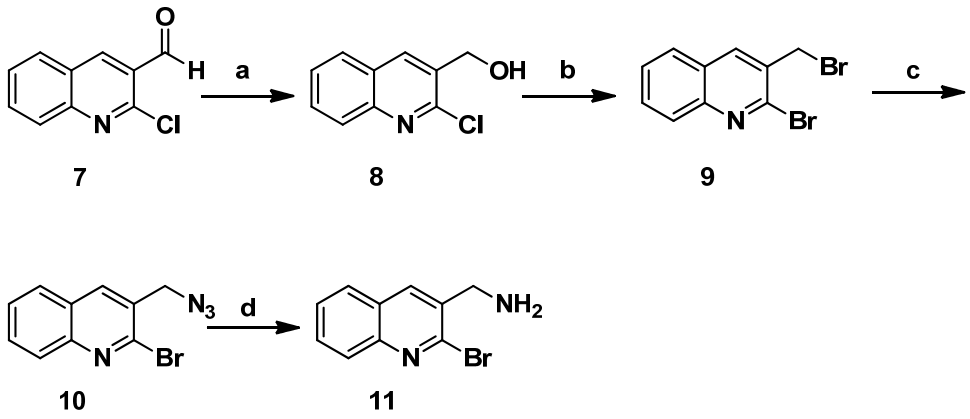


Scheme 4

As per retrosynthetic plan depicted in scheme 4, the (+)-camptothecin **1** could be synthesized from diester **2** by selective reduction followed by lactonization and enantioselective hydroxylation. The diester **2** could be accessed from diester **3** by intramolecular Heck coupling and it was envisioned as the key intermediate. The key intermediate **3** could be accessed by aromatization of **4**, which in turn can be synthesized by Michael addition, condensation and Knoevenagel cyclisation sequence of quinoline amine **5** on *α,β*-unsaturated ketone **6**.

2.2.4 Results and Discussion

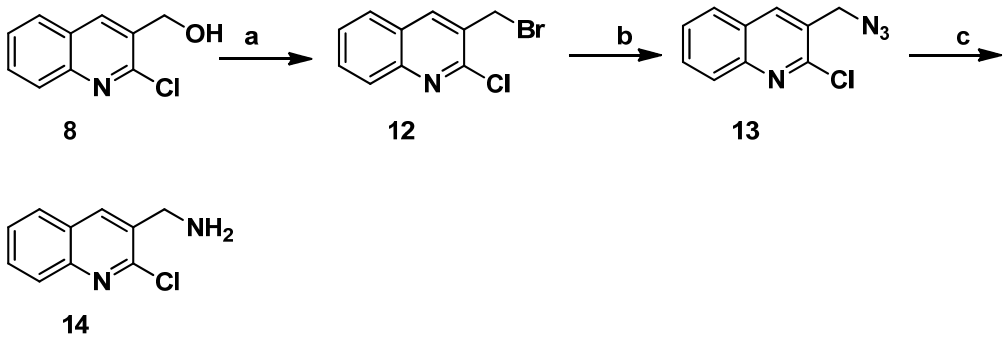
According to planned retrosynthetic analysis, the journey began with the synthesis of quinoline amine **5**. Meth-Cohn's[17] quinoline aldehyde **7** with a formyl group at 3-position and the halide at 2-position for the functionalization *i.e.* C-C bond formation, given the flexibility and simplicity for the analogues preparation, appeals to be ideal starting material to do away with the shortcomings of the earlier approaches such as usage of 2-aminobenzaldehyde, regiochemistry problems encountered in Friedlander condensation and the usage of expensive starting materials like acridine, propargyl amine and DMAD.



Scheme 5: ***Reagents and conditions****: a) $NaBH_4$, MeOH, °C, 1 h, 90%; b) PBr_3, reflux, 4 h, 72%; c) NaN_3, DMF, rt, 17 h, 85%; d) PtO_2, EtOH, H_2, rt, 2 h, 94%.*

Chloroquinoline aldehyde **7** was realized by Vilsmeier-Haack reaction on acetanilide using dimethylformamide and phosphorous oxychloride. The aldehyde **7** was converted to required quinoline amine **11** (Scheme 5) by following literature procedure.[18] Aldehyde **7** on treatment with $NaBH_4$ in methanol afforded alcohol **8.** The alcohol **8** was

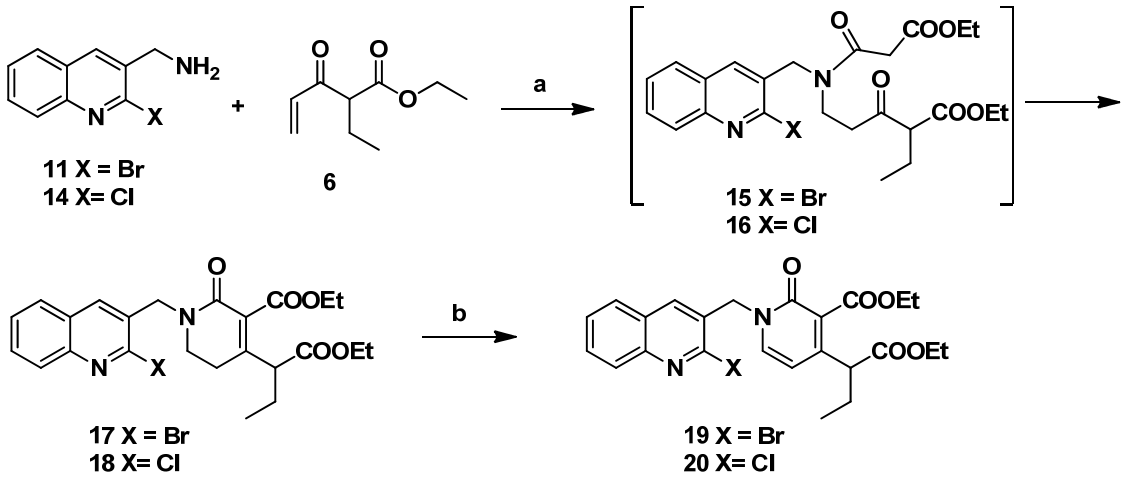
refluxed with PBr_3 to afford di-bromo compound **9** in good yield. The bromo compound **9** was subjected to treatment with NaN_3 in DMF at room temperature to furnish the azide **10**. The absorbance band at 2103 cm^{-1} in the IR spectrum of **10** showed the incorporation of azide moiety, which subsequently on reduction using PtO_2 under hydrogen atmosphere in ethanol afforded required bromo quinoline amine **11**. Amine **11** was characterized by using spectral methods and the data were in complete agreement with reported values.[18]



Scheme 6: ***Reagents and conditions****: a) PBr_3 (1 equiv.), DCM, reflux, 4 h, 72%; b) NaN_3, DMF, rt, 17 h, 85%; c) PtO_2, EtOH, H_2, rt, 2 h, 94%.*

Since the retrosynthetic analysis involved Heck cyclization as one of the key transformations, to check the reactivity of substituted chloroquinoline, it was planned to synthesise chloroquinoline **14**. Chloroquinoline amine **14** was prepared from alcohol **8**, wherein the alcohol **8** on treatment with 1 equivalent of PBr_3 in DCM afforded the bromide **12**. It was subjected to treatment with NaN_3 in DMF at room temperature to furnish the azide **13**, which subsequently on reduction using PtO_2 under hydrogen atmosphere in ethanol afforded required chloroquinoline amine **14** (Scheme 6). The spectral data of the amine **14** were in complete agreement with reported values.[18]

With the synthesis of quinoline amines **11** and **14** completed, which will act as Michael donor in tandem reactions, the Michael acceptor *α, β*-unsaturated ketone **6** was synthesized form acrolein (described in section I of this chapter) and the stage was set to perform one-pot tandem aza-Michael reaction, condensation with ethyl malonyl chloride followed by intramolecular "Knoevenagel" cyclization.



Scheme 7: ***Reagents and conditions****: a) K_2CO_3 (4 equiv.), ethyl malonyl chloride, DCM, 0 °C-rt, 8 h, 65%; b) DDQ, 1,4-dioxane, reflux, 24 h, 95%.*

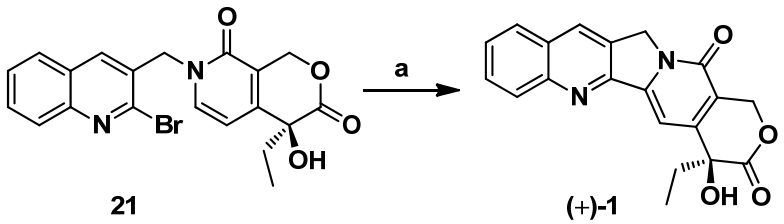
Thus, the α,β-unsaturated ketone **6** was subjected to one-pot Michael addition, condensation and Knoevenagel cyclization wherein it was treated with quinoline amine **11** at room temperature, and after 30 minutes, addition of 4 eq. of K_2CO_3 followed by the addition of ethyl malonyl chloride at 0 °C and stirring at room temperature for 8 h afforded dihydropyridone **17** in 65 % yield *via* the intermediate **15**. Formation of dihydropyridone **17** was confirmed by using spectroscopic methods. IR spectrum showed presence of carbonyl functionalities by revealing absorptions at 1734 and 1680 cm^{-1} for ester and amide carbonyls respectively. ^{1}H NMR spectrum of **17** showed two triplets at δ 0.92 (J = 7.4 Hz) and 0.97 (J = 7.2 Hz) together integrating for three protons and a multiplet at δ 1.76-1.99 integrating for two protons attributed to ethyl group protons which originated from Michael acceptor. The multiplets that appeared at δ 2.34-2.58 and 3.65-3.78 integrating for two protons each were assigned to methylene protons in the dihydropyridone ring. The rest of the protons resonated at expected positions. The mass spectrum of compound **17** showed the m/z peaks at 504: 506 (1:1) $(M + H)^+$ and 526:528 (1:1) $(M + Na)^+$ confirming the structure of **17**.

Same reactions under similar conditions were performed on amine **14** which resulted in the similar outcome affording **18** in comparable yield.

Having synthesized the required dihydropyridones **17** and **18** in a short sequence, they were subjected to aromatization using DDQ as oxidant in 1, 4-dioxane to furnish excellent yields of pyridones **19** and **20** respectively. ^{1}H NMR spectrum of **19** showed appearance of

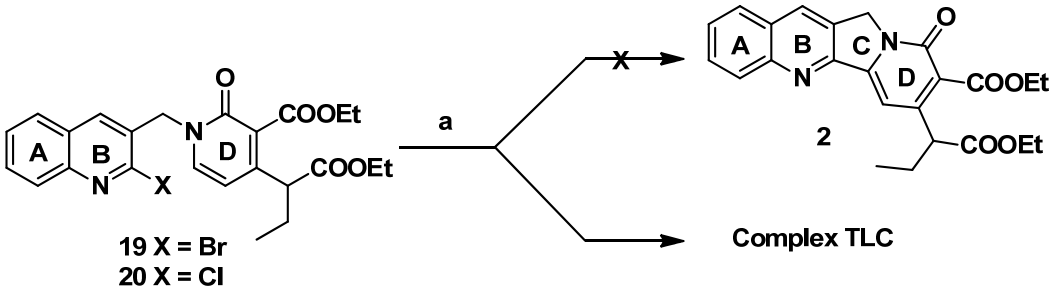
two new doublets at δ 6.37 (d, *J* = 7.2 Hz, 1H) and 7.61 (d, *J* = 7.2 Hz, 1H) which were attributed to pyridone ring protons adjacent to each other thereby confirming oxidation. The triplet at δ 3.50 integrating for one proton was assigned to proton α to ethyl ester ($CH_3CH_2\underline{CH}COOEt$). Three signals appeared as triplet at δ 0.92, 1.24 and 1.39 integrating for three protons each, two quartets at δ 4.14 and 4.41 integrating for two protons each and two multiplets at δ 1.69-1.83 and 1.96-2.06 for diastereotopic protons adjacent to chiral center which were attributed to three ethyl group protons. Mass spectrum of **19** showed the *m/z* peaks at 524 and 526 (1:1) $(M + Na)^+$ confirmed the structure of pyridone **19**. The pyridone **20** was prepared from dihydropyridone **18** in a similar way.

Having synthesized the required pyridones **19** and **20** in a short sequence, stage was set to form C-C bond to obtain C ring so that it can be further elaborated to the target molecule. To construct C ring it was decided to exploit the Heck cyclization. Comins[19] utilized Heck coupling for the total synthesis of camptothecin **1** (Scheme 8).



Scheme 8: ***Reagents and conditions****: a) $Pd(OAc)_2$, TBAB, KOAc, DMF, 86%.*

Therefore it was planned to apply same conditions for synthesis of ABCD ring. Thus, pyridone **19** was subjected to Heck coupling using $Pd(OAc)_2$, TBAB and KOAc in DMF at reflux condition but it led to complex TLC pattern (Scheme 9). The pyridone **20** also failed to give the desired product under these conditions.



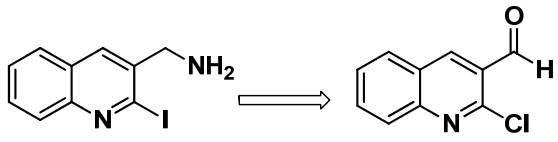
Scheme 9: ***Reagents and conditions****: a) $Pd(OAc)_2$, TBAB, KOAc, DMF, 100-120 ^oC.*

Hence, efforts were directed to get ABCD skeleton **2** by performing the reactions under different conditions for Heck cyclization (Table 1). However, most of the different reaction conditions tried (entry 1-5, Table 1) ended up with complex TLC patterns, while use of $Pd(OAc)_2$, Na_2CO_3 as base and PPh_3 in DMF gave required product **2** but the yield of the product was very discouraging. Hence, efforts were directed to improve the yield of the transformation (entry 6 and 7) but the results were not much encouraging.

Table 1.

Sr. No.	Catalyst	Base	Solvent	PTC	Temp ^oC	Observation
1	$Pd(OAc)_2$	KOAc	DMF	TBAB/TBAI	90-110	Complex TLC
2	$Pd(OAc)_2$	KOAc	CH_3CN	TBAB/TBAI	reflux	Complex TLC
3	$Pd(OAc)_2$	K_2CO_3	DMF	TBAB	90-120	Complex TLC
4	$Pd(OAc)_2$	K_2CO_3	CH_3CN	TBAB	RT-reflux	Complex TLC
5	$Pd(OAc)_2$	Et_3N	DMF/CH_3CN	TBAB	90-120	Complex TLC
6	$Pd(OAc)_2$	Na_2CO_3	DMF	PPh_3	80	>10% yield
7	$Pd(OAc)_2$	Na_2CO_3	DME	PPh_3	reflux	>12% yield

Since the bromo and chloro compounds did not react well under the conditions tried to effect Heck coupling, it was decided to perform the Heck reaction on iodo compound based on the propensity of the iodides to undergo facile Heck reactions. Thus, to synthesize of iodo amine **22,** again Meth-Cohn's[17] quinoline aldehyde **14** was preferred as the starting material (Scheme 10).

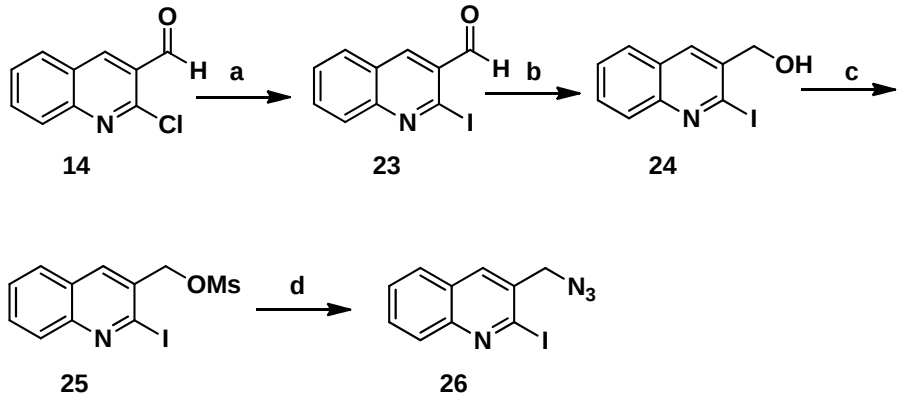


22 **14**

Scheme 10

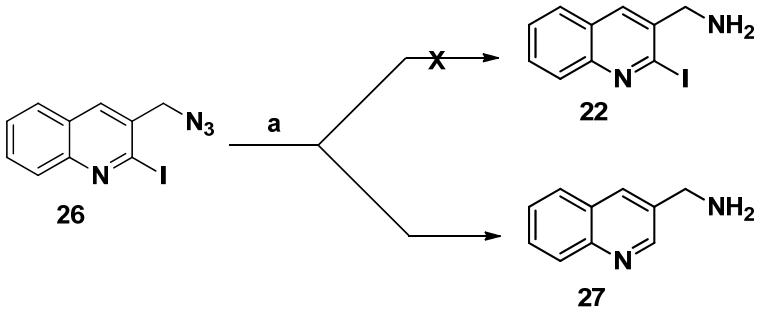
Thus, chloro aldehyde **14** was converted into iodo azide **26** by following literature[20] procedure. Chlorine atom was replaced by iodine using NaI in acetonitrile to afford iodo aldehyde **23**. The aldehyde **23** on treatment with $NaBH_4$ in methanol afforded alcohol **24.**

Alcohol **24** on *O*-mesylation using Et_3N, MsCl afforded **25**, which on treatment with NaN_3 in DMF at room temperature furnished the corresponding azide **26** in 95% yield (Scheme 11). Spectral data for azide were in complete agreement with those reported in literature.[20]



Scheme 11: ***Reagents and conditions****: a) NaI, Cat. HCl, acetonitrile, reflux, 5 h, 95%; b) $NaBH_4$, methanol, 30 min, 85%; c) Et_3N, MsCl, DCM, 0 °C, 20 min, quanti.; d) NaN_3, DMF, rt, 1 h, 95%.*

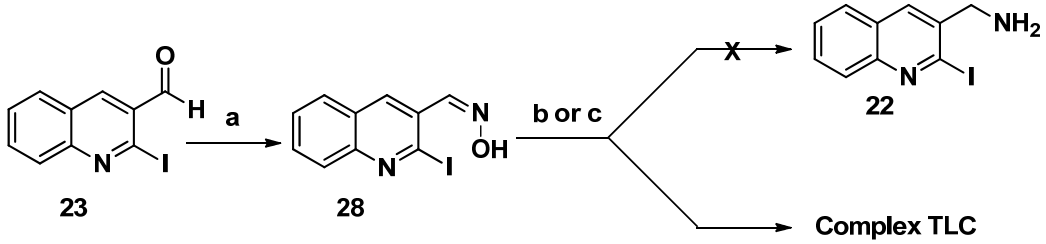
Having azide **26** in hand, next task was the reduction of azide to amine **22**. Same reaction conditions were applied for this transformation as in chloro azide **13** and bromo azide **10** but unfortunately hydrogenation over PtO_2, did not yield the desired amine **22**, instead dehalogenated amine **27** was observed (Scheme 12)**.**



Scheme 12: ***Reagents and conditions****: a) PtO_2, H_2, rt, 1 h, 94%.*

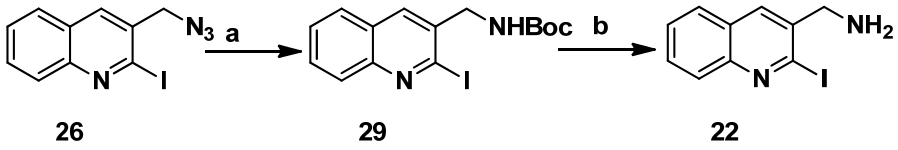
Failure of this reduction made it mandatory to shift to an alternative synthetic strategy. It was thought to synthesise amine **22** in short sequence. Accordingly aldehyde **23** was treated with hydroxyl amine hydrochloride and sodium acetate in ethanol to give corresponding oxime **28** which was subsequently exposed to reduction using Pd/C in methanol but unfortunately it ended up in a complex reaction mixture. Also reduction of

oxime was carried out using LAH in THF but unfortunately under this condition also the reaction ended up in complex reaction mixture (Scheme 13).



Scheme 13: ***Reagents and conditions****: a) Hydroxylamine hydrochloride, NaOAc, ethanol, rt, 90%; b) Pd/C, H_2, ethanol; c) LAH, THF, 0 °C-rt.*

In spite of failing to synthesise amine **22** in short sequence, it was decided to go ahead with the original plan *i. e.* reduction of azide **26** to amine **22**. Thus azide **26** was subjected to reduction using Schrödinger's protocol using TPP in THF:H_2O (8:2) as solvent system at room temperature to afford amine **22**, but R_f values of amine and side product TPP oxide were same so it was very difficult to purify the product, and hence the amine was protected as its Boc derivative for purification using Boc anhydride, triethyl amine in DCM to furnish compound **29** (Scheme 14**).** IR spectrum of the product **29** indicated the presence of a carbamate by revealing absorption at 1708 cm^{-1}.

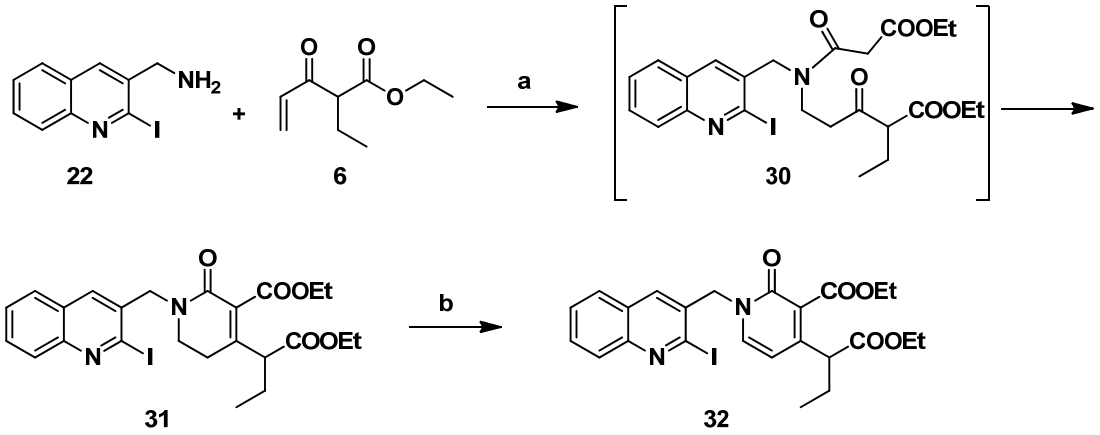


Scheme 14: ***Reagents and conditions****: a) i) TPP, THF:H_2O (8:2), rt; ii) Boc-anhydride, Et_3N, DCM, 1 h, 85%, (over two steps); b) TFA, DCM, 0 °C-rt, 1 h, 90%.*

The ^{1}H NMR spectrum of **29** showed signal corresponding to Boc group at δ 1.46 as a singlet integrating for nine protons. The doublet at δ 4.44 integrating for two protons was attributed to benzylic protons (Ar$\underline{CH_2}$NH-). The broad singlet at δ 5.28 integrating for one proton was assigned to amide proton. ^{13}C NMR along with DEPT spectra of **29** showed signals at δ 28.3, 79.9 and 155.6 which were assigned to Boc group carbons. Signal at δ 47.7 corresponded to benzylic (Ar$\underline{CH_2}$NH-) carbon. The rest of the proton and carbon signals were present at expected positions. Lastly mass spectrum of **29** showed the

peaks at *m/z* 385 and 407 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively and elemental analysis data were in good agreement with the proposed structure. Finally Boc deprotection was carried out using TFA in DCM to afford required iodo amine **22** in excellent yield (Scheme 14). Absence of peak corresponding to carbonyl group in the IR spectrum and presence of absorption at 3345 cm^{-1} confirmed the deprotection. ^1H NMR spectrum of **22** displayed the absence of peaks corresponding to Boc group. The signal that appeared at δ 3.96 as a singlet integrating for two protons was assigned to benzylic protons while the signal that appeared at δ 7.98 (s, 1H) was assigned to quinoline proton at C-4 position. The remaining aromatic protons showed two doublets at δ 7.75 and 8.00 integrating for one proton each having coupling constant 8.5 Hz and two triplets at δ 7.53 and 7.65 integrating for one proton each having coupling constant 8.0 Hz. Structure of **22** was further confirmed by its ^{13}C NMR and DEPT spectra, which showed only one methylene ($-CH_2-$) and five methine (-CH-) carbons. Finally, mass spectrum confirmed the formation of **22** by exhibiting a peak at 285 $(M + 1)^+$ and in case of elemental analysis the experimental values were in good agreement with the theoretical values.

Having required amine **22** in hand, next goal was to perform tandem one-pot reaction employing same reaction conditions described earlier for bromo and chloro amines **11** and **14.** Thus the *α,β*-unsaturated ketone **6** was subjected to one-pot Michael addition, with quinoline amine **22** in DCM at room temperature and after 30 minutes 4 equiv. K_2CO_3 followed by the ethyl malonyl chloride were added at 0 ^oC and the reaction mixture was stirred at room temperature for 8 h to afford dihydropyridone **31** in 65 % yield *via* the intermediate **30** (Scheme 15).



Scheme 15: ***Reagents and conditions****: a) K_2CO_3, DCM, ethyl malonyl chloride, 0 ^oC-rt, 8 h, 65%.; b) DDQ, 1, 4-dioxane, reflux, 24 h, 91%.*

In support of the confirmation of formation of intermediate **30**, it was isolated and characterized using spectroscopic techniques. IR spectrum of **30** showed absorptions at 1735, 1710 and 1681 cm^{-1} which indicated the presence of three different types of carbonyls. ^{1}H NMR spectrum of **30** showed the signals that appeared at δ 0.88 and 0.93 (2t, *J* = 7.2, 3H) (due to rotamers $\underline{CH_3}CH_2CH$-) and δ 1.21-1.34 (m, 6H) (–$COOCH_2\underline{CH_3})_2$ were attributed to methyl protons. The two singlets that appeared at δ 3.39 and 3.78 integrating for two protons due to mixture of rotamers were attributed to methylene (-$CO\underline{CH_2}CO$-) group protons thus confirming the condensation with malonyl chloride. The characteristic aromatic proton signals appeared at δ 7.56 and 7.61 (2t, *J* =7.5, 1H), 7.67-7.76 (m, 1H), 7.80-7.84 (m, 1H) and 7.98-8.21 (m, 2H) thereby confirming Michael addition. ^{13}C NMR along with DEPT spectra of **30** revealed it to be a mixture of rotamers showing doubling of peaks *viz.* at δ 166.9, 167.0, 167.2, 168.0, 169.3, 169.5, 203.1 and 204.2 which were assigned to four carbonyl carbons, while rest of proton and carbon peaks resonated at expected positions and finally the structure of **30** was confirmed by its mass spectra and elemental analysis. The *m/z* peaks at 569 and 591 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively were observed in mass spectrum and in elemental analysis the experimental values were in good agreement with the theoretical values.

Formation of **31** was deduced by spectroscopic methods. IR spectrum showed no peak corresponding to the ketone carbonyl while ester and amide carbonyls showed peaks at expected positions at 1734 cm^{-1} and 1657 cm^{-1} respectively thereby confirming intramolecular Knoevenagel cyclization. ^{1}H NMR spectrum of **31** revealed following characteristic resonances: Two triplets appeared at δ 1.31 and 1.37 integrating for three protons each and those were assigned to the protons of two ester methyls. Two triplets at δ 0.93 and 0.98 integrating for three protons due to conformers were assigned to ($\underline{CH_3}CH_2CH$-) protons. Multiplets at δ 2.32-2.56 and 3.65-3.73 integrating for two protons each were assigned to ring methylene protons. Two quartets at δ 4.22 and 4.36 integrating for two protons each were assigned to ester methylene protons. Benzylic protons appeared as multiplets at δ 4.51-5.01 integrating for two protons while quinoline protons resonated in aromatic region at expected positions. Structure of **31** was further supported by its mass spectrum and elemental analysis, the *m/z* peak at 573 corresponding to $(M + Na)^+$ was observed in mass spectrum and in elemental analysis the experimental values were in good agreement with the theoretical values.

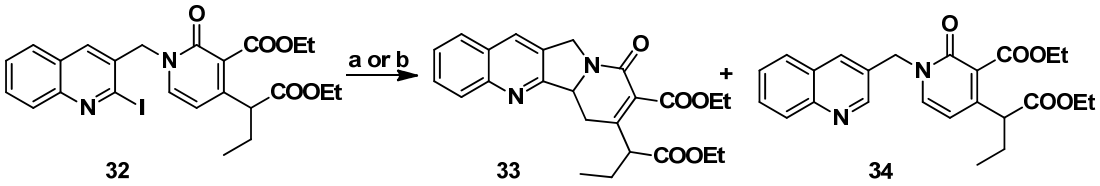
Having synthesized the required pyridone **31** having iodine by a short sequence, it was subjected to aromatization using DDQ as oxidant in refluxing 1,4-dioxane as solvent for 24 h, to afford pyridone **32** in 91% yield (Scheme 15). The structure of pyridone **32** was confirmed by spectral analysis. IR spectrum showed absorptions at 1735 and 1665 cm^{-1} signifying the presence of ester and amide carbonyl functionalities respectively. ^{1}H NMR spectrum of **32** showed appearance of two new signals at δ 6.39 (d, *J* = 7.3 Hz, 1H) and 7.62 (d, *J* = 7.3 Hz, 1H) which were assigned to vicinal pyridone ring protons thereby confirming oxidation. The triplet which appeared at δ 3.51 integrating for one proton was assigned to proton α to ethyl ester ($CH_3CH_2\underline{CH}COOEt$). Three signals appeared as triplets at δ 0.93, 1.25 and 1.39 was integrating for three protons each, two quartets at δ 4.13 and 4.42 integrating for two protons each and two multiplets at δ 1.69-1.84 and 1.97-2.11 integrating for one proton each for diastereotopic protons adjacent to chiral center were attributed to three ethyl group protons. The singlet at δ 5.34 integrating for two protons was assigned to the benzylic protons adjacent to the quinoline ring. ^{13}C NMR spectrum of **32** displayed 24 peaks corresponding to 24 carbons. DEPT spectrum showed presence of three methyl and four methylene carbons. Finally the mass spectrum of **32** showed the *m/z* peaks at 549 $(M + H)^+$ and 571 $(M + Na)^+$ and elemental analysis results were also found to be in good agreement with the calculated values.

Having the iodo pyridone **32** in hand, stage was set to form C ring of camptothecin **1**. Yet again it was decided to perform the intramolecular Heck reaction for the cyclization. Pyridone **32** was subjected to Heck coupling employing different conditions as on pyridones **19** and **20** (Table 1) but frustratingly results were same as shown in Table 1.

Having failed in Heck cyclization, it was decided to go for alternative reaction for c-c bond formation. Comins[21] employed radical cyclization for C ring formation of camptothecin **1**. Similarly, pyridone **32** was subjected to radical cyclization using *tri*-butyltin hydride, with AIBN as radical initiator in benzene or toluene at room temperature to reflux conditions to afford the expected compound **33** in 10% yield along with dehalogenated compound **34** in >10% yield (Scheme 16).

Though the desired cyclization was achieved, the yield and selectivity was extremely unacceptable. To improve yield of reaction, a variety of conditions were tried by changing addition sequence, rate of addition and addition temperature. Unfortunately

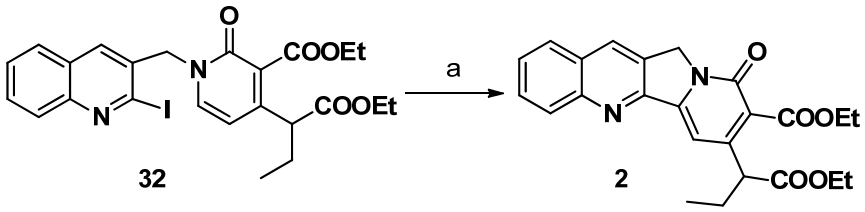
none of the trials gave satisfactory results. In all cases, either reaction ended up with complex reaction mixture or very low yield of required compound **33**.



Scheme 16: ***Reagents and conditions****: a) Bu_3SnH, AIBN, benzene, rt to reflux; b) Bu_3SnH, AIBN, toluene, rt to reflux.*

In spite of failing to improve yield of radical cyclization on pyridone **32**, it was decided to go for original plan *i. e.* Heck cyclization. Accordingly it was decided to change solvent from conventional to ionic liquid.[22] A literature search revealed the application of poly(ethylene glycol) (PEG) having molecular weight 2000 as an efficient reaction medium for Pd-catalyzed Heck reaction.[23] Instead of going for ionic liquid, it was decided to apply these conditions (PEG) for Heck coupling on pyridone **32**.

Gratifyingly, pyridone **32** was subjected to Heck coupling using PEG 2000 as solvent, triethylamine and $Pd(OAc)_2$ at 90 ^oC to afford the pyridone **2** in 84% yield (Scheme 17).

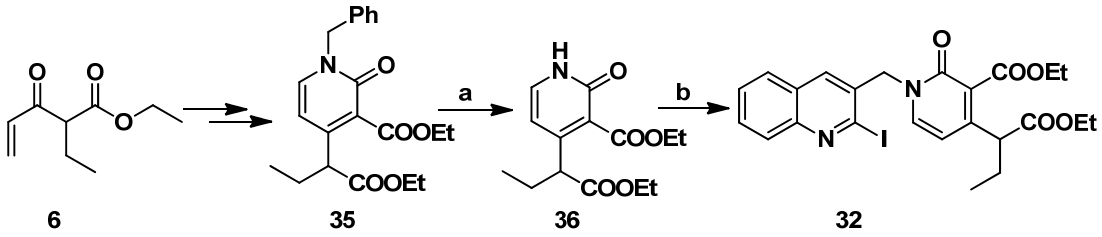


Scheme 17: ***Reagents and conditions****: a) PEG-2000, Et_3N, $Pd(OAc)_2$, 90 ^oC, 10 h, 84%.*

The formation of compound **2** was confirmed by spectral data. IR spectrum of **2** showed strong absorption bands at 1735, 1727 and 1649 cm^{-1} indicating the presence of aliphatic ester, aromatic ester and amide functionality respectively. ^1H NMR showed singlet at δ 7.50 integrating for one proton and was assigned to pyridone proton thereby confirming coupling to have taken place. The triplet at δ 3.73 integrating for one proton was assigned to proton α to ethyl ester. The three triplets at δ 0.99, 1.26 and 1.43 were assigned to three methyl protons. Two quartets at δ 4.19 and 4.47 integrating two protons each were assigned to ester methylene protons. The singlet at δ 5.25 integrating for two

protons was assigned to the benzylic protons adjacent to the quinoline ring, while rest of the protons resonated at expected positions. ^{13}C NMR revealed 24 carbon signals corresponding to the proposed structure. The compound **2** is a common key intermediate in our previous approaches for camptothecin **1**.[24,25] All the data of **2** were in complete agreement with reported data.

Alternatively diester compound **32** could be obtained from compound **35**, which was synthesized from α,β-unsaturated compound **6** (described in section I of this chapter). Accordingly, the compound **35** was subjected to *N*-debenzylation using $Pd(OH)_2$ at 50 ^oC in ethanol under hydrogen atmosphere to afford the amine **36** in 96% yield (Scheme 18).



Scheme 18: ***Reagents and conditions****: a) $Pd(OH)_2$, EtOH, 50 ^oC, 5 h, 96%. b) t-BuO^-K^+,* ***25****, DME, reflux, 8 h****,*** *86%.*

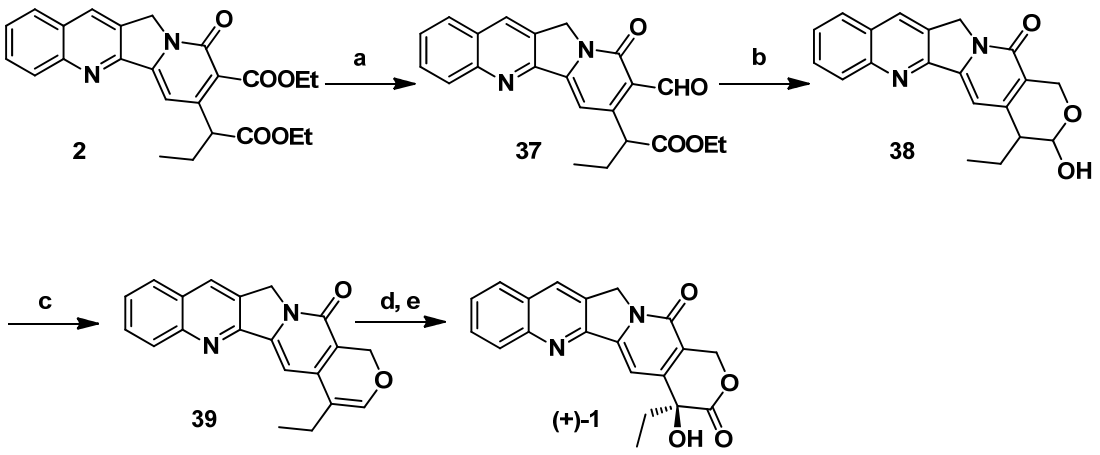
Formation of pyridone **36** was confirmed by spectroscopic techniques. ^1H and ^{13}C NMR spectra showed absence of aromatic protons and carbon resonances corresponding to benzyl group, while all other proton and carbon peaks resonated at expected positions in respective spectra in accordance with the proposed structure **36**. Finally the mass spectrum of **36** showed the *m/z* peaks at 282 $(M + 1)^+$ and 304 $(M + Na)^+$ and elemental analysis was also found to be in good agreement with the calculated values.

Having pyridone **36** in hand, it was subjected to condensation with mesyl compound **25** using potassium tertiary butoxide as the base in DME as solvent at reflux temperature to afford required pyridone **32** in 86% yield. The pyridone **32** thus obtained was identical to the one obtained earlier (Scheme 15) in all respects.

Since the pyridone **2** has been converted to (+) camptothecin by this group[25,26] *via* lactol **38** and enol ether **39** and enantioselectivity was achieved using Sharpless dihydroxylation (Scheme 19). This constitutes a formal synthesis of (+)-camptothecin **1**.

Thus, the enol ether **39** was treated with catalytic amount of OsO_4 and $(DHQD)_2$-PYR, 3 equivalent $K_3Fe(CN)_6$ as a re-oxidant, 3 equivalent K_2CO_3, 1 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 hours by this group.[26] However, the yield was 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]



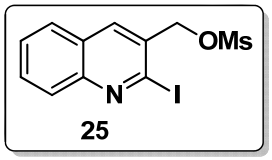
Scheme 19: ***Reagents and conditions****: a) DIBAL-H (3.0 equiv), dry THF, -60 ^oC, 2 h, 83%; b) $NaBH_4$, THF-H_2O (9:1), 0 ^oC, 0.5 h, 90%; c) MsCl, Et_3N, anhydrous THF, rt, 24 h, 92%; d) $(DHQD)_2$-PYR (cat.), OsO_4 (cat.), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $CH_3SO_2NH_2$ (1.0 equiv), t-BuOH-H_2O (1:1), 0 ^oC; e) I_2 (12.5 equiv), $CaCO_3$ (12.5 equiv), CH_3OH-H_2O (10:1), rt, 24 h.*

2.2.5 Conclusion

Enantioselective formal synthesis of (+)-camptothecin was achieved employing one-pot tandem aza-Michael addition-condensation with ethyl malonyl chloride and intramolecular "Knoevenagel" reaction and Heck cyclization as the key step. Another important feature of this synthesis is the installation of the chiral center in an enantioselective manner employing Sharpless dihydroxylation as the key step at the end.

2.2.6 Experimental

(2-Iodoquinolin-3-yl) methyl methanesulfonate (25)



25

To a solution of (2-iodoquinolin-3-yl) methanol **24** (10 g, 35.20 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added triethylamine (9.7 mL, 70.4 mmol) and after five minutes of stirring mesyl chloride (4.0 mL, 52.82 mmol) was added dropwise and the temperature was raised to room temperature. After 20 minutes, the mixture was quenched with saturated solution of ammonium chloride and extracted twice with dichloromethane. The combined organic layers were washed with 10% $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the product **25** in quantitative yield (12.7 g) as a yellow solid.

Mol. Formula **:** $C_{11}H_{10}INO_3S$ (MW: 363.17).

Melting Point **:** 111-113 ^oC.

IR (Neat) **:** 1605, 1351, 1171, 860 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.14 (s, 3H), 5.37 (s, 2H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.13 (s, 1H).

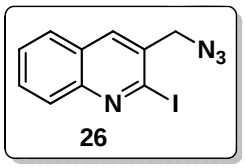
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 38.0, 72.7, 121.4, 126.5, 127.8, 127.9, 128.3, 129.8, 131.0, 136.6, 148.9.

Mass (ESI) m/z **:** 364 $(M + H)^+$.

Elemental analysis **:** Calculated: C, 36.38; H, 2.78; N, 3.86, I, 34.94%

: Found: C, 36.35; H, 2.75; N, 3.84, I, 34.89%

3-(Azidomethyl)-2-iodoquinoline (26)



26

To (2-iodoquinolin-3-yl) methyl methanesulfonate **25** (5 g, 13.7 mmol) dissolved in dimethylformamide (28 mL), was added sodium azide (0.97 g, 15.1 mmol) at 0 ^oC. After one hour, the reaction was quenched with water (80 mL), extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and the residue was filtered through a silica bed with ethyl acetate/pet ether (1:9) to afford the azide **26** as a yellow solid (5.5 g, 95%).

Mol. Formula **:** $C_{10}H_7IN_4$ (MW: 310.09).

Melting Point **:** 60-61 ^{o}C.

IR ($CHCl_3$) **:** 2103, 1612, 1151 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 4.60 (s, 2H), 7.59 (t, *J* = 6.9 Hz, 1H), 7.73 (t, *J* = 6.9 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 8.0 (s, 1H), 8.05 (d, *J* = 6.9 Hz, 1H).

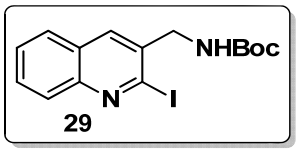
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 57.4, 122.9, 127.0, 127.7 (2C), 128.5, 130.5, 132.0, 135.2, 148.4.

Mass (ESI) m/z **:** 311 $(M + H)^{+}$, 333 $(M + Na)^{+}$.

Elemental analysis **:** Calculated: C, 38.73; H, 2.28; I, 40.92; N, 18.07%

: Found: C, 38.71; H, 2.22; I, 40.92; N, 18.01%

***tert*-Butyl ((2-iodoquinolin-3-yl) methyl) carbamate (29)**



29

To a solution of azide **26** (3 g, 9.6 mmol) in a mixture of THF/H_2O (40:10 mL) was added triphenylphosphine (3.8 g, 14.5 mmol). After 3 hours, the reaction mixture was extracted with dichloromethane, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude amine. The crude amine was dissolved in dry dichloromethane (40 mL) and triethylamine (4.0 mL, 28.8 mmol) was added. After 5 minutes of stirring the Boc-anhydride (2.64 mL, 11.5 mmol) was added dropwise. After 1 h, the reaction mixture was quenched with saturated solution of ammonium chloride and extracted with dichloromethane. The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification on silica gel using pet ether/ethyl acetate (9:1) afforded the carbamate **29** as a white solid (3.1 g, 85%).

Mol. Formula **:** $C_{15}H_{17}IN_2O_2$ (MW: 384.21).

Melting Point **:** 142-144 ^{o}C.

IR ($CHCl_3$) **:** 3453, 3019, 1708, 1588, 1215, 860 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.46 (s, 9H), 4.44 (d, *J* = 6.1 Hz, 2H), 5.28 (bs, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H).

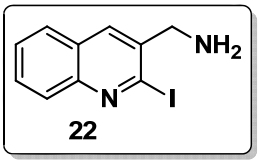
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 28.3 (3C), 47.7, 79.9, 123.8, 127.1, 127.3, 127.6, 128.2, 130.0, 134.6, 135.1, 148.5, 155.6.

Mass (ESI) m/z **:** 385 $(M + H)^+$, 407 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 46.89; H, 4.46; I, 33.03; N, 7.29%

: Found: C, 46.87; H, 4.44; I, 33.05; N, 7.28%

(2-Iodoquinolin-3-yl) methanamine (22)



22

To a solution of **29** (2 g, 5.2 mmol) in anhydrous CH_2Cl_2 (15 mL), was added trifluoroacetic acid (2.1 mL, 26 mmol) at 0 ^oC and the mixture was stirred at rt for 1 h. After completion of reaction (TLC), solvent was evaporated to furnish amine **22** (1.3 g, 90%), which was pure enough for further use.

Mol. Formula **:** $C_{10}H_9IN_2$ (MW: 284.10).

IR (Neat) **:** 3345, 1588, 1352, 1215, 862 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.96 (s, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.98 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H).

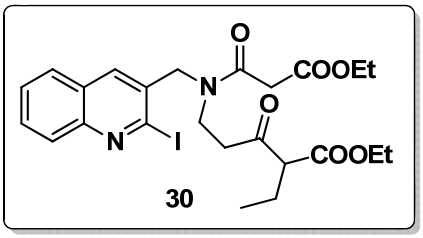
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 49.4, 124.6, 127.0, 127.2, 127.4, 127.5, 128.5, 129.9 133.8, 148.4.

Mass (ESI) m/z **:** 285 $(M + H)^+$.

Elemental analysis **:** Calculated: C, 42.28; H, 3.19; I, 44.67; N, 9.86%

: Found: C, 42.21; H, 3.15; I, 44.61; N, 9.81%

Ethyl 5-(3-ethoxy-*N*-((2-iodoquinolin-3-yl)methyl)-3-oxopropanamido)-2-ethyl-3-oxopentanoate (30)



30

To a stirred solution of amine **22** (2.5 g, 8.7 mmol) in dry CH_2Cl_2 (10 mL), *α,β*-unsaturated keto compound **6** (1.45 g, 8.7 mmol) was added dropwise at room temperature and allowed to stir for 30 min. After the completion of the reaction (TLC), K_2CO_3 (1.2 g, 8.7 mmol) was added followed by dropwise addition of ethyl malonyl chloride (1.3 mL, 9.6 mmol) at 0 °C. The mixture was stirred at room temperature until completion (1 h, TLC), and then was filtered and the residue was washed with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered and

concentrated on a rotary evaporator under diminished pressure. The resulting residue was purified by flash column chromatography (SiO_2) using ethyl acetate/pet ether (3:7) as an eluent to afford dihydropyridone **30** as a colorless liquid (3.45 g, 70%).

Mol. Formula **:** $C_{24}H_{29}IN_2O_6$ (MW: 568.40).

IR (Neat) **:** 1735, 1710, 1681, 1600, 1435, 1220, 856 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 and 0.93 (2t, *J* = 7.2 Hz, 3H), 1.21-1.34 (m, 6H), 1.77-1.91 (m, 2H), 2.03-2.56 (m, 1H), 2.80-3.10 (m, 1H), 3.38 and 3.40 (2t, *J* = 7.2 Hz, 1H), 3.64-3.73 (m, 2H), 3.39 and 3.78 (2s, 2H), 4.09-4.39 (m, 4H), 4.62-5.02 (m, 2H), 7.56 and 7.61 (2t, *J* = 7.5 Hz, 1H), 7.67-7.76 (m, 1H), 7.80-7.84 (m, 1H), 7.98-8.21 (m, 2H). (Mixture of rotamers)

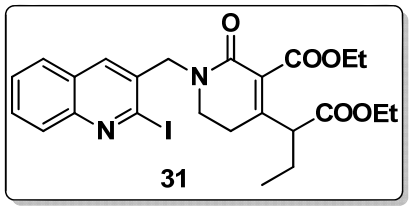
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.8, 11.9, 14.0, 14.1, 21.4, 21.5, 29.6, 39.7, 40.1, 40.9, 41.2, 42.6, 42.9, 51.8, 56.7, 60.5, 60.7, 61.4, 61.6, 61.7, 121.8, 123.2, 127.0, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 130.1, 130.5, 131.7, 131.9, 133.1, 134.4, 148.7, 148.8, 166.9, 167.0, 167.2, 168.0, 169.3, 169.5, 203.1, 204.2. (Mixture of rotamer)

Mass (ESI) m/z **:** 569 $(M + H)^+$, 591 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 50.71; H, 5.14; I, 22.33; N, 4.93%

: Found: C, 50.69; H, 5.15; I, 22.31; N, 4.92%

Ethyl 4-(1-ethoxy-1-oxobutan-2-yl)-1-((2-iodoquinolin-3-yl) methyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (31)



31

Method A: To the stirred solution of diester **30** (2 g, 3.51 mmol) in dry dichloromethane (10 mL), was added K_2CO_3 (1.4 g, 10.5 mmol) and allowed to stir for 5 h at room temperature. After the disappearance of starting material (TLC), the reaction was quenched with addition of saturated solution of ammonium chloride 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 which resulted in

the residue which was purified by flash column chromatography (SiO_2) eluting with ethyl acetate/pet ether (3:7) as eluent to yield dihydropyridone **31** (1.7 g, 92%).

Method B: To a stirred solution of amine **30** (2 g, 7.03 mmol) in dry CH_2Cl_2, keto compound **6** (1.19 g, 7.03 mmol) was added dropwise at room temperature and allowed to stir for 20 min. After the completion of the reaction (TLC), K_2CO_3 (3.8 g, 28.12 mmol) was added followed by drop wise addition of ethyl malonyl chloride (1.05 mL, 7.73 mmol) at 0 °C. The mixture was stirred at room temperature until completion (8 h, TLC), and then it was filtered and the residue was washed with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under diminished pressure. The resulting residue was purified by flash column chromatography (SiO_2) using ethyl acetate/pet ether (3:7) as an eluent to afford the dihydropyridone **31** (2.5 g, 65%) as yellowish thick oil.

Mol. Formula **:** $C_{24}H_{27}IN_2O_5$ (MW: 550.39).

IR (Neat) **:** 1734, 1657, 1605, 1450, 1365, 1235, 867 cm^{-1}.

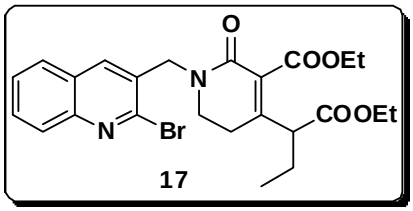
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.93 and 0.98 (2t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.3 Hz, 3H), 1.37 (t, *J* = 7.3 Hz, 3H), 1.75-1.97 (m, 2H), 2.32-2.56 (m, 2H), 3.25-3.40 (m, 1H), 3.65-3.73 (m, 2H), 4.22 (q, *J* = 7.3 Hz, 2H), 4.36 (q, *J* = 7.3 Hz, 2H), 4.51-5.01 (m, 2H), 7.53-7.56 (m, 1H), 7.65-7.72 (m, 1H), 7.77-7.81 (m, 1H), 7.85-8.07 (m, 2H).

Mass (ESI) m/z **:** 573 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 52.37; H, 4.94; N, 5.09; I, 23.06%

: Found: C, 52.38; H, 4.94; N, 5.08; I, 22.99%

Ethyl 1-((2-bromoquinolin-3-yl)methyl)-4-(1-ethoxy-1-oxobutan-2-yl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (17)



17

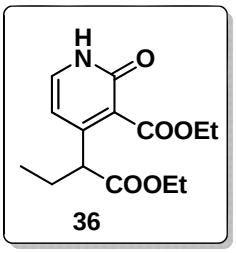
Mol. Formula **:** $C_{24}H_{27}BrN_2O_5$ (MW: 503.39).

IR (Neat) **:** 1734, 1680, 1600, 1450, 1365, 1235, 867 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.92 and 0.97 (2t, *J* = 7.4 Hz, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.37 (t, *J* = 7.3 Hz, 3H), 1.76-1.99 (m, 2H), 2.34-2.58 (m, 2H), 3.25-3.40 (m, 1H), 3.65-3.78 (m, 2H), 4.22 (q, *J* = 7.3 Hz, 2H), 4.36 (q, *J* = 7.3 Hz, 2H), 4.51-5.01 (m, 2H), 7.53-7.56 (m, 1H), 7.65-7.72 (m, 1H), 7.77-7.81 (m, 1H), 7.85-8.07 (m, 2H).

Mass (ESI) m/z **:** 504 and 506 $(M + H)^+$, 526:528 $(M + Na)^+$.

Ethyl 4-(1-ethoxy-1-oxobutan-2-yl)-2-oxo-1,2-dihydropyridine-3-carboxylate (36)



36

To a well-stirred solution of compound **35** (1 g, 2.69 mmol) in EtOH (30 mL), was added 10% $Pd(OH)_2$ (0.075 g, 0.53 mmol) and the reaction mixture was allowed to stir at 50 ^oC under hydrogen ballon. The progress of reaction was monitored by TLC (5 h) and 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* to furnish the desired amine **36** as thick oil (0.727 g, 96%).

Mol. Formula **:** $C_{14}H_{19}NO_5$ (MW: 281.30).

IR (Neat) **:** 1735, 1718, 1695, 1629, 1521, 1477, 1217 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.65-1.87 (m, 1H), 1.93-2.14 (m, 1H), 3.50 (t, *J* = 7.5 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 6.39 (d, *J* = 6.8 Hz, 1H), 7.43 (d, *J* = 6.8 Hz, 1H), 13.4 (bs, 1H).

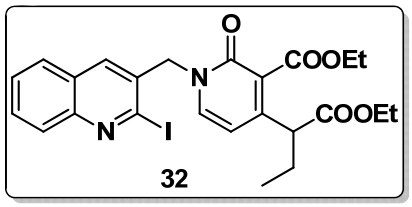
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.8, 14.0, 14.1, 25.7, 49.9, 61.2, 61.6, 105.6, 125.0, 135.6, 151.2, 162.2, 165.8, 171.7.

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

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

: Found: C, 59.76; H, 6.82; N, 4.96%.

Ethyl 4-(1-ethoxy-1-oxobutan-2-yl)-1-((2-iodoquinolin-3-yl)-methyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (32)



32

Method A: To the stirred solution of dihydropyridone **31** (2 g, 3.63 mmol) in anhydrous 1, 4-dioxane (20 mL), was added DDQ (0.90 g, 3.99 mmol) and reaction mixture was refluxed till the completion of reaction (24 h, TLC). The reaction mixture was diluted with ethyl acetate and quenched with addition of 10% $NaHCO_3$ solution, the organic phase was separated and aqueous phase was extracted with ethyl acetate (3 x 20 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-pet ether to obtain pyridone **32** (1.81 g, 91%).

Method B: To the stirred solution of **36** (0.3 g, 1.06 mmol) in 10 mL of dry DME at 25 ºC was added KO*t*Bu (0.179 g, 1.59 mmol). The resulting yellow suspension was stirred at ambient temperature for 30 min, and then mesyl compound **25** (0.42 g, 1.16 mmol) was added dropwise in dry DME. After completion of reaction (TLC, 2 h), the reaction mixture was cooled and quenched with water. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (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/pet ether to obtain pyridone **32** (0.5 g, 86%) as yellow sticky solid.

Mol. Formula **:** $C_{24}H_{25}IN_2O_5$ (MW: 548.37).

IR (Neat) **:** 1735, 1718, 1665, 1600, 1521, 1350, 856 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.69-1.84 (m, 1H), 1.97-2.11 (m, 1H), 3.51 (t, *J* = 7.5 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 5.34 (s, 2H), 6.39 (d, *J* = 7.3 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 8.37 (s, 1H).

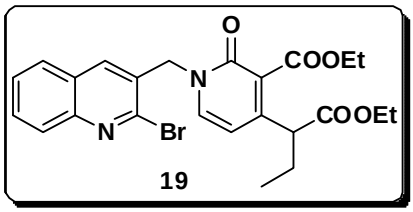
^{13}C NMR ($CDCl_3$, 100 MHz) : δ 11.8, 14.0, 14.1, 25.7, 49.7, 50.4, 61.2, 61.7, 104.9, 125.9, 126.7, 127.0, 127.3, 127.9, 128.1, 130.9, 138.3, 140.5, 147.2, 149.45, 149.48, 159.5, 165.7, 171.17.

Mass (ESI) m/z **:** 549 $(M + H)^+$, 571 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 52.57; H, 4.60; I, 23.14; N, 5.11%

: Found: C, 52.53; H, 4.63; I, 23.11; N, 5.08%

Ethyl 1-((2-bromoquinolin-3-yl)methyl)-4-(1-ethoxy-1-oxobutan-2-yl)-2-oxo-1,2-dihydropyridine-3-carboxylate (19)



19

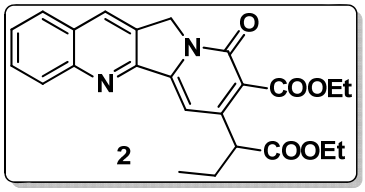
Mol. Formula **:** $C_{24}H_{25}BrN_2O_5$ (MW: 501.37).

IR (Neat) **:**1735, 1718, 1664, 1600, 1521, 1350, 856 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.69-1.83 (m, 1H), 1.96-2.06 (m, 1H), 3.50 (t, *J* = 7.5 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 5.33 (s, 2H), 6.37 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 6.9 Hz, 1H), 7.73 (t, *J* = 6.9 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 8.36 (s, 1H).

Mass (ESI) m/z **:** 524 and 526 $(M + Na)^+$.

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



2

A mixture of pyridone **32** (0.2 g, 0.36 mmol), PEG-2000 (4 g), triethylamine (0.1 mL, 0.72 mmol) and $Pd(OAc)_2$ (0.004 g, 0.018 mmol) was placed in a 10 mL round bottomed flask and stirred at 80 ^oC. After completion of the reaction (10 h, TLC), the reaction mixture was cooled and water was added and extracted with cold diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The generated residue was purified by flash column chromatography (SiO_2) eluting with 80% ethyl

acetate-petroleum ether as a solvent system to yield pyridone **2** as a pale yellow solid (0.128 g, 84% yield).

Mol. Formula **:** $C_{24}H_{24}N_2O_5$ (MW: 420.46).

Melting point **:** 171-173 ^oC (Lit. 172-173 ^oC).

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

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.99 (t, *J* = 7.4 Hz, 3H), 1.26 (t, *J* = 6.9 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.85-2.07 (m, 1H), 2.12-2.34 (m, 1H), 3.73 (t, *J* = 7.7 Hz, 1H), 4.19 (q, *J* = 6.9 Hz, 2H), 4.47 (q, *J* = 7.2 Hz, 2H), 5.25 (s, 2H), 7.50 (s, 1H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.83 (t, *J* = 7.3 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 8.27 (d, *J* = 8.2 Hz, 1H), 8.39 (s, 1H).

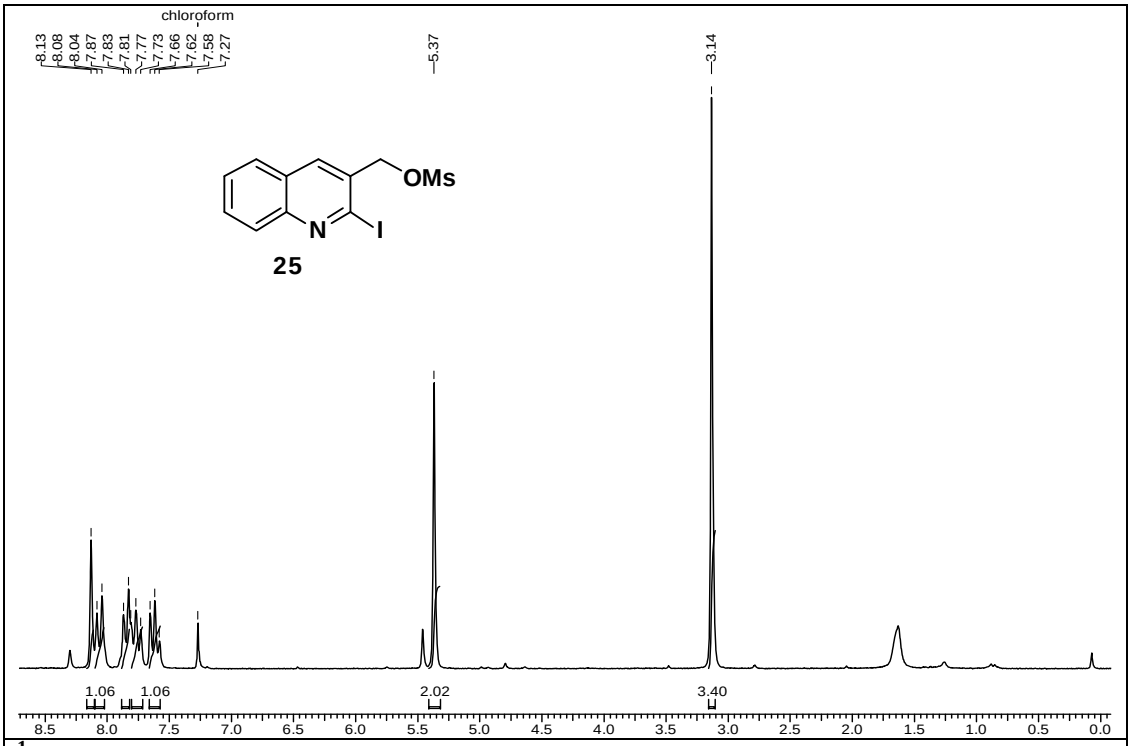
^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 12.0, 14.1, 14.2, 25.7, 49.9, 50.0, 61.1, 61.5, 99.6, 125.2, 127.8, 127.9, 128.0, 128.8, 129.5, 130.4, 130.9, 146.0, 148.5, 150.3, 152.0, 158.0, 165.7, 171.6.

Mass (ESI) m/z **:** 421 $(M + 1)^+$, 443 $(M + Na)^+$.

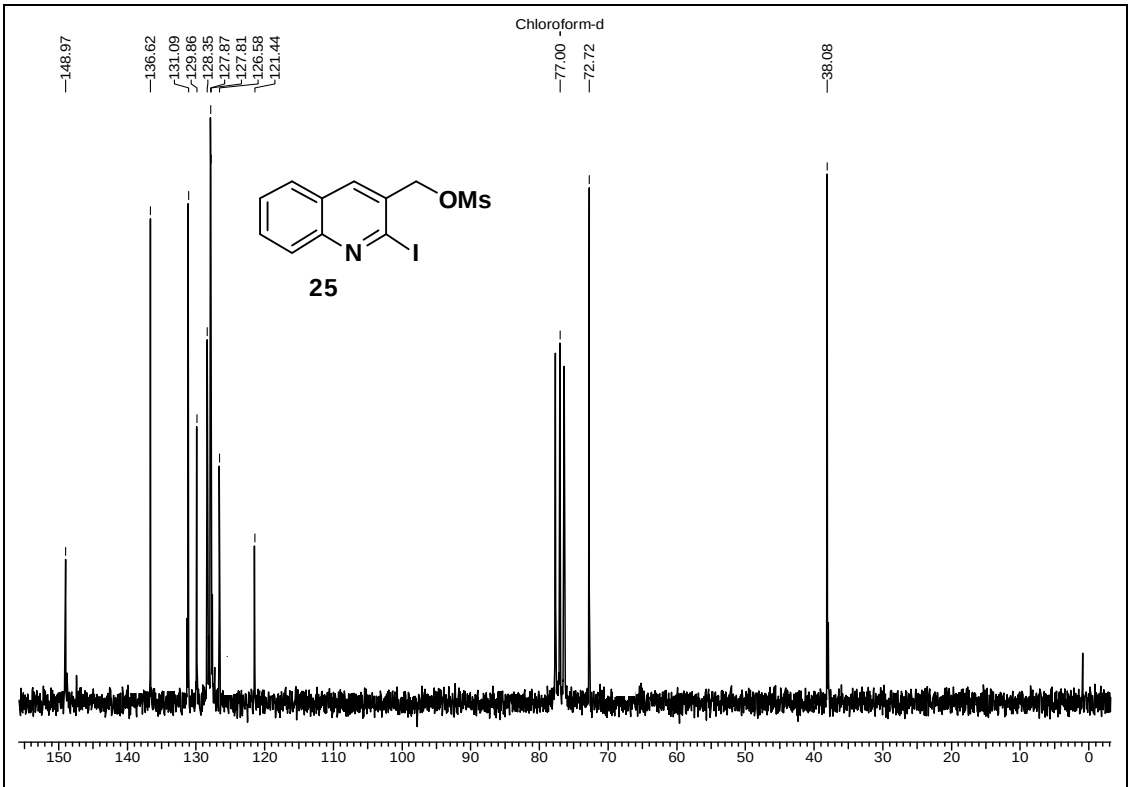
Elemental analysis **:** Calculated: C, 68.56; H, 5.75; N, 6.66%

: Found: C, 68.56, H, 5.74, N, 6.65%

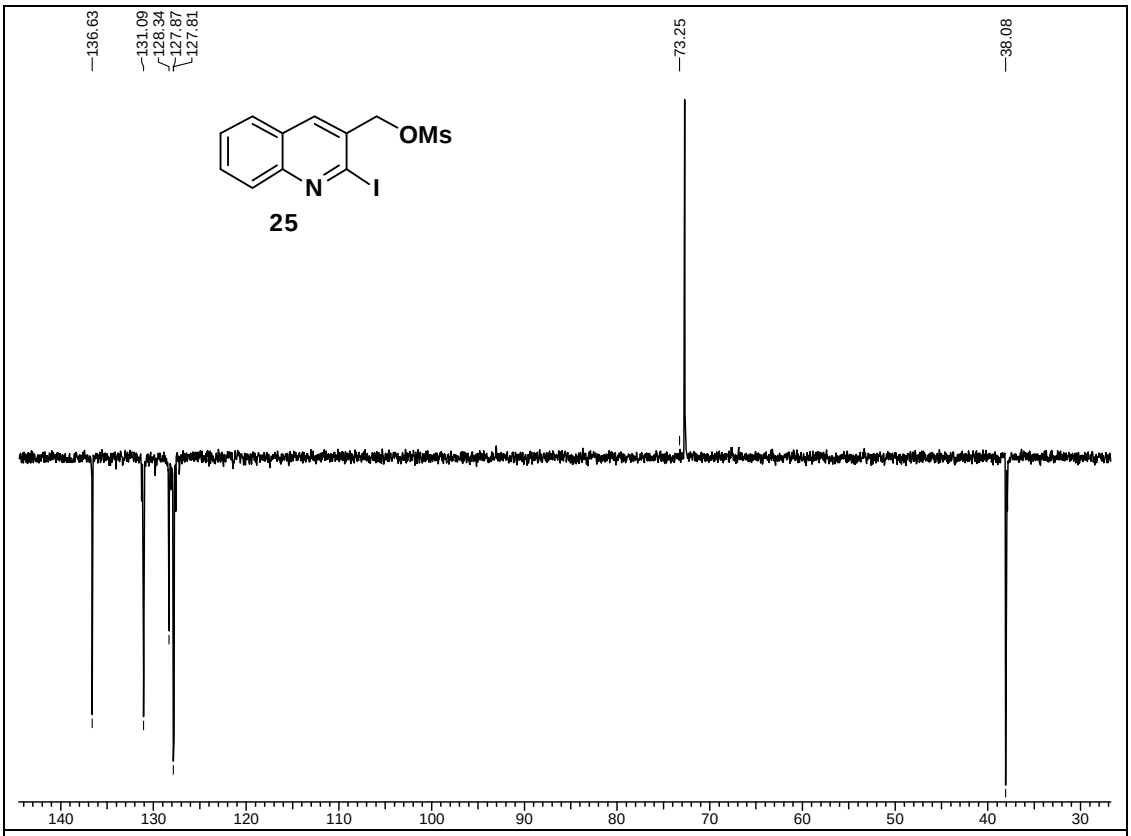
2.2.7 Spectra



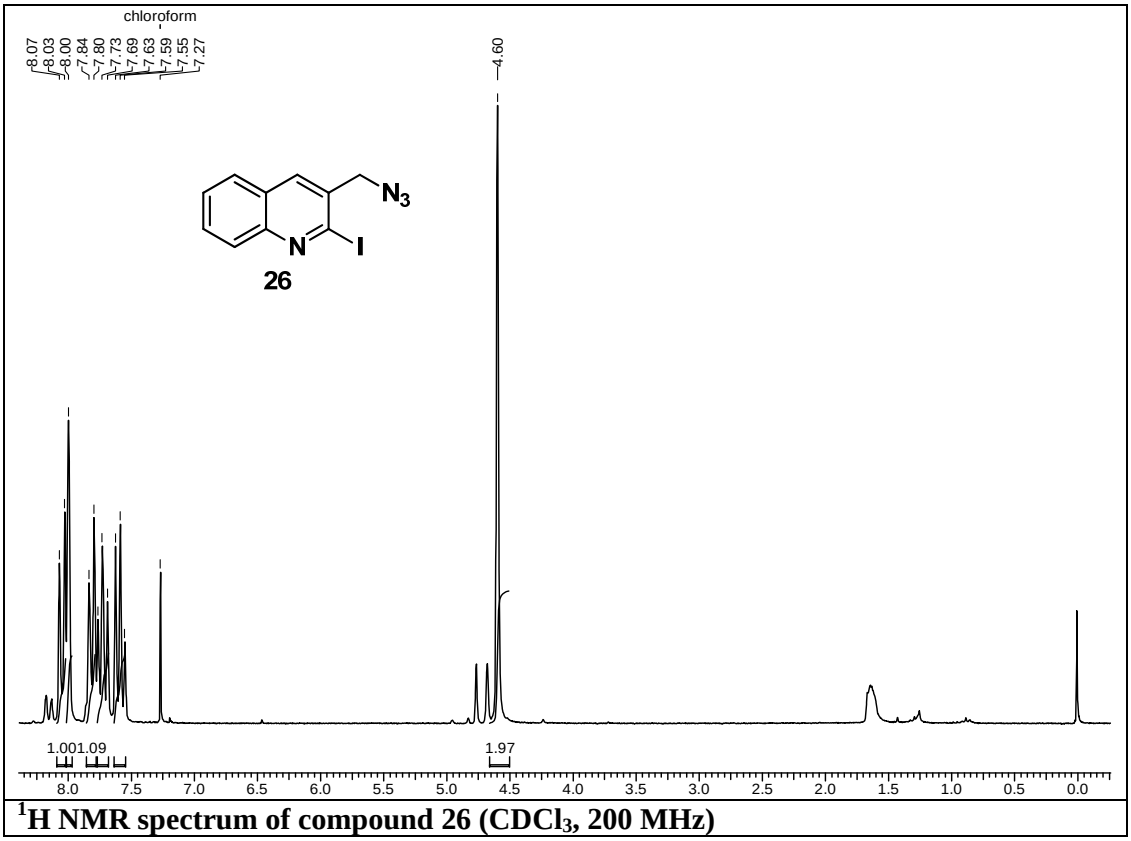
^{1}H NMR spectrum of compound 25 ($CDCl_3$, 200 MHz)



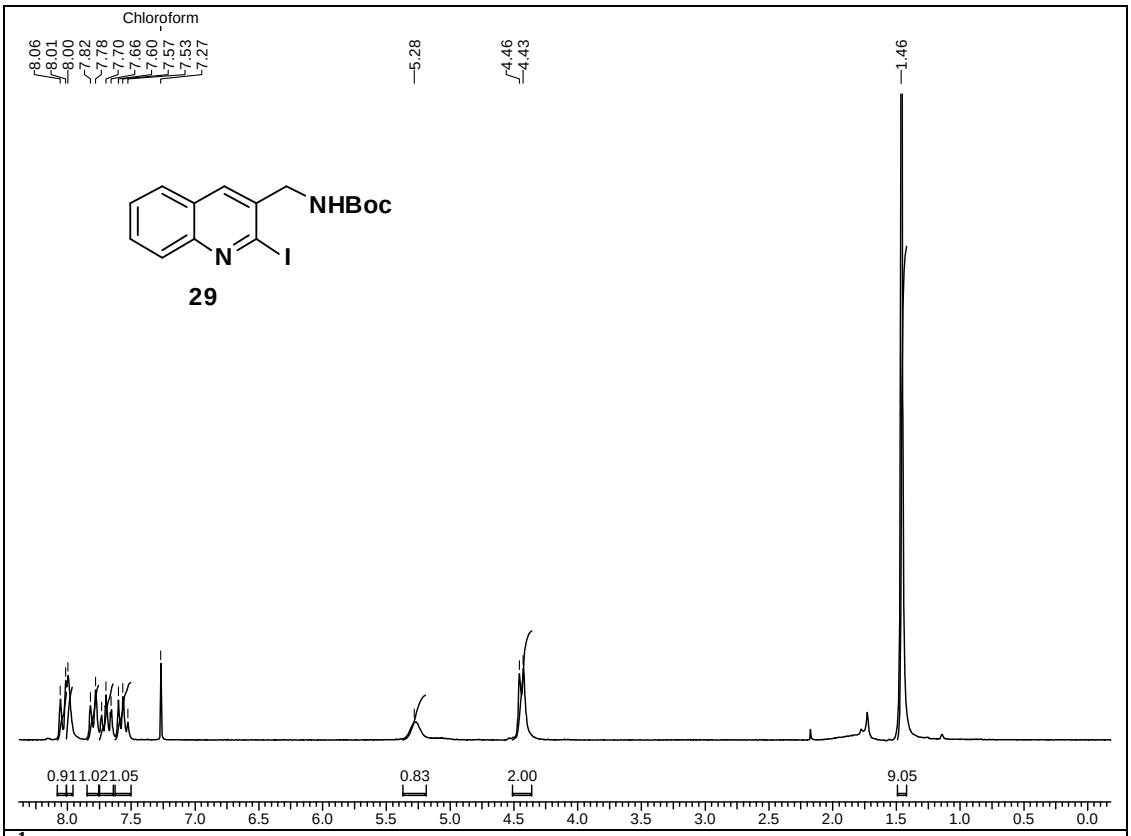
^{13}C NMR spectrum of compound 25 ($CDCl_3$, 50 MHz)



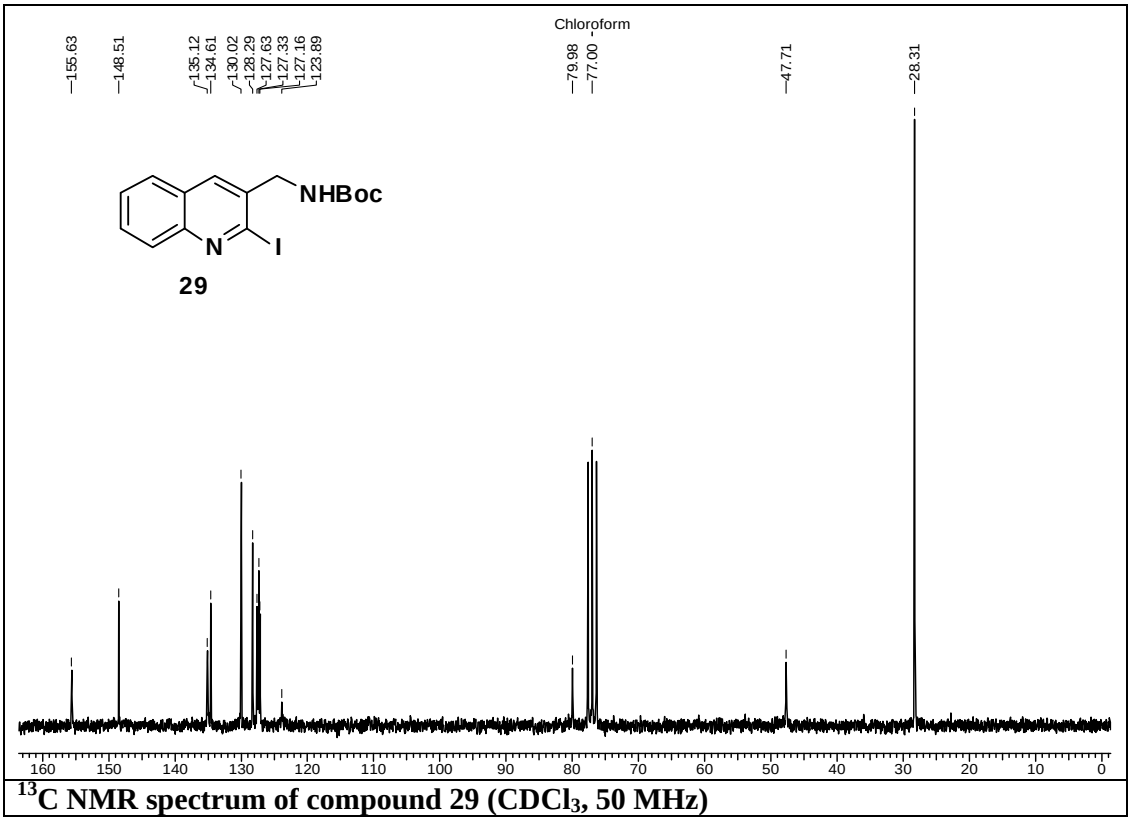
DEPT spectrum of compound 25 ($CDCl_3$, 50 MHz)



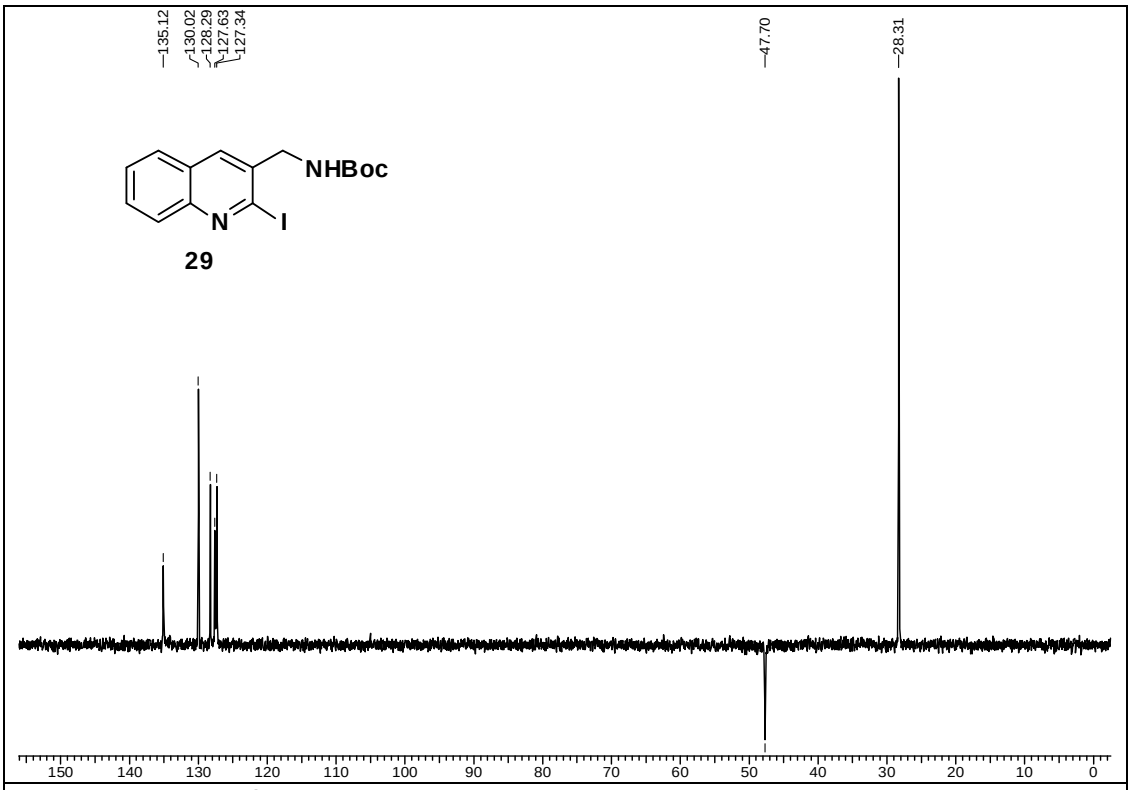
^{1}H NMR spectrum of compound 26 ($CDCl_3$, 200 MHz)



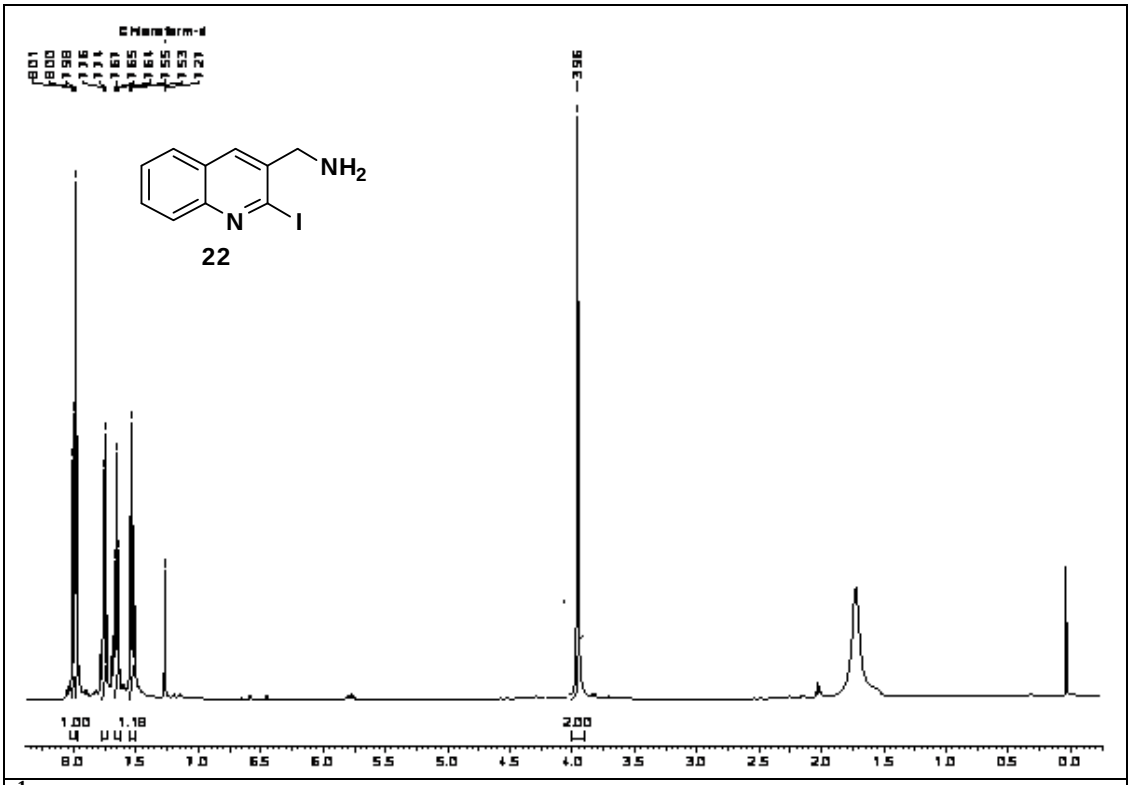
^{1}H NMR spectrum of compound 29 ($CDCl_3$, 200 MHz)



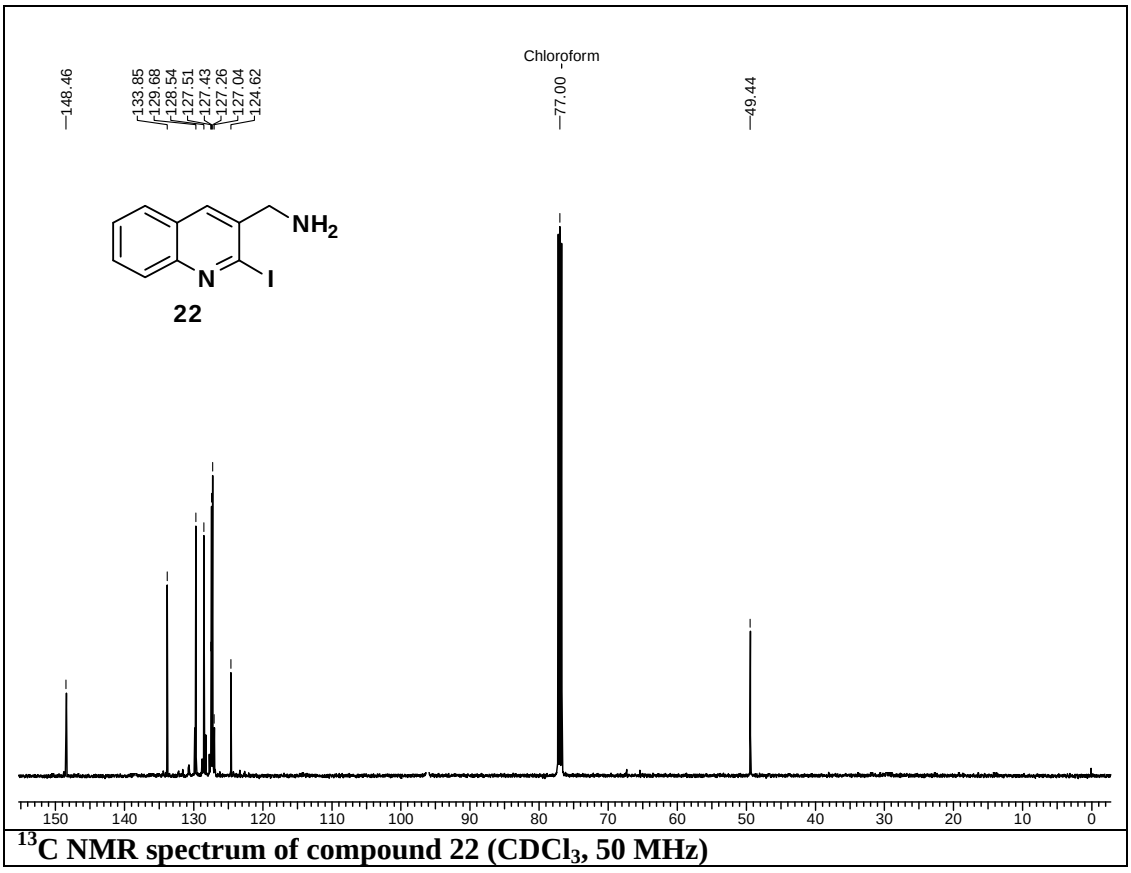
^{13}C NMR spectrum of compound 29 ($CDCl_3$, 50 MHz)



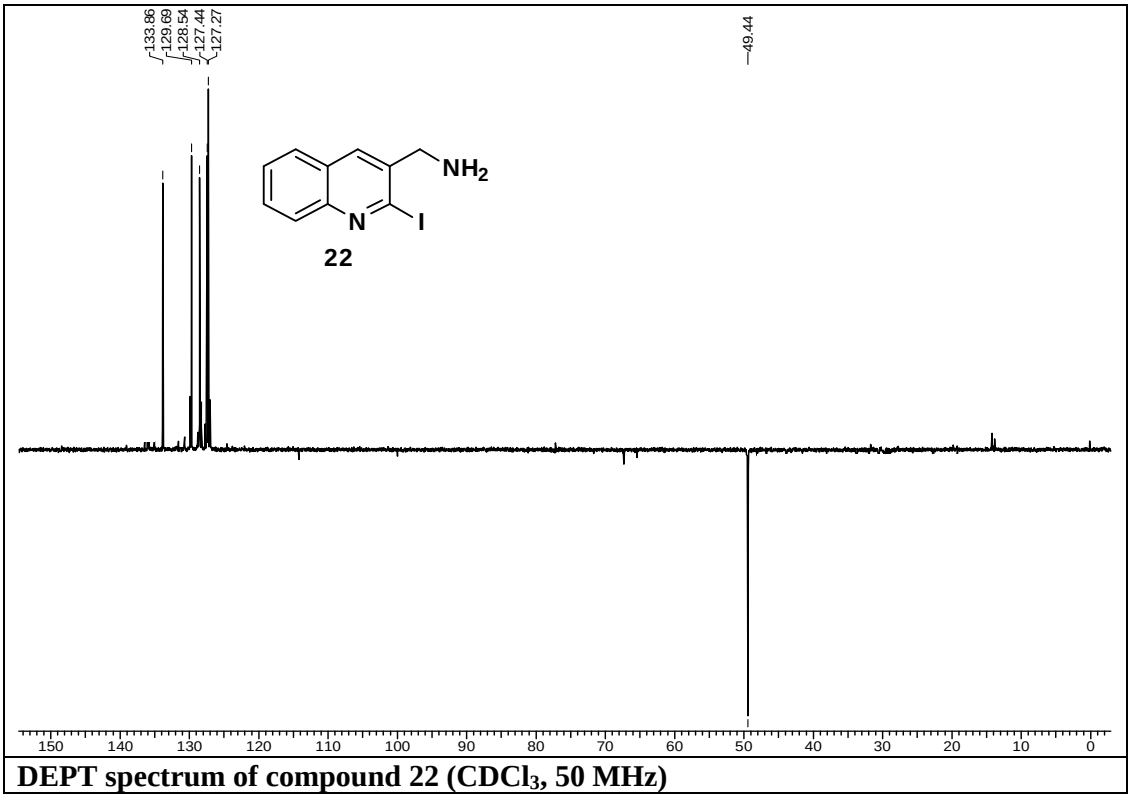
DEPT spectrum of compound 29 ($CDCl_3$, 50 MHz)



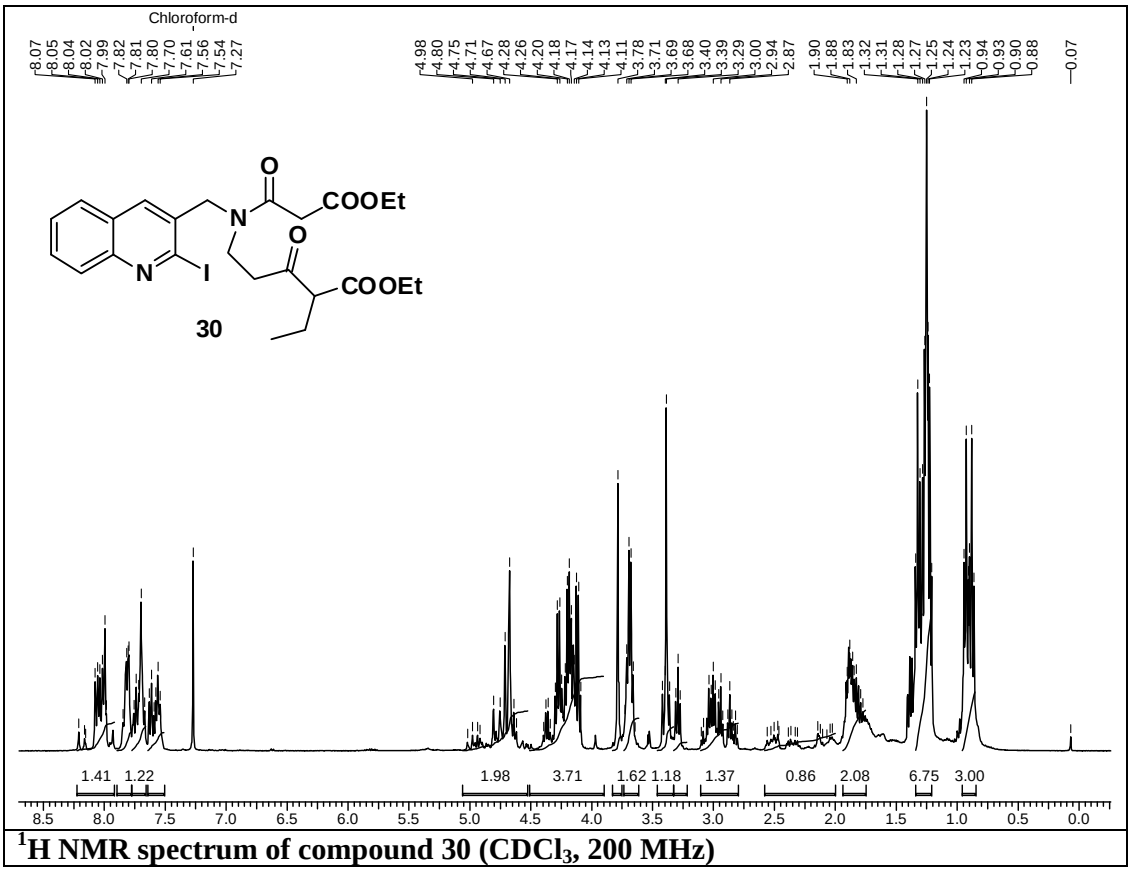
^{1}H NMR spectrum of compound 22 ($CDCl_3$, 200 MHz)



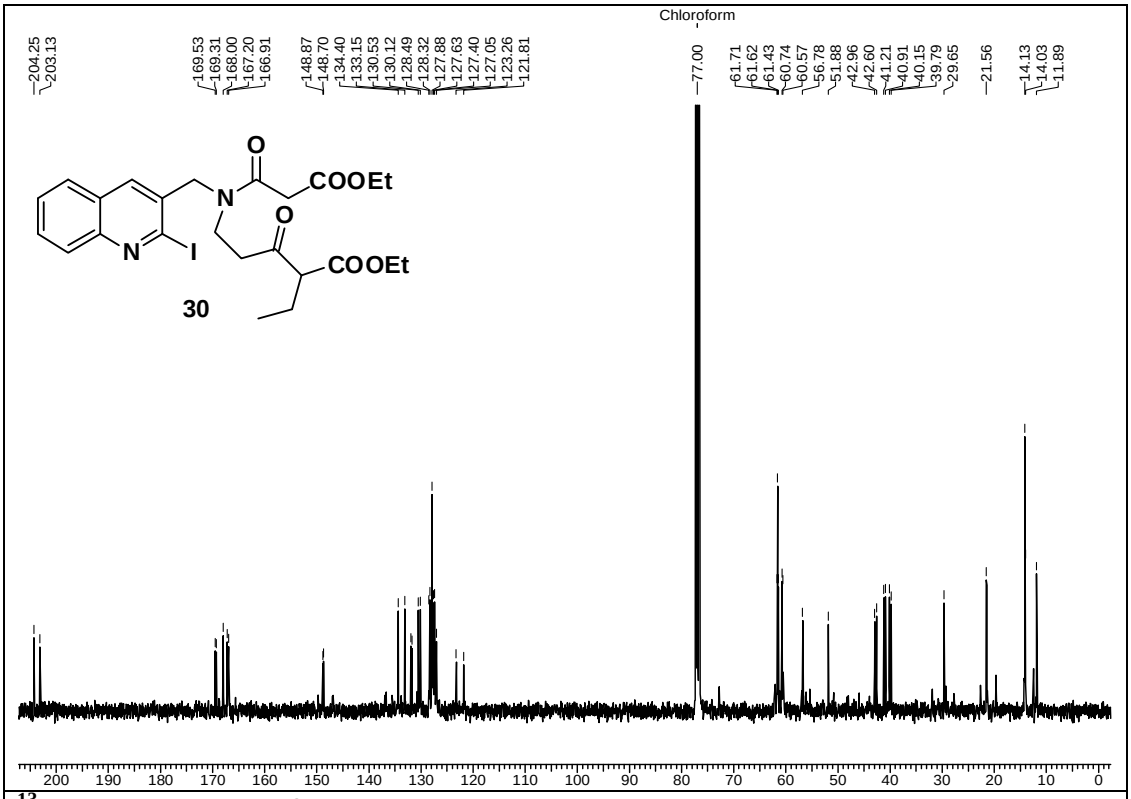
^{13}C NMR spectrum of compound 22 ($CDCl_3$, 50 MHz)



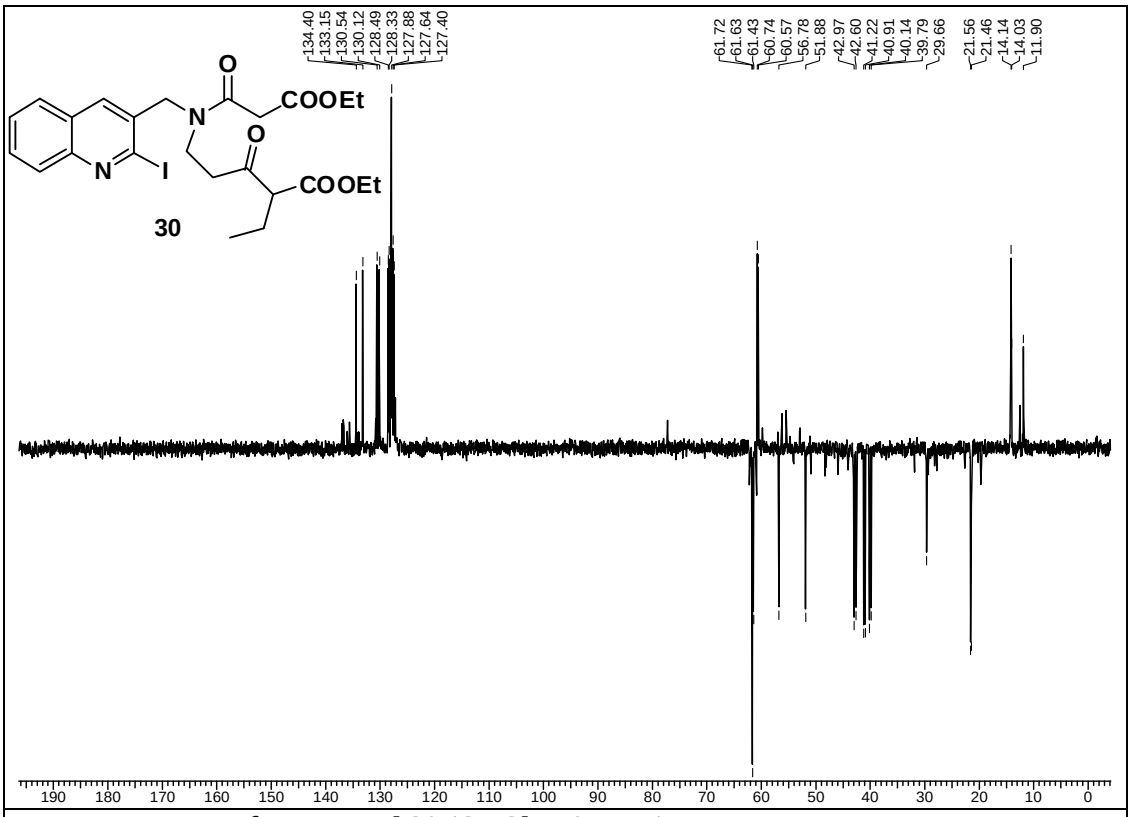
DEPT spectrum of compound 22 ($CDCl_3$, 50 MHz)



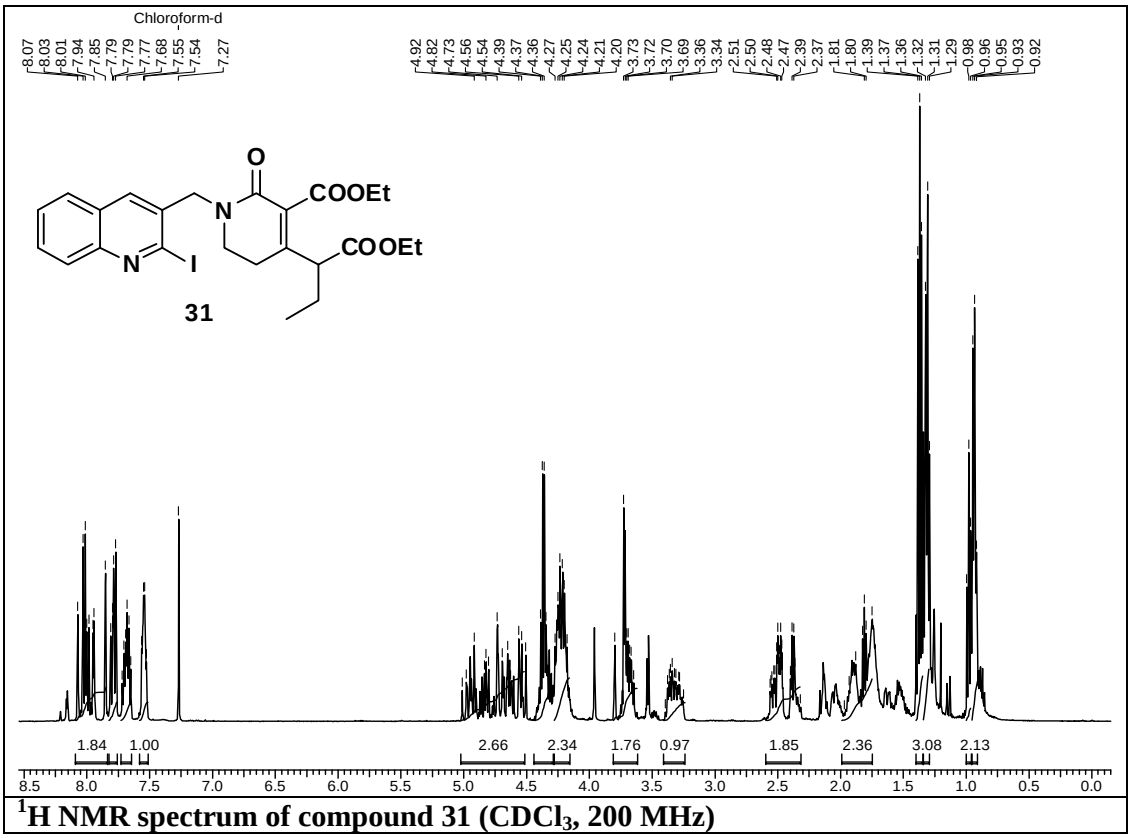
^{1}H NMR spectrum of compound 30 ($CDCl_3$, 200 MHz)



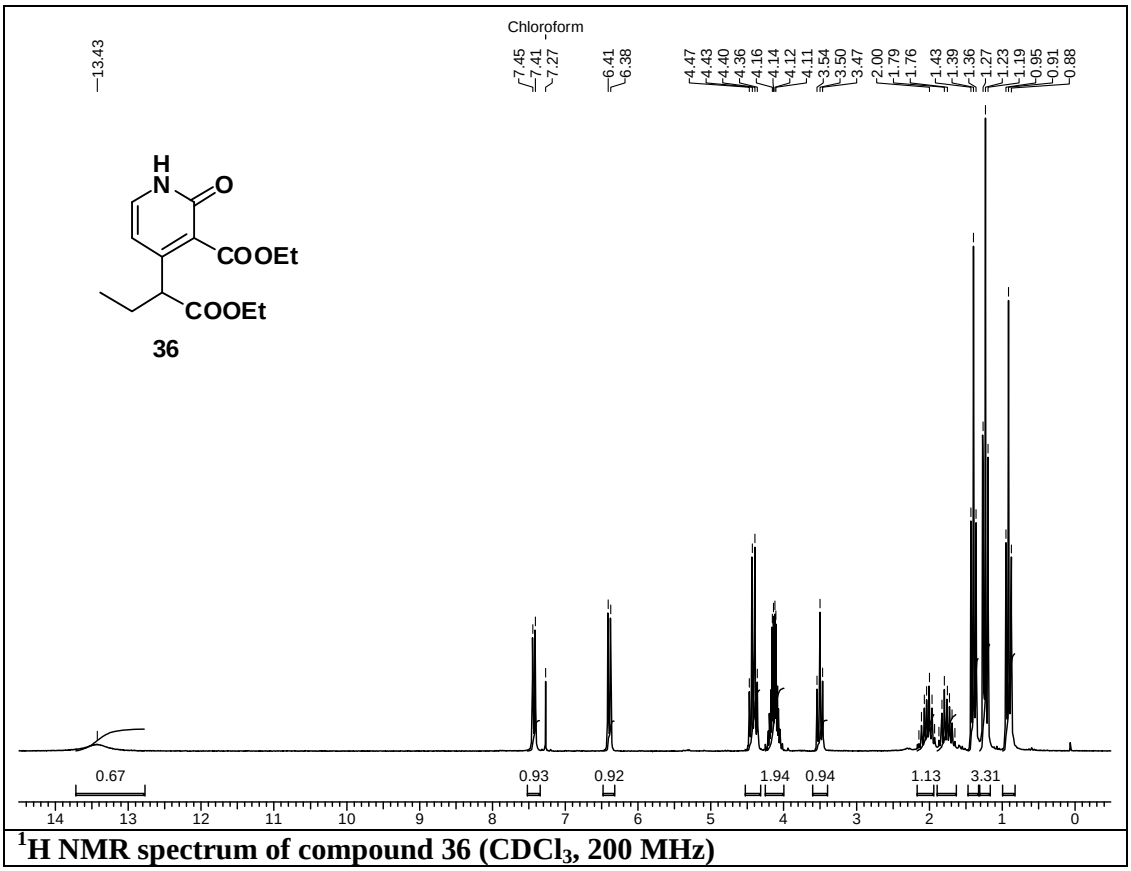
^{13}C NMR spectrum of compound 30 ($CDCl_3$, 50 MHz)



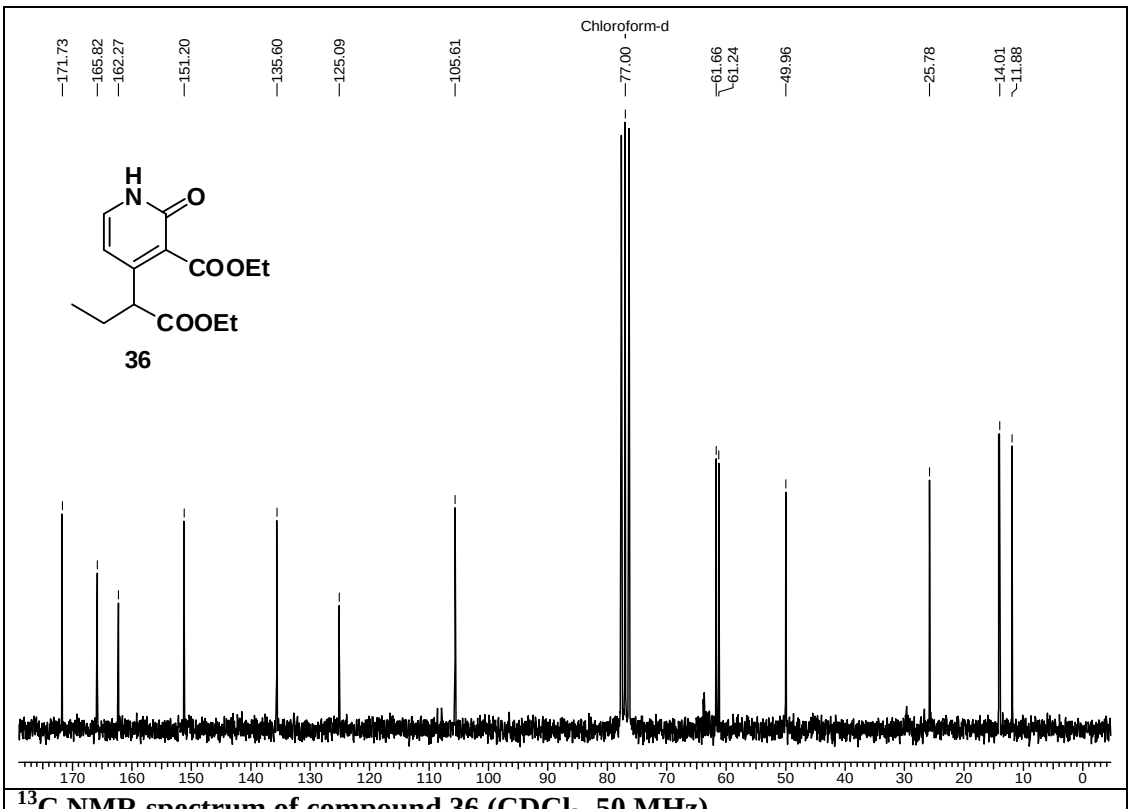
DEPT spectrum of compound 30 ($CDCl_3$, 50 MHz)



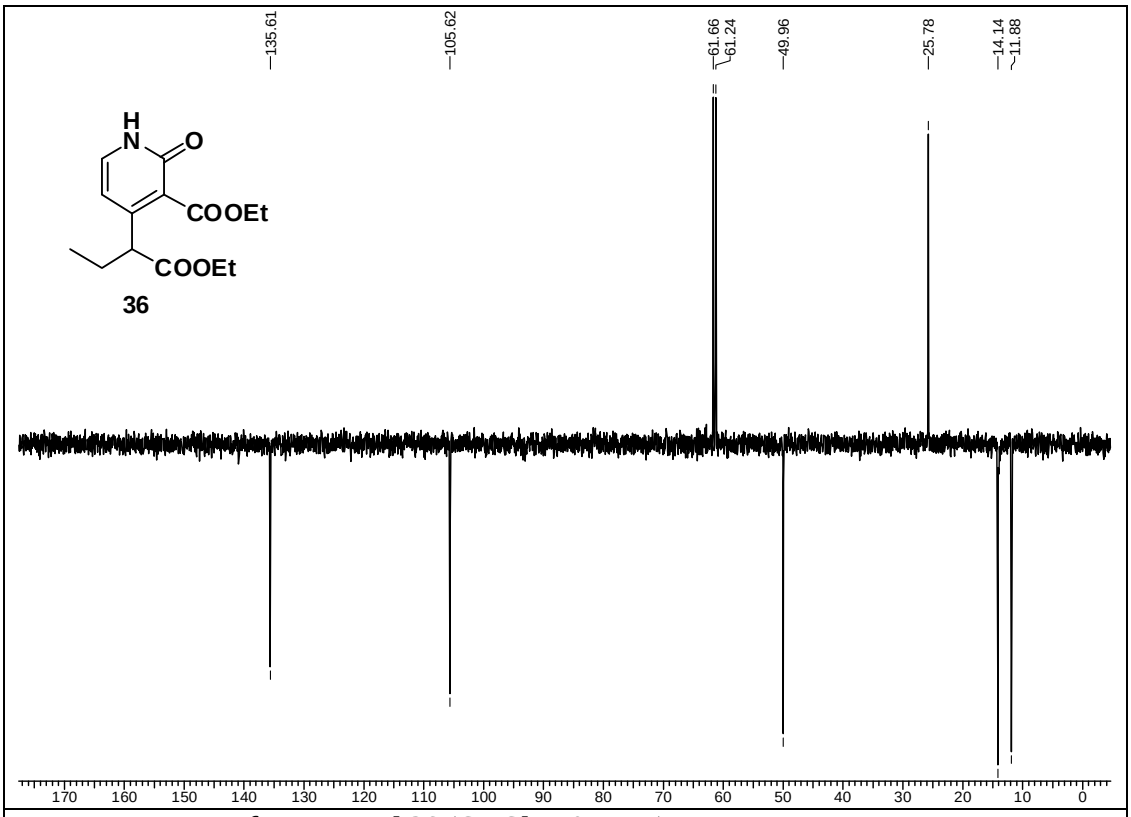
^{1}H NMR spectrum of compound 31 ($CDCl_3$, 200 MHz)



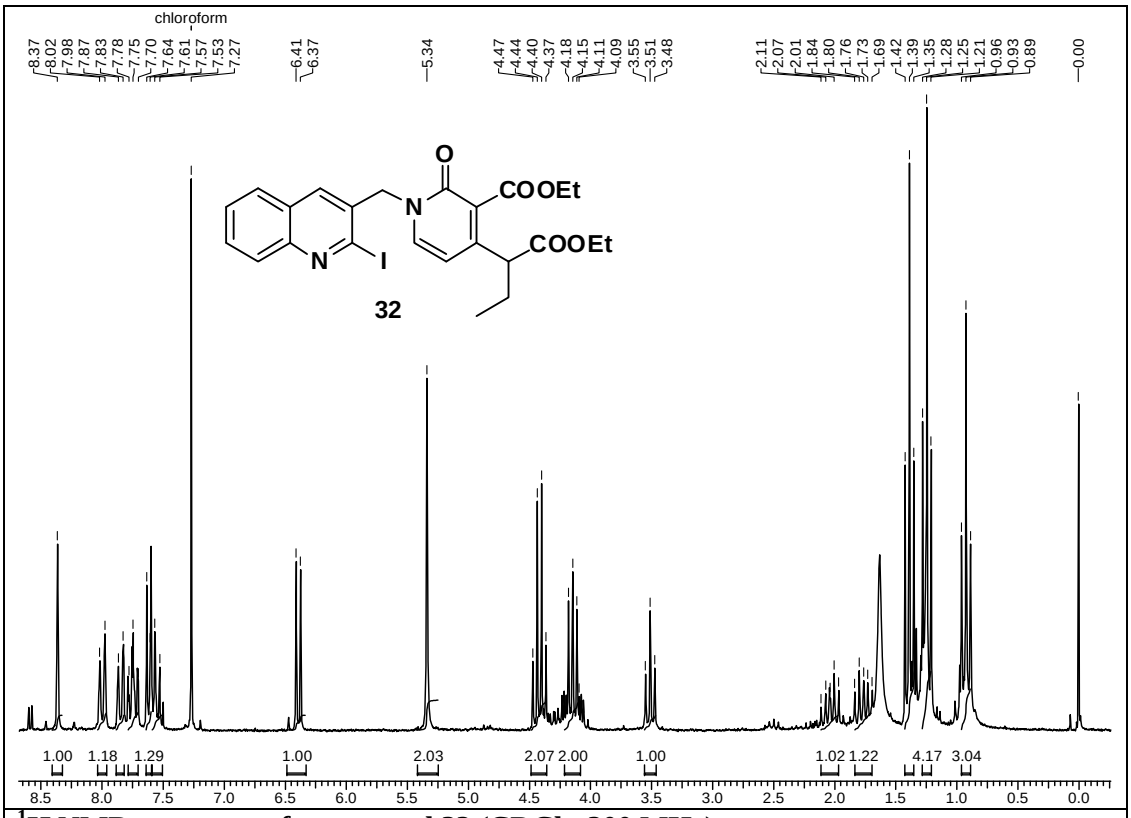
^{1}H NMR spectrum of compound 36 ($CDCl_3$, 200 MHz)



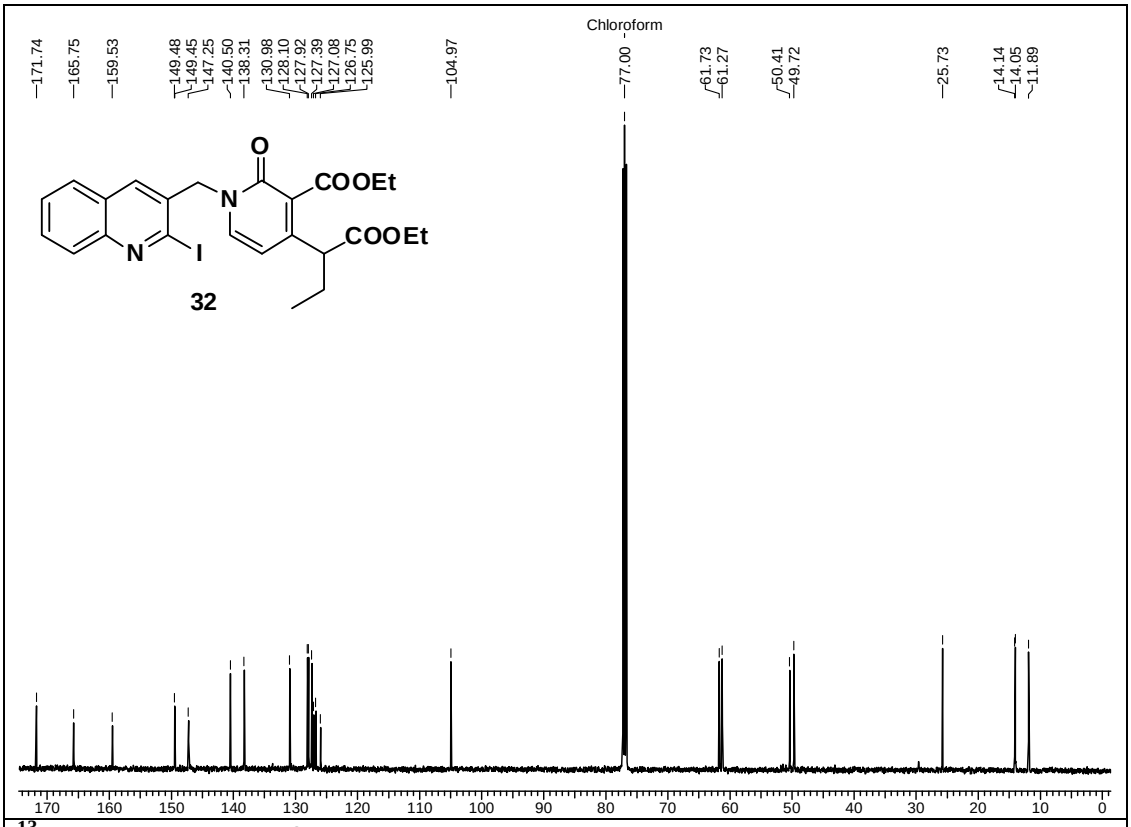
^{13}C NMR spectrum of compound 36 ($CDCl_3$, 50 MHz)



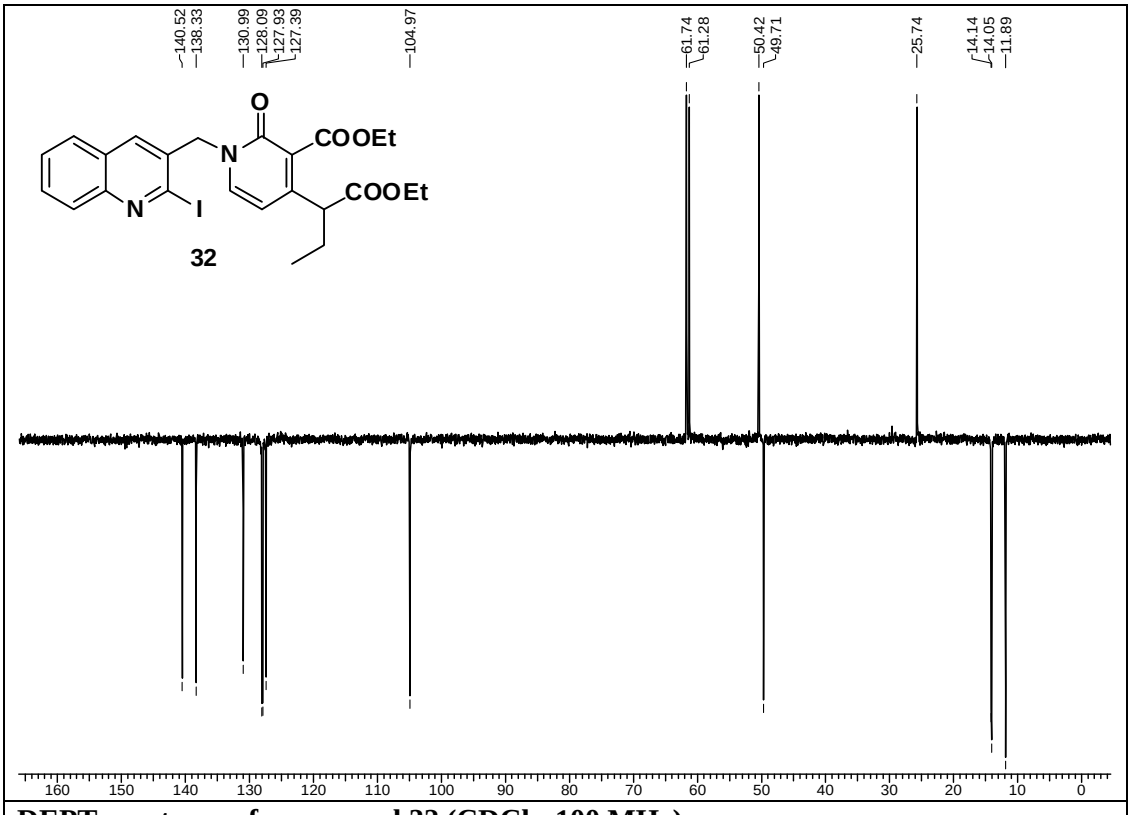
DEPT spectrum of compound 36 ($CDCl_3$, 50 MHz)



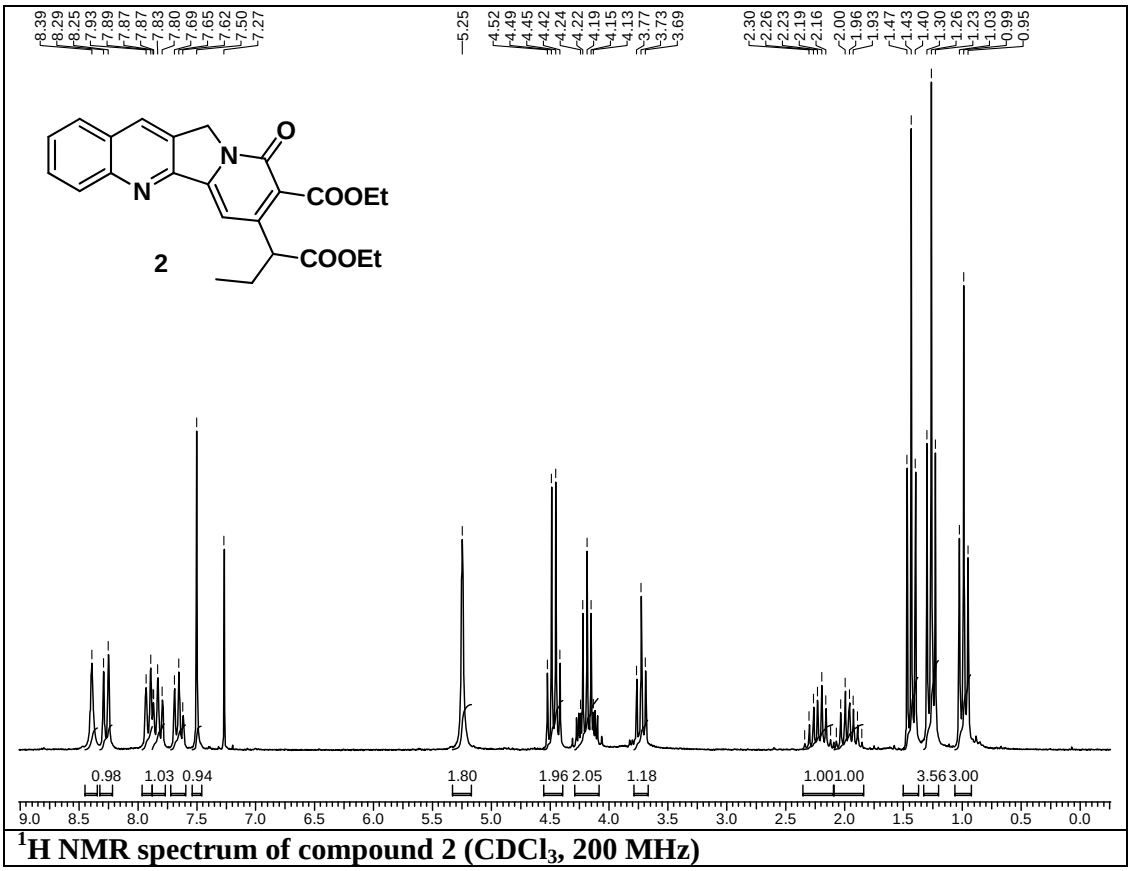
^{1}H NMR spectrum of compound 32 ($CDCl_3$, 200 MHz)



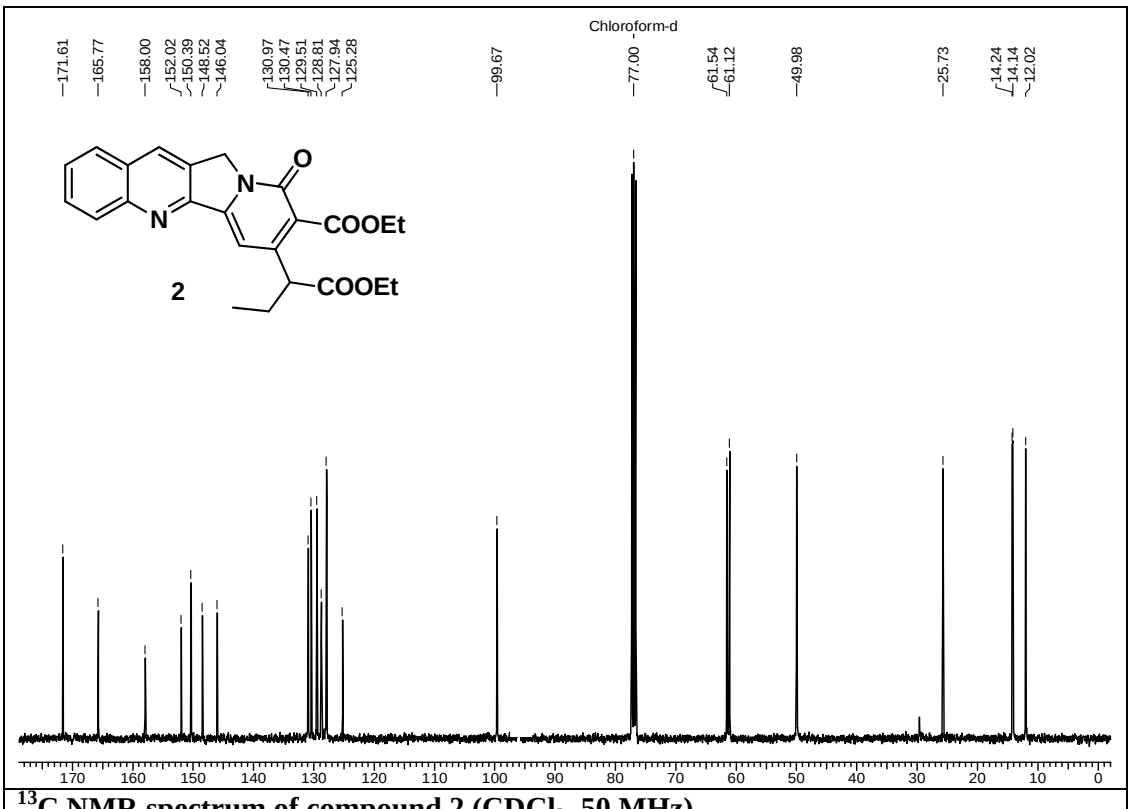
^{13}C NMR spectrum of compound 32 ($CDCl_3$, 100 MHz)



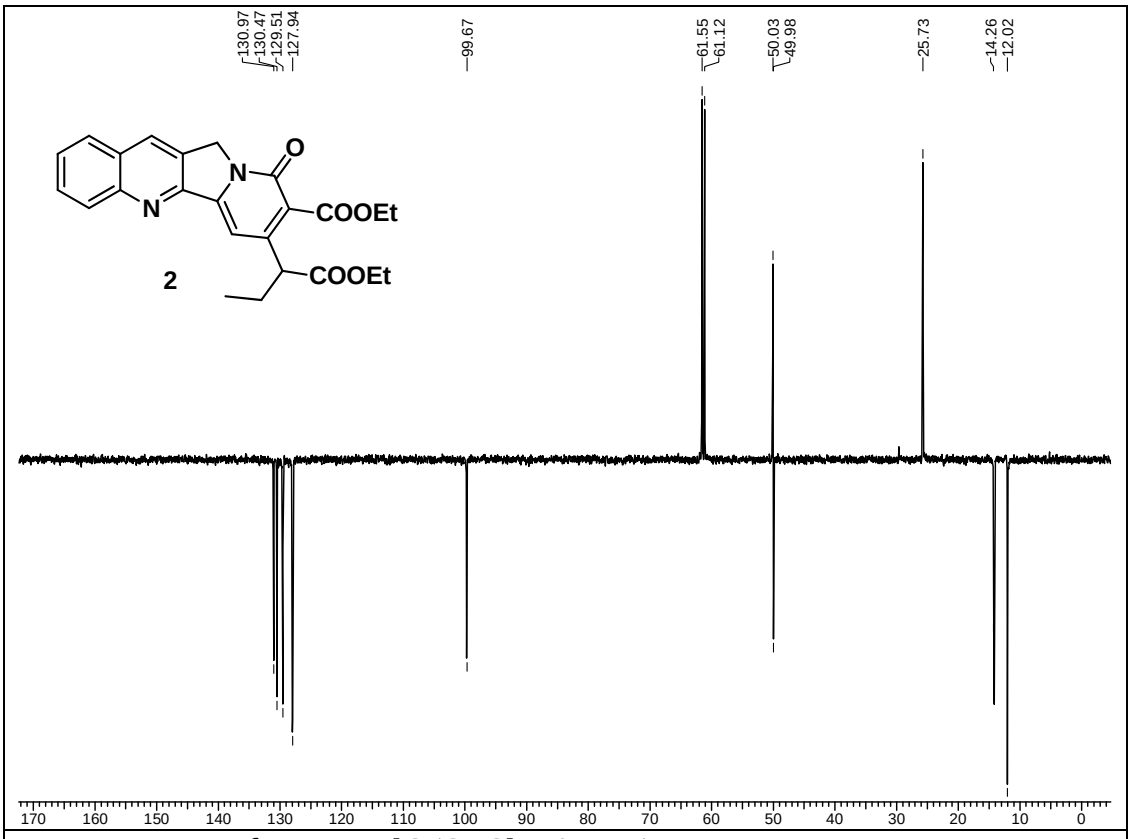
DEPT spectrum of compound 32 ($CDCl_3$, 100 MHz)



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



^{13}C NMR spectrum of compound 2 ($CDCl_3$, 50 MHz)



DEPT spectrum of compound 2 ($CDCl_3$, 50 MHz)

2.2.8 References

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Chapter 2. Tandem one-pot reaction approaches towards the synthesis of camptothecin

Section 3

Formal synthesis of camptothecin via tricyclic lactone as key synthon

2.3.1 Summary

The present section deals with the formal total synthesis of (±)-camptothecin **1** *via* tricyclic lactone **3**, which is most versatile synthon for the synthesis of camptothecin and its analogues.

2.3.2 Introduction

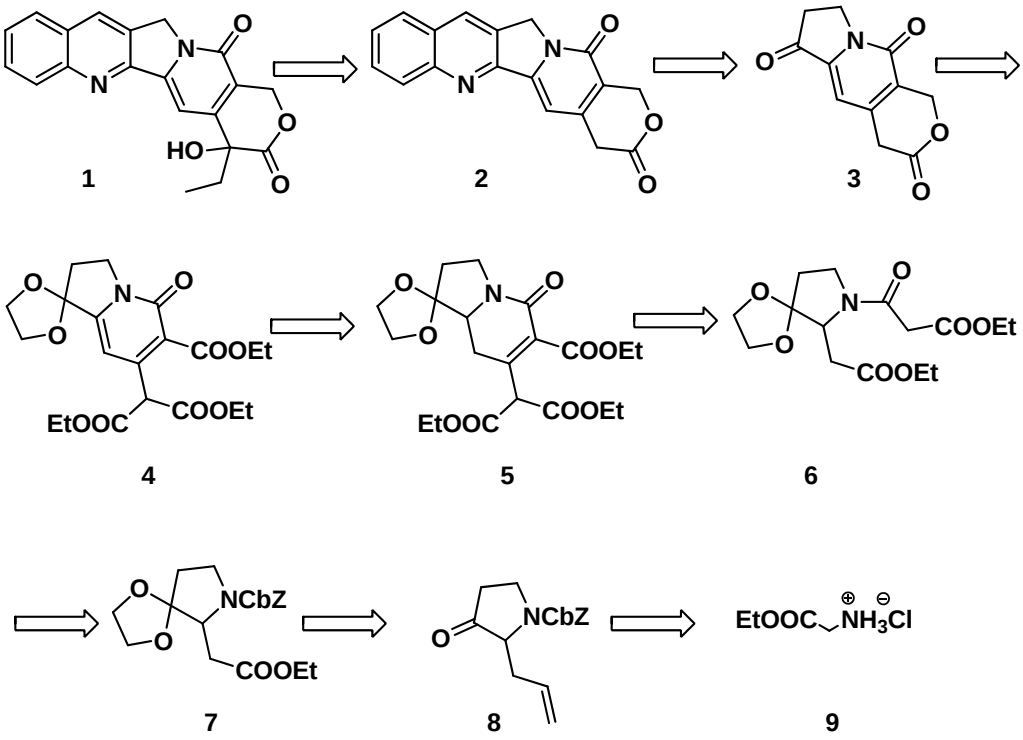
The clinical use of camptothecin has been limited owing to its insolubility and toxicity, but extensive structure-activity relationship studies have identified its various analogues having better solubility and with equal or better antitumor activity, which resurged the interest of the chemists as well as oncologists. The New York academy of science organized two international meetings devoted exclusively to camptothecin in the year 1996 and 2000.[1,2] As of 2003 August, of the 2255 cancer clinical trials recorded, 5.3% comprises of camptothecin derived drugs, including irinotecan[3] and topotecan[4] either as single agents or in combination with other anticancer agents.[5] Stimulated by the excellent biological activity, unique mode of action and challenging structure it has been the compound of choice spanning four decades for both medicinal as well as synthetic chemists. 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 counterparts either predominantly through Friedlander coupling or by radical or Heck cyclization respectively. Thinking on these lines, it was envisioned to synthesize the CDE-ring fragment, which is most versatile synthon for the synthesis of camptothecin and its analogues.

2.3.3 Present work

As described in earlier sections, racemic as well as enantioselective synthesis of camptothecin **1** was achieved by convergent (*via* DE synthon) and linear manner employing tandem one-pot reactions. In this section the formal synthesis of (±)-camptothecin **1** *via* CDE tricyclic lactone followed by coupling with suitable AB-ring counterparts, predominantly through Friedlander coupling to get pentacyclic frame of camptothecin **1**, is described.

As shown in the retrosynthetic analysis (Scheme 1), camptothecin **1** could be synthesized from pentacyclic lactone **2** by alkylation followed by hydroxylation, which in

turn could be obtained from tricyclic lactone **3** *via* Friedlander coupling. Tricyclic lactone **3** could be realized from pyridone **4** *via* lactone formation followed by decarboxylation.



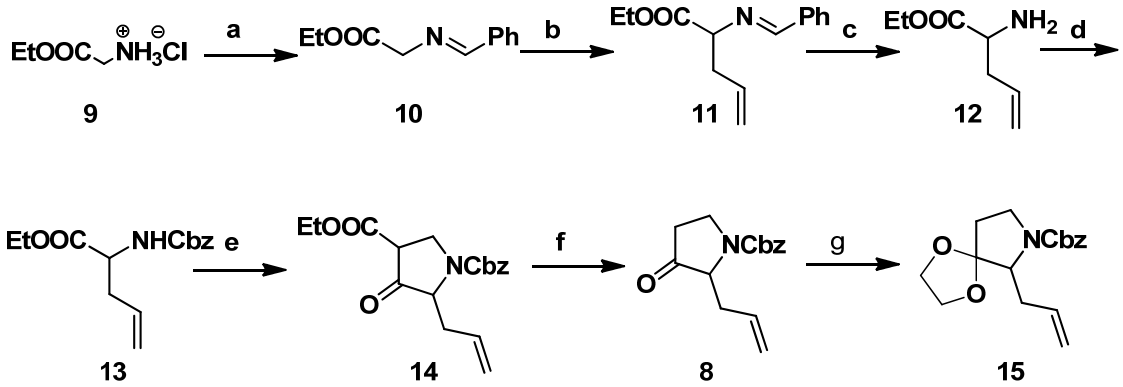
Scheme 1

Pyridone **4** could be synthesised by oxidation of dihydropyridone **5**, which in turn could be realized from diester **6** *via* cyclization. The diester **6** could be accessed from compound **7** by Cbz deprotection and condensation. Compound **7** could be synthesised from urethane **8**, which in turn could be synthesized from commercially available glycine ethyl ester hydrochloride salt **9**.

2.3.4 Results and discussion

According to planned retrosynthetic analysis, the intermediate **8** was synthesized from readily available ethyl ester of glycine hydrochloride **9** as per reported procedure[6] described by this group (Scheme 2). Glycine ester hydrochloride **9** was subjected to imine formation with triethylamine and benzaldehyde in DCM to afford imine **10** in 98% yield. Alkylation of O'Donnell's Schiff's base **10** with allyl bromide in presence of $TBAHSO_4$ as phase transfer catalyst using 10% aq NaOH furnished the allylated Schiff's base **11** in excellent yield. Acidic hydrolysis of the **11** liberated the free amine **12**, which in turn was protected as a carbamate **13** using CbzCl with K_2CO_3 as a base in DCM in 96% yield.

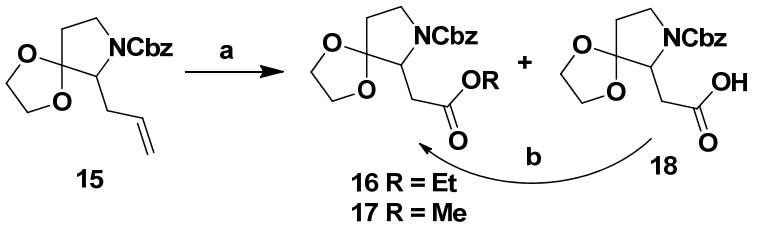
Urethane **13** underwent one-pot Michael addition followed by Dieckmann cyclization with ethyl acrylate using NaH as a base to afford the keto ester **14** in 72% yield. Keto ester **14** without purification was subjected to decarboxylation under Krapcho's conditions[7] to furnish the keto compound **8** in 78% yield. Keto compound **8** was protected as its acetal using ethylene glycol to afford urethane **15** in 90% yield. The structures of compounds **10** to **15** were confirmed by spectral analysis and were in complete agreement with literature data.[6, 8]



Scheme 2: ***Reagents and conditions:*** *a) Et_3N (1.2 equiv), PhCHO (0.9 equiv), molecular sieves, dry CH_2Cl_2, 0 ^oC, 1 h, 98%; b) 10% NaOH, 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), benzyl chloroformate (1.1 equiv), anhydrous CH_2Cl_2, 0 ^oC, 1 h, 91 %; e) NaH (1.2 equiv), ethyl acrylate (1.2 equiv), C_6H_6, rt, 1 h, reflux, 2-3 h, 72%; f) NaCl (4.0 equiv), DMSO-H_2O (3:1), 120-130 ^oC, 6 h, 78%; g) 1, 2-Ethane diol, PTSA, benzene, reflux, 8 h, 90%.*

Having urethane **15** (C ring) in hand, next task was to build D ring of camptothecin **1**. Thus urethane **15** was subjected to oxidative cleavage by using catalytic osmium tetroxide followed by $NaIO_4$ to afford the crude aldehyde, which on treatment with oxone[9] in methanol/ethanol at room temperature afforded corresponding ester urethane **16** in 60% yield along with acid **18** in 25% yield (Scheme 3). The formation of ester **16** and acid **18** was confirmed by spectroscopic data. IR spectrum of **16** displayed strong absorption band at 1734 cm^{-1} which indicated the presence of ester carbonyl. ^1H NMR spectrum of ester **16** showed signal at δ 1.26 as a triplet integrating for three protons and was assigned to methyl group ($\underline{CH_3}CH_2CO$-) protons. In addition to these peaks, three multiplets appeared at δ 1.88-2.21 (-$\underline{CH_2}CH_2N$-), 2.38-2.85 (-CO$\underline{CH_2}$CH-) and 3.35-3.59 (-COCH$_2\underline{CH}$-)

integrating for five protons. The triplet at δ 3.80 integrating for two protons was assigned to methylene protons next to ring nitrogen. The multiplet that appeared at δ 3.98-4.22 integrating for six protons was assigned to acetal and ester methylene protons which were merged, while benzylic and aromatic protons resonated at δ 5.07-5.23 as multiplet integrating for two protons and a singlet at δ 7.33 integrating for five protons respectively. ^{13}C NMR and DEPT spectra revealed it to be a mixture of rotamers by revealing doubling of some peaks. Peaks that appeared at δ 154.4, 154.5 (-NCO-) and 170.7 (-COOEt) were assigned to two carbonyl groups. Finally the structure of **16** was confirmed by mass spectral and elemental analysis. The mass spectrum of **16** showed the *m/z* peaks at 350 $(M + 1)^+$ and 372 $(M + Na)^+$. Elemental analysis was also found to be in good agreement with calculated values.

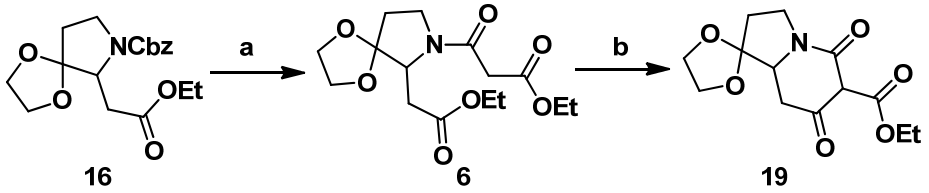


Scheme 3: ***Reagents and conditions:*** *a) i) OsO_4, acetone:H_2O, $NaIO_4$, 3 h; ii) Oxone, ethanol, rt, 16 h, 60%; b) Diazomethane, diethyl ether, 0 ^oC -rt, 95%.*

Acid **18** was also characterized by using spectral techniques. IR spectrum showed presence of acid by revealing a characteristic absorption at 3410 cm^{-1}. ^{1}H NMR spectrum of **18** showed signal at δ 5.12-5.17 as a multiplet integrating for two protons which was assigned to benzylic protons, while aromatic protons showed singlet at δ 7.34 integrating for five protons. The doublet of doublet at 2.41 integrating for one proton was assigned to methine proton. Rest of the protons resonated at expected positions as multiplets. ^{13}C NMR and DEPT spectra revealed it to be a mixture of rotamers. Its mass spectrum revealed a peak of $(M + H)^+$ at 322, and $(M + Na)^+$ at 344 which confirmed the formation of acid **18**. Finally, acid was confirmed by converting it into required ester by treatment with diazomethane to afford methyl ester **17** in 95% yield (Scheme 3).

Having requisite ester **16** in hand, next task was the Cbz deprotection and condensation. Thus, ester **16** was subjected to Cbz deprotection by using $Pd/C/H_2$ at 60 psi pressure followed by condensation with ethyl malonyl chloride using K_2CO_3 as the base in dry DCM to afford the amide **6** in 88% yield over two steps (Scheme 4)**.** The formation of

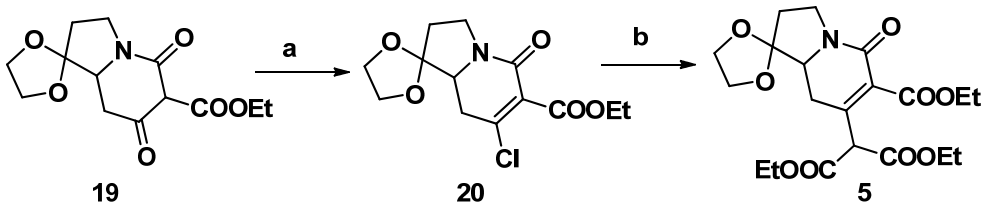
6 was confirmed by spectral analysis. IR spectrum of **6** showed the absorption bands at 1731 and 1647 cm^{-1} corresponding to ester and amide carbonyl respectively.



Scheme 4: ***Reagents and conditions:*** *a) i) Pd/C, ethanol, 60 psi, 2 h; ii) K_2CO_3, DCM, ethyl malonyl chloride, 0 °C, rt, 88%; b) NaH, ethanol, 0 °C-rt, 3 h, 98%.*

^{1}H NMR spectrum of **6** displayed the disappearance of singlet corresponding to aromatic protons while appearance of two new triplets at δ 1.26 and 1.28 integrating for three protons each were assigned to two ester methyl group protons, confirming the deprotection of Cbz and condensation with ethyl malonyl chloride, while rest of proton peaks resonated at expected positions. ^{13}C NMR along with DEPT spectra of **6** revealed it to be a mixture of rotamers. The mass spectrum of **6** showed *m/z* peaks at 330 and 352 corresponding to $(M + H)^+$, and $(M + Na)^+$ respectively. Elemental analysis was also found to be in good agreement with calculated values.

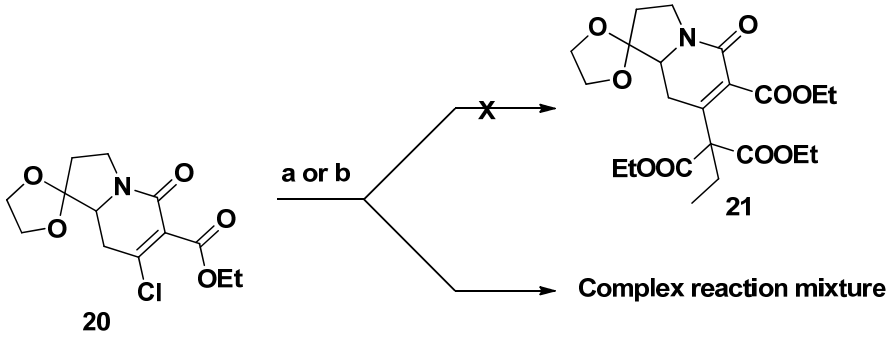
Amide **6** was treated with sodium hydride in ethanol at 0 °C-rt to yield the cyclised compound which existed in keto form **19**. The formation of **19** was confirmed by its IR spectrum (revealed characteristic absorptions at 1732, 1710, 1654 cm^{-1}), and without purification it was immediately subjected to next reaction with $POCl_3$ in anhydrous dichloromethane at reflux temperature to furnish chloro compound **20**. The resulting chloro compound **20** was unstable, so straight away it was subjected to addition-elimination reaction by treatment with diethyl malonate using sodium hydride as the base in anhydrous benzene at room temperature, overnight, to afford the product **5** in 65% yield (Scheme 5). IR spectrum of **5** showed a strong absorption band at 1732 cm^{-1} indicating the presence of ester functionality. The ^{1}H NMR spectrum of **5** displayed multiplet at δ 1.25-1.38 integrating for nine protons which was assigned to ester methyl groups. Singlet that appeared at δ 4.77 integrating for one proton was assigned to the proton flanked between two ester carbonyls thus confirming addition of diethyl malonate.



Scheme 5: ***Reagents and conditions:*** *a) $POCl_3$, DCM, reflux, 4 h; b) NaH, diethyl malonate, dry benzene, rt, overnight, 65%.*

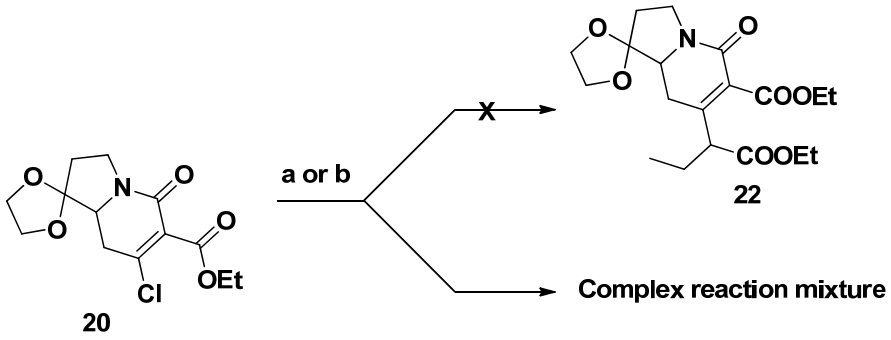
Other characteristic resonances were observed at δ 2.47 (dd, *J* = 16.8 and 5.05 Hz, 1H), 2.66 (dd, *J* = 13.7 and 16.8 Hz, 1H), 3.86 (dd, *J* = 13.7 and 5.05 Hz, 1H) assigned to protons at chiral center and adjecent diastereotopic protons, multiplets at δ 3.94-4.03 and 4.19-4.38 integrating for four and six protons respectively were assigned to acetal protons and ester methyl group protons, multiplets at δ 2.04-2.08 and 3.48-3.74 integrating for two protons each assigned to methyl protons in five membered ring containing nitrogen. ^{13}C NMR along with DEPT spectra of **5** showed seven peaks for eight methylene carbons. Peaks at δ 65.2 and 113.4 were ascribed to acetal carbons while rest of carbons associated with compound resonated at expected values. The mass spectrum of compound **5** showed the *m/z* peaks at 426 $(M + H)^+$ and 448 $(M + Na)^+$ and elemental analysis was in good agreement with calculated values.

As camptothecin **1** has ethyl group at C-20, it was thought to introduce ethyl group during addition-elimination steps. Accordingly, chloro compound **20** was subjected to addition-elimination with diethyl 2-ethylmalonate using strong bases like LDA and NaH in THF at -78 ^oC to room temperature but unfortunately it led to a complex reaction mixture (Scheme 6).



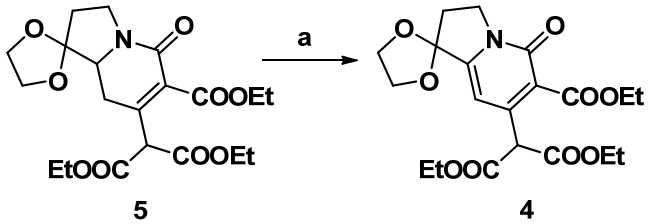
Scheme 6: ***Reagents and conditions:*** *a) LDA, THF, diethyl 2-ethylmalonate, -78 ^oC -rt; b) NaH, THF, diethyl 2-ethylmalonate, -78 ^oC -rt.*

Having failed in addition of diethyl 2-ethylmalonate, it was thought to introduce ethyl group by utilizing ethyl butyrate. Thus, chloro compound **20** was subjected to addition-elimination with ethyl butyrate using LDA as a strong base in THF at -78 ^{0}C to room temperature but unfortunately reaction ended up with complex reaction mixture (Scheme 7).



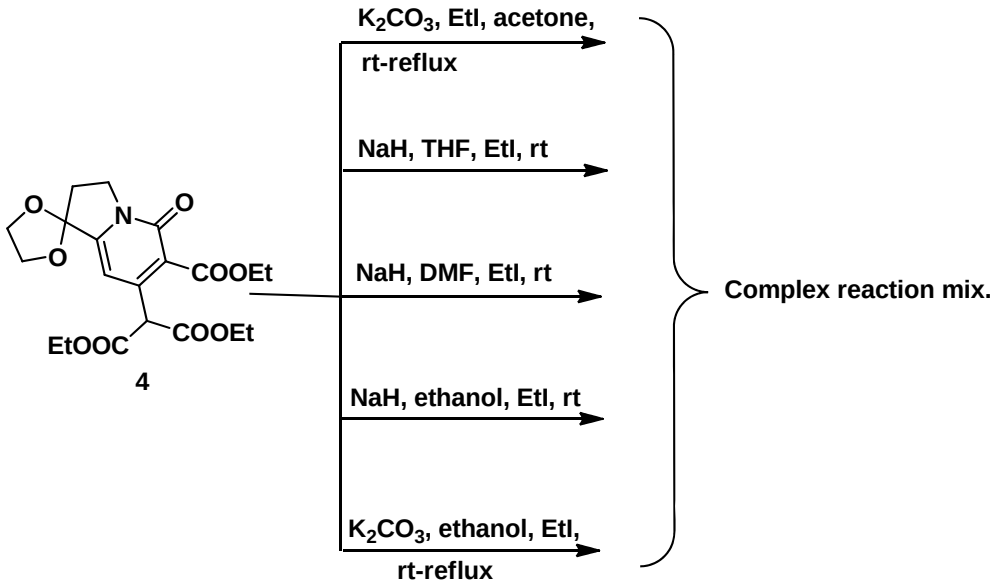
Scheme 7: ***Reagents and conditions:*** *a) LDA, THF, ethyl butyrate, -78 ^{o}C -rt.*

Since addition-elimination of diethyl 2-ethylmalonate and ethyl butyrate failed, it was thought to go ahead with triester **5** and to introduce ethyl group at later stages. Accordingly, triester **5** was subjected to the aromatization using DDQ as oxidant in 1, 4-dioxane at reflux conditions for 48 h to afford the pyridone **4** in 96% yield (Scheme 8). IR spectrum of **4** showed a strong absorption band corresponding to carbonyl. The ^{1}H NMR spectrum of **4** showed the disappearance of three doublet of doublets integrating for one proton each and appearance of one new singlet at δ 6.47 integrating for one proton which was assigned to aromatic proton thus confirming the aromatization. ^{13}C NMR along with DEPT spectra of **4** revealed the presence of two methine carbons at δ 54.4 and 100 which were assigned to tertiary methine and aromatic methine carbon respectively, while rest of the carbons resonated in agreement with proposed structure and lastly structure of compound **4** was confirmed by mass spectral and elemental analysis. The mass spectrum of compound **4** displayed the *m/z* peaks at 424 $(M + 1)^+$ and 446 $(M + Na)^+$ and its elemental analysis was also found to be in good agreement with calculated values.



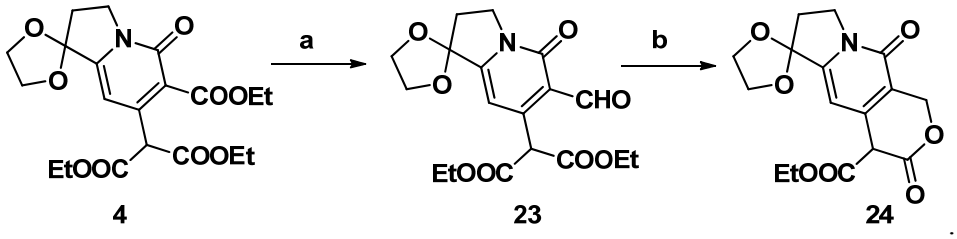
Scheme 8: ***Reagents and conditions:*** *a) DDQ, 1,4-dioxane, reflux, 48 h, 96%.*

Having the pyridone **4** in hand, attention was turned to introduction of ethyl group at required position. But under various conditions tried, the desired transformation could not be achieved; instead it ended up in a complex reaction mixture (Scheme 9).



Scheme 9

Having failure in introduction of ethyl group, it was thought to build lactone ring first. In that direction, the next task was to selectively reduce heteroaromatic ester to aldehyde. Earlier[6] the selective reduction of heteroaromatic ester in presence of aliphatic ester employing DIBAL-H was accomplished by this group. Therefore, pyridone **4** was subjected to selective reduction of aromatic ester using 3 eq. of DIBAL-H in THF as solvent at -60 ^{o}C to afford selectively reduced aromatic aldehyde **23** in 82% yield (Scheme 10).

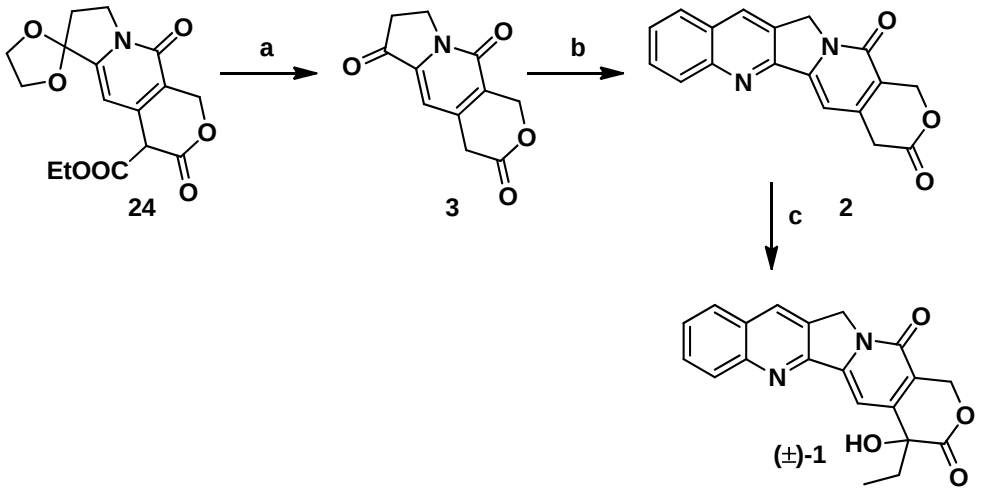


Scheme 10: ***Reagents and conditions:*** *a) DIBAL-H, THF, -60 ^{o}C, 2 h, 82%; b) $NaBH_4$, THF:H_2O (9:1), 0 ^{o}C, 5 min, 90%.*

IR spectrum of **23** showed a strong absorption band at 2720 cm^{-1} indicating the presence of aldehydic CH strech. The ^{1}H NMR spectrum of **23** displayed the absence of peaks corresponding to aromatic ester and a new singlet that appeared at δ 10.47 integrating for one proton was assigned to aldehyde proton. The deshielded singlet at δ 6.08 integrating for one proton was assigned to proton α to two carbonyls (-CO<u>CH</u>CO-). The triplet at δ 1.28 integrating for six protons and quartet at δ 4.24 integrating for four protons having coupling constant 7.2 Hz was assigned to aliphatic ester group protons. The multiplet at δ 4.12-4.18 integrating for six protons was assigned to acetal and methylene protons next to nitrogen. The triplet at δ 2.43 integrating for two protons was assigned to methylene in five membered ring. ^{13}C NMR along with DEPT spectra of **23** revealed the presence of aldehyde carbonyl carbon by resonance at δ 192.1 while rest of the carbons associated with structure resonated at expected positions. The mass spectrum of compound **23** displayed the *m/z* peaks at 380 $(M + H)^+$ and 402 $(M + Na)^+$ and its elemental analysis was also found to be in good agreement with calculated values.

With aldehyde **23** in hand, a reduction followed by cyclization would give the desired tricyclic lactone **24**. Thus aldehyde **23** on treatment with 1 eq. of sodium borohydride in THF:H_2O (9:1) at 0 ^{o}C for 5 min furnished the lactone **24** in 90% yield (Scheme 10). IR spectrum of **24** showed strong absorption bands at 1734, 1722 and 1647 cm^{-1} indicating the presence of ester, lactone and amide functionalities respectively. The ^{1}H NMR spectrum of **24** displayed the absence of peaks corresponding to aldehyde, and the presence of two new doublets that appeared at δ 5.36 and 5.52 (J = 15.8 Hz) which were attributed to the lactone methylene protons. The shielded singlet at δ 4.50 integrating for one proton was assigned to proton α to carbonyl group. ^{13}C NMR spectrum of **24** revealed the presence of 16 carbons and DEPT spectrum displayed six methylene carbons and only one methyl carbon. The mass spectrum of lactone **24** showed the *m/z* peaks at 336 and 358 corresponding to $(M + H)^+$ and $(M + Na)^+$ respectively. Elemental analysis was also found to be in good agreement with calculated values.

Having tricyclic lactone **24** in hand, acetal deprotection, ester hydrolysis and decarboxylation was achieved in one pot by refluxing lactone **24** with 10% HCl for 6 h to afford the tricyclic lactone **3** in 82% yield (Scheme 11). IR spectrum of **3** showed strong absorption bands at 1722, 1710 and 1667 cm^{-1} indicating the presence of lactone, ketone and amide carbonyls respectively.



Scheme 11: ***Reagents and conditions:*** *a) 10% HCl, 90-100 ^{o}C, 6 h, 82%; b) Ref. 10; c) Ref. 11, 12, 13.*

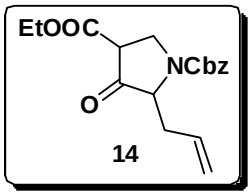
The ^{1}H NMR spectrum of **3** showed the absence of peaks corresponding to ester, and the presence of two new singlets that appeared at δ 3.66 and 5.44 integrating for two protons each were assigned to lactone methylene protons. The two triplets at δ 2.97 and 4.35 integrating for two protons each having coupling constant 7.0 Hz were assigned to methylene protons in five membered ring containing nitrogen. ^{13}C NMR along with DEPT spectra of **3** revealed the presence of four methylene carbons and one methine carbon. The mass spectrum of **3** showed the *m/z* peaks at 219 and 242 corresponding to $(M)^{+}$ and $(M + Na)^{+}$ respectively. Lactone **3** is the common intermediate in Shamma's synthesis[10] which could be converted to (±)-camptothecin **1** by a three-step sequence *i.e.* Friedlander condensation with 2-amino benzaldehyde to give pentacyclic core **2** which on alkylation and hydroxylation furnished (±)-camptothecin **1**.[11,12,13] This constitutes a formal synthesis of camptothecin.

2.3.5 Conclusion

In conclusion, a formal synthesis of (±)-camptothecin *via* tricyclic lactone **3**, which is versatile synthon for synthesis of camptothecin and its analogues, employing simple reaction conditions and from cheap, commercially available starting material with an overall yield of 12.1% is achieved.

2.3.6 Experimental

1-Benzyl 3-ethyl 5-allyl-4-oxopyrrolidine-1, 3-dicarboxylate (14)



To the stirred suspention of of sodium hydride (1.73 g, 36 mmol) (50% suspention prewashed with dry pet ether 2 x 10 mL) in dry benzene (100 mL), was added urethane **13** (10 g, 36 mmol) in dry benzene (50 mL). The reaction mixture was stirred till evolution of hydrogen ceased. To the generated sodium salt was dropwise added ethyl acrylate (4.2 mL, 39.6 mmol) in benzene (50 mL), over 20 min. The mixture was allowed to stir at room temperature for 30 mins and then refluxed for 2 h. The reaction mixture was quenched with 10% HCl and organic phase was separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL) and combined organic phases were dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure to furnish crude β-keto ester **14** which on purification by column chromatography (SiO_2) using 25% ethyl acetate in pet ether as eluent furnished β-keto ester **14** (8.5 g, 72%) as colorless oil.

Mol. Formula : $C_{17}H_{19}NO_5$ (MW: 331.36).

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

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.45-3.00 (m, 2H), 3.75 (d, *J* = 6.5 Hz, 2H), 4.00-4.55 (m, 4H), 4.95-5.40 (m, 2H), 5.20 (s, 2H), 5.70 (m, 1H), 7.35 (s, 5H).

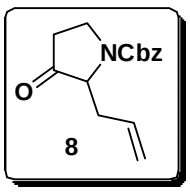
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.1, 14.2, 14.3, 34.3, 35.5, 45.3, 45.9, 48.9, 49.1, 53.3, 60.6, 62.1, 62.2, 67.0, 119.2, 119.7, 120.1, 128.0, 128.2, 128.3, 128.6, 131.6, 131.8, 132.2, 136.3, 136.5, 136.8, 154.3, 154.5, 154.8, 166.2, 167.5, 169.2 (Mixture of rotamers).

Mass (ESI) m/z **:** 354 $(M + Na)^+$.

Elemental analysis : Calculated: C, 65.24; H, 6.39; N, 4.23%

: Found: C, 64.35; H, 6.20; N, 4.40%

Benzyl 2-allyl-3-oxopyrrolidine-1-carboxylate (8)



To the stirred solution of β-keto ester **14** (10 g, 30.1 mmol) in DMSO:H_2O (3:1), was added NaCl (7 g, 120 mmol) and the mixture was stirred under reflux for 3 h. The reaction mixture was cooled and water (50 mL) was added and extracted twice with ethyl acetate (3 x 30

mL). The combined organic phases were dried over anhydrous sodium sulphate, filterd and concentrated under reduced pressure to furnish keto compound **8** (6.1 g, 78%) as yellow oil, which was pure enough for further use.

Mol. Formula **:** $C_{15}H_{17}NO_3$ (MW: 259.30).

IR ($CHCl_3$) **:** 1722, 1702, 1216, 1053, 762, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.34-2.70 (m, 4H), 3.49-3.73 (m, 1H), 3.87-4.14 (m, 2H), 4.99-5.26 (m, 4H), 5.54-5.74 (m, 1H), 7.36 (s, 5H).

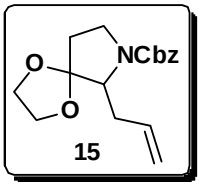
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 35.4, 35.9, 42.0, 61.7, 67.0, 119.4, 127.8, 128.0 (2C), 128.3 (2C), 131.6, 136.1, 154.7, 212.5.

Mass (ESI) m/z **:** 260 $(M + H)^+$, 282 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 69.48; H, 6.61; N, 5.40%

: Found: C, 69.57; H, 6.73; N, 5.34%

Benzyl 6-allyl-1,4-dioxa-7-azaspiro[4.4]nonane-7-carboxylate (15)



15

A mixture of keto compound **8** (15 g, 57.84 mmol), ethylene glycol (4.8 mL, 186.72 mmol) and catalytic amount of PTSA (500 mg) in benzene was refluxed azeotropically for 8 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution. The aquoues layer was further extracted with ethyl acetate (2 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was column chromatographed using pet ether/ethyl acetate (9:1) to provide compound **15** (15.79 g, 90%) as colorless thick oil.

Mol. Formula **:** $C_{17}H_{21}NO_4$ (MW: 303.35).

IR (Neat) **:** 2894, 1692, 1416, 763, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.86-2.50 (m, 4H), 3.45-3.52 (m, 2H), 3.67-3.80 (m, 1H), 3.86-4.08 (m, 4H), 4.95-5.18 (m, 4H), 5.57-5.94 (m, 1H), 7.36 (s, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 32.0, 32.7, 34.8, 35.5, 42.8, 61.8, 62.0, 63.6, 64.5, 65.0, 66.3, 66.6, 113.7, 114.3, 117.0, 126.5, 126.9, 127.4, 127.6, 128.1, 134.4, 134.5, 136.3, 136.5, 154.6, 154.8. (mixture of rotamers).

Mass (ESI) (m/z) **:** 304 $(M + H)^+$.

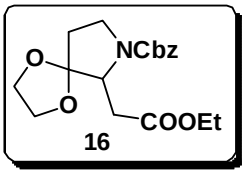
Elemental analysis **:** Calculated C, 63.88; H, 8.93; N, 8.28%

: Found: C, 63.49; H, 8.60; N, 8.21%

Benzyl 6-(2-methoxy-2-oxoethyl)-1,4-dioxa-7-azaspiro[4.4]nonane-7-carboxylate (16) and 2-(7-((benzyloxy) carbonyl)-1,4-dioxa-7-azaspiro[4.4]nonan-6-yl)acetic acid (18)

To the stirred solution of olefin **15** (8.0 g, 26.37 mmol) in acetone-water (50 mL, 3:1), was added catalytic amount of OsO_4 at room temperature and stirred for 10 minutes. The reaction mixture became black coloured. $NaIO_4$ (14.1 g, 65.93 mmol) was added portionwise and reaction mixture was left to stir for 3 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 (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to furnish aldehyde. The generated crude aldehyde (assuming 100% conversion) was treated with oxone (17.8 g) in ethanol (20 mL) under argon atmosphere and allowed to stir at room temperature. After the completion of reaction (16 h, TLC) the solvent was removed on rotary evaporator under reduced pressure and the resultant residue was dissolved in H_2O (25 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue thus obtained was purified by flash column chromatography (SiO_2) using first ethyl acetate/pet ether (4:6) as an eluent to furnish the ester **16** as a viscous yellow liquid (5.3 g, 60%). Eluting further ethyl acetate/petroleum ether (8:2) furnished acid **18** (2.1 g, 25%).

Benzyl 6-(2-methoxy-2-oxoethyl)-1,4-dioxa-7-azaspiro[4.4]nonane-7-carboxylate (16)



16

Mol. Formula **:** $C_{17}H_{23}NO_6$ (MW: 349.38).

IR (Neat) **:** 1734, 1654, 1464, 753, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.88-2.21 (m, 2H), 2.38-2.85 (m, 2H), 3.35-3.59 (m, 1H), 3.80 (t, *J* = 6.0 Hz, 2H), 3.98-4.22 (m, 6H), 5.07-5.23 (m, 2H), 7.33 (s, 5H).

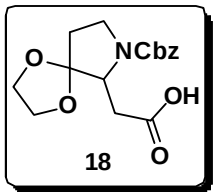
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.0, 31.7, 32.4, 35.7, 36.7, 42.9, 43.0, 59.0, 59.3, 60.0, 64.2, 65.3, 66.5, 66.6, 113.5, 114.1, 127.4, 127.6, 127.7, 128.2, 136.3, 136.4, 154.4, 154.5, 170.7.

Mass (ESI) m/z **:** 350 $(M + H)^+$, 372 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 61.88; H, 6.64; N, 4.01%

: Found: C, 62.01; H, 6.62; N, 3.99%

2-(7-((Benzyloxy) carbonyl)-1, 4-dioxa-7-azaspiro[4.4]nonan-6-yl)acetic acid (18)



Mol. Formula **:** $C_{16}H_{19}NO_6$ (MW: 321.33).

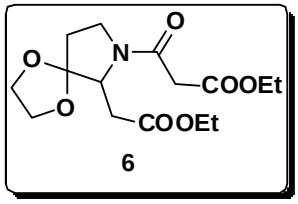
IR (Neat) **:** 3410, 1705**,** 1691, 1424, 748, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.90-2.28 (m, 2H), 2.41 (dd, *J* = 10.5 and 5.9 Hz, 1H), 2.65-2.95 (m, 1H), 3.35-3.59 (m, 2H), 3.81-4.10 (m, 5H), 5.12-5.17 (m, 2H), 7.34 (s, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 31.7, 32.5, 35.7, 36.5, 43.0, 59.0, 59.3, 64.4, 65.4, 66.8, 113.5, 114.2, 127.5, 127.7, 127.8, 128.3, 136.2, 154.7, 176.1, 176.2.

Mass (ESI) m/z **:** 322 $(M + H)^+$, 344 $(M + Na)^+$.

Ethyl 3-(6-(2-ethoxy-2-oxoethyl)-1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-3-oxopropanoate (6)



The carbamate **16** (5 g, 14.9 mmol) was taken in methanol (30 mL) and was subjected to hydrogenation at 60 psi pressure with Pd/C (10%, 0.1 g) as the catalyst for 2 h. After completion of reaction, the reaction mixture was filtered through a celite bed and the filtrate was concentrated under reduced pressure to furnish quantitative yield of amine. To the stirred solution of amine in anhydrous DCM, was added K_2CO_3 (2.26 g, 16.4 mmol) followed by ethyl malonyl chloride (2.1 mL, 16.4 mmol) at 0 ^oC and left to stir at room temperature under nitrogen atmosphere till the completion of reaction. The reaction mixture was diluted with water and the DCM layer separated. The aqueous layer was extracted with DCM (3 x 30 mL). Combined organic

layers were washed with aq. $NaHCO_3$, brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (SiO_2) using ethyl acetate/pet ether (4:6) as eluent to afford the ester **6** (4.1 g, 88%) as a pale yellow oil.

Mol. Formula **:** $C_{15}H_{23}NO_7$ (MW: 329.35).

IR (Neat) **:** 1731, 1647, 1416, 1173 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.95-2.59 (m, 4H), 2.83 (dd, *J* = 3.4 and 16.1 Hz, 1H), 3.34 and 3.41 (2s, 2H), 3.48-3.59 (m, 2H), 3.77-4.05 (m, 4H), 4.07-4.31 (m, 4H).

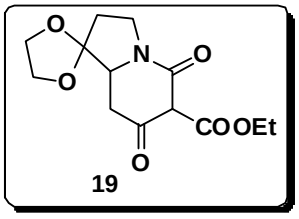
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.7, 13.9, 30.8, 32.5, 34.6, 37.2, 41.3, 41.4, 42.2, 43.9, 58.7, 59.5, 60.1, 60.5, 61.1, 64.1, 64.3, 65.2, 112.9, 113.9, 164.8, 165.0, 166.9, 167.0, 170.2, 170.5. (Mixture of rotamers)

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

Elemental analysis **:** Calculated: C, 54.70; H, 7.04; N, 4.25%

: Found: C, 54.65; H, 6.99; N, 4.23%

Ethyl 5',7'-dioxohexahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-indolizine]-6'-carboxylate (19)



19

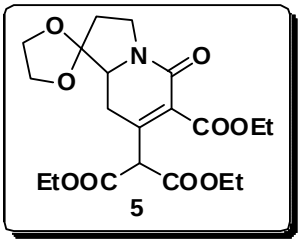
50% NaH (0.167 g, 6.97 mmol) was washed with dry petroleum ether (2 x 5 mL). Absolute ethanol (30 mL) was added dropwise at 0 ^oC followed by gradual addition of amide **6** (2 g, 6.39 mmol) and allowed to stir for 2-3 h at room temperature. After the disappearance of starting material (TLC), the reaction was quenched by 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 to afford keto compound **20** as a thick yellow liquid (1.6 g, 98%).

Mol. Formula **:** $C_{13}H_{17}NO_6$ (MW: 283.28).

IR (Neat) **:** 1732, 1710, 1654, 1168 cm^{-1}.

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

Diethyl 2-(6'-(ethoxycarbonyl)-5'-oxo-3', 5', 8', 8a'-tetrahydro-2'*H*-spiro[1,3]dioxolane-2,1'-indolizin]-7'-yl)malonate (5)



5

To a well-stirred solution of keto compound **19** (1 g, 3.53 mmol) in anhydrous CH_2Cl_2 (10 mL), was added $POCl_3$ (0.33 mL, 3.53 mmol) dropwise at room temperature. The resultant mixture was refluxed under argon atmosphere till the completion of reaction (4 h, TLC). After the completion of reaction, the reaction mixture was cooled to room temperature and reaction was quenched by the addition of saturated $NaHCO_3$ at 0 ^oC. 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 under diminished pressure to afford the crude chloro compound **20**. The crude chloro compound **20** was used as such for next reaction.

To the stirred suspension of 50% NaH [(0.101 g, 4.23 mmol), prewashed with anhydrous petroleum ether (3 x 5 mL)], dry benzene (15 mL) was added followed by gradual addition of diethyl malonate (0.64 g, 4.23 mmol) at room temperature and stirred for 30 minutes. The crude chloro compound **20** in dry benzene was added dropwise over 15 min and the reaction mixture was allowed to stir overnight at room temperature. After the completion of reaction (TLC), reaction was quenched by addition of saturated NH_4Cl solution. 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 (4:6) as an eluent to furnish the compound **5** as a viscous yellow liquid (0.97 g, 65 %).

Mol. Formula **:** $C_{20}H_{27}NO_9$ (MW: 425.17).

IR (Neat) **:** 1732, 1664, 1629, 1444, 1215 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25-1.38 (m, 9H), 2.04-2.08 (m, 2H), 2.47 (dd, *J* = 16.8 and 5.05, 1H), 2.66 (dd, *J* = 13.7 and 16.8 Hz, 1H), 3.48-3.74 (m, 2H), 3.86 (dd, *J* = 13.7 and 5.05 Hz, 1H), 3.94-4.03 (m, 4H), 4.19-4.38 (m, 6H), 4.77 (s, 1H).

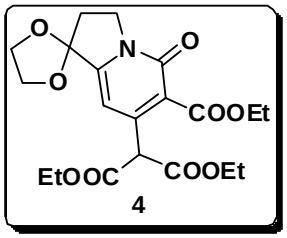
^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.85, 13.87, 13.9, 25.8, 33.5, 41.9, 55.0, 59.5, 61.6, 62.10, 62.17, 65.2 (2C), 113.4, 130.8, 143.2, 159.5, 164.7, 165.7, 166.3.

Mass (ESI) m/z **:** 426 $(M + H)^+$, 448 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 56.46; H, 6.40; N, 3.29%

: Found: C, 56.45; H, 6.39; N, 3.31%

Diethyl 2-(6'-(ethoxycarbonyl)-5'-oxo-3',5'-dihydro-2'*H*-spiro[[1,3]dioxolane-2,1'-indolizin]-7'-yl) malonate (4)



4

A mixture of dihydropyridone **5** (0.5 g, 1.17 mmol) and DDQ (0.293 g, 1.29 mmol) in anhydrous 1, 4-dioxane (20 mL) was refluxed till the completion of reaction (48 h, TLC). The reaction mixture was diluted with ethyl acetate and filtered. The filtrate was quenched with aqueous $NaHCO_3$ solution. The organic phase was separated and aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The generated residue was purified by flash column chromatography (SiO_2) eluting with ethyl acetate/pet ether (6:4) as a solvent system to yield pyridone **4** as a pale yellow liquid (0.47 g, 96 %).

Mol. Formula **:** $C_{20}H_{25}NO_9$ (MW: 423.15).

IR ($CHCl_3$) **:** 1735, 1654, 1602, 1508, 1251 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28 ((t, *J* = 7.20 Hz, 6H), 1.38 (t, *J* = 7.07 Hz, 3H), 2.39 (t, *J* = 6.95 Hz, 2H), 4.23 (q, *J* = 7.20, 2H), 4.24 (q, *J* = 7.20, 2H), 4.40 (q, *J* = 7.07, 2H), 4.09-4.18 (m, 6H), 4.88 (s, 1H), 6.47 (s, 1H).

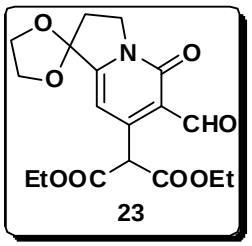
^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8 (2C), 14.0, 33.5, 45.0, 54.4, 61.7, 62.2 (2C), 65.5 (2C), 100.0, 112.8, 124.7, 144.8, 149.6, 157.9, 165.4, 166.3 (2C).

Mass (ESI) m/z **:** 424 $(M + H)^+$, 446 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 56.73; H, 5.95; N, 3.31%

: Found: C, 56.71; H, 5.94; N, 3.32%

Diethyl 2-(6'-formyl-5'-oxo-3',5'-dihydro-2'*H*-spiro[[1,3]dioxolane-2,1'-indolizin]-7'-yl) malonate (23)



23

The compound **4** (0.2 g, 0.476 mmol) was taken in dry THF (20 mL) under argon atmosphere and temperature lowered to –60 ^{o}C. DIBAL-H (2M solution in toluene, 0.710 mL, 1.41 mmol) was added dropwise and left to stir at same temperature till the completion of reaction (TLC). The reaction was quenched at –60^{0}C with an equal amount of methanol and water as that of DIBAL-H and then warmed to room temperature. The gelatinous precipitate was filtered through the celite and washed thoroughly with THF. The filtrate was concentrated under reduced pressure and resultant residue was purified by flash column chromatography (SiO_2) eluting with the mixture of ethyl acetate/petroleum ether (5:5) as a solvent system to deliver the aldehyde **23** (0.146 g, 82%) as yellowish thick oil.

Mol. Formula **:** $C_{18}H_{21}NO_8$ (MW: 379.13).

IR (Neat) **:** 2720, 1732, 1718, 1699, 1253 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, *J* = 7.2 Hz, 6H), 2.43 (t, *J* = 6.7 Hz, 2H), 4.12-4.18 (m, 6H), 4.24 (q, *J* = 7.2 Hz, 4H), 6.08 (s, 1H), 6.39 (s, 1H), 10.47 (s, 1H).

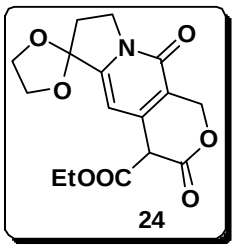
^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9 (2C), 33.4, 45.1, 52.9, 62.1 (2C), 65.7 (2C), 101.1, 113.0, 121.5, 150.1, 154.0, 161.9, 166.9 (2C), 192.1.

Mass (ESI) m/z **:** 380 $(M + H)^+$, 402 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 56.99; H, 5.58; N, 3.69%.

: Found: C, 56.97; H, 5.60; N, 3.70 %.

Ethyl 3',10'-dioxo-1',3',4',7',8',10'-hexahydrospiro[[1,3]dioxolane-2,6'-pyrano[3,4-f]indolizine]-4'-carboxylate (24)



24

To the stirred solution of aldehyde **23** (0.1 g, 0.263 mmol) in THF/H_2O (9:1) at 0 ^{o}C, was added $NaBH_4$ (0.004 g, 0.131 mmol) and stirred for 5 min. The reaction was quenched with 10% HCl and extracted with chloroform. The organic layer was separated and aqueous phase further extracted with 2 x 10 mL of chloroform. 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 (7:3) as an eluent to furnish the compound **24** as viscous yellow liquid (0.079 g, 96%).

Mol. Formula **:** $C_{16}H_{17}NO_7$ (MW: 335.31).

IR (Neat) **:** 1734, 1722, 1647, 1350, 1150 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, *J* = 7.0 Hz, 3H), 2.41 (t, *J* = 6.7 Hz, 2H), 4.12-4.15 (m, 6H), 4.17 (q, *J* = 7.0 Hz, 2H), 4.50 (s, 1H), 5.36 (d, *J* = 15.8 Hz, 1H), 5.52 (d, *J* = 15.8 Hz, 1H), 6.24 (s, 1H).

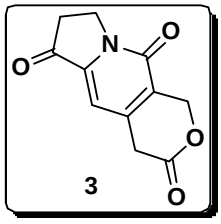
^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 29.6, 33.9, 44.9, 52.0, 63.1, 65.6, 66.7, 98.8, 112.9, 121.0, 140.7, 149.3, 157.5, 164.9, 165.1.

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

Elemental analysis **:** Calculated: C, 57.31; H, 5.11; N, 4.18%

: Found: C, 57.21; H, 5.01; N, 4.12%

7,8-Dihydro-1*H*-pyrano[3,4-*f*]indolizine-3,6,10(4*H*)-trione (3)



To the lactone **24** (0.05 g, 0.149 mmol) was added 10% HCl (10 mL) and refluxed for 6 h till the completion of reaction (TLC). The reaction mixture was cooled and 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/pet ether (9:1)) to afford tricyclic lactone **3** (0.026 g, 82%) as oil, which was gradually converted to white solid.

Mol. Formula **:** $C_{11}H_9NO_4$ (MW: 219.19).

IR (Neat) **:** 1722, 1710, 1667, 1310, 1125 cm^{-1}.

Melting point **:** 51-52 ^oC

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 2.97 (t, *J* = 7.0 Hz, 2H), 3.66 (s, 2H), 4.35 (t, *J* = 7.0 Hz, 2H), 5.44 (s, 2H), 6.75 (s, 1H).

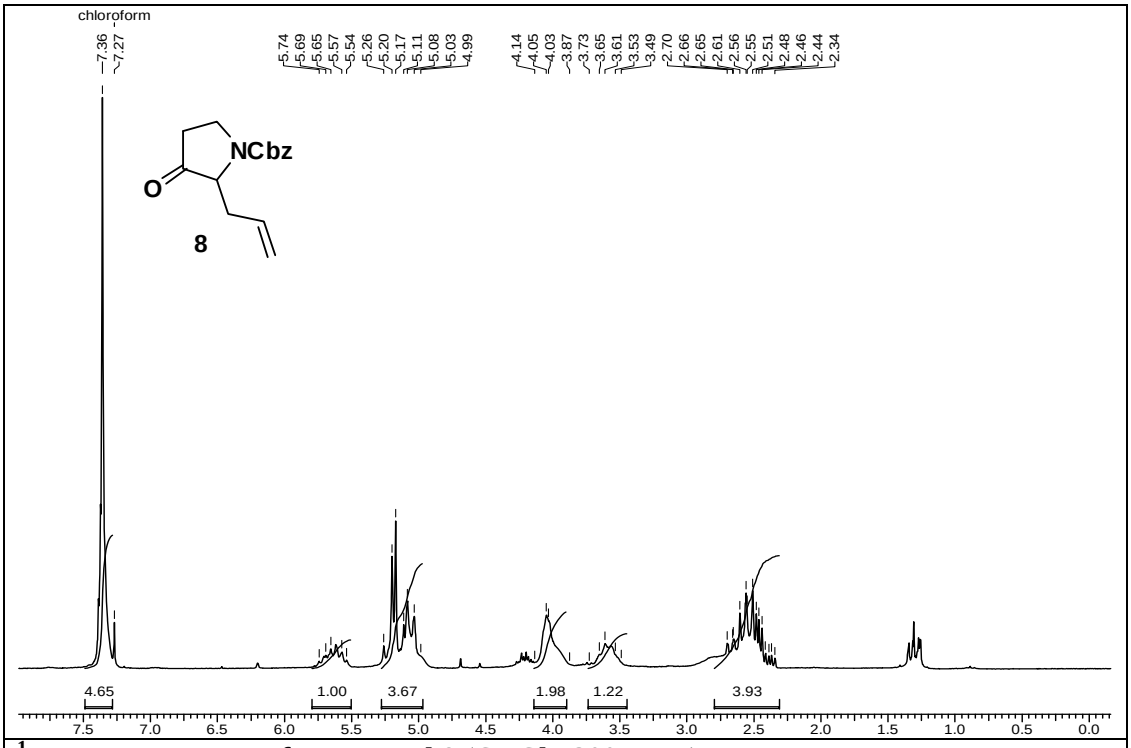
^{13}C NMR ($CDCl_3$, 100 MHz): δ 33.6, 34.1, 42.1, 66.2, 102.5, 126.6, 139.6, 142.4, 157.7, 167.2, 195.8.

Mass (ESI) m/z **:** 219 $(M)^+$, 242 $(M + Na)^+$.

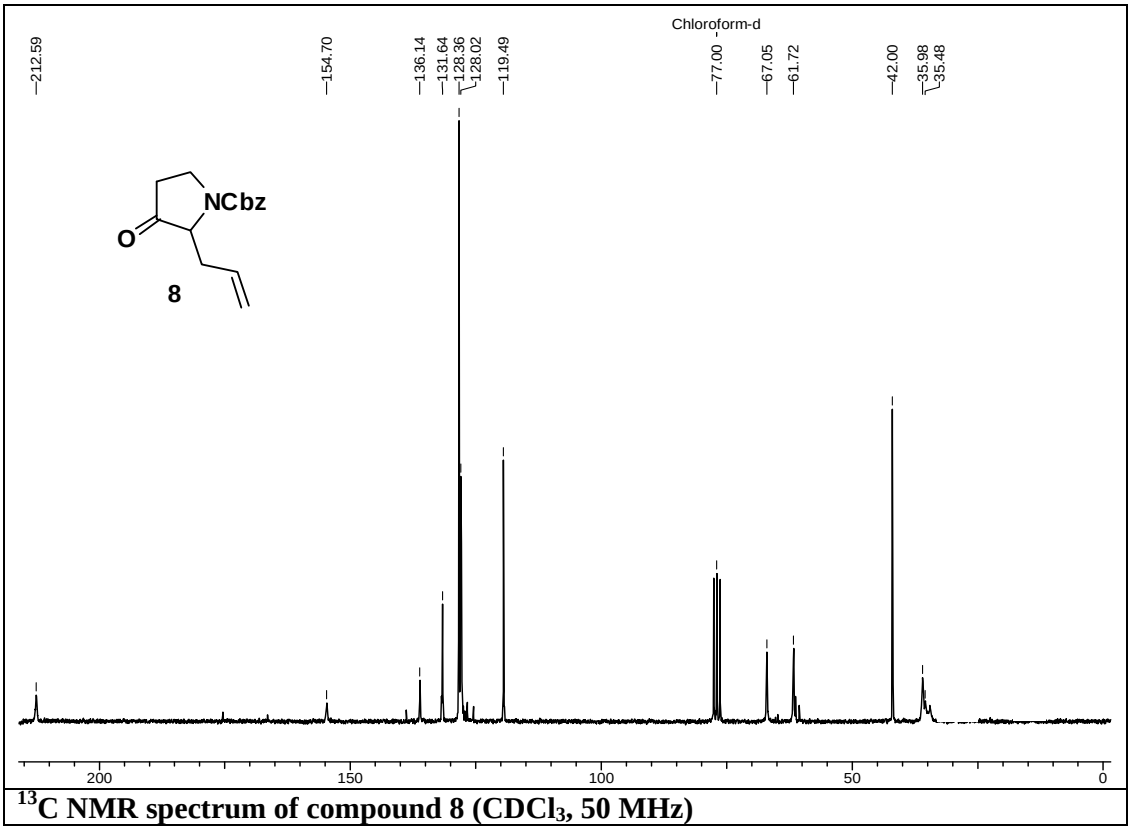
Elemental analysis **:** Calculated: C, 60.27; H, 4.14; N, 6.39%

: Found: C, 60.25; H, 4.04; N, 6.29%

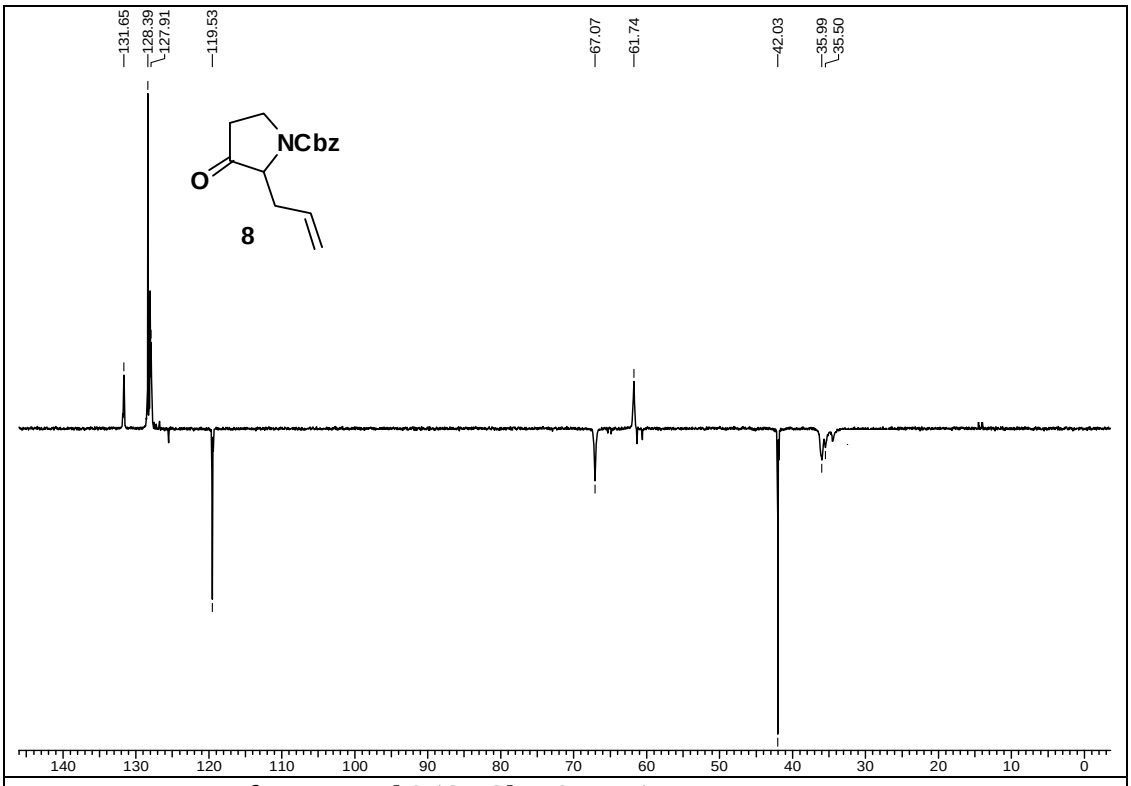
2.3.7 Spectra



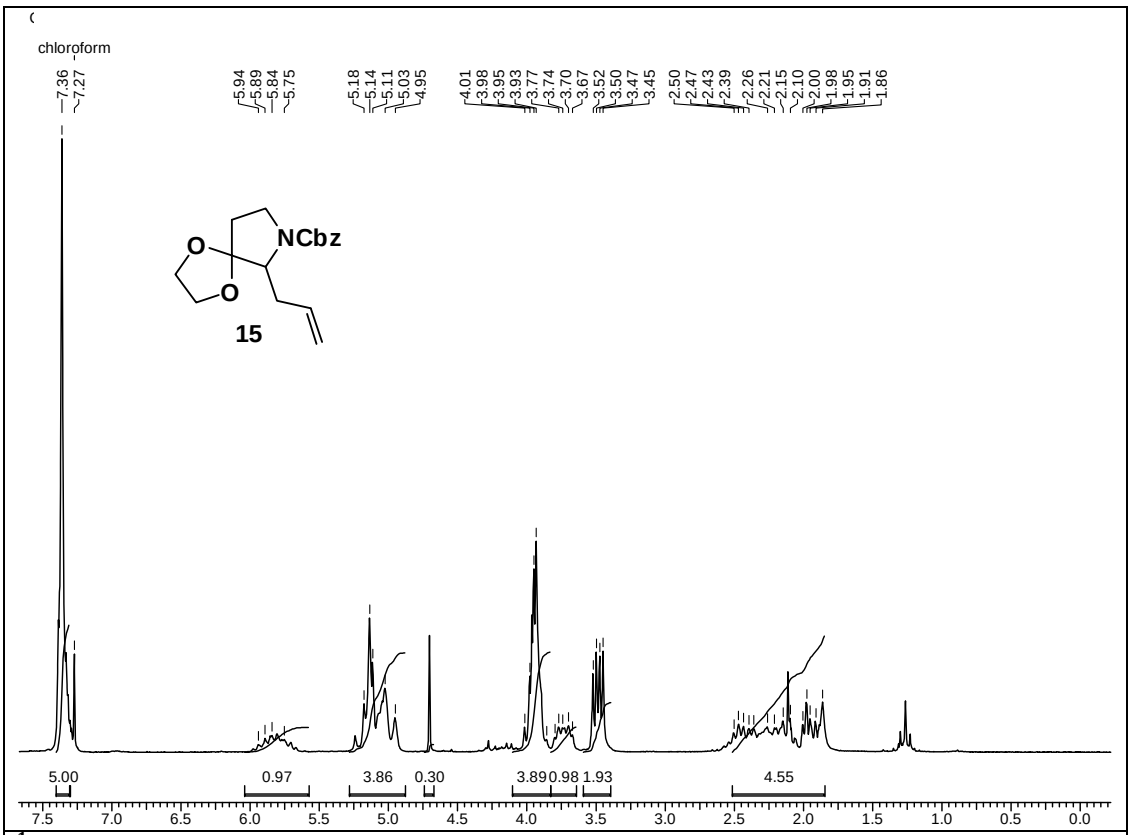
^{1}H NMR spectrum of compound 8 ($CDCl_3$, 200 MHz)



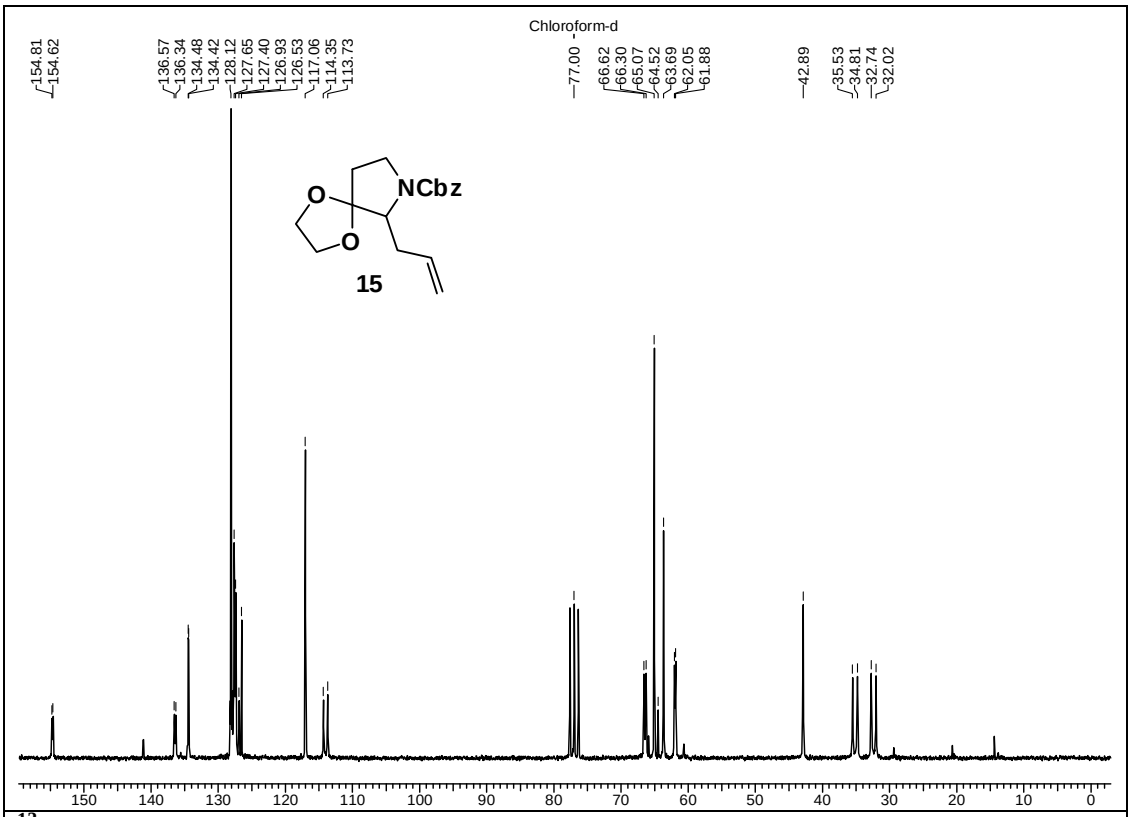
^{13}C NMR spectrum of compound 8 ($CDCl_3$, 50 MHz)



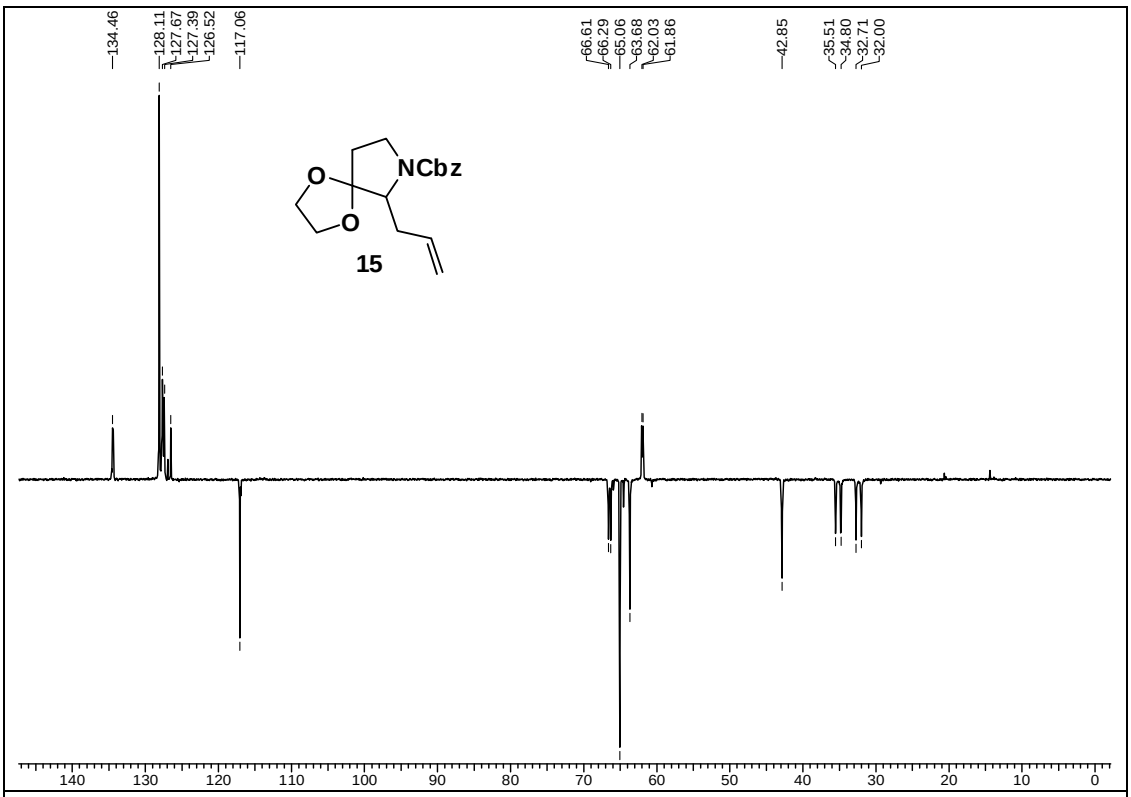
DEPT spectrum of compound 8 ($CDCl_3$, 50 MHz)



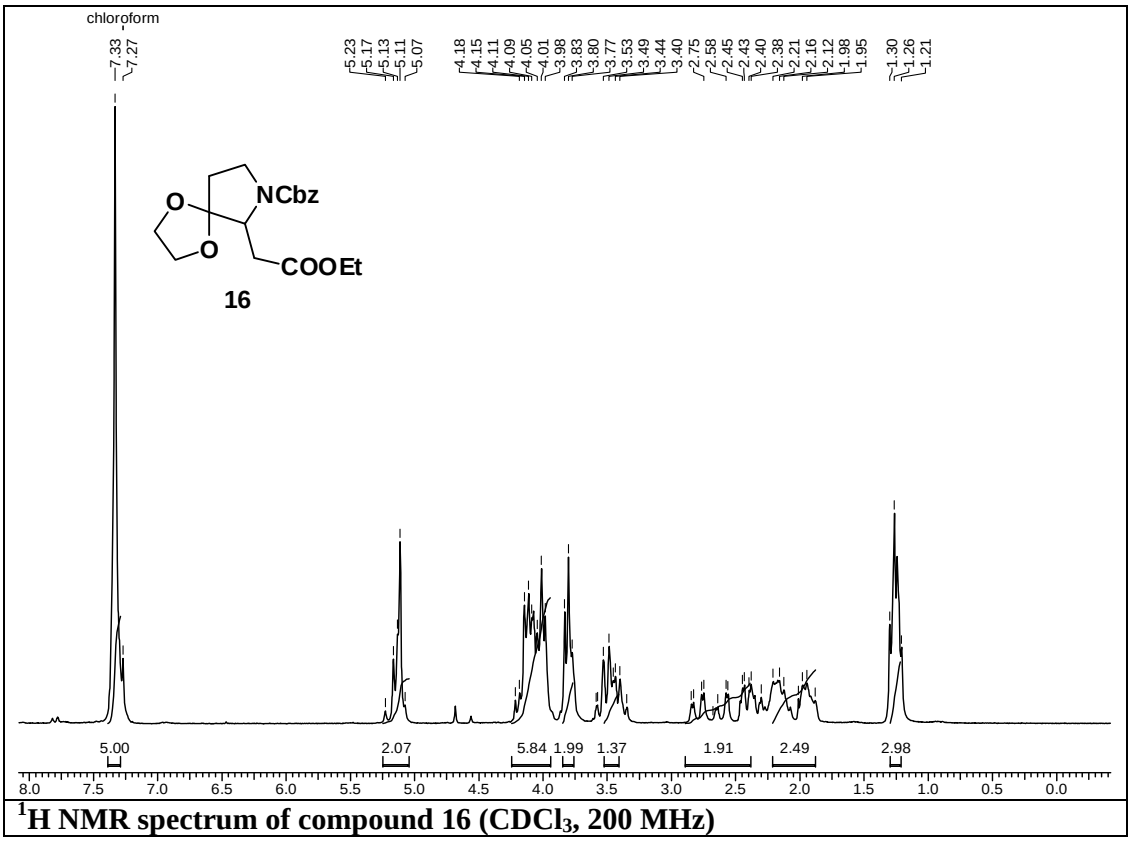
^{1}H NMR spectrum of compound 15 ($CDCl_3$, 200 MHz)



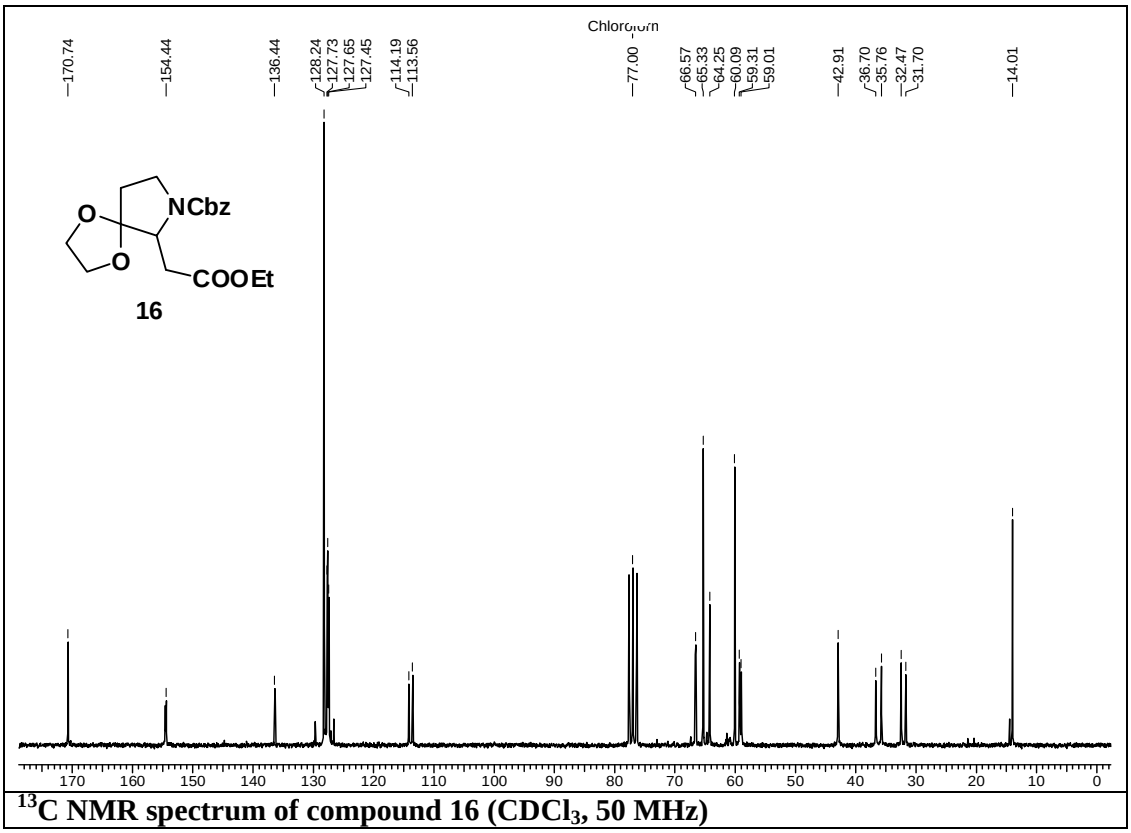
^{13}C NMR spectrum of compound 15 ($CDCl_3$, 50 MHz)



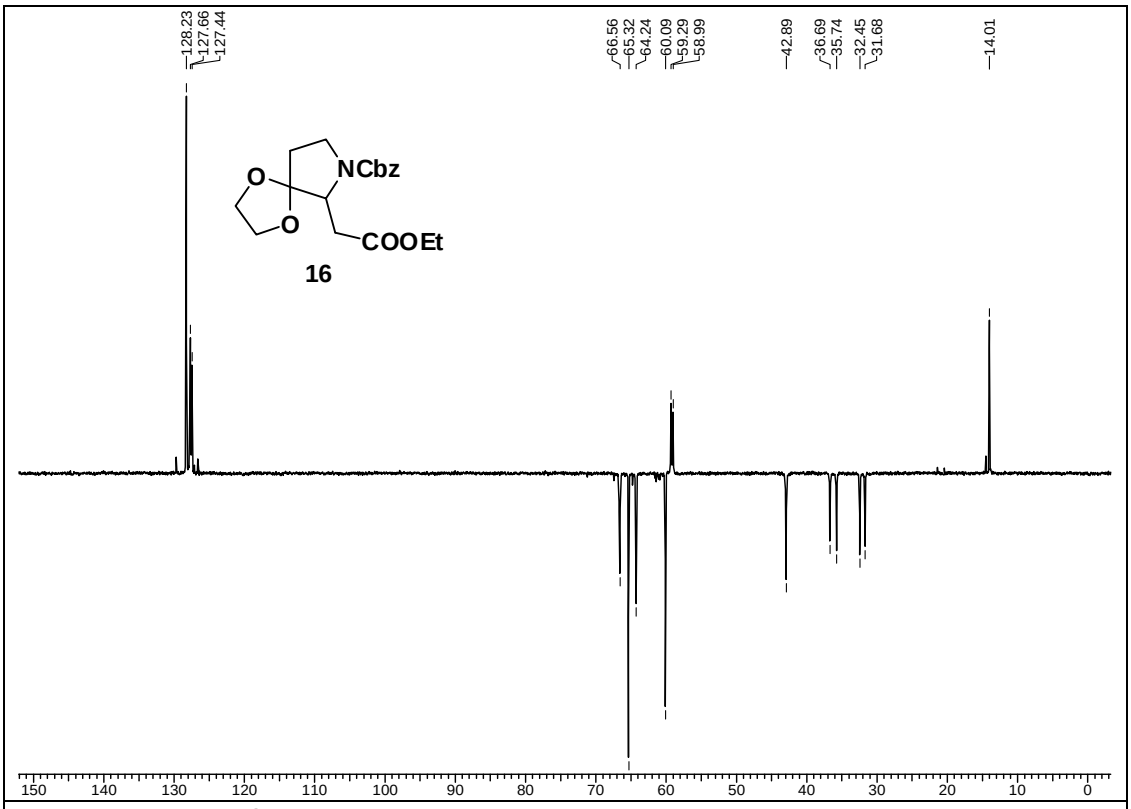
DEPT spectrum of compound 15 ($CDCl_3$, 50 MHz)



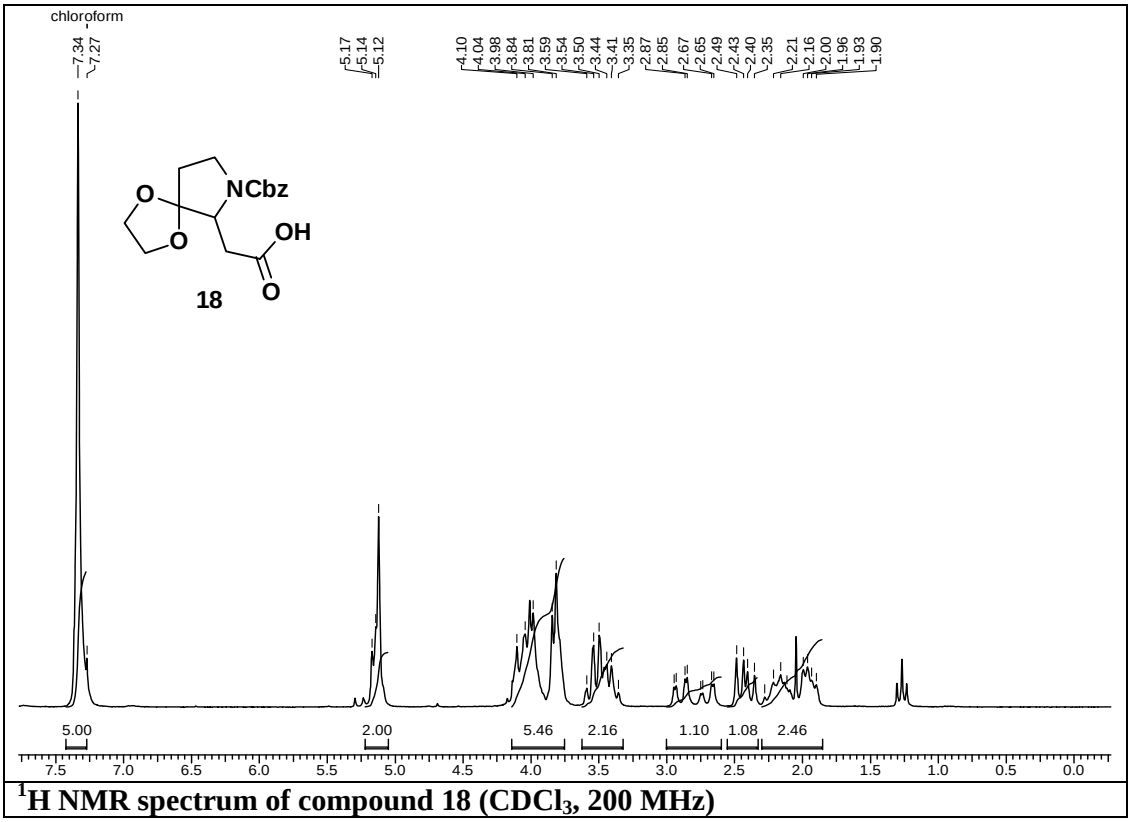
^{1}H NMR spectrum of compound 16 ($CDCl_3$, 200 MHz)



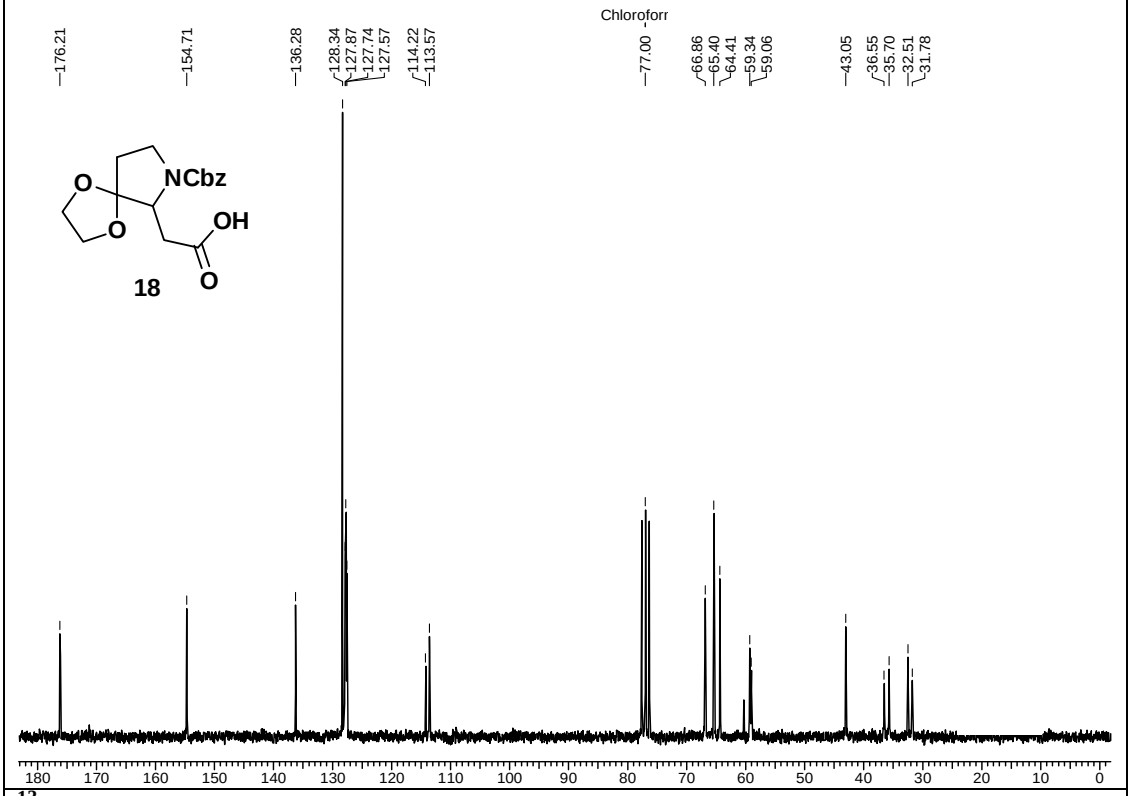
^{13}C NMR spectrum of compound 16 ($CDCl_3$, 50 MHz)



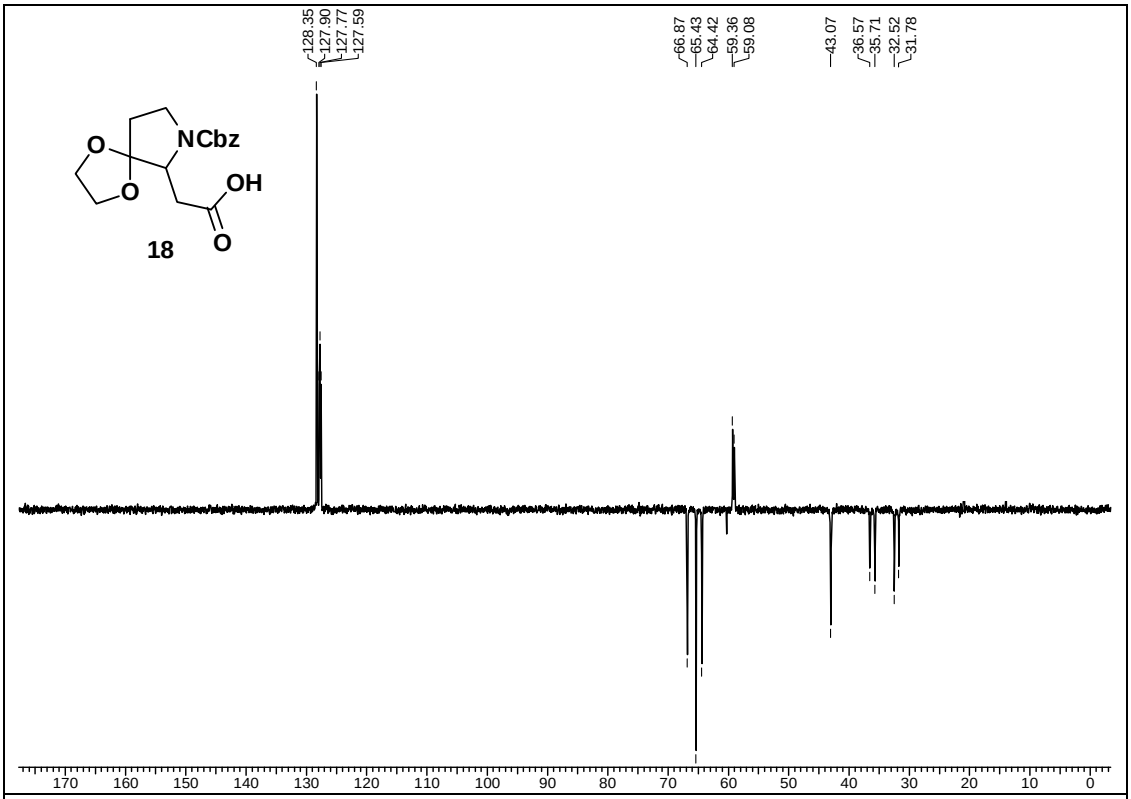
DEPT spectrum of compound 16 ($CDCl_3$, 50 MHz)



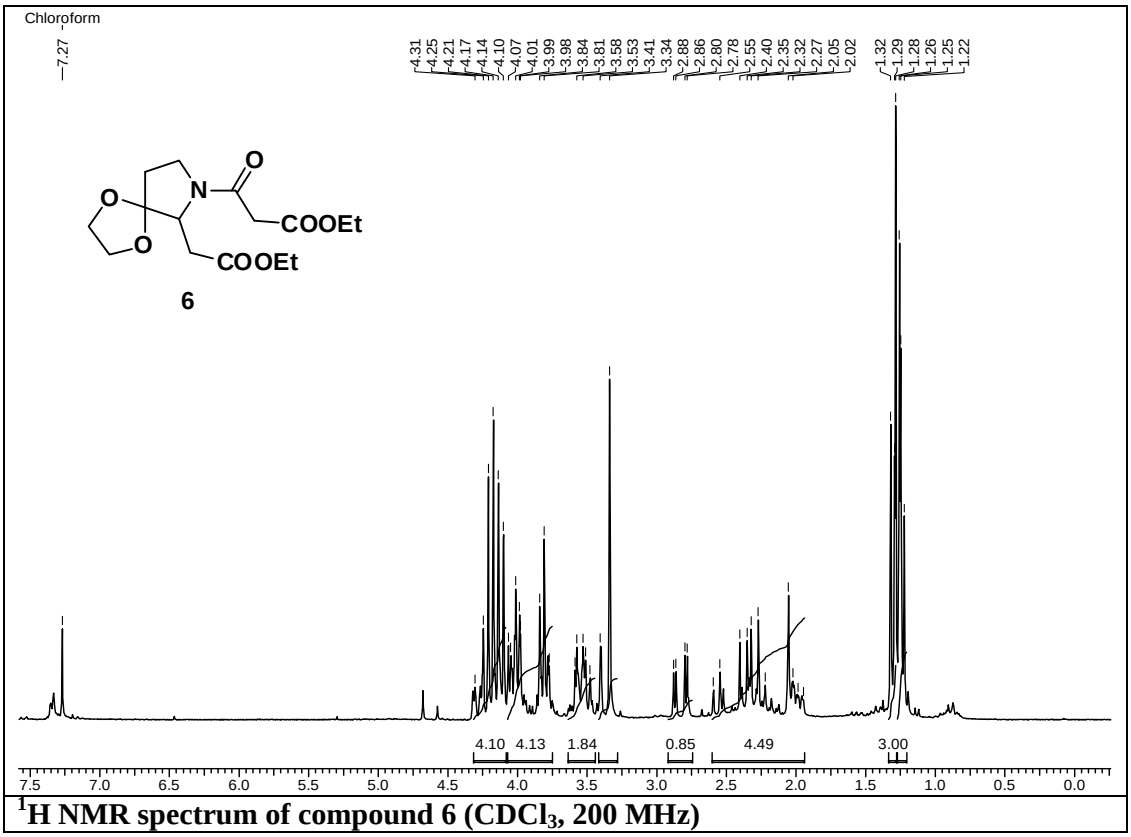
^{1}H NMR spectrum of compound 18 ($CDCl_3$, 200 MHz)



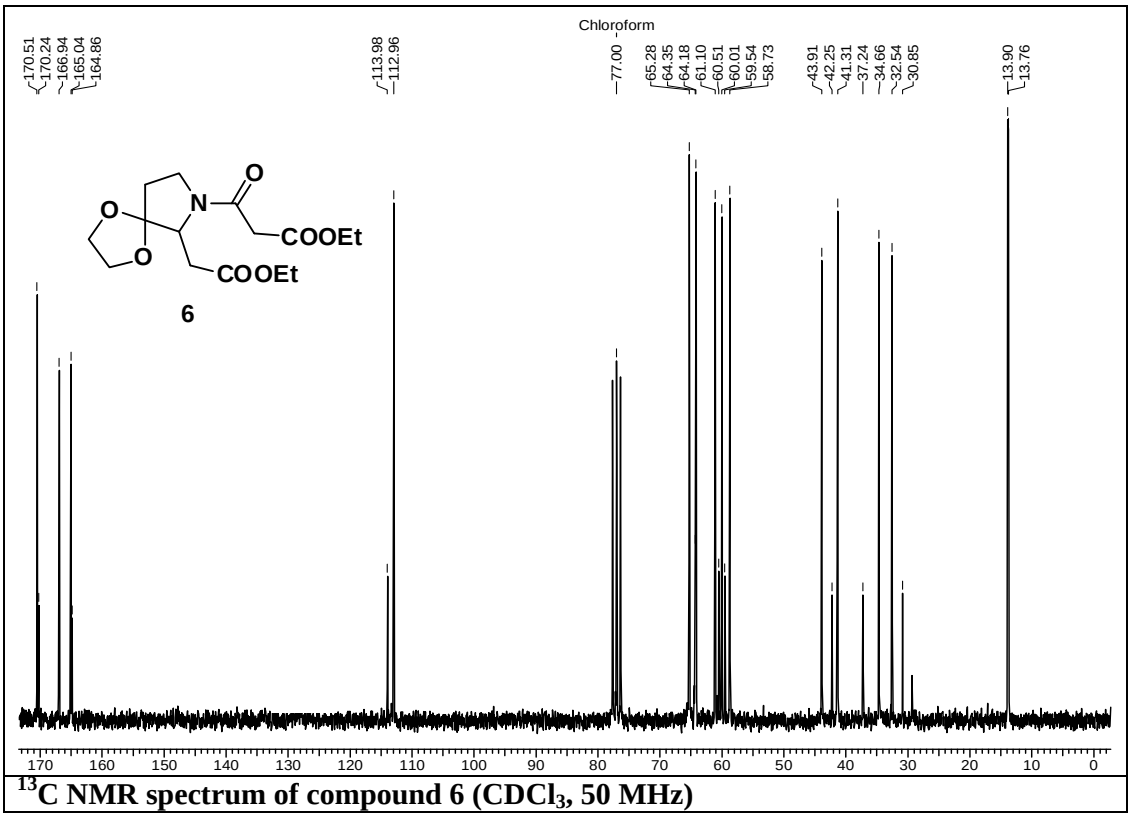
^{13}C NMR spectrum of compound 18 ($CDCl_3$, 50 MHz)



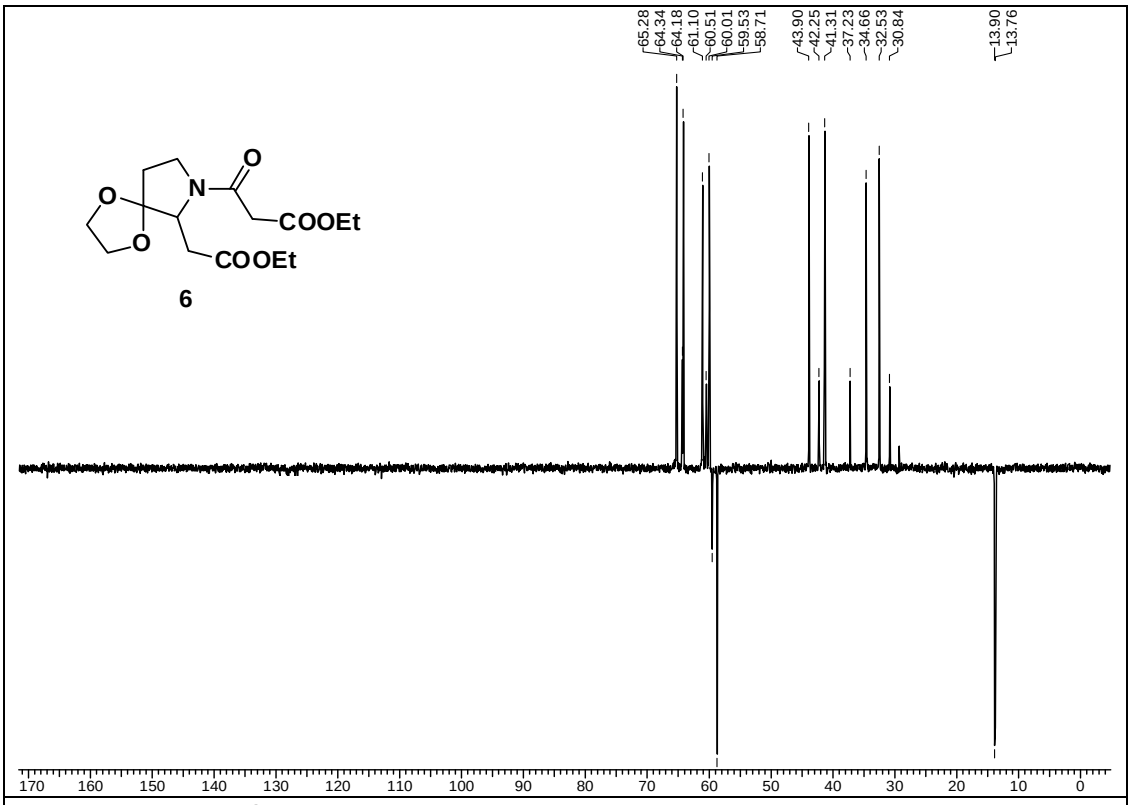
DEPT spectrum of compound 18 ($CDCl_3$, 50 MHz)



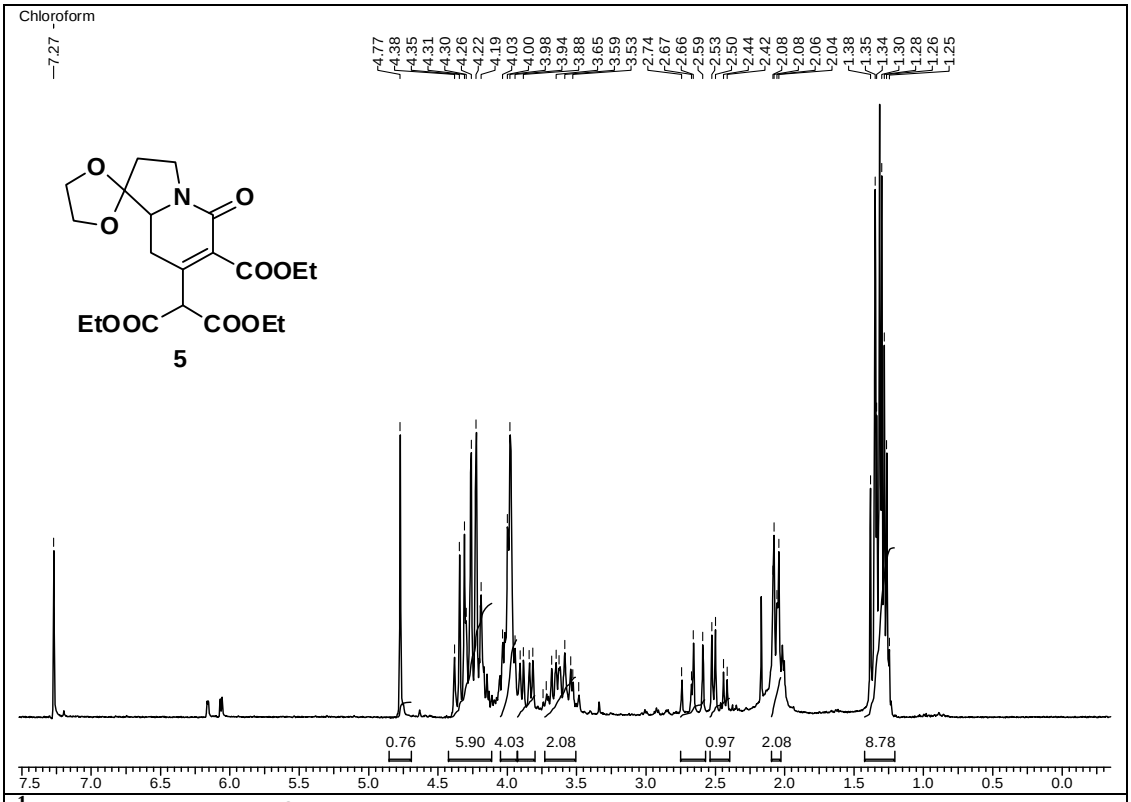
^{1}H NMR spectrum of compound 6 ($CDCl_3$, 200 MHz)



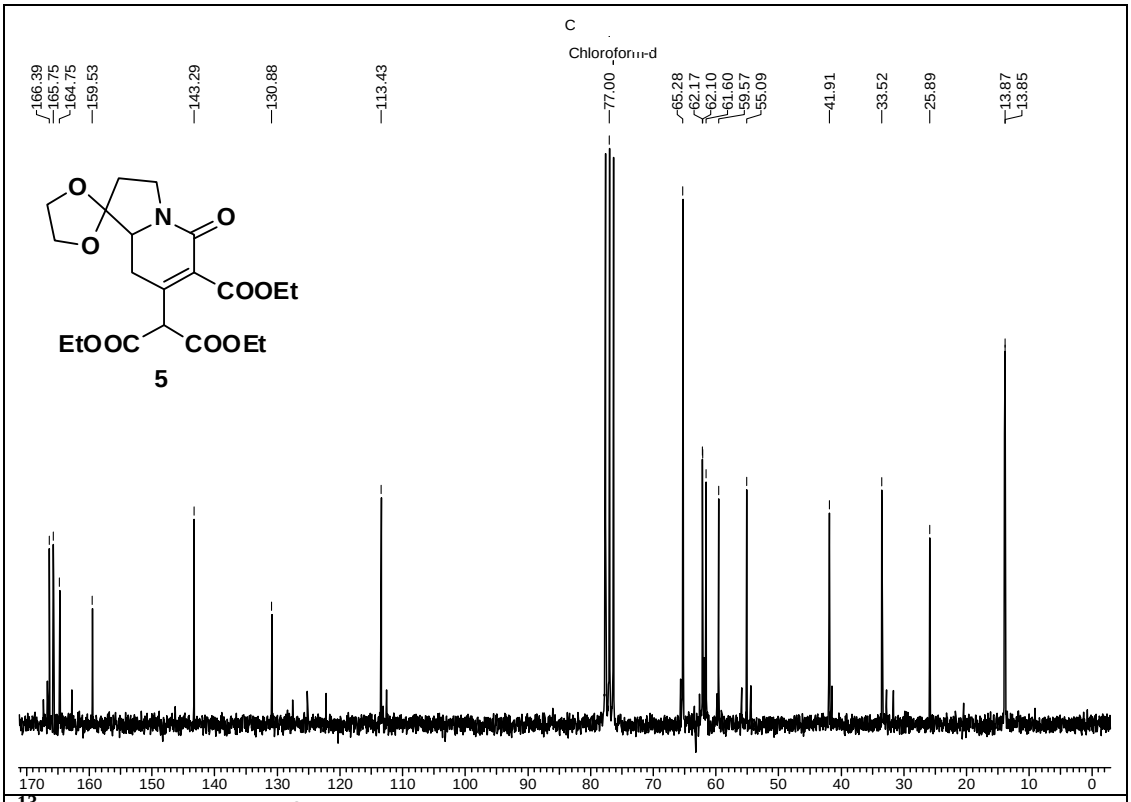
^{13}C NMR spectrum of compound 6 ($CDCl_3$, 50 MHz)



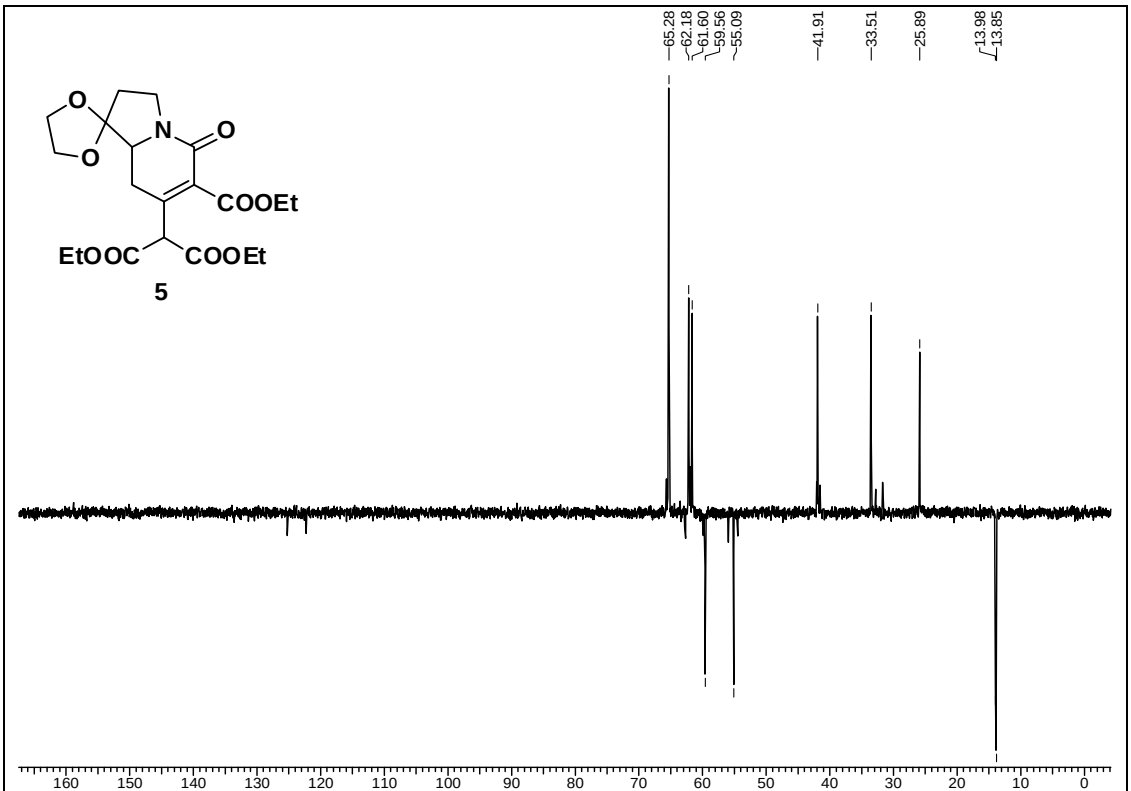
DEPT spectrum of compound 6 ($CDCl_3$, 50 MHz)



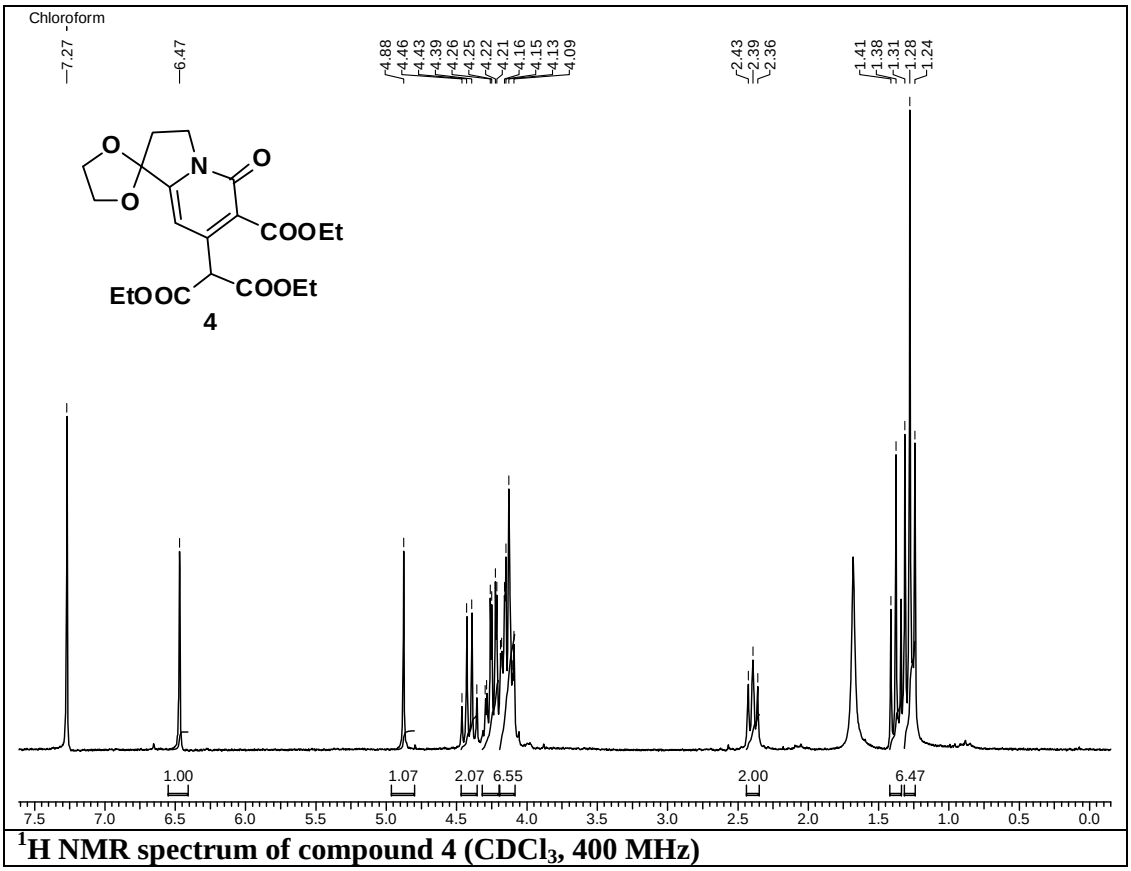
^{1}H NMR spectrum of compound 5 ($CDCl_3$, 200 MHz)



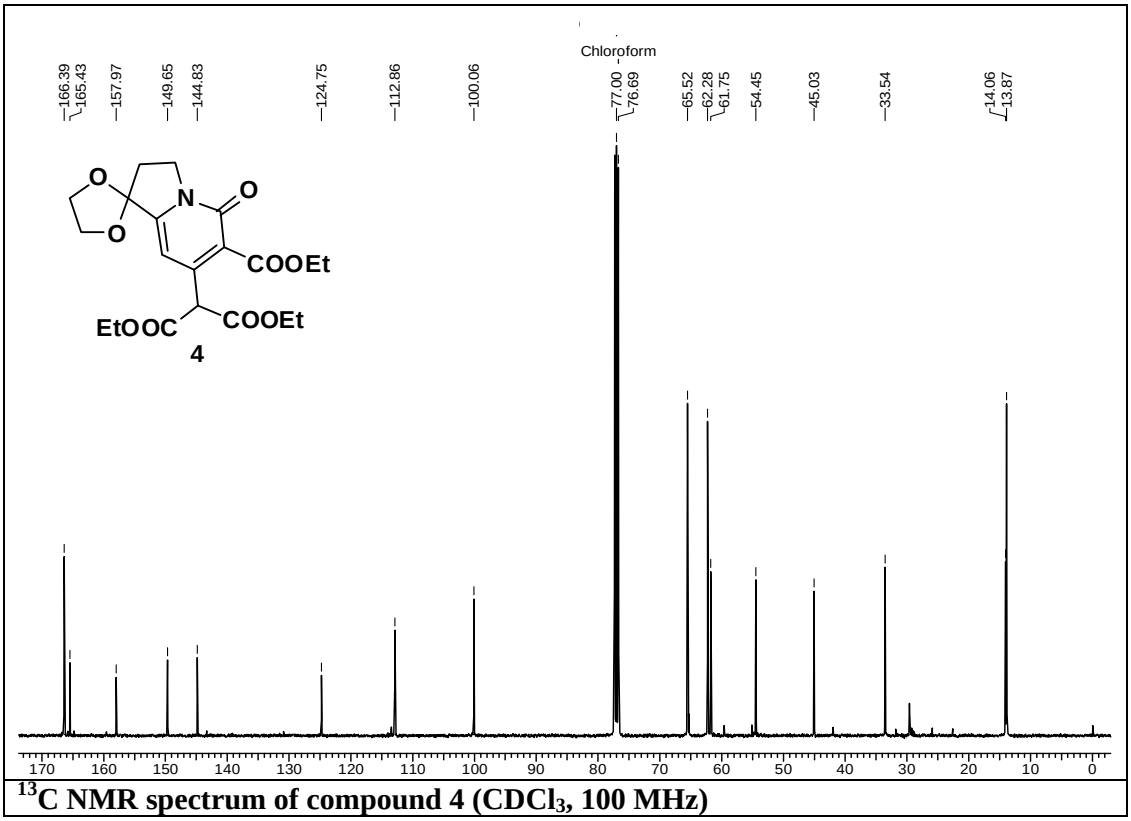
^{13}C NMR spectrum of compound 5 ($CDCl_3$, 50 MHz)



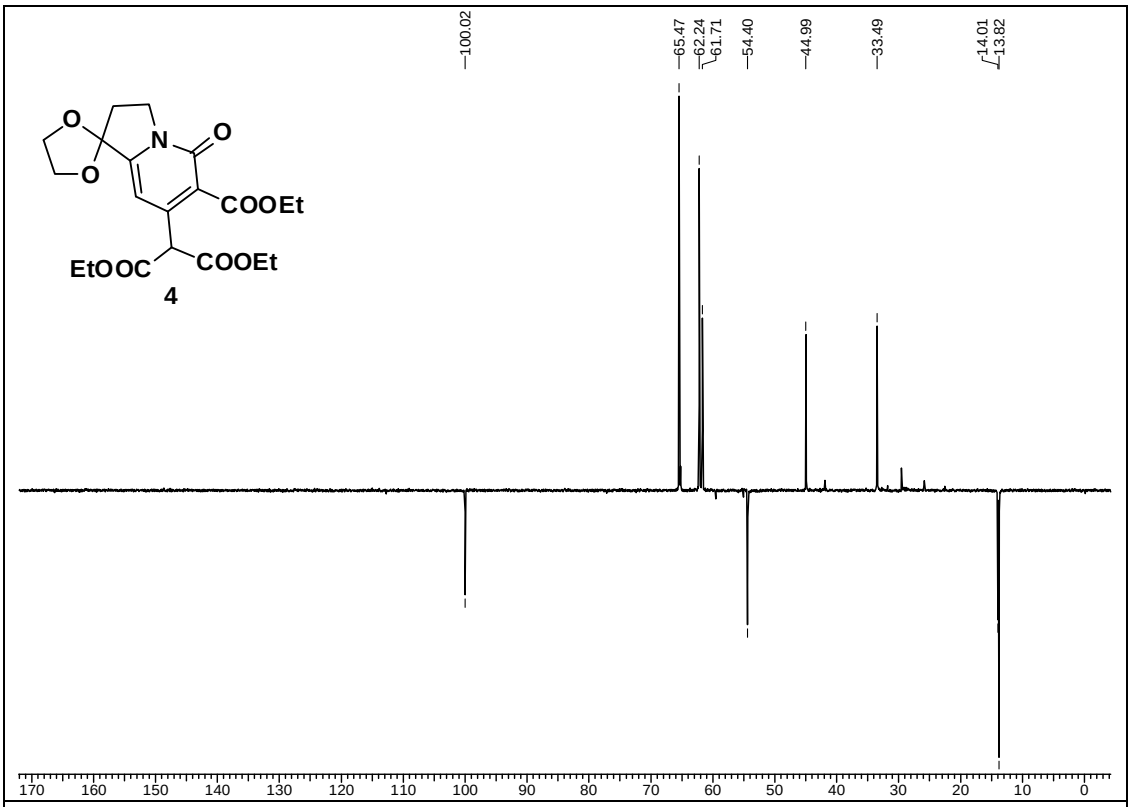
DEPT spectrum of compound 5 ($CDCl_3$, 50 MHz)



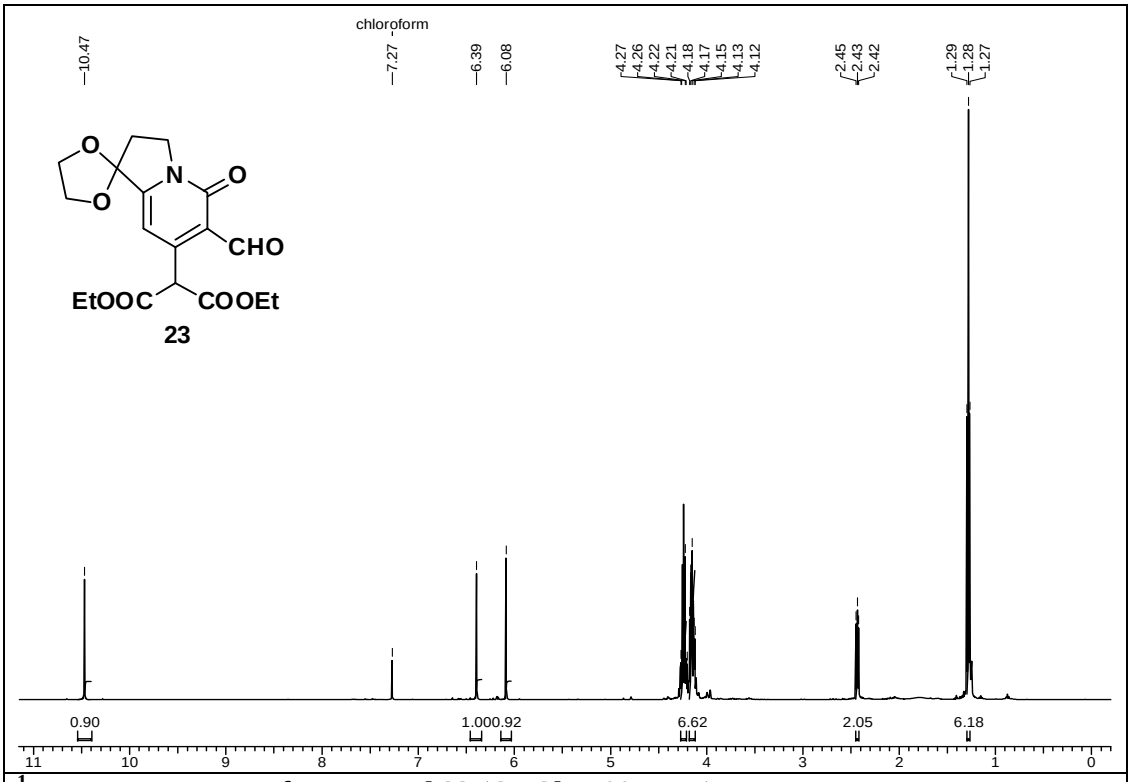
^{1}H NMR spectrum of compound 4 ($CDCl_3$, 400 MHz)



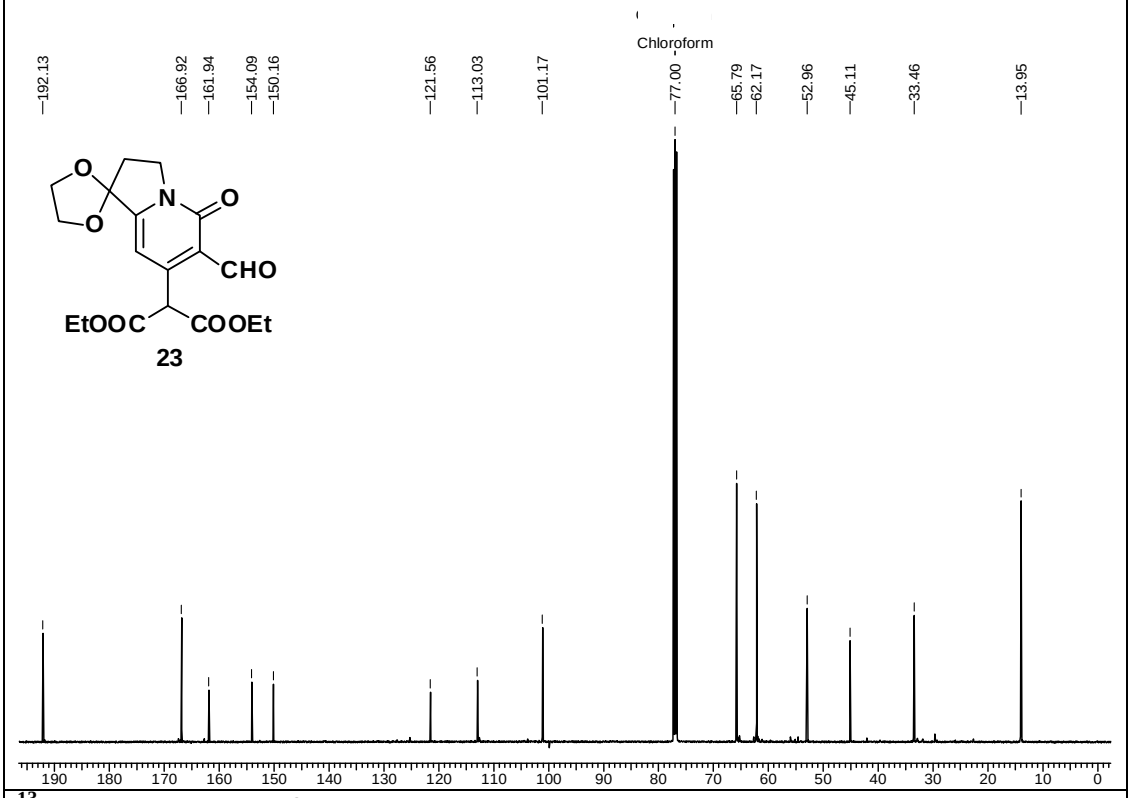
^{13}C NMR spectrum of compound 4 ($CDCl_3$, 100 MHz)



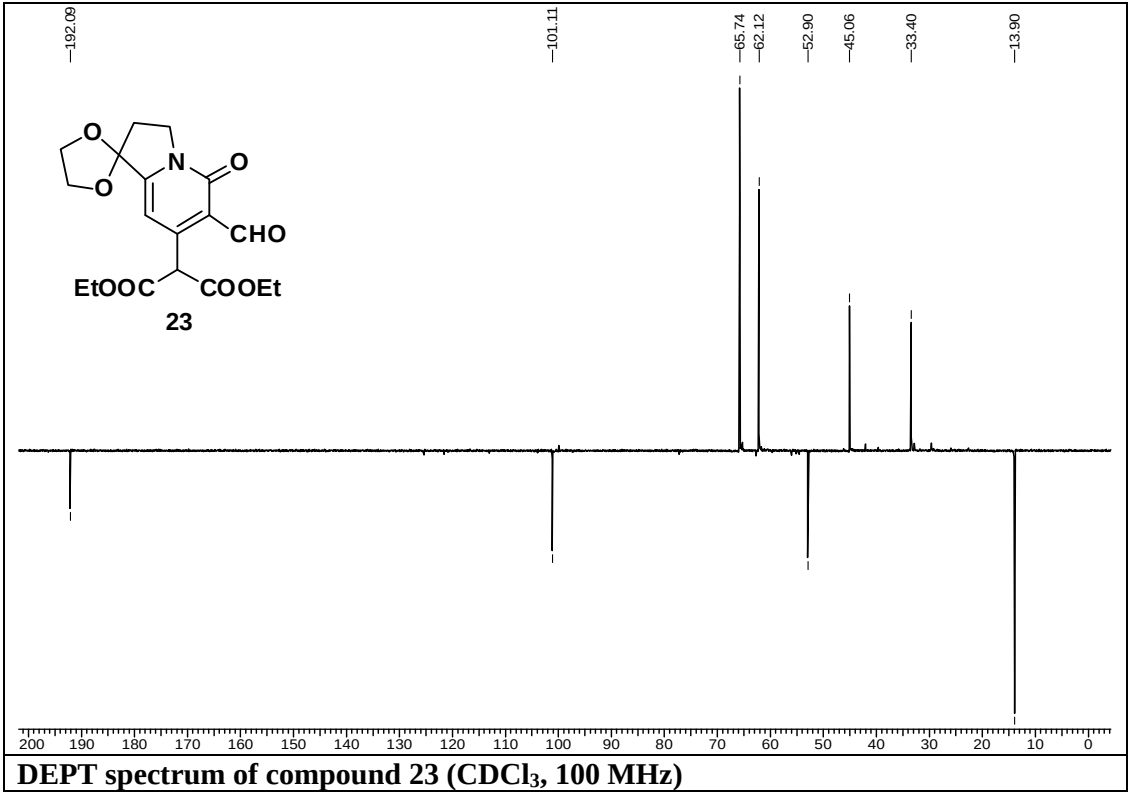
DEPT spectrum of compound 4 ($CDCl_3$, 100 MHz)



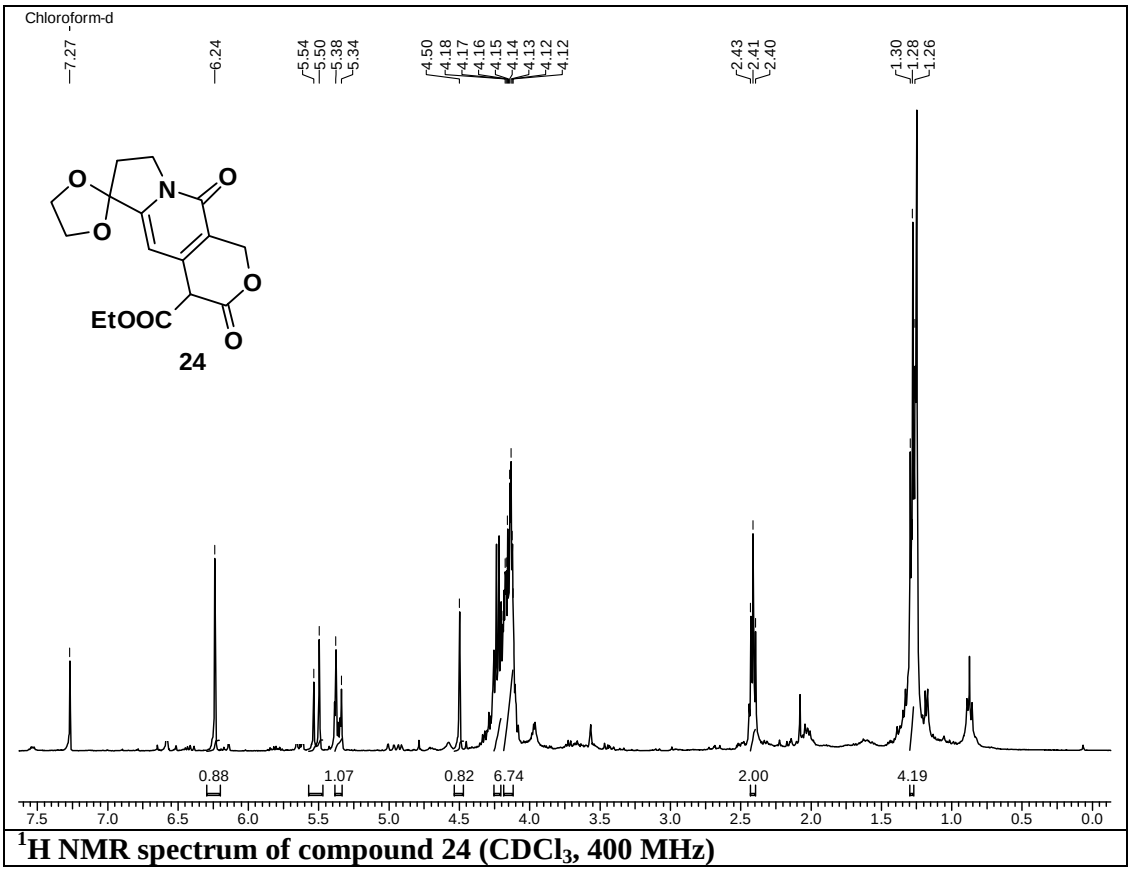
^{1}H NMR spectrum of compound 23 ($CDCl_3$, 400 MHz)



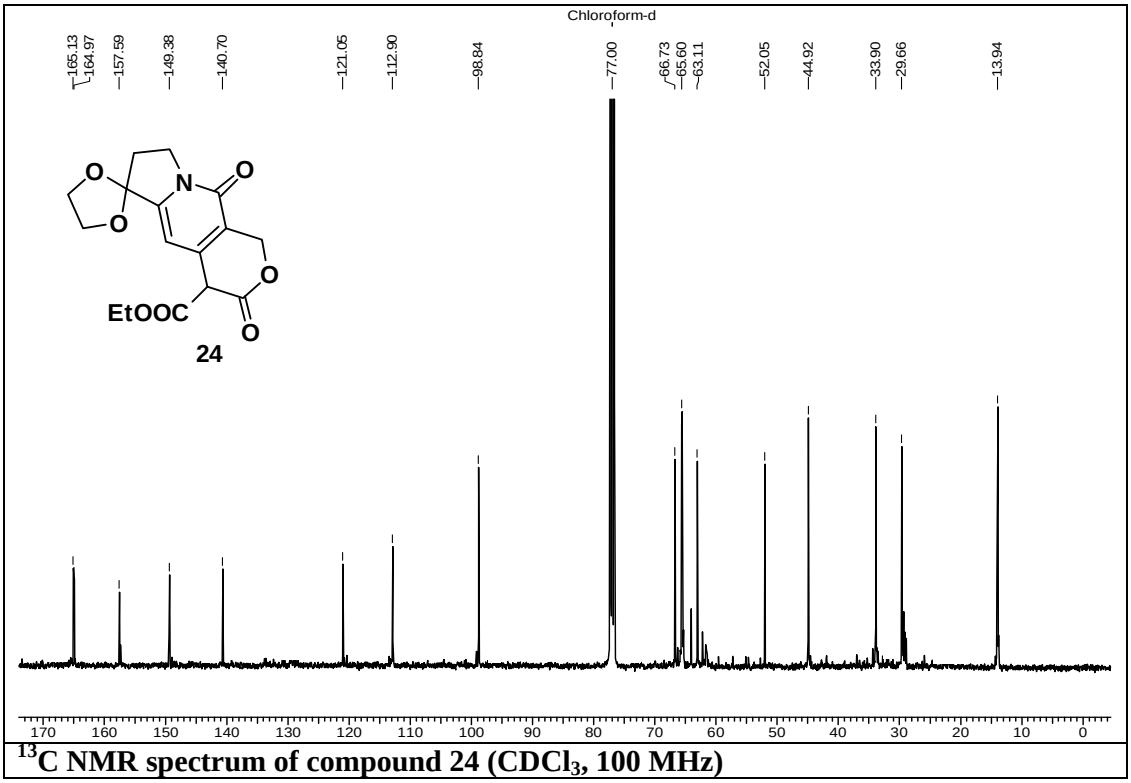
^{13}C NMR spectrum of compound 23 ($CDCl_3$, 100 MHz)



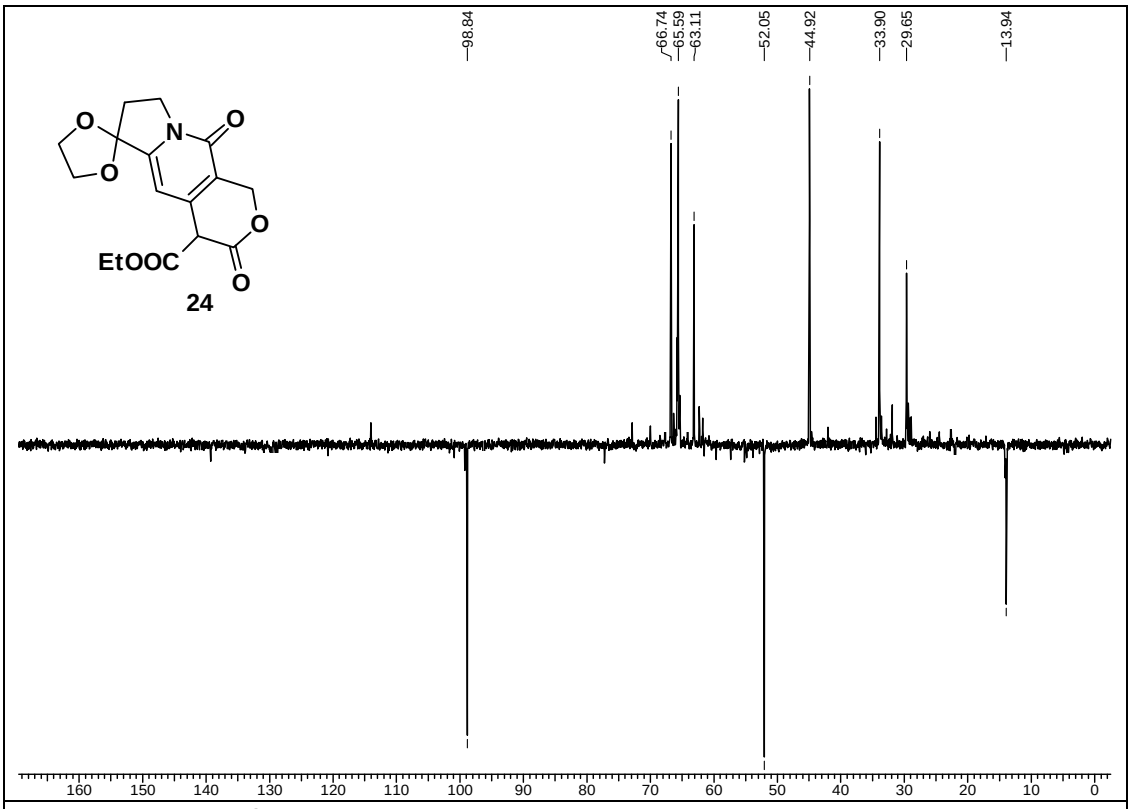
DEPT spectrum of compound 23 ($CDCl_3$, 100 MHz)



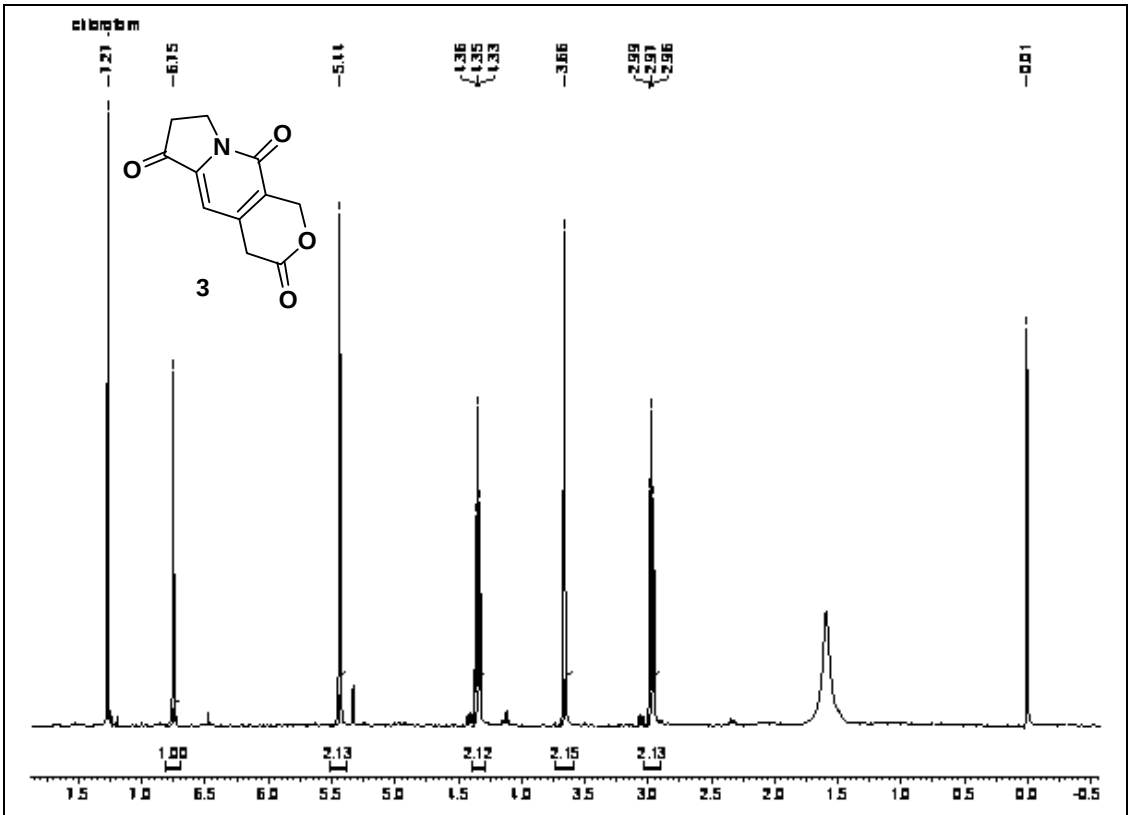
^{1}H NMR spectrum of compound 24 ($CDCl_3$, 400 MHz)



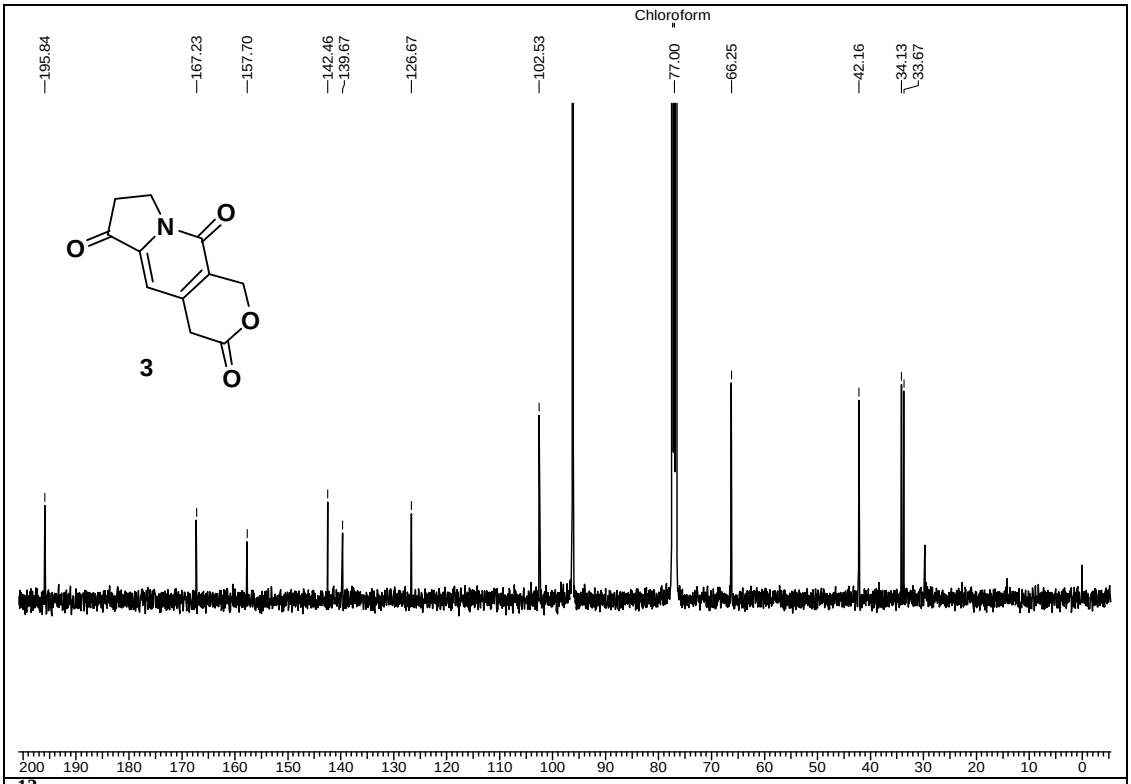
^{13}C NMR spectrum of compound 24 ($CDCl_3$, 100 MHz)



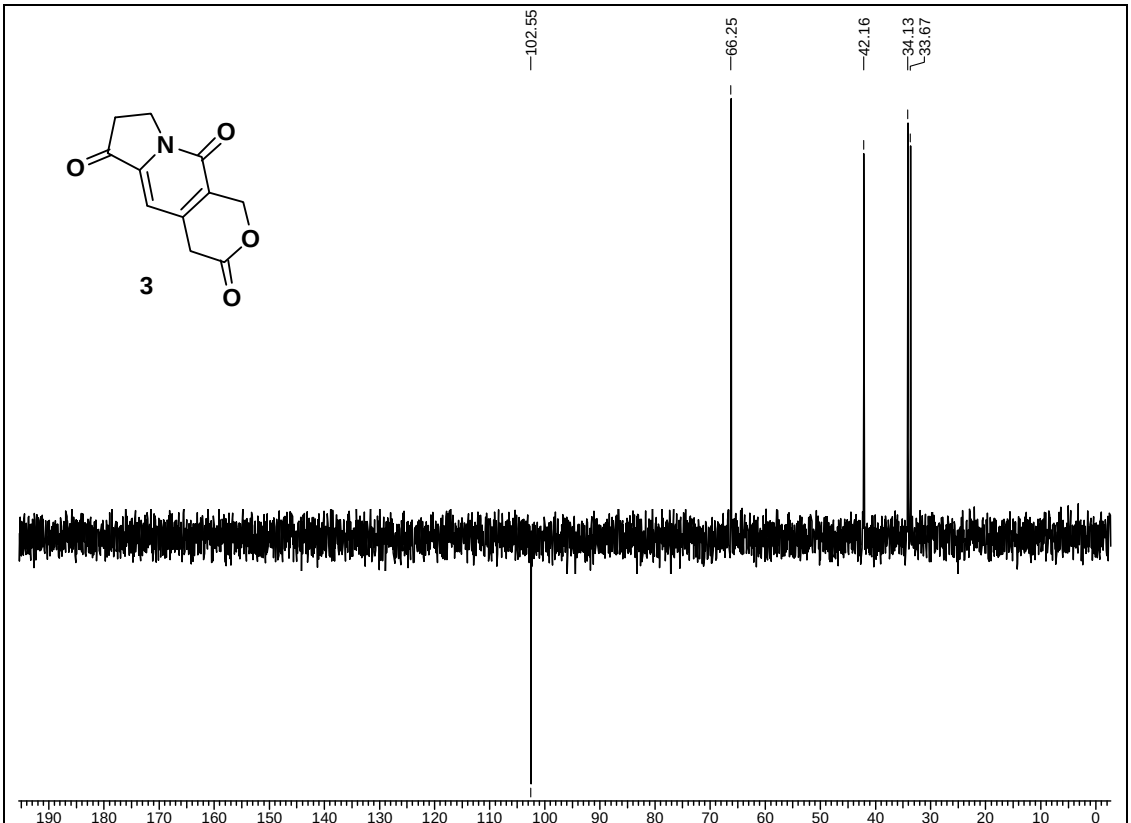
DEPT spectrum of compound 24 ($CDCl_3$, 100 MHz)



^{1}H NMR spectrum of compound 3 ($CDCl_3$, 400 MHz)



^{13}C NMR spectrum of compound 3 ($CDCl_3$, 100 MHz)



DEPT spectrum of compound 3 ($CDCl_3$, 100 MHz)

2.3.8 References

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Chapter 3. Synthetic studies towards α-cuparenone

Section 1

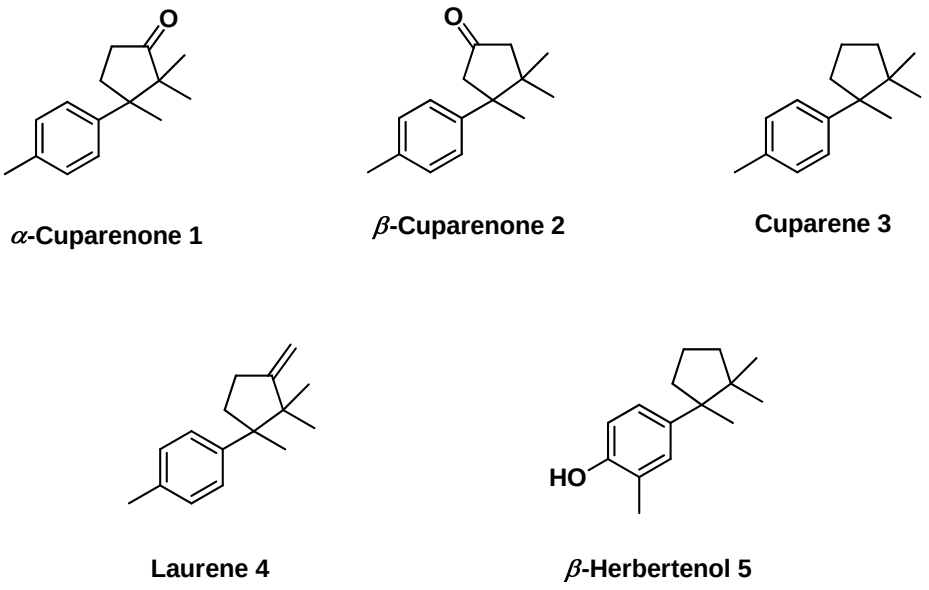
α-Cuparenone: A family of sesquiterpene-A brief review

3.1.1 Summary

The present section deals with general introduction of bicyclic sesquiterpenes along with detailed review on synthesis emphasizing mainly the synthetic approaches towards α-cuparenone, a bicyclic terpene isolated from *Thuja orientalis* (Mayurpankhi).

3.1.2 Introduction

α-Cuparenone **1**, β-cuparenone **2**, cuparene **3,** laurene **4** and herbertenol **5** are bicyclic sesquiterpenes belonging to cuparene family. First two compounds **1** and **2** were isolated from *Thuja orientalis* (Mayurpankhi) by Sukh Dev and Chetty[1] in 1964. Cuparene **3** was isolated by Erdtman and Enzellz[2] in 1958. Laurene **4** was isolated by Irie and co-workers[3] while β-herbertenol **5** was isolated from *Herberta adunsa* by Matsuo and co-workers.[4]



α-Cuparenone 1 **β-Cuparenone 2** **Cuparene 3**

Laurene 4 **β-Herbertenol 5**

Figure 1

These compounds pose a challenge to synthetic organic chemists due to the presence of two contiguous quaternary centers in a cyclopentane ring.

3.1.3 Synthesis of α-cuparenone: literature survey

Owing to its challenging structure having two contiguous quaternary centers in a cyclopentane ring, several syntheses of α-cuparenone are reported in the literature employing various strategies. In many cases, the synthesis of α-cuparenone has been used as a demonstration of the novelty and efficiency of new methodology. These several syntheses of α-cuparenone can be broadly classified into following categories.

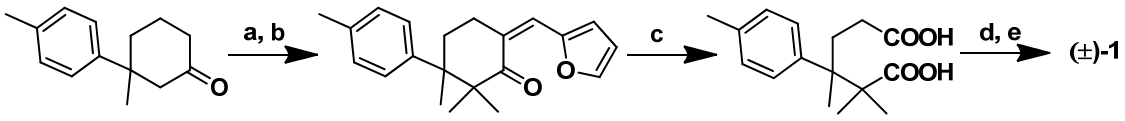
1. Dieckmann cyclization[5-12]
2. *Via* 1, 4-dicarbonyl compounds[13-21]
3. Ring expansion[22-30]
4. Use of transition metal catalysts[31,32]
5. Michael addition[11,12,33-35]
6. Miscellaneous [36-45]

Since review on synthesis of all categories up to 1997 has been covered by Sachindra S. Patil[46] from this group, only those syntheses of racemic and optically pure α-cuparenone reported after 1997 and some representative syntheses have been described in this present section.

Raphael's Approach

Raphael and co-workers[5] have reported the first total synthesis of α-cuparenone in seven steps with overall yield of 18%, employing Dieckmann cyclization as key step.

Scheme 1 : Raphael *et al. J. Chem. Soc.* **1962**, 1558.



6 7 8

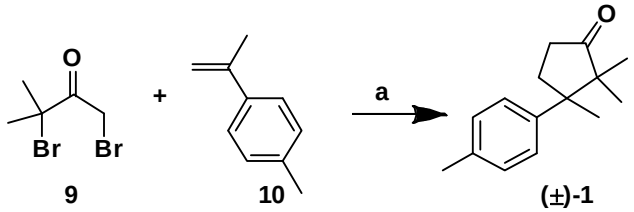
Reagents and conditions: *a) Furfuraldehyde, EtOH, aq. NaOH, rt, 2 h; b) t-BuOK, CH_3I, rt; c) O_3, AcOH, H_2O_2, H_2SO_4; d) i) CH_2N_2, ether, 0 ^oC; ii) Benzene, t-BuOK, reflux, 6 h; e) i) AcOH, HCl, H_2O, 4 h; ii) Heat, 100 ^oC, MeOH, NaOH.*

The less hindered methylene of ketone **6** was protected *via* aldol condensation with 2-furfuraldehyde. The resulting enone was subjected to gem-dimethylation to get enone **7**. Ozonolysis of compound **7** afforded substituted adipic acid **8**. The acid **8** on esterification followed by Dieckmann cyclization, hydrolysis and decarboxylation afforded α-cuparenone **1**.

Noyori's Approach

In this communication Noyori *et al.*[31] have reported an elegant one-step synthesis of α-cuparenone using transition metal catalyst.

Scheme 3: Noyori *et al. Tetrahedron Lett.* **1978**, *19,* 993.



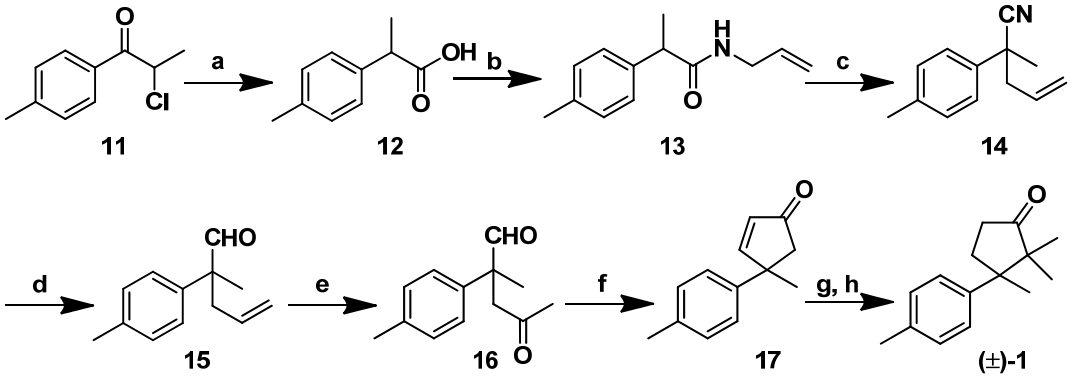
Reagents and conditions: *a) $Fe_2(CO)_9$, benzene, 55 ^oC, 1 h, argon, 18%.*

Dibromoketone **9** was treated with 2-*p*-tolyl-1-propene **10** in presence of $Fe_2(CO)_9$ directly to afford the α-cuparenone **1**, though in very low yield (18%). This is the shortest and most well-designed synthesis of α-cuparenone involving dipolar cycloaddition of oxa-allyl cation to construct five membered ring.

Chavan's 1st Approach

This group[20] synthesized (±)-α-cuparenone employing aza-Claisen rearrangement.

Scheme 3: Chavan *et al*. *Tetrahedron Lett.* **1996**, *37,* 2629.



Reagents and conditions: *a) hv, 2-methyl oxirane, aq. acetone 6 h, 70%; b) $SOCl_2$,*

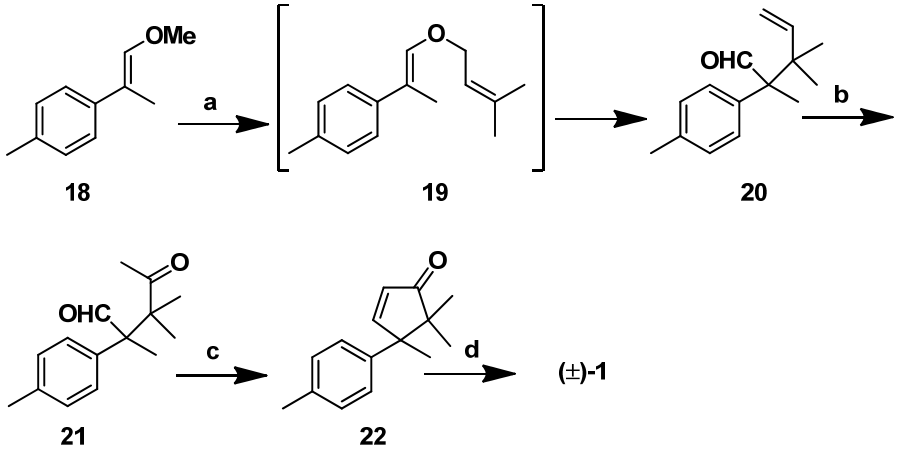
benzene, allylamine, Et_3N; c) PPh_3, CH_3CN, CCl_4, Et_3N, 24 h, 80%; d) DIBAL-H, benzene, ambient temp., 70%; e) Wacker oxidation, 63%; f) KOH, EtOH, rt, 98%; g) NaH, MeI (excess), 65%; h) Pd-C, H_2, rt, 98%.

α–Chloro-4-methyl propiophenone **11** was converted to α-*p*-tolyl propionic acid **12** by facile photochemical rearrangement, in the presence of propylene oxide as an acid scavenger. α-*p*-Tolyl propionic acid **12** was converted to allyl amide **13** by reacting it with thionyl chloride followed by allylamine. Aza-Claisen rearrangement[47] of compound **13** mediated by triphenyl phosphine and CCl_4 furnished unsaturated nitrile **14**, which on partial reduction and hydrolysis afforded aldehyde **15**. Wacker oxidation of compound **15** gave ketone **16** which was followed by intramolecular aldol condensation and dehydration to give cyclopentanone **17**. Gem-dimethylation of compound **17** followed by hydrogenation completed the total synthesis of α-cuparenone **1**. Thus the total synthesis was completed in eight steps with an overall yield of 14%.

Kulkarni's Approach

Kulkarni *et al.*[21] have reported a short and efficient total synthesis of (±)-α-cuparenone employing a tandem enol ether exchange Claisen rearrangement.

Scheme 4: Kulkarni *et al*. *Tetrahedron*, **1997**, *53*, 3167.



Reagents and conditions: *a) Prenyl alcohol, TFA (10%), toluene, reflux, 18 h, 69%; b) $PdCl_2$ (10%), $CuCl_2$ (10%), O_2, H_2O:DME (1:9), rt, 2 h, 81%; c) KOH, MeOH, rt, 2 h, 87%; d) Pd/C, AcOEt, H_2, rt, 8 h, 94%.*

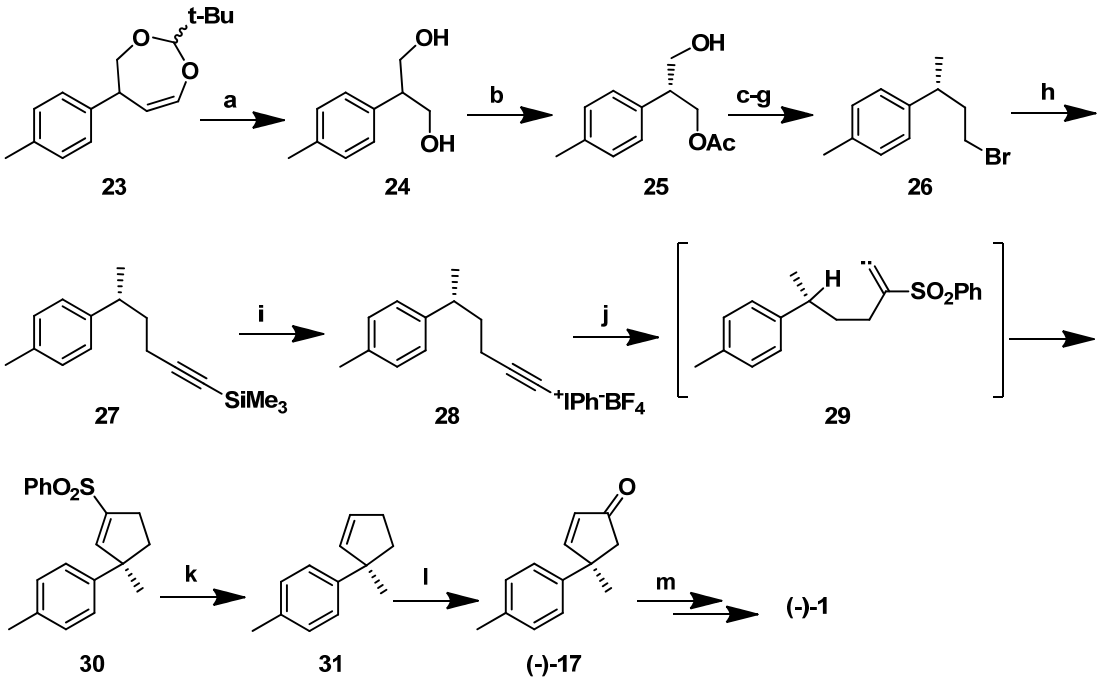
Accordingly, enol ether **19** was prepared by enol ether exchange from **18** and subsequent Claisen rearrangement using trifluoroacetic acid in refluxing toluene gave aldehyde **20** *via* **19**. Wacker oxidation of aldehyde **20** afforded ketoaldehyde **21**, which on

aldol condensation gave **22** and hydrogenation of **22** afforded the (±)-α-cuparenone **1**. Thus the total synthesis of (±)-α-cuparenone was completed in four steps with an overall yield of 43%.

Shishido's Approach

Shishido and coworkers[40] have reported an efficient and enantiocontrolled formal total synthesis of (-)-α-cuparenone by employing an asymmetric construction methodology for formation of the benzylic quaternary stereogenic centre.

Scheme 5: Shishido *et al. Chem. Commun*, **1997**, 1167.



Reagents and conditions: *a) O_3, $NaBH_4$, CH_2Cl_2, -78 to 0 °C, 84%; b) Vinyl acetate, PPL, Et_2O, rt, 84%; c) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, $NaBH_4$, Me_2SO, 60 °C, 73%; d) MsCl, i-Pr_2NEt, CH_2Cl_2, rt, 88%; e) KCN, 18-crown-6, Me_2SO, 60 °C, 90%; f) DIBAL-H, hexane–CH_2Cl_2 (1:1), -78 °C then 1M HCl, $NaBH_4$, MeOH, 75%; g) Ph_3P, CBr_4, CH_2Cl_2, -40 °C, 94%; h) t-BuLi, HC≡$CSiMe_3$, THF, HMPA, -78-0 °C, 69%; i) $(PhIO)_n$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; j) $PhSO_2Na$, H_2O, 0 °C, 83% (over two steps); k) Na–Hg (5%), MeOH, sonication, rt, 70%; l) PDC, t-BuOOH, celite, benzene, 10 °C, rt, 72%; m) Ref. 15.*

Accordingly, treatment of 2-*tert*-butyl-4, 5-dihydro-5-(4-methylphenyl)-1, 3-dioxepine **23**[48] with ozone followed by reductive workup with $NaBH_4$ gave prochiral 1, 3-

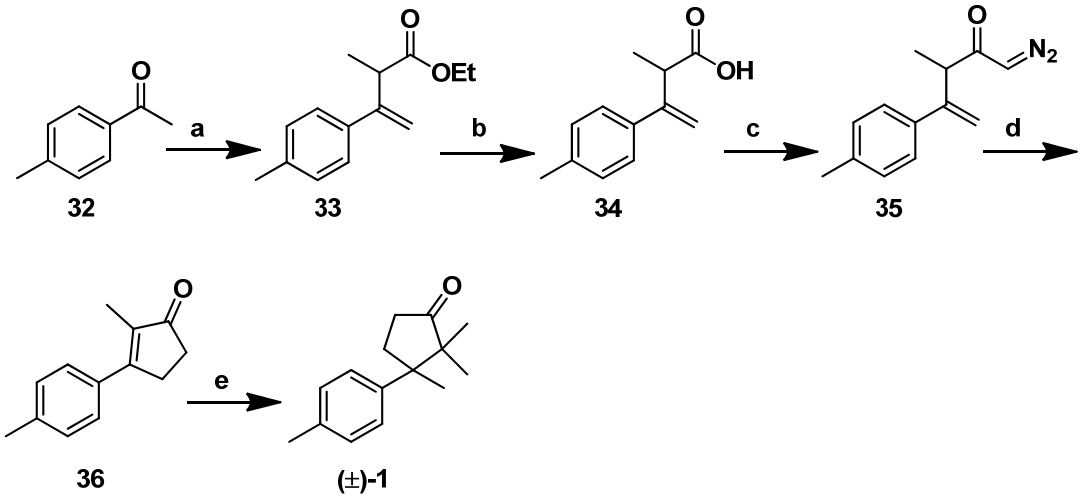
diol **24**. Diol **24** on asymmetric acetylation using porcine pancreatic lipase (PPL) and vinyl acetate gave monoacetate **25**. Removal of hydroxy moiety in **25** by tosylation and subsequent reduction gave alcohol, which on mesylation and subsequent cyanation, DIBAL-H reduction, and further reduction of the aldehyde thus obtained with $NaBH_4$ gave one carbon elongated alcohol, which was converted to bromide **26** by using CBr_4 and triphenylphosphine. Reaction of bromide with lithium trimehylsilylacetylide produced the alkynylsilane **27** in 69% yield.

The construction of quaternary stereogenic center was carried out *via* [1, 5] C-H insertion reaction of the alkylidene carbene. Thus, treatment of **27** with iodosylbenzene in the presence of boron trifluoride diethyl etherate in DCM at 0 ^oC followed by treatment with aq. sodium tetrafluoroborate provided the iodonium tetrafluoroborate **28**, which was exposed to aq. sodium benzenesulfinate at 0 ^oC to give the cyclised vinyl sulfone **30** *via* the alkylidene carbene intermediate **29**. Reductive removal of benzenesulfonyl moiety in **30** under sonication afforded **31**. Oxidation of allylic methylene was carried out using PDC in presence of *tert*-butylhydroperoxide and celite to furnish enone **17** which is an intermediate in the cuparenone synthesis and can be converted to (-)-α-cuparenone.[17] Thus this synthetic sequence constitutes a formal synthesis of (-)-α-cuparenone.

Chavan's 2nd Approach

This is the second short and simple approach from this group.[41] Central to this approach is construction of a substituted cyclopentenone *via* acid catalyzed decomposition of β,γ-unsaturated-α-diazoketone.

Scheme 6 : Chavan *et al. Tetrahedron* **1999,** *55*, 13417.



Reagents and conditions: *a) i) Ethyl 2-bromopropionate, Zn, ether; ii) H^+, 97%; b)*

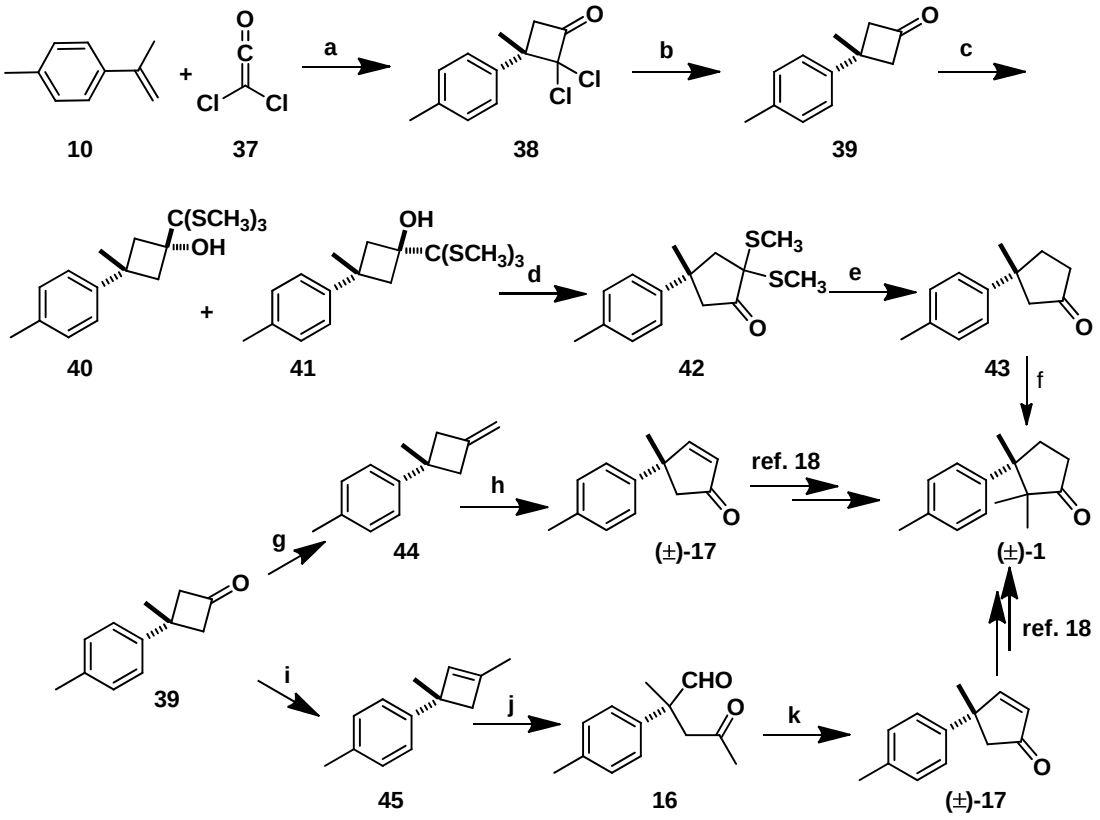
KOH/EtOH-H_2O; c) i) $SOCl_2$, benzene; ii) CH_2N_2, ether, quant; d) $BF_3.Et_2O$, DCM, 0 ^oC, quant; e) i) Me_3Al, $Ni(acac)_2$, THF, rt, 85%; ii) NaH, diglyme, MeI, 68%.

Accordingly, Reformatsky reaction of 4-methylacetophenone **32** and ethyl 2-bromopropionate furnished the β,γ-unsaturated ester **33**. Saponification of ester **33** gave acid **34** followed by treatment with $SOCl_2$ to give corresponding acid chloride. Reaction of acid chloride with diazomethane gave β,γ-unsaturated-α-diazoketone **35**. Cyclization was carried out by using $BF_3.Et_2O$ to furnish cyclopentenone **36**. 1,4-Conjugate addition with trimethylaluminum[49] followed by alkylation[50] furnished α-cuparenone **1**. Thus total synthesis was achieved in five steps with an overall yield 56%.

Ho's approach

Ho *et al.*[28] reported the synthesis of α-cuparenone applying ring expansion approach based on symmetry considerations.

Scheme 7: Ho *et al. Can. J. Chem.* 75, **1997**, 621.



Reagents and conditions: *a) Sonication, 76%; b) Zn dust, NaI, AcOH, 80-90 ^oC, 84%; c) [Tris(methylthio)methyl]lithium, 95%; d) Lithium hydroxide, copper perchlorate-*

acetonitrile complex; e) Raney nickel, EtOH, reflux, 85%; f) ref. 7 g) One carbon Wittig; h) Thallium (III) nitrate trihydrate; i) MeMgI; j) Ozonolysis; k) Aldol.

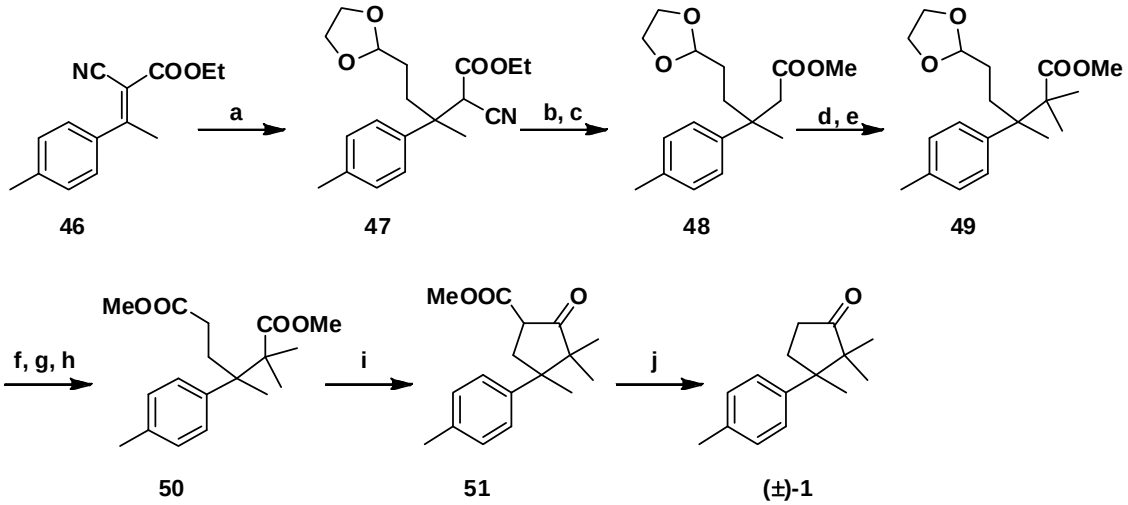
Accordingly, synthesis started with 2+2 cycloaddition of α,*p*-dimethylstyrene **10** with dichloroketene **37** under ultrasonic irradiation to obtain compound **38**, which on dechlorination afforded symmetric ketone **39**. Ketone **39** on treatment with [tris(methylthio)methyl]lithium afforded mixture of *cis* and *trans*-hydroxythio-orthoesters **40** and **41**. Both **40** and **41** on treatment with LiOH, copper (I) perchlorate-acetonitrile complex gave ring enlarged ketone **42**. Desulfurization of **42** gave ketone **43** which on methylation gave α-cuparenone **1**.

Alternatively **39** was converted to **44** by Wittig reaction followed by treatment with thallium (III) nitrate trihydrate to afford **17**. Compound **17** is well known precursor for synthesis of α-cuparenone.[20] Also, compound **39** was subjected to reaction with methyl magnesium iodide, dehydration, ozonolysis and aldolization to afford known precursor **17** for the synthesis of α-cuparenone.[20]

Mukherjee's Approach

This communication[11] deals with synthesis of rac-α-cuparenone using α,α–dimethylation of the ester **48** as the key step.

Scheme 8: Mukherjee *et al. Tetrahedron Lett.* **1999***, 40,* 4733.



Reagents and conditions: *a) 3,3-Ethylenedioxypropylmagnesium bromide, CuBr.Me_2S, THF, Et_2O, 0 to 25 ^oC, 50%; b) KOH, $HOCH_2CH_2OH$, H_2O, reflux, then H_3O^+, then heat*

190 ^{o}C; c) CH_2N_2, Et_2O, 0 ^{o}C, 75%; d) LDA (1 equiv), THF, -20 ^{o}C, MeI, HMPA, -78 ^{o}C, 95%; e) LDA (1.7 equiv), HMPA (2 equiv), THF, 0 ^{o}C; MeI, 0 ^{o}C, 92%; f) AcOH-H_2O (4:1), 25-60 ^{o}C; g) Jones reagent, Me_2CO, 0-25 ^{o}C; h) CH_2N_2, Et_2O, 0 ^{o}C; i) t-BuOK, C_6H_6, reflux; j) DMSO, NaCl, 155 ^{o}C, 75% .

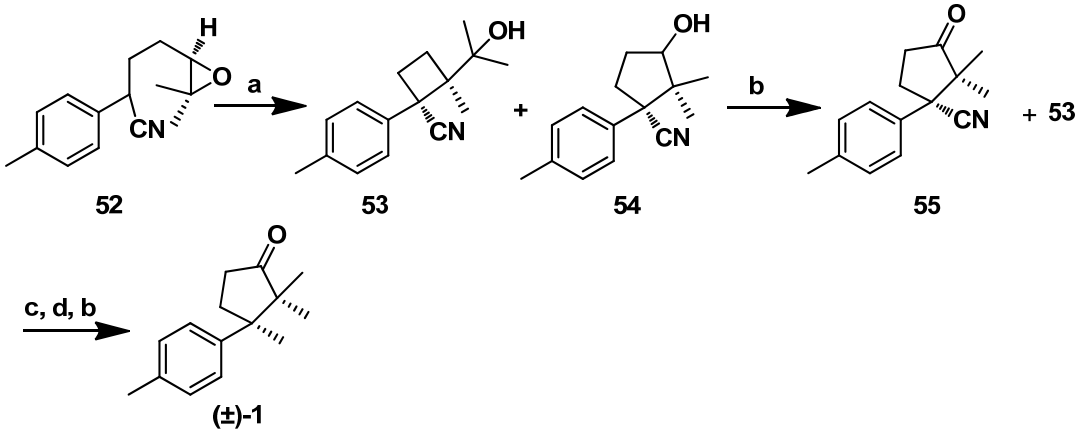
Accordingly, conjugate addition of 3, 3-ethylenedioxypropylmagnesium bromide to the unsaturated cyano-ester **46** provided **47**. Hydrolysis, decarboxylation and esterification afforded ester **48** in 75% overall yield. The ester **48** was alkylated with MeI to provide the ester **49**. After a few functional group transformations, the resultant diester **50** was subjected to Dieckmann cyclization to afford β-ketoester **51**. Finally decarbomethoxylation of **51** afforded (±)-α-cuparenone.

Later in 2003, the same authors have reported synthesis of (±)-α-cuparenone using similar synthetic strategy (Mukherjee *et al.* ARKIVOC **2003**, ix, 104–114).[12]

Maldonado's Approach

Maldonado *et al.*[29] reported the total synthesis of (±)-α-cuparenone using epoxynitrile anion cyclization reaction as the key step.

Scheme 9: Maldonado *et al. Chem. Lett.* **2000**, *5*, 512.



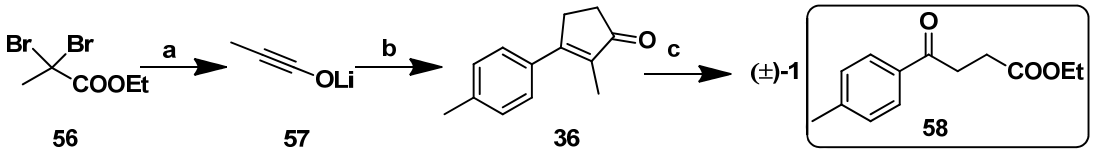
Reagents and conditions: *a) LHMDS, benzene, reflux, 60%; b) PCC, DCM, rt; c) DIBAL-H; d) $NH_2NH_2.H_2O$, KOH, ethylene glycol, heat.*

Accordingly, cyclization of epoxynitrile **52** was carried out using LiHMDS in refluxing benzene to afford cyclobutane **53** and cyclopentanol **54** in 60% yield. Oxidation using PCC gave ketone **55** along with unreacted **53**. Ketone **55** on DIBAL-H reduction furnished aldehyde alcohol followed by Wolff-Kishner reduction and PCC oxidation afforded (±)-α-cuparenone **1**.

Sindo's Approach

In this communication Sindo *et al.*[10] reported the synthesis of (±)-α-cuparenone by utilizing novel tandem [2 + 2] cycloaddition-Dieckmann condensation *via* ynolate anion.

Scheme 10: Sindo *et al*. *J. Org. Chem.* **2001**, *66*, 7818.



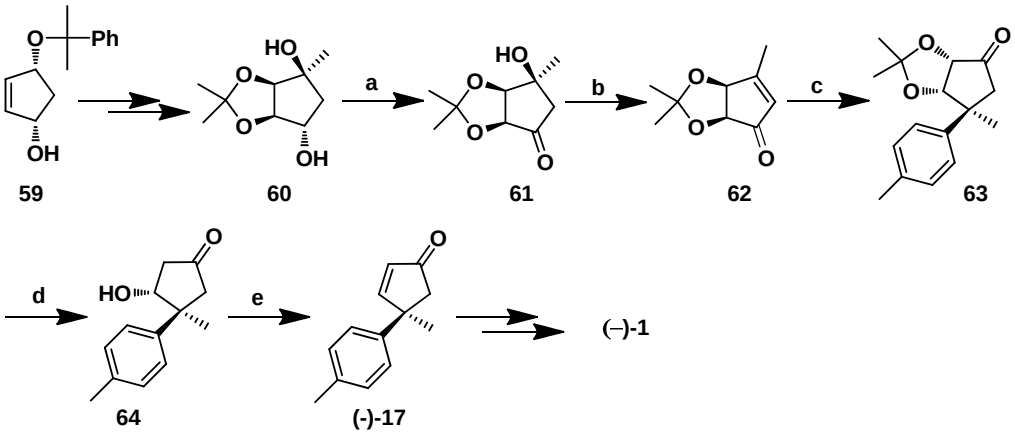
Reagents and conditions: *a) n-BuLi, THF, 78%; b) i)* **58***, -78 °C, 76%; ii) 3% HCl-EtOH, reflux; c) i) Me_3Al, $Ni(acac)_2$; ii) NaH, MeI, 65% (over two steps).*

Thus, ethyl 2, 2-dibromopropionate **56** was treated with *n*-BuLi in THF to get methyl substituted ynolate **57**. One-pot reaction of the methyl-substituted ynolate **57** with ethyl 4-oxo-4-(4-methylphenyl) butanoate **58** afforded cyclopentenone **36.** The 1,4-conjugate addition with trimethylaluminum followed by alkylation furnished α-cuparenone.

Ogasawara's Approach

In this communication Ogasawara *et al.*[42] reported an efficient enantioselective route to (-)-α-cuparenone utilizing a chiral cyclopentanoid **59** as a starting material.

Scheme 11: Ogasawara *et al*. *Tetrahedron Lett.* **2000**, *41*, 2639.



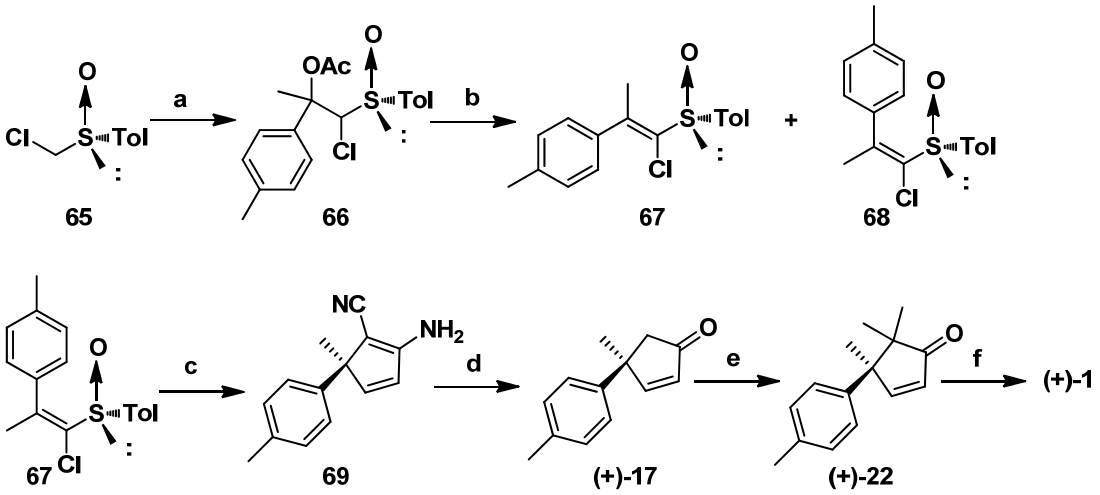
Reagents and conditions: *a) PCC, CH_2Cl_2, 90%; b) AcOH, 40 °C, 93%; c) 4-MeC_6H_4MgBr, $CuBr.SMe_2$, HMPA, TMSCl, THF, -78°C, then TBAF, THF, 87%; d) Al–Hg, EtOH, 91%; e) 10% HCl:dioxane (1:1), 40 °C, 81%..*

Thus, enantiopure diol (-)-**60** was accomplished from **59**[51] by using enantiodivergent functional group transformation. Oxidation of **60** with PCC afforded *β*-hydroxyketone **61**, which on dehydration gave enone **62.** Treatment of **62** with Grignard reagent in presence of copper (I) bromide and TMS-chloride allowed convex face selective 1,4-addition to afford cyclopentanone **63** having benzylic quaternary stereogenic center. Conversion of **63** into known key intermediate to synthesis of (-)-*α*-cuparenone was carried out by reductive cleavage of *α*-oxyketone **63** using aluminium amalgam to afford *β*-hydroxyketone **64** which on treatment with dil. HCl afforded enone **17** from which (-)-*α*-cuparenone has been obtained in two steps.[17, 34]

Satoh's Approach

Satoh *et al.*[43] reported asymmetric synthesis of 4,4-disubstituted 2-cyclopentenones from optically active 1-chlorovinyl *p*-tolyl sulfoxides and its application to the asymmetric total synthesis of (+)-*α*-cuparenone.

Scheme 12: Satoh *et al*. *Tetrahedron*: *Asymmetry* **2003**, *14*, 281.



Reagents and conditions: *a) i) LDA, 4-methyl acetophenone, -50 °C, 98%; ii) Acetic anhydride, pyridine, DMAP, 95%; b) $LiNPh_2$, THF, 93%; c) $LiCH_2CN$, THF, 75%; d) H_3PO_4, AcOH-H_2O, 93%; e) NaH, MeI (excess), DMF, 72%; f) Pd-C, H_2, rt, 97%.*

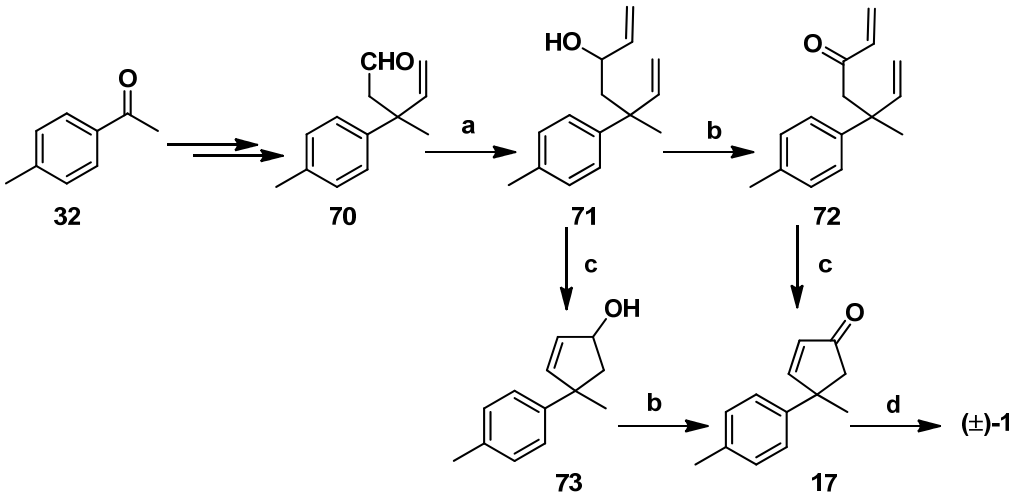
Enantiomerically pure (*R*)-(-)-**65** was treated with LDA at −50 °C followed by 4-methylacetophenone to afford the hydroxy compound, which was acetylated to afford the acetate **66** in 95% yield. The reaction of the acetate with lithium diphenylamide gave 93% yield of the desired 1-chlorovinyl *p*-tolyl sulfoxides **67** and **68** in 3:1 ratio. The major

isomer **67** was treated with cyanomethyllithium to give optically active enaminonitrile **69** in 75% yield. The enaminonitrile **69** was heated under reflux with H_3PO_4 in acetic acid to give the desired cyclopentenone **17** in 93% yield, which was dimethylated followed by hydrogenation in ethyl acetate with catalytic Pd–C to give (+)-α-cuparenone **1.**

Srikrishna's Approach

In this communication Srikrishna *et al.*[44] reported the methodology to synthesise sesquiterpenes employing a combination of Claisen rearrangement and ring closing metathesis reactions.

Scheme 13: Srikrishna *et al*. *Synlett* **2002**, 340.



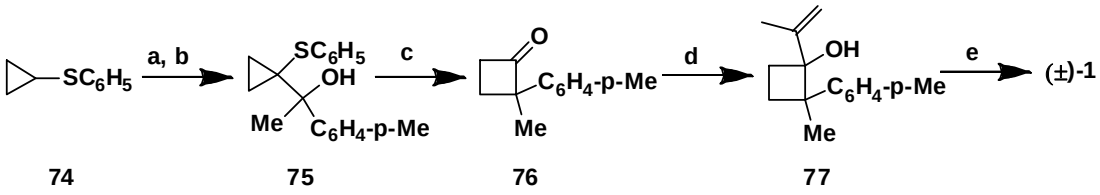
Reagents and conditions: *a) CH_2=CHMgBr, THF, rt, 92%; b) PCC, NaOAc, CH_2Cl_2, rt, 97%; c) Grubbs' catalyst, CH_2Cl_2, rt, 3 h, 93%; d) Ref. 15.*

Thus, reaction of the aldehyde **70**, obtained from 4-methylacetophenone[39] **32** in three steps, with vinylmagnesium bromide in THF furnished a 1:1 diastereomeric mixture of the dienol **71**, in 92% yield. Oxidation of **71** with PCC and sodium acetate furnished the dienone **72**. RCM of the dienone **72** with Grubbs' catalyst [PhCH=$RuCl_2(PCy_3)_2$] in methylene chloride was slow (18 h, 55–60% conversion), hence the reaction was carried out using dienol **71**. Reaction of the dienol **71** with 6 mol% of Grubbs' catalyst [PhCH=$RuCl_2(PCy_3)_2$] in methylene chloride at room temperature for 3 h furnished the RCM product, cyclopentenol **73** in 97% yield. Oxidation of the cyclopentenol **73** with PCC furnished the cyclopentenone **17** in 93% yield, The cyclopentenone **17** has already been transformed into (±)-α-cuparenone,[17] *via* alkylation and hydrogenation.

Piras' Approach

In this communication Piras *et al.*[30] reported the short synthesis of (±)-α-cuparenone *via* 2,2-dimethyl cyclopentanones which are prepared by acid catalyzed ring expansion of isopropenylcyclobutanols.

Scheme 14: Piras *et al*. *Chem. Commun.* **2005**, *30*, 3853.



Reagents and conditions: *a) n-BuLi, THF, -78 ^{o}C; b) MeCOC$_6$H$_4$-p-Me; c) PTSA, benzene, reflux; d) Prop-1-en-2-ylmagnesium bromide, THF, 0-20 ^{o}C; e) PTSA, benzene, reflux.*

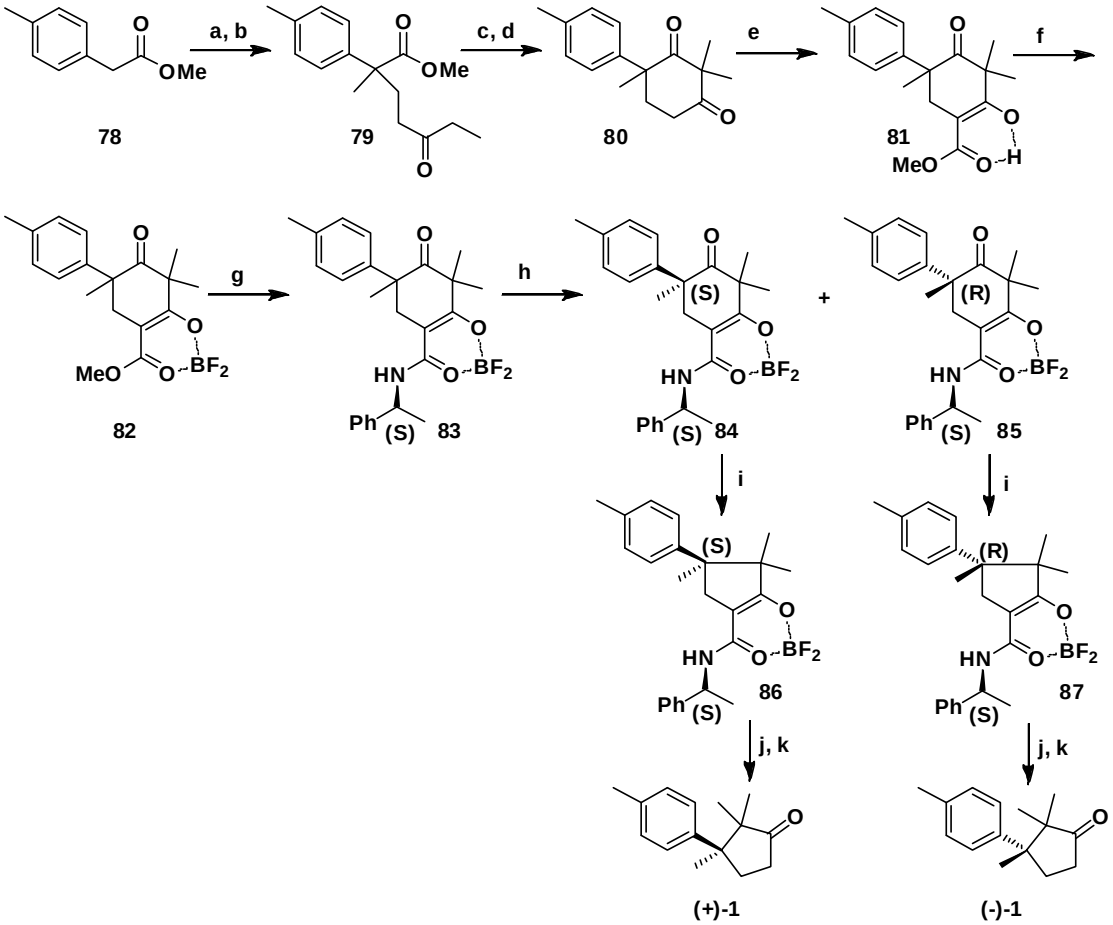
Thus, formation of the alcohol **75** by reaction of lithium cyclopropylphenyl sulfide **74** with 4-methyl acetophenone and its ring expansion by refluxing in benzene in the presence PTSA led to cyclobutanone **76**. The cyclobutanone **76** was then reacted with isopropenylmagnesium bromide to give the corresponding cyclobutanol **77**. Finally, treatment of **77** with a stoichiometric amount of PTSA in benzene gave excellent yields of the expected (±)-α-cuparenone **1**.

Garibay's approach

Garibay and coworkers[45] reported the solid to solid reactions for the stereospecific synthesis of (+)- and (-)-isomers of α-cuparenone utilizing photo-induced decarbonylation of crystalline hexasubstituted ketones with adjacent stereogenic quaternary centers.

As a starting point, racemic cyclohexanedione **80** was prepared in four steps from methyl 2-*p*-tolylacetate **78**. To prepare the enantiomerically pure natural products a classical resolution of (±)-**80** *via* the diastereomeric difluorodioxaborinane complexes of β-keto-*(S)*-(α)-methylbenzylamide **83** was performed. β-Ketoester **81** was obtained in 92% yield by selective C-acylation of (±)-**80** with methyl cyanoformate, and subsequent treatment with $BF_3.OEt_2$ gave difluorodioxaborinane (±)-**82** in 98% yield. Reaction of (±)-**82** with (-)-(*S*)-(α)-methylbenzylamine in acetonitrile yielded 80% of diastereomers **83**. Separation by column chromatography (EtOAc/hexane 2:8) led to pure **84** and **85**

Scheme 15: Garibay *et al*. *Angew. Chem. Int. Ed.* **2007**, *46*, 6485.



Reagents and conditions: *a) KH, MeI, THF, 0 °C, 92%; b) LDA, ethyl vinyl ketone, THF, 0 °C, 81 %; c) Na, MeOH, reflux, 99%; d) KH, MeI, DMF, 75 °C, 81%; e) LiHMDS, MeO(CO)CN, 92%; f) $BF_3.OEt_2$, toluene, 100%; g) (S)-(a)-Methylbenzylamine, MeCN, 80%; h) Silica gel chromatography (EtOAc/hexane 2:8); i) hν, suspension of nanocrystals in aq. CTAB solution, 80%; j) $MeCO_2Na$, EtOH, 70 °C, >98%; k) 6 M HCl, 100 °C, 90%.*

. Finally syntheses of (+)- and (-)-(α)-cuparenone were completed by parallel UV/Vis irradiation of suspended nanocrystals of (+)-(*S,S*)-**84** and (-)-(*S,R*)-**85** in aqueous cetyltrimethylammonium bromide (CTAB) solutions to lead to the clean formation of the (α)-cuparenone ketoamide derivatives (+)-(*S,S*)-**86** and (-)-(*S,R*)-**87** with 100% stereoselectivity in 80% yield. Removal of the BF_2 unit with NaOAc in ethanol followed by amide hydrolysis and decarboxylation gave the (*S*)-(+)-**1** and (*R*)-(-)-**1** each in 90% yield.

3.1.4 References

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Chapter 3. Synthetic studies towards *α*-cuparenone

Section 2

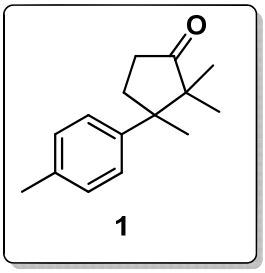
Synthesis of (±)-α-cuparenone employing one-pot cyclopetannulation

3.2.1 Summary

The present section deals with the total synthesis of (±)-α-cuparenone. Novel convenient and short synthesis of (±)-α-cuparenone employing cyclopentannulation has been achieved starting from commercially available cheap starting material like 4-methylbenzyl cyanide.

3.2.2 Introduction

α-Cuparenone **1** is a sesquiterpene isolated from Mayurpankhi tree (*Thuja orientalis*)[1] and liverwort mania fragrans.[2] Its structure and absolute configuration were determined by Sukh Dev and Chetty[1] in 1964.



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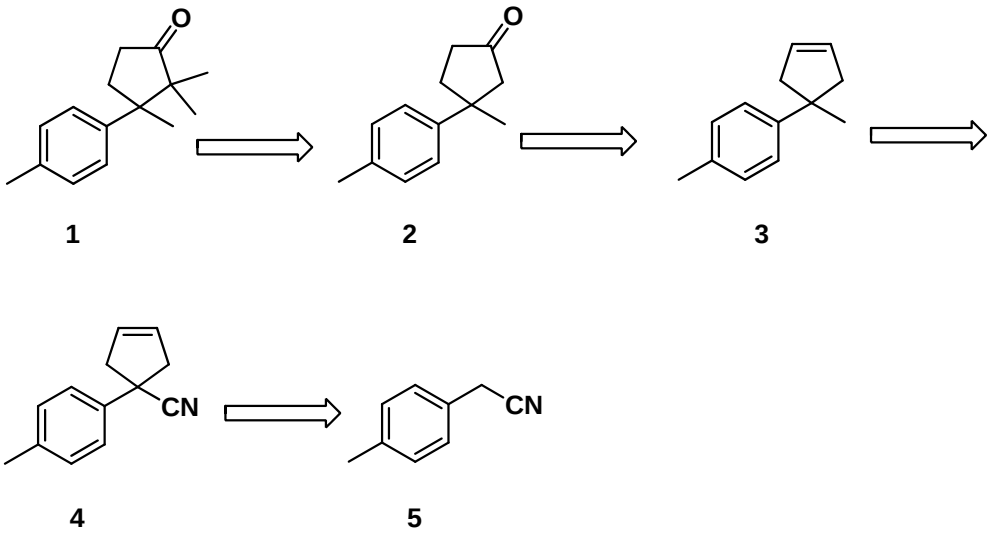
The structure of α-cuparenone **1** is quite interesting as it has a five membered ring having two contiguous quaternary centers. This makes α-cuparenone a good synthetic challenge to organic chemist. Although variety of approaches have been employed for the synthesis of α-cuparenone, all the reported syntheses have their own advantages and disadvantages and very few of them construct the five membered rings. There still exists need to develop a simple, practical and efficient synthesis of α-cuparenone. Continued interest in synthesis of cyclopentanoid natural products led to the synthesis α-cuparenone employing one-pot cyclopentannulation starting from cheap and commercially available starting material like 4-methylbenzyl cyanide.

3.2.3 Present work

According to retrosynthetic analysis depicted in scheme 1, α-cuparenone **1** could be achieved from selective gem-dialkylation of cyclopentanone **2**, which in turn could be obtained from cyclopentene **3** having the required quaternary methyl by employing hydroboration-oxidation sequence.

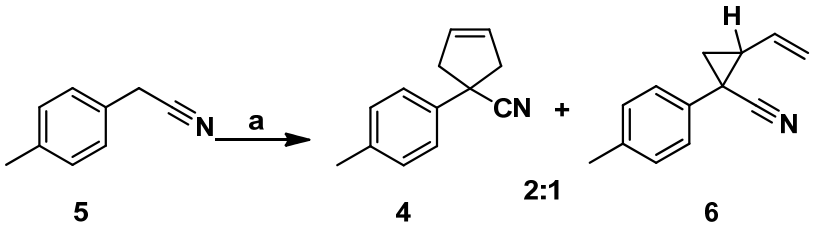


Scheme 1

The corresponding cyclopentene **3** could be synthesized from the cyclopentene **4** having cyano group at quaternary center, which in turn could be synthesized from commercially available 4-methylbenzyl cyanide **5** by employing cyclopentannulation using *cis*-1, 4-dichlorobut-2-ene (Scheme 1).

3.2.4 Results and discussion

Accordingly, synthesis was initiated from 4-methylbenzyl cyanide **5** which was subjected for cyclopentannulation with *cis*-1, 4-dichlorobut-2-ene using NaH as base in THF at room temperature to furnish cyclopentene ring **4** along with side product **6** as a mixture in 2:1 ratio which was inseparable on column chromatography (Scheme 2).

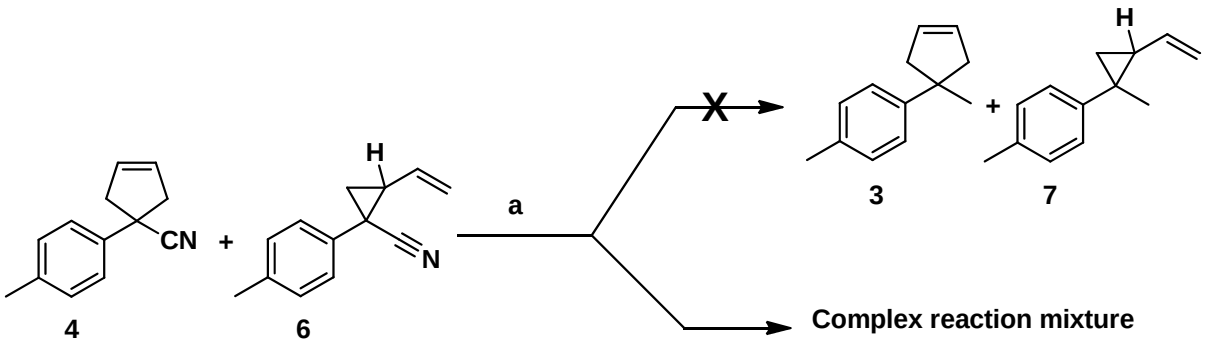


Scheme 2. ***Reagents and conditions:*** *a) NaH, cis-1,4-dichlorobutene, THF, rt, 8 h, 80%.*

The formation of mixture of compounds **4** and **6** was confirmed by spectroscopic data. IR spectrum of the mixture of **4** and **6** displayed strong absorption band at 2238 cm^{-1} indicating the presence of -CN functionality. ^1H NMR spectrum also showed it to be a mixture of compounds and showed the multiplets at δ 1.69-1.83 and 2.09-2.21 which were attributed to cyclopropane protons in structure **6,** while the broad doublets at δ 2.93 and 3.31 having the coupling constant 15.1 Hz were attributed to methylene protons in cyclopentene ring of structure **4**. The multiplets at δ 5.30-5.41 and 5.71-5.89 were attributed to olefinic protons in structure **6** while singlet at δ 5.83 was assigned to olefinic protons in compound **4**. The integration values clearly indicated that the ratio of compounds **4** and **6** was 2:1. For confirmation of the structure, the mixture was separated on gas chromatography where it showed two separate peaks which were in the ratio 2:1. Finally, the structure of both the compounds **4** and **6** was confirmed by GC mass spectrum. The mass spectrum of both the compounds exhibited *m/z* peak at 183 $(M)^+$ which confirmed that the compounds **4** and **6** are the isomers of each other.

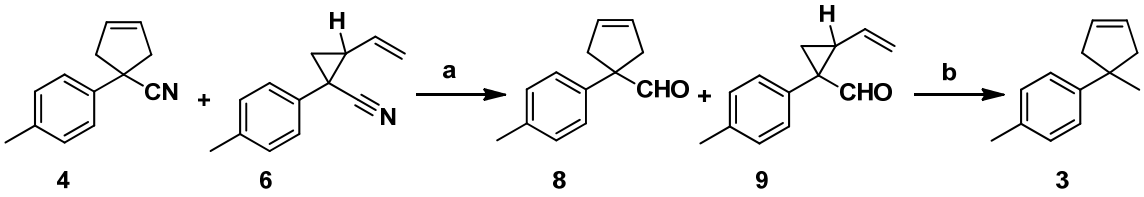
Though these compounds could not be separated at this stage, it was understandable that this mixture could be readily separated at hydroboration-oxidation step. As **4** on reduction –oxidation would lead to ketone while **6** would lead to acid. So the mixture was carried forward with the hope that it would be possible to separate the compounds at hydroboration-oxidation step.

Next it was thought to introduce methyl group at the place of cyano functionality and it can be realised by the reductive alkylation of cyano compound using lithium naphthalenide[3] reaction. Subjecting the mixture of substrates **4** and **6** to reductive alkylation using naphthalene, lithium metal and methyl iodide in THF led to a complex reaction mixture (Scheme 3).



Scheme 3: ***Reagents and conditions:*** *a) Naphthalene, lithium metal, THF, CH_3I, rt.*

Having failure in introduction of methyl group in one step, it was thought to solve the problem by using two-step strategy for reduction of –CN functionality. Accordingly DIBAL-H reduction of the mixture of cyano compounds **4** and **6** into corresponding aldehydes **8** and **9** was achieved at –78 ^{o}C, and the product without purification was further reduced under Huang-Minlon[4] reaction condition to furnish the required olefin intermediate **3** having one of the quaternary center (Scheme 4). Formation of single compound was confirmed by spectroscopic methods. IR spectrum showed no peak corresponding to the –CN functionality.



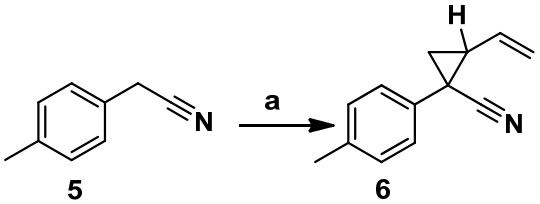
Scheme 4: ***Reagents and conditions:*** *a) DIBAL-H, DCM, -78 ^{o}C, 1 h; b) $NH_2NH_2.H_2O$, NaOH, diethylene glycol, 180 ^{o}C, 8 h, 60% (over two steps).*

^{1}H NMR spectrum of compound **3** showed the presence of a new singlet that appeared at δ 1.32 integrating for three protons which was attributed to methyl protons attached to quaternary center while signal that appeared at δ 5.71 was attributed to olefinic protons and signals at δ 2.45 (d, *J* = 14.2 Hz, 2H) and 2.73 (d, *J* = 14.2 Hz, 2H) were attributed to cyclopentene protons. A singlet integrating for three protons appeared at δ 2.30 which was attributed to aryl methyl protons. ^{13}C NMR spectrum of **3** also exhibited the absence of signals of nitrile carbons and revealed new signal that appeared at δ 20.8 which was assigned

to quaternary methyl carbon. DEPT spectrum of **3** showed presence of two methyl carbons while rest of the carbon peaks associated with the compound were seen at expected positions and finally the structure of **3** was confirmed by mass spectrum and elemental analysis. The mass spectrum showed the *m/z* peak at 173 $(M+1)^+$. Elemental analysis was also found to be in good agreement with the calculated values.

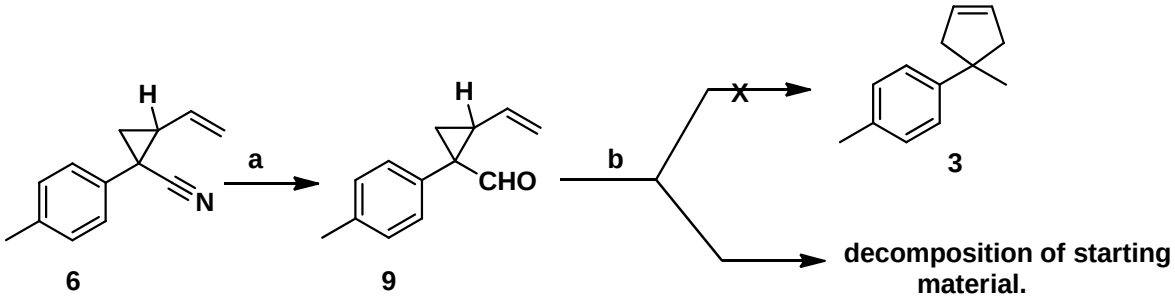
Formation of a single product in Huang-Minlon reduction was initially surprising but it was thought that the cyclopropane product **9** may undergo vinyl-cyclopropane rearrangement[5] to furnish cyclopentene **3**. In order to confirm the occurrence of vinyl-cyclopropane rearrangement, it was planned to prepare the compound **6** in pure form and subject it to the reaction conditions. Accordingly compound **6** was synthesized from 4-methylbenzyl cyanide by using sodium hydride and *trans*-1, 4-dibromobut-2-ene in THF as the solvent in 85% yield (scheme 5).

The compound **6** was characterized by spectroscopic methods. IR spectrum showed absorption at 2237 cm^{-1} signifying the presence of nitrile functionality. ^1H NMR spectrum showed signals that appeared in olefinic region at δ 5.30-5.41 as multiplet integrating for two protons (-CH=$\underline{CH_2}$) and δ 5.71-5.88 as multiplet integrating for one proton (-$\underline{CH}$=CH_2). The signals that appeared at δ 1.69–1.83 (m, 2H) and 2.09-2.21 (m, 1H) were attributed to the vinylic and cyclopropane protons. ^{13}C NMR spectrum of **6** showed the signals that appeared at δ 20.9, 22.8 and 33.4 corresponding to cyclopropane ring carbons while the signals at δ 118.4 and 134.3 were ascribed to vinylic carbons. Additionally DEPT experiment also showed presence of two methylene carbons, while rest of the protons and carbons associated with the compound resonated at their expected positions. Finally appearance of a peak at *m/z* 206 $(M + Na)^+$ in the mass spectrum (ESI) and elemental analysis confirmed the structure of compound **6**.



Scheme 5: ***Reagents and conditions:*** *a) NaH, trans-1, 4-dibromobutene, THF, rt, 8 h, 85%.*

Having the compound **6** in hand as the sole product, it was planned to subject the compound **6** for further reactions. Accordingly, the compound **6** was subjected to reduction with DIBAL-H in DCM at –78 ^{o}C to furnish aldehyde **9,** which without purification was further subjected to Huang-Minlon[4] reduction. Unfortunately, the required cyclopentene intermediate **3** was not obtained even after several trials with starting material undergoing decomposition (Scheme 6).

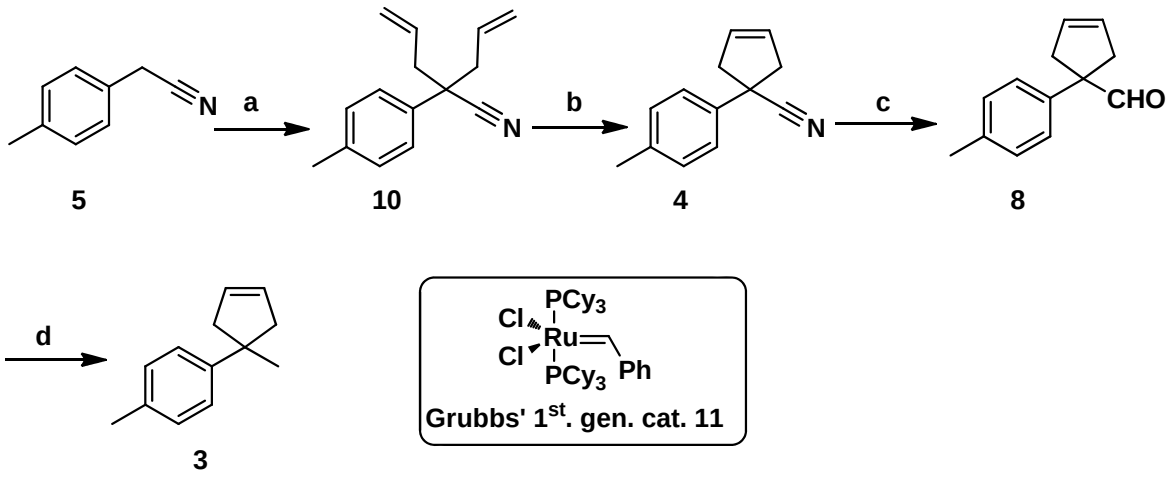


Scheme 6 : *Reagents and conditions:* *a) DIBAL-H, DCM, -78 ^{o}C, 1 h; b) $NH_2NH_2.H_2O$, NaOH, diethylene glycol, 180 ^{o}C, 8 h.*

Hence it was concluded that under Huang-Minlon conditions, the compound **9** decomposed due to strain in the cyclopropane ring. This observation explained the isolation of the cyclopentene intermediate **3**, as the sole product from Huang-Minlon reduction of mixture of compounds **8** and **9** (Scheme 4) in 60% yield (based on the conversion of **4** to **3**).

Since during direct formation of cyclopentene **4** a mixture of isomers was obtained, an alternative approach was attempted to overcome this problem. Accordingly, **5** was dialkylated with allylbromide using NaH as base in THF to furnish the diallylated compound **10** in 86 % yield (Scheme 7). IR spectrum of the product **10** indicated the presence of a nitrile group by revealing absorption at 2237 cm^{-1}. ^{1}H NMR spectrum showed signals that appeared in olefinic region at δ 5.11-5.19 (m, 4H), multiplet integrating for four protons (-CH=$\underline{CH_2}$) and δ 5.56-5.72 multiplet integrating for two protons (-$\underline{CH}$=CH_2). The multiplet which appeared at 2.66-2.70 integrating for four protons (-$\underline{CH_2}$-CH=CH_2) was attributed to the allylic methylene protons while rest of the proton peaks associated with the compound resonated at expected positions. ^{13}C NMR and DEPT spectra of compound **10** showed the signals that appeared at δ 44.1 ($\underline{CH_2}$-CH=CH_2), 131.7 (CH_2-$\underline{CH}$=CH_2) and 119.9 (CH_2-CH=$\underline{CH_2}$) corresponding to allyl

chain carbons and signal at δ 47.1 showed presence of quaternary carbon while rest of the carbons associated with the compound resonated at their expected positions. Finally the mass spectrum of **10** showed the *m/z* peak at 234 $(M + Na)^+$ and elemental analysis was also found to be in good agreement with the calculated values.

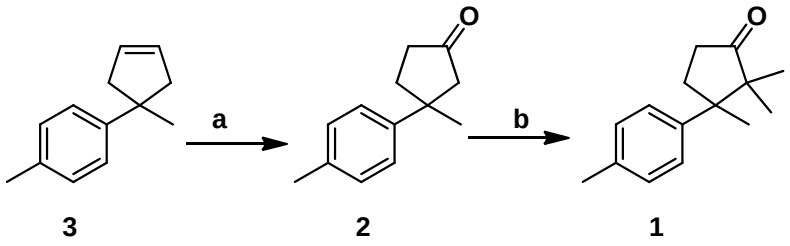


Scheme 7 : *Reagents and conditions:* *a) NaH, allyl bromide, THF, rt, 86%; b) Grubbs' 1st gen. cat., DCM, 3 h, 96%; c) DIBAL-H, DCM, -78 °C, 1 h; d) $NH_2NH_2.H_2O$, NaOH, diethyleneglycol, 180 °C, 8 h, 60% (over two steps).*

The ring-closing metathesis on **10** was carried out in the presence of 10 mol % of Grubbs' 1st generation catalyst[6] **11** in DCM at room temperature. The required cyclopentene **4** was obtained in 96% yield (Scheme 7). IR spectrum of the product **4** indicated the presence of a cyano group by revealing absorption at 2238 cm^{-1}. ^1H NMR spectrum showed absence of allyl group protons and the presence of new signal that appeared in the olefinic region at δ 5.83 as a singlet integrating for two protons which was attributed to cyclopentene ring protons thus confirming the ring closing metathesis. ^{13}C NMR and DEPT spectra of compound **4** showed a signal at δ 124.8 for –CN while the signal at 129.4 was attributed to cyclopentene olefinic carbons. Rest of the protons and carbons associated with the compound **4** resonated at expected positions. Finally the mass spectrum of **4** showed the *m/z* peak at 206 $(M + Na)^+$ and elemental analysis was also found to be in good agreement with the calculated values. DIBAL-H reduction of the compound **4** at –78 °C furnished aldehyde **8**, which without

purification was further reduced under Huang-Minlon[4] reaction conditions to furnish required olefin intermediate **3** having methyl at quaternary center (Scheme 7).

Having successfully synthesized the requisite olefin **3** as the sole product, stage was set to complete the total synthesis of target compound **1**. Accordingly, the olefin **3** was subjected to hydroboration[7]-oxidation[8] sequence using $BH_3.Me_2S$, H_2O_2-NaOH, IBX to furnish cyclopentanone **2** in 85% yield (Scheme 8).



Scheme 8 : ***Reagents and conditions:*** *a) i) $BH_3.SMe_2$, THF, H_2O_2, 3 N NaOH; ii) IBX, DMSO, 12 h, 85%; b) LiHMDS, MeI, DME, HMPA, 3 h, 70%.*

IR spectrum of the product **2** indicated the presence of a carbonyl group by revealing absorption at 1720 cm^{-1} confirming hydroboration-oxidation. ^1H NMR spectrum showed no peak in the olefinic region while appearance of peaks at δ 2.46 and 2.65 as a doublet integrating for one proton each, having geminal coupling constant 17.7 Hz, was attributed to methylene protons between carbonyl and quaternary center. The methylene protons next to carbonyl and quaternary center showed multiplets at δ 2.21-2.29 and 2.32–2.37 respectively integrating for two protons each. ^{13}C NMR spectrum of compound **2** showed a signal that appeared at δ 217.8 corresponding to carbonyl carbon, while rest of the proton and carbon peaks associated with the compound **2** resonated at expected positions. Finally, the mass spectrum of **2** showed the *m/z* peak at 189 $(M + 1)^+$ and elemental analysis was also found to be in good agreement with the calculated values.

The ketone **2** on regioselective alkylation using MeI and LiHMDS as a hindered base, cat. HMPA in DME afforded the target compound (±)-α-cuparenone **1** in 70% yield. The IR spectrum of **1** showed characteristic absorption at 1725 cm^{-1} for the ketone carbonyl. The ^1H NMR displayed all the four methyls, as singlets at δ 0.61, 1.17 and 1.26 for methyls on

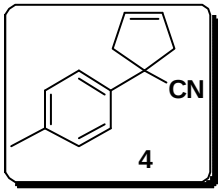
cyclopentanone ring and δ 2.35 for Ar-CH_3. The multiplets at δ 1.86-1.97 integrating for one proton, 2.41-2.52 integrating for two protons and 2.58-2.71 integrating for one proton were assigned to the protons in cyclopentanone ring. Aromatic protons appeared at δ 7.14-7.30 as multiplet integrating for four protons. ^{13}C NMR and DEPT spectra of compound **1** showed the signals at δ 18.3, 20.8, 22.1 and 25.3 which were attributed to four methyl carbons while signals that appeared at δ 29.6 and 33.7 were attributed to methylene carbons in cyclopentanone ring. The rest of the protons and carbons associated with the compound **1** resonated at expected positions. Finally the mass spectrum of **1** showed the *m/z* peak at 216 (M^+) and base peak at 145 while the elemental analysis was also found to be in good agreement with the calculated values. All the spectral data of the α-cuparenone were in good agreement with literature reported values[9] for natural (±)-α-cuparenone.

3.2.5 Conclusion

In conclusion, a very efficient and practical synthesis of (±)-α-cuparenone has been accomplished in which all the reaction sequences are easy to perform, essentially mild and proceed in excellent yields. One of the shortest and efficient synthesis of the (±)-α-cuparenone has been achieved in five steps in 28% overall yield.

3.2.6 Experimental

1-*p*-Tolylcyclopent-3-enecarbonitrile (4)



Method A: To the suspension of 60% NaH (3.05 g, 76 mmol) (washed with dry petroleum ether 2-3 times) in dry THF (20 mL) at 0 ^{o}C was added 4-methylbenzyl cyanide **5** (5 g, 38 mmol) in dry THF (10 mL) and stirred for 30 min. Then *cis*-1,4-dichlorobut-2-ene (4.7 g, 38 mmol) in dry THF (10 mL) was added drop wise over 20 min and reaction was stirred at room temperature for 8 h. On completion of the reaction (TLC), it was quenched by the addition of saturated ammonium chloride solution, extracted with ethyl acetate (3 x 40 mL) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by flash column chromatography (SiO_2) using 3% ethyl acetate/petroleum ether as eluent to afford yellow oil consisting of mixture of compounds **4** and **6** (5.52 g, 80%) in the ratio of 2:1.

Method B: The Grubbs' 1st generation catalyst (194 mg, 1 mol %) was added to a degassed homogeneous solution of allyl compound **10** (500 mg, 2.36 mmol) in dry DCM (50 mL) under an atmosphere of argon. The resulting mixture was stirred at room temperature for 4 h. On completion of the reaction, the solvent was removed under vacuum and the product was purified by flash column chromatography (SiO_2) using 2% ethyl acetate/petroleum ether as eluent to provide thick colourless oil **4** (390 mg, 92%).

Mol. Formula : $C_{13}H_{13}N$ (MW 183.10).

IR (Neat) : 817, 1514, 1640, 2238, 3029 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.36 (s, 3H), 2.93 (d, *J* = 15.0 Hz, 2H), 3.31 (d, *J* = 15.0 Hz, 2H), 5.83 (s, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H).

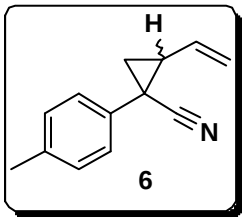
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.7, 44.5, 48.0 (2C), 124.8, 125.0 (2C), 128.2 (2C), 129.4 (2C), 137.2, 138.2.

Mass (ESI) m/z : 183 $(M)^+$, 206 $(M + Na)^+$.

Elemental analysis : Calculated: C, 85.21; H, 7.15; N, 7.64%

: Found: C, 84.84; H, 6.98; N, 7.12%

1-*p*-Tolyl-2-vinylcyclopropanecarbonitrile (6)



To the suspension of 60% NaH (3.6 g, 76 mmol) (washed with dry petroleum ether) in dry THF (20 mL) at 0 ^{o}C, was added 4-methylbenzyl cyanide **5** (5 g, 38 mmol) in dry THF (25 mL) and stirred for 30 min. Then *trans*-1,4-dibromobut-2-ene (8.16 g, 38 mmol) in dry THF (10 mL) was added drop wise over 20 min and the reaction mixture was stirred at room temperature for 8 h. On completion of the reaction, it was quenched by the addition of saturated ammonium chloride solution and extracted with ethyl acetate (3 x 40 mL) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash column chromatography using 3% ethyl acetate-petroleum ether as eluent to afford compound **6** (5.8 g, 85%) as yellow oil.

Mol. Formula **:** $C_{13}H_{13}N$ (MW: 183.25).

IR (Neat) **:** 817, 1216, 1514, 1640, 2237, 3019 cm^{-1}.

^{1}H NMR ($CDCl_3$ 200 MHz) **:** δ 1.69–1.83 (m, 2H), 2.09-2.21 (m, 1H), 2.36 (s, 3H), 5.30-5.41 (m, 2H), 5.71-5.88 (m, 1H), 7.09-7.25 (m, 4H).

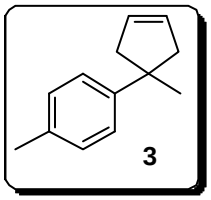
^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 20.9, 21.4, 22.8, 33.4, 118.4, 120.1, 125.4 (2C), 129.5 (2C), 132.6, 134.3, 137.3.

Mass (ESI) m/z **:** 183 $(M)^+$, 206 $(M + Na)^+$.

Elemental analysis **:** Calculated: C, 85.21; H, 7.15; N, 7.64%

: Found: C, 84.99; H, 7.05; N, 7.32%

1-Methyl-4-(1-methylcyclopent-3-enyl) benzene (3)



The mixture of compounds **4** and **6** (4 g, 21 mmol) was taken in dry DCM (30 mL) under argon atmosphere and temperature was lowered to –78 ^{o}C. DIBAL-H (44.0 mmol, 22 mL, 2M solution in toluene) was added drop wise and left to stir at same temperature till the completion of the reaction. After completion of reaction, it was quenched at –78 ^{o}C with the drop wise addition of 2N HCl and then warmed to the room temp. The organic layer was separated and the aqueous

layer was extracted with DCM (3 x 20 mL). Combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the mixture of aldehydes **8** and **9** which was used as such without further purification.

To the stirred solution of crude mixture of aldehydes **8** and **9** obtained above in diethylene glycol (20 mL) was added hydrazine monohydrate (3.85 mL, 88 mmol) and sodium hydroxide (3.52 g, 88 mmol). The reaction mixture was heated to reflux for 8 h and after completion of the reaction, it was diluted with water (10 mL) and extracted using ethyl acetate (3 x 25 mL). Combined organic layers were then washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford a residue which was purified by flash column chromatography (SiO_2) using 2% ethyl acetate/petroleum ether as eluent to obtain compound **3** (2.2 g, 60%).

Mol. Formula **:** $C_{13}H_{16}$ (MW: 172.27).

IR (Neat) **:** 816, 1215, 1650, 2926, 3019 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.32 (s, 3H), 2.30 (s, 3H), 2.45 (d, *J* = 14.2 Hz, 2H), 2.73, (d, *J* = 14.2 Hz, 2H), 5.71 (s, 2H), 7.06 (d, *J* = 8.34 Hz, 2H), 7.20 (d, *J* = 8.34 Hz, 2H).

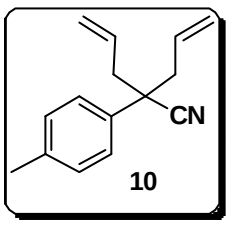
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.8, 31.3, 45.7, 47.7 (2C), 125.8 (2C), 128.8 (2C), 129.3 (2C), 134.6, 148.6.

Mass (ESI) m/z **:** 173 $(M + H)^+$.

Elemental analysis **:** Calculated**:** C, 90.64; H, 9.36%

: Found**:** C, 90.75; H, 9.48%

2-Allyl-2-*p*-tolylpent-4-enenitrile (10)



10

To the suspension of 60% NaH (0.68 gm, 16.7 mmol) (washed with dry petroleum ether 2-3 times) in dry THF (10 mL) was added 4-methylbenzyl cyanide **5** (1.0 g, 7.6 mmol) in dry THF (10 mL) at 0 ^oC and stirred for 30 min. Allyl bromide (1.49 mL, 16 mmol) in dry THF (5 mL) was added drop wise over 5 min and reaction mixture was stirred at room temperature for 8 h. On completion of the reaction it was quenched by the addition of

saturated ammonium chloride solution, extracted with ethyl acetate (3 x 20 mL) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash column chromatography using ethyl acetate/petroleum ether (3:97) as eluent to afford compound **10** (1.3 g, 86%) as yellowish oil.

Mol. Formula **:** $C_{15}H_{17}N$ (MW: 211.30).

IR (Neat) **:** 815, 1642, 1514, 2237, 2982 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.37 (s, 3H), 2.66-2.70 (m, 4H), 5.11-5.19 (m, 4H), 5.56-5.72 (m, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H).

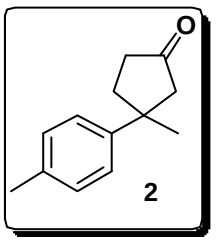
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.9, 44.1 (2C), 47.1, 119.9 (2C), 121.5, 126.0 (2C), 129.4 (2C), 131.7 (2C), 134.6, 137.3.

Mass (ESI) m/z **:** 234 $(M + Na)^+$.

Elemental analysis **:** Calculated**:** C, 85.26; H, 8.11; N, 6.63%

: Found**:** C, 84.82; H, 8.05; N, 6.59%

3-Methyl-3-*p*-tolylcyclopentanone (2)



To the solution of olefin **3** (300 mg, 1.7 mmol) in anhydrous THF (15 mL) at 0 ^oC, $BH_3.SMe_2$ (0.331 mL, 3.4 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4h. It was then cooled to 0 ^oC and treated with aqueous NaOH (2.8 mL, 8.7 mmol) and 30% H_2O_2 (0.98 mL, 8.7 mmol). The reaction mixture was allowed to warm to room temperature. After 3 h the volatile materials were removed under reduced pressure and residue was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford alcohol which was used as such without further purification.

To the stirred solution of alcohol in dry DMSO (10 mL), were added IBX (732 mg, 2.6 mmol) and left to stirr at room temperature for 4 h. After completion of the reaction, the reaction mixture was diluted with water and extracted using diethylether (3 x 20 mL). Combined organic layers were then washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford residue which was purified by flash

column chromatography using 5% ethyl acetate/petroleum ether as eluent to afford compound **2** as white solid (0.276 g, 85%).

Mol. Formula **:** $C_{13}H_{16}O$ (MW**:** 188.27).

Melting point **:** 58-60 ^{o}C.

IR ($CHCl_3$) **:** 815, 1246, 1614, 1720, 3019 cm^{-1}.

^{1}H NMR ($CDCl_3$ 200 MHz) **:** δ 1.39 (s, 3H), 2.21-2.29 (m, 2H), 2.35 (s, 3H), 2.32–2.37 (m, 2H), 2.46 (d, *J* = 17.7 Hz, 1H), 2.65 (d, *J* = 17.7 Hz, 1H), 7.12-7.22 (m, 4H).

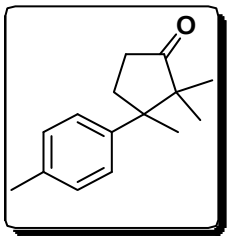
^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 20.7, 29.3, 35.8, 36.5, 43.3, 52.1, 125.1 (2C), 129.0 (2C), 135.5, 145.3, 217.8.

Mass (ESI) m/z **:** 189 $(M + H)^{+}$.

Elemental analysis **:** Calculated: C, 82.84; H, 8.57%

: Found: C, 82.75; H, 8.54%

2, 2, 3-Trimethyl-3-*p*-tolylcyclopentanone (1)



To the stirred solution of ketone **2** (200 mg, 1.0 mmol) in dry DME (20 mL), was added LiHMDS (371 mg, 2.2 mmol) and catalytic amount of HMPA and stirred for few minutes. Then methyl iodide (0.325 mL, 5.0 mmol) in dry DME (2 mL) was added drop wise and reaction mixture was stirred for 3 h. After completion, the reaction was quenched by addition of saturated ammonium chloride solution and extracted with ethyl acetate (3 x 50 mL) and washed with brine solution. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash column chromatography using 3% ethyl acetate/petroleum ether as eluent to furnish desired target molecule **1** (152 mg, 70%) as a colorless oil.

Mol. Formula **:** $C_{15}H_{20}O$ (MW: 216).

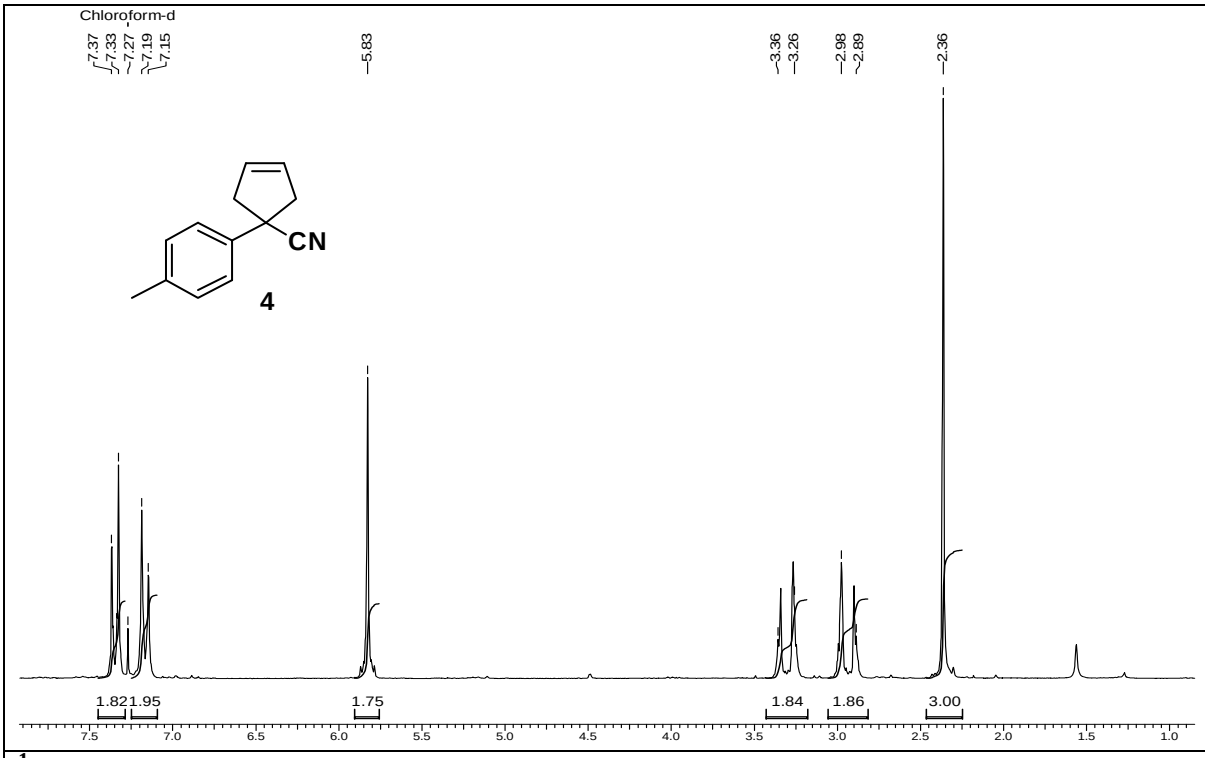
IR (Neat) **:** 815, 1460, 1510, 1725, 2960 cm^{-1}.

^{1}H NMR ($CDCl_3$ 200 MHz) : δ 0.61 (s, 3H), 1.17 (s, 3H), 1.26 (s, 3H), 1.86-1.97 (m, 1H), 2.35 (s, 3H), 2.41-2.52 (m, 2H), 2.58-2.71 (m, 1H), 7.14-7.30 (m, 4H).

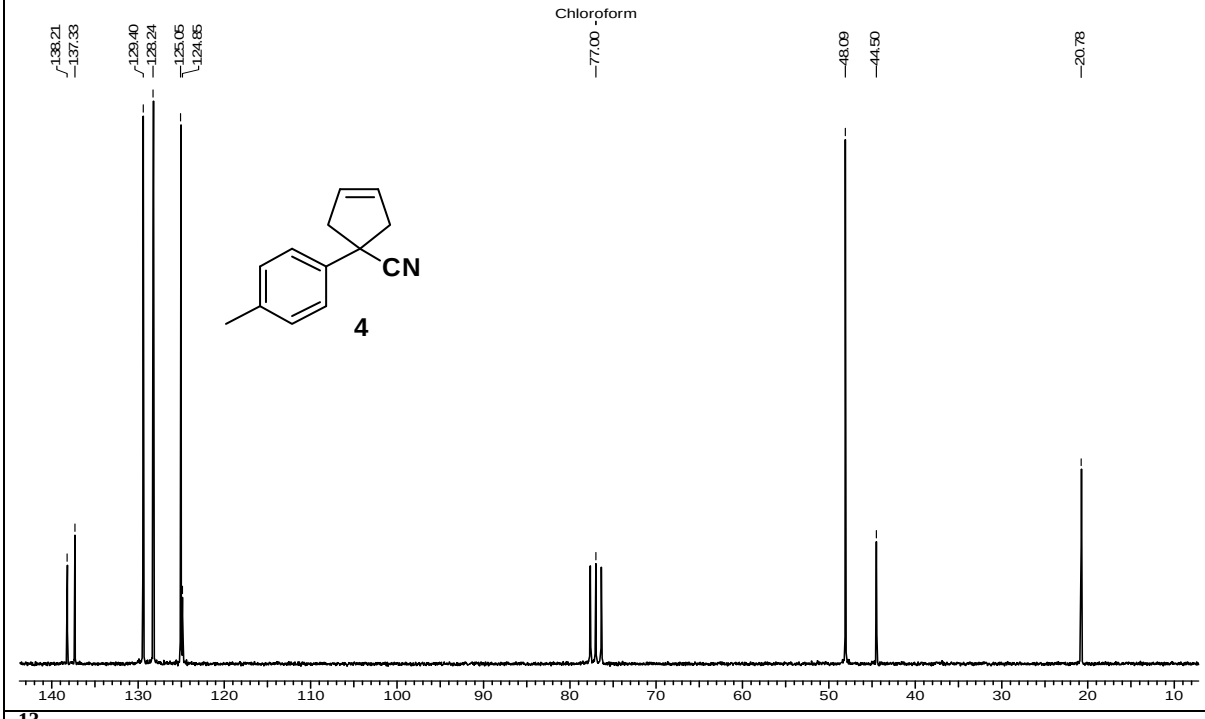
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 18.3, 20.8, 22.1, 25.3, 29.6, 33.7, 48.3, 53.2, 126.3 (2C), 128.9 (2C), 135.8, 141.9, 222.7.

Mass (ESI) m/z : 216 (M^+, 75%).

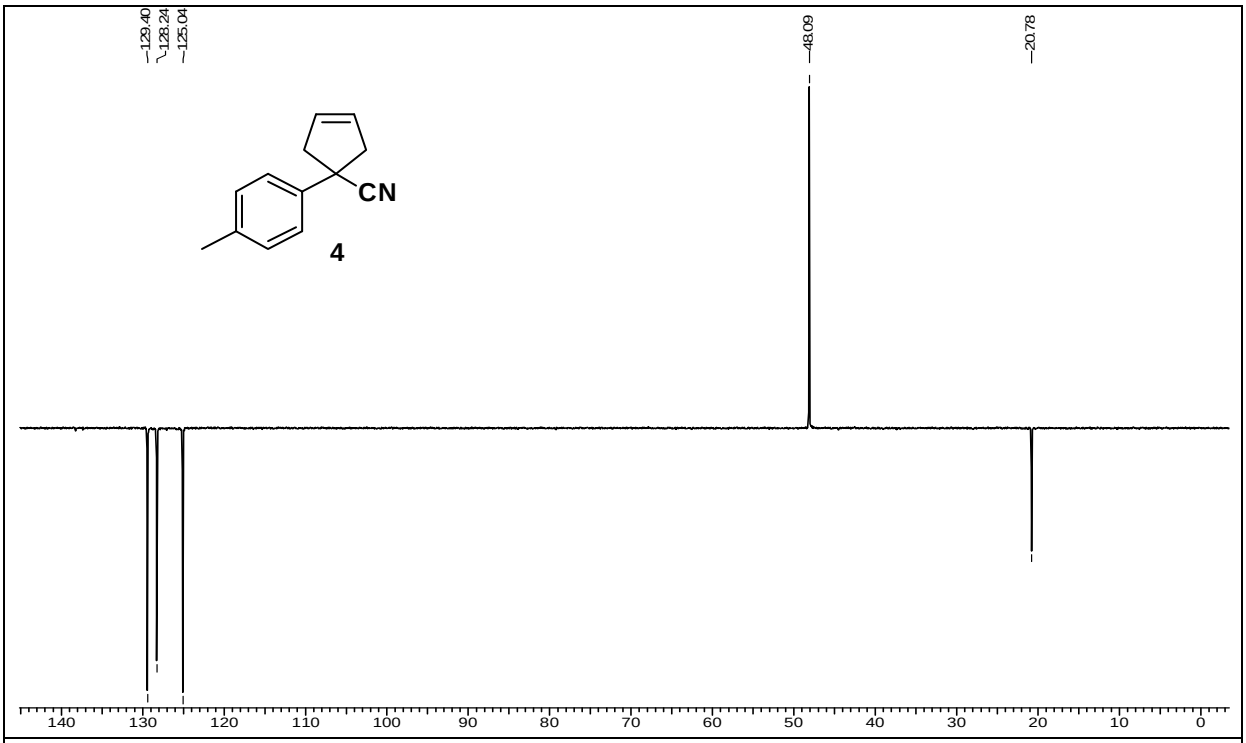
3.2.7 Spectra



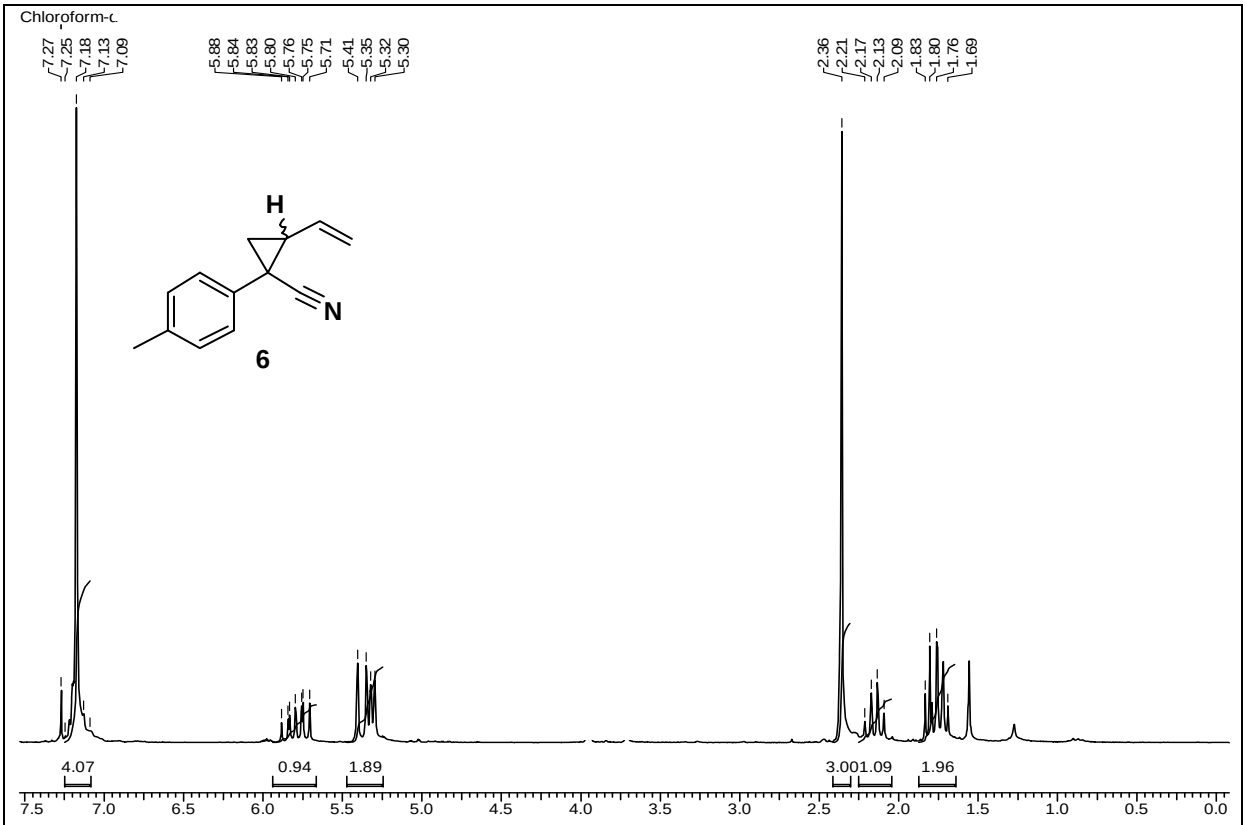
^{1}H NMR spectrum of compound 4 ($CDCl_3$, 200 MHz)



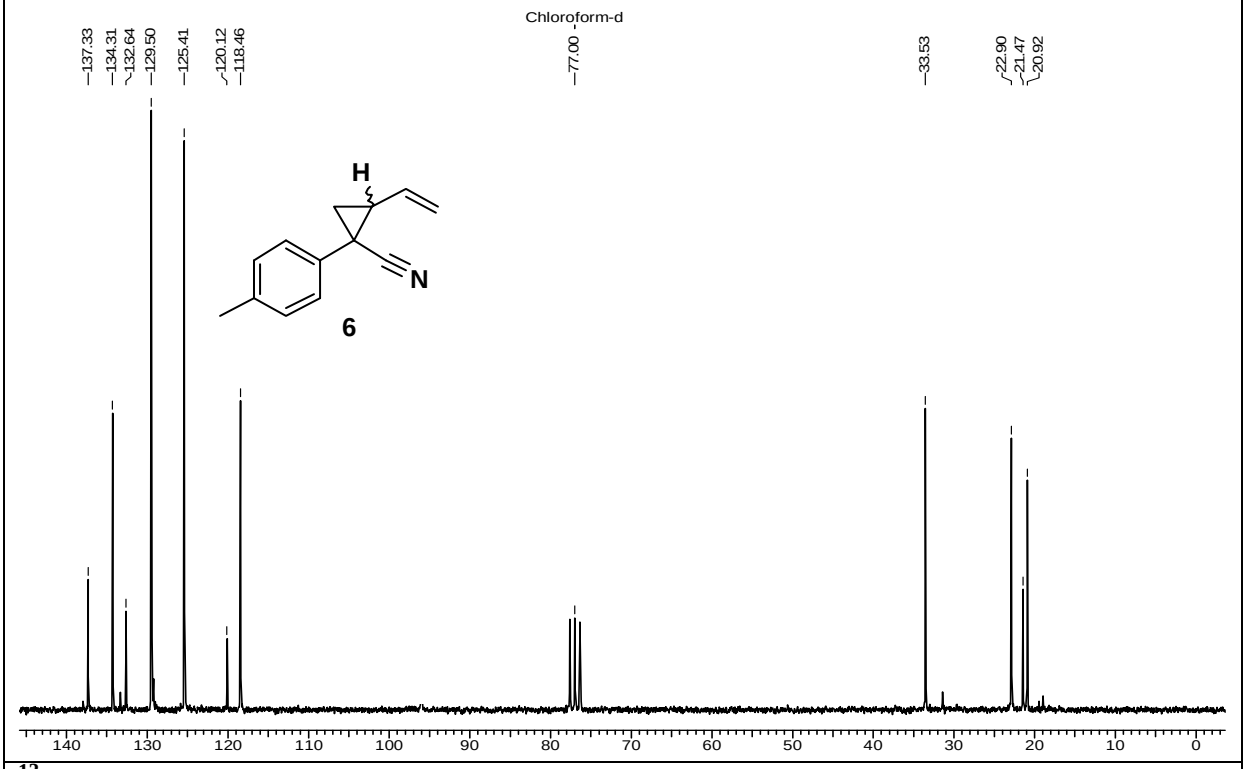
^{13}C NMR spectrum of compound 4 ($CDCl_3$, 50 MHz)



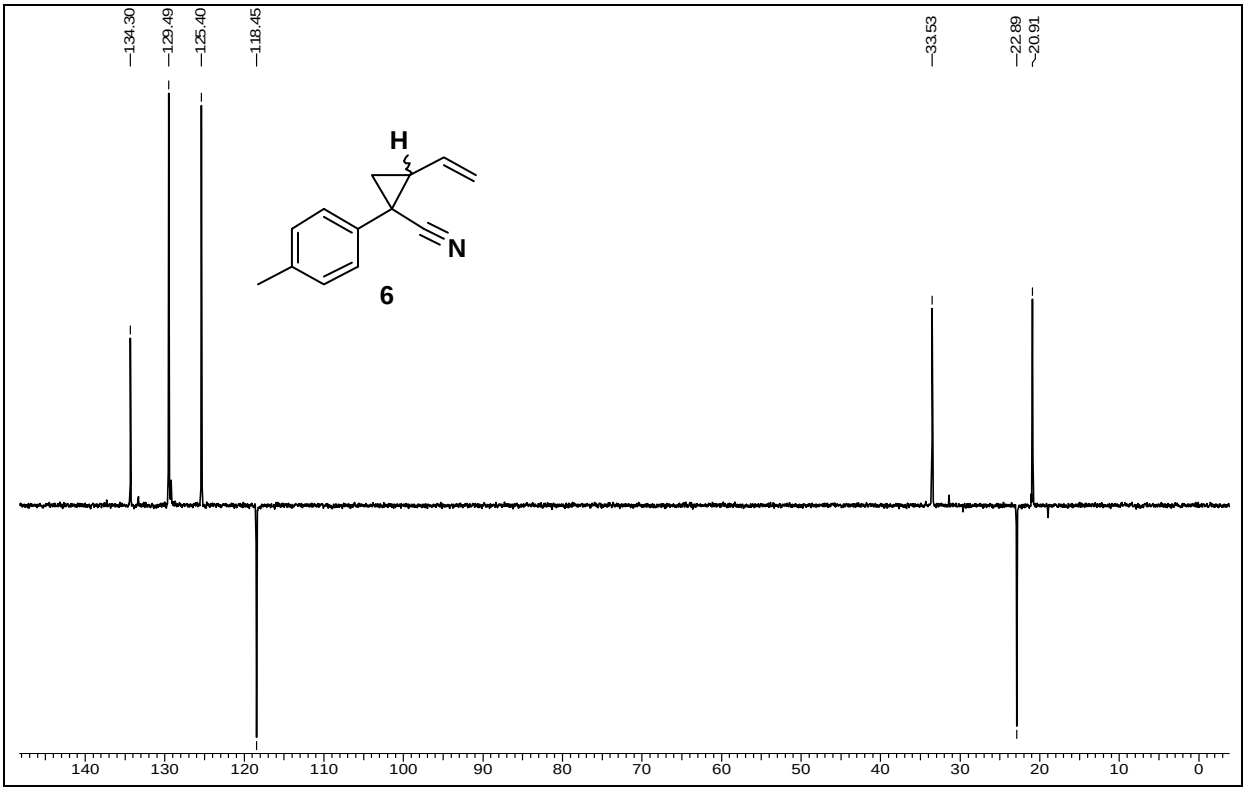
DEPT spectrum of compound 4 ($CDCl_3$, 50 MHz)



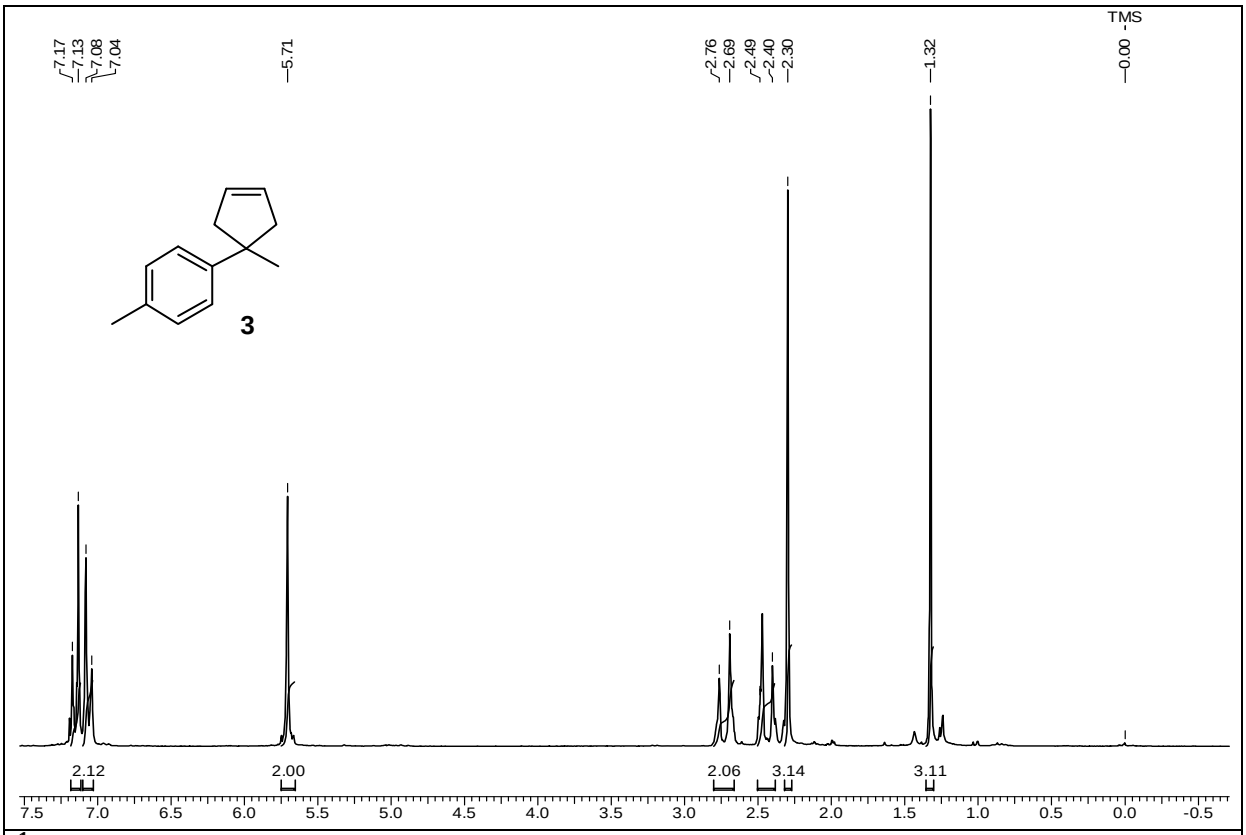
^{1}H NMR spectrum of compound 6 ($CDCl_3$, 200 MHz)



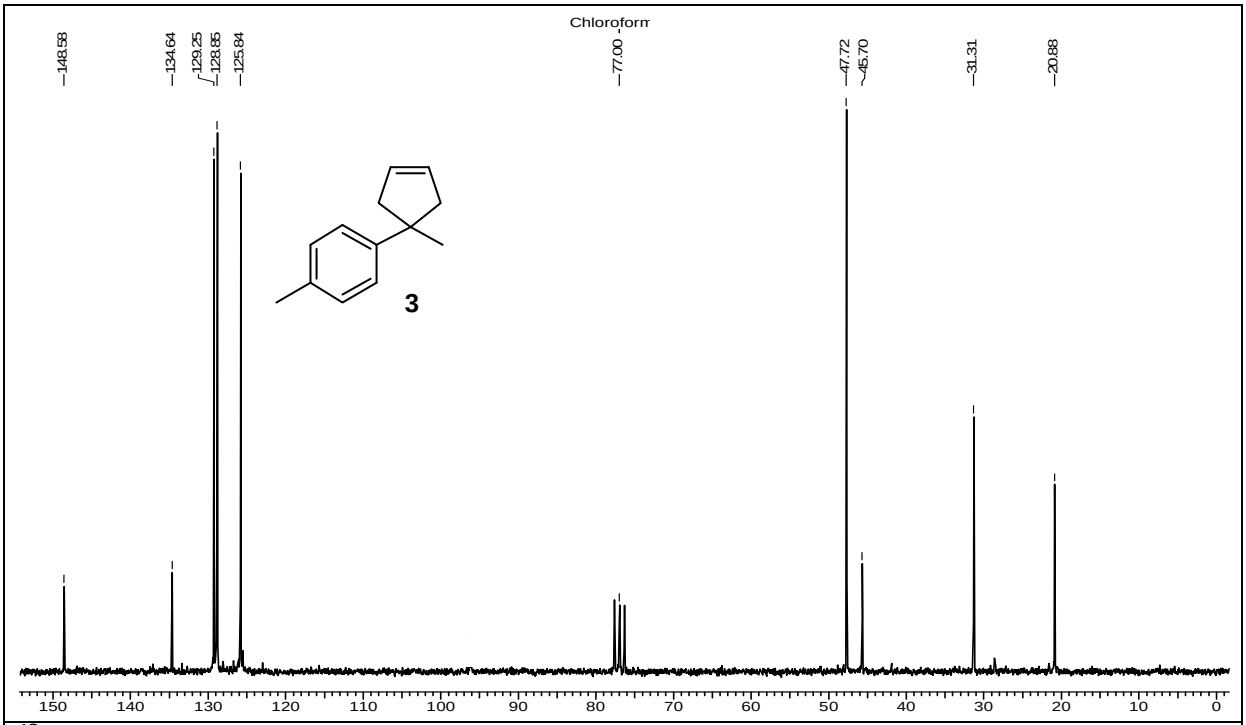
^{13}C NMR spectrum of compound 6 ($CDCl_3$, 50 MHz)



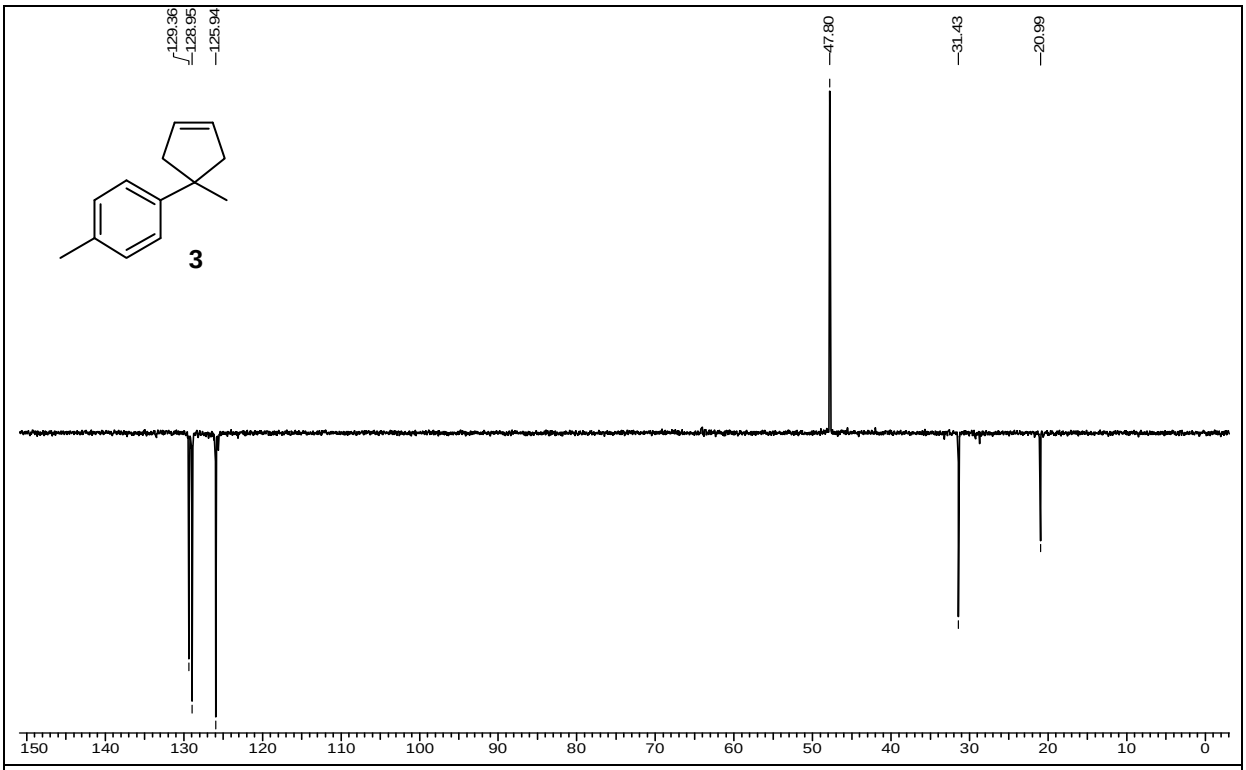
DEPT spectrum of compound 6 ($CDCl_3$, 50 MHz)



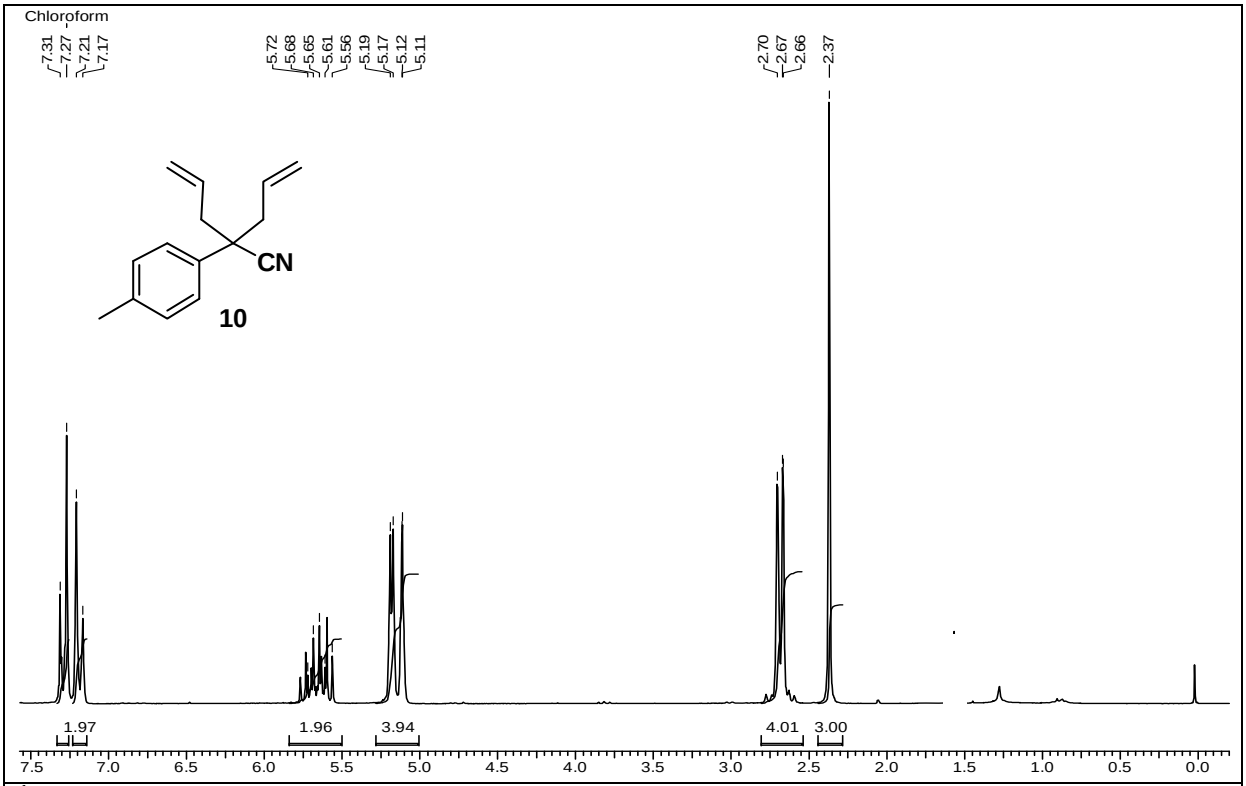
^{1}H NMR spectrum of compound 3 ($CDCl_3$, 200 MHz)



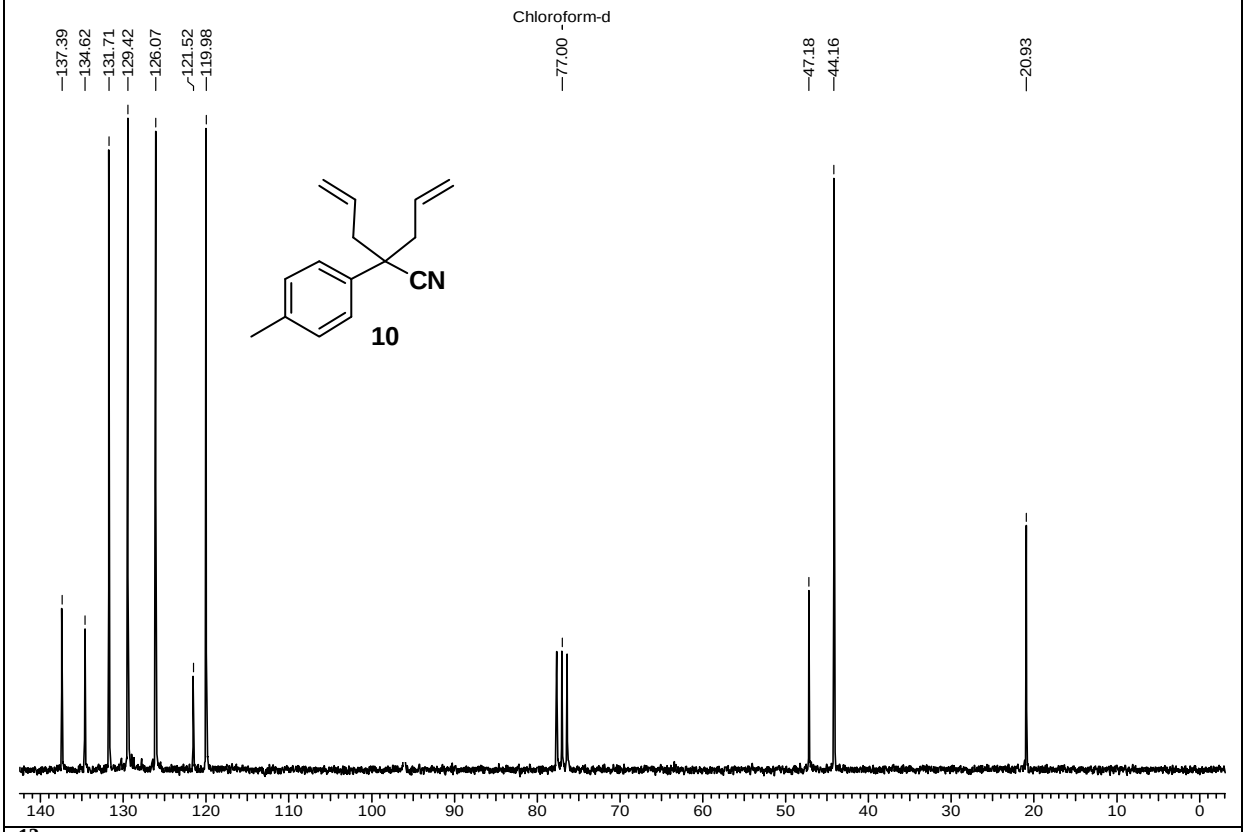
^{13}C NMR spectrum of compound 3 ($CDCl_3$, 50 MHz)



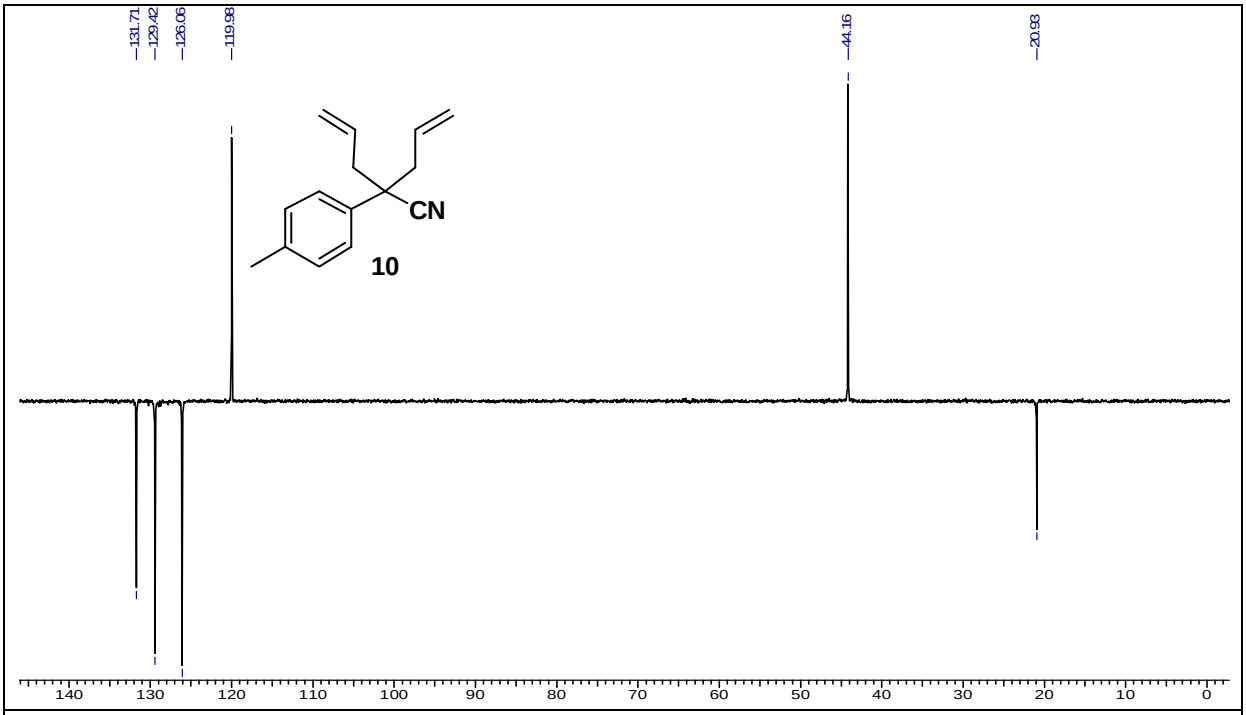
DEPT spectrum of compound 3 ($CDCl_3$, 50 MHz)



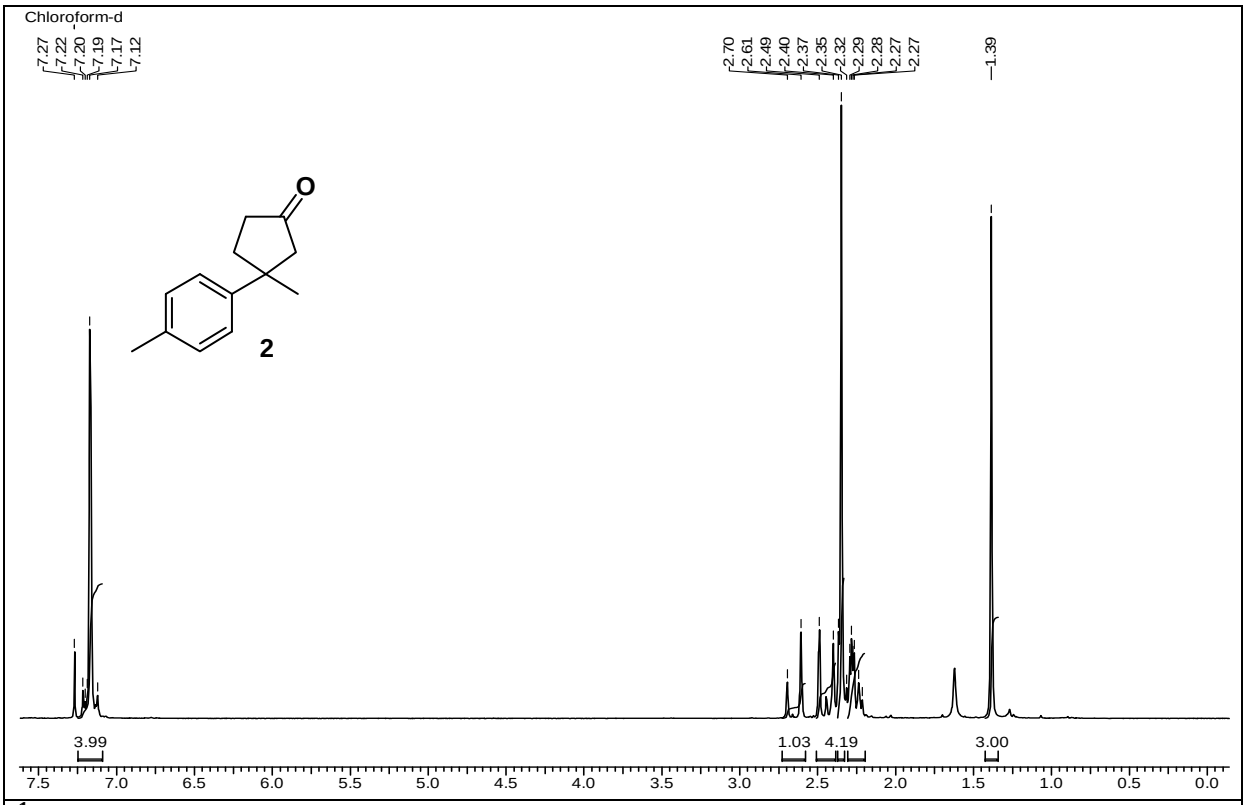
^{1}H NMR spectrum of compound 10 ($CDCl_3$, 200 MHz)



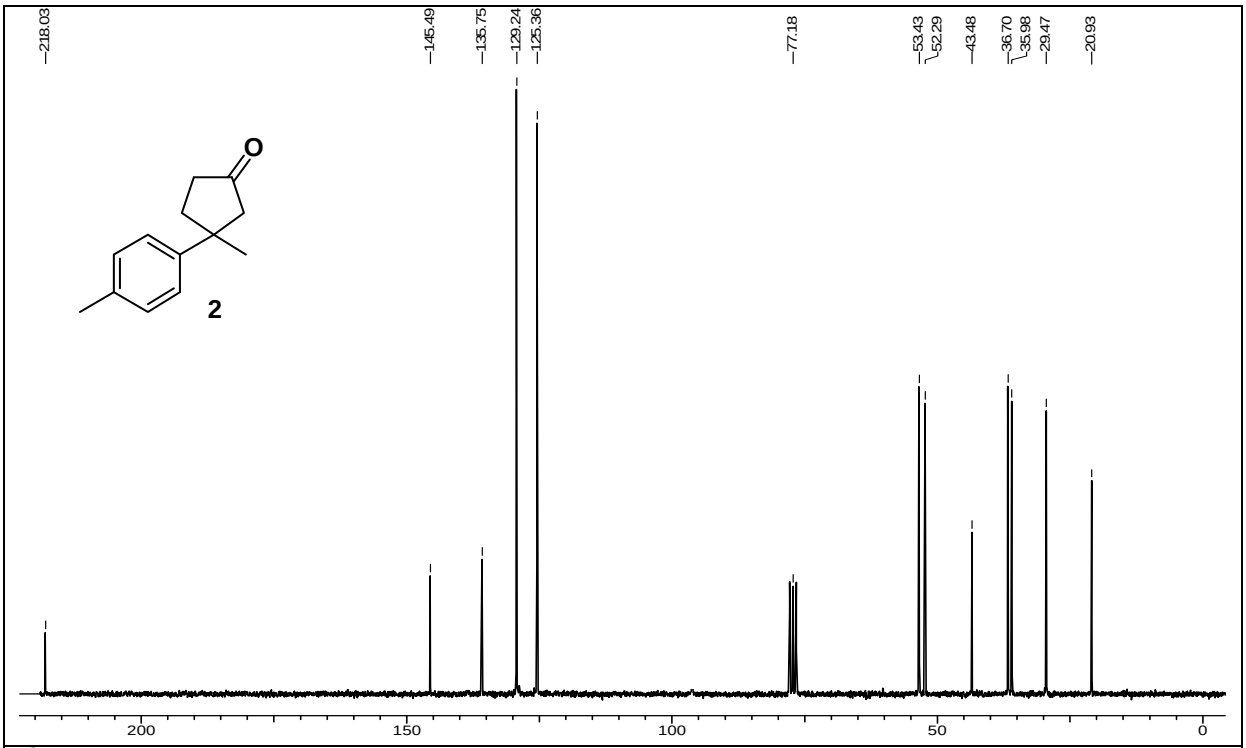
^{13}C NMR spectrum of compound 10 ($CDCl_3$, 50 MHz)



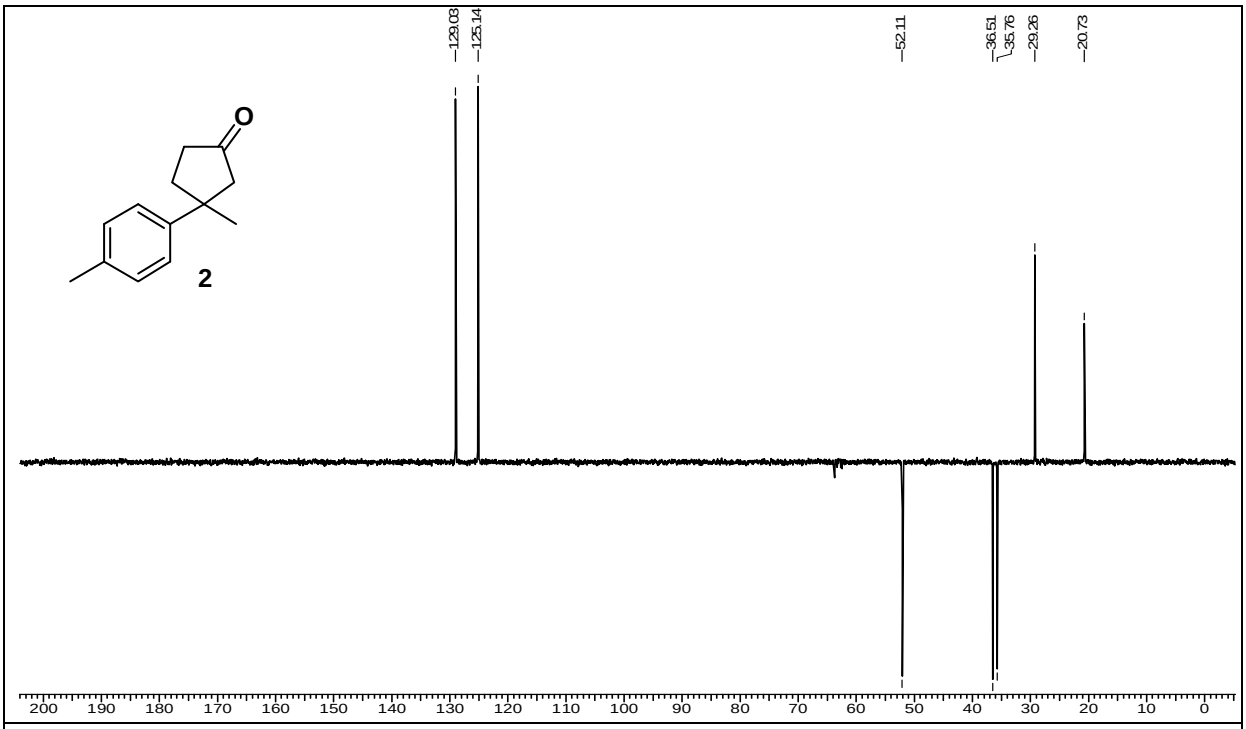
DEPT spectrum of compound 10 ($CDCl_3$, 50 MHz)



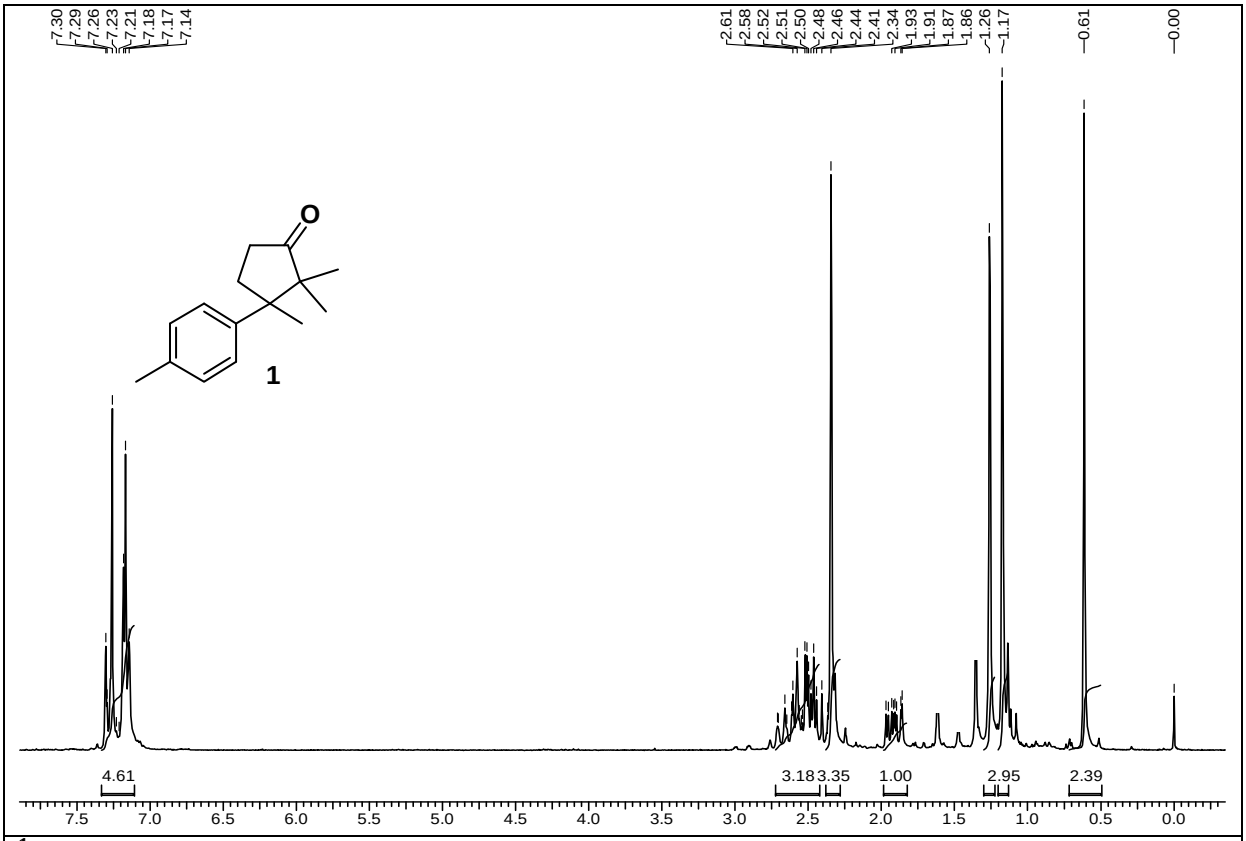
^{1}H NMR spectrum of compound 2 ($CDCl_3$, 200 MHz)



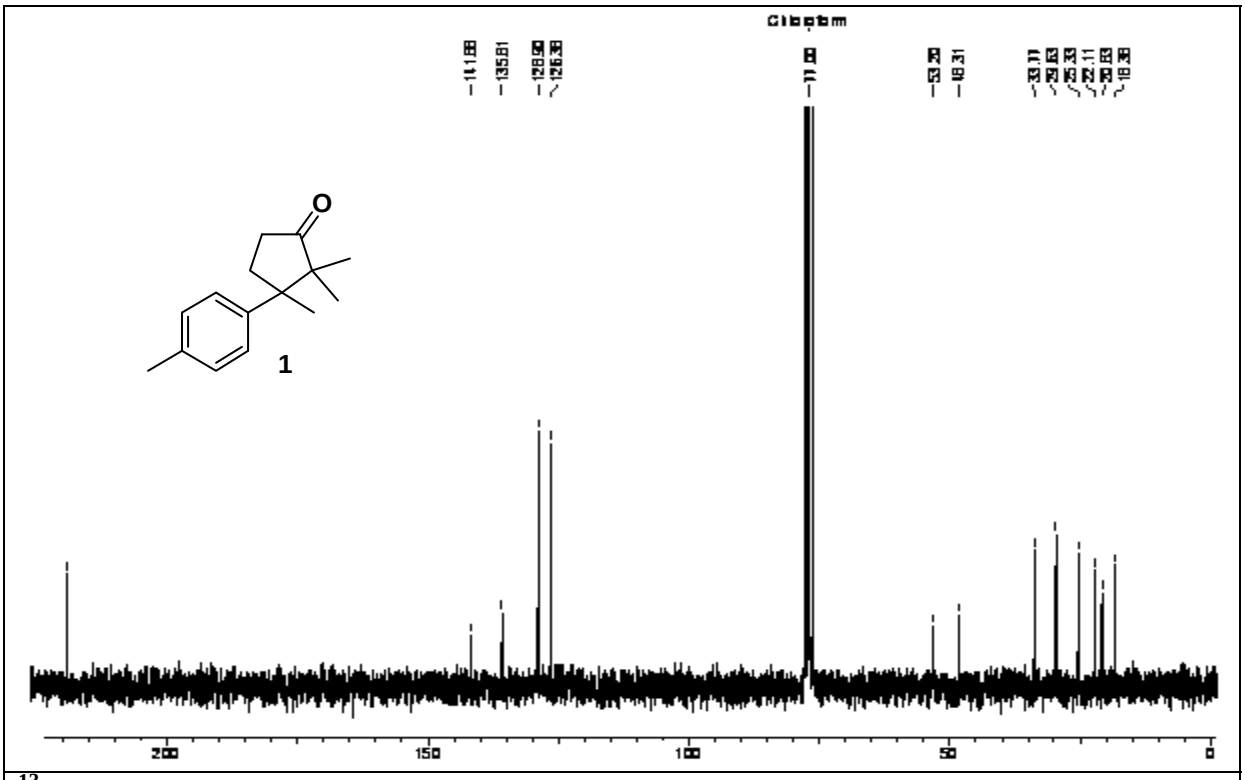
^{13}C NMR spectrum of compound 2 ($CDCl_3$, 50 MHz)



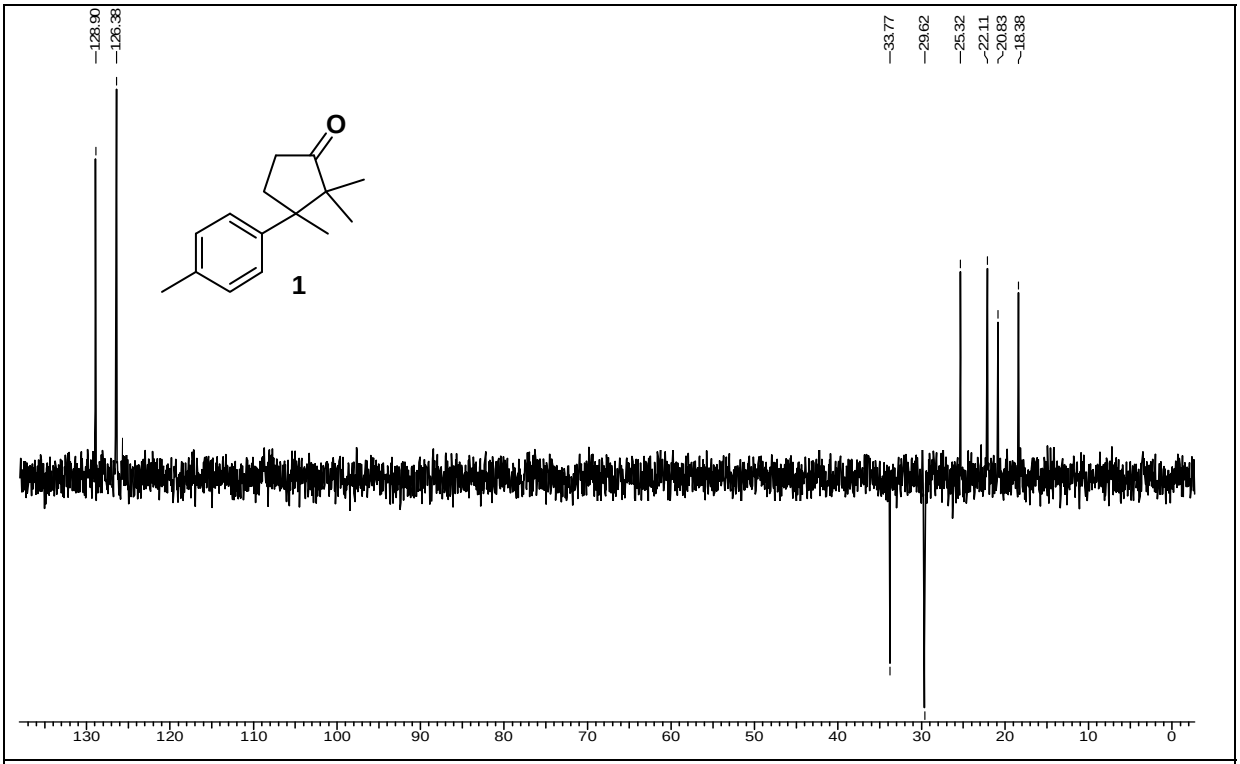
DEPT spectrum of compound 2 ($CDCl_3$, 50 MHz)



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



^{13}C NMR spectrum of compound 2 ($CDCl_3$, 50 MHz)



DEPT spectrum of compound 2 ($CDCl_3$, 50 MHz)

3.2.8 References

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Chapter 3. Synthetic studies towards *α*-cuparenone

Section 3

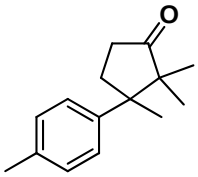
Synthesis of (±)-α-Cuparenone employing gem-diallylation and RCM

3.3.1 Summary

The present section deals with the total synthesis of (±)-α-cuparenone. New expedient and short synthesis of (±)-α-cuparenone has been achieved starting from commercially available cheap starting material 4-methyl acetophenone.

3.3.2 Introduction

As described in section I of this chapter the synthesis of α-cuparenone **1** is a good synthetic challenge. In keeping with the interest in the expedient construction of the naturally occurring cyclopentane ring[1] and the utilisation of ring closing metathesis,[2] it was decided to apply RCM for the efficient synthesis of α-cuparenone.

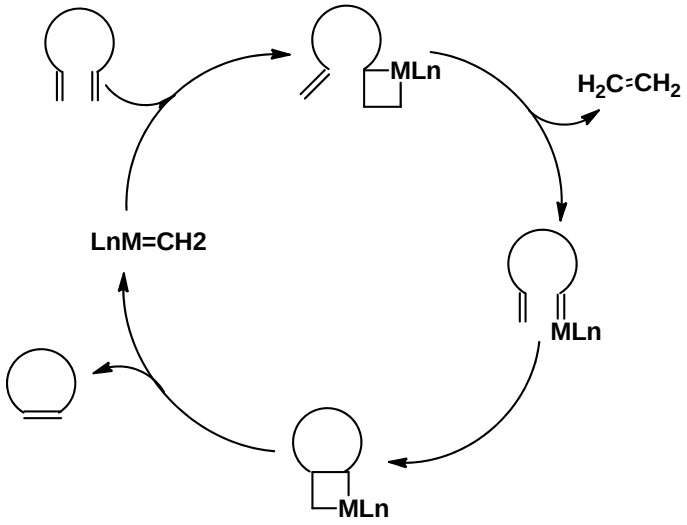


1

Olefin metathesis is one of the most important tools in the hands of the organic chemist[3] for the formation of C-C bond and it is gaining increasing importance due to introduction of new and efficient catalysts that are more air stable and have been successfully used for the preparation of both carbocyclic as well as heterocyclic ring systems. More importantly, small, medium and large rings[4] have been constructed efficiently and thus it has become a reliable tool for natural product synthesis. Also they have high functional group compatibility and activity thus becoming potentially synthetically more useful.[3]

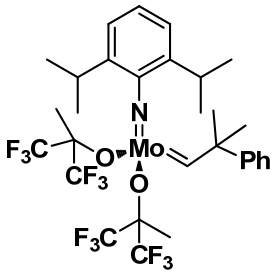
Olefin metathesis is a disproportionation process involving bond formation, bond breakage and reorganization. It was first reported by Anderson and Merckling[5] in 1955, where Ti(IV) metal catalysts were used for polymerization of norbornene. Later on, after introduction of Mo and Ru based catalysts by Schrock[6] and Grubbs[7] which are air stable and are tolerant to diverse functional groups, olefin metathesis has become popular in organic synthesis as well.

Scheme-1 depicts the postulated mechanism for ring closing metathesis reaction, which involves an iterative process of [2+2] cycloaddition and cycloreversion between the olefins, metal alkylidene and metallocyclobutane species.

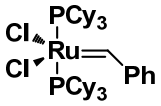


Scheme 1

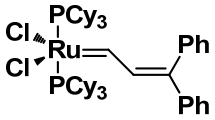
The numerous catalysts were developed by Tebbe, Schrock and Grubbs for different kinds of metathesis reactions, which are tolerant to different functional groups and which have wide range in chemical area and their uses are described.



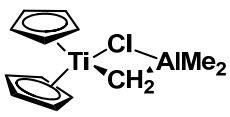
Schrock's catalyst 2



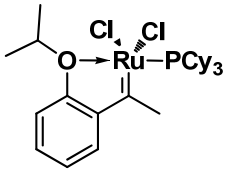
Grubbs' 1st generation cat. 3



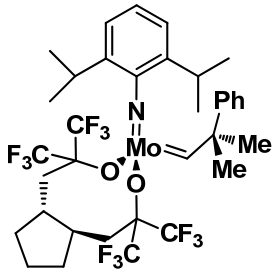
Grubbs' catalyst 4



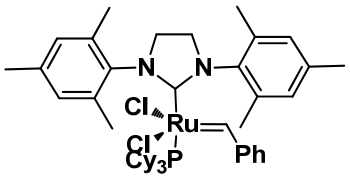
Tebbe's reagent 5



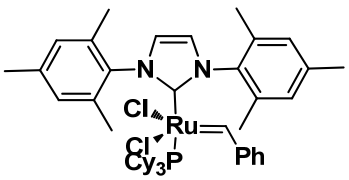
Grubbs-Hoveyda catalyst 6



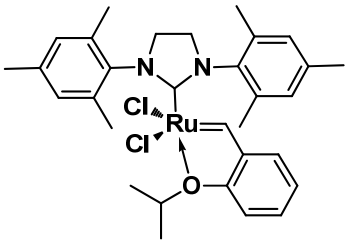
Catalyst for chiral metathesis 7



Grubbs' 2nd generation cat. 8



Grubbs' catalyst 9



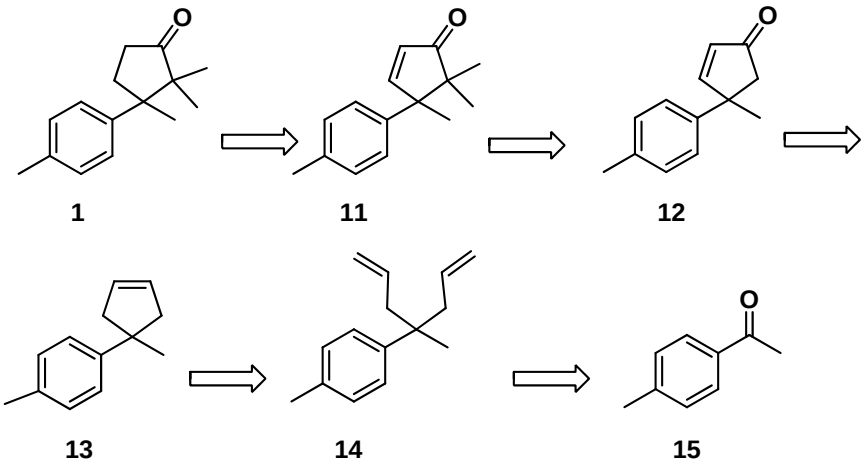
Grubbs-Hoveyda
2nd gen. catalyst 10

Scheme 2

3.3.3 Present work

Having successful in synthesis of racemic α-cuparenone employing cyclopentannulation where carbon bearing aryl ring acts as a nucleophile involves simple dialkylation to construct cyclopentene ring as the key step, this section deals with the synthesis of α-cuparenone employing one-pot gem-diallylation of acetophenone, where the carbon bearing aryl group serves as an electrophile, followed by RCM on the resulting substrate to construct the cyclopentene ring. This was elaborated to short and efficient synthesis of α-cuparenone.

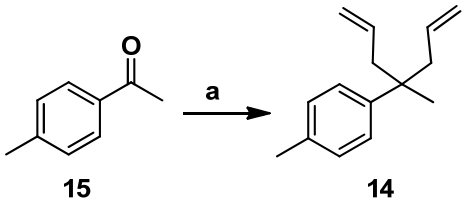
According to retrosynthetic analysis depicted in scheme 3, α-cuparenone could be achieved from reduction of enone **11**, which in turn could be accessed by dialkylation of **12** and enone **12** could be accessed by PDC oxidation of cyclopentene ring **13**. Cyclopentene ring **13** could be synthesized from diallyl compound **14** *via* ring closing metathesis and compound **14** in turn could be synthesized from commercially available 4-methyl acetophenone **15** by employing one-pot gem-diallylation.



Scheme 3

3.3.4 Results and discussion

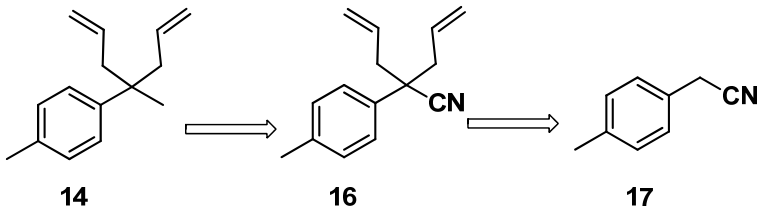
According to proposed retrosynthetic plan, synthesis started from 4-methyl acetophenone **15**, which on treatment with $InCl_3$,[8] allyl trimethylsilane and TMS-Cl in ethylene dichloride as a solvent at room temperature furnished diallyl compound **14** in 30% yield (Scheme 4).



Scheme 4: ***Reagents and conditions:*** *a) $InCl_3$, Me_3SiCl, allyltrimethylsilane, EDC, 8 h, 30%.*

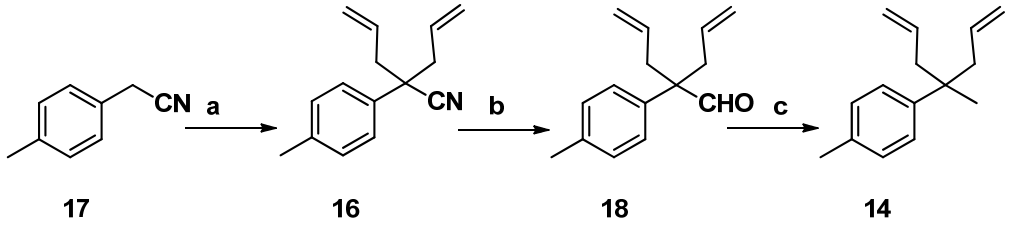
The formation of **14** was ascertained by spectral analysis. ^{1}H NMR spectrum of **14** displayed a singlet at δ 1.23 integrating for three protons and was assigned to quaternary methyl group. Signals at δ 2.46 (dd, *J* = 6.6, 13.8 Hz, 2H) and 2.25 (dd, *J* = 6.6, 13.8 Hz, 2H) were attributed to the methylene group of allyl moieties (-$\underline{CH_2}$-CH=CH_2)$_2$, multiplets in olefinic region at δ 4.89-4.99 (-CH_2-CH=$\underline{CH_2}$)$_2$ integrating for four protons and δ 5.40-5.60 (-CH_2-$\underline{CH}$=CH_2)$_2$ integrating for two protons were attributed to olefinic protons of allyl groups while singlet at δ 2.30 corresponded to aryl methyl group. This was further confirmed by its ^{13}C and DEPT spectra, which showed a signal at δ 40.2 for the quaternary carbon bearing aryl group. Signals at δ 117.0 and 135.1 showed presence of olefinic carbons while rest of the protons and carbons associated with the compound resonated at expected positions. Finally the structure of **14** was confirmed by mass spectral and elemental analysis. The mass spectrum of **14** showed the *m/z* peak at 223 $(M + Na)^+$. In case of elemental analysis the experimental values were found to be in good agreement with its theoretical values.

Though the required diallyl compound was synthesized in one pot, yield of the reaction was not satisfactory. To improve the yield alternative strategy was adopted wherein it was thought to synthesise diallyl compound from 4-methylbenzyl cyanide (Scheme 5). Accordingly, 4-methylbenzyl cyanide **17** was dialkylated with allyl bromide and NaH to furnish the diallylated compound **16** (Scheme 6).



Scheme 5

DIBAL-H reduction of the compound **16** at –78 ^{o}C in DCM gave aldehyde **18**. The formation of aldehyde was confirmed by spectroscopic methods. IR spectrum showed presence of aldehyde group by revealing absorptions at 2720 and 1715 cm^{-1}. ^{1}H NMR spectrum showed singlet integrating for one proton at δ 9.49 and was attributed to aldehydic proton and in ^{13}C NMR spectrum signal that appeared at δ 201.4 indicated the presence of carbonyl group while rest of the protons and carbons associated with the compound resonated at expected positions. Finally, the mass spectrum of **18** showed the *m/z* peak at 215 $(M + H)^{+}$. Aldehyde **18** was further reduced under Huang-Minlon[9] reaction condition to furnish required diallyl compound **14** (Scheme 6). Formation of compound **14** was confirmed by using spectroscopic methods.



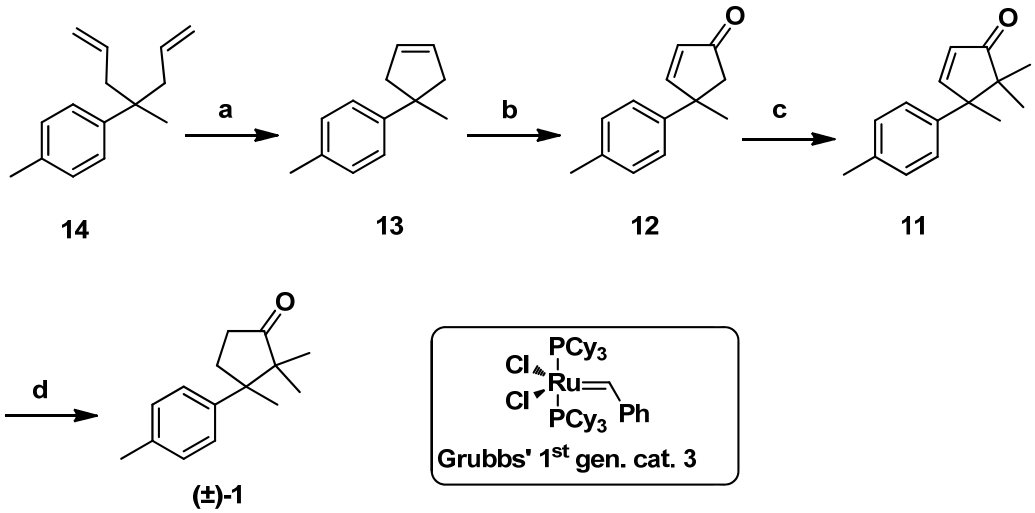
Scheme 6 : *Reagents and conditions:* *a) NaH, allyl bromide, THF, RT, 86%; b) DIBAL-H, DCM, -78 ^{o}C, 1 h; c) $NH_2NH_2.H_2O$, NaOH, diethylene glycol, 180 ^{o}C, 8 h, 60% (over two steps).*

The allyl compound **14** thus obtained was identical to the one obtained by gem-diallylation of 4-methyl acetophenone **15** (Scheme 4).

Having successfully synthesised requisite diallyl compound **14**, it was planned to construct the cyclopentene ring employing ring closing metathesis. Accordingly performing ring closing metathesis on diallyl compound **14** by using 1st generation Grubbs' catalyst[10] afforded the required key intermediate **13** (Scheme 7). ^{1}H NMR spectrum showed singlet at δ 5.71 integrating for two protons which was attributed to olefin protons in cyclopentene ring, while all other peaks associated with the olefinic

protons of allyl groups vanished confirming the RCM reaction. Singlets which appeared at δ 1.32 and 2.32 integrating for three protons each were attributed to methyl groups attached to quaternary center and aryl methyl moiety. ^{13}C NMR spectrum along with DEPT spectrum showed the absence of the carbons belonging to the allyl groups and the presence of new signal that appeared at δ 129.3 which was assigned to cyclopentene olefin carbons. Signal which appeared at δ 45.7 indicated the presence of quaternary methyl carbon and finally the structure of **13** was confirmed by mass spectrum and elemental analysis. The mass spectrum of **13** showed the *m/z* peak at 173 $(M + H)^+$. Elemental analysis was also found to be in good agreement with calculated values.

With the cyclopentene unit **13** in hand, an easy and straightforward conversion into corresponding enone **12** could be realised by the PDC oxidation[11] of the alkene **13.** Subjecting the substrate **13** to react with PDC in pyridine at 100 ^oC for 7 h rendered the product **12** in 65% yield (Scheme 7).



Scheme 7: ***Reagents and conditions:*** *a) Grubbs' cat. 1st generation, DCM, rt, 5 h, 90%; b) PDC, pyridine, 100 ^oC, 7 h, 65%; c) NaH, DMF, CH_3I (excess), rt, 12 h, 70%; d) H_2-Pd/C, EtOH, piperidine, 4 h, quantitative yield.*

The structure of enone **12** was confirmed by IR, NMR and mass spectroscopy. The IR spectrum of enone **12** showed absorption at 1720 cm^{-1} signifying the presence of keto functionality. ^{1}H NMR spectrum of enone **12** revealed two singlets, one at δ 1.63

integrating for three protons and other at δ 2.34 integrating for three protons, which were attributed to quaternary methyl (C-$\underline{CH_3}$) and aryl methyl (Ar-$\underline{CH_3}$) respectively. The methylene protons α to carbonyl showed a doublet at δ 2.58 with coupling constant J = 7 Hz and the olefinic protons appeared at δ 6.20 (d, J = 5.5 Hz, 1H) and 7.67 (d, J = 5.5 Hz, 1H). Aromatic protons appeared as a singlet at δ 7.16 integrating for four protons, thus confirming the enone **12**. All the signals observed for enone **12** were in complete agreement with the values reported for **12**.[12]

The alkylation of enone **12** with NaH and methyl iodide in DMF at ambient temperature afforded alkylated enone **11** in 70% yield. The formation of compound **11** was confirmed by spectroscopic methods. IR spectrum showed absorption at 1713 cm^{-1} for enone carbonyl. ^{1}H NMR spectrum showed three signals which appeared at δ 0.55 (s, 3H), 1.20 (s, 3H) and 1.49 (s, 3H) for methyl groups present on cyclopentenone ring and a signal that appeared at δ 2.35 (s, 3H) for methyl group attached to aromatic ring. Two olefinic doublets appeared at δ 6.25 (d, J = 7 Hz, 1H) and 7.75 (d, J = 7 Hz, 1H) which were attributed to enone protons and a multiplet at δ 7.10 (m, 4H) was assigned to four aromatic protons as reported in literature[13] thus confirming the structure of alkylated enone **11**.

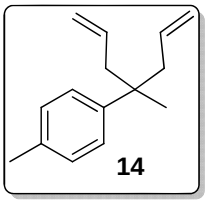
Finally total synthesis of (±)-α-cuparenone was achieved by reduction of enone with 10% Pd/C in dry ethanol in presence of catalytic piperidine in 98% yield. The α-cuparenone **1** thus obtained was identical to the one obtained from previous approach (chapter 3, section 2) in all respect. All the spectral data of the synthetic cuparenone were in good agreement with literature reported values[12, 1b] for natural (±)-α-cuparenone **1**.

3.3.5 Conclusion

In conclusion, the synthesis of α-cuparenone has been accomplished in concise and efficient fashion in five steps employing one-pot gem-diallylation and ring closing metathesis as key steps under simple reaction conditions and from commercially readily available 4-methyl acetophenone as starting material.

3.2.6 Experimental

1-Methyl-4-(4-methylhepta-1,6-dien-4-yl)benzene (14)



Method A: To the mixture of $InCl_3$ (412 mg, 1.8 mmol), trimethylsilyl chloride (0.228 mL, 1.8 mmol) and allyltrimethyl silane (18 mL, 11.1 mmol) in dry DME (15 mL), was added 4-methyl acetophenone (5 g, 32.2 mmol) solution in DME and the reaction mixture was stirred for 6 h at room temp. After completion of the reaction, it was quenched by saturated solution of sodium bicarbonate and extracted with ethyl acetate. Organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered, concentrated *in vacuo* and the residue was purified by flash column chromatography, eluting with petroleum ether to furnish desired compound **14** (2.2 g, 30%).

Method B: To the stirred solution of aldehyde **18** (2 g, 9.3 mmol) in diethylene glycol (30 mL) was added hydrazine monohydrate (1.8 mL, 37.3 mmol) and sodium hydroxide (1.4 g, 37.3 mmole). The reaction mixture was heated to reflux for 8 h and after completion of the reaction, it was diluted with water (10 mL) and extracted using ethyl acetate (3 x 25 mL). Combined organic layers were then washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford a residue which was purified by flash column chromatography using 2% ethyl acetate/pet ether as eluent to afford compound **14** (1.2 g, 65%) as a colorless thick oil.

Mol. Formula **:** $C_{15}H_{20}$ (MW**:** 200.32).

IR (Neat) **:** 815, 1019, 1218, 1638, 3005 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.23 (s, 3H), 2.30 (s, 3H), 2.46 (dd, *J* = 6.6, 13.8 Hz, 2H)**,** 2.25 (dd, *J* = 6.6, 13.8 Hz, 2H)**,** 4.89-4.99 (m, 4H), 5.40-5.60 (m, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H).

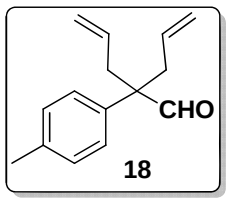
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.8, 24.2, 40.2, 46.9 (2C), 117.0 (2C), 126.2 (2C), 128.7 (2C), 134.9, 135.1 (2C), 144.0.

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

Elemental analysis **:** Calculated**:** C, 89.94; H, 10.06%

: Found: C, 89.86; H, 9.87%

2-Allyl-2-(*p*-tolyl) pent-4-enal (18)



A stirred solution of **16** (2 g, 9.4 mmol) in dry DCM under argon atmosphere was cooled to –78 ^{o}C and DIBAL-H (18.9 mmol, 14.6 mL, 2M solution in toluene) was added drop wise and left to stir at same temperature till the completion of the reaction. After completion of reaction, it was quenched at –78 ^{o}C with the drop wise addition of 2N HCl and then warmed to the room temp. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 30 mL). Combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford aldehyde **18** in quantitative yield (2.02 g) which was pure enough for further use.

Mol. Formula **:** $C_{15}H_{18}O$ (MW: 214.30).

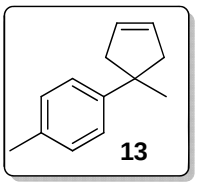
IR (Neat) **:** 815, 1460, 1510, 1715, 2720, 2960 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.36 (s, 3H), 2.69 (d, *J* = 7.2 Hz, 4H), 5.04-5.12 (m, 4H), 5.46-5.67 (m, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 9.49 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.9, 36.6 (2C), 56.3, 118.7 (2C), 127.4 (2C), 129.5 (2C), 132.7 (2C), 134.8, 137.0, 201.4.

Mass (ESI) m/z **:** 215 $(M + H)^{+}$.

1-Methyl-4-(1-methylcyclopent-3-enyl) benzene (13)



The Grubbs' 1st generation catalyst (194 mg, 1 mol %) was added to a degassed homogeneous solution of allyl compound **14** (500 mg, 2.36 mmol) in dry DCM (50 mL) under an atmosphere of argon. The resulting mixture was stirred at room temperature for 4 h. On the completion of the reaction (TLC), the solvent was removed under vacuum and purified by flash column chromatography (SiO_2) using 2% ethyl acetate/petroleum ether as eluent to provide **7** as thick colorless oil (390 mg, 92%).

Mol. Formula **:** $C_{13}H_{16}$ (MW: 172.27).

IR (Neat) **:** 816, 1215, 1650, 2926, 3019 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.32 (s, 3H) 2.30 (s, 3H), 2.45 (d, *J* = 14.2 Hz, 2H), 2.73, (d, *J* = 14.2 Hz, 2H), 5.71 (s, 2H), 7.06 (d, *J* = 8.34 Hz, 2H), 7.20 (d, *J* = 8.34 Hz, 2H).

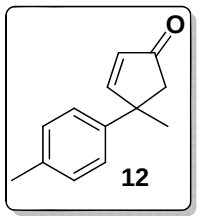
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.8, 31.3, 45.7, 47.7 (2C), 125.8 (2C), 128.8 (2C), 129.3 (2C), 134.6, 148.6.

Mass (ESI) m/z **:** 173 $(M + H)^+$.

Elemental analysis **:** Calculated**:** C, 90.64; H, 9.36%

: Found**:** C, 90.75; H, 9.48%

4-Methyl-4-*p*-tolylcyclopent-2-enone (12)



To a solution of compound **13** (150 mg, 0.87 mmol) in pyridine (5 mL), PDC (262 mg, 1.04 mmol) was added. Reaction mixture was heated at 100 ^oC for 8 h and then cooled, filtered through a short silica gel column and eluted with more DCM. Evaporation of solvent and purification of residue over a flash silica gel column using 4% ethyl acetate/pet ether as eluent furnished the enone **15** as oil (96 mg, 65%).

Mol. Formula **:** $C_{13}H_{14}O$ (MW: 186.25)

IR (Neat) **:** 815, 1246, 1614, 1720, 3019 cm^{-1}.

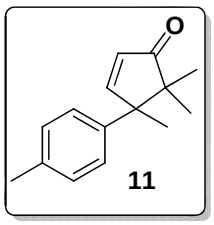
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.63 (s, 3H), 2.34 (s, 3H), 2.58 (d, *J* = 7.0 Hz, 2H), 6.20 (d, *J* = 5.5 Hz, 1H), 7.16 (s, 4H), 7.67 (d, *J* = 5.5 Hz, 1H).

Mass (ESI) m/z **:** 187 $(M + H)^+$.

Elemental analysis **:** Calculated: C, 83.83; H, 7.58%

: Found: C, 83.82; H, 7.55%

4,5,5-Trimethyl-4-*p*-tolylcyclopent-2-enone (11)



A solution of enone **12** (75 mg, 0.4 mmol) in anhydrous DMF (10 mL) was added drop wise over 15 min period to a suspension of sodium hydride (21 mg) in DMF (2 mL) and the reaction mixture was stirred at ambient temperature under the nitrogen atmosphere for 30 min. Methyl iodide (600 mg, excess) was added drop wise and reaction mixture was stirred for 15 h. Methanol was added to quench the reaction and it was diluted with ether (5 mL) and filtered. The solid was washed with ether 2-3 times.

Combined organic solution was evaporated under vacuum and the resultant oily residue was purified by column chromatography over neutral alumina in ethyl acetate/pet ether as the eluent to afford the ketone **11** (53 mg, 65%) as a viscous liquid.

Mol. Formula **:** $C_{15}H_{18}O$ (MW 214.14).

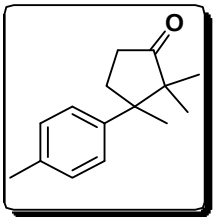
IR (Neat) **:** 816, 1019, 1123, 1384, 1459, 1513, 1594, 1713, 2917 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.55 (s, 3H), 1.20 (s, 3H), 1.49 (s, 3H), 2.35 (s, 3H), 6.25 (d, *J* = 7 Hz, 1H), 7.75 (d, *J* = 7 Hz, 1H), 7.10 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.2, 21.2, 26.0, 26.6, 51.8, 54.8, 126.9 (2C), 129.3 (2C), 129.5, 136.6, 140.5, 169.08, 215.1.

Mass (ESI) m/z **:** 215 $(M + H)^+$.

2, 2, 3-Trimethyl-3-*p*-tolylcyclopentanone (1)



A mixture of ketone **11** (50 mg, 0.24 mmol), 10% palladium on carbon (10 mg) and 2 drops of piperidine in dry ethanol was shaken at room temperature under 1 atm hydrogen on Parr hydrogenation unit until the gas uptake had ceased. The reaction mixture was filtered, the catalyst was washed with ethanol and combined organic layer was evaporated and purified by flash column chromatography using 3% ethyl acetate/petroleum ether as eluent to furnish the desired target molecule **1** in quantitative yield (0.051g).

Mol. Formula **:** $C_{15}H_{20}O$ (MW 216.32).

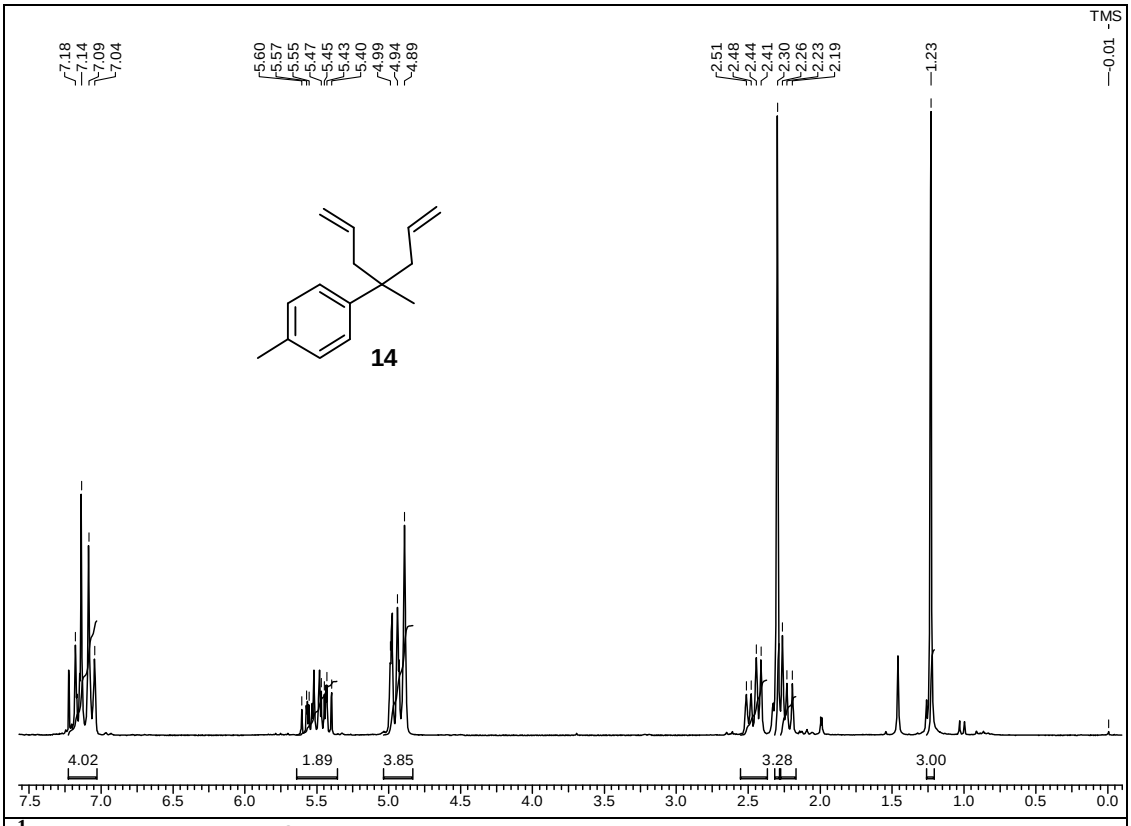
IR (Neat) **:** 815, 1460, 1510, 1725, 2960 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.61 (s, 3H), 1.17 (s, 3H), 1.26 (s, 3H), 1.86-1.97 (m, 1H), 2.35 (s, 3H), 2.41-2.52 (m, 2H), 2.58-2.71 (m, 1H), 7.14-7.30 (m, 4H).

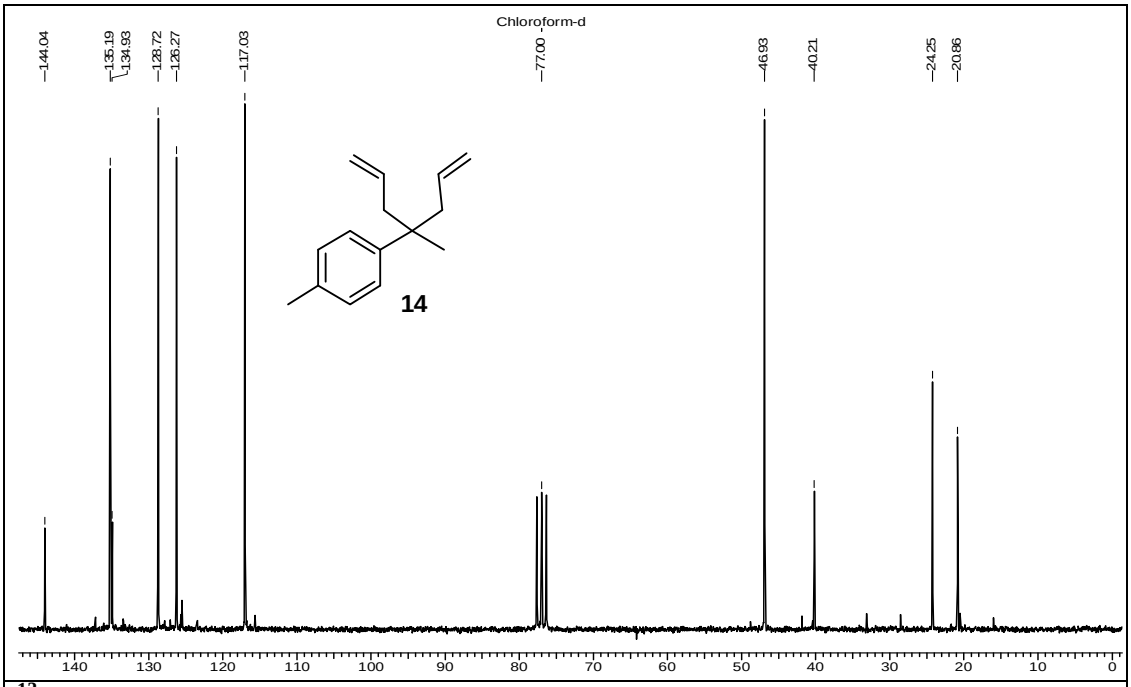
^{13}C NMR ($CDCl_3$, 50MHz) : δ 18.3, 20.8, 22.1, 25.3, 29.6, 33.7, 48.3, 53.2, 126.3 (2C), 128.9 (2C), 135.8, 141.9, 222.7.

Mass (ESI) m/z **:** 216 (M^+, 75%).

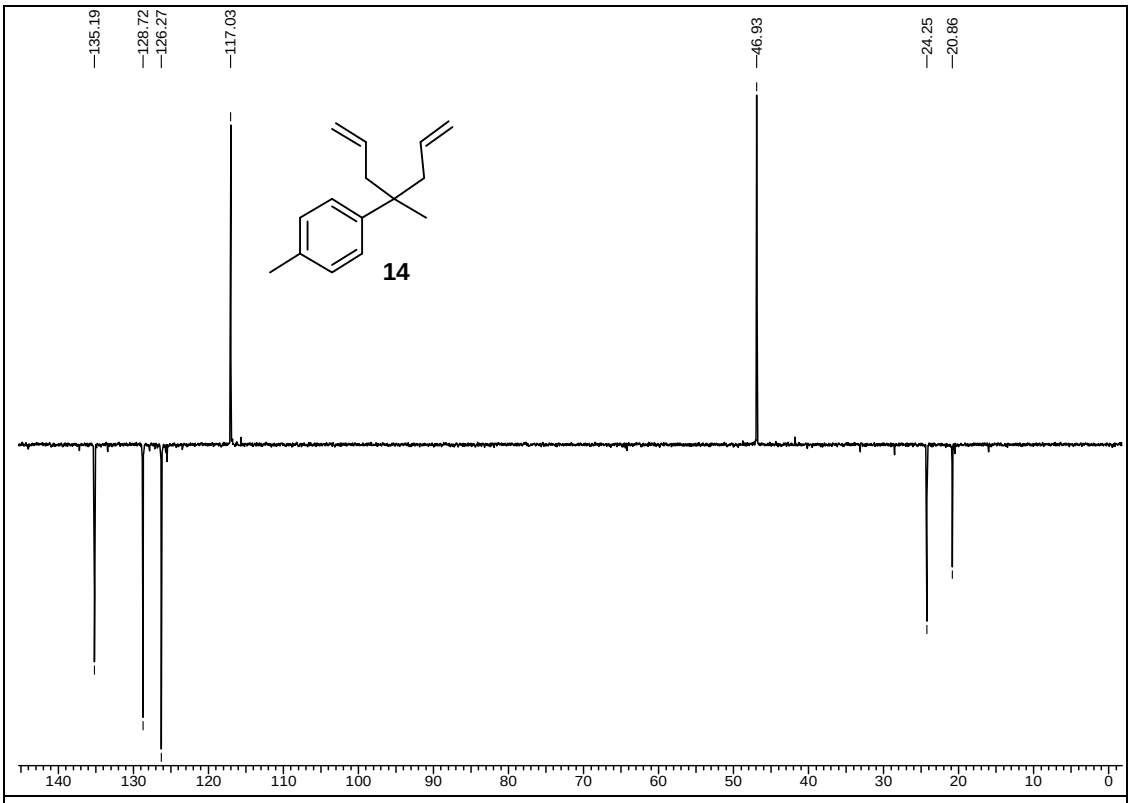
3.3.7 Spectra



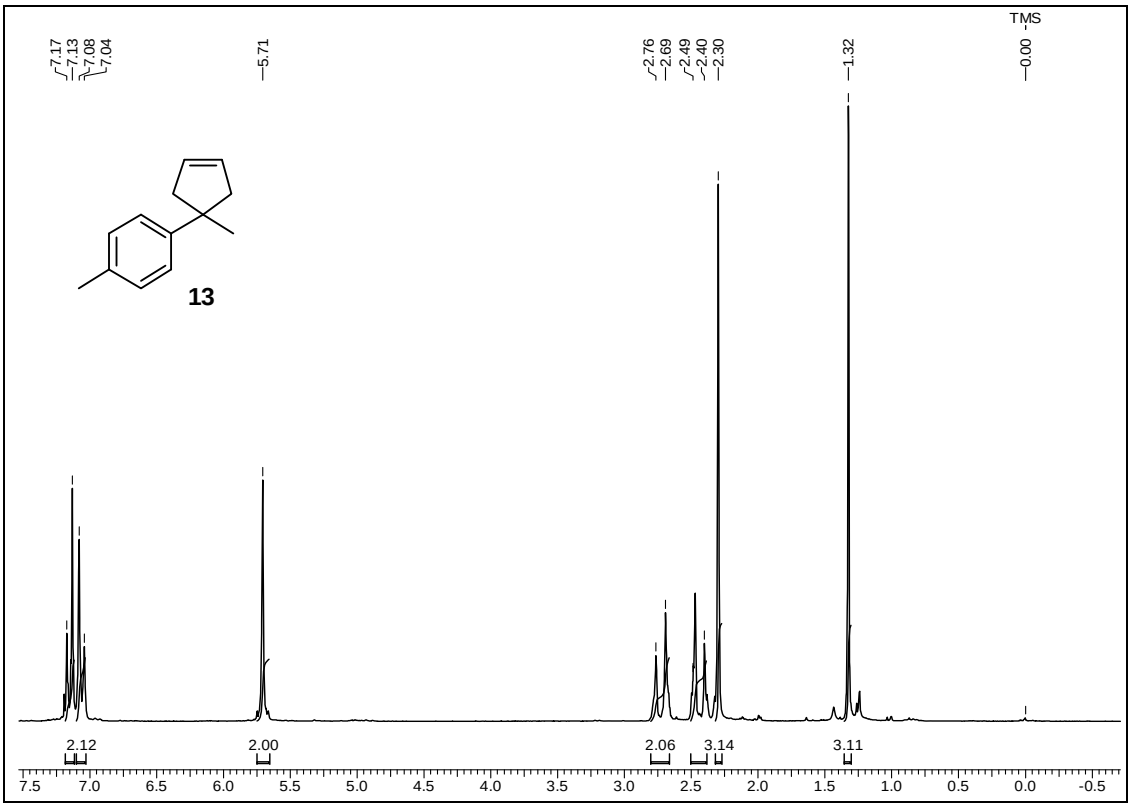
^{1}H NMR spectrum of compound 14 ($CDCl_3$, 200 MHz)



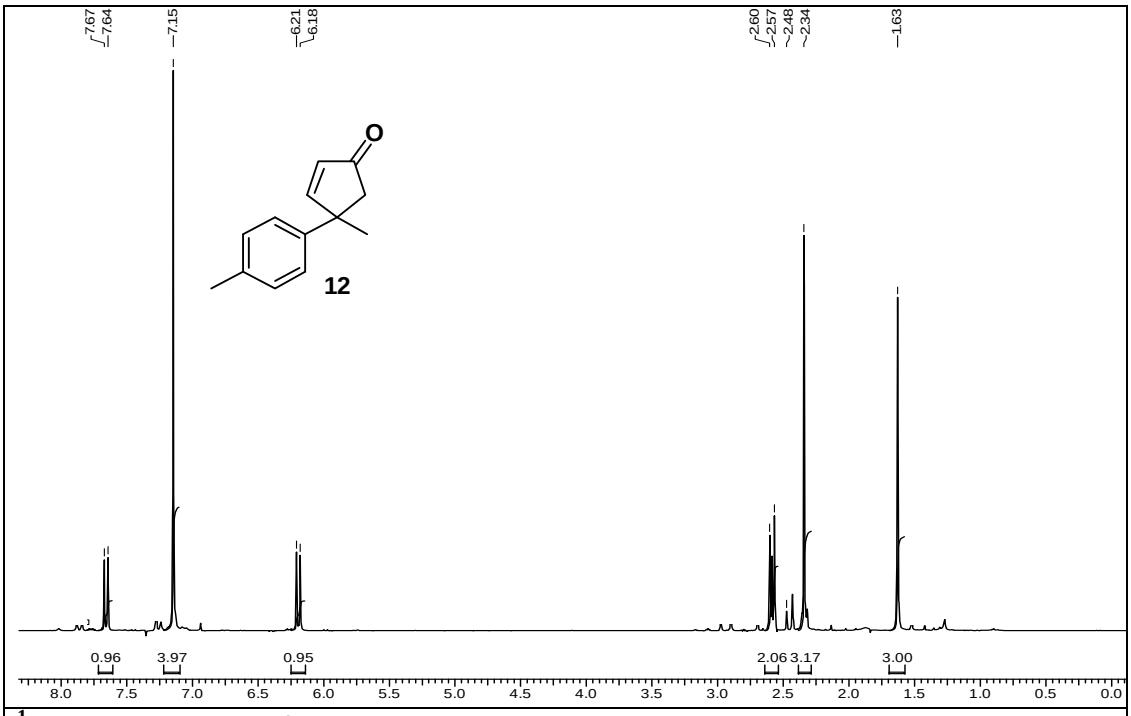
^{13}C NMR spectrum of compound 14 ($CDCl_3$, 50 MHz)



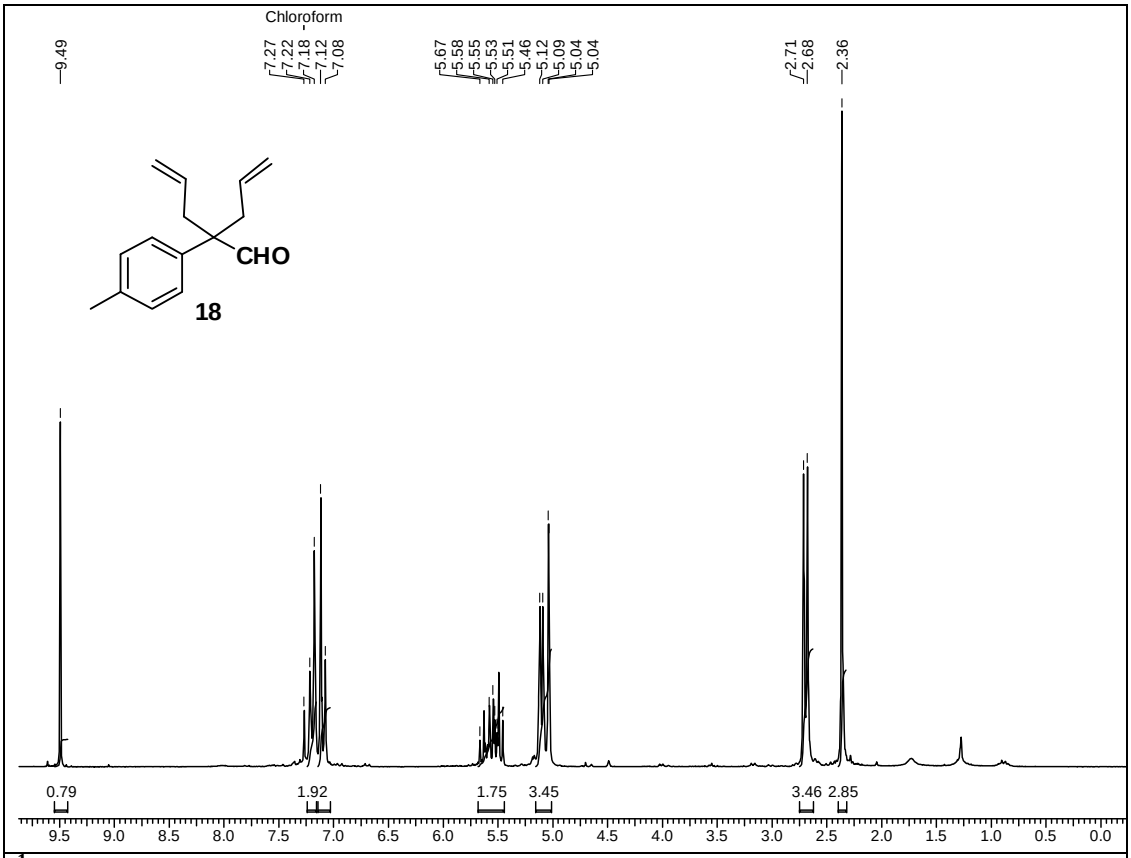
DEPT spectrum of compound 14 ($CDCl_3$, 50 MHz)



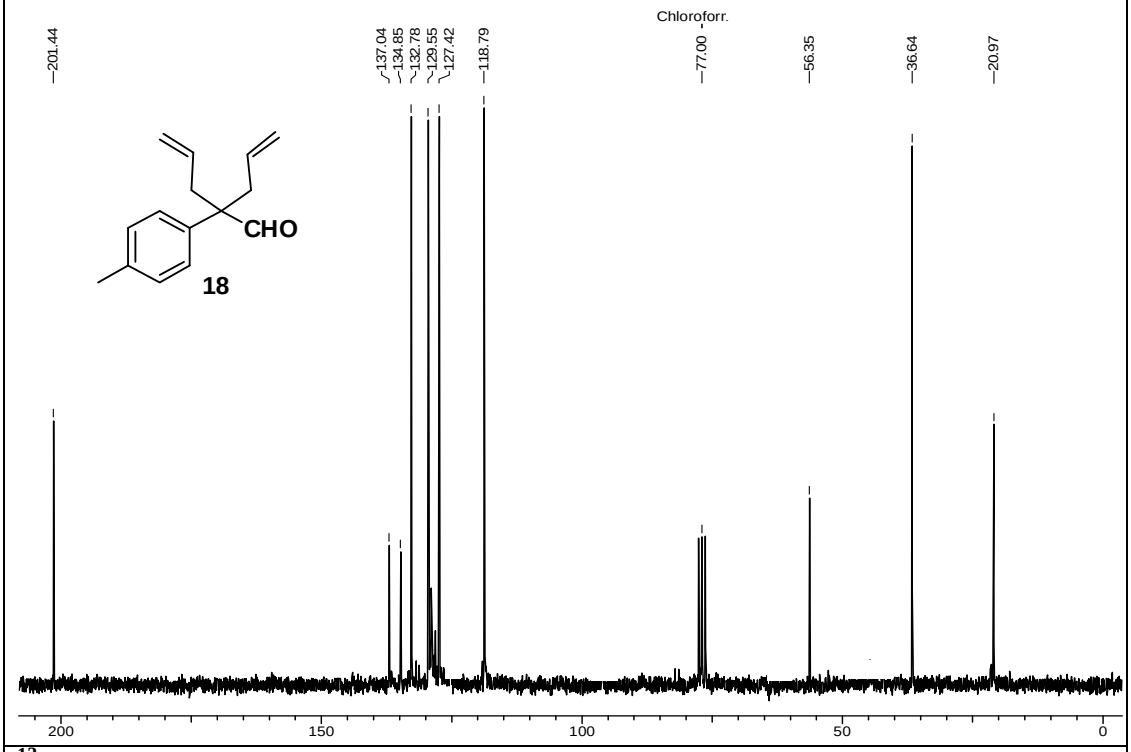
^{1}H NMR spectrum of compound 13 ($CDCl_3$, 200 MHz)



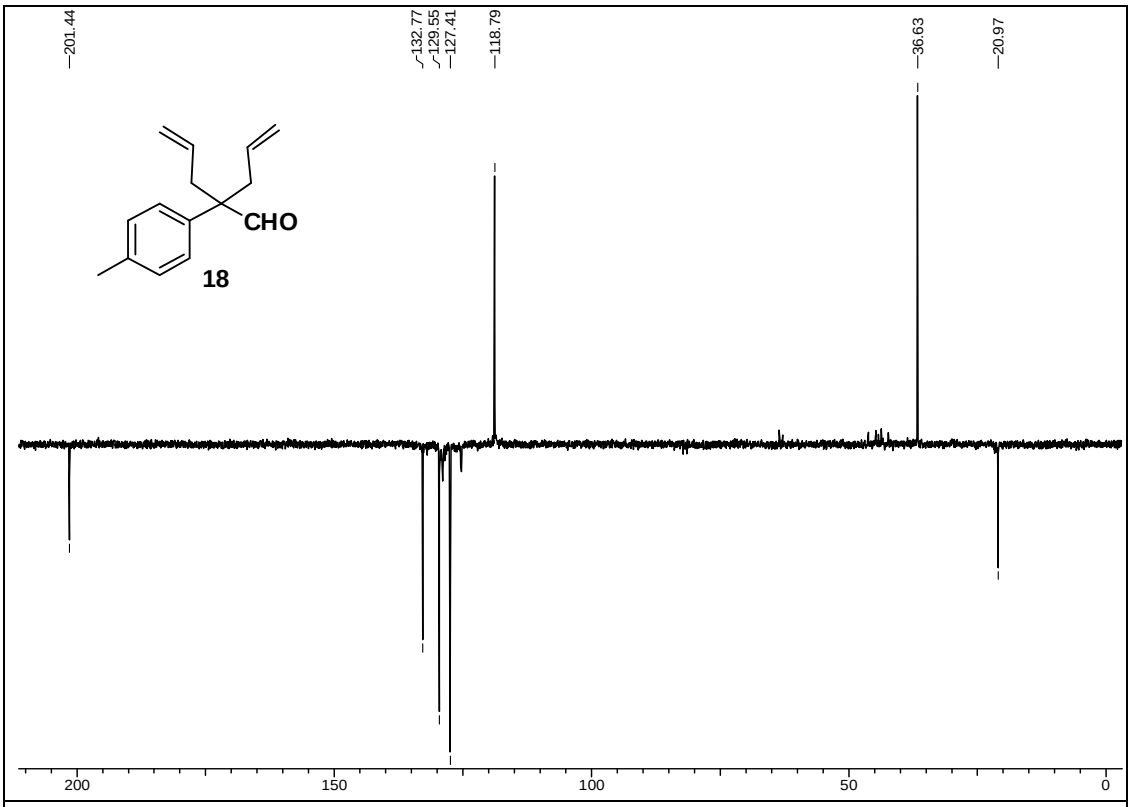
^{1}H NMR spectrum of compound 12 ($CDCl_3$, 200 MHz)



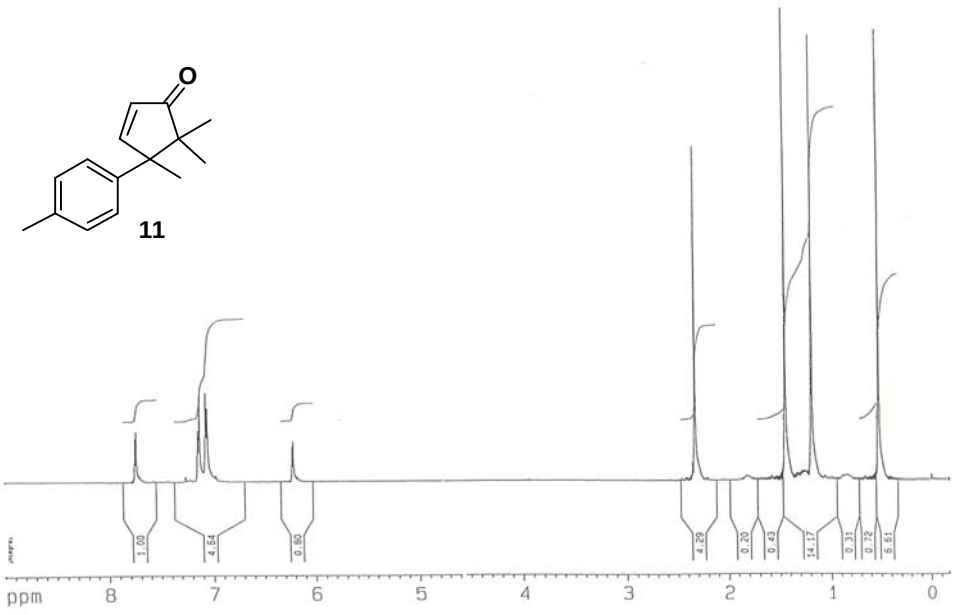
^{1}H NMR spectrum of compound 18 ($CDCl_3$, 200 MHz)



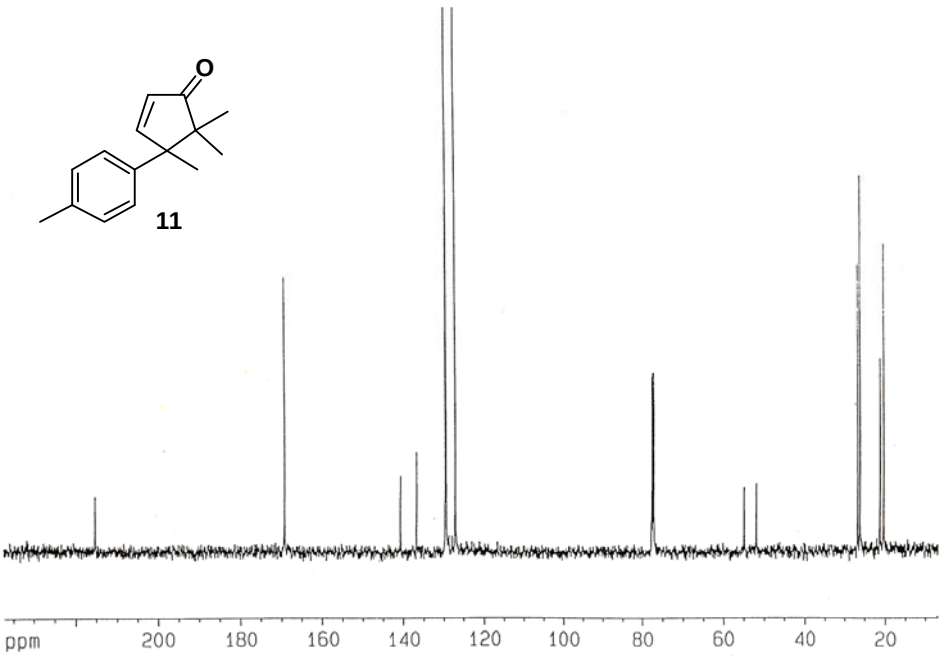
^{13}C NMR spectrum of compound 18 ($CDCl_3$, 50 MHz)



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



^{1}H NMR spectrum of compound 11 ($CDCl_3$, 200 MHz)



^{13}C NMR spectrum of compound 11 ($CDCl_3$, 50 MHz)

3.3.8 References

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List of publications

1. Formal synthesis of (±)-camptothecin *via* tricyclic lactone as key synthon. Chavan, S. P.; **Dhawane A. N**.; Kalkote, U. R. *Tetrahedron Lett.* **2010**, *51,* 3099-1101.

2. Tandem Aza-Michael-Condensation-Aldol Cyclization Reaction: Approach to the Construction of DE Synthon of (±)-Camptothecin. Chavan, S. P.; **Dhawane, A. N**.; Kalkote, U. R. *Synlett*, **2008**, 2781-2784.

3. A facile total synthesis of (±)-α-cuparenone employing diallylation and RCM as key steps. Chavan, S. P.; **Dhawane, A. N**.; Kalkote, U. R. *Tetrahedron Lett.* **2007**, *48*, 965-966.

4. An Efficient and Practical Total Synthesis of (±)-α-Cuparenone. Chavan, S. P.; **Dhawane, A. N.**; Kalkote, U. R. *Synthesis*, **2007**, 3827-3830.

5. Total Synthesis of Pulchellalactam *via* RCM Strategy. Chavan, S. P.; **Dhawane A. N.;** Pathak A. B.; Kalkote, U. R. *Synth. Commun.* **2007**, 37, 1503-1510.

6. Sodium Tetrafluoroborate as a New and Highly Efficient Catalyst for One-pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Thiones. B. P. Bandgar, V. T. Kamble, S. N. Bavikar and **Dhawane A. N.** *J. Chin. Chem. Soc.* ***2007****, 54, 2, 1.*