STUDIES TOWARDS ANTITUMOR QUINOLINE DERIVATIVES AND DEVELOPMENT OF USEFUL SYNTHETIC METHODOLOGIES

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By

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DEDICATED TO MY

ALL

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CERTIFICATE

Certify that the work incorporated in this Thesis entitled STUDIES TOWARDS ANTITUMOR QUINOLINE DERIVATIVES AND DEVELOPMENT OF USEFUL SYNTHETIC METHODOLOGIES submitted by MR. ANIL KUMAR SHARMA, was carried out by him under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

July 2001 S. P. CHAVAN

Research Guide

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ANIL KUMAR SHARMA

Abbreviations

Ac	Acetyl
Al	Aluminium
Ar	Aryl
B.P.	Boiling point
CPD	Cyclopentadiene
CuCl	Cuprous chloride
DBU	1, 8-Diazabicyclo-[5,4,0]-undec-7-ene
DMF	Dimethyl formamide
DMSO	Dimethyl Sulphoxide
EtOAc	Ethyl acetate
$FeCl_3$	Ferric chloride
g	Gram/s
hr	Hour/s
IR	Infra Red
Mg	Magnesium
mg	milligram
MS	Mass spectrum
NaH	Sodium hydride
NaI	Sodium iodide
NMR	Nuclear Magnetic Resonance
OsO_4	Osmium teroxide
Ph	Phenyl
PTSA	p-Toluene sulphonic acid
SiO_2	Silica gel
$TBAHSO_4$	Tetrabutyl ammonium hydrogen sulphate
THF	Tetrahydrofuran
TMSCl	Trimethyl silyl chloride

General Remarks

All melting points and boiling points are uncorrected and the temperature are in centigrade scale.

The compound numbers and scheme numbers given in each chapter refer to that particular chapter only.

All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.

Organic layers were dried over anhydrous sodium sulphate (Na_2SO_4).

TLC analysis were carried out on glass plates using silica gel : GF-254 and the plates were analysed by keeping in iodine or under UV light.

In cases where chromatographic purification were done, SiO_2 or alumina was used as stationary phase.

The IR spectrum was recorded on Perkin-Elmer infrared spectrophotometer model 683B.

The ^{1}H NMR and ^{13}C NMR were recorded on varian Bruker WH 90 (22.63 MHz) or Brucker AC 200 (50 MHz) or MSL 300 (75 MHz) or DRX 500 MHz (125 MHz). Figures in the parantheses correspond to ^{13}C frequencies. ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million from internal standard (tetramethylsilane) on δ scale.

TUMORS

According to *Willis*

"A tumor is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after the cessation of the stimuli which evoked the change".

Tumors may vary widely in shape, size and colour. Sometimes they form a well-defined nodule in the interior of an organ or tissue, or they rise half-way above the surface as a hemispherial projection; in other cases they are connected with the tissue of origin by a narrow pedicle. Tumors are mainly of two types. These are **benign tumors** and **malignant tumors**; the latter are called **cancers**, which ultimately kill the host. Benign tumors do not do so except when they interfere with the function of a vital organ. The rate of growth, the biochemical and, morphological properties of normal tissue and of benign or malignant tumors are different, and generally the characteristics of benign tumors approximate that of normal tissues.

The term carcinoma designates malignant tumors which arise from cells of epithelial tissues regardless of the germ layer. *e.g.* the term adenocarcinoma denotes a tumor of glandular origin which is unequivocally malignant. Cancer cells usually are larger than the cells of the corresponding normal tissues. Because the sets of chromosomes are not homologously paired or exactly twice or four times that number, but that the different chromosomes are present in different numbers and the nucleus is, therefore genetically unbalanced, which involves the thickening, breaking, stickiness, and bridge formation of chromosomes.

Some Antitumor compounds

Antitumor compounds of natural origin are being reported in the literature around the world. Hundreds of compounds have been discovered so far, most of them are of natural origin. Some compounds which are used in the clinics to combat cancer, are as**Bleomycin**, **Actinomycin**, **Daunorubicin**, **Adriamycin**, **Mitomycin**, **Vinblastine sulphate**, **Vincristine sulphate**, and recently introduced **Camptothecin** and its

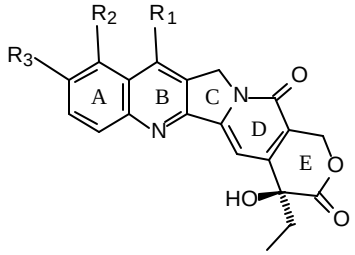
derivatives in drug categories. Camptothecin has found a new shelf under the category of anticancer drugs and forms a separate class as **antitumor quinoline derivatives**

CAMPTOTHECIN AND ITS ANALOGS

Introduction

Most of the anticancer drugs employed clinically exert their antitumor effect by inhibiting nucleic acid (DNA or RNA) or protein synthesis. This inhibition can occur through cross linking of bases in DNA or binding to and activation of enzymes necessary for the synthetic processes. It can also occur by substitution of bases in nucleic acids with inactive analogs or through breakage of DNA by antitumor drugs.

New drug development has as its major goal, the enhancement of therapeutic activity of a drug i.e. maximising antitumor activity and minimising toxicity. Although Camptothecin **1** has potent antitumor activity, it has serious problems with solubility and toxicity. The clinical trials of this alkaloid were carried out using its water soluble sodium salt **2**, in which E-lactone ring was cleaved by NaOH, but its severe toxicity to bone marrow and bladder ruled out the salt **2** as a drug for the cancer treatment. Camptothecin derivatives such as Topotecan **3**, Irinotecan **4** *etc*. began to be used as clinical antitumor agents to enhance the therapeutic activity.



2

1. $R_1=R_2=R_3=H$
Camptothecin

3. $R_1=H$ $R_2= CH_2NMe_2HCl$ $R_3= OH$
Topotecan

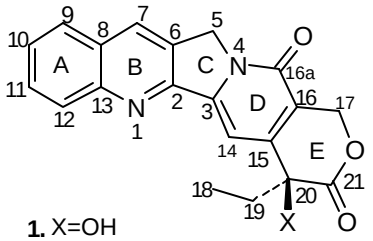
4. $R_1=C_2H_5$ $R_2= H$ $R_3=$ OCO(4-piperidinyl piperidine)
Irinotecan (CPT-11)

5. $R_2=NH_2$
9-amino Camptothecin

Isolation:

Camptothecin **1**, was isolated by Wall *et al*[1]. in 1966 from the stem wood of the tree *Camptotheca acuminata decene* (Nysaceae), a tree widely distributed in the southern part of China. 10-hydroxy camptothecin **14e** and 10-methoxy camptothecin **14f** were isolated from stem wood of *C. acuminata*[2] Camptothecin **1**, 9-methoxy camptothecin **13f** and other related alkaloid like mappicine were isolated from *Nothapodytes foetida* (Icacinaceae).[3,4] Camptothecin **1** and 10-hydroxy camptothecin **14e** were isolated from *Ophiorrhiza mungos* (Rubiaceae).[5] Gunasekera *et. al.*[6] isolated camptothecin **1** and 10-methoxy camptothecin **14f** from *Ervatamia leyneana* (Apocynaceae). 11-hydroxy camptothecin **15e** and 11 methoxy camptothecin **15f** were isolated from the fruits of *C.acuminata,*[7] in addition to camptothecin **1** , 10-hydroxy camptothecin **14e** and 10-methoxy camptothecin **14f**.

Characterisation:

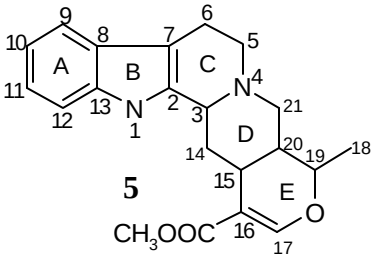


1. X=OH

1a.X=$OCOCH_3$

1b.X=Cl

1c.X= $OCOCH_2I$



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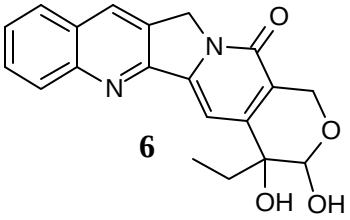
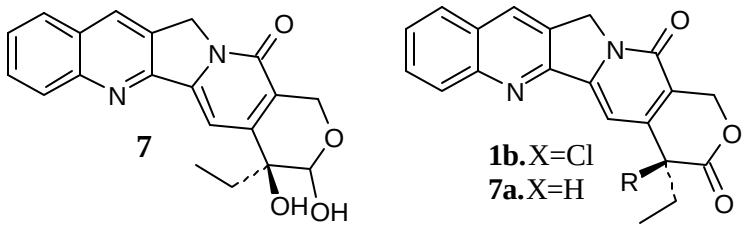


6

The Le Men Taylor[8] numbering system was used for camptothecin based on the probable biogenetic relationship with Ajmalicine **5**. The pyridone carbonyl carbon in **1** has been

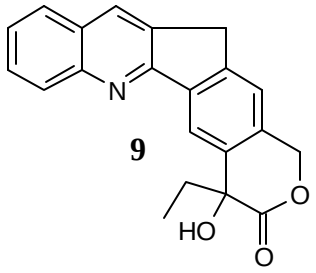
designated 16a, although this atom was not assigned a number in the Le Men Taylor scheme. The structure of **1** was deduced from its spectral properties (UV, IR, 1H NMR, MS) and certain chemical properties (formation of mono-O-acetate **1a**, reaction with $SOCl_2$ and pyridine to give 20-chloro camptothecin **1b**, rapid saponification to a sodium salt that gave **1** on acidification and reduction with sodium borohydride at room temperature to the lactol **6**. The X-ray crystallographic analysis of its 20-iodoacetate derivatives established that **1** is 4(S)-ethyl-4-hydroxy-1H-pyrano(3', 4':6, 7) indolizino(1, 2-b) quinoline-3, 14 (4H, 12H)-dione.

Structure-Activity relationship:



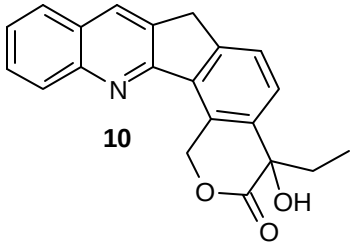
Wall *et al.*[9] established early in the chemical investigation of camptothecin **1** that the ring E α-hydroxy lactone of **1** is the most critical structural feature with respect to the alkaloid's antitumor activity *in vitro* and against L1210 and P388 *in vivo* assays. Camptothecin hemilactol **7,** 20-chlorocamptothecin **1b** and 20-deoxycamptothecin **7a** were completely inactive in such assays. Whereas the substitution of the 20-ethyl group by allyl, propargyl or benzyl resulted in good increase in life span for L1210 leukemic mice. The 20(S)-enantiomeric configuration as found in natural camptothecin is prerequisite for antitumor activity, whereas 20(R) isomer showed one-tenth the cytotoxic activity and was marginally active *in vivo.*

Camptothecin sodium salt[10] **2** formed by dissolving camptothecin **1** in NaOH showed marked activity against a variety of animal tumors but its activity was only one-tenth than of **1**.



9

The pyridone ring D is essential for antitumor activity. Thus, the compound **9** which has same spatial identity with camptothecin **1** showed at least 40-60 fold decrease in activity, while **10** was inactive[11]. Danishefsky *et. al.*[12] prepared isocamptothecin **11a** and isohomocamptothecin **11b**. Compound **11a** showed a slight activity *in vitro* whereas **11b** was completely inactive.



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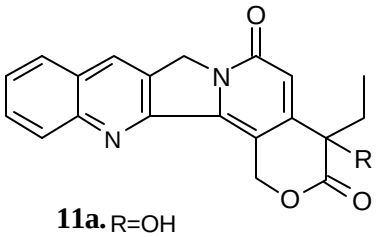
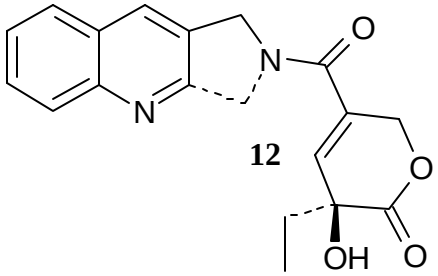
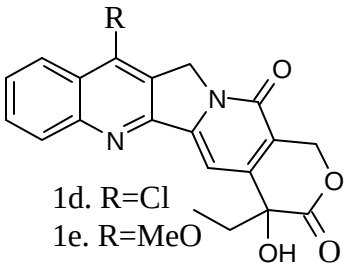


11a. R=OH
11b. R=CH_2OH

The presence of C and D rings are essential as compound **12** was found inactive, but the substitution in the ring C leads to complete inactivation.[13]

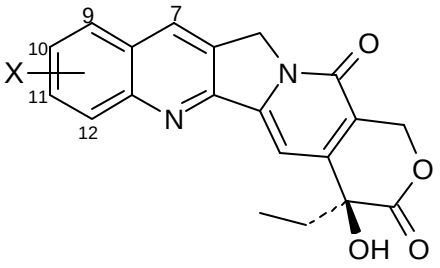


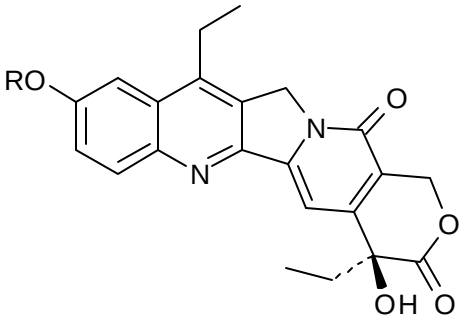
The substitution in ring A and B shows different level of antitumor activity. The *dl*-7-chlorocamptothecin **1d** exhibits , more activity than *dl*-**1**, but *dl*-7 methoxy analog **1e** was inactive. 10-hydroxy and 10-methoxy camptothecin (**14e** and **14f**) were found to be active whereas substitution at position 11 leads to compounds of relatively low activity while a substitution at position 12 results in inactivation.[14a,b]



Sawada *et. al.*[15] prepared a number of A ring substituted camptothecin and observed different cytotoxicity and antitumor activity.

Cytotoxicity of A-ring modified Camptothecin (KB Cell *in vitro*)





13a. X=9-NO_2 **14a.** X=10-NO_2 **17a.** R=H

13b. X=9-NH_2 **14b**. X=10-NH_2 **17b.** R=Pr

13c. X=9-Cl **14c.** X=10-Cl **17c.** R=CH_2Ph

13d. X=9-Br **14d**. X=10-Br

13e. X=9-OH **14e.** X=10-OH

13f. X=9-OMe **14f.** X=10-OMe

15a. X=11-NO_2 **16a.** X=12-NO_2

15b. X=11-NH_2 **16b**. X=12-NH_2

15c. X=11-Cl **16c.** X=12-Cl

15d. X=11-Br **16d.** X=12-Br

15e. X=11-OH **16e.** X=12-OH

15f. X=11-OMe **16f.** X=12-OMe

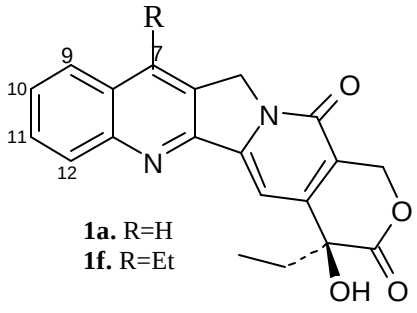
Table: 1

Cytotoxicity of A-ring modified camptothecin (KB cell *in vitro*)

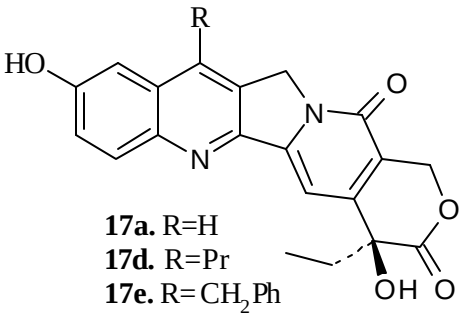
Compound no. (ED50 of the test sample/ED50 of 8) :substituents						
Substituted Position	NO_2	NH_2	Cl	Br	OH	OMe
9.	3a(1.7)	13b(1.0)	13c(0.5)	13d(0.5)	13e(0.9)	13f(0.7)
10	14a(1.6)	14b(0.3)	14c(0.8)	14d(0.6)	14e(0.7)	14f(0.8)
11	15a(10.3)	15b(1.3)	15c(1.0)	15d((0.9)	15e(0.5	15f(0.8)
12	16a(150.0)	16b(125.0)	16c(189)	16d(17.1)	16e(58.3)	16f(5.9)

From **table 1** it is evident that significant cytotoxicity was discovered in the derivatives having electron withdrawing chloro and bromo substituents at the 9 position and electron donating hydroxyl and amino groups at the 10 position.

Antitumor activity of 20 (S)-Camptothecin derivatives (L1210 *in vitro*)



1a. R=H
1f. R=Et



17a. R=H
17d. R=Pr
17e. R= CH_2Ph

Comp. No.	Substituents R	X	T/C% [a] Total dose (mg/kg) 2.5	5	10	25	50	100	150	250
1	H	H	-	112	127	168	84	-	-	-
1[b]	-	-	-	-	180	313	120	-	-	-
						(4/10) [c]				
1d	Et	H	111	147	179	249	87	-	-	-
						(9/10) [c]				
13f	H	9-OMe	163	229	155	-	-	-	-	-
13c	H	9-Cl	-	-	-	129	185	-	-	-
14e	H	10-OH	123	130	152	145	99	-	-	-
14f	H	10-OMe	168	215	147	-	-	-	-	-
17a	Et	10-OH	120	128	138	158	158	169	180	111
17a[b]			-	-	-	176	304	-	-	-
							(2/6)			
17d	Pr	10-OH	-	-	-	140	146	-	-	-
17e	CH_2Ph	10-OH	-	-	141	148	147	87	-	-

Table: 2

a)T/C%=(the mean survival time of tested mice)/(the mean survival time of control mice)multiplied by 100 b) administered as suspension. c) number of cured mice/tested mice, - not tested.

The sodium salt of 7-ethyl camptothecin (**1f** Na) showed higher T/C% than that of (**1**-Na). In the corresponding 10-hydroxy derivatives 7-ethyl, 10-hydroxyl camptothecin **17a** (**17a**-Na 0.4 ED_{50} /ED_{50} of **1**-Na, KB cells *in vitro*) also showed higher activity than **14e**, and its TI value was the largest (TI : therapeutic index; maximum tolerance dose/ minimum effective dose, calculated from the dose response curves; **1**-Na, 3.1; **1d**-Na, 12.5; **14e**-Na, 8.96; **17d**, 50).

Systematic modification and evalution of the ring A modified camptothecins, gave a

highly potent derivative, **17a** which has a 7-ethyl and an additional hydroxyl group. The 7-ethyl group tended to increase the antitumor activity, while the hydroxyl group reduced it.

Mode of Action

Eukaryotic DNA topoisomerases I and II are essential nuclear enzymes responsible for the organisation and modulation of the topological features of DNA. So that a cell may replicate, transcribe, and repair genetic information. Topoisomerase I functions by creating transient single-stranded nicks in DNA supercoils relieving torsional strain that has accumulated during DNA replication and transcription. Intracellular levels of topoisomerase I are elevated in number of human solid tumors, relative to the respective normal tissues, suggesting that variation in topoisomerase I levels are tumor type specific. Thus, topoisomerase I represents a promising target for the development of new cancer chemotherapeutic agents against a number of solid human tumors.[16]

Camptothecin acts as antitumor agent due to the inhibition of topoisomerase. It stabilizes the complex between DNA and topoisomerase I, thus interfering with the religation process. Studies have shown a correlation between the ability to cause stabilisation of a DNA-topoisomerase intermediate, DNA strands breaks, and antitumor effects of several camptothecin analogs.

As shown in the **table 3** among the camptothecin derivatives the only one which exhibit antitimor activity without inhibiting topoisomerase I is CPT-11 **4**, which does not inhibit topoisomerase at concentration 120 times greater than the CC_{50} of camptothecin. It is 50 times less potent than camptothecin as a cytotoxic agent and about 10 times less potent as an antitumor agent. When tested at a high enough dose, however, CPT-11 **4** is as efficacious as camptothecin **1** in L1210 *in vivo* and has been reported to be effective in a spectrum of animal tumor models. These results suggests that CPT-11 **4** may be

converted to 7-ethyl 10-hydroxy camptothecin **17a** upon hydrolysis *in vivo* and has potent cytotoxic activity and has efficacy against L1210 leukemia *in vivo* similar to that

observed for CPT-11 **4**.[17]

Table 3:

Topoisomerase I inhibition, Cytotoxicity and antitumor activity of 7- and 10-substituted Camptothecin.

[a] conc. that produced 50% DNA cleavage in the presence of topoisomerase I. [c] conc. that inhibited the proliferation of L1210 cells by 50% upon continuous exposure. [d] maximally tolerated dose (μ mol/kg) in mice bearing L1210 leukemia. [e]increase in life span of mice bearing L1210 leukemia, relative to untreated control, when treated at the MTD.

Hypothetical model of the interaction of Camptothecin with topoisomerase I and plasmid DNA:[18]

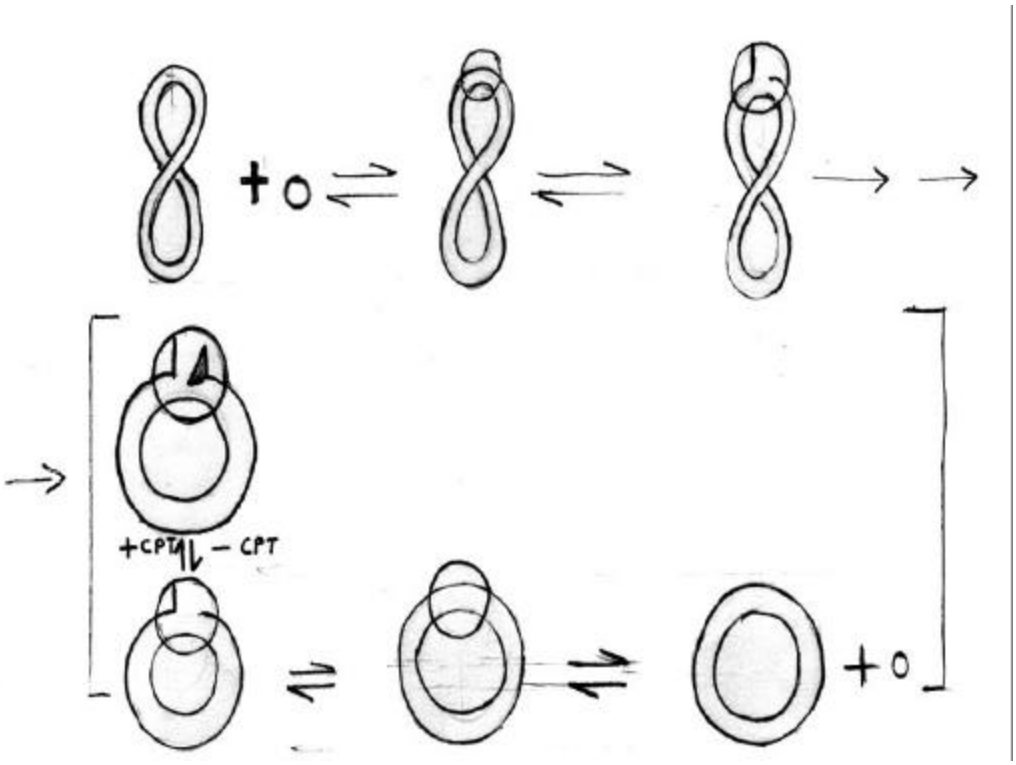
When supercoiled DNA is relaxed by catalytic amount of topoisomerase I , the reaction pathway shown in **fig.1** must be repeated over several cycles, creates a single-stranded nick, unwinds the supercoils, reseals the DNA backbone, and then dissociates

R_1	R_2	CC_{50}[a], µM	IC_{50}, nM	MTD	%ILS
CH_3CN	CH_3	0.5	.5	.5	0±1
$CH_2CH_2NH_2$	CH_3	3.0	9	8	33
H	$CH_2CH_2N(Cbz)CH_3$	2.0	2	28	2
H	$CH_2CH_2NHCH_3$	0.4	4	22	3
$OONC_5H_9.NC_5H_9$	CH_2CH_3	>100	200	45	38
OH	CH_2CH_3	0.8	.9	6	44
H	H	0.82±0.07	3±4	2	18±6

from the DNA. The free enzyme can then bind to another supercoiled DNA substrate for another cycle or to a relaxed DNA molecules leading to product inhibition. Camptothecin decreased the initial velocity of the relaxation reaction but did not inhibit the enzyme irreversible, since all of the DNA was eventually relaxed in its presence. This was consistent with the reversible binding of camptothecin to an enzyme-DNA complex.

Analysis of camptothecin-induced DNA breaks show that topoisomerase I is covalently linked to the 3’ end of the broken DNA. Thus, camptothecin inhibits the

fig. 1



catalytic activity of mammalian DNA topoisomerase I. The inhibition of nucleic acid synthesis in vivo may be related to the formation of this drug-induced cleavable complex.

Biogenesis:

Studies of Sheriha & Rapport[19] and Hutchinson *et. al.*[20] proved that camptothecin 1 is derived from tryptamine and secologninn, the established biosynthetic precursor of monoterpene indole alkaloids found in several higher plants.

Mevalonate is converted by the way of geraniol and loganin into secologninn **19**, which combines with tryptamine **18** to form strictosidine (isovincoside) **20**. Strictosidine **20** is then lactonised to the lactam strictosamide, which *via* reduction to the corresponding derivatives and oxidative cleavage by molecular oxygen or H_2O_2 yields the keto lactam. The intramolecular cyclisation of lactam produced a pyrroloquinoline derivative, which in turn through a sequence of oxidation-reduction steps is transformed into camptothecin.

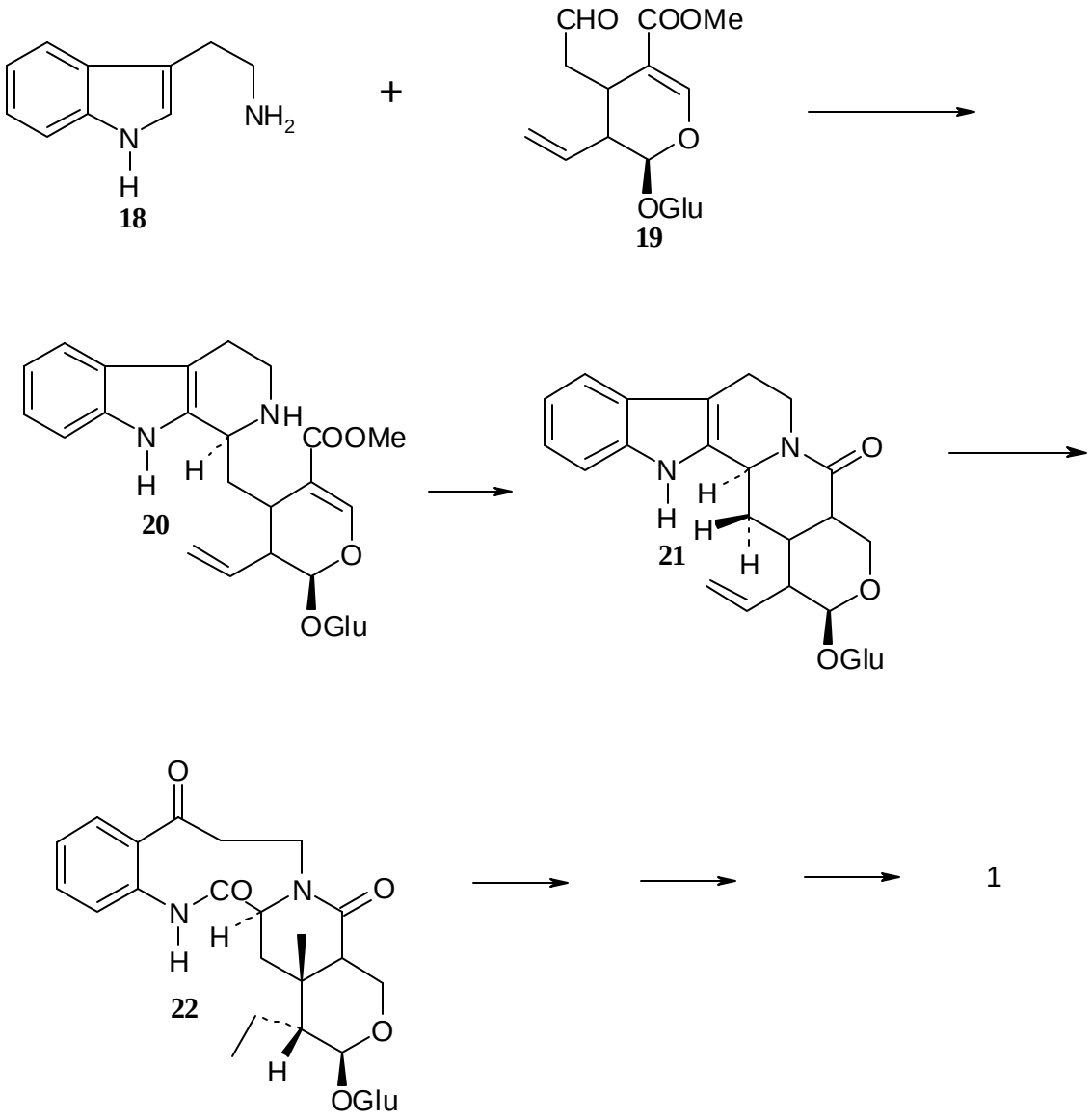


fig. 2

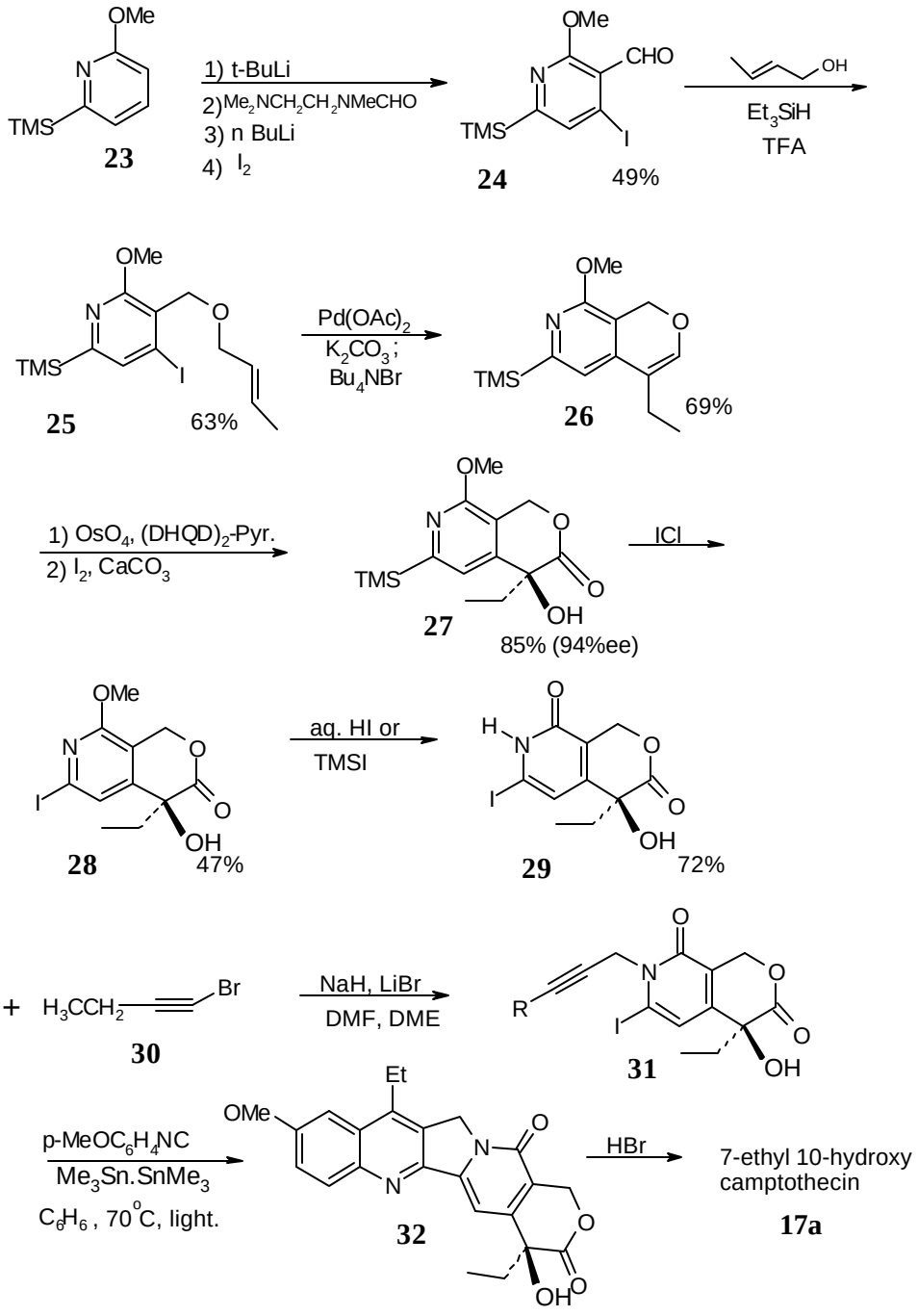
Synthesis of Camptothecin analogs (Literature survey)

A number of publications are flooded in the literature describing the total synthesis of camptothecin,[e.g.21-25] but only a few reports are available till date towards the synthesis of its analogs, because of more complexities in the derivatives as compared to its parent molecule, camptothecin. A and B ring substituted camptothecins are obtained either by chemical modification of camptothecin or by total synthetic routes.

The following section briefly describes some of the reported routes employed for the synthesis of camptothecin analogues.

Scheme 1:[26]

Curran *et. al.* (**Angew Chem. Int. Ed. Engl.** 1995, 34, 2683)



The authors employed 2-bromo 6-methoxy pyridine as the starting material

towards the formation of 7-ethyl 10-hydroxy camptothecin, which was then quenched with TMSCl to provide **23**. The compound **23** was then converted in one step to iodoaldehyde **24** by following the procedure of Comins. The E-ring was then introduced by a sequence of reductive etherification to form **25** and subsequent Heck reaction to give enol ether **26**. The Sharpless asymmetric hydroxylation of **26** produced **27** in 85% yield and 94% *ee*. Exchange of the TMS group in **27** for iodine occurred upon exposure to ICl, which upon demethylation using aqueous HI provided lactone **29**.

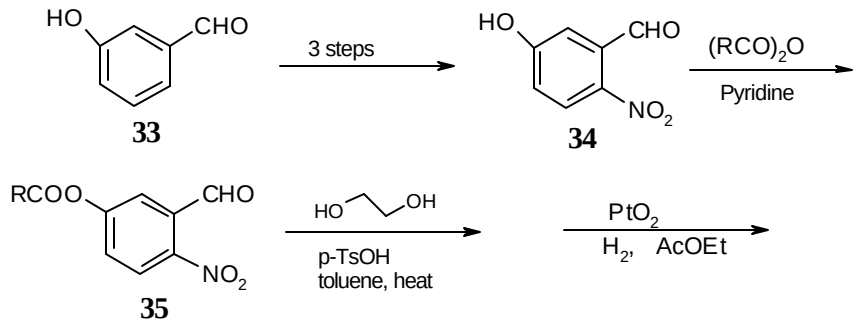
The lactone **29** was N-propargylated with methyl propargyl bromide **30** and the resulting product **31** was treated with p-methoxyphenylisonitrile under the satandard conditions. This is the key step in the synthesis which establishes simultaneous C-D ring fromation. Demethylation of the product **32** with HBr then gave 7-ethyl 10-hydroxy camptothecin **17a** (scheme-1).

Scheme 2:[27]

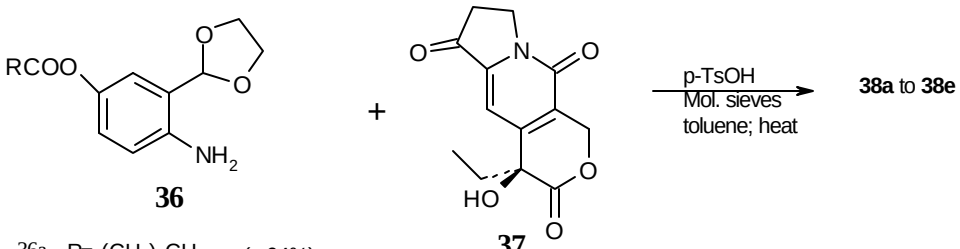
Takayama *et. al.* (Biorg. Med. Chem. Lett. 415-418 1998)

This synthesis (scheme-2) was aimed to prepare (20S)-10-hydroxy camptothecin derivatives carrying the long chain fatty acid esters. The key step of this synthesis was Friedlander condensation of the protected benzaldehyde with **37**.

Nitration of the compound **33** with concentrated HNO_3/H_2SO_4 followed by alkaline hydrolysis gave 5-hydroxy-2-nitro benzaldehyde **34** in three steps. The compound **34** was then acylated with five different fatty acid anhydride *i.e.* capric-, lauric-, palmitic-, stearic-, and arachidic anhydride to give the corresponding esters **35a**-**35e** in good to moderate yields. After that aldehyde functionality in **35a**-**35e** was respectively protected as ethylene acetal, the nitro group was reduced by catalytic hydrogenation (H_2 /PtO_2) to afford the primary amine **36a**-**36e** which were then condensed with chiral tricyclic ketone **37** for the formation of CDE ring system in **38a**-**38e**.



35a. R= $(CH_2)_8CH_3$; (y.53%)
35b. R= $(CH_2)_{10}CH_3$; (y.74%)
35c. R= $(CH_2)_{14}CH_3$; (y.85%)
35d. R= $(CH_2)_{16}CH_3$; (y.68%)
35e. R= $(CH_2)_{18}CH_3$; (y.70%)



36a. R= $(CH_2)_8CH_3$; (y.64%)
36b. R= $(CH_2)_{10}CH_3$; (y.74%)
36c. R= $(CH_2)_{14}CH_3$; (y.85%)
36d. R= $(CH_2)_{16}CH_3$; (y.68%)
36e. R= $(CH_2)_{18}CH_3$; (y.70%)

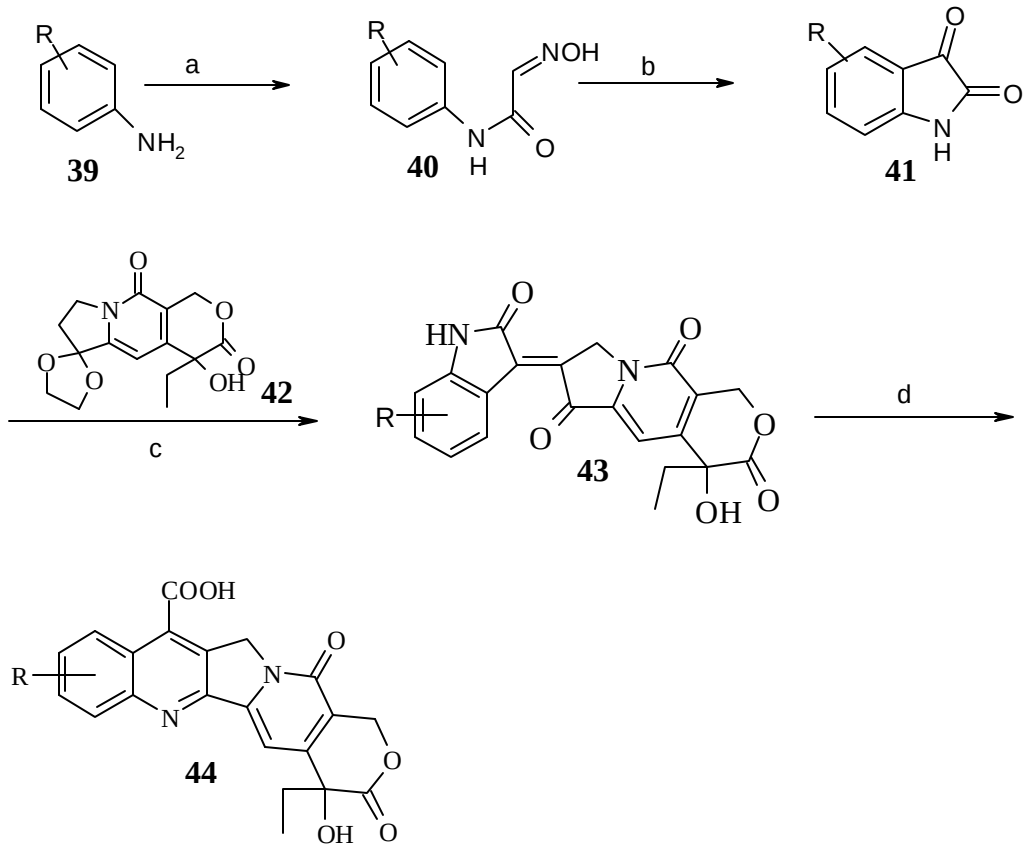
Scheme 3:[13]

Lackey *et. al.* (J. Med. Chem. 38, 906-911, 1995)

In this synthesis (scheme-3) the cyclisation of ∝-oximinolide **40** to substituted isatin and its further condensation with CDE skeleton was the key step towards the synthesis of substituted Camptothecin.The formation of an ∝-oximinolide was accompanied by condensation of chloral hydrate, hydroxylamine, and substituted aniline **39** which was

cyclised with concentrated sulphuric acid to form substituted isatin **41**. Equimolar amount of tricyclic ketal **42** and substituted isatin **41** were combined in an aqueous acid medium and stirred at room temperature for between 2 to 40 hours, which on heating

reacted further to form 7-carboxylic acid **42**.



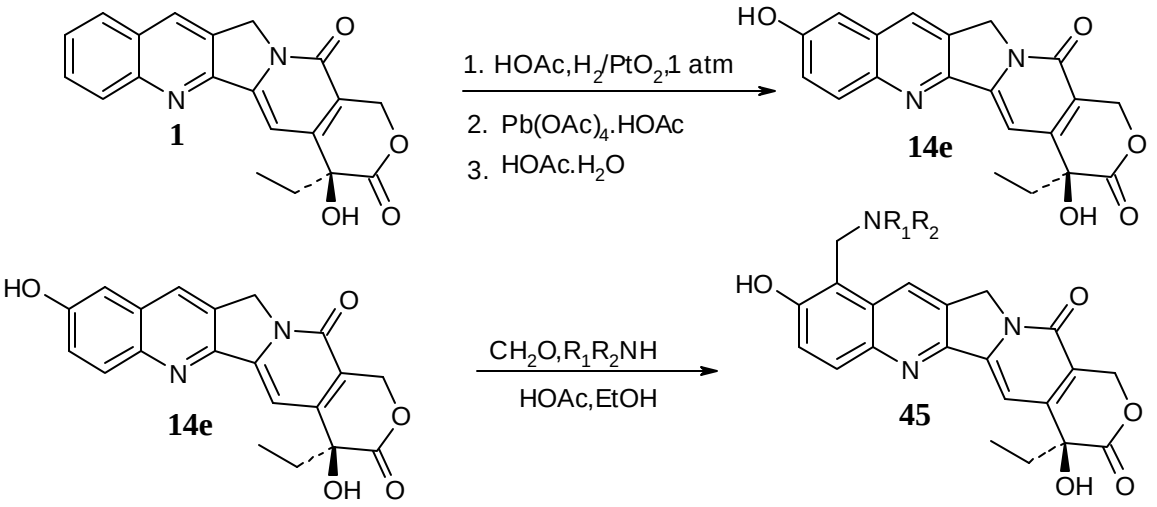
Reagents: (a) chloral hydrate, hydroxylamine, H_2O/HCl; (b) conc. H_2SO_4, $BF_3.Et_2O$, or $H_4P_2O_7$/heat; (c) HOAc, HCl, room temp.; (d) HOAc, conc. HCl, 105ºC.

Scheme 4:[17]

Kingsbury *et. al.* (J. Med. Chem. 34, 98-107, 1991)

The authors achieved the synthesis of substituted camptothecin by semisynthetic sequence involving natural camptothecin, as well as the synthetic routes.

Thus, 10-hydroxy camptothecin **14e** was prepared from 20(S)-Camptothecin **1** by a reduction-oxidation sequence (scheme-4a). Controlled catalytic reduction of camptothecin produced 1, 2, 6, 7-tetrahydro camptothecin which because of air sensitivity, was treated with lead tetraacetate followed by hydrolysis with acetic acid-

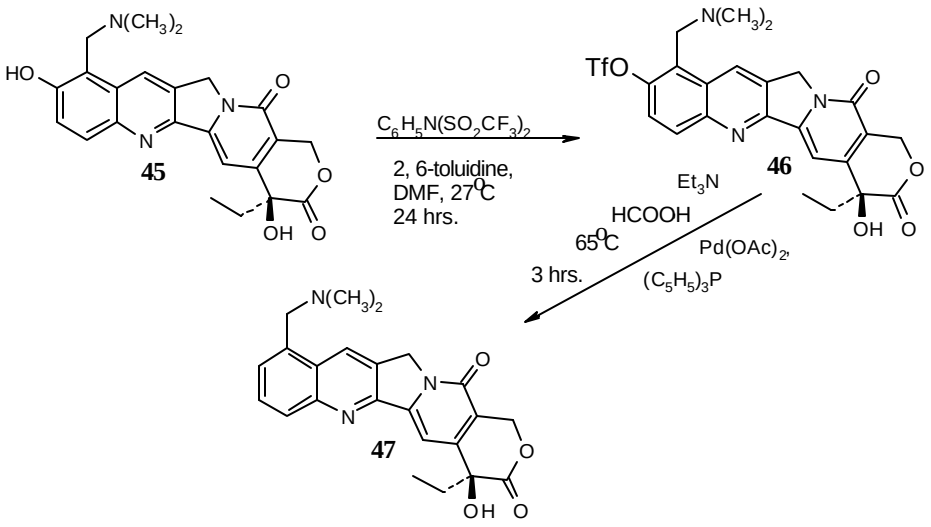


Scheme: 4a

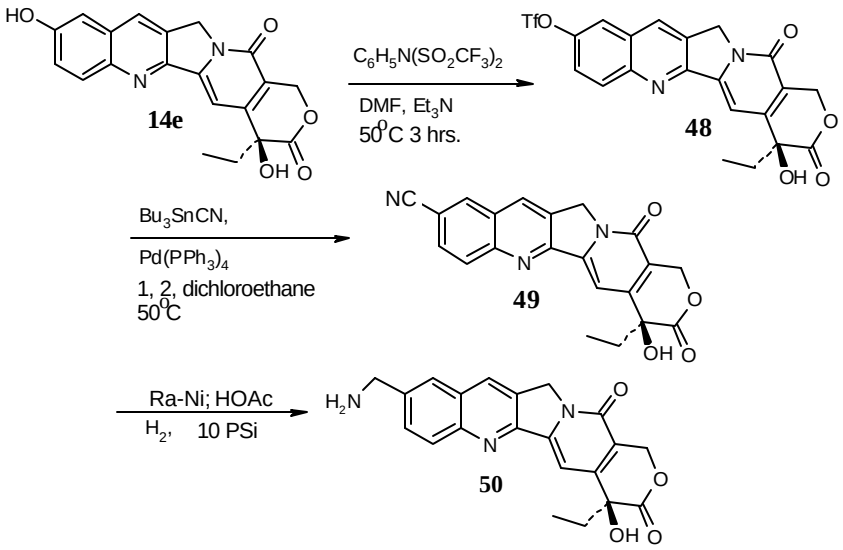
water resulted in the formation of 10- hydroxy camptothecin **14e**. N-substituted 9-(amino alkyl)-10-hydroxy camptothecins **45** were prepared using Mannich reaction from 10-hydroxy camptothecin **14e**, whereas only N-substituted 9-(amino alkyl) camptothecin **47** was obtained by removing hydroxyl group using palladium-catalysed reduction of aryl triflate (scheme-4b). This triflate **46** in turn was prepared from the reaction of 9-(amino alkyl) 10-hydroxy camptothecin **45** with N-phenyl trifluoromethane sulphonamide.

10-(aminomethyl) camptothecin **50** was prepared (scheme-4c) from 10-hydroxy camptothecin **14e** by reaction of N-phenyl trifluoromethane sulphonamide with **14e** to give a quantitative yield as crude triflate **48**, which was converted to 10-cyano camptothecin **49** by the palladium catalysed cyanation, which on catalytic reduction furnished 10-(amino methyl) camptothecin.

Scheme: 4b



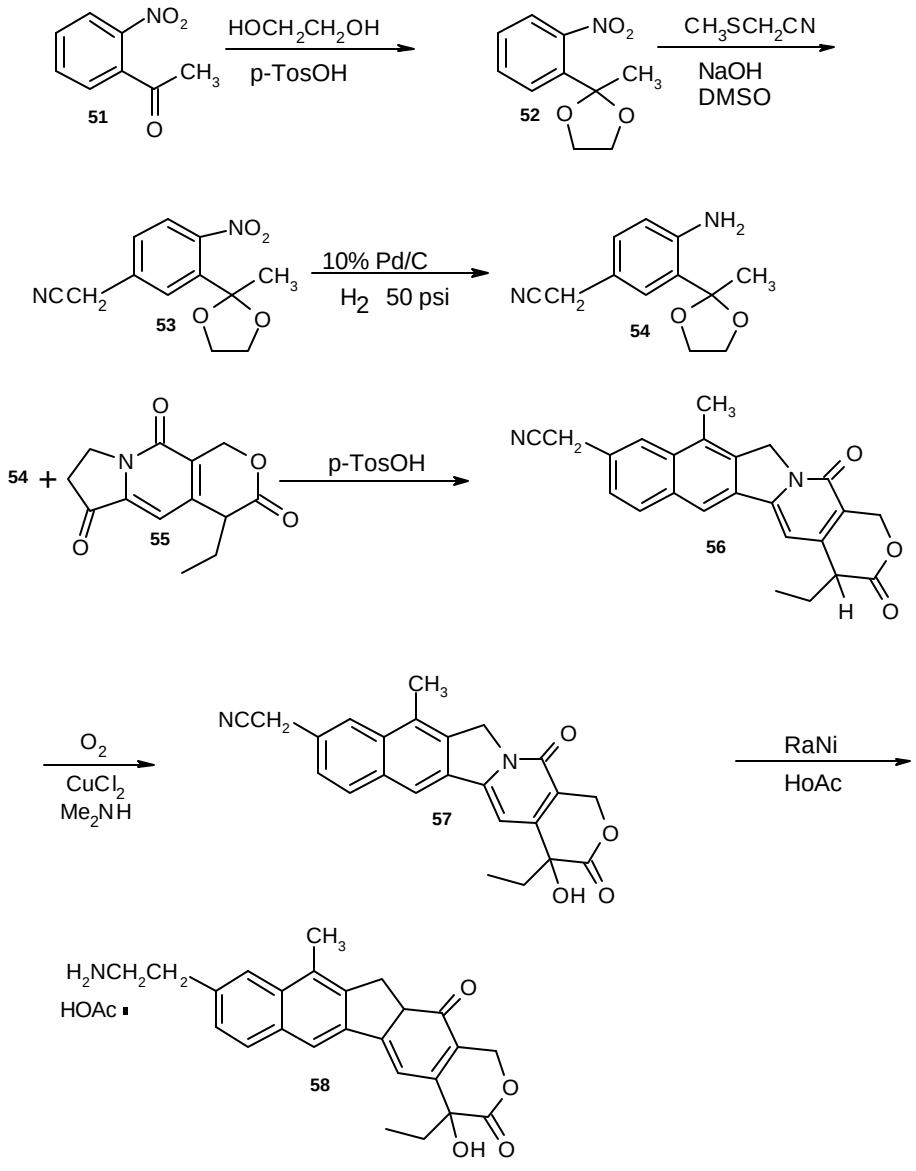
Scheme: 4c



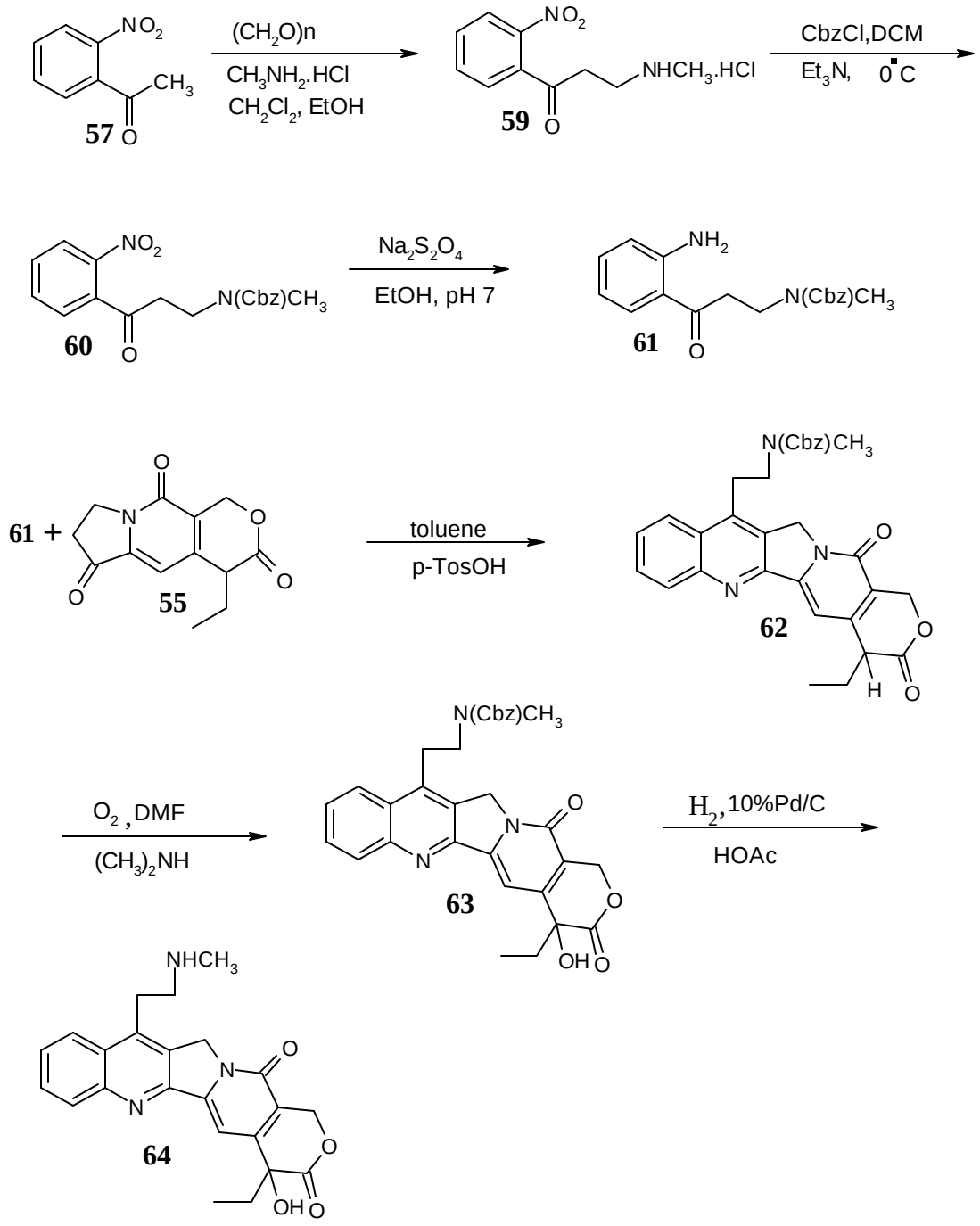
7-substituted camptothecin were prepared (scheme-4c) by condensing tricyclic ketone **55** with the appropriate aromatic amino ketones and the resulting deoxycamptothecin

derivative was hydroxylated with oxygen in the presence of cupric chloride.

Scheme: 4d

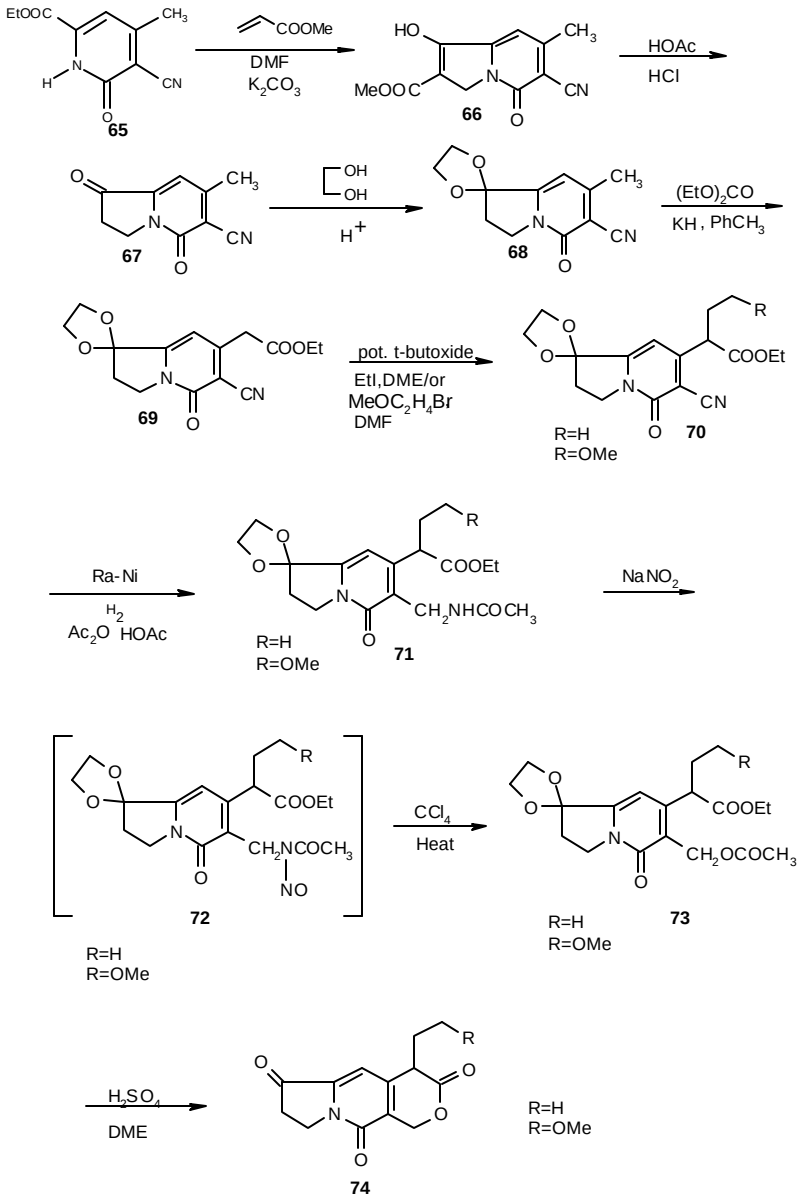


Scheme : 4e


NO2
CH3
O
57
(CH2O)n
CH3NH2.HCl
CH2Cl2, EtOH
NHCH3.HCl
59
CbzCl,DCM
Et3N, 0°C
NO2
N(Cbz)CH3
60
Na2S2O4
EtOH, pH 7
NH2
N(Cbz)CH3
61
61 +
55
toluene
p-TosOH
N(Cbz)CH3
62
O2 , DMF
(CH3)2NH
N(Cbz)CH3
63
H2, 10%Pd/C
HOAc
NHCH3
64
OH

Scheme 5:[28]

Monroe E. *Wall et. al.* (J. Med. Chem. 29, 1553, 1986)



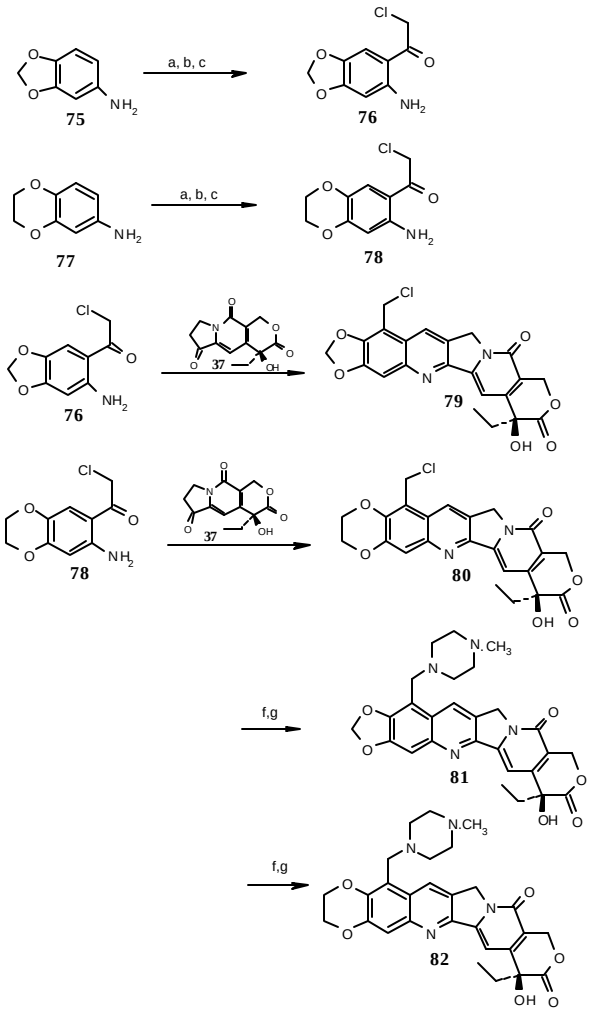
To synthesis 11-methoxy camptothecin **15f** (scheme-5), substituted pyridone **65** was taken as the starting material, and was converted to the bicyclic pyridone **66** by treatment with methyl acrylate and K_2CO_3 in DMF. Hydrolysis and decarboxylation were effected by refluxing in a mixture of HOAc and conc. HCl under N_2. The ketone **67** was then converted into ketal **68**. Ethylation was accomplished by using potassium t-butoxide, and ethyl iodide to furnish **70**. Catalytic hydrogenation of the nitrile **70** in the presence of Raney Ni in a mixture of acetic anhydride and acetic acid gave the amide **71**. Removal of the catalyst by filtration followed by the addition of $NaNO_2$ to the filtrate furnished the N-nitroso derivative **72**, which decomposed on heating in an inert solvent (CCl_4) leading to the formation of acetate **73**. The diester **73** was lactonised by 2N H_2SO_4 in dimethoxyethane with simultaneous deketalisation to give ketone **74**. Friedlander condensation of this ketone with 4-methoxy-2-amino benzaldehyde in the presence of acid catalyst furnished substituted 20-deoxy camptothecin which was oxidised to *dl*-11-methoxy camptothecin **15f** by passing O_2 through a solution of compound in DMF in the presence of $CuCl_2$.

Scheme 6:[16]

Luzzio *et. al.* (J. Med. Chem. 38, 395, 1995)

The authors prepared substituted camptothecin and using the corresponding substituted aniline as the starting material.

N-Acetylation of 3, 4-(methylene dioxy) aniline **75** was carried out with acetic anhydride followed by a directed $ZnCl_2$-catalysed Friedel-Crafts acylation with chloroacetyl chloride on the anilide to provide á-chloroacetophenone **76**. Hydrolysis of the acetamide group, using aqueous acid produced the requisite 2'-amino-2-chloro-4',5'-(methylene dioxy)acetophenone **76**. In the ethylene dioxy series 1, 4-benzo-dioxane-6-amine was reacted with chloroacetonitrile in the presence of BF_3 and catalytic anhydrous $AlCl_3$ producing the corresponding 2'-amino-2-chloro-4',5'-(ethylene dioxy) acetophenone **78** was formed in one step. The 2'-amino-2-chloro-4', 5'-(methylene

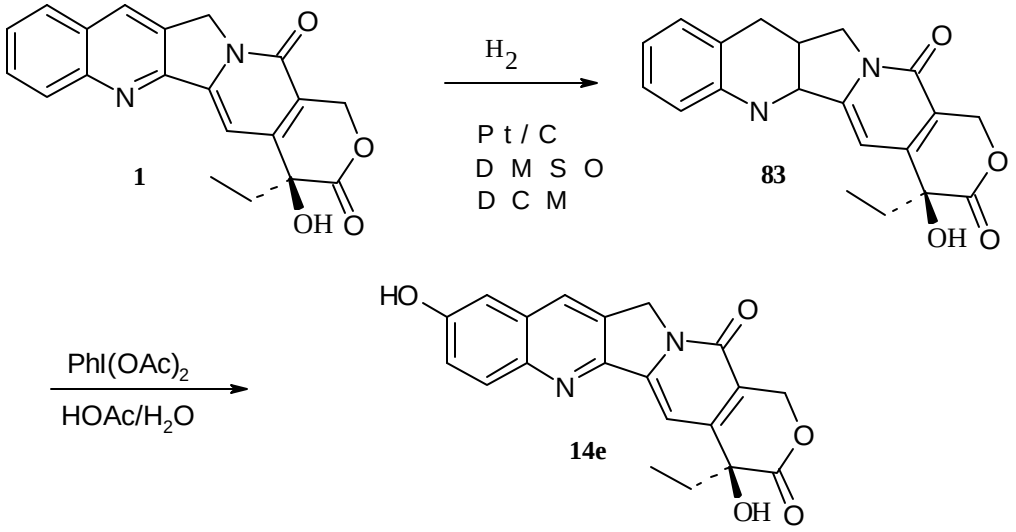


Reagents: (a) AcCl, Na_2CO_3; (b) $ClCH_2COCl$, $ZnCl_2$, CH_3NO_2, 100ºC; (c) conc,HCl, ethanol, 80ºC; (d) $ClCH_2CN$, BCl_3, CH_2Cl_2, 4ºC; (e) p-TSA, tol., 100ºC; (f) 1-methyl piperazine, DMF, RT; (g) CF_3COOH.

dioxy)acetophenone and 2'-amino-2-chloro-4', 5'-(ethylene dioxy) acetophenone were reacted with the tricyclic keto lactone under PTSA catalysed Friedlander condensation conditions to yield the corresponding 7-(chloromethyl)-10, 11-(methylene dioxy)-(20S)-camptothecin **79** and 7-(chloromethyl)-10, 11-(ethylenedioxy)-(20S)-camptothecin **80** respectively. The respetive chlorides were displaced with 4-methyl piperazine to provide the corresponding tertiary amines.

Scheme 7:[29]

Wood *et. al.* (JOC 60, 5739, 1995)



This method describes a convenient way to functionalise camptothecin to 10-hydroxy camptothecin on a large scale. Catalytic hydrogenation of **1** over platinum in mildly acidic solution gave 1,2,6,7-tetrahydro camptothecin **83** which on oxidation with (iodobenzene diacetate) in 1:1 acetic acid/H_2O provided 10-hydroxy camptothecin **14e**. This reaction sequence can be performed on large scale and leads to formation of clean products. The 10-hydroxycamptothecin (14e) is a key synthon for topotecan and can also be utilised for the synthesis of irinotecan and other bioactive camptothecin derivatives as well.

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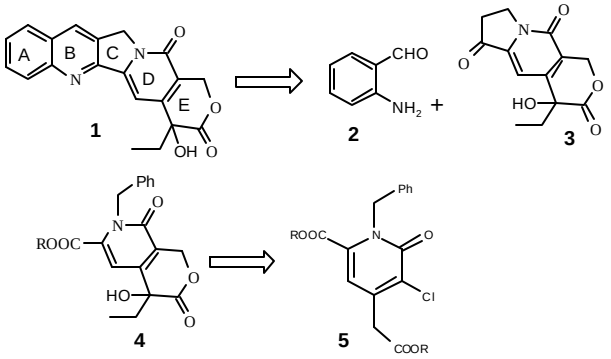
Section: 2

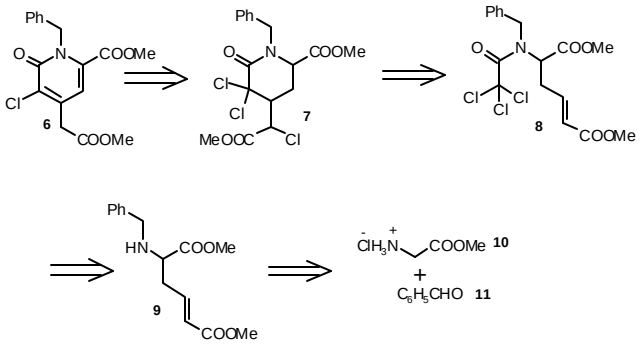
Part I

Preparation of 4-methyl N-substituted pyridone: An important precursor towards the formation of camptothecin.

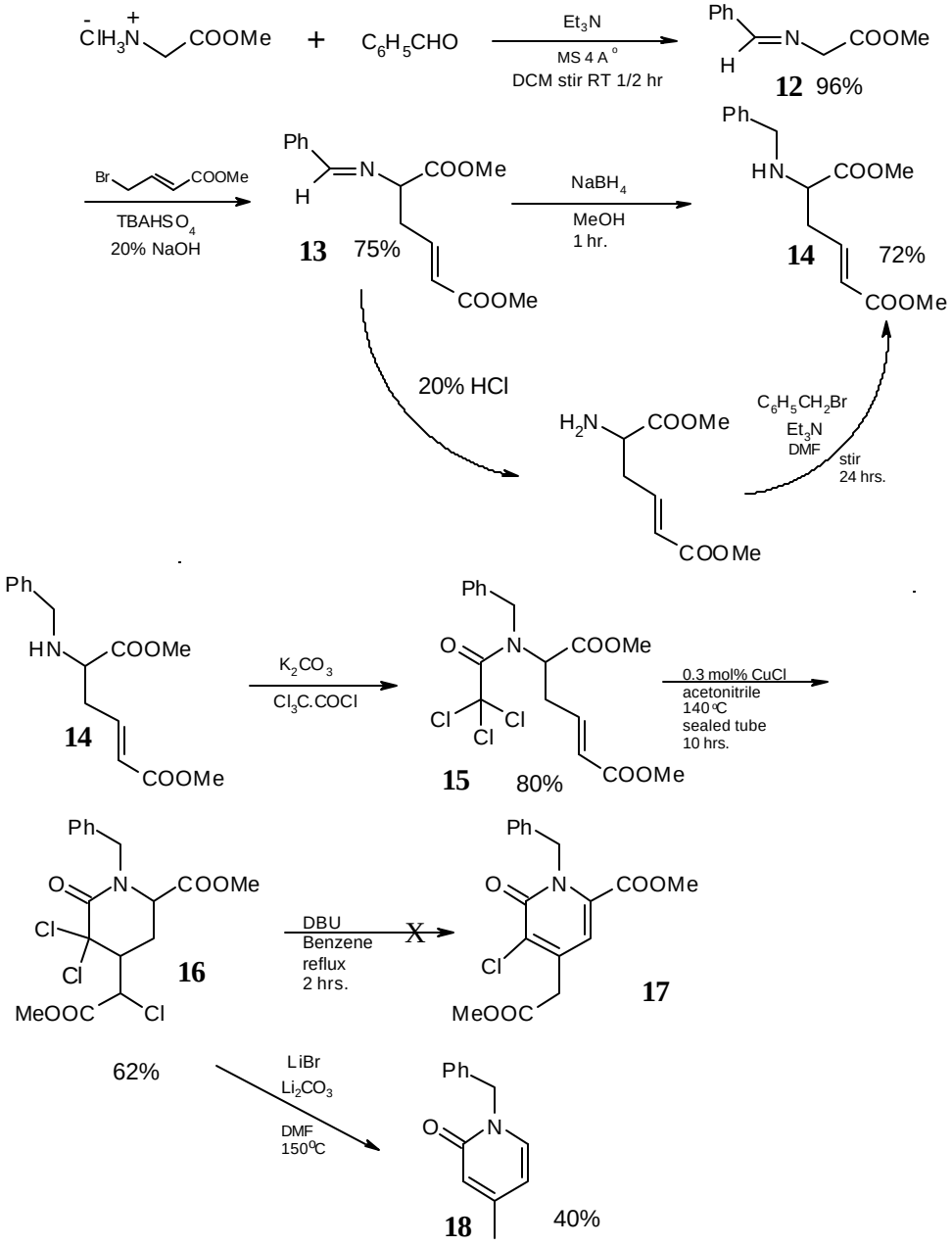


Scheme 1

In an approach towards the synthesis of camptothecin, it was envisaged that pyridone **6** would be a key synthon. The pyridone **6** in turn could be accessed readily by the metal catalysed cyclisation of the trichloro compound **8**. The construction of pyridone ring as a model molecule was anticipated as the ideal way to ascertain the feasibility of intramolecular C-C bond formtion reaction prior to synthesis of quinoline moiety.The following reterosynthetic strategy was adopted.



Scheme 2



Scheme 3

Alkylation of Schiff's base of glycine ester[1] **12** with 4-bromo methyl crotonate furnished compound **13** in 75% yield using 20% NaOH[2] solution in the presence of catalytic

amount of $TBAHSO_4$. The alkylated product on treatment with $NaBH_4$ in MeOH furnished amine **14** in 72% yield. The amine **14** was also prepared by the hydrolysis of alkylated product using 20% HCl solution followed by the condensation with benzyl bromide in the presence of triethyl amine and DMF as the solvent. The amine **14** was then condensed with trichloroacetyl chloride in the presence of K_2CO_3 as the base to furnish amide **15** in 80% yield. Intramolecular free radical cyclisation of **15** with CuCl (0.3 mol%)[3] as the catalyst in CH_3CN at 140°C under sealed tube conditions provided the desired chlorocompound **16** in 62% yield.

With the desired cyclised compound **16** in hand there was now a need to aromatise the ring. The following two reagents were chosen to effect desired transformation.

When compound **16** was subjected to aromatisation using DBU (2 eq.) in benzene as solvent, a complex mixture was formed and desired compound **17** could not be obtained.

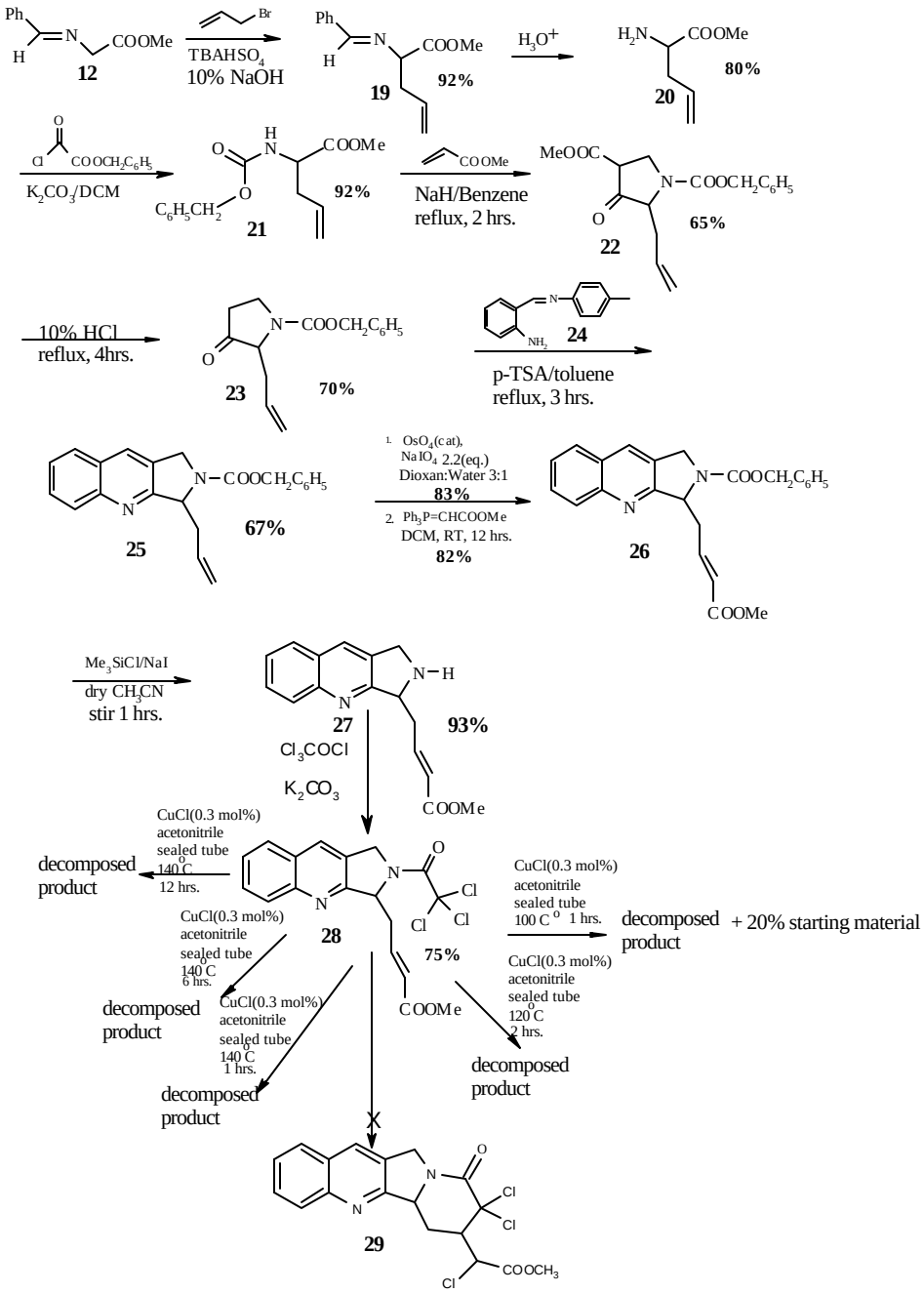
Treatment of compound **16** with LiBr-Li_2CO_3 in DMF at 150°C,[4] provided the aromatic compound **18** whose spectral analysis revealed the lack of ester group. Analysis of IR of compound **18** showed absence of peaks at 1744 cm^{-1} indicating the absence of ester group. The ^1H NMR spectrum revealed a peak at 2.2 ppm integrating for 3 protons indicative of the presence of heteroaromatic methyl group. The presence of a singlet at 6.4 ppm and 2 doublets at 6.0 & 7.2 ppm with coupling constant of 7 Hz. confirmed the structure of **18** to be N-benzyl 4-methyl pyridone. The structure was further confirmed by the presence of a peak at 199 in mass spectral analysis. Formation of pyridone **18** in 40% is noteworthy as it involves 5 sequential steps involving 2 dehydrohalogenations, 2 decarboxylations and bond reorganisation step. With pyridone as model molecule in hand, efforts were directed towards the synthesis ABC and D ring.

The Schiff's base of glycine ester **12** on treatment with allyl bromide under phase transfer conditions using tetrabutyl ammonium hydrogen sulphate as the catalyst furnished alkylated Schiff's base **19** in 92% yield (scheme-4). The ^1H NMR of **19**

showed the presence of multiplet at 2.6 ppm which was assigned to CH_2 group adjacent to allylic proton, the doublet at 5.1 ppm integrating for 2 protons was assigned to the 2 terminal olefinic protons, whereas the multiplet between 5.25 and 5.7 ppm was assigned to the third olefinic proton.

Hydrolysis of **19** using 10% HCl solution furnished amine **20** in 80% yield, which was protected as its urethane **21** employing benzyl chloroformate[5] in presence of K_2CO_3 as the base in 92% yield. In proton NMR spectra the singlet at 5.1 ppm was assigned to the benzylic proton ($\underline{H_2}\underline{C}C_6H_5$). The compound **21** was subjected to tendem Michael-Dieckmann reaction [6,7] with ethyl acrylate as the Michael acceptor employing NaH as the base to furnish ethyl keto ester **22** in 70% yield, whereas the yield was 65% when methyl acrylate was used as the Michael acceptor to furnish methyl keto ester. The keto ester was then refluxed in 10% HCl for 4 hrs. to provide pyrrolidine **23** as a product of hydrolysis-decarboxylation reaction. Friedlander condensation of **23** with N(o-amino benzylidine)p-toluidine[8] **24**, in toluene using PTSA as the catalyst furnished quinoline **25** in 67% yield. In ^1H NMR spectrum the multiplet at 4.7-5.1 ppm integrating for 4 protons was assigned to 2 terminal olefinic protons and 2 protons benzylic to quinoline ring. Oxidative cleavage of **25** employing osmium tetroxide (cat.) and $NaIO_4$ in dioxane/water system furnished aldehyde which without purification was subjected to Wittig olefination with phosphorane (prepared from 2-chloroacetate and triphenyl phosphine) provided α, β-unsaturated ester **26** in 82% yield. In ^1H NMR spectrum the multiplet at 6.5 to 6.8 ppm was assigned to β olefinic proton of α, β-unsaturated ester group.

The urethane **26** was deprotected using 10 eq. of trimethyl silyl iodide (prepared from 10 eq. of TMSCl and 10 eq. of NaI)[9] in dry acetonitrile under N_2 atmosphere at room temperature furnished amine **27** within an hour. The crude amine **27** was then condensed with trichloroacetyl chloride in the presence of K_2CO_3 in dichloromethane as the solvent provided amide **28** in 75%. The compound **28** was then subjected to intramolecular free radical cyclisation using CuCl cat. (0.3 mol%) in sealed tube as depicted in scheme-4. Dissappointedly several attempts to cyclise **28** to **29** met with


12
TBAHSO4
10% NaOH
19
92%
H3O+
20
80%
K2CO3/DCM
21
92%
NaH/Benzene
reflux, 2 hrs.
22
65%
10% HCl
reflux, 4hrs.
23
70%
24
p-TSA/toluene
reflux, 3 hrs.
25
67%
1. OsO4(cat), NaIO4 2.2(eq.) Dioxan:Water 3:1
83%
2. Ph3P=CHCOOMe DCM, RT, 12 hrs.
82%
26
Me3SiCl/NaI
dry CH3CN
stir 1 hrs.
27
93%
Cl3COCl
K2CO3
CuCl(0.3 mol%) acetonitrile sealed tube 140 C 12 hrs.
decomposed product
28
75%
CuCl(0.3 mol%) acetonitrile sealed tube 100 C 1 hrs.
decomposed product + 20% starting material
CuCl(0.3 mol%) acetonitrile sealed tube 140 C 6 hrs.
decomposed product
CuCl(0.3 mol%) acetonitrile sealed tube 140 C 1 hrs.
decomposed product
CuCl(0.3 mol%) acetonitrile sealed tube 120 C 2 hrs.
decomposed product
29

Scheme 4

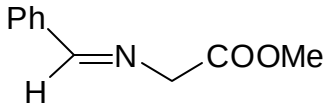
with failure. Since **28** could not be cyclised to **29** this route to synthesize camptothecin was abondoned.

Conclusion :

Although the cyclisation reaction failed to achieve the tetracyclic framework of camptothecin, 4-methyl pyridone could be readily accessed following the above mentioned methodology. Occurrence of dehydrohalogenation as well as removal of two carbomethoxy groups in one pot is the noteworthy feature of this transformation. 4-Methyl pyridone **18** can potentially serve as a synthon towards the synthesis of camptothecin.

Experimental Procedure :

Methyl N-(phenyl methylene)b -vinyl alaninate 12:[1]

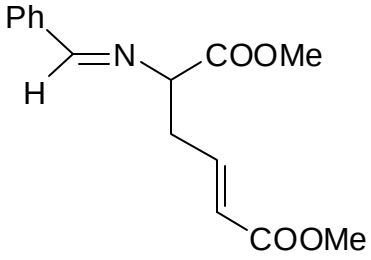


12

To a solution of 15.68g (0.125 mol) of glycine methyl ester hydrochloride and 12.62g (0.125 mol) of triethyl amine in 50 ml of dry DCM in the presence of 5g of Molecular sieves (4 A°), was added 10.6g (0.1 mol) of benzaldehyde. The reaction mixture was stirred for 0.5 hr at room temperature. At the end of reaction, 100 ml of water was added to dissolve triethyl ammonium hydrochloride, the organic layer was separated and the resulting aqueous solution was then extracted wth 2x50 ml portions of dichloromethane. The combined organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator to furnish Schiff's base **12** as colourless oil in 96% yield.

^{1}H NMR (200 MHz); 4.35 (s, 2H); 3.9 (s, 3H); 7.3-7.8 (m, 5H); 8.2 (s, 1H).

Dimethyl 5-[-phenyl methylidene amino]-2-hexenedioate 13:[2]



13

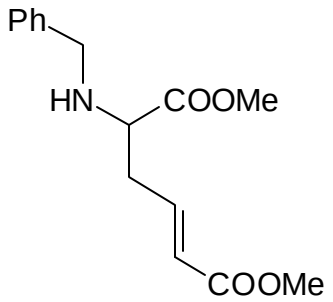
To a 10g (56 mmol) of Schiff's base **12** and 12.5g (70 mmol) of methyl 4-bromo crotonate in 50 ml DCM was added, 50 ml of 20% sodium hydroxide solution followed

by catalytic $TBAHSO_4$ 1.9g (5.6 mmol). The two phase system was stirred at room temperature for 40 mins. The dichloromethane layer was separated and the aqueous layer extracted with 2x50 ml portions of dichloromethane. The combined dichloromethane layer was dried over anhydrous Na_2SO_4, and filtered. Concentration of the organic layer on rotary evapoator furnished 11.3 g of alkylated Schiff's base **13** as colourless oil in 75% yield.

IR (neat) ν cm^{-1}: 1700, 1640, 1440.

^{1}H-NMR (200 MHz): δ 2.75 (m, 2H); 3.65 (s, 3H); 4.35 (t, 1H); 5.9 (d, 1H, J=16 Hz.); 6.85 (dt, 1H) 6.8-7.7 (m, 5H).

Dimethyl 5-benzyl amino-2-hexene dioate 14:



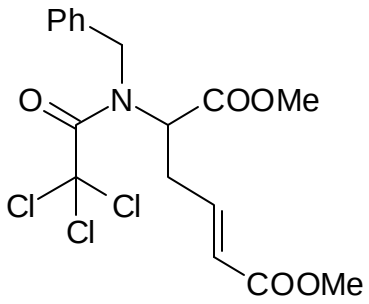
14

To a 10g (37.7 mmol) of alkylated Schiff's base **13** in 50 ml of dry MeOH, was added in small portion of 1.1g (30 mmol) of sodium borohydride under ice cooling. After stirring for 0.5 hr the solution was then concentrated on rotary evaporator, the resulting residue was quenched with 50 ml of water and extracted with 3x25 ml protions of ethyl acetate. The combined organic layer was dried (anhydrous Na_2SO_4), filtered and then concentrated on rotary evaporator. Purification of the residue thus obtained by column chromatography (SiO_2) furnished 7.25g amine **14** as viscous oil in 72% yield.

IR (neat) ν cm^{-1}: 3373, 3059, 1729, 1657, 1440.

^{1}H-NMR (200 MHz): δ 1.9 (br s, 1H); 2.5 (m, 2H); 3.4 (t, 1H); 3.7 (s, 2H); 3.8 (s, 6H); 5.9 (d, 1H); 6.9 (m, 1H); 7.3 (m, 5H).

Dimethyl 5-benzyl(trichloromethyl)carboxamido-2-hexenedioate 15:



15

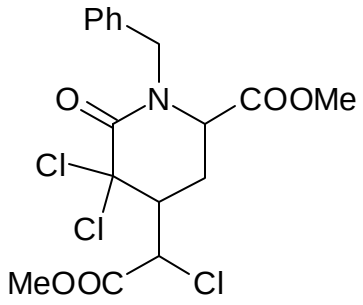
To a stirred solution of 5g (18.7 mmol) of amine **14** and 1.46g (37.4 mmol) of K_2CO_3 in 50 ml. of dichloromethane, was added 4.2g (23.4 mmol) of trichloroacetyl chloride dropwise at 0°C. The reaction mixture was stirred overnight, at room temperature, quenched with 50 ml of water and extracted with 2x25 ml portions of dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator. Purification by column chromatography over silica gel using 20% EtOAc-pet.ether as eluent furnished 6.2g of amide **15** as a viscous liquid in 80% yield.

IR (neat) ν cm^{-1}: 1724, 1680, 1496, 1456, 1436, 1360, 1224.

^{1}H-NMR (200 MHz): δ 2.8 (m, 1H); 3.0 (m, 1H); 3.7 (t, 1H); 3.75 (s, 6H); 5.0 (s, 1H); 5.75 (d, 1H –CH=CH-COOMe); 6.7 (m, 1H –CH=CH-COOMe); 7.35 (m, 5H aromatic ring).

Mass (m/e): 408, 386, 362, 276, 171, 91.

Methyl(1-benzyl-5,5-dichloro-4-chloro(methyl oxycarbonyl)methyl-6-oxohexahydro-2-pyridine carboxylate 16:[3]



16

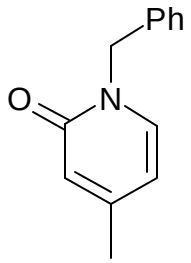
In a glass tube on 10 ml capacity 2g (4.8 mmol) of amide **15**, 2.3 mg (0.3 mol%) of CuCl in 5 ml of CH_3CN were introduced. The end of the glass tube was then sealed and closed in steel bomb, and was then kept at 140°C for 10 hrs. The resulting black coloured solution was then cooled and concentrated. To the residue 20 ml water was added and aqueous layer was extracted with 3x20 ml EtOAc, the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator. Column purification of the residue provided 1.24g (62% yield) of cyclic product **16** as a viscous liquid.

IR (neat) ν cm^{-1}: 2923, 1744, 1686, 1437, 1209.

^{1}H-NMR (200 MHz): δ 2.45 (m, 2H), 3.4 (m, 1H), 3.8 (m, 2H), 3.9 (s, 6H), 4.15 (m, 1H), 4.9 (d, 1H), 5.5 (m, 1H),7.3 (m, 5H).

Mass (m/e): 408, 386, 328, 216, 121, 91, 77.

4-Methyl N-benzylpyridone 18:[4]



18

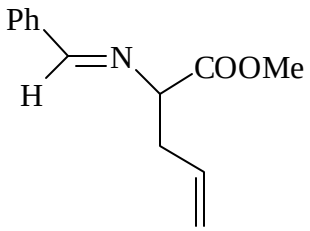
To a 0.5g (1.2 mmol) of amide **16** in 5 ml of DMF was added 0.13g (1.5 mmol) of LiBr and 0.11g (1.5 mmol) of Li_2CO_3. The solution was heated at 150°C for 0.5 hr, and was then cooled to room temperature and 25 ml of water was added to it. The aqueous solution was extracted with 3x25 ml of EtOAc and finally washed with 25 ml. of brine solution followed by 25 ml of water. The organic layer was separated dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator. Purification by column chromatography (SiO_2) afforded 0.095g of pyridone **18** as a viscous oil in 40% yield.

^{1}H-NMR (200 MHz): δ 2.2 (s, 3H), 5.1 (s, 2H), 6.0 (d, 1H, J=7Hz olefinic), 6.4 (s, 1H olefinic), 7.2 (d, 1H, J=7Hz olefinic), 7.4 (m, 5H aromatic).

^{13}C NMR (50 MHz): 22(s), 52(t), 108.7(d), 119(d), 128(d), 128.5(d), 129(d), 136(d), 136.5(s), 151(s) 162.5(s).

Mass (m/e): 199, 182, 122, 110, 91, 64.

Ethyl N-(phenyl methylene)-b -vinyl alaninate 19:[2]



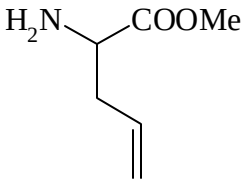
19

To a 10g (56.5 mmol) solution of methyl N-(phenyl methylene) glycinate **12** in 100 ml of DCM, was added 8.6g (70.6 mmol) of allyl bromide, followed by addition of 100 ml of 10% NaOH solution and 2g (5.65 mmol) of tetrabutyl ammonium hydrogen sulphate in catalytic amount. The reaction mixture was stirred for 0.75 hr at room temperature. The organic phase was separated and the aqueous layer was extracted with 2x50 ml portions of dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude syrup thus obtained was redissolved in CCl_4 (50 ml) and washed with water. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to get 11.2g of crude alkylated Schiff's base **19** in 92% yield as viscous oil.

IR (neat) cm^{-1}: 1730, 1620.

^{1}H-NMR (200 MHz): δ 2.6 (t, 2H, J=7.5 Hz -$\underline{CH_2}CH=CH_2$), 3.75 (s, 3H –COO$\underline{CH_3}$), 5.1 (d, 2H, J=5.18 Hz CH_2-CH=$\underline{CH_2}$), 5.3-5.7 (m, 1H, -CH_2-$\underline{CH}$=CH_2), 7.2 (s, 5H aromatic).

Methyl 2-aminopentenoate 20:



20

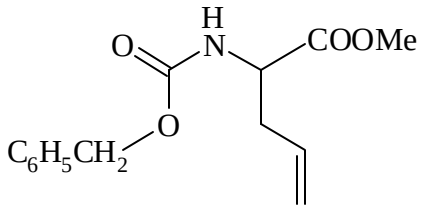
The crude Schiff's base **19** was stirred with 75 ml of 10% HCl for ½ hr at the end of

which 30 ml of EtOAc was added to the reaction mixture. The solution was again stirred for 2-3 minutes. The aqueous layer was separated and extracted again with 2x30 ml portions of EtOAc. The aqueous layer was then cooled and neutralised with ammonia solution (40%) and was then extracted with 3x30 ml portions of dichloromethane. The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated under reduced pressure to provide 5.3g of crude amino ester **20** in 80% yield as viscous oil.

IR (neat) cm^{-1}: 1730, 3400.

^{1}H-NMR (200 MHz): δ 1.9 (br s, 2H $-NH_2$), 2.6 (t, 2H, J=7.5 Hz $\underline{H_2C}$-CH=CH_2), 3.75 (s, 3H $-CH_3$), 5.1 (d, 2H J=5.18 Hz olefinic), 5.4 (m, 1H, -CH_2-$\underline{CH}$=CH_2).

Methyl-2-(benzoyloxy carbonyl amino)-4-pentenoate 21:[5]



21

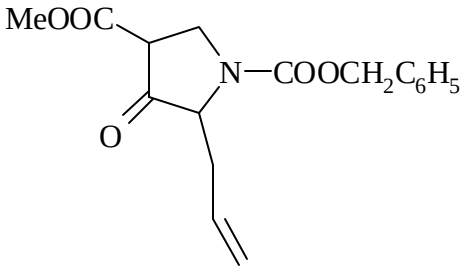
To a stirred solution of 5.3g (41mmol) of amino ester **20** in 50 ml of dry dichloromethane under N_2 atmosphere at 0°C, was added 11g (82 mmol) of K_2CO_3 followed by slow addition of 7g (41 mmol) benzyl chloroformate. The mixture was stirred for 2 hrs and on completion of reaction (TLC), 100 ml of water was added. The organic layer was separated whereas aqueous layer was extracted with 2x25 ml of dichloromethane. The combined organic layer was the dried and concentrated under reduced pressure. Column chromatography (SiO_2) of the residue using 20% EtOAc-pet ether as the eluent furnished 9.9g of pure urethane **21** in 92% yield as viscous oil.

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

^{1}H-NMR (200 MHz): δ 2.46 (t, 2H J=7.5 Hz $\underline{CH_2}$-CH=CH_2), 3.75 (s, 3H, COO$\underline{CH_3}$),

4.46 (m, 1H), 5.1 (s, 2H, $\underline{CH_2}Ph$), 5.35 (d, 2H, J=5.18 Hz CH_2-CH=$\underline{CH_2}$), 5.55-5.85 (m, 1H, CH-$\underline{CH}$=CH_2), 7.4 (s, 5H).

1-Benzyl 3-methyl 5-allyl-4-oxotetrahydro-1H-1, 3-pyrrole dicarboxylate 22:[6,7]



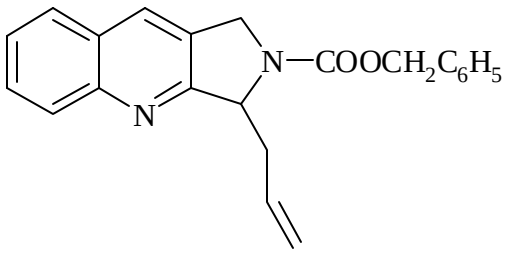
22

To a stirred suspension of 1.6g (68 mmol) of NaH (50% suspension in oil prewashed with 3x10 ml of dry pet-ether) in 100 ml of dry benzene was added 9g (34 mmol) of urethane **21** dropwise under N_2 atmosphere at room temperature. The reaction mixture was stirred till evolution of hydrogen ceased. To the generated sodium salt was added 3.17g (37.4 mmol of methyl acrylate in 20 ml benzene dropwise, the reaction mixture was stirred for 0.5 hr, which was then refluxed for 2 hrs It was then quenched with 50 ml of saturated solution of ammonium chloride, the organic layer was separated and the water layer was extracted with 2x50 ml of EtOAc. The combined organic layer was then dried (anhydrous Na_2SO_4), filtered and concentrated. Purification by column chromatography (SiO_2) using 25% EtOAc-pet ether as eluent furnished 7.34g methyl keto ester **22** in 65% yield as viscous liquid.

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

^{1}H NMR (200 MHz):δ 1.3(t, 3H, J=7.5 Hz $COOCH_2\underline{CH_3}$), 2.6 (m, 2H, $\underline{CH_2}$-CH=CH_2), 3.75 (d, J=7 Hz 2H), 4.0-4.55 (m, 3H), 5-5.4 (m, 2H), 5.2 (s, 2H, $\underline{CH_2}Ph$), 5.65 (m, 1H CH_2-$\underline{CH}$=CH_2), 7.35 (s, 5H).

2-(Benzyloxycarbonyl)-3-(2-propenyl)-1, 3-dihydro-2H-pyrrolo [3, 4b]quinoline 25:[8]



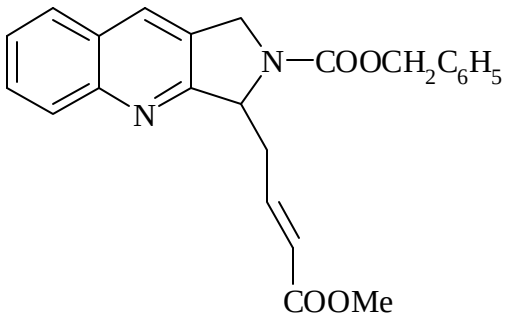
25

To a 5g (15.1 mmol) of β-ketoester, 50 ml of 10%HCl solution was added and the mixture was refluxed for 4 hrs. The reaction mixture was cooled and extracted with 3x30 ml portions of dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to provide 2.7 g of pyrrolidinone in 70% yield. To a solution of 2.7 g of crude pyrrolidinone in 25 ml of dry toluene, was added 2.8g (13.1 mmol) of N-(o-aminobenzilidine)-p-toluidine and the mixture refluxed for 0.5 hr with azeotropic removal of water using Dean-Stark apparatus. After half an hour, 0.3g of PTSA (catalytic amount) was added and the mixture was again refluxed for 3 hrs. The reaction mixture was then cooled and quenched with 10%$NaHCO_3$ and the organic phase was separated and the aqueous phase was further extracted with 2x25 ml portions of EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish crude quinoline. Purification by column chromatography over silica gel using 30% EtOAc-pet. ether as eluent provided 2.5g of quinoline **25** in 67% yield as viscous liquid.

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

^1H NMR (200 MHz):δ 2.8-3.3(m, 2H, $\underline{CH_2}$-CH=CH_2), 4.7-5.1 (m, 4H), 5.3 (s, 2H, $\underline{CH_2}$Ph), 5.3-5.6 (m, 1H, CH_2-$\underline{CH}$=CH_2), 7.3-7.5 (m, 5H, Ph), 7.6 (t, 1H), 7.75 (t, 1H), 7.8 (d, 1H), 8.0 (d, 1H), 8.1 (m, 1H).

Benzyl 3-[3-methloxy carbonyl-2-propenyl]-2, 3-dihydro-1H-pyrrolo[4, 3-b] quinoline-2-carboxylate 26:



26

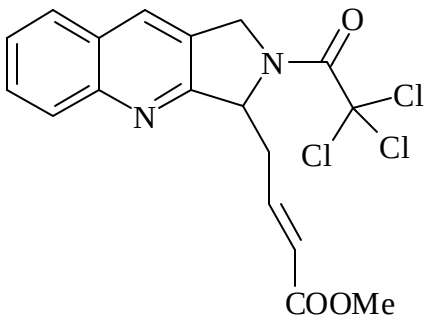
To a stirred solution of 2g (5.8 mmol) of quinoline **25** in 15 ml of 1,4-dioxane and 5 ml of water was added catalytic amount of OsO_4 and was stirred continuously for 5 min, a black coloured complex appeared. To this complex was added 2.7g (12.8 mmol) of $NaIO_4$ in small portion at a time and the solution was stirred further for 4 hrs. Water was added and crude aldehyde was extracted with 2x25 ml of ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish 1.7g of aldehyde in 83% yield. To a crude solution of 1.4g (4.9 mmol) g of aldehyde in 20 ml of dichloromethane was added 2.0g (6 mmol) of Wittig salt, the solution was stirred at room temperature, under N_2 atmosphere for 6 hrs. The reaction mixture was then concentrated and purified by column chromatography (SiO_2) to furnish 1.6 g of α,β-unsaturated ester **26** in 82% yield as brown coloured solid. m.p. 106°C.

IR (neat) cm^{-1}: 3014, 2945, 1705, 1680, 1500, 1400, 1347, 1314, 1274, 1211.

^{1}H NMR (200 MHz): δ 3.1-3.4 (m, 2H, >C-$\underline{CH_2}$-CH), 3.6 (s, 3H, -COO$\underline{CH_3}$), 4.7-5.2 (m, 3H), 5.35-5.45 (m, 2H), 5.6-5.8 (m, 1H), 6.5-6.8 (m, 1H), 7.26-7.5 (m, 5H), 7.6 (t, 1H), 7.75 (t, 1H), 7.85 (d, 1H), 7.9-8.2 (m, 2H).

Mass (m/e): 402, 371, 325, 303, 259, 168, 91.

Methyl 4-[2-(2, 2, 2-trichloroacetyl)]-2, 3-dihydro-1H-pyrrolo[4, 3-b] quinoline-2-butenoate 28:[9]



28

To a stirred solution of 1g (2.5 mmol) of urethane **26** and 3.7g (25 mmol) of NaI in dry acetonitrile, was added 2.7g (25 mmol) of Me_3SiCl dropwise under N_2 atmosphere and stirred for 1 hr at room temperature. After completion of reaction (TLC) 25 ml of 20% solution of $Na_2S_2O_3$ was added and aqueous phase was extracted with 3x30 ml. portions of EtOAc. The combined organic layer was washed with 50 ml of saturated solution of NaCl and finally with 50 ml of water, dried over anhydrous Na_2SO_4, filtered and was then concentrated to frunish 0.63g of crude amine in 93% yield.

To this ice cold stirred solution of 0.63g (2.4 mmol) of amine in 25 ml of dichloromethane, was added 0.65g (48 mmol) of K_2CO_3 and 0.54g (3 mmol) of trichloro acetylchloride dropwise. The solution was stirred for 4 hrs and at the end of reaction 25 ml of water was added. The organic layer was then separated and the aqueous layer was extracted with dichloromethane (2x25 ml). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to furnish a residue, which on column purification furnished 0.66g of pure amide **28** in 75% yield as a viscous liquid.

IR (neat) cm^{-1}: 2976, 2937, 1716, 1667, 1571, 1437, 1372, 1324, 1268, 1211, 1170.

^1H NMR (200 MHz): δ 3.1-3.4 (m, 2H, >CH-$\underline{CH_2}$-CH=), 3.6 (s, 3H, -COO$\underline{CH_3}$), 5.2 (d, J=17 Hz 1H), 5.5-5.7 (m, 3H), 5.85 (m, 1H), 6.5 (m, 1H), 7.55 (t, 1H), 7.8 (d, 1H), 8.1 (d, 1H).

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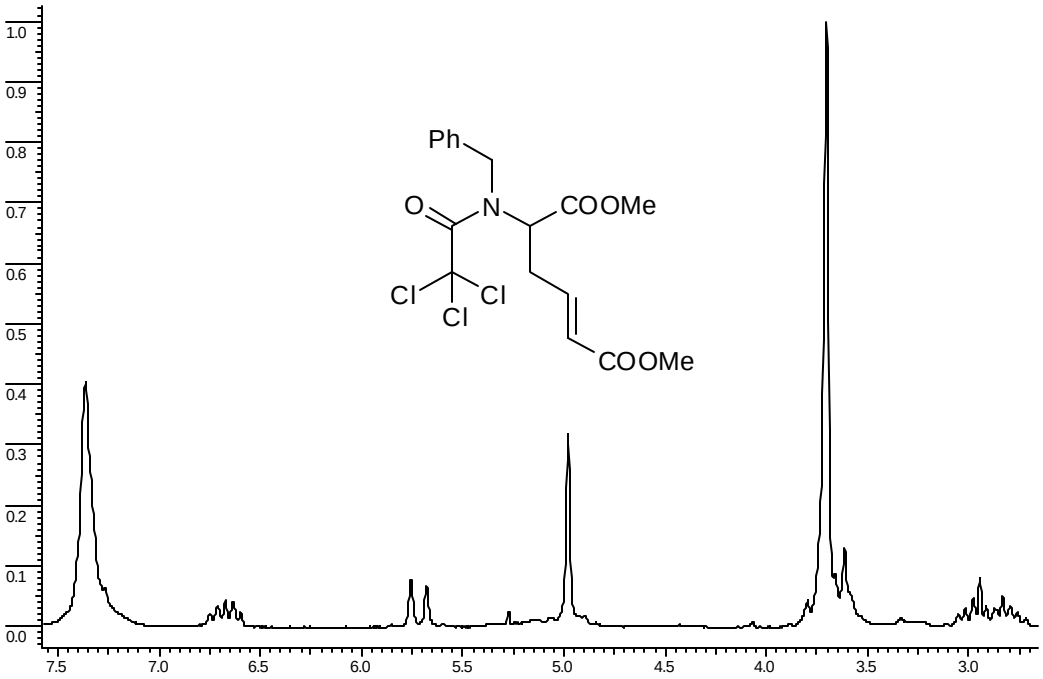
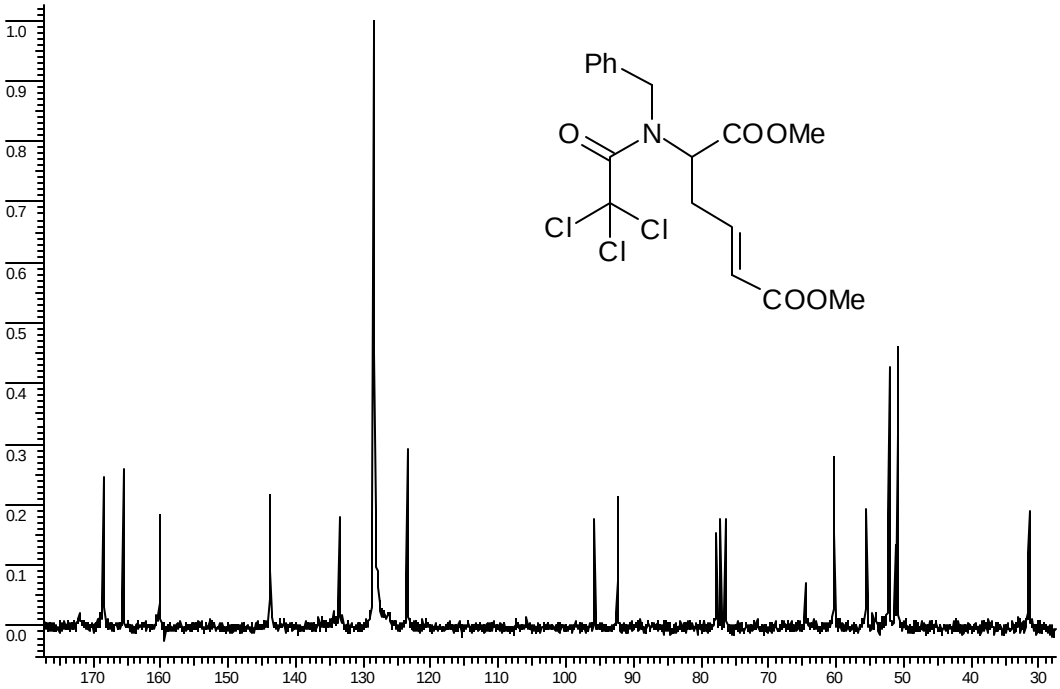
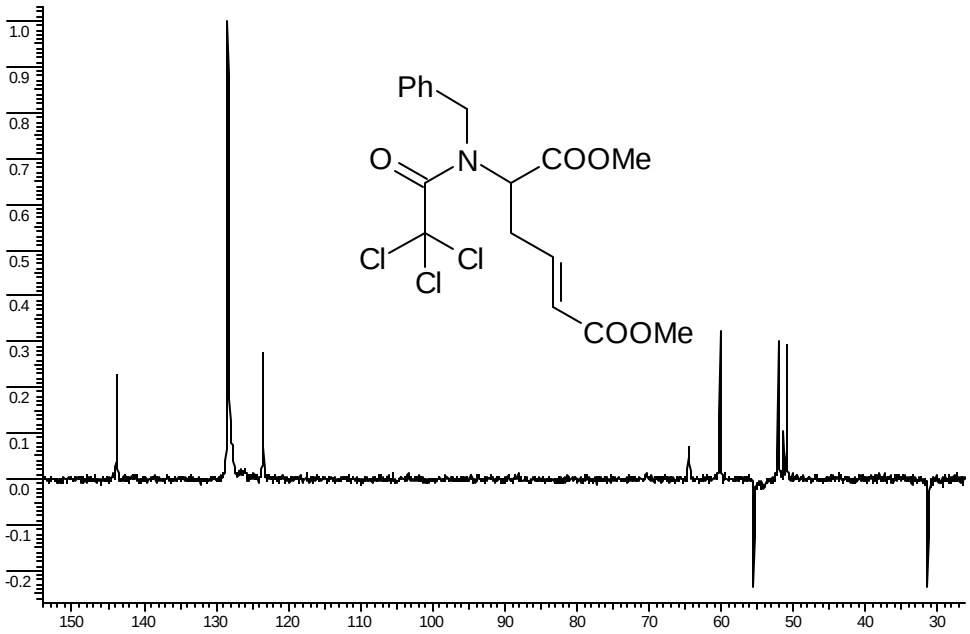


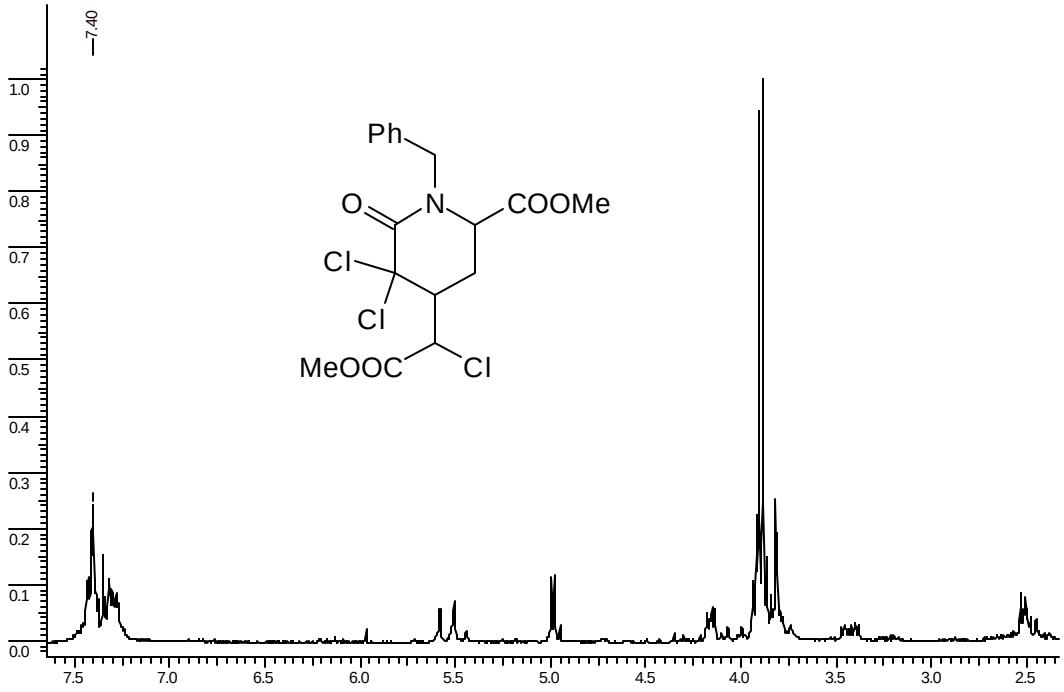
^{1}H NMR spectrum of dimethyl 5-benzyl(trichloromethyl)carboxamido-2-hexenedioate 4 ($CDCl_3$ 200 MHz)



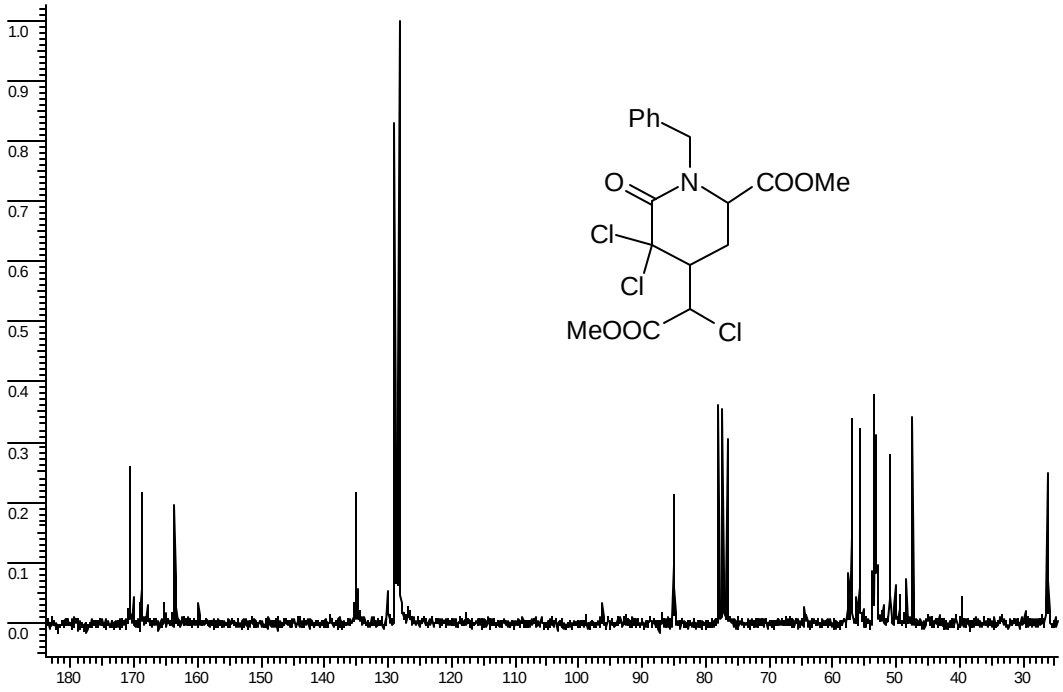
^{13}C NMR of dimethyl 5-benzyl(trichloromethyl)carboxamido-2-hexenedioate 4 ($CDCl_3$ 50 MHz)



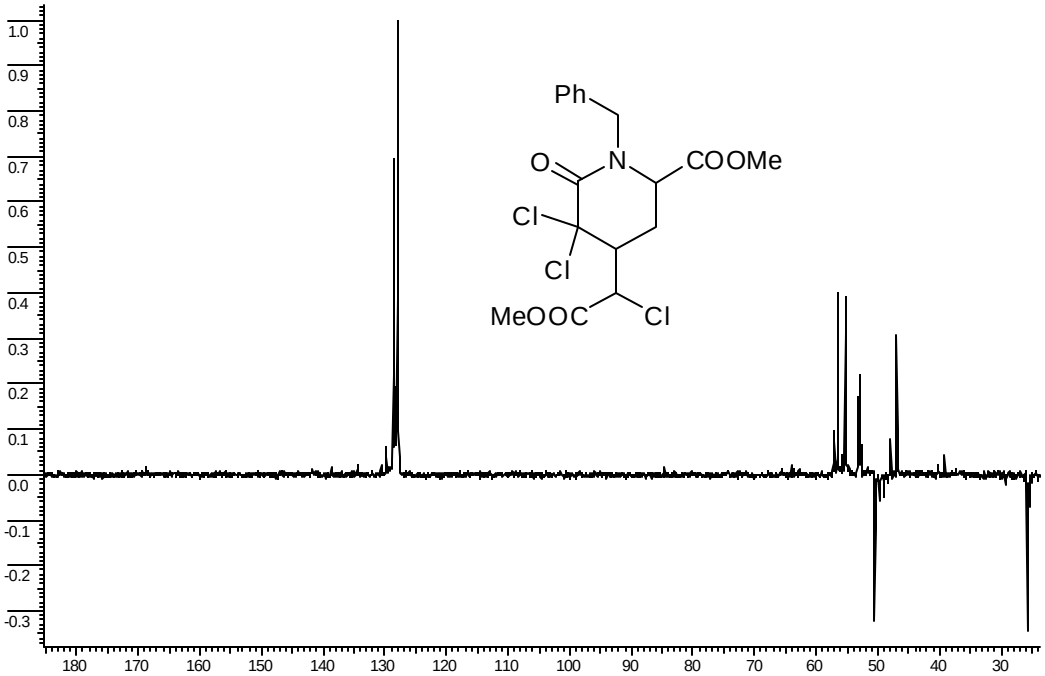
DEPT of dimethyl 5-benzyl(trichloromethyl)carboxamido-2-hexenedioate 4 ($CDCl_3$ 50 MHz)



^{1}H NMR of methyl(1-benzyl-5,5-dichloro-4-chloro(methyl oxycarbonyl)methyl-6-oxohexahydro-2-pyridine carboxylate 5 ($CDCl_3$ 200 MHz)

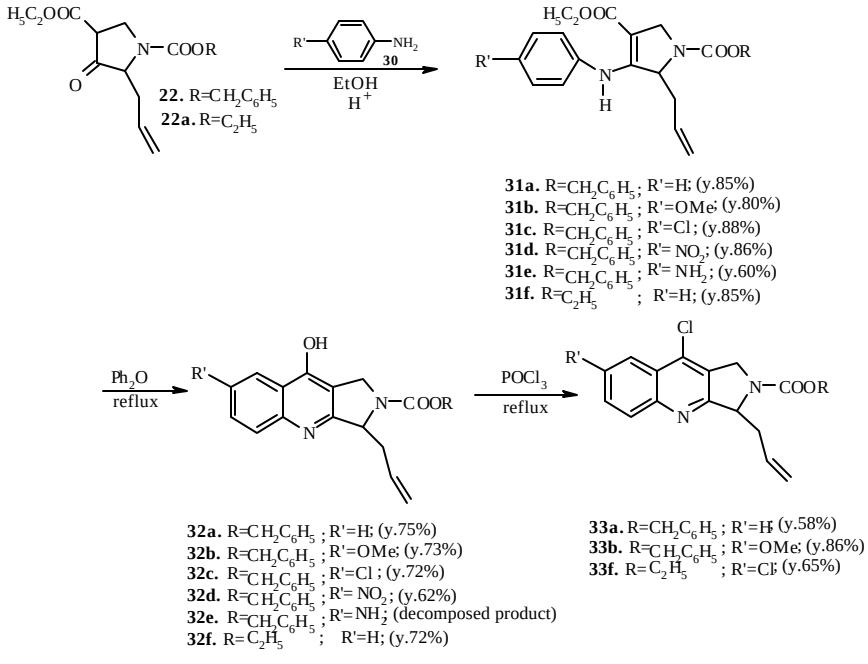


^{13}C NMR of methyl(1-benzyl-5,5-dichloro-4-chloro(methyl oxycarbonyl)methyl-6-oxohexahydro-2-pyridine carboxylate 5 ($CDCl_3$ 50 MHz)



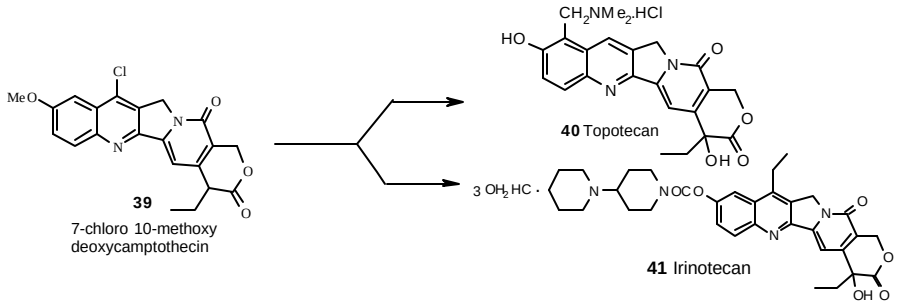
Part : 2

Having failed to get the desired pyridone from the trichlorocompound by the above scheme, attempts were diverted towards the formation of quinoline through another route. Most of the earlier routes employ substituted amino benzaldehydes in Friedlander condensation to synthesize the quinoline. Since substituted aminobenzaldehydes are not readily available and their instability prompted us to access variously substituted quinolines and camptothecin. Accordingly, the keto esters, were condensed with aniline or substituted aniline in the presence EtOH and two drops of dil. HCl, furnished enamines (**31a**-**31f**) which were then cyclised in the presence of diphenyl ether at temperature ranges between 240°C to 260°C to provide hydroxy quinoline (**32a**-**32f**). After considerable experimentation it was found that the temperature plays a critical role in the success of the reaction. The crucial part in this reaction was to maintain the temperature, as below 240°C the reaction doesn't start whereas at elevated temperature beyond 260°C it starts to decompose.[1]



Scheme 5

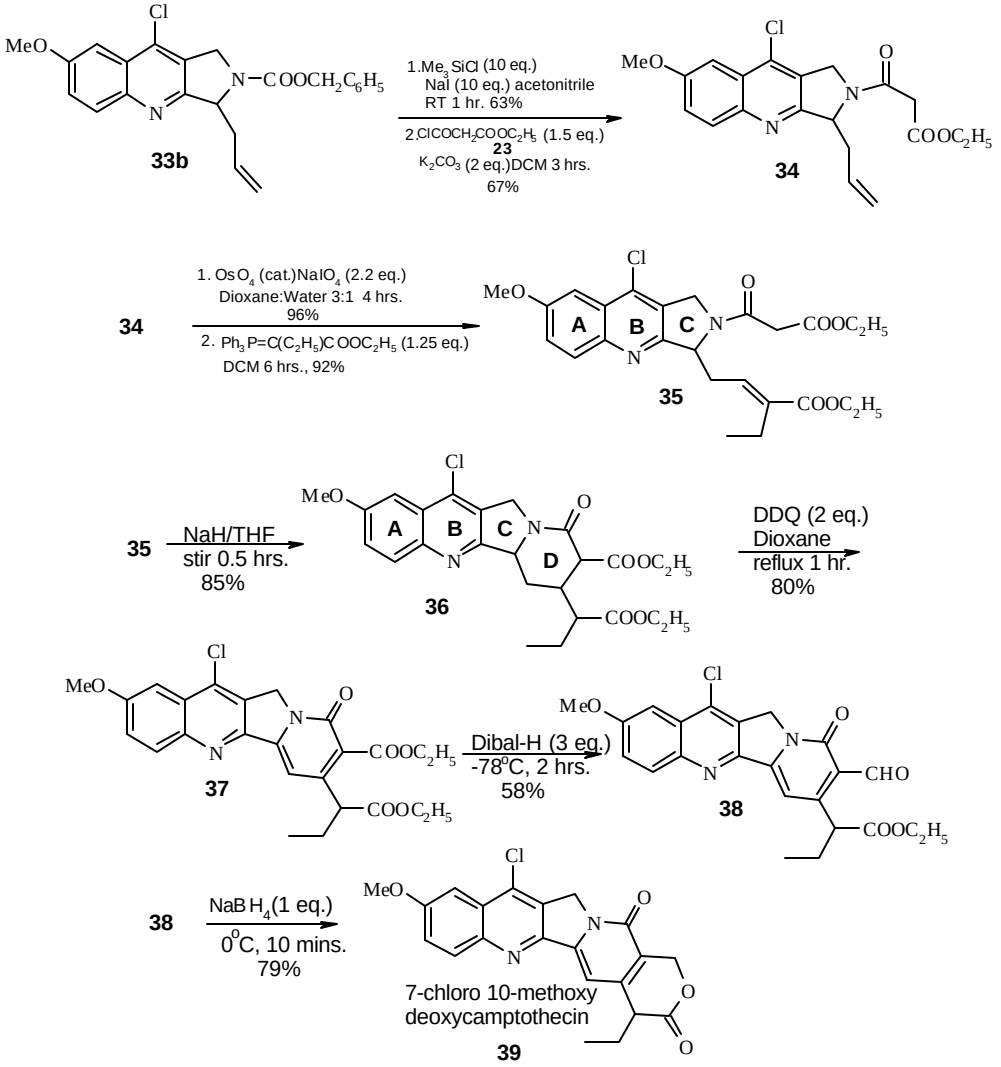
Having the desired quinoline in hand, a number of other derivatives were prepared to establish the efficacy of the protocol as shown in the **scheme 5**. These phenols were then subjected to reaction with $POCl_3$ to furnish chloroquinoline (**33a-33f**) . From **scheme 5**, it is evident that various substituted quinolines could be cyclised with equal ease. Compound **33b** has bifunctionality incorporated in the quinoline ring which could be used to access two commercially important derivatives of camptothecin *viz.* topotecan & irinotecan. Compound **33b** was therefore chosen as an important precursor towards the total synthesis of disubstituted deoxycamptothecin.



Scheme 6

Thus, compound **33b** was subjected to treatment with excess TMSI (10 equivalents) in acetonitrile at room temperature. The TLC analysis after one hour showed the complete consumption of starting material with the formation of benzyl iodide as a side product. The amine was then condensed with carbethoxy acetyl chloride[2] in dry dichloro methane with K_2CO_3 as the base to furnish amide **34** in 67% yield. Oxidative cleavage of **34** using osmium tetroxide (in catalytic amount) and $NaIO_4$ in dioxane/water system furnished aldehyde in 96% yield, which without purification was directly subjected to Wittig olefination with phosphorane (prepared from α-bromobutyrate and triphenyl phosphine).[3] The α, β-unsaturated ester **35** was formed in 92% yield. The ^1H NMR of **35** showed triplet at 0.85 ppm and multiplet at 2.20 ppm integrating for 3 and 2 protons respectively which were assigned to the ethyl functionality α to the ester. The olefinic proton appeared at 6.95 ppm as a triplet integrating for 1 proton. IR spectrum showed absorption at 1714.6 cm^{-1} suggesting the presence of α, β-unsaturated ester.

Having assembled the requisite carbon framework required for camptothecin skeleton, the compound **35** was then subjected for intramolecular Michael reaction as it had all the functionalities required to effect the-D ring construction according to the protocol developed in our laboratory.[6] Thus treatment of **35** with NaH in dry THF at room temperature furnished tetrahydropyridone **36** in 85% yield.



Scheme 7

The ^{1}H NMR spectrum of **36** showed doublet at 3.6 ppm (J=8.0 Hz) integrating

for 1 proton which was assigned to the active methine proton (NCO.CH-COOEt). The doublets at 4.75 ppm and 5.2 ppm (J=16.1 Hz) and doublet of doublet at 5.50 ppm all integrating for 1 proton each was assigned to the 3 pyrrolidine protons. The IR spectrum showed absorption at 1732 cm^{-1} and 1658.7 cm^{-1} suggesting the presence of saturated ester and lactum functionality respectively.

Following the reported procedure,[3] the compound **36** was subjected to oxidation using 2 equivalents of DDQ in refluxing dioxane, to furnish pyridone **37** in 80% yield. The ^1H NMR spectrum of 28 showed triplet at δ 3.75 integrating for 1 proton which was assigned to proton α to ethyl ester (CH_3CH_2CHCOOEt). The singlet at 5.3 ppm integrating for 2 protons was assigned to the 2 benzylic protons of the quinoline ring. The singlet at 7.45 ppm integrating for 1 proton was assigned to the pyridone proton.

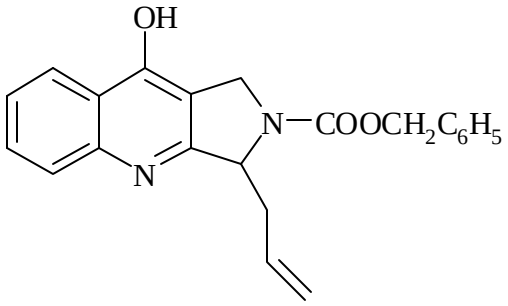
Analogous to Kraiss's[4] method for selective reduction of diester, selective reduction of heteroaromatic ester was established in our laboratory earlier[5], after careful experimentation, conditions were established for selective reduction of heteroaromatic ester over aliphatic ester. Thus when the compound **37** was treated with 3 equivalents of Dibal-H at -78°C in dry toluene for 2 hrs, aromatic aldehyde **38** was formed in 58% yield with a small amount of polar inseparable products. The ^1H NMR spectrum of **38** showed that the disappearance of peaks at 1.45 ppm and 4.15 ppm and the appearance of peak as a singlet at 10.61 ppm clearly indicative the conversion of heteroaromatic ethyl ester to an aldehyde **38**. Having achieved the selective functionalisation of aromatic ester to aldehyde, the next task was to further reduce the aldehyde to alcohol and lactonisation to construct E ring of camptothecin. Accordingly, the treatment of aldehyde **38** with 1 equivalent of $NaBH_4$ in THF/H_2O at O°C furnished lactone **39** in good yield. In the ^1H NMR spectrum of **39** the triplet resonating at 3.65 ppm and integrating for 1 proton was assigned to proton α ethyl moiety. The 2 gem coupled doublets at 5.4 ppm and 5.6 ppm each integrating for 1 proton was assigned to the 2 α protons next to the oxygen (-CH_2-O-). The IR spectrum showed absorption at 1743.5 cm^{-1} and 1662.5 cm^{-1} corresponding to the

lactone and pyridone carbonyls respectively.

In conclusion, a short and efficient synthesis of disubstituted deoxycamptothecin has been achieved in 14 short steps starting from glycine ester. A noteworthy feature of this synthesis is that this derivative in turn could serve as an important synthon common for the synthesis of other two commercially important derivatives of camptothecin *viz*. irrinotecan and topotecan without putting any extra efforts to introduce substituents at 7 and 10 position, which would otherwise, become very difficult directly from camptothecin.

Experimental Procedure :

Benzyl 3-allyl-9-hydroxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate 32a:



32a

To a 2g (6.04 mmol) of â-keto ester in 10 ml of ethyl alcohol was added 0.56 g (7.55 mmol) of aniline, followed by the addition of 1 drop of dil. HCl. The solution was refluxed for 15 hrs. The reaction mixture was then cooled and concentrated on rotary evaporator. The residue was then mixed with 25 ml 10% HCl solution, extracted with 2x25 ml portions of dichloromethane. The organic layer was then washed with 25ml of saturated solution of $NaHCO_3$ and finally with 25 ml of water. The solution was then dried (anhydrous Na_2SO_4), filtered and concentrated to furnish a residue, which on column purification furnished 2.0g of enamine in 85% yield.

The solution of 1g (2.8 mmol) of enamine in 25ml of diphenyl ether was refluxed for 0.5 hr. The temperature was maintained between 240ºC to 260ºC. After the completion of reaction, diphenyl ether was removed under high vacuum distillation. The residue on column purification (SiO_2) by EtOAc as eluent furnished 0.67g of phenol **32a** in 75% yield as a sticky solid.

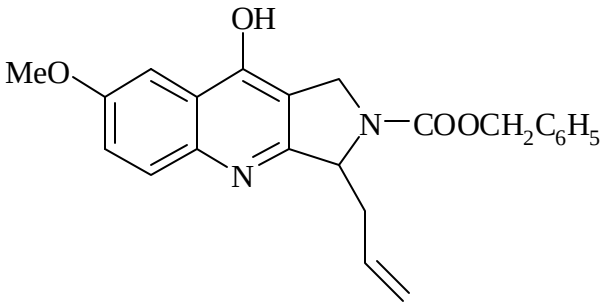
IR cm^{-1}: 1705, 1630, 1580, 1472, 1355.

^1H NMR (200 MHz):δ 2.7-3.2(m, 2H), 4.4-5.2(m, 3H). 5.3(s, 2H –$\underline{CH_2}$Ph), 5.35-5.5(m, 2H), 5.5-5.58(m, 1H), 7.3(m, 6H), 7.55(t, J=7.5 Hz 1H), 7.75(t, J=8 Hz 1H), 8.4(d,

J=8 Hz 1H), 12.95(br s, 1H aromatic –OH).

^{13}C NMR (50 MHz): 36 (t), 37 (t), 50.3 (t), 62.8 (d), 67.5 (t), 120 (t), 124 (d), 125 (d), 131 (d), 132 (d), 136.5 (s), 141 (s), 151 (s), 154 (s), 174 (s).

Benzyl 3-allyl-9-hydroxy 7-methoxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate 32b:



32b

To a 2g (6.04 mmol) of â-keto ester in 10 ml of ethyl alcohol was added 0.93g (7.55 mmol) of p-anisidine, followed by the addition of 1 drop of dil.HCl. The solution was refluxed for 15 hrs. The reaction mixture was then cooled and concentrated on rotary evaporator. The residue was then mixed with 25 ml 10% HCl solution, extracted with 2x25 ml portions of dichloromethane. The organic layer was then washed with 25 ml of saturated solution of $NaHCO_3$ and finally with 25 ml of water. The solution was then dried over anhydrous Na_2SO_4, filtered and concentrated to furnish a residue which on column purification furnished 2.4g of condensation product in 80% yield. The solution of 1g (2.4 mmol) of enamine in 150 ml of diphenyl ether was refluxed in boiling diphenyl ether for 15 minutes. After the completion of reaction, diphenyl ether was removed under high vacuum distillation. The residue on column purification by EtOAc as eluent furnished 0.65g of phenol **32b** in 73% yield as white coloured solid. m.p. 222.6°C.

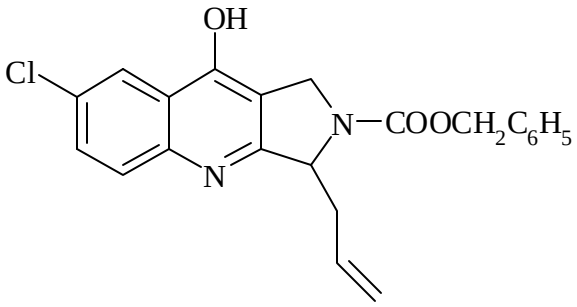
^{1}H NMR (200 MHz):δ 2.5-3.00(m, 2H), 3.8(s, 3H – O<u>Me</u>), 4.3-5.00(m,5H), 5.2(s, 2H, -<u>CH$_2$</u>Ph), 5.2-5.5(m, 1H), 6.8-7.8(m, 8H), 12.2 (br s, 1H phenolic-OH).

^{13}C NMR (50 MHz):35.44(t), 36.83(t), 50.76(t), 55.2(q), 61.75(d), 66.97(t), 119.76(t),

120.6(d), 126.6(d), 127.96(d), 128.98(d), 131.67(d), 156.11(s), 172.47(s).

Mass: 390, 349, 254, 214, 199, 171, 91.

Benzyl 3-allyl-9-hydroxy 7-chloro 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate 32c:



32c

To a 2g (6.04 mmol) of â-keto ester in 10 ml of ethyl alcohol was added 0.96g (7.55 mmol) of p-chloro aniline, followed by the addition of 1 drop of dil.HCl. The solution was refluxed for 15 hrs. The reaction mixture was then cooled and concentrated on rotary evaporator. The residue was then mixed with 25 ml 10% HCl solution, extracted with 2x25 ml portions of dichloromethane. The organic layer was then washed with 25ml of saturated solution of $NaHCO_3$ and finally with 25 ml of water. The solution was then dried and concentrated which on column purification furnished 2.4g of enamine in 88% yield.

The solution of 1g (2.8 mmol) of enamine in 25ml of diphenyl ether was refluxed for 0.5 hr. The temperature was maintained between 240ºC to 260ºC. After the completion of reaction, diphenyl ether was removed under high vacuum distillation. The residue on column purification by EtOAc as eluent furnished 0.65g of phenol **32c** in 72% yield as yellow coloured sticky solid.

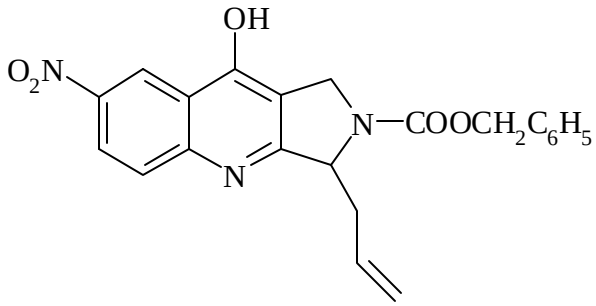
IR cm^{-1}:1708, 1633, 1566, 1463, 1407.

^1H NMR (200 MHz): δ 2.7-3.3 (m, 2H, -$\underline{CH_2}$-CH=CH_2), 4.4-5.2 (m, 3H), 5.3 (s, 2H,–CH_2Ph), 5.55 (m, 1H, -CH_2-$\underline{CH}$=CH_2), 7.35 (s, 5H, aromatic), 7.55 (d, J=8 Hz 1H), 7.65 (d, J=8 Hz 1H), 8.3 (s, 1H), 12.85 (br s, 1H).

^{13}C NMR (50 MHz):36.26 (t), 37.4 (t), 50.63 (t), 62.95 (d), 67.84 (t), 120 (t), 121 (d), 124 (d), 126.6 (d), 127.97 (d), 128.78 (d), 131.39 (d), 132.68 (d), 139 (s, -C-Cl), 151.31 (s), 154.66 (s), 173.3 (s).

Mass: 394, 353, 219, 183, 91.

Benzyl 3-allyl-9-hydroxy 7-nitro 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate 32d:



32d

To a 1.5g (4.5 mmol) of â-keto ester in 10 ml of ethyl alcohol was added 0.78g(5.60 mmol) of p-nitroaniline,followed by the addition of 1 drop of dil. HCl. The solution was refluxed for 15 hrs. The reaction mixture was then cooled and concentrated on rotary evaporator. The residue was then mixed with 25 ml 10% HCl solution, extracted with 2x25 ml portions of dichloromethane. The organic layer was then washed with 25 ml of saturated solution of $NaHCO_3$ and finally with 25 ml of water. The solution was then dried and concentrated which on column purification furnished 1.8g of condensation product in 86% yield. The solution of 1g .(2.2 mmol) of enamine in 25 ml of diphenyl ether was refluxed in boiling diphenyl ether for 45 minutes. After the completion of reaction, diphenyl ether was removed under high vacuum distillation. The residue on column purification by EtOAc as eluent furnished 0.56g of phenol **32d** in 62% yield. m.p. 231.5° C.

IR cm^{-1}:3203, 3018, 1701, 1641, 1471, 1456, 1340, 1227, 1072.

^{1}H NMR (200 MHz):δ 2.7-3.3 (m, 2H), 4-4.3 (m, 2H), 4.35-5.00 (m, 3H), 5.5 (m, 1H), 7.2 (m, 5H, Ph), 7.35 (d, 1H J=8 Hz), 8.25 (d, 1H J=8 Hz), 8.9 (s, 1H), 12.35 (br s,1H).

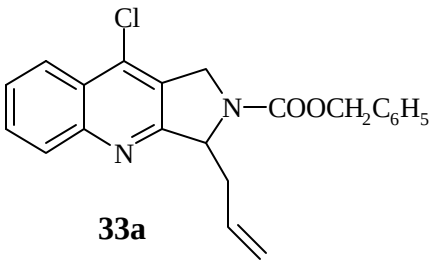
^{13}C NMR (50 MHz):34.88 (t), 36.21 (t), 49.99 (t), 62.49 (d), 66.68 (t), 119.65 (t), 120.68(d), 121.67 (d), 126.19(d), 127.85 (d), 128.36 (d), 128.95 (d), 131.96 (d), 136.92 (s), 142.81 (s), 144.17 (s), 150.41 (s), 153.69 (s), 171.99 (s).

Mass: 405, 364, 271, 230, 184, 91.

General procedure for chlorination of phenol:

To a 1 mmol solution of phenol in 10 ml of diphenylether, was added 1.2 mmol of $POCl_3$. The solution was then refluxed for 4 hrs. After completion of reaction, it was cooled and quenched with 25 ml of ice cold water. The solution was then neutralised with 25 ml of liquor ammonia solution and extracted with 25x3 ml portions of EtOAc. The organic layer was then concentrated and the compound was purified through column chromatography (SiO_2).

Benzyl 3-allyl-9-chloro 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate 33a:



33a

Appearance : viscous liquid.

Yield: 58%

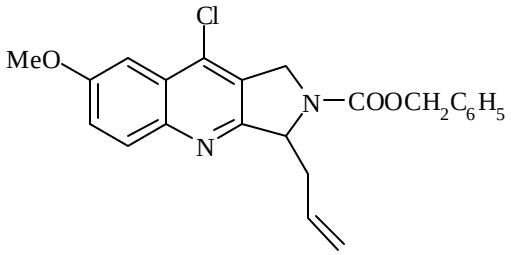
IR cm^{-1}: 1715, 1626, 1590, 1411, 1385, 1260.

^{1}H NMR (200 MHz): δ 2.7-3.3 (m, 2H), 4.3(m, 1H), 4.6-5.2 (m, 4H), 5.3 (s, 1H), 5.5 (m, 1H), 7.4(m, 5H), 7.7(t, J=7 Hz 1H), 7.9 (t, J=7 Hz 1H), 8.2 (d, J=8 Hz 1H), 8.3 (d, J=8 Hz 1H).

^{13}C NMR (50 MHz): 37.00(t), 38.36(t), 50.0(t), 64.05(d), 67.0(t), 120(t), 123.5(d), 127.3(d), 128(d), 130(d), 132(d), 136(s), 149(s), 154.81(s), 162(s).

Mass: 378, 245, 202, 91.

Benzyl 3-allyl-9-chloro-7-methoxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate 33b:



33b

Appearance : viscous liquid.

Yield: 86%

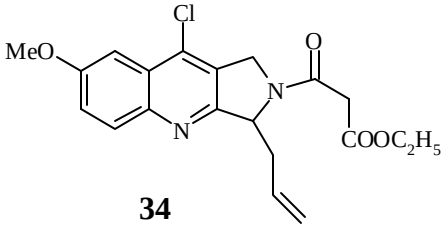
IR cm^{-1}: 1702, 1622, 1502, 1456, 1424, 1180.

^{1}H NMR (200 MHz):δ 2.7-3.4(m, 2H), 4.05(s, 3H –O<u>Me</u>), 4.6-5(m, 4H), 5.3(s, 2H), 5.5(m, 1H –<u>CH</u>=CH_2), 7.4(m, 7H), 8.1(br s. 1H).

^{13}C NMR (50 MHz): 36.85 (t), 38.21 (t), 50.16 (d), 55.38 (q), 63.17 (d), 63.72 (d), 66.88 (t), 100.99 (d), 118.93 (t), 122.39 (d), 126.1 (d), 127.97 (d), 128.38 (d), 130.69 (d), 132.16 (d), 136.57 (s), 144.99 (s), 154.05 (s), 158.37 (s).

Mass: 408, 367, 274, 232, 198, 91.

Ethyl-2-carbethoxy acetyl 3-allyl-9-chloro-7-methoxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline 34:



34

To a stirred solution of 1.2g (2.9 mmol) of chloroquinoline **33b** and 4.4g (29 mmol) of NaI in dry acetonitrile, was added 3.2g (29 mmol) of Me_3SiCl dropwise under N_2 atmosphere. The reaction mixture was stirred for 1 hr, and after completion of reaction (TLC) 25 ml of 20% solution of $Na_2S_2O_3$ was added and aqueous phase was extracted with 3x30 ml portions of EtOAc. The combined organic layer was then mixed with 50 ml of 20% solution of HCl, whereby pure amine goes into the aqueous layer. The aqueous layer was further extracted with 2x20 ml portions of EtOAc. The aqueous layer was then neutralized with 50 ml of liquor ammonia, which was then extracted with 3x20 ml portions of DCM. The combined organic layer was then dried using Na_2SO_4, filtered and concentrated to furnish 0.51g of pure amine in 63% yield as viscous liquid.

To this ice cold stirred solution of 0.51g (1.86 mmol) of amine in 25 ml of dichloromethane, was added 0.52g (3.72 mmol) of K_2CO_3 and 0.42g (2.79 mmol) of carbethoxyacetyl chloride dropwise. The solution was stirred for 3 hrs, and at the end of reaction 25 ml of water was added. The organic layer was then separated and the aqueous layer was extracted with dichloromethane (2x25 ml). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to furnish a residue which on column purification furnished 0.49g of amide **34** as viscous oil in 67% yield.

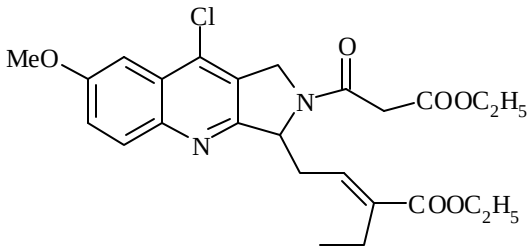
IR cm^{-1}:1660.

^{1}H NMR (200 MHz):δ 0.8 (t, 3H J=8 Hz $\underline{H_3C}CH_2$), 2.8-3.3 (m, 2H $\underline{H_2C}$-CH=CH_2), 3.35 (d, 1H J=2 Hz $\underline{H_2C}COOC_2H_5$), 3.6 (d, 1H J=2 Hz $\underline{H_2C}COOC_2H_5$), 4.0 (s, 3H $\underline{H_3C}$-O), 4.25 (q, 2H, J=7 Hz COO$\underline{CH_2}CH_3$), 4.3 (t, J=6 Hz 1H), 4.8-5.15 (m, 2H), 5.15-5.7 (m, 2H), 6.9 (m, 1H), 7.15 (s, 1H), 7.45 (d, J=8 Hz 1H), 8.05 (d, J=8 Hz 1H).

^{13}C NMR (50 MHz): 13.82 (q), 36.08 (t), 39.06 (t), 41.89 (t), 50.93 (t), 51.63 (t), 55.30 (q), 61.26 (t), 63.39 (d), 100.88 (d), 102.87 (d), 119 (t), 120.03 (d), 121.76 (d), 127.13 (d), 128.19 (d), 131.65 (d), 131.87 (d), 145.12 (s), 157.36 (s), 158.32 (s), 164.49 (s), 166.81 (s).

Mass: 388, 233.

Ethyl-2-carbethoxy acetyl 9-chloro-7-methoxy 1, 3-dihydro-2H-pyrrolo[4, 3-b]quinoline-3-[(2-alkyl)-2-butenoate] 35:



35

To a stirred solution of 0.45g (1.16 mmol) of amide **34** in 6ml of 1, 4-dioxane and 2 ml of water was added, a catalytic amount of OsO_4 and was stirred continuously for 5 mins, a black coloured complex appeared. To this complex was added 0.55g (2.55 mmol) of $NaIO_4$ in small portions at a time, the solution was stirred further for 4 hrs. After completion of reaction, 10 ml of water was added and the crude aldehyde was extracted with 2x25 ml of ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish 0.45g of aldehyde in 96% yield. To a crude solution of 0.45g (1.15 mmol) of aldehyde in 10 ml of dichloromethane was added 0.54g (1.43 mmol) of Wittig salt (prepared from α bromobutyrate and triphenyl phosphine), the solution was stirred at room temperature under N_2 atmosphere for 6 hrs. The reaction mixture was then concentrated under reduced pressure to furnish a residue which on column purification (SiO_2) furnished 0.52g of α, β-unsaturated ester **35** in 92% yield as a viscous oil.

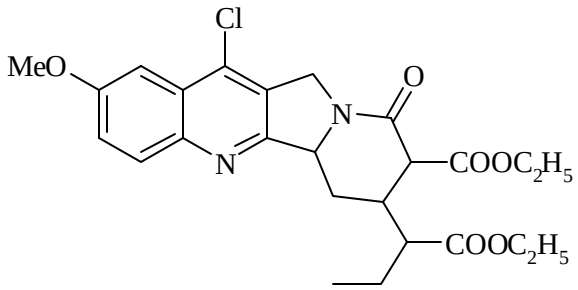
IR cm^{-1}: 1714.6.

^{1}H NMR (200 MHz):δ 0.8 (t, 3H J=8 Hz $\underline{H_3C}$-CH_2), 1.2 (t, 3H J=7 Hz -$COOCH_2\underline{CH_3}$), 1.3 (t, 3H J=7 Hz -$COOCH_2\underline{CH_3}$), 2.2 (m, 3H), 3.1 (m, 1H), 3.4 (d, J=2 Hz 1H), 3.6 (d, J=2 Hz 1H), 3.95 (s, 3H $\underline{H_3C}$-O), 4.1 (q, 2H J=7 Hz –$COO\underline{CH_2}CH_3$), 4.25 (q, 2H J=7 Hz $COO\underline{CH_2}CH_3$), 4.4-5.1 (m, 2H), 5.5 (d, 1H J=17 Hz), 6.5 (t, 1H J=7 Hz olefinic), 6.9 (s, 1H), 7.45 (d, J=7 Hz 1H), 8.05 (d, J=7 Hz 1H).

^{13}C NMR (50 MHz): 13.6 (q), 13.8 (q), 19.67 (t), 31.28 (t), 41.50 (t), 41.94 (t), 50.91 (t), 52.05 (t), 55.4 (q), 59.99 (t), 61.32 (t), 62.20 (t), 63.15 (d), 101.05 (d), 101.71 (d), 122.99 (d), 126.23 (s), 126.5 (s), 130.53 (d), 134.24 (d), 145.23 (s), 157.51 (s), 158.54 (s), 159.35 (s), 164.71 (s), 166.99 (s).

Mass: 347, 233, 91.

7-[1-Ethoxycarbonyl)-propyl]-5b, 6, 7, 8, 9, 11-hexahydro-8-(ethoxycarbonyl)-indolizino[1,2-b] chloro methoxy quinoline-9-one 36:



36

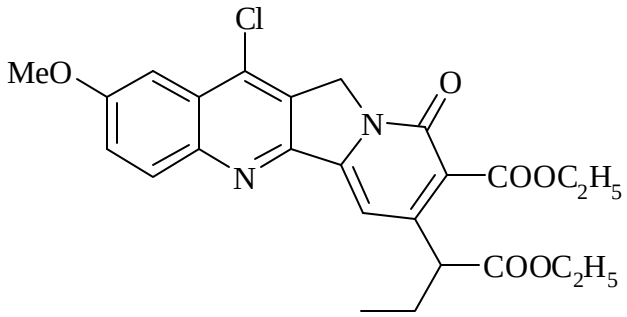
To a stirred suspension of 0.038g (1.6 mmol) of NaH (50% suspension in oil prewashed with 3x5 ml of dry pet.ether) in 5ml of dry THF was added 0.4g (0.82 mmol) of compound **35** in 2ml of THF dropwise. The solution was stirred for 45 minutes. At the end of the reaction 10 ml saturated solution of ammonium chloride was added. The aqueous layer was extracted with 3x10 ml of EtOAc. The combined organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Column purification (SiO_2) of the residue furnished 0.34g of tetrahydropyridone **36** in 85% yield as a viscous liquid.

IR cm^{-1}: 1732, 1658.7.

^{1}H NMR (200 MHz):δ 1.00 (t, 3H J=7 Hz $-H_2C\underline{CH_3}$), 1.3 (t, 3H J=7 Hz $-COOCH_2\underline{CH_3}$), 1.35 (t, J=7 Hz $-COOCH_2\underline{CH_3}$), 1.65-2.1 (m, 2H $\underline{CH_2}CH_3$), 2.25-3.0 (m, 2H), 3.6(d, 1H J=8 Hz CO$\underline{CH}$COOEt), 4.0 (s, 3H O$\underline{CH_3}$), 4.25 (m, 2H COO$\underline{CH_2}CH_3$), 4.5-5.5 (m, 2H), 7.45 (m, 2H), 8.0 (d, J=8 Hz 1H).

^{13}C NMR (50 MHz): 12.19 (q), 14.02 (q), 23.07 (t), 28.62 (t), 35.2 (d), 48.3 (t), 49.09 (d), 51.7 (d), 55.23 (q), 59.3 (d), 60.26 (t), 61.07 (t), 100.99 (d), 122.61 (d), 127.09 (s), 131.28 (d), 135.77 (s), 145.62 (s), 159.11 (s), 166.57 (s), 169.69 (s), 173.99 (s).
Mass: 488, 413, 299, 246.

8-(Ethoxycarbonyl)-7-[1-(ehoxycarbonyl)propyl]-9, 11-dihydroxyindolizino [1, 2b] chloro methoxy quinoline-9-one 37:



37

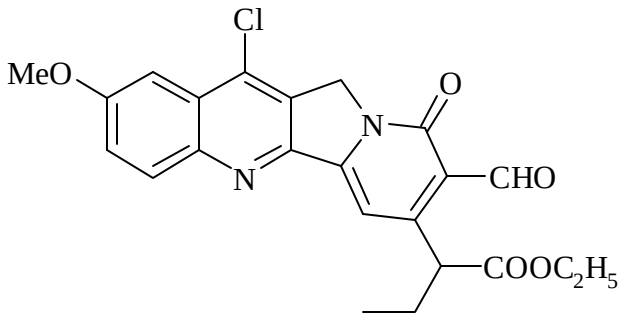
To a solution of 0.2g (0.41 mmol) of tetrahydropyridone **36** in 5 ml of dioxane was added 0.19g (0.82 mmol) of DDQ. The solution was refluxed for 1 hr. After completion of the reaction the mixture was cooled and diluted with 10 ml of benzene followed by the addition of 10 ml of saturated solution of $NaHCO_3$. The organic layer was separated whereas the aqueous layer was further extracted with 2x10 ml of benzene. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish a residue which on column purification (SiO_2) furnished 0.16g of pyridone **37** as yellow coloured solid in 80% yield. m.p. 222.6°C.
IR cm^{-1}: 1606, 1558.7, 1732.
^{1}H NMR (200 MHz): δ 1.05 (t, 3H J=7.5 Hz $CH_2\underline{CH_3}$), 1.25 (t, 3H J=7.5 Hz $COOCH_2\underline{CH_3}$), 1.45 (t, 3H J=7 Hz $COOCH_2\underline{CH_3}$), 1.95 (m, 1H, $CH_2\underline{CH_3}$), 2.25 (m, 1H $CH_2\underline{CH_3}$), 3.75 (t, 1H J=8 Hz), 4.05 (s, 3H $\underline{H_3C}$-O), 4.2 (q, 2H J=7 Hz), 4.5 (q, 2H J=8

MHz), 5.3 (s, 2H $N\underline{CH_2}$), 7.35 (s), 7.45 (s), 7.52 (d 1H J=8 Hz), 8.15 (d 1H J=8 Hz).

^{13}C NMR (50 MHz): 11.96 (q), 14.2 (q), 14.3 (q), 25.75 (t), 50.01 (d), 55.67 (q), 61.51 (t), 61.9 (t), 99.2 (d), 101.06 (d), 124.04 (d), 124.99 (s), 128.01 (s), 131.72 (d), 135.54 (s), 145.8 (s), 149.29 (s), 150.54 (s), 157.85 (s), 159.89 (s), 165.65 (s), 171.56 (s).

Mass : 484, 439, 382, 265.

8-(Formyl)-7-[1-(ethoxycarbony)propyl]-9, 11-dihydroindolizino [1, 2b]-chloro methoxy quinoline-9-one 38:



38

To a 0.03g (0.06 mmol) of pyridone **37** in 12 ml of dry toluene was added 0.094 ml (0.18 mmol) of Dibal-H (2M solution in toluene) dropwise at -78°C under argon atmosphere. The mixture was allowed to stir at -78°C for an additional 2 hrs. The reaction was quenched with 0.094 ml MeOH and 0.025 ml water, the reaction mixture was then warmed to room temperature. The gelatinous precipitate was filtered through celite and the celite washed thoroughly with ethyl acetate. Concentration of the solution on rotary evaporator furnished crude aldehyde, which was purified by column chromatography using 50% ethyl acetate-pet.ether as eluent to furnish 0.016g of pure aldehyde **38** in 58% yield as a viscous liquid.

IR cm^{-1}: 1732, 1678, 1652, 1625, 1514.

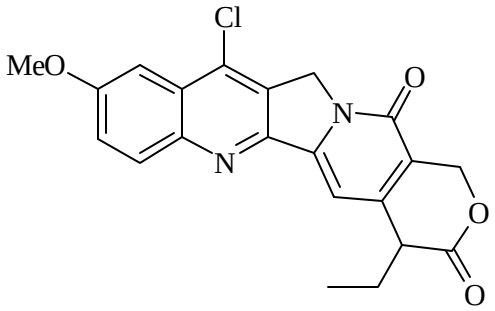
^1H NMR (200 MHz): δ 1.05 (t, 3H, J=7 Hz $H_2C\underline{CH_3}$), 1.25 (t, 3H J=7 Hz $COOCH_2\underline{CH_3}$), 1.9 (m, 1H), 2.25 (m, 1H), 4.05 (s, 3H OMe), 5.15 (t, 1H J=7 Hz), 5.35 (s, 2H, $N\underline{CH_2}$),

7.3 (s, 1H), 7.5 (s, 1H), 7.55 (d, 1H), 8.1 (d, 1H), 10.6 (s, 1H –CHO).

^{13}C NMR (50 MHz): 11.69 (q), 13.82 (q), 25.62 (t), 46.80 (d), 49.96 (t), 55.62 (q), 66.76 (t), 100.2 (d), 101.2 (d), 124.21 (d), 127.7 (s), 128.55 (s), 131.72 (d), 135.54 (s), 146.01 (s), 148.69 (s), 157.95 (s), 160.19 (s), 161.96 (s), 171.99 (s), 191.73 (d).

Mass : 440, 395, 366.

Deoxy-4-ethyl-1H-pyrano[3', 4':6, 7]indolizino[1, 2b] chloro methoxy quinoline-3, 14[4H, 12H]-dione 39:



39

To 0.007g (0.016 mmol) of aldehyde **38** in 2 ml of THF and 0.2 ml of H_2O at 0°C was added 0.0006g (0.016 mmol) of $NaBH_4$ and stirred for 10 mins. The reaction mixture was quenched with 3 ml of 10% HCl and extracted with chloroform. The organic layer was separated and aqueous layer was further extracted with 2x5 ml portions of chloroform. The combined organic layer was then dried over Na_2SO_4, filtered and then concentrated under reduced pressure, the residue on column purification using 60% ethyl acetate-pet.ether as eluent furnished 0.005g of deoxycamptothecin **39** in 79% yield as sticky yellowish solid. m.p. 264.5°C.

IR cm^{-1}:1743.5, 1662.5, 1608.5, 1242.1.

^{1}H NMR (200 MHz):δ 1.1 (t, 3H J=7 Hz $\underline{H_3C}CH_2$), 2.15 (m, 2H), 3.65 (t, 1H, J=6.2 Hz), 4.05 (s, 3H $O\underline{CH_3}$), 5.35 (s, 2H $N\underline{CH_2}$), 5.38 (d, 1H, J=16.68 Hz), 5.58 (d, 1H, J=16.68 Hz), 7.1 (s, 1H), 7.5 (s, 1H),7.55 (d, 1H J=8 Hz), 8.1 (d, 1H J=8 Hz).

^{13}C NMR (125 MHz): 11 (q), 24.99 (t), 45.57 (d), 49.79 (t), 55.59 (q), 65.70 (t), 99.22 (d). 101.31 (d), 120.33 (s), 123.99 (d), 127.70 (s), 131.36 (d), 135.85 (s), 145.71 (s), 146.96 (s), 149.28 (s), 159.74 (s), 170.42 (s).

Mass : 396, 325, 265.

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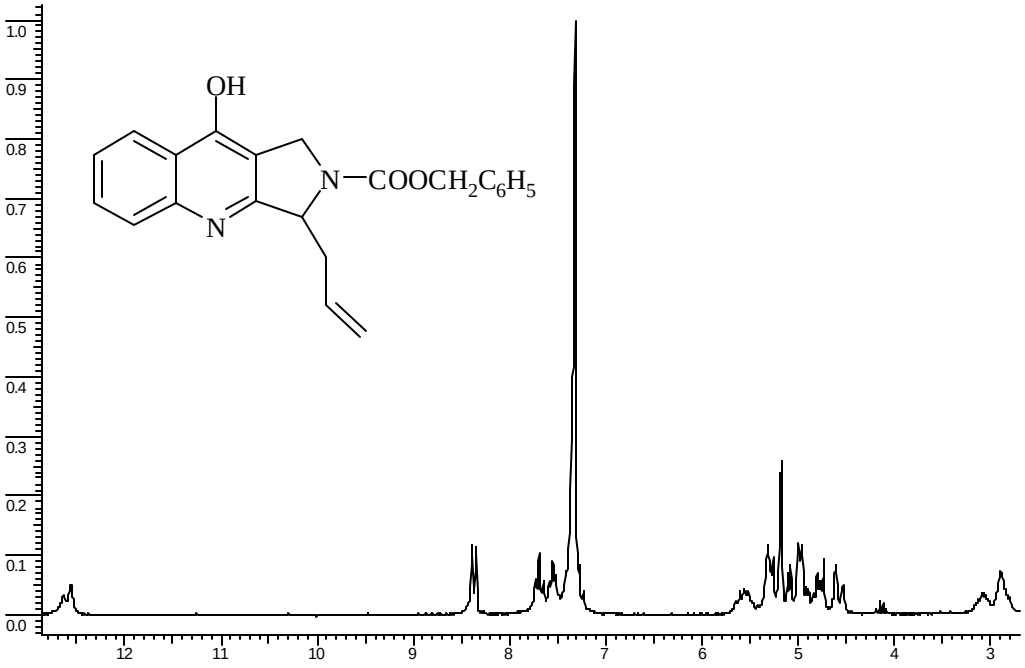
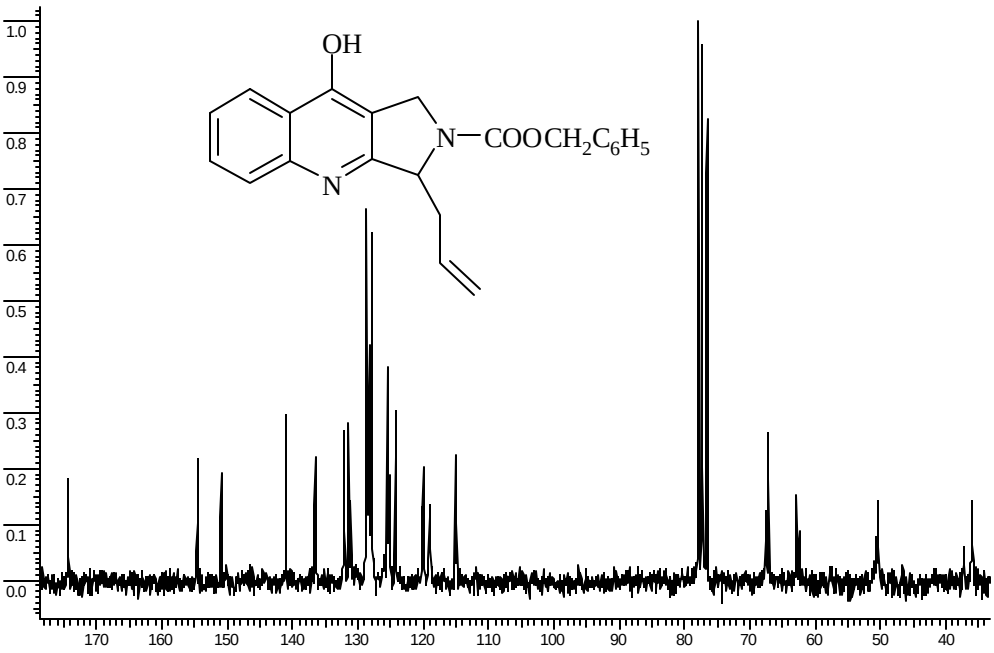
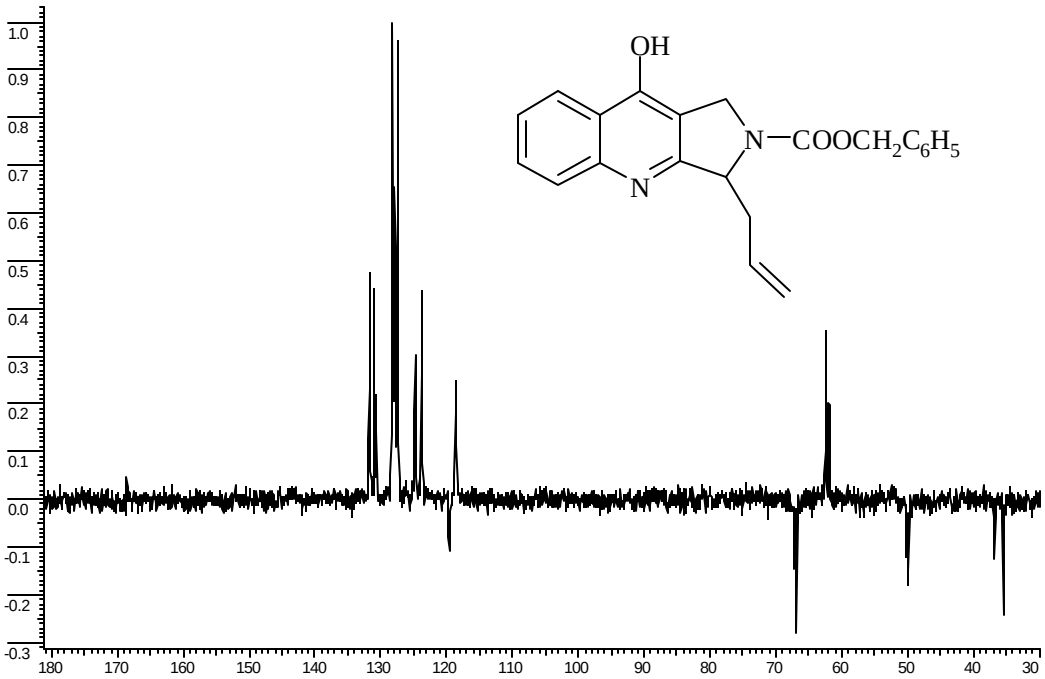


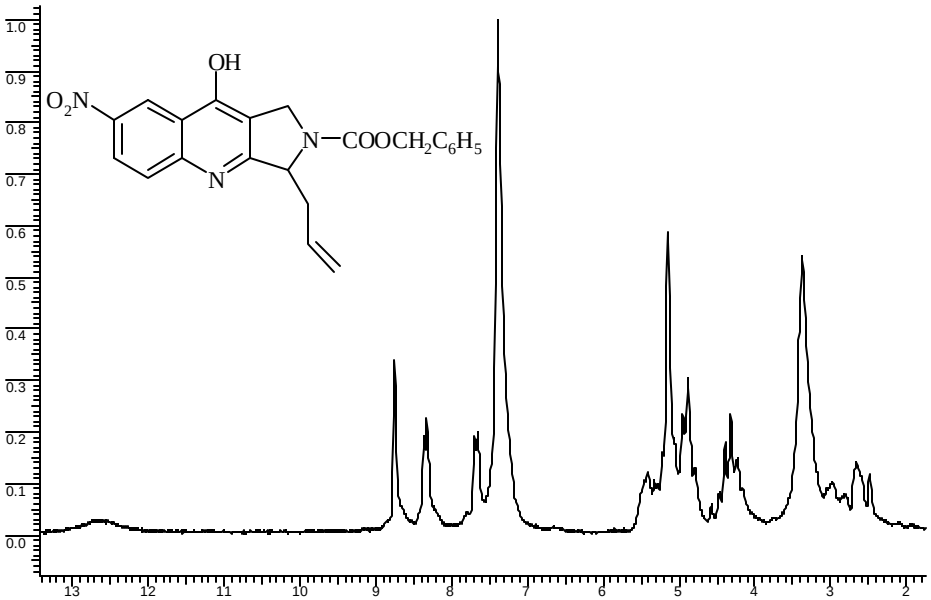
. ^{1}H NMR of benzyl 3-allyl-9-hydroxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate 32a ($CDCl_3$ 200 MHz)



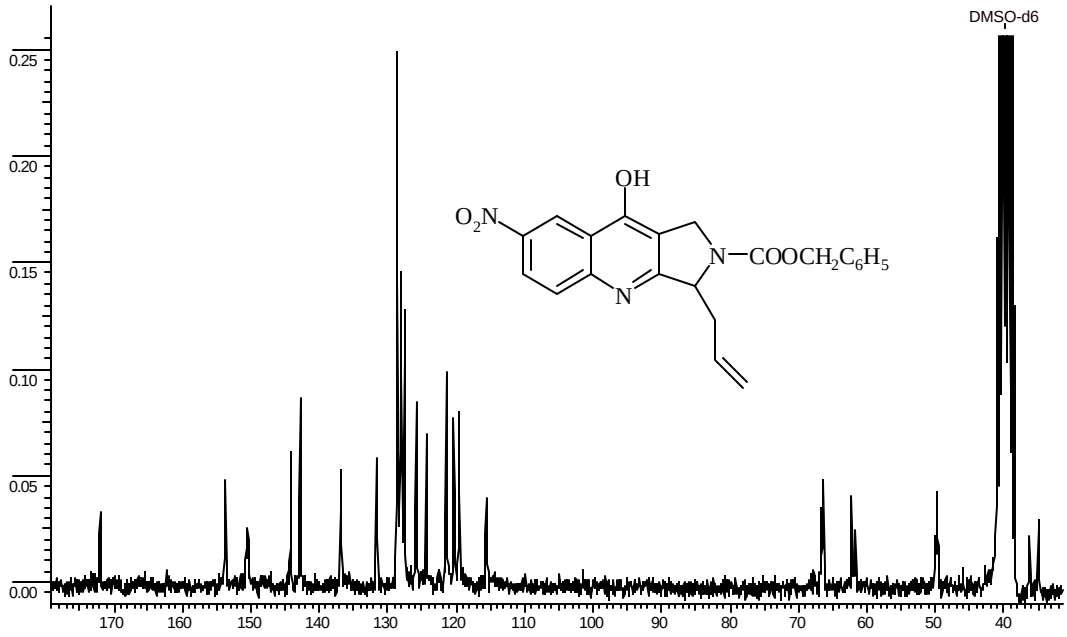
.^{13}C NMR of benzyl 3-allyl-9-hydroxy 2, 3-dihydro-1H-pyrrolo[4, 3-b] quinoline-2 carboxylate ($CDCl_3$ 200 MHz)



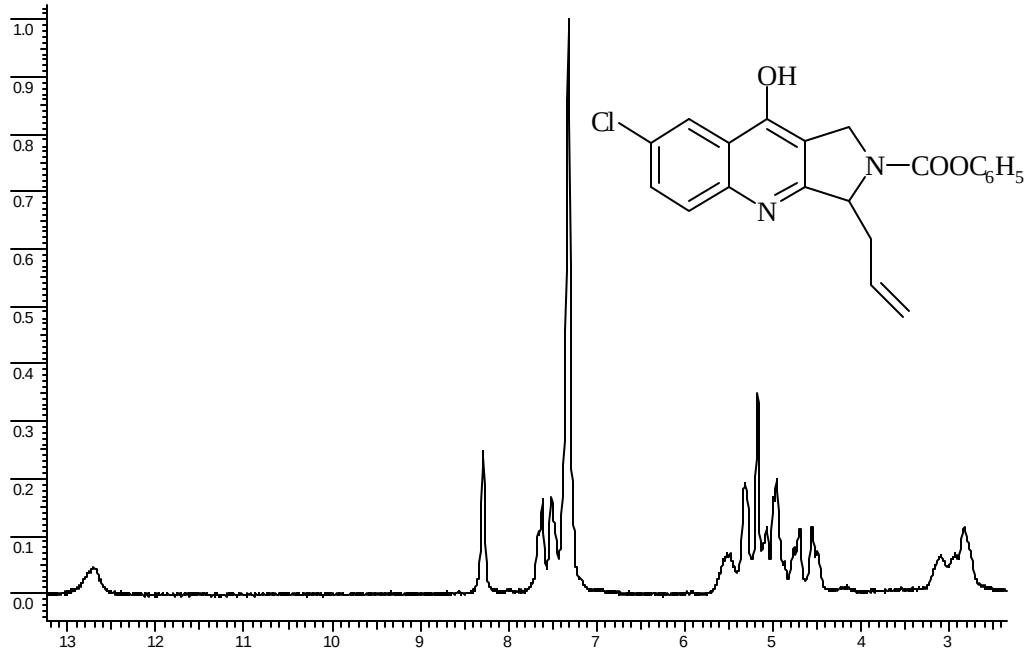
. Dept of benzyl 3-allyl-9-hydroxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate ($CDCl_3$ 200 MHz).



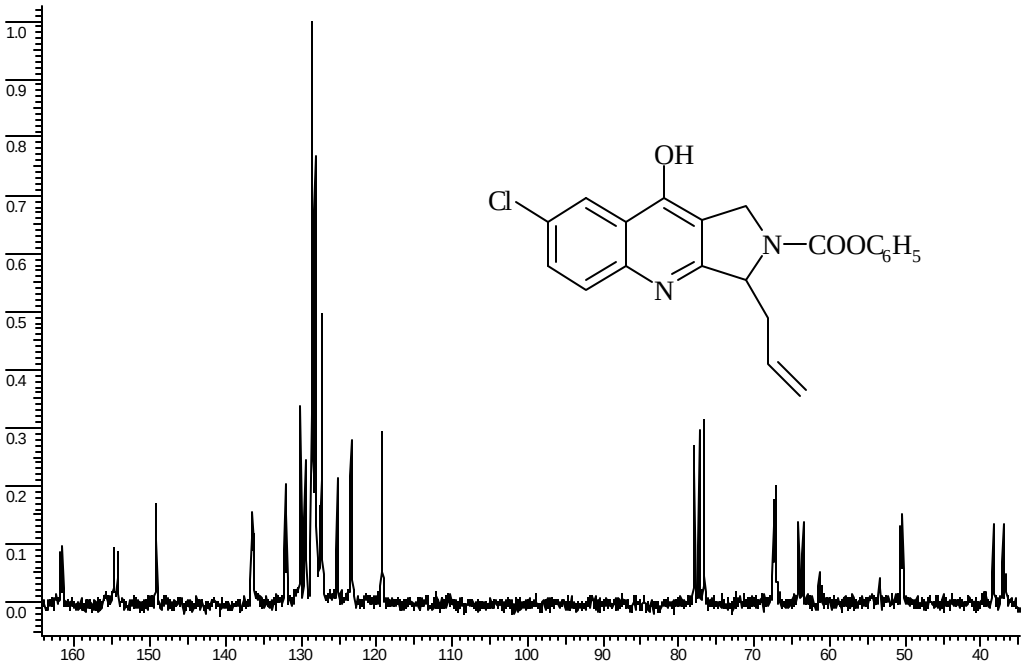
^{1}H NMR of benzyl 3-allyl-9-hydroxy 7-nitro 2, 3-dihydro-1H-pyrrolo[4,3-b] quinoline-2-carboxylate ($CDCl_3$ 200 MHz)



.^{13}C NMR benzyl 3-allyl-9-hydroxy 7-nitro 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate (DMSO-d6 200 MHz)

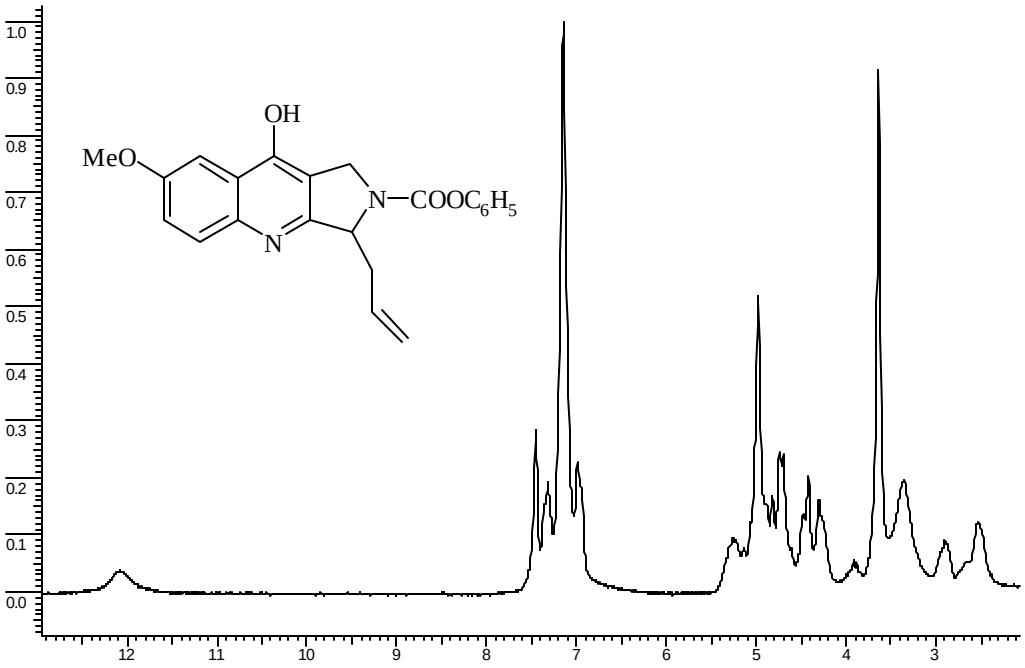


^{1}H NMR benzyl 3-allyl-9-hydroxy 7-chloro 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate ($CDCl_3$ 200 MHz)

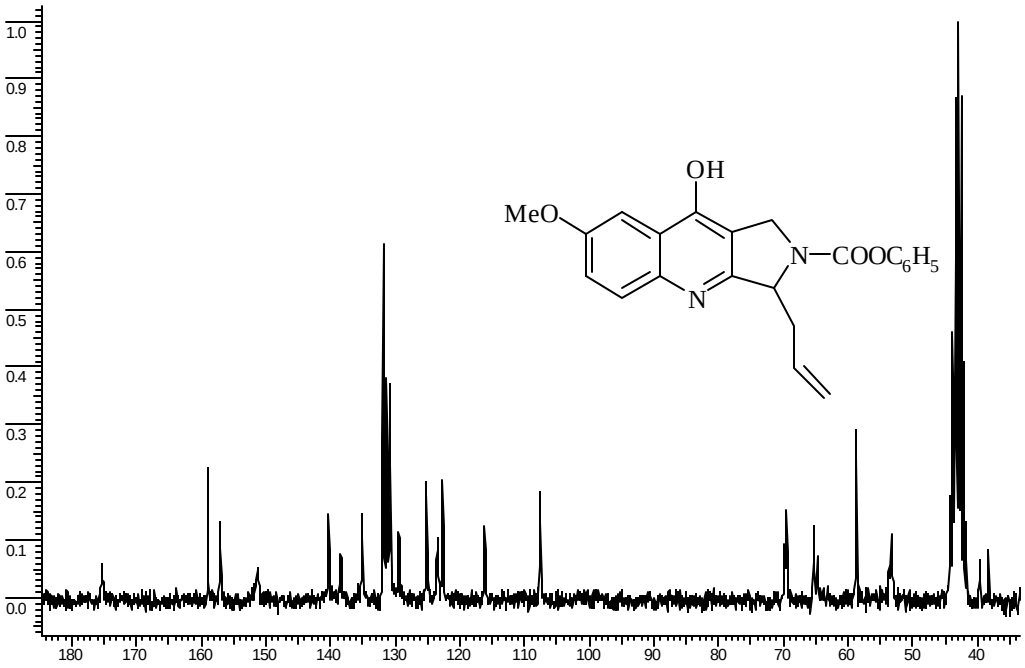


^{13}C NMR benzyl 3-allyl-9-hydroxy 7-chloro 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate ($CDCl_3$ 200 MHz)

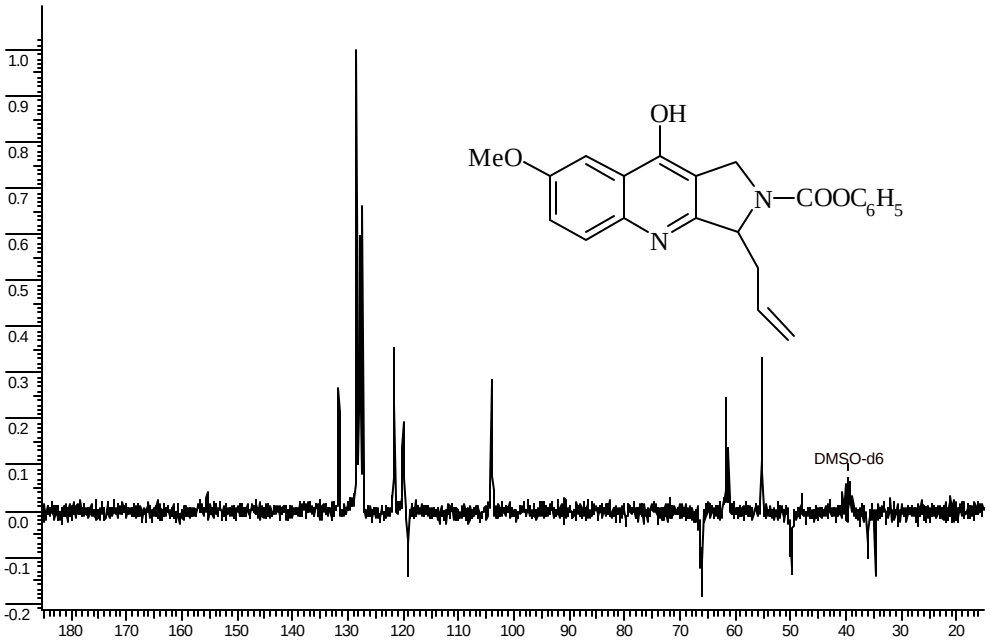
DEPT of benzyl 3-allyl-9-hydroxy 7-chloro 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate ($CDCl_3$ 200 MHz)



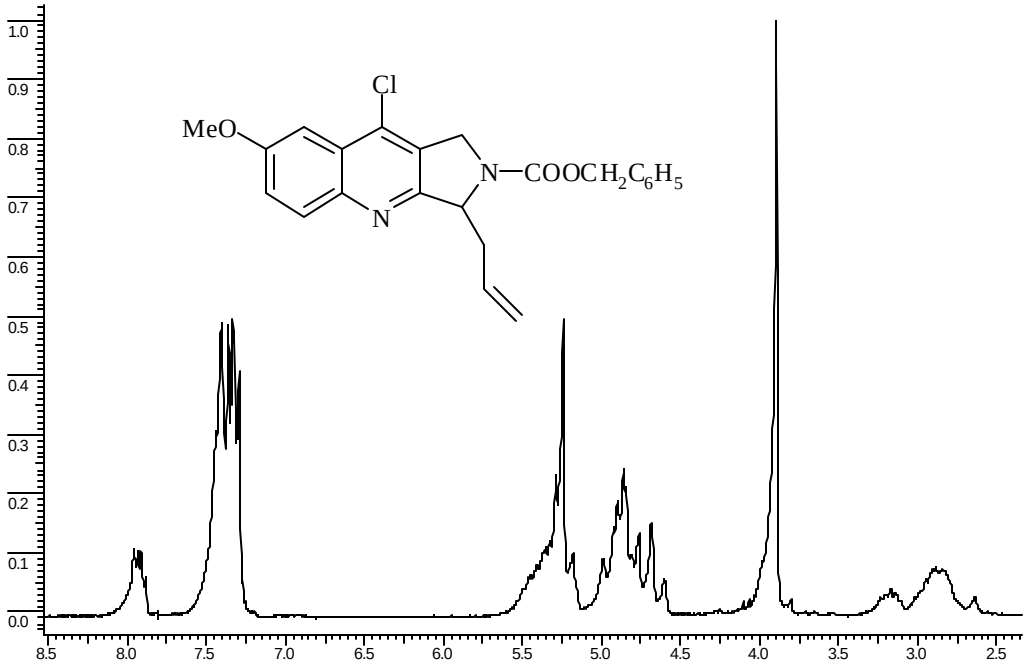
^{1}H NMR benzyl 3-allyl-9-hydroxy 7-methoxy 2, 3-dihydro-1H-pyrrolo[4, 3-b] quinoline-2-carboxylate ($CDCl_3$ 200 MHz)



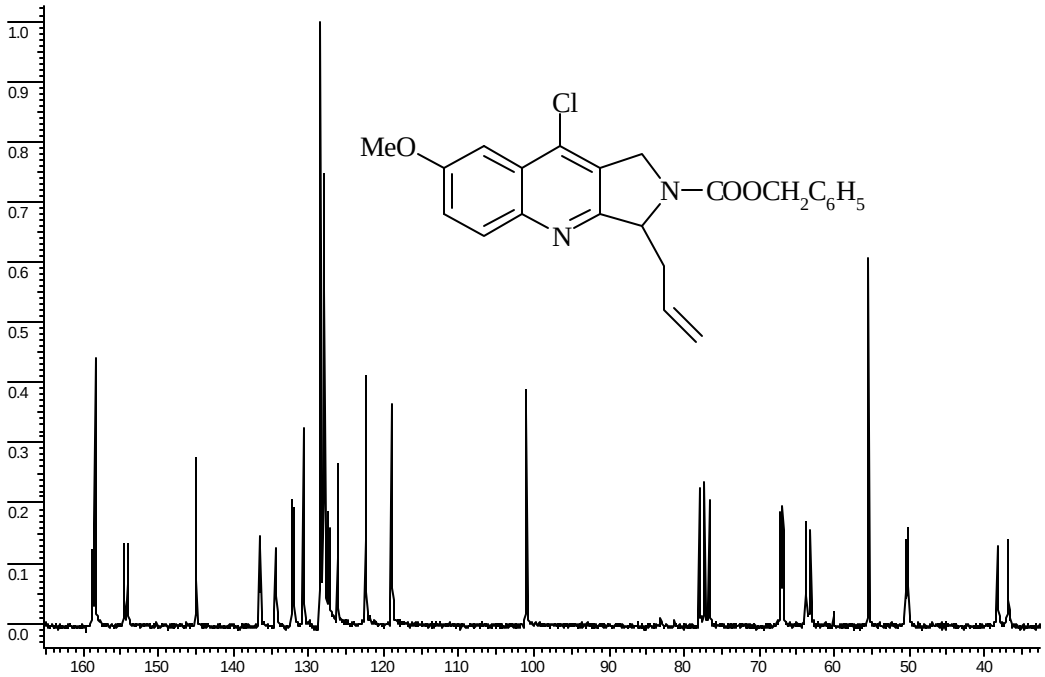
^{13}C NMR benzyl 3-allyl-9-hydroxy 7-methoxy 2, 3-dihydro-1H-pyrrolo[4, 3-b] quinoline-2-carboxylate ($CDCl_3$ 200 MHz)



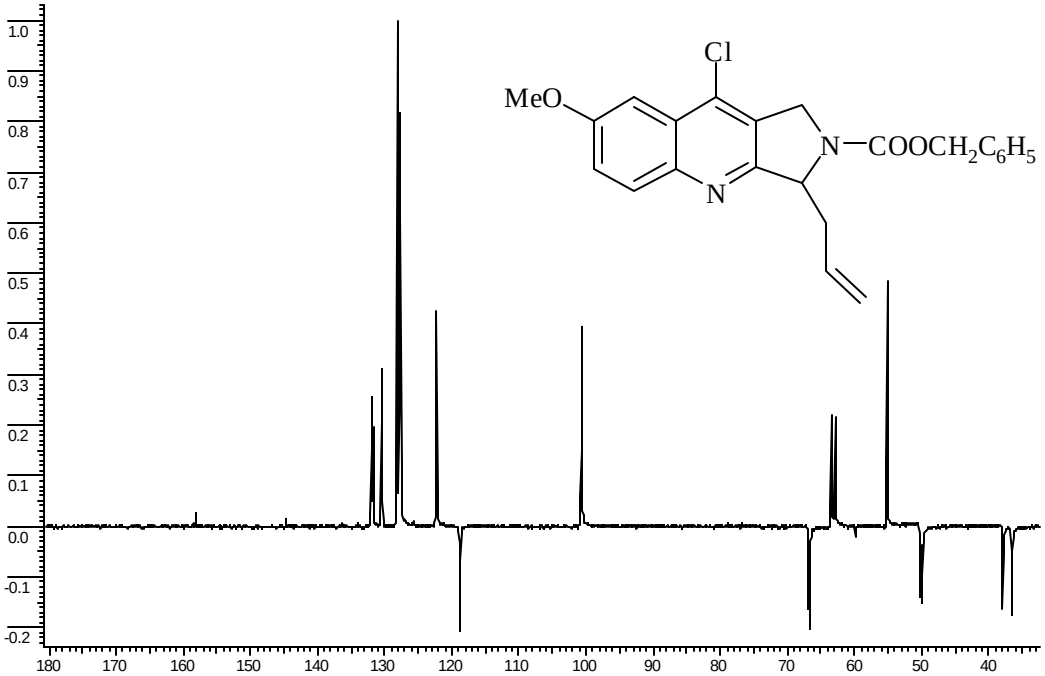
DEPT of benzyl 3-allyl-9-hydroxy 7-methoxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate (DMSO-d6 200 MHz)



^{1}H NMR benzyl 3-allyl-9-chloro-7-methoxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate ($CDCl_3$ 200 MHz)



^{13}C NMR of benzyl 3-allyl-9-chloro-7-methoxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate ($CDCl_3$ 200 MHz)



DEPT of benzyl 3-allyl-9-chloro-7-methoxy 2, 3-dihydro-1H-pyrrolo[4, 3-b]quinoline-2-carboxylate ($CDCl_3$ 200 MHz)

Chapter 2:

Section (a) :

Use of $FeCl_3$ and $FeCl_3$ adsorbed on silica as efficient Lewis acid catalyst in Ionic Diels-Alder reactions of α, β-unsaturated acetals.

The Diels-Alder reactions is a very powerful tool in the arsenal of synthetic chemists. This reaction, due to its generality, efficiency and excellent regio- and stereocontrol has been extensively utilized for construction of six membered rings. The ionic Diels-Alder reaction, which was first observed by Gassman *et al.*[1] is another variant of the Diels-Alder reaction which involves ionic intermediates (cations) as extremely powerful dienophiles. Advantages of the ionic Diels-Alder reaction over conventional Diels-Alder reactions is the excellent stereo, and regioselectivity exhibited by them. Dienophiles utilised in ionic Diels-Alder reactions are neutral species which are transiently converted to charged species *in situ* and undergo facile Diels-Alder reaction to furnish the neutral adducts. Thus, the dienophiles which are unstable and/or undergo polymerization under normal Diels-Alder reactions can be handled efficiently and conveniently as their acetals which are stable and can be stored without decomposition. A variety of Bronsted Acids and Lewis acid TfOH,[2] TMSOTf,[3] $CF_3SO_3Si(CH_3)_3$,[4] $BF_3(OEt)_2$,[5] $Et_3O^+BF_4$,[6] trifluoro acetic anhydride,[7] CF_3SO_3H,[8] electro-generated acid,[9] $TiCl_4$-$Ti(Oi\text{-}Pr)_4$,[11] I_2,[12] $LiClO_4$,[13] $LiClO_4$ (or Nafion-H)[14a] and very recently $InCl_3$[14b] (after completion of the present work) have been utilised as catalysts to effect 4Π+2Π cycloaddition . Although a variety of acids[4,8,9,11,13,14a-b] are known to catalyse the ionic Diels-Alder reactions, most of them are either very strong, and employ harsh conditions as well as involve use of hazardous reagents and involve unattractive reaction conditions thereby limiting their usage.

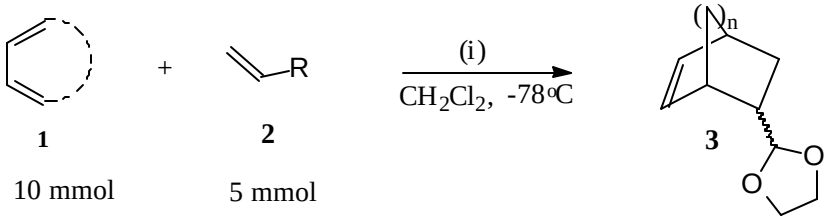
Literature methods :

Literature methods describing ionic Diels-Alder reactions have been categorized and presented according to the acids/reagents used to effect these reactions.

(1). Ionic Diels-Alder reaction of α , β -unsaturated acetals using triflic acid :[2]

Gassman, P. G.; Singleton, D. A.; Wilwerding, J. J.; Chavan, S. P.; *J. Am. Chem. Soc.* **1987,** *109,* 2182-2184.

Scheme 1:



1 **2** **3**

10 mmol 5 mmol

(a) R = $-CH(OC_2H_5)_2$ 31 - 61 %

(b) R = 63 -100 %

(i). 0.1 mmol (2 mol %) of triflic acid in 1,1,2-trichloro-1,2,2-trifluoro ethane.

Different types of 1, 3-dienes and acetals in dichloromethane at -78ºC with 2 mol% of triflic acid in 1, 1, 2-trichloro-1, 2, 2-trifluoroethane were shown to give good yields of the corresponding Diels-Alder adducts as shown in the above scheme-1. In this study acetals derived from ethylene glycol were shown to furnish high yields of the adducts.

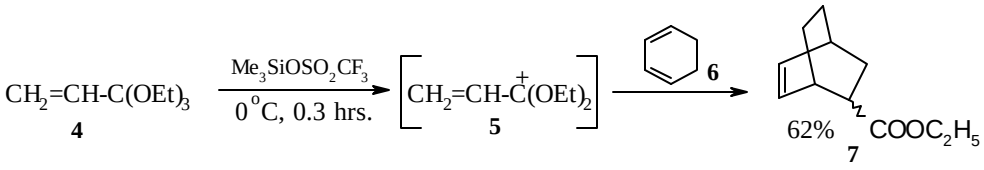
(2). Using trimethyl silyl triflate with acyclic orthoesters (triethyl orthoacrylate) dienophiles :[3]

Gassman, P. G ; Chavan S.P.; *J. Org. Chem.* **1988,** *53,* 2392-2394.

Scheme 2:

Later the concept of ionic Diels-Alder reaction was extended to acyclic orthoesters.

Thus 3, 3, 3-triethoxy propene (triethyl orthoacrylate) was added to a series of 1, 3 dienes in the presence of trimethyl silyl triflate at –78 to 0ºC to produce 53-83% yields



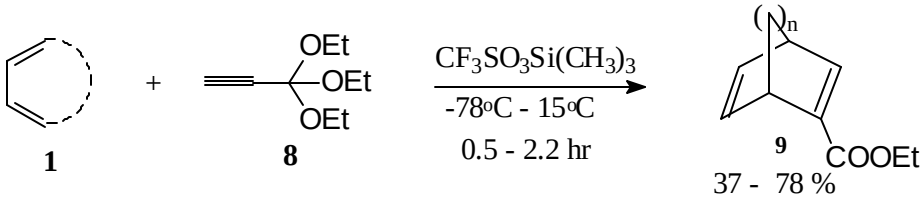
of the adduct.

As shown in the above **scheme 2,** 1, 1-diethoxy allyl cation **5** is an extremely powerful dienophile in Diels-Alder reaction under very mild conditions. In their study the intermediacy of **5** was demonstrated by trapping experiments as well as spectral analysis.

(3). Using trimethylsilyl triflate as Lewis acid with triethyl orthopropiolate : [4]

Gassman, P. G.; Chavan, S. P.; *Tetrahedron Letters,* **1988**, *29*, 3407-3410.

Scheme 3:

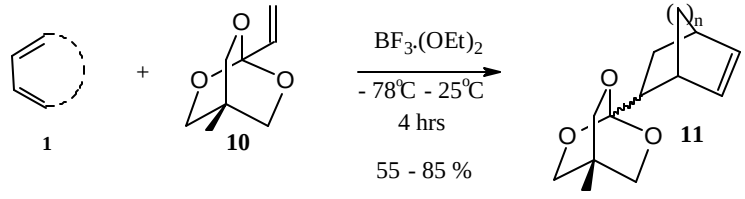


The use of allyl cation and propargyl cations as powerful low-temperature dienophiles in the Diels-Alder reactions was established by now. An extension of this concept was used in this methodology which involved the cycloaddition of acrolein acetals and vinyl ortho esters ot 1, 3-dienes at low-temperature. Thus, 3, 3, 3-triethoxypropyne (triethyl orthopropiolate) was added to a series of 1, 3-dienes at low temperature in the presence of trimethylslilyl triflate to yield the 4Ï+2Ï products of the formal addition of ethyl propiolate to the 1, 3-dienes.

(4). Using boron trifluoride-diethyl ether : [5]

Gassman, P. G; Chavan. S. P. *J. Chem. Soc. Chem. Commun*, **1989,** 837

Scheme 4:

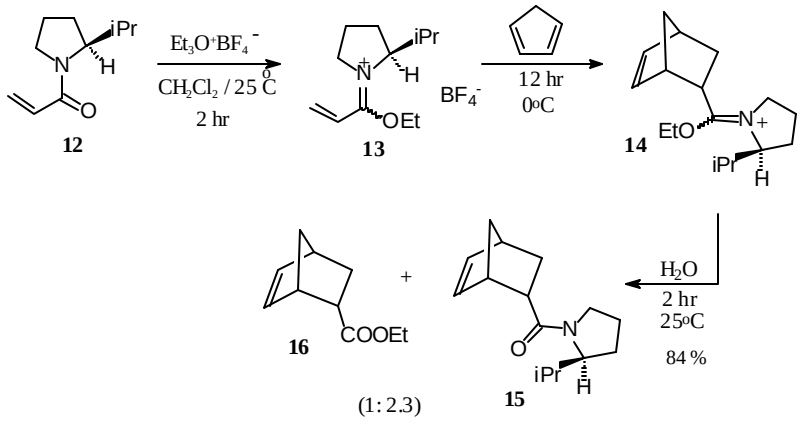


Here the concept was extended to cyclic orthoester and the present study indicated the retention of cyclic orthoester in the product. The authors reported that cyclic orthoester, 1-vinyl-4-methyl-2, 6, 7-trioxabicyclo[2.2.2]octane underwent cycloaddition reactions with various cyclic and acyclic 1, 3-dienes at low temperature with boron trifluoride-diethyl ether as catalyst, to furnish Diels-Alder adduct with overall retention of orthoester protecting group in moderate to good yields.

(5). Diels-Alder reactions involving amides using $Et_3O^+BF_4^-$: [6]

Jung, M. E.; Vaccaro, W. D.; Buszek, K. R. *Tetrahedron Letters*, **1989,** *30*, 1893-1896

Scheme 5:



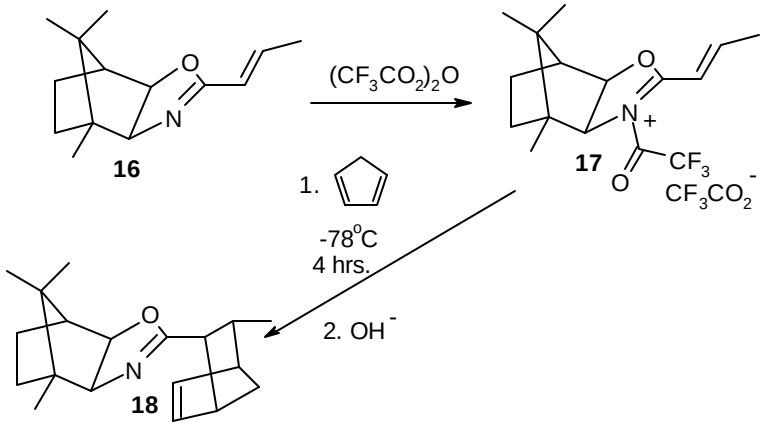
The optically active vinyl alkoxy iminium salt with cyclopentadiene were reacted to give the optically active amides in high yields and with good diastereoselectivity.

(6). Reactions involving oxazoline using trifluoro acetic anhydride :[7]

Povilhes. A.; Uriate, E; *et al. Tetrahedron Letters*, **1989,** *30,* 1395.

Scheme 6:

The authors used chiral á, â-unsaturated oxazoline which was activated with trifluoro acetic anydride as potent dienophiles in the Diels-Alder reactions. The oxazoline on reaction with trifluoro acetic anhydride generates very reactive á, â-unsaturated acyl immonium intermediate **15** which reacts with 1, 3-dienes to give the corresponding Diels-Alder adducts exclusively as *endo* isomer.



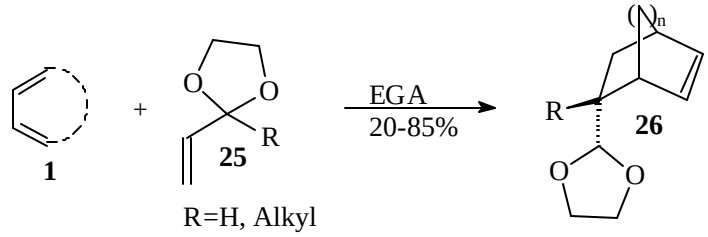
(7). Electrogenerated acid :[8]

Inokuchi, T.; Toru, S.; Sin-ichi, T. *J.Org, Chem* , **1990**, *55,* 3958

Scheme 7:

The electrogenerated acid catalysed reactions of enone acetals and 1, 3-dienes was performed by using electrodes in dichloromethane containing lithium perchlorate and tetrabutyl ammonium perchlorate as a source of acid catalyst. The electrolysis was carried out at -78 C under a constant applied voltage of 15V for 0.2F/mol of electricity.

A variety of cyclic and acyclic dienes were reacted with α, β-unsaturated acetals to furnish the corresponding adducts in moderate to excellent yields.

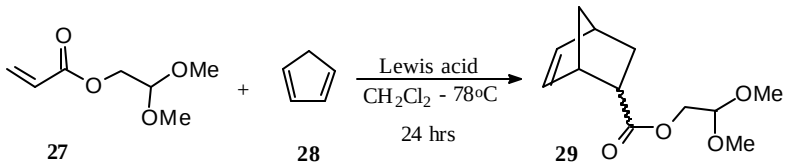


(8). Using different Lewis acid with dienophiles from 2, 2-dimethoxy-ethyl acrylate, 2-oxopropyl acrylate or 2-oxocyclopentyl acrylate : [9]

Hashimoto,Y.; Saigo. K.; Nagashima, T.; Kobayashi, K.; Hasegawa, M. *Tetrahedron*, **1993,** 6349.

Scheme 8:

On treatment with a Lewis acid, 2, 2-dimethoxy ethyl acrylate was readily transformed into a reactive cationic dienophile, and it reacted with dienes under mild conditions to give Diels-Alder adducts in good yields with high stereo- and/or regioselectivity.



A mixture of endo and exo isomers as shown in the table 1

Table 1

The Diels-Alder Reactions of 2, 2-Dimethoxy ethyl acrylate with 1, 3-cyclopentadiene in the presence of various Lewis acids

No.	Lewis acids	Yield (%)	*endo : exo*
1.	$TiCl_4$	85	25 : 1
2.	Me_3SiOTf	41	34 : 1
3.	$BF_3.OEt_2$	21	69 : 1
4.	$SnCl_4$	28	11 : 1
5.	$GaCl_3$	84	45 : 1

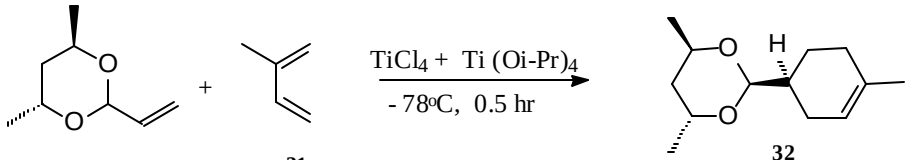
(9). Use of $TiCl_4$/Ti(O i-Pr)$_4$ as Lewis acid catalyst :[10]

Sammakia, T. and Berliner, M. A. *J. Org. Chem*. **1994,** *59,* 6890-6891.

Scheme 9:

Chiral á, â-unsaturated acetals derived from 2, 4-pentanediol were shown to undergo Diels-Alder reactions in the presence of equimolar mixture of $TiCl_4$ and Ti(O i-Pr)$_4$ with dienes. The advantages of this catalyst are as follows.

It is very mild and has to be used in greater than stoichiometric quantities. However, under these conditions no decomposition of the starting materials was observed. It therefore provides products in good selectivities and yields under mild conditions.



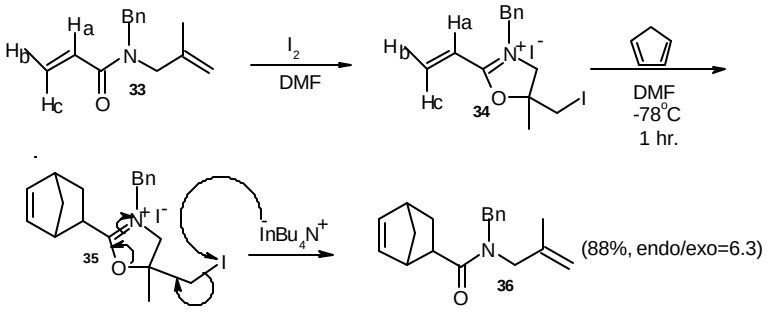
30 **31** **32**

(7.5 : 1)

(10). Using I_2 as Lewis acid :[11]

Kitagawa, O.; Aoki, K.; Inove, T.; Taguchi, T. *Tetrahedron Letters*, **1995,** *36*, 593-596.

Scheme 10:

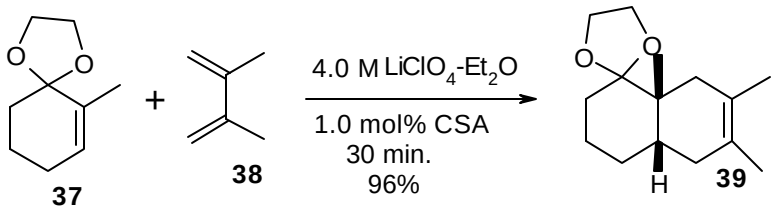


The Diels-Alder reaction of N-allylic enamide and á, â-unsaturated lactam derivatives proceeded in the presence of I_2 at low temperature through a cationic iodolactonisation intermediate.

(11). 4M $LiClO_4$ and 1 mol% Camphor sulphonic acid :[12]

Grieco, P. A.; Collins, J. L.; Handes, S. T. *Synlett*, **1995,** 1155-1157

Scheme 11:



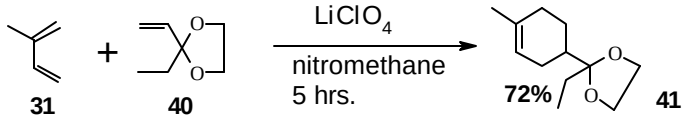
Ketals and orthoesters of unsaturated ketones and esters, respectively, undergo inter- and intramolecular ionic Diels-Alder reactions in the presence of 4.0-5.0M $LiClO_4$-diethyl ether containing a few mol% of camphor sulphonic acid.

12). Use of $LiClO_4$ as Lewis acid :[13a]

Vankar, P. S.; Reddy, M. V.; Kumareswaran, R.; Pitre, S. V.; Roy, R.; Vankar, Y. D *Tetrahedron*, **1999,** *55*, 1099-1110.

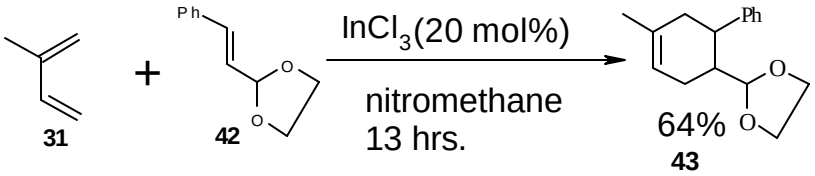
Scheme 12 :

A variety of achiral olefinic acetals were shown to react with isoprene and cyclopentadiene to form the cycloadducts in good to excellent yields when catalysed by 4M $LiClO_4$ in nitromethane or by Nafion-H in dichloromethane.



(13). Use of Indium trichloride as Lewis acid :[13b] Reddy, G.; Kumareswaran, R.; Vankar, Y. D. *Tetrahedron Letters,* **2000,** *41*, 10333-
10336.

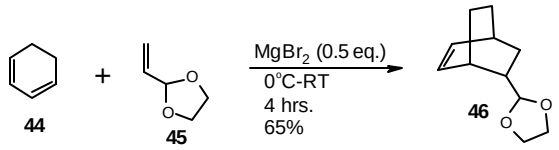
Scheme 13 :



After completion of the present work. Vankar et. al. have demonstrated the utility of $InCl_3$ as an efficient Lewis acid catalyst. Indium trichloride (20 mol%) in nitromethane allows ionic Diels-Alder reaction of a variety of 2, 3-olefinic acetals to form the corresponding cycloadducts in good yields with good *endo* selectivities.

(14). Use of $MgBr_2$ as Lewis acid :[14]

Ph. D. thesis of Krishna S. Ethiraj submitted to University of Pune June 1998



Our group has already demonstrated the utility of $MgBr_2$ as Lewis acid in ionic Diels-Alder reaction. The oxophilic propensity of $MgBr_2$[15,16] was exploieted and $MgBr_2$ was shown to be a mild reagent to effect ionic Diels-Alder reaction. Good to excellent yields

of the adduct were obtained by utilising $MgBr_2$ as Lewis acid.

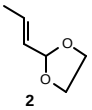
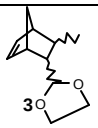
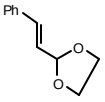
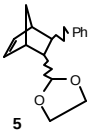
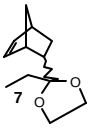
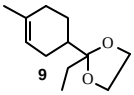
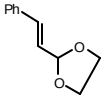
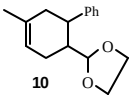
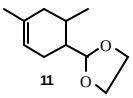
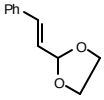
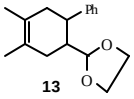
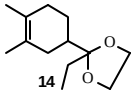
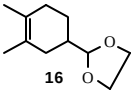
Present work :

$FeCl_3$ is a unique reagent which can function efficiently both as a Lewis acid as well as an oxidant. During the course of our study in the Diels-Alder reaction we became interested in exploring the utility of $FeCl_3$ as the Lewis acid due to its ready availability and its price. The use of $FeCl_3$ as Lewis acid is very well documented in the literature,[17a-d] however, its utility has not been explored in ionic Diels-Alder reactions. We subjected the α,β-unsaturated acetals to Diels-Alder reaction with both cyclic and acyclic dienes in the presence of $FeCl_3$ as a Lewis acid. It was observed that reaction of 2 equivalents of cyclopentadiene **1** with 2-(-propenyl) 1, 3-dioxolane **2** as the dienophile in dry dichloromethane at room temperature for 4 hrs. using 0.1 eq. $FeCl_3$ furnished 2-(bicyclo[2.2.1]hept-5-ene-2-yl 3-methyl) dioxolane **3** in 82% yield. The product was formed as a mixture of *exo* and *endo* adducts. In the ^1H NMR spectrum, the emergence of doublets at 4.2 and 4.7 indicated that the ratio of *endo* to *exo* is 5.7:1.

In order to generalise the utility of $FeCl_3$ as the catalyst, a variety of acetals were subjected to reactions with a variety of cyclic and acyclic dienes. Excellent to moderate yields were obtained as shown in table1, entries 1-9. In order to test the generality and limitations of our methodology we subjected α,β-unsaturated acetals (entries 1, 2 and 3) substituted at different positions to the ionic Diels-Alder reaction. It was observed that acetals derived from aldehydes as well as ketones participated well in the ionic Diels-Alder reactions (entries 1-3 table 1). With isoprene **8** as diene (10 eq.), (entry 6) reaction with 2-(1-propenyl)-1, 3-dioxolane **2** as dienophile at 0°C, the adduct 2-(1, 5 dimethyl-1-cyclohexen-4-yl) dioxolane **11** was obtained in only 37% yield, but on increasing the amount of catalyst to 0.3 eq., and decreasing the amount of diene from 10 eq. to 1.5 eq. and reaction time to 1.5 hrs., the yield was increased to 65%. Further increasing the amount of catalyst furnished only polymerized product. It is pertinent to mention that the yield obtained with the reaction of 2, 3-dimethyl butadiene with **6** using $FeCl_3$ as the catalyst was better than the one obtained by the use of electrogenerated acid[10] as well as

Table: 1

Cycloaddition reactions of dienes and dienophiles using $FeCl_3$ as catalyst

Entry	Diene	Dienophile	Product	Method	Yield % (*Endo:Exo*)
1	 **1**	 **2**	 **3**	1a	82** (85:15)
2		 **4**	 **5**	1a	73** (3:1)
3		 **6**	 **7**	1a	83* (3:1)
4	 **8**		 **9**	1b	79**
5			 **10**	1b	45**
6			 **11**	1b 1d	37** 65
7	 **12**		 **13**	1a	45
8			 **14**	1a	43
9		 **15**	 **16**	1c	65

*Method: 1a. diene:dienophile, 2:1, $FeCl_3$, (0.1eq.), DCM, RT, 4 hrs. 1b. diene:dienophile, 10:1, $FeCl_3$, (0.1eq.), DCM, 0°C, 4hrs. 1c. diene:dienophile, 2:1, $FeCl_3$, (0.15eq.), DCM, RT, 4 hrs. 1d. diene:dienophile, 1.25:1, $FeCl_3$, (0.3eq.), DCM, 0°C-RT, 1.5 hrs, 6:1 (regioisomers). * reported in the literature (ref. 10). **reported in the literature (ref. 11b)*

$Yb(OTf)_3$, $Sc(OTf)_3$[11b] which were recently shown to be inactive in ionic Diels-Alder reactions with a similar dienophile (entry 8). In general it was observed that cyclic dienes participate well as compared to acyclic dienes.

Another point worthy of note is that the reaction of acyclic dienophile *i.e.* 3, 3-

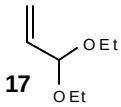
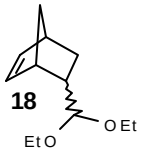
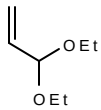
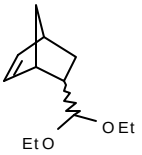
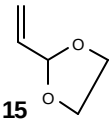
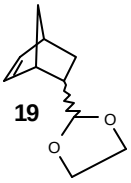
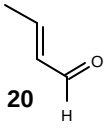
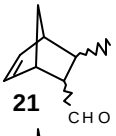
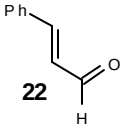
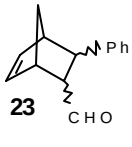
diethoxy-1-propene **17** with acyclic dienes under similar reaction conditions as compared with the corresponding cyclic acetal 2-ethenyl-1, 3-dioxolane **15** furnished only polymerised product with $FeCl_3$ (0.1 eq.) as the catalyst. Extensive polymerization was also observed when the reaction between 3, 3 diethoxy-1-propene **17** and cyclopentadiene (2 eq.) **1** was performed using 0.1 eq. of catalyst. Decreasing the amount of catalyst and lowering the temperature of reaction to -70°C did not lead to the formation of desired product.

Having failed to get the desired cycloaddition product it was thought that the very high reactivity of the *in situ* generated dienophile, its tendency to undergo facile undesired reactions, coupled with the harsh nature of the Lewis acid were responsible for these polymerisation reactions. The reactivity of $FeCl_3$ could be readily moderated by its adsorption on silica, which acted as solid support for this Lewis acid catalyst. In literature the use of $FeCl_3$ adsorbed on silica is well known in some other chemical transformation.[18a-e] It was gratifying to note that dramatic results were achieved (Table II) when 0.1 mol% $FeCl_3$ adsorbed on silica (5% by wt.) was used in the reaction of cyclopentadiene **1** with 3, 3-diethoxy-1-propene **17** at -70°C, to produce the corresponding cycloadduct, 5-(1, 1-diethoxymethyl) bicyclo[2.2.1] hept-2-ene[4] **18** in excellent yield (86%), with very high *endo* selectivity (*endo*:*exo*=98:2). When the same reaction was performed at room temperature although the yield was increased (92%), however, it was accompanied by a slight erosion of *endo* selectivity (*endo*:exo=96:4) Employing 2-ethenyl-1, 3-dioxolane **15** as the dienophile with cyclopentadiene **1** using 0.5 mol% $FeCl_3$ adsorbed on silica (5% by wt.), the corresponding adduct 2-(bicyclo[2.2.1]-hept-5-ene-2-dioxolane[10] **19** was obtained in 90% yield as a mixture of *endo*: *exo* (2.75:1) isomers with the *endo* adduct being major. The difference in diastereoselectivity between **15** and **17** with cyclopentadiene may be attributed to the steric interaction of the complexed **17** with Lewis acid with cyclopentadiene in the transition state. It was also observed that the reaction of cyclopentadiene **1** with 3, 3-diethoxy-1-propene **17** using only silica as catalyst (500% by weight) did not furnish the

desired product even in traces. This confirms that, it is only $FeCl_3$ which acts as catalyst in ionic Diels-Alder reactions but its activity can be reduced on its adsorption on silica. In an attempt to increase the yield of the ionic Diels-Alder reaction, acyclic dienes (*viz.* isoprene, 2, 3-dimethyl butadiene) were subjected to treatment with acetal 2-(1-propenyl)-1, 3-dioxolane **2** in the presence of $FeCl_3/SiO_2$, however no improvement in the yield of the adduct was observed, instead yields were drastically reduced to 5% when 1 mol% of $FeCl_3$ adsorbed on silica (5% by wt.) was used as catalyst.

Table:II

Cycloaddition reactions of dienes and dienophiles using $FeCl_3$ adsorbed on silica as catalyst.

Entry	Diene	Dienophile	Product	Method	Yield % (*Endo:Exo*)
10		 **17**	 **18**	IIa	86* (49:1)
11				IIb	92* (24:1)
12		 **15**	 **19**	IIc	90** (2.75:1)
13		 **20**	 **21**	IId	80*** (3:1)
14		 **22**	 **23**	IId	78*** (3:1)

Methods: IIa:. diene:dienophile, 2:1, $FeCl_3$ (1.0 mol%) adsorbed on silica (5% by wt.), DCM, -70°C 2 hrs. IIb:. diene:dienophile, 2:1, $FeCl_3$ (0.5 mol%) adsorbed on silica (5% by wt.), DCM, 0°C-RT, 4 hrs. IIc: diene:dienophile, 2:1, $FeCl_3$ (0.6 mol%) adsorbed on silica (5% by wt.), DCM, 0°C-RT 2 hrs IId. diene:dienophile, 2:1, $FeCl_3$ (1.0 mol%) adsorbed on silica (5% by wt.), DCM, 0°C-RT 4 hrs.(reported in the literature ref.4). **(reported in the literature ref.10). ***(reported in the literature ref. 19).*

Therefore, $FeCl_3/SiO_2$ as the catalyst not only increased the efficiency of the above reactions but its utility could be readily extended to the cycloaddition with the enone and enals. Thus the reaction of cyclopentadiene **1** with crotonaldehyde **20** using 1 mol% of $FeCl_3$ on silica produced the corresponding adduct[15] **21** in 80% yield (entry 13 Table 2). The ratio of *endo*/*exo* as determined by 1H-NMR was ≈ 3:1. An analogous reaction of the dienophile cinnamaldehyde **22** with cyclopentadiene **1** in the presence of 1 mol% of catalyst furnished a 3:1 mixture of *endo* and *exo* isomers[19] in 78% yield (entry 14, Table 2).

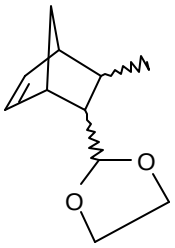
In conclusion, we have demonstrated, the utility of $FeCl_3$ as an efficient Lewis acid catalyst and established a mild protocol for the ionic Diels-Alder reaction of 1,3-dienes with various dienophiles. Additionally one can moderate and fine-tune the reactivity of $FeCl_3$ by adsorbing it on silica gel. $FeCl_3$ adsorbed on silica not only avoids polymerisation but enhances the *endo* selectivity as well in Diels-Alder reactions yields. Additionally the heterogeneous nature of the catalyst coupled with its potential reusability makes the work up procedure extremely simple involving mere filtration.

Experimental:

(a). General Procedure for Ionic Diels-Alder reaction using $FeCl_3$ as catalyst:

To a 6.25 mmol/10 mmol/50 mmol of diene in 20 ml. of dry dichloromethane under nitrogen atmosphere, 5 eq. of dienophile was added followed by the addition of 0.5 to 0.3 eq. of anhydrous $FeCl_3$. Reaction mixture was stirred at room temperature and monitored by tlc. After completion of reaction, the mixture was quenched with 25 ml. of water, extracted with dichloromethane (3x25 ml.), dried over anhydrous Na_2SO_4 and filtered. The filtrate on concentration under reduced pressure furnished a crude residue. Column purification (SiO_2) of the residue afforded Diels-Alder product as viscous oil.

2-(3-Methyl Bicyclo[2.2.1] hept-5-en-2-yl)-1, 3-dioxolane 3:



To a freshly cracked solution of 0.330 gm (5 mmol) of cyclopentadiene **1** in 20 ml of dry dichloromethane under N_2 atmosphere at 0°C, was added 0.285 gm (2.5 mmol) of 2-(1-propenyl)-1,3-dioxolane **2** followed by the addition of 0.40 gm (0.1eq.) of $FeCl_3$. Reaction mixture was gradually warmed upto RT, and stirred continuously for 4 hrs. After monitoring by tlc, the reaction mixture was quenched with 25 ml. of water and extracted with dichloromethane (3x25 ml.). It was then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to furnish a crude residue. Column chromatography (SiO_2) of the residue using 5% ethyl acetate-pet.ether as eluent provided 0.267 gm of 2-(bicyclo[2.2.1] hept-5-en-2-yl 3-methyl) dioxolane **3** in 82% yield. The ratio of *endo* to *exo*, as observed from 1H-NMR was ≈ 34:6 (5.67).

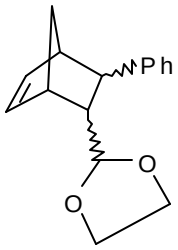
IR (neat) cm^{-1}: 3060, 1360, 1660, 1080, 940, 746.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.15 (d, 3H, J=8 Hz, -CH_3), 1.25-1.45 (m, 2H), 1.50-1.70 (m, 2H), 2.45 (br s, 1H), 2.9 (br s, 1H), 3.75-4.05 (m, 4H, -$\underline{OCH_2CH_2O}$-), 4.25 (d, 1H, J=10.8 Hz) distinct peak for *exo* isomer 4.8 (d, 1H, J=8 Hz), 6.0 (dd, 1H, J=6 Hz), 6.25 (dd, 1H, olefinic, J=6 Hz).

^{13}C-NMR (50 MHz, $CDCl_3$) δ: 21.3 (q), 36.37 (d), 44.75 (d), 46.05 (t), 48.72 (d), 52.10 (d), 64.71 (t), 108.45 (d), 133.05 (d), 138.15 (d).

Mass (m/e):180, 165, 114.

2-(Bicyclo[2.2.1]hept-5-en-2-yl 3-phenyl) dioxolane 5:



To a freshly cracked stirred solution of 0.33gm (5 mmol) of cyclopentadiene **1** in 20 ml. of dry dichloromethane under N_2 atmosphere at 0°C, was added 0.44g (2.5 mmol) of 2-(3-phenyl-2-vinyl)-1, 3-dioxolane **5**, followed by the addition of 40 mg (0.1 eq.) of $FeCl_3$. The reaction mixture was stirred overnight at room temperature. After completion of reaction, usual work-up and column chromatography(SiO_2) furnished 0.44g of 2-(bicyclo[2.2.1]hept-5-en-2-yl 3-phenyl) dioxolane **5** in 73% yield.

Yield: 73%.

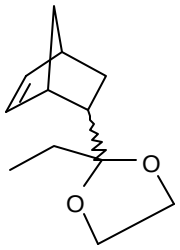
IR (neat) cm^{-1}: 2970, 1681, 1625, 1600, 1496, 1404, 1332, 1145, 1109.

^{1}H-NMR (200 MHz, $CDCl_3$): 1.6 (d, 1H, J=8 Hz), 1.8 (d, 1H, J=8 Hz), 2.3 (m, 1H), 2.55 (m, 1H), 2.9 (br s, 1H), 3,2 (br s, 1H), 3.75-4.05 (m, 4H, -O$\underline{CH_2CH_2}$O-), 4.45 (d, 1H J=10.8 Hz), 6.3 (dd, 1H, J=6 Hz, olefinic), 6.45 (dd, 1H olefinic, J=6 Hz) 7.00-7.6 (m, 5H aromatic). *Exo* isomer showed distinct peaks at 0.8δ (d, 1H, J=8 Hz) and at 4.9δ (d, 1H, J=8 Hz) along with other overlapped peaks of *endo* isomer.

^{13}C-NMR (50 MHz, $CDCl_3$) δ: 44.7 (d), 46.4 (d), 46.76 (t), 48.85 (d), 50.8 (d), 64.7 (t), 108.37 (d), 125.5 (d), 127.6 (d), 128 (d), 134.76 (d), 137.9 (d), 144.7 (s).

Mass : 242, 176, 104, 91, 66.

2-(Bicyclo[2.2.1]hept-5-en-2yl)-2-ethyl dioxolane 7:



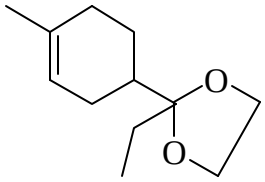
To a freshly cracked solution of 0.33g (5 mmol) of cyclopentadiene **1** in 20 ml of dry dichloromethane under N_2 atmosphere was added 0.32g (2.5 mmol) of 2-ethyl, 2-vinyl-1, 3-dioxolane **6** followed by addition of 20 mg (0.05 eq.) of $FeCl_3$ at 0° C. Reaction mixture was stirred at room temperature for 5 hrs. and monitored by tlc. After completion of reaction, usual work-up and purification through column chromatography (SiO_2) afforded 0.402g of a mixure of *endo* and *exo* 2-(bicyclo[2.2.1]hept-5-en-2yl)-2-ethyl dioxolane **7** in 83% yield as a viscous oil.

IR (neat) cm^{-1}: 3066, 2970, 1630, 1340, 1073, 922, 725.

^{1}H-NMR (200MHz. $CDCl_3$) δ 0.90 (t, 3H, J=9 Hz, -CH_2-$\underline{CH_3}$, *exo* isomer), 1.05 (t, 3H, J=8 Hz, -CH_2-$\underline{CH_3}$, *endo* isomer), 1.35-1.45 (m, 2H), 1.56 (q, 2H –$\underline{CH_2}$-CH_3), 1.6-1.8 (m, 2H), 2.45 (m, 1H), 2.8 (br s, 1H), 2.9 (br s, 1H), 3.82-4.05 (m, 4H, -O$\underline{CH_2CH_2}$-O), 5.95 (dd, 1H, olefinic, J=6 Hz, J=3 Hz), 6.15 (dd, 1H, J=6 Hz, J=3 Hz, olefinic). In addition the peaks of *exo* isomers are overlapping with the *endo* isomers.

Mass (m/e): 194, 181, 165, 129, 102, 101, 100, 99, 91, 77, 66.

2-(1-Methyl-1-cyclohexen-4-yl)-2-ethyl dioxolane 9:



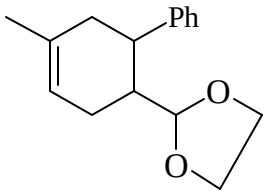
To a stirred solution of 1.7g (25 mmol) of isoprene **8** at 0°C and N_2 atmosphere, was added 0.32g (2.5 mmol) of 2-vinyl-1, 3-dioxolane followed by the addition of 40 mg (0.1 eq.) of $FeCl_3$. The reaction mixture was stirred for 4 hrs. After completion of reaction and usual workup and column purification (SiO_2) furnished 0.387g of 2-(1-methyl-1-cyclohexen-4-yl)-2-ethyl dioxolane in 79% yield.

IR (Neat) cm^{-1}:2980, 2875, 1640, 1370, 1150, 1045, 940..

^{1}H-NMR (200MHz, $CDCl_3$) δ: 0.90 (t, 3H, J=8Hz, -CH_2.$\underline{CH_3}$), 1.25-1.45 (m, 2H), 1.60-1.75 (br m, 5H), 4.0 (m, 4H, -O$\underline{CH_2}\underline{CH_2}$-O), 5.40 (br m, 1H, olefinic).

Mass (m/e): 196, 101, 99, 57.

2-(4-Methyl-6-phenyl-3-cyclohexenyl)-1, 3-dioxolane 10:



To a stirred solution of 1.7g (2.5 mmol) of isoprene **8** in 20 ml. DCM under ice cooling at N_2 atmosphere, was added 0.44g (2.5 mmol) of 1-(1, 3-dioxolan-2-yl)-2-phenyl-1-ethene **5**. Reaction mixture was stirred for 4 hrs. After completion of reaction, usual work-up and column chromatography (SiO_2) furnished 0.275g of 2-(4-methyl-6-phenyl-3-cyclohexenyl)-1, 3-dioxolane in 45% yield.

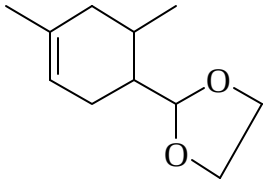
IR (neat) cm^{-1}:3010, 2891, 1600, 1492, 1452, 1398, 1217, 1141.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.75 (s, 3H, $-CH_3$), 2.1-2.4 (m, 4H), 2.9 (m, 1H), 3.6-4.0 (m, 4H, -O$\underline{CH_2}\underline{CH_2}$O-), 4.55 (d, 1H), 5.5 (br s, 1H, olefinic) 7.0-7.5 (m, 5H aromatic).

^{13}C-NMR (50 MHz, $CDCl_3$) δ: 23.2 (d), 23.3 (t), 38.67 (t), 41.21 (d), 41.8 (d), 64.84 (t), 104 (d), 119.94 (d), 125.86 (d), 127.55 (d), 128.1 (d), 132.7 (s), 144.72 (s).

Mass : 244, 182, 167, 91, 73.

2-(4, 6 Dimethyl-3-cyclohexenyl)-1, 3- dioxolane 11:



To a stirred solution of 0.218g (3.2 mmol) of isoprene **8** in 30 ml of dichloromethane at 0°C, under N_2 atmosphere, was added 0.285g (2.5 mmol) of 2-(1-propenyl)-1, 3-dioxolane **2** followed by the addition of 0.121 mg (0.3 eq.) of $FeCl_3$. The reaction mixture was stirred for 1.5 hrs. After completion of reaction, usual work-up and column purification (SiO_2) afforded a mixture of 0.295g of 2-(4, 6 dimethyl-3-cyclohexenyl)-1, 3- dioxolane **11** in 65% yield. Two regioisomers were observed in the ratio of 1:6 by ^{1}H NMR spectroscopy.

Yield: 65%

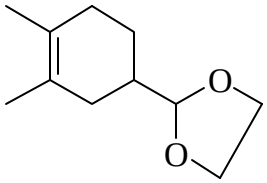
IR (Neat) cm^{-1}: 2958, 2887, 1685, 1442, 1377, 1400, 1120, 1099.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.05 (d, 3H J=6Hz), 1.65 (s, 3H), 1.75-1.9 (m, 6H), 3.75-4.05 (m, 4H –O-$\underline{CH_2}$-$\underline{CH_2}$-O-), 4.92 (d, 1H J=6Hz), 5.32 (br s, 1H, olefinic).

^{13}C NMR (50 MHz) 19.97(q), 23.98(q), 24.31(t), 29.9(d), 38.61(t), 42.76(d), 65.19(t), 105.62(d), 119.92(d), 132.82(s).

Mass(m/e): 182, 167, 120, 91, 73.

2-(3, 4-Dimethyl-3-cyclohexenyl)-1, 3-dioxolane 16:



To a stirred solution of 0.41g (5 mmol) of 2, 3-dimethylbutadiene **12** in 20 ml. of dry dichloromethane at 0°C and N_2 atmosphere was added, 0.25g (2.5 mmol) of 2-vinyl-1, 3-dioxolane **15**. The reaction mixture was stirred for 4 hrs. After completion of reaction and usual work-up and column purification (SiO_2) furnished 0.296g of 2-(3, 4-dimethyl 3-cyclohexenyl)-1, 3-dioxolane **16** in 65% yield.

IR (Neat) cm^{-1}: 2984, 2880, 1500, 1377, 1151, 1044, 948 cm-1.

^{1}H-NMR (200MHz, $CDCl_3$) δ 1.23-1.33 (m, 1H), 1.59 (s, 3H), 1.61 (s, 3H), 1.75-2.00 (m, 4H), 2.89 (m, 1H), 3.87-3.96 (m, 4H –O$\underline{CH_2}$-$\underline{CH_2}$O-), 4.5 (d, 1H).

Preparation of Catalyst ($FeCl_3$ adsorbed on Silica):

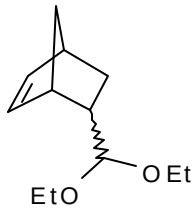
Silica gel (1g 60-120 mesh s. d. fine chemicals ltd. India) was added to a solution of anhydrous $FeCl_3$ (50 mg) in 0.5 ml of dichloromethane at room temperature. The solvent was removed on rotary evaporator to achieve homogenous adsorption. Finally, the yellow powder was the dried under vacuum (0.1 mmHg) for 30 mins to furnish a yellow powder.

(b). General Procedure for Ionic Diels-Alder reaction using $FeCl_3$ adsorbed on silica as catalyst:

To a 10 mmol of diene in 20 ml. of dry dichloromethane under nitrogen atmosphere, 5 mmol. of dienophile was added followed by the addition of 0.5 to 1 mol%. of anhydrous $FeCl_3$ adsorbed on silica (5% by weight). Reaction mixture was stirred at

room temperature and monitored by tlc. After completion of reaction, the mixture was quenched with 25 ml. of water, extracted with dichloromethane (3x25 ml.), dried over anhydrous Na_2SO_4, which on concentration under reduced pressure furnished a crude residue. Column purification afforded Diels-Alder product as viscous oil.

5-Diethoxy methyl bicyclo[2.2.1]hept-2-ene 18:

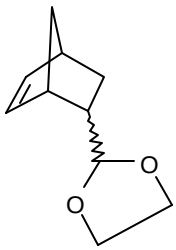


To a freshly cracked stirred solution of 0.33g (5 mmol) of cyclopentadiene **1** at 0°C under N_2 atmosphere, was added 0.325g (2.5 mmol) of 3, 3-diethoxy-1-propene **17** follwed by the addition of 0.5 mol% of $FeCl_3$ adsorbed on silica (5% by weight). Reaction mixture was stirred at room temperature for 4 hrs. After completion of reaction tlc, usual work-up and column purification (SiO_2) furnished 0.42g of 5-diethoxy methyl bicyclo[2.2.1]hept-2-ene **18** in 86% yield besides 8% of aldehyde as the side product.

IR (Neat) cm^{-1}: 3062, 1118, 1058, 932, 721.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.83 (m, 1H), 1.16 (t, 3H, J=7.5 Hz), 1.23 (t, 3H, J=7.5 Hz), two sets, 1.32-1.45 (br, m, 2H), 1.83 (m, 1H), 2.42 (m, 1H), 2.48 (br s, 1H), 2.88 (br s, 1H), 3.44-3.74 (m, 4H), 3.87 (d, 1H, J=9.3 Hz), 5.96 (dd, 1H, J=5.6, and J=3.0 Hz), 6.15 (dd, 1H, J=5.6 and 3.0 Hz). The emergence of doublets at 3.87 and 4.4 δ at the ratio of 24:1 clearly establishes the formation of *endo* and *exo* isomers respectively.

2-(Bicyclo[2.2.1] hept-5-en-2-yl)-1, 3 dioxolane 19:



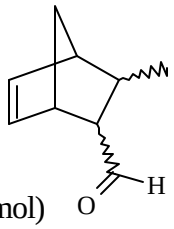
To a freshly cracked stirred solution of 0.33g (5 mmol) of cyclopentadiene in 20 ml. of dichloromethane at 0°C under N_2 atmosphere, was added 0.25g (2.5 mmol) of 2-vinyl-1, 3-dioxolane follwed by the addition of 0.6 mol% of $FeCl_3$ adsorbed on silica (5% by weight). Reaction mixture was stirred for 2 hrs., and monitored by thin layer chromatography. After completion of reaction, the reaction mixture was quenched with 20 ml. of water, then extracted with dichloromethane (3x25 ml), dried over anhydrous sodium sulphate and finally concentrated under reduced pressure. Column chromatography (SiO_2) of the residue using 5% EtOAc-Pet.ether as eluent furnished 0.374g of 2-(bicyclo[2.2.1] hept-5-en-2-yl)-1, 3 dioxolane **19** as viscous oil in 90% yield.

IR (Neat) cm^{-1}: 3065,1930, 1335, 1107, 980, 835.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.92 (m, 1H), 1.24 (d, 1H), 1.40 (m, 1H), 1.87 (m, 1H), 2.19 (m, 1H), 2.82 (br s, 1H), 2.97 (br s, 1H), 3.7-4.0 (m, 4H, $-OCH_2CH_2O-$), 4.2 (d, 1H, J=10.8 Hz), 5.97 (dd, 1H, J=6 Hz, J=2 Hz, olefinic), 6.15 (dd, 1H, J=6 Hz, J=-2 Hz olefinic). The emergence of peaks at 4.2 and 4.7 δ in the ratio of 2.75:1 clearly establishes the formation of *endo* and *exo* isomers respectively.

Mass (m/e): 166(6), 125(11), 100(24), 99(81), 91(12), 86(9), 77(17), 73(89), 66(100), 55(19).

3-Methyl bicyclo[2.2.1]hept-5-ene-2-carbaldehyde 21:



To a solution of 0.33g (5 mmol) of cyclopentadiene at 0°C under N_2 atmosphere, was added 0.175g (2.5 mmol) of crotonaldehyde followed by the addition of 1.0 mol% of $FeCl_3$ adsorbed on silica (5% by weight). Reaction mixture was stirred at room temperature for 4 hrs. After completion of reaction tlc, usual work-up and column purification (SiO_2) furnished 0.0.272g of 3-methyl bicyclo[2.2.1]hept-5-ene-2-carbaldehyde **21** in 80% yield.

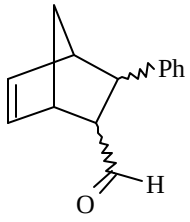
IR (Neat) cm^{-1}: 2960, 2930, 2872, 1719, 1456, 1332, 1215, 1179.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.25(d, 3H, J=8 Hz, $-CH_3$,), 1.3-1.7 (m, 2H), 2.4 (m, 1H), 2.6(br s, 1H), 3.25 (br s, 1H), 6.0 (dd, 1H, J=6 Hz, olefinic), 6.25 (dd, 1H, J=6 Hz., olefinic), 9.4 (s, 1H *endo*-CHO), 9.85 (s, 1H, *exo*-CHO).

^{13}C-NMR (50 MHz, $CDCl_3$) δ: 20.93 (q), 36.41 (d), 45.52 (d), 46.3 (t), 49.16 (d), 61.48 (d), 132.71 (d), 138.6 (d). 204.94 (d).

Mass : 137, 111, 83, 71, 67.

3-Phenyl bicyclo[2.2.1]hept-5-ene-2-carbaldehyde 23:



To a stirred solution of 0.33g (5 mmol) of cyclopentadiene at 0°C under N_2

atmosphere, was added 0.29g (2.5 mmol) of cinnamalaldehyde follwed by the addition of 1.0 mol% of $FeCl_3$ adsorbed on silica (5% by weight). Reaction mixture was stirred at room temperature for 4 hrs. After completion of reaction (TLC), usual work-up and column purification (SiO_2) furnished 0.35g of 3-phenyl bicyclo[2.2.1]hept-5-ene-2-carbaldehyde **23** in 78% yield.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.9 (d, 3H, J=8 Hz, -CH_3 *endo*), 1.25 (d, 3H, J=8 Hz, -CH_3, *exo*), 1.3-1.7 (m, 2H), 2.4 (m, 1H), 2.6(br s, 1H), 3.25 (br s, 1H), 3.87 (d, 1H, J=9.3 Hz, 6.0 (dd, 1H, J=6 Hz, olefinic), 6.25 (dd, 1H, J=6 Hz., olefinic), 9.4 (s, 1H *endo*-CHO), 9.85 (s, 1H, *exo*-CHO).

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Tetrahedron, **1985,** *41*, 413. d. Patney, H. K. *Tetrahedron Letters*, **1991,** 2259. e. Jempty, T. C. ; Gogins, K. A. ; Mazur, Y. ; Miller, L. L. *J. Org. Chem*., **1981,** *46*, 4545.

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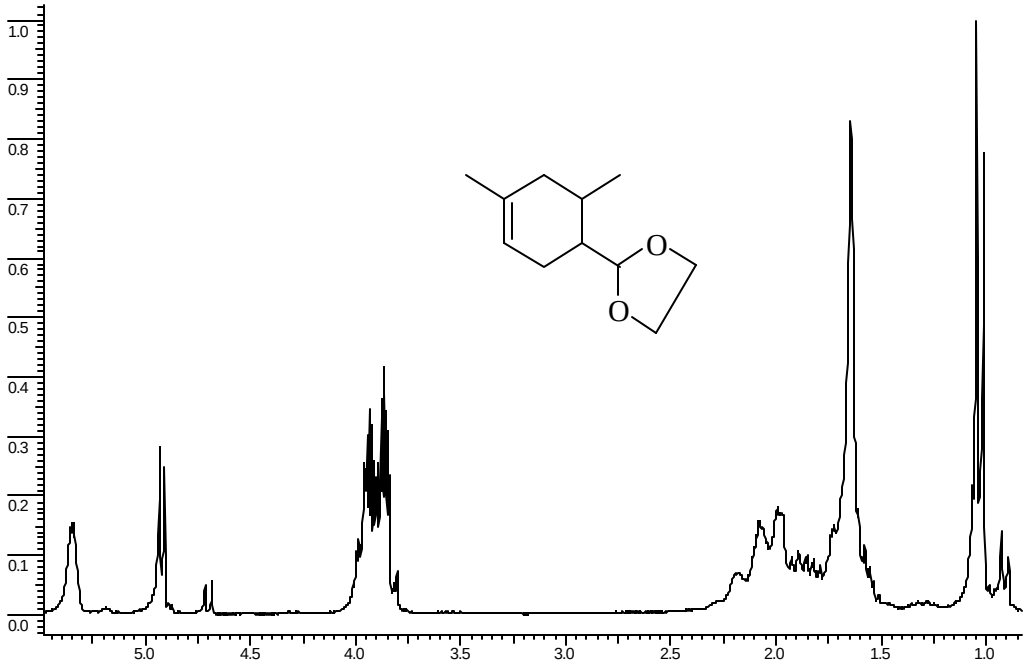
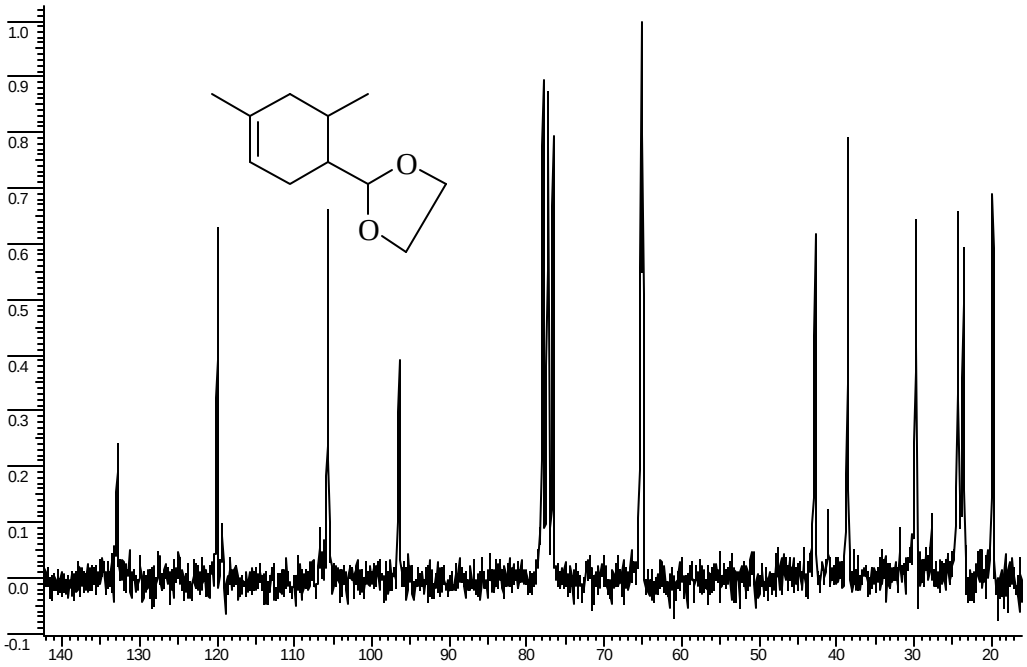
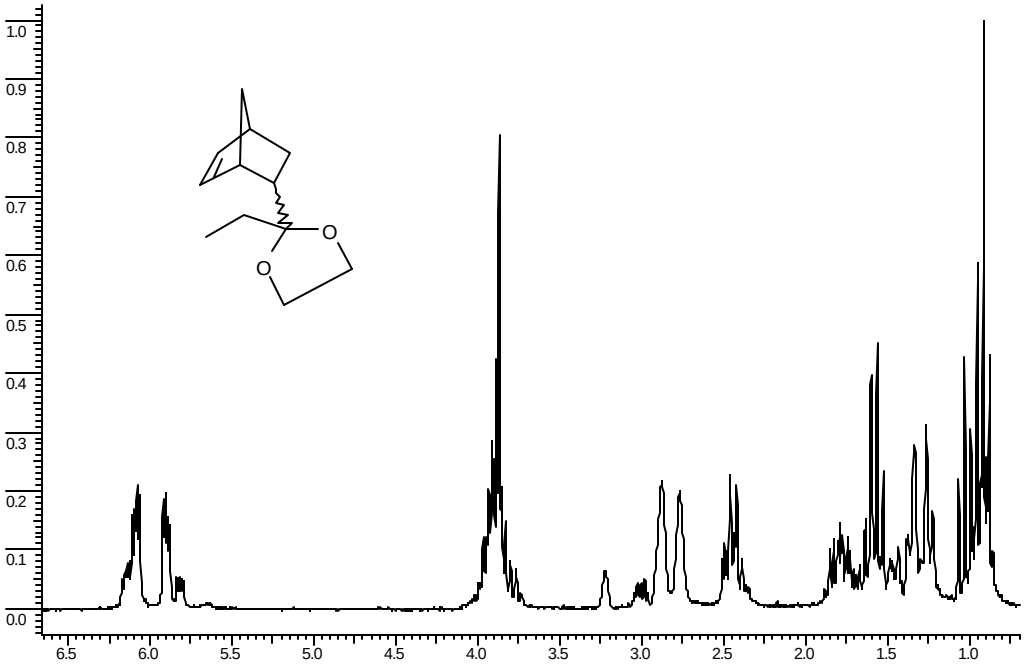


^{1}H NMR of 2-(4, 6 Dimethyl-3-cyclohexenyl)-1, 3- dioxolane ($CDCl_3$ 200 MHz)

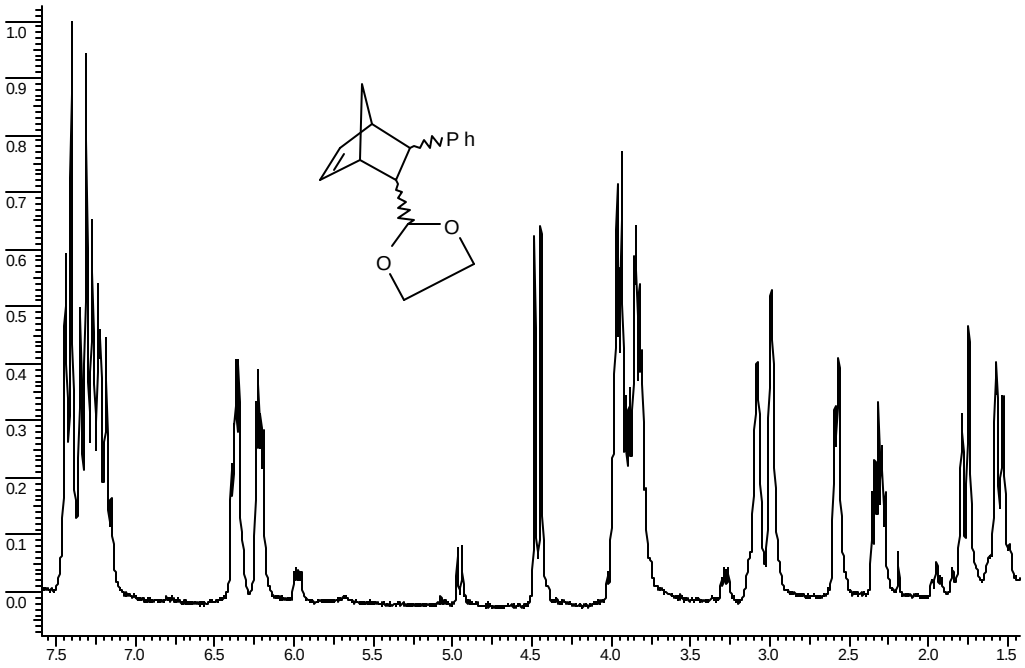


^{13}C NMR of 2-(4, 6 Dimethyl-3-cyclohexenyl)-1, 3- dioxolane ($CDCl_3$ 200 MHz)

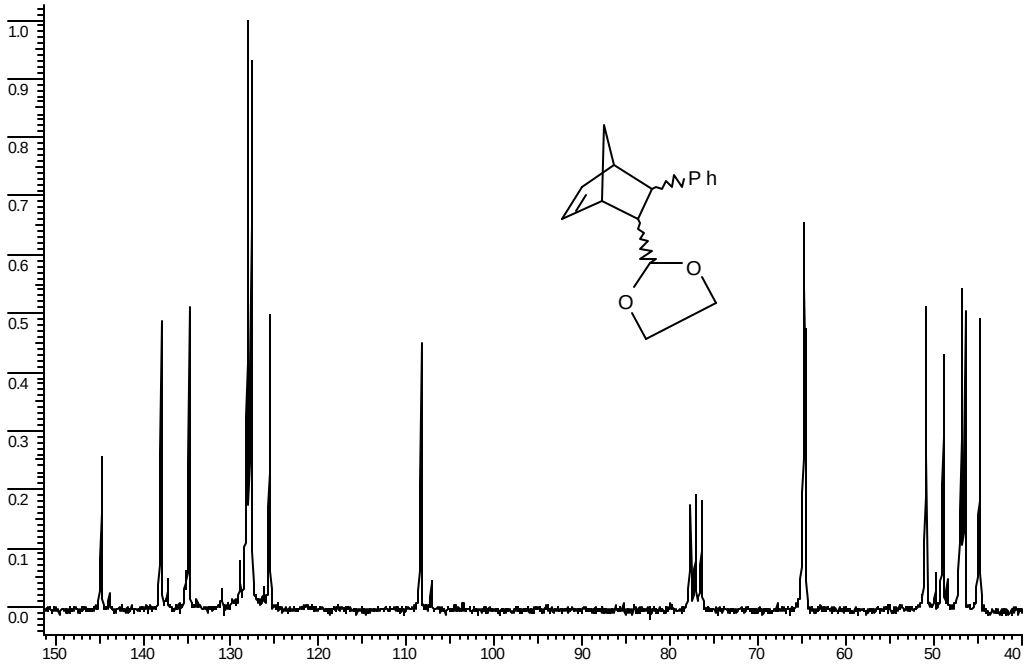
DEPT of 2-(4, 6 Dimethyl-3-cyclohexenyl)-1, 3- dioxolane ($CDCl_3$ 200 MHz)



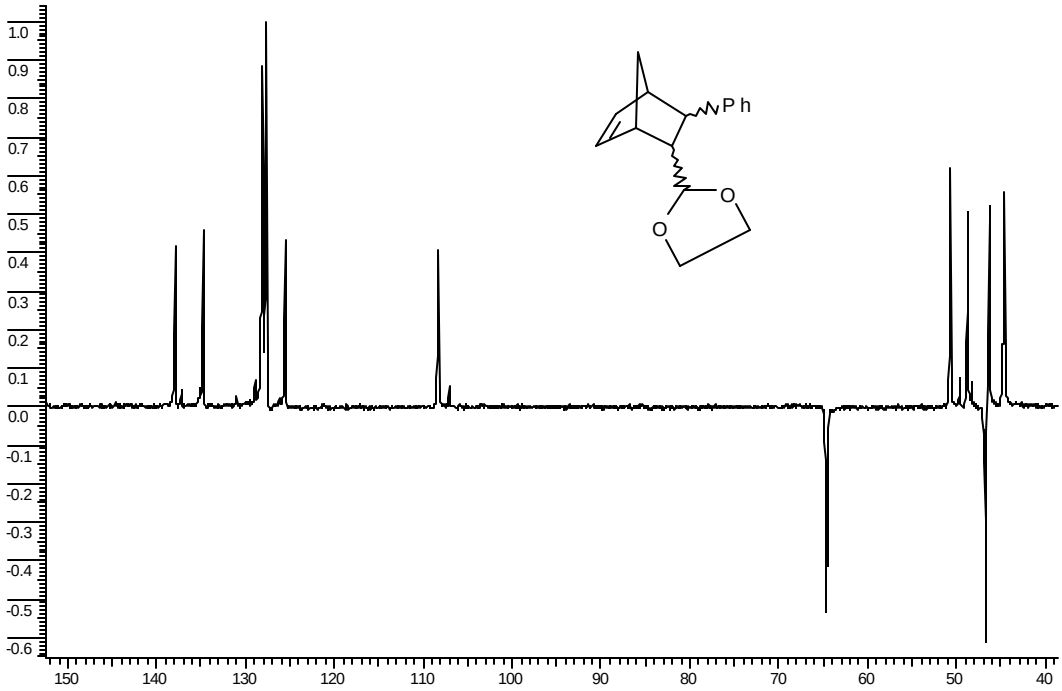
^{1}H NMR 2-(Bicyclo[2.2.1]hept-5-en-2yl)-2-ethyl dioxolane ($CDCl_3$ 200 MHz)



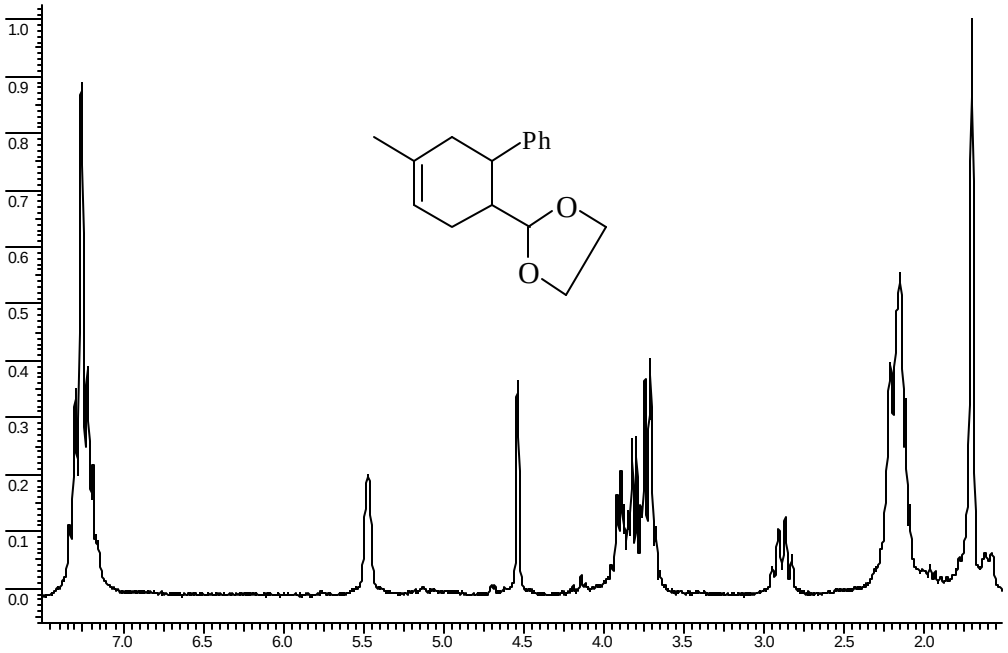
^{1}H NMR 2-(Bicyclo[2.2.1]hept-5-en-2-yl 3-phenyl) dioxolane ($CDCl_3$ 200 MHz)



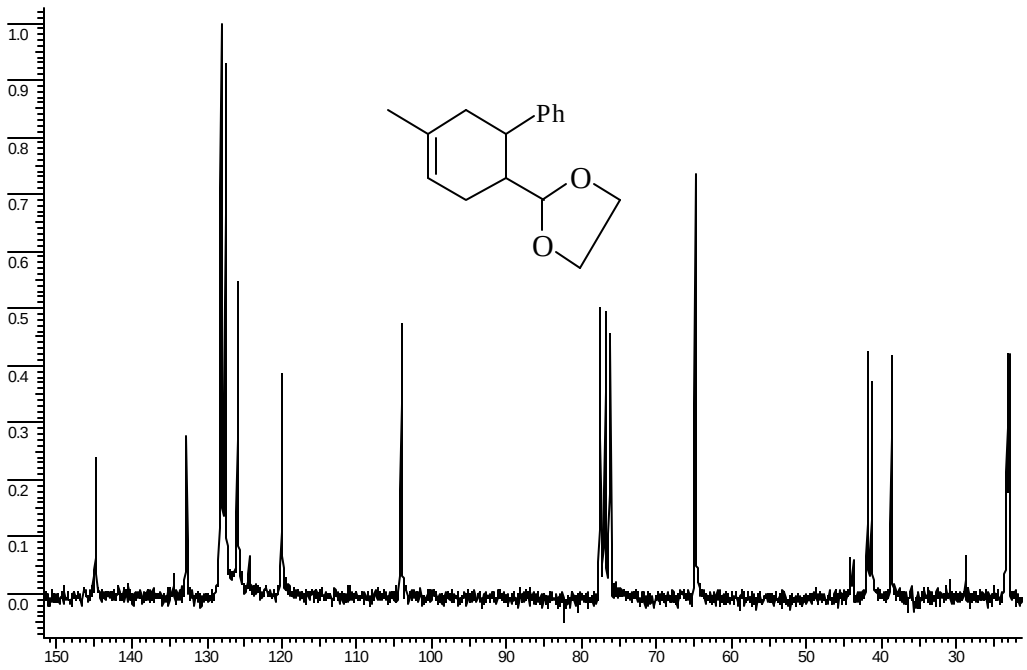
^{13}C NMR 2-(Bicyclo[2.2.1]hept-5-en-2-yl 3-phenyl) dioxolane ($CDCl_3$ 200 MHz)



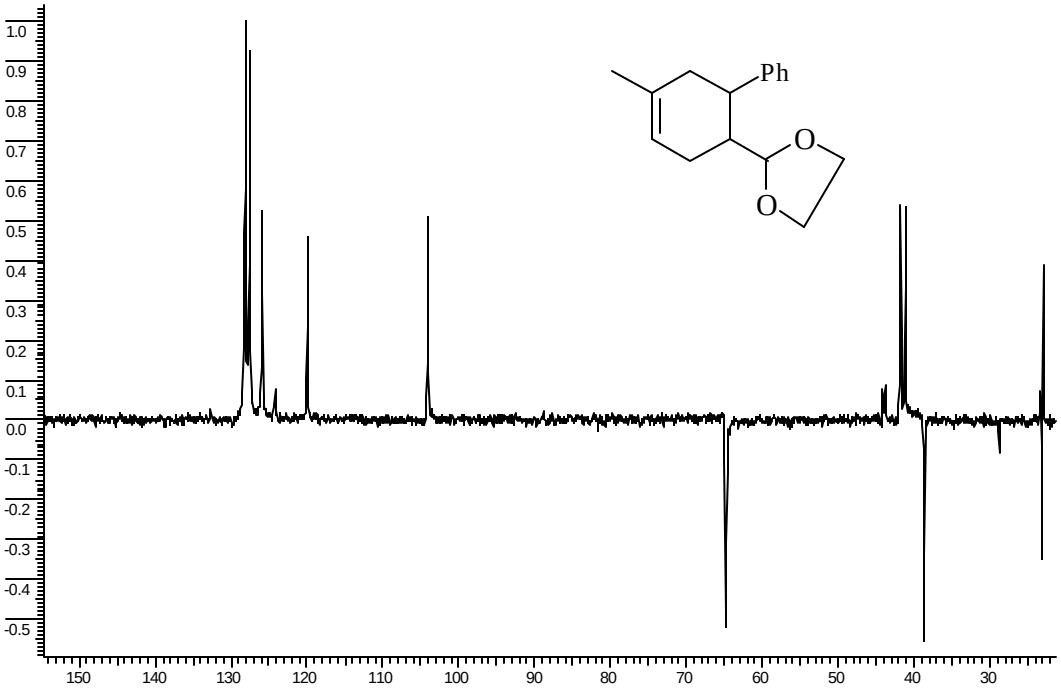
DEPT 2-(Bicyclo[2.2.1]hept-5-en-2-yl 3-phenyl) dioxolane ($CDCl_3$ 200 MHz)



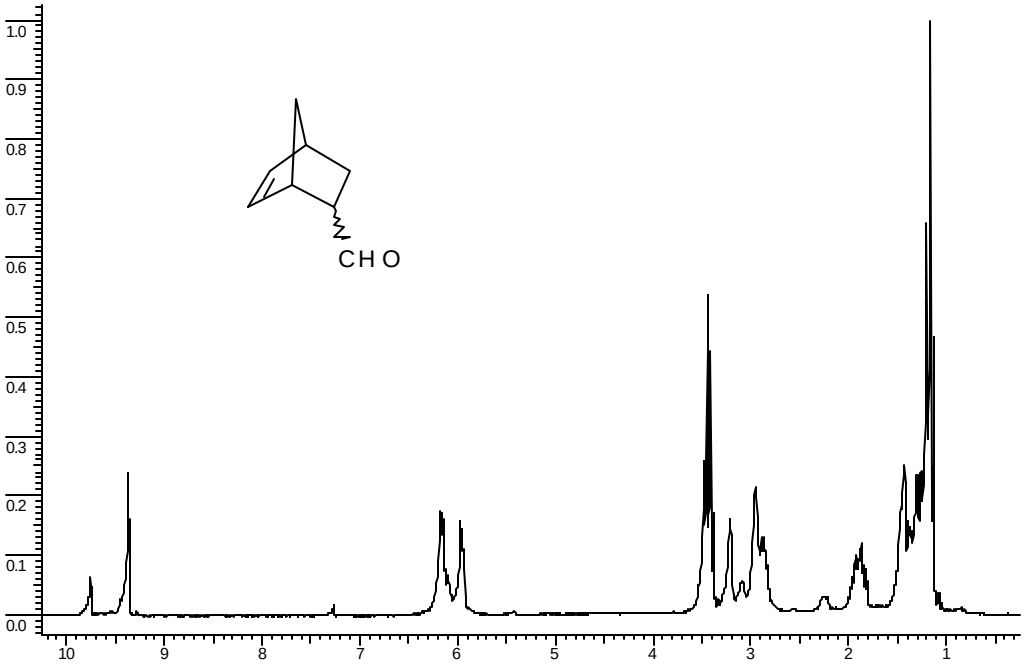
^{1}H NMR 2-(4-Methyl-6-phenyl-3-cyclohexenyl)-1, 3-dioxolane ($CDCl_3$ 200 MHz)



^{13}C NMR 2-(4-Methyl-6-phenyl-3-cyclohexenyl)-1, 3-dioxolane ($CDCl_3$ 200 MHz)



DEPT NMR 2-(4-Methyl-6-phenyl-3-cyclohexenyl)-1, 3-dioxolane ($CDCl_3$ 200 MHz)



^{1}H NMR 3-Methyl bicyclo[2.2.1]hept-5-ene-2-carbaldehyde ($CDCl_3$ 200 MHz)

Chapter 2:

Section b:

Iodolactonisation and iodoetherification of b, g-unsaturated acid and alcohol using $FeCl_3$ and NaI

Iodolactonisation and iodoetherification are crucial reactions in organic synthetic sequence as well as in structure elucidation. Iodolactonisation has been elegantly utilised for stereoselective functional group incorporation and manipulation in Corey's prostaglandin synthesis[1] as well as in the total synthesis of the tumor inhibitors *e.g.* vernolepin and vernomenin,[2] vitamin D_2 and D_3[3] synthesis. Likewise iodoetherification is used in some important organic synthesis *e.g.* prostacyclin.[4] In structure determination also iodolactonisation and iodoetherification of isomeric mixtures give a quantitative conversion of *endo* acid to an iodolactone and iodoether respectively, whereas, the *exo* isomer proved to be inert thus enabling the proportions of *endo* and *exo* to be determined, as well as the separation and structure determination of these two isomers.

The conversion of β, γ-or γ, δ-unsaturated acid into iodolactone was first reported by Bougault[5] by dissolving unsaturated acid in aq. $NaHCO_3$ and treating the solution with a solution of I_2 in KI. A number of other methods as shown above are also reported in the literature to effect iodolactonisation and iodoetherification like, cyanogen iodide,[6] iodosuccinimide,[8] N-I(collidine)$_2^+ClO_4^-$,[9] $Na_2S_2O_8$[10] *etc*. The standard iodolactonisation procedure requires substantial quantities of potassium iodide in addition to iodine and long reaction times. We have developed a new approach to generate iodonium ion using NaI with $FeCl_3$ as the oxidant. This iodonium ion forms weakly polarized complex with the double bond. The reaction probably occurs as a synchronous process in which the complex bond is converted into a valence bond and ring closure takes place by the attack

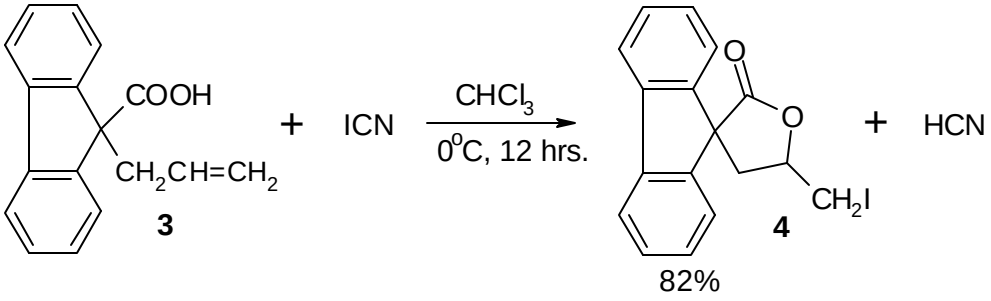
of electron-donating alcohol or carboxylic acid to the β-carbon atom.

Literature methods:

The following section deals with the reported methods to effect iodolactonisation/iodoetherification.

1. Using ICN in iodolactonisation :[6]

Richard, T. A; Kenneth L. *J. Am. Chem. Soc.,* **1953**, 1048.

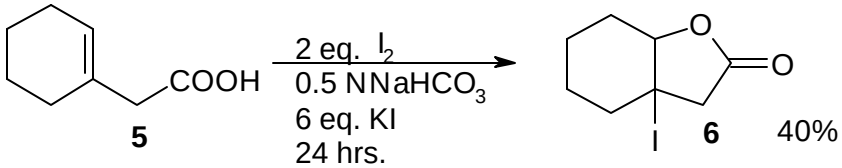


Scheme 1

Cyanogen iodide reacts with ã, ä-unsaturated acids (2, 2-diphenylpenten-4-oic acid, 9-allyl-9-fluorocarboxylic acid and penten-4-oic acid) to furnish corresponding ä-iodo-ã-pentanolactone.

2. Using I_2 and KI in the presence of $NaHCO_3$:[7]

Tamelen V. and Shamma, M. *J. Am. Chem. Soc.,* **1954,** 2315.



Scheme 2

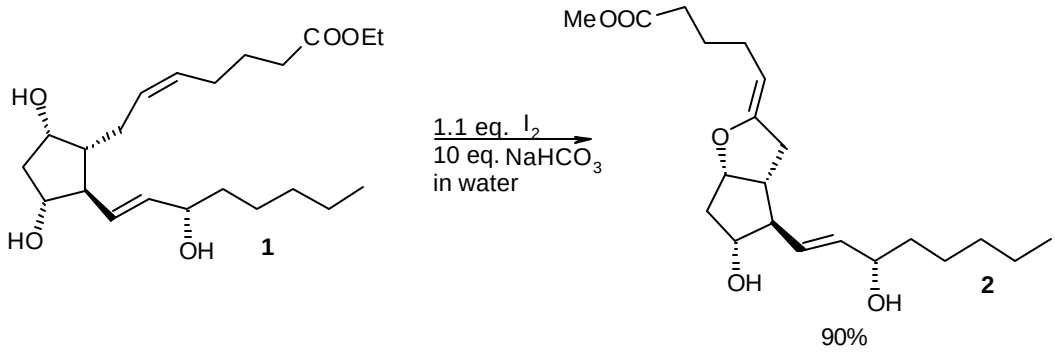
Tamelen *et. al.* in their study of iodolactonisation treated certain â, ã and ã, ä-unsaturated acids to yield five-membered iodolactone on treatment with iodine-potassium

iodide in $NaHCO_3$ solution at room temperature. It is pertinent to note that both I_2 as well as KI are used in excess.

3. Iodoetherification using I_2 :[4]

Norman, W. *Tetrahedron Letters,* **1977,** 2805.

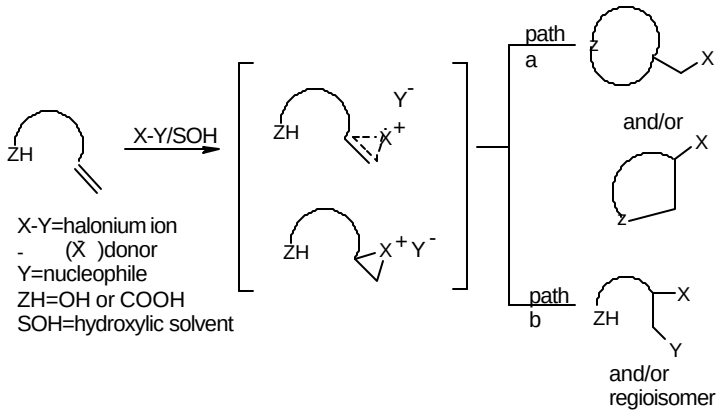
The author used I_2 for iodoeherification as the key step for the synthesis of prostaglandin (5, 6-didehydro-9-deoxy-6, 9 á-epoxy prostaglandin).



Scheme 3

4. Using $I(Collidine)_2^+ClO_4^-$:[9]

Robert, D. E; Joseph, W. M; Herman, S. *Synthesis*, **1988** 862.

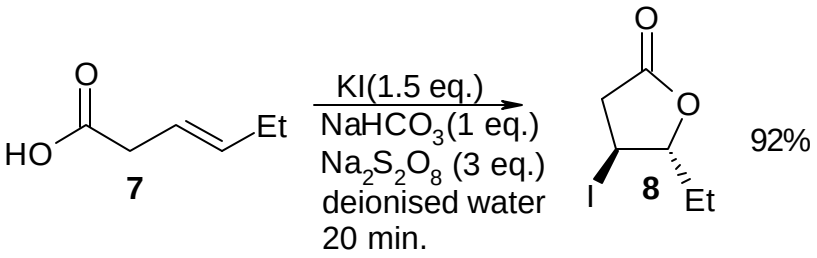


Scheme 4

$I(Collidine)_2^+ClO_4$ was used to react with unsaturated alcohols and carboxylic acids in dichloromethane at ambient temperature to furnish three to seven-membered ring iodoether and four-to seven-membered-ring iodo lactones, respectively, in moderate yields generally with high regioselectivity.

Using $Na_2S_2O_8$ and KI :[10]

April, C. R; Robert, C. M. April; M. S. *Synlett*, **1993**, 899.

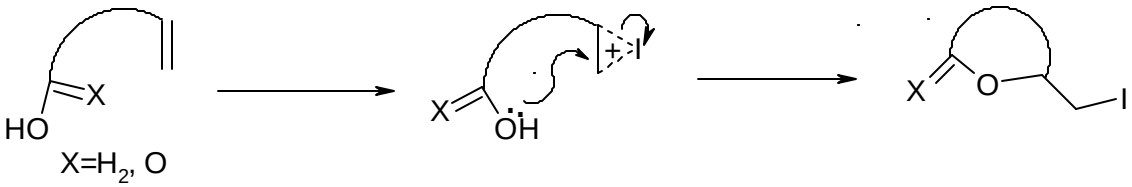


Scheme 5

In this study it was shown that oxidation of KI with sodium persulphate in the presence of salts of â, ã-and ã, ä-unsaturated carboxylic acids affords ã-lactone in high yields at ambient temperature and with short reaction times.

Present Work:

$FeCl_3$ enjoys a unique place as a reagent by virtue of its dichotomy to act as an efficient Lewis acid as well as an oxidant. Due to our interest in successful demonstration of $FeCl_3$ as an efficient Lewis acid in catalysing ionic Diels-Alder reactions, we decided to exploit its oxidative power in development of methodology for iodoetherification as well as iodolactonisation. It was surmised that $FeCl_3$ could oxidize KI to iodonium ion or iodine and in turn could act like a Lewis acid to activate the iodine thus generated. If both olefin and alcohol/acid were to be present in the same molecule, it would lead to cyclisation to genarate heterocycles as depicted in **scheme 1.**



scheme 1

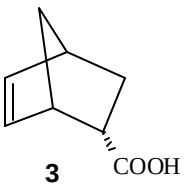
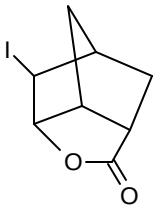
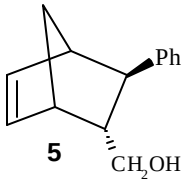
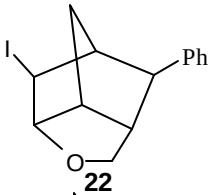
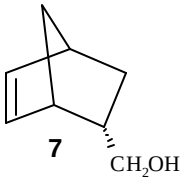
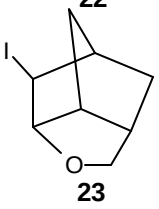
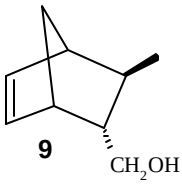
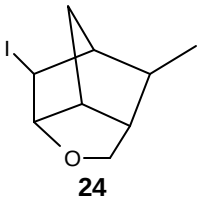
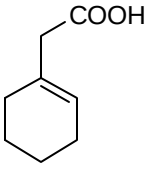
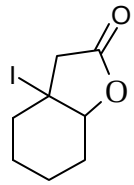
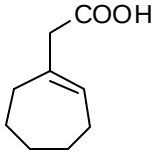
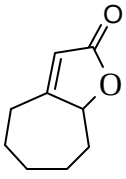
Compound **3** was taken as the substrate to test the hypothesis. Thus, when 3 (as a mixture of *endo*:*exo* isomers in the ratio of 3:1) was treated with KI/$FeCl_3$ in CH_3CN at 82ºC, the *endo* isomer underwent iodolactonisation whereas the *exo* isomer remained unreacted the iodolactone was obtained in 86% yield (based on *endo* isomer), whereas the *exo* isomer (based on endo isomer) was recovered unreacted. Similarly, a mixture of the *endo* and *exo* alcohols (entries 2-4) were also subjected to the iodoetherification and the yields are based on the *endo* isomer.

In order to establish the efficacy and generality of the protocol developed by us, we subjected a variety of olefinic acids/alcohols to the reaction conditions. Good to excellent yields of iodoetherification and iodolactonisation reactions were observed. The results of the present study are summarized in **table 1**. A noteworthy feature of cyclisation of cyclic

olefin (entry 6) is the exclusive formation of butenolide, presumably arising from the elimination of the initially formed iodolactone under the reaction conditions. In order to confirm the formation of butenolide, it was synthesized by an unambiguous way following a methodology[11] previously developed by us (scheme 7).

Table : 1

Role of $FeCl_3$ /NaI mediated by Iodoetherification and Iodoesterification

Entry	Substrate	Product	Yield
1.	 **3**	 **21**	86%
2.	 **5**	 **22**	93%
3.	 **7**	 **23**	94%
4.	 **9**	 **24**	100%
5.	 **14**	 **25**	76%
6.	 **18a**	 **26**	75%

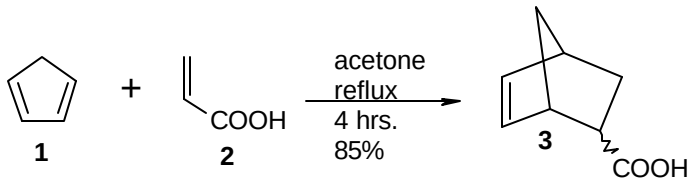
Thus, we have established $FeCl_3$/NaI as an efficient reagent to effect

iodolactonisation as well as iodoetherification. The efficiency, generality and ease of operation of the present protocol would be a useful addition to the practising organic chemist.

PREPARATION OF SUBSTRATES :

Preparation of Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 3:

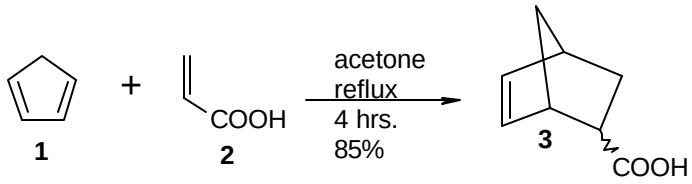
The compound **3** was prepared from a reaction of cyclopentadiene **1** and acrylic acid **2**. The reaction mixture was refluxed for 4 hrs. in acetone to furnish bicyclo[2.2.1] hept-5-ene-2-carboxylic acid **3** in 85% yield, (*endo*:*exo*=3:1).



Scheme 2

2-Hydroxymethyl, 3-phenyl bicyclo[2.2.1]hept-5-ene 5:

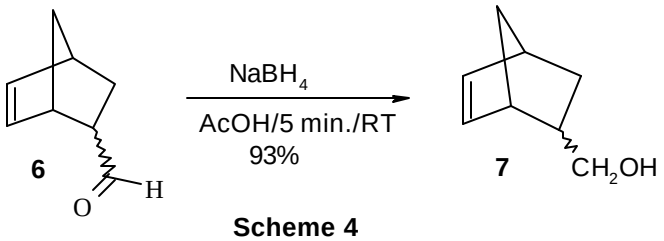
2-Hydroxymethyl, 3-phenyl bicyclo[2.2.1]hept-5-ene **5** was formed as a mixture of *endo* and *exo* isomer (3:1) from 3-phenyl bicyclo[2.2.1]hept-5-ene-2-carbaldehyde **4** (a Diels-Alder adduct of cyclopentadiene **1** and cinnamaldehyde) by reducing it with $NaBH_4$ in 87% yield.



Scheme 3

2-Hydroxy methyl bicyclo[2.2.1]hept-5-ene 7:

It was prepared as a mixture of *endo*:*exo* (3:1) from bicyclo[2.2.1]hept-5-ene-2-carbaldehyde **6** (a condensation product of cyclopentadiene **1** and acrolein) by reducing it

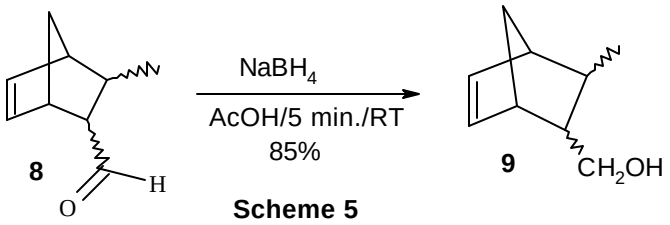


Scheme 4

with $NaBH_4$ as shown in the following **scheme 4**.

Preparation of 2-hydroxymethyl 3-methyl bicyclo[2.2.1]hept-5-ene 9:

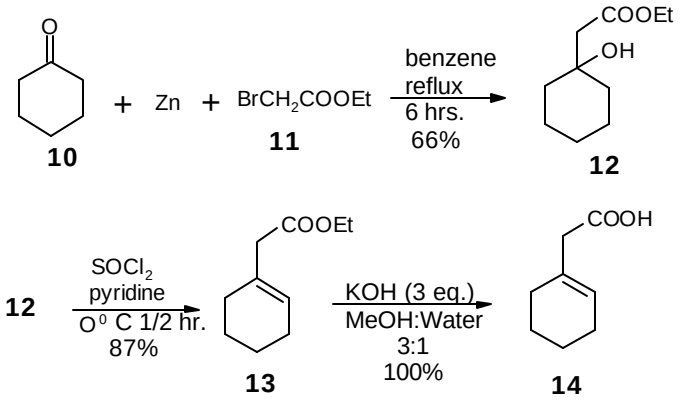
2-Hydroxymethyl 3-methyl bicyclo[2.2.1]hept-5-ene **9** was prepared as a mixture of *endo*:*exo*=3:1 isomers by the reduction of 3-methyl bicyclo[2.2.1]hept-5-ene-2-carbaldehyde **8** using $NaBH_4$ as the reducing agent. The reaction proceeded within 5 minutes to furnish 2-hydroxymethyl 3-methyl bicyclo[2.2.1]hept-5-ene **9** in 85% yield.



Scheme 5

Preparation of 2-(1-cyclohexenyl) acetic acid 14:

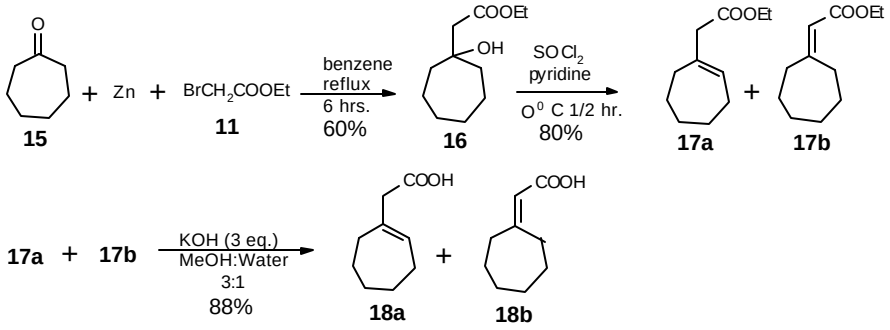
The â, ã-unsaturated acid **14** was prepared by the Reformatasky reaction involving ethyl bromo acetate **11** and cyclohexanone by refluxing for 6 hrs. to furnish hydroxy compound **12** in 66% yield. The compound **12** on dehydration using thionyl chloride and pyridine as dehydrating agent furnished alkene **13** in 87% yield. The ester group of **13** was then hydrolysed using 3 eq. of KOH in $MeOH/H_2O$ system to furnish 2-(1-cyclohexenyl) acetic acid **14** in 100% yield.



Scheme 6

Preparation of 2-(1-cycloheptenyl) acetic acid 18a:

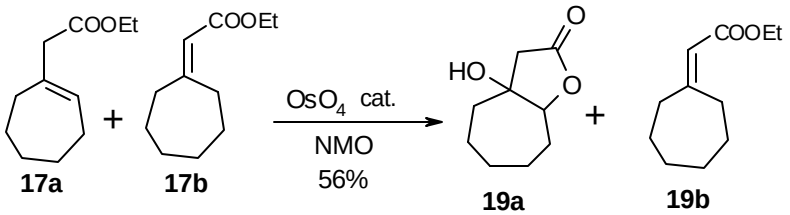
Cycloheptanone **15** on Reformatasky reaction with ethyl bromo acetate **11** and zinc provided hydroxy compound **16** in 60% yield. The compound **16** was then dehydrated using thionyl chloride and pyridine to furnish a mixture of á, â- **17a** and â, ã-unsaturated esters **17b** in 80% yield. The mixture of esters without separation (separation was difficult because of identical rf value on tlc plate) was subjected to hydrolysis using 3 eq. of KOH in MeOH/H_2O system to furnish a mixture of acids **18a** and **18b** (4:1) respectively.

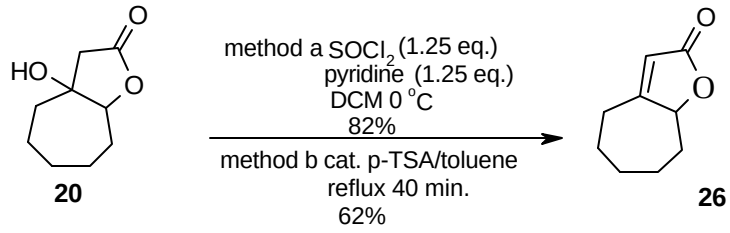


Scheme 7

Preparation of authentic butenolide 39:

The mixture of **17a** á, â- and **17b** â, ã-unsaturated esters respectively was subjected for dihydroxylation using catalytic OsO_4 and NMO to furnish unexpected hydroxy lactone **19a** while the unreacted á, â- unsaturated ester **17a** was recovered. The hydroxy compound **19a** was then dehydrated using catalytic p-TSA in refluxing toluene to furnish butenolide **26** in 62% yield.





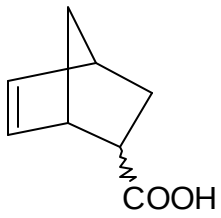
Scheme 8

Experimental:

General Procedure for iodoetherification, iodolactonisation and butenolide formation:

To a 2 mmol of β, γ-unsaturated alcohol or acid was added 4 mmol of anhydrous $FeCl_3$ and 4 mmol of NaI in 25 ml of acetonitrile. The solution was refluxed for 4-6 hrs. The reaction was then quenched with water, extracted with 3x20 ml. portion of dichloromethane. The organic solution was then successively washed with 25 ml saturated solution of $Na_2S_2O_3$., 25 ml of brine and finally with 25 ml of water. The organic solvent was dried over anhydrous Na_2SO_4, filtered and was then removed on rotary evaporator under reduced pressure and the residue thus obtained was purified by column chromatography (SiO_2) to furnish the corresponding iodoether or iodolactone (or butenolide) respectively.

Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 3:



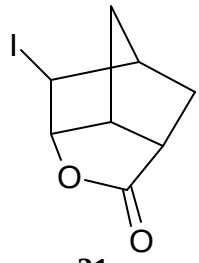
3

To a 3.67g (55.56 mmol) of freshly cracked cyclopentadiene **1** in 25 ml. of acetone was added, 2g (27.78 mmol) of acrylic acid **2**. The solution was refluxed for 4 hrs. After completion of reaction the solution was concentrated, which on column purification furnished 3.26g of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **3** as mixture of *endo* and *exo* isomer (*endo* being the major one) in 85% yield.

IR cm^{-1}: 2500-3700 (broad hump), 1699, 1416, 1276.

^1H NMR (200 MHz) : 1.2-1.6 (m, 3H), 1.8-2.0 (m, 1H), 2.75-3.05 (m, 2H), 3.25 (br s, 1H). 6.0 (m, 1H olefinic), 6.2 (m, 1H olefinic).

9-Iodo-5-oxa tricyclo[4.2.1.$0^{3,7}$]nonan-4-one 21:



21

To a 1g (7.25 mmol) of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **3** in 20 ml of acetonitrile, was added 2.34g (14.5 mmol) of anhydrous $FeCl_3$ and 2.17g (14.5 mmol) of NaI. The solution was refluxed for 4 hrs. After completion, the reaction mixture was cooled and 25 ml of saturated solution of $NaHCO_3$ was added. The organic compound was extracted using 3x25 ml of EtOAc. The combined organic layer was then washed successively, with 25 ml of brine solution and 25 ml of water. The organic layer was dried over anhydrous Na_2SO_4, filtered and on concentration and column purification (SiO_2) furnished 1.64g of 9-iodo-5-oxa tricyclo[4.2.1.$0^{3,7}$]nonan-4-one **21** in 86% yield.

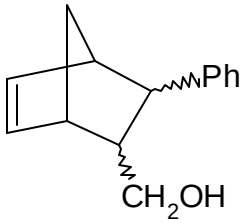
IR cm^{-1}: 1735, 1160, 1060.

^{1}H-NMR (200 MHz): 1.6-1.95 (m, 2H), 1.95-2.2 (m, 1H), 2.35 (d, 1H J=16 Hz) 2.5 (dd, 1H J=16Hz, J=4Hz), 2.7 (br s, 1H), 3.17 (m, 1H), 3.9 (m, 1H), 5.17 (m, 1H).

^{13}C-NMR (50 MHz): 30.2 (d), 34.09 (t), 36.85 (d), 37 (t), 46.41 (d), 46.42 (d), 88.38 (d), 178.7 (s).

Mass: 264, 167, 137, 127, 91, 79, 66.

2-Hydroxymethyl, 3-phenyl bicyclo[2.2.1]hept-5-ene 5:



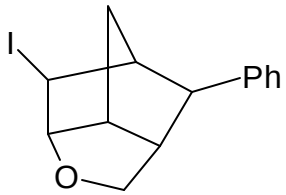
5

To a 1g (5 mmol) ice cold solution of 3-phenyl bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde **4** in 10 ml of acetic acid, was added 0.575g (15 mmol) of $NaBH_4$ in small portion with continuous stirring. Reaction mixture was stirred further for 10 min. At the end of the reaction, the solution was neutralized by adding saturated solution of $NaHCO_3$. The organic compound was isolated using 3x25 ml portions of EtOAc. The combined organic layer was then dried over anhydrous Na_2SO_4, filtered and on concentration and column purification (SiO_2) furnished 0.88g of 2-hydroxymethyl, 3-phenyl bicyclo[2.2.1]hept-5-ene **5** in 87% yield.

IR cm^{-1}: 3200, 3010, 1631, 1590, 1470.

^1H NMR (200 MHz) : 1.6 (m, 1H), 1.75-2.0 (m, 2H), 2.1 (m, 1H), 2.6 (m, 1H), 2.9 (br s, 1H), 3.06 (br s, 1H), 3.35 (m, 1H), 3.65 (m, 1H), 6.15 (m, 1H olefin), 6.35 (m, 1H olefin), 7.05-7.5 (m, 5H aromatic).

2-Iodo-9-phenyl-4-oxa-tricyclo[4.2.1.$0^{3,7}$]nonane 22:



22

To a 0.5g (2.5 mmol) solution of 2-hydroxy methyl 3-phenyl bicyclo[2.2.1]hept-5-ene **5** in 10 ml of acetonitrile was added, 0.8g (5 mmol) of anhydrous $FeCl_3$ and 0.75g (5 mmol) of NaI. The solution was refluxed for 6 hrs. After completion of the reaction and usual work-up, furnished 0.74g of 2-iodo-9-phenyl-4-oxa-tricyclo[$4.2.1.0^{3,7}$]nonane **22** in 93% yield.

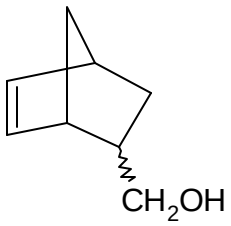
IR cm^{-1}: 3057, 2971, 2875, 1494, 1293, 1249, 1218, 1140, 1058.

^{1}H NMR (200 MHz) : 2.15 (m, 2H), 2.55 (br s, 1H), 2.72 (m, 3H), 3.85 (m, 3H), 4.8 (m, 1H), 7.1-7.45 (m, 5H aromatic).

^{13}C NMR (50 MHz):34.58 (t), 37.29 (d), 45.05 (d), 46.61 (d), 50.63 (d), 54.14(d), 73.86 (t), 89.00 (d) 126.08 (d), 126.81 (d), 128.27 (d), 143.01 (s).

Mass: 326, 234, 199, 169, 141, 115, 91, 77

2-Hydroxy methyl bicyclo[2.2.1]hept-5-ene 7:



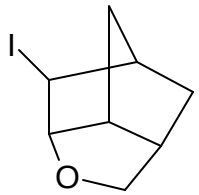
7

To a stirred ice cold solution of 1g (8.2 mmol) of bicyclo[2.2.1]hept-5-ene-2-carbaldehyde **6** in 10 ml of CH_3COOH was added, 0.93g (24.6 mmol) of $NaBH_4$ in small portion. The solution was stirred further for 10 minutes at the same temperature. After completion of the reaction and usual work-up furnished 0.95g of 2-hydroxy methyl bicyclo[2.2.1]hept-5-ene **7** in 93% yield as a mixture of *endo* and *exo* isomers (3:1).

IR cm^{-1}: 3341, 3046, 1717, 1410, 1248.

^{1}H NMR (200 MHz) : 1.25 (m, 2H), 1.47 (d, 1H J=8H), 1.8 (m, 1H), 2.25 (m, 2H), 2.5-3.0 (m, 2H), 3.1-3.5 (m, 1H), 3.5-4.0 (m, 1H), 5.95 (m, 1H olefinic), 6.1 (m, 1H olefinic).

2-Iodo-4-oxa tricyclo[4.2.1.$0^{3,7}$]nonane 23:



23

To a stirred solution of 0.5g (4 mmol) of 2-hydroxy methyl bicyclo[2.2.1]hept-5-ene **7** in 10 ml acetonitrile was added, 1.3g (8 mmol) of $FeCl_3$ and 1.2g (8 mmol) of sodium iodide. The solution was then refluxed for 4 hrs. After completion of reaction and usual work-up furnished 0.89g of 2-iodo-4-oxa tricyclo[4.2.1.$0^{3,7}$]nonane **23** in 94% yield.

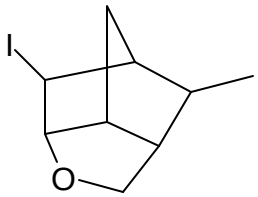
IR cm^{-1}: 2946, 1445 1060, 910.

^{1}H-NMR (200 MHz): 1.24 (d, 1H J=11Hz), 1.75 (d, 1H J=11 Hz), 1.95-2.3 (m, 2H), 2.35 (m, 2H), 2.65 (br s, 1H), 3.5-3.9 (m, 3H), 4.7 (d, 1H J=6Hz).

^{13}C NMR (50 Hz): 36.68 (t), 36.97 (d), 37.41 (t), 37.49 (d), 43.81 (d), 46.49 (d), 73.73 (t), 89.17 (d).

Mass: 250, 167, 123, 93, 79.

2-Iodo-9-methyl-4-oxa tricyclo[4.2.1.$0^{3,7}$]nonane 24:



24

To a solution of 0.5g (3.6 mmol) 2-hydroxymethyl 3-methyl bicyclo[2.2.1]hept-5-ene **9** in 10 ml of acetonitrile was added, 1.17g (7.2 mmol) of anhydrous $FeCl_3$ and 1.08g

(7.2 mmol) of NaI. The solution was refluxed for 5 hrs. After completion of reaction and usual work-up furnished 0.96g of 2-iodo-9-methyl-4-oxa tricyclo[4.2.1.$0^{3,7}$]nonane **24** in 100% yield.

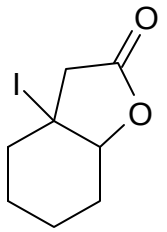
IR cm^{-1}: 1214, 1067, 1027, 759.

^{1}H NMR(200 MHz): 1.07 (d, 3H J=8Hz), 1.48 (m, 1H), 1.85 (m, 1H), 1.95 (br s, 1H), 2.1 (d, 2H J=8Hz), 2.58 (m, 1H), 3.6 (br s, 1H), 3.7 (m, 2H), 4.65 (m, 1H).

^{13}C NMR (50 MHz): 31.18 (q), 44.77 (t), 48.31 (d), 54.23 (d), 56.79 (d), 56.94 (d), 60.79 (d), 83.92 (t), 99.03 (d).

Mass: 264, 167, 137, 127, 119, 107, 91, 79.

3-Iodo perhydro cyclohexa[b] furan-2-one 25:



25

To stirred solution of 0.5g (3.5 mmol) of 2-(1-cyclohexenyl) acetic acid **14** in 10 ml of acetonitrile was added, 1.15g (7.0 mmol) of anhydrous $FeCl_3$ and 1.07 (7.0 mmol) of NaI. The solution was refluxed for 6 hrs. After completion of reaction and usual work-up furnished 0.722g of 3_a-iodo perhydro cyclohexa[b] furan-2-one **25** in 76% yield.

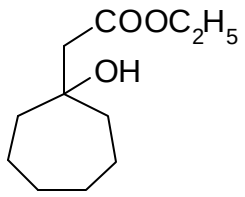
IR cm^{-1}: 1786, 1237, 1200, 1156, 755.

^{1}H NMR (200 MHz): 1.65 (m, 6H), 1.9-2.4 (m, 3H), 2.85-3.4 (m, 2H), 4.8 (m, 1H).

^{13}C NMR (50 MHz): 19.35 (t), 22.22 (t), 24.50 (t), 37.18 (s), 39.53 (t), 50.23 (t), 86.29 (d), 174.29 (s).

Mass: 266.

Ethyl-2-(1-hydroxy cycloheptyl) acetate 16:



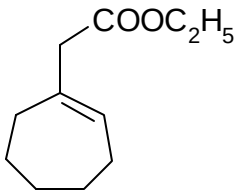
16

To a refluxed solution of 2g (17.85 mmol) of cycloheptanone **15** in 25 ml benzene and 1.16g (53.55 mmol) of Zn, was added a solution of 3.72g (22.3 mmol) of ethyl bromoacetate **11** in 25 ml benzene dropwise. The solution was then refluxed further for 6 hrs. After completion of reaction, the reaction mixture was cooled and quenched with 25 ml of 10% HCl solution. The solution was then filtered and the organic layer was separated, whereas aqueous layer was extracted with 3x25 ml portions of ethyl acetate. The combined organic layer was then dried over anhydrous Na_2SO_4, filtered and on concentration on rotary evaporator and column purification (SiO_2) furnished 2.2g of ethyl-2-(1-hydroxy cycloheptyl) acetate **16** in 62% yield.

IR cm^{-1}: 3523, 2925, 1716, 1201.

^{1}H NMR (200 MHz) : 1.25 (t, 3H $-COOCH_2\underline{CH_3}$), 1.3-1.95 (m, 12H), 2.47 (s, 2H-$\underline{CH_2}COOCH_2CH_3$), 3.3 (br s 1H –OH), 4.15 (q, 2H $-COO\underline{CH_2}CH_3$).

Ethyl 2-(1-cycloheptenyl) acetate 17a:



17a

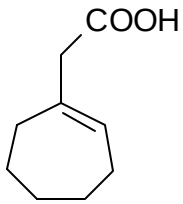
To an ice cold solution of 1.8g (5.56 mmol) of ethyl-2-(1-hydroxy cycloheptyl)

acetate **16** and 0.9g (6.94 mmol) of pyridine in 10 ml of dichloromethane was added, 1.73g (6.94 mmol) of $SOCl_2$ dropwise. The mixture was stirred for 0.5 hrs. After completion of reaction, 25 ml of saturated solution of $NaHCO_3$ was added. The organic layer was separated whereas the aqueous layer was extracted with 3x15 ml portions of dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and on concentration and column purification (SiO_2) furnished 1.47g mixture of ethyl 2-(1-cycloheptenyl) acetate **17a** and á, â-unsaturated ester in 90% yield.

IR cm^{-1}: 2925, 1737, 1716, 1635, 1446, 1147.

^1H NMR (200 MHz) : 1.25 (t, 3H), 1.35-1.9 (m, 6H), 2-2.25 (m, 2H), 2.35 (m, 1H), 2.85 (m, 1H), 2.95 (s, 2H), 4.15 (q, 2H), 5.7 (m, 1H olefinic).

2-(1-Cycloheptenyl) acetic acid 18a:



18a

To a 1g (5.5 mmol) solution of the mixture of á, â-and â, ã-ester in 15 ml of MeOH/Water (3:1) system was added, 0.92g (16.5 mmol) of powdered potassium hydroxide. The reaction mixture was refluxed for 4 hrs. After completion of the reaction, the reaction mixture was cooled and 25 ml of saturated $NaHCO_3$ was added. The solution was then extracted with 3x25 ml portions of EtOAc. The aqueous layer was then neutralized with 15 ml. of dil. H_2SO_4 which was then extracted with 3x25 ml. portions of dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and was then concentrated on rotary evaporator under reduced pressure. The residue thus obtained on purification by column chromatography (SiO_2) furnished 0.78g of the acid as

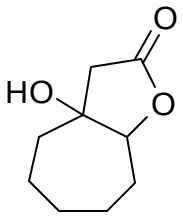
a (1:4) mixture of á, â-and â, ã-acids in 92% yield.

IR cm^{-1}: 3500-2500 (broad hump), 1686, 1627, 1417, 1256, 877.

^1H NMR (200 MHz) : 1.35-2.25 (m, 8H), 2.4 (m, 2H), 2.95 (m, 2H), 5.65 (m, 1H olefinic) 11.05 (br s, 1H -COOH).

Mass : 154, 137, 126, 94, 79, 67.

3-Hydroxy perhydro cyclohepta[b] furan-2-one 20:



20

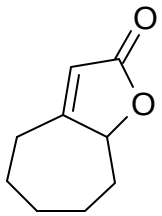
A 20 ml test tube was charged with 0.546g (3 mmol) of -unsaturated ester and 0.526 (4.5 mmol) N-methylmorpholine N-oxide (NMO) in acetonitrile-water mixture (9:1, 5 ml.) and a catalytic amount of osmium tetroxide in toluene was injected into it. The reaction was monitored by TLC. After stirring for 12 hrs at room temperature, solid sodium metabisulfite ($Na_2S_2O_5$) was added and the mixture stirred for further 0.5 hr. The reaction mixture was filtered and the solid washed with chloroform (30 ml). The combined organic layer was washed with 10% HCl (10 ml), dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under vacuum. The residue thus obtained was chromatographed over silica gel using 20% ethyl acetate-pet.ether to furnish 0.36g of cyclic hydroxy compound **20** in 60% yield.

IR cm^{-1}: 3454, 2935, 2862, 1770, 1245, 1197, 908, 731.

^1H NMR (200 MHz) : 1.1-1.5 (m, 1H), 1.5-1.9 (m, 6H), 1.95-2.5 (m, 3H), 2.65 (s, 2H), 2.9 (br s, 1H), 4.4 (m, 1H).

^{13}C NMR (50 MHz): 23.47 (t), 25.23 (t), 25.5 (t), 36.52 (t), 45.3(t), 78.24 (s), 86.84 (d), 176.6 (s).

4,5,6,7,8,8a-Hexahrdro-cyclohepta[b]furan-2-one 26



26

To a solution of 0.5g (3.25 mmol) of 2-(1-cycloheptenyl) acetic acid **18a** in 10 ml of acetonitrile was added, 1.05g (6.5 mmol) of anhydrous $FeCl_3$ and 0.97g (6.5 mmol) of NaI. The solution was refluxed for 12 hrs. After completion of reaction and usual work-up and column purification (SiO_2) 0.37g of butenolide **26** was obtained in 75% yield.

IR cm^{-1}: 2937, 1751, 1626, 1446, 1452, 1355, 1190.

^{1}H NMR (200 MHz) : 1.1-1.65 (m, 4H), 1.65-2.00 (m, 3H), 2.25 (m, 1H), 2.7 (m, 2H), 4.95 (m, 1H), 5.75(s, 1H).

^{13}C-NMR (50 MHz): 25.49 (t), 26.03 (t), 28.62 (t), 29.57 (t), 33.32 (t), 84.52 (d), 115.5 (d), 172.93 (s), 174.54 (s).

Mass : 152, 123, 95, 81, 67.

Conversion of 20 into 26 :

Method a:

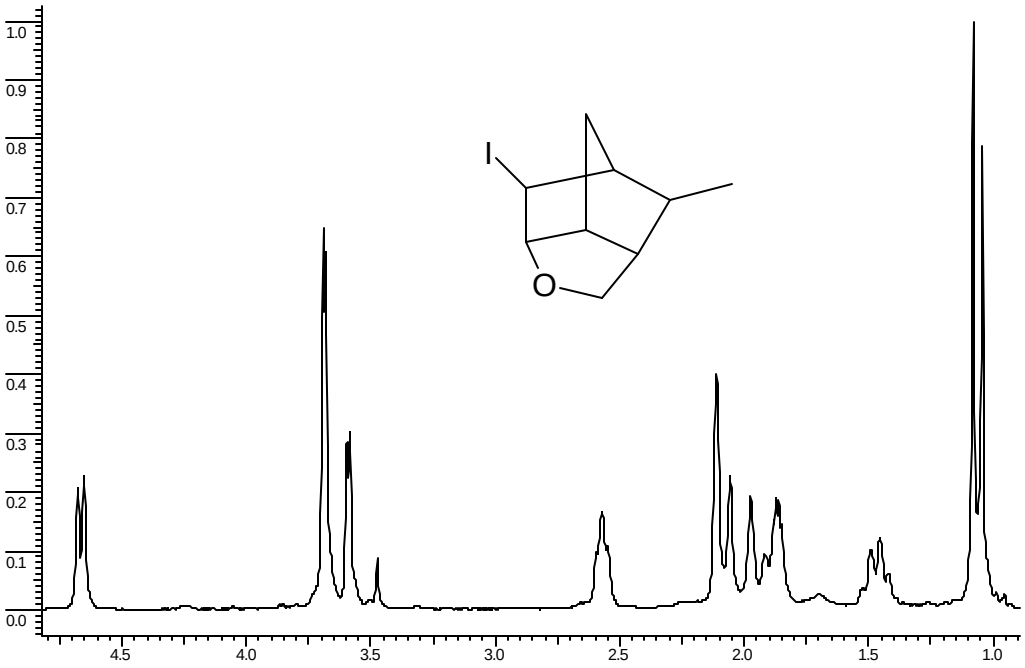
To a ice cold solution of 0.2g (1.3 mmol) of 3_a-hydroxy perhydro cyclohepta[b] furan-2-one and 0.13g (1.6 mmol) of pyridine in 5 ml of dichloromethane was added, 0.19g (1.6 mmol) of $SOCl_2$ dropwise. The mixture was stirred for 0.5 hrs. After completion of reaction, 10 ml of saturated solution of $NaHCO_3$ was added. The organic layer was separated whereas the aqueous layer was extracted with 3x10 ml portions of dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and on concentration under reduced pressure and column purification (SiO_2) 0.145g of butenolide **26** was obtained in 82% yield.

Method b:

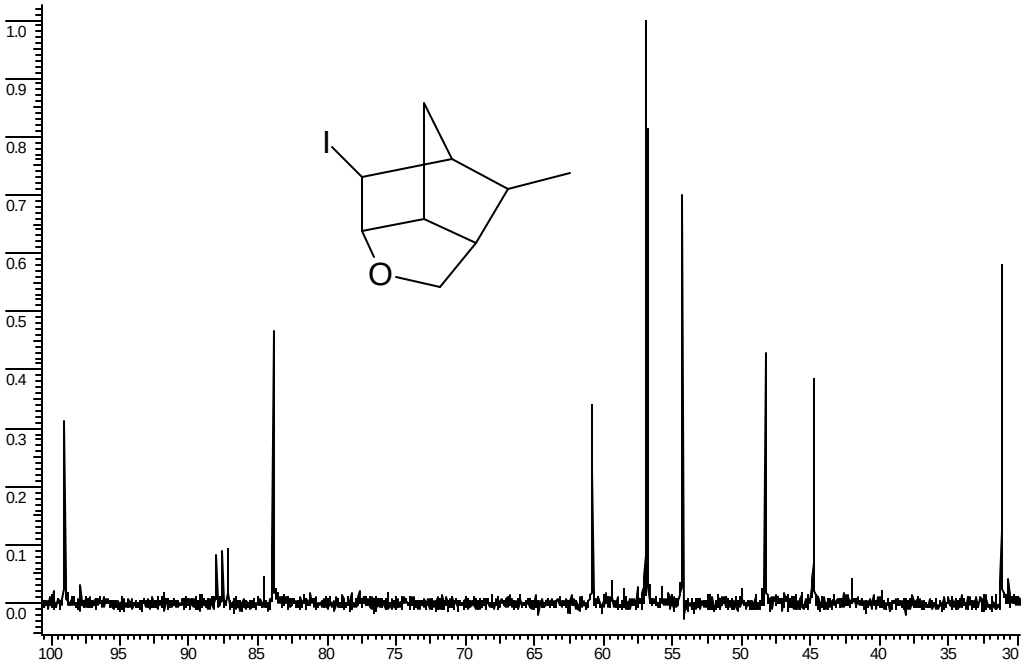
To a solution of 0.2g (1.3 mmol) of 3_a-hydroxy perhydro cyclohepta[b] furan-2-one in 5 ml of toluene, was added a catalytic amount of p-TSA. The mixture was refluxed for 40 mins. The solution was then cooled and neutralized with 5 ml saturated solution of $NaHCO_3$. The organic layer was separated and the water layer was extracted with 3x5 ml of ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and on concentration and column purification (SiO_2) furnished 0.11g of butenolide **26** in 62% yield.

References:

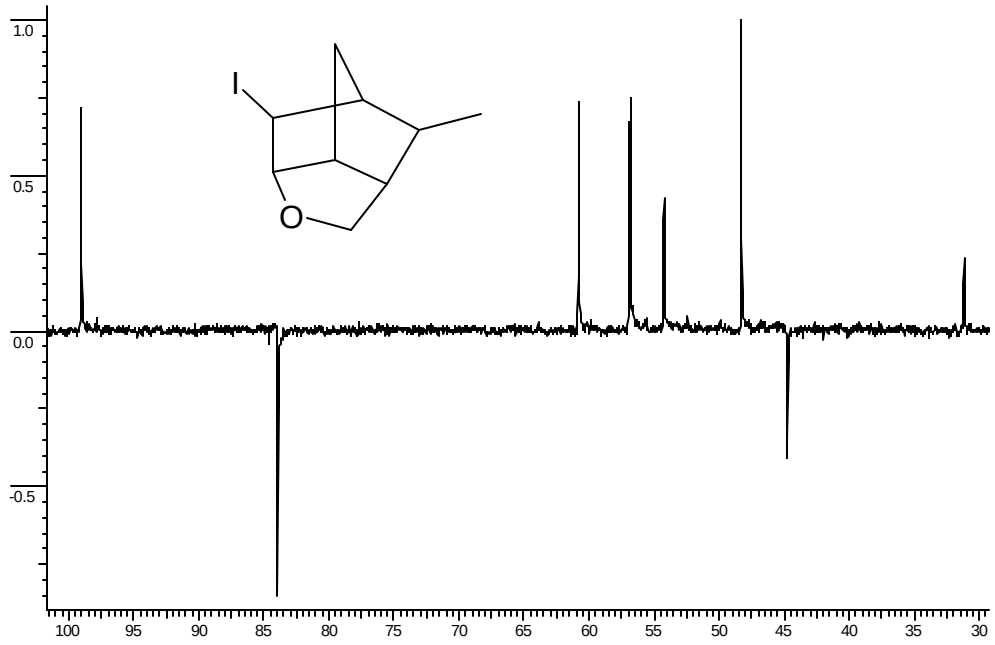
1. Corey, E. J; Noyori, R. *Tetrahedon Letters,* **1970**, 311.
2. Denishefsky, S; Schuda, P. et. al*. J. Am. Chem. Soc***, 1977,** 6066.
3. Lythgoe, B; Nanbudiry, M. E.; Tideswell, J. *Tetrahedron Letters,* **1977**, 3685.
4. Norman, W. *Tetrahedron Letters,* **1977,** 2805.
5. Bougault, M. J; *Compt. Rend*., **1904**, 139, 864.
6. Richard, T. A; Kenneth L.*J. Am. Chem. Soc*, **1953**, 1048.
7. Tamelen V. and Shamma, M. *J. Am. Chem. Soc.*, **1954,** 215.
8. Bartlett, P. D; Myerson, J. *J. Am. Chem. Soc,* **1978,** 100, 3950.
9. Robert, D. E; Joseph, W. M; Herman, S. *Synthesis,* **1988** 862.
10. April, C. R; Robert, C. M. April; M. S. *Synlett*, **1993**, 899.
11. Chavan, S. P.; Zubaidha, P. K.; Ayyangar, N. R. *Tetrahedron Letters,* **1992,** 4605.



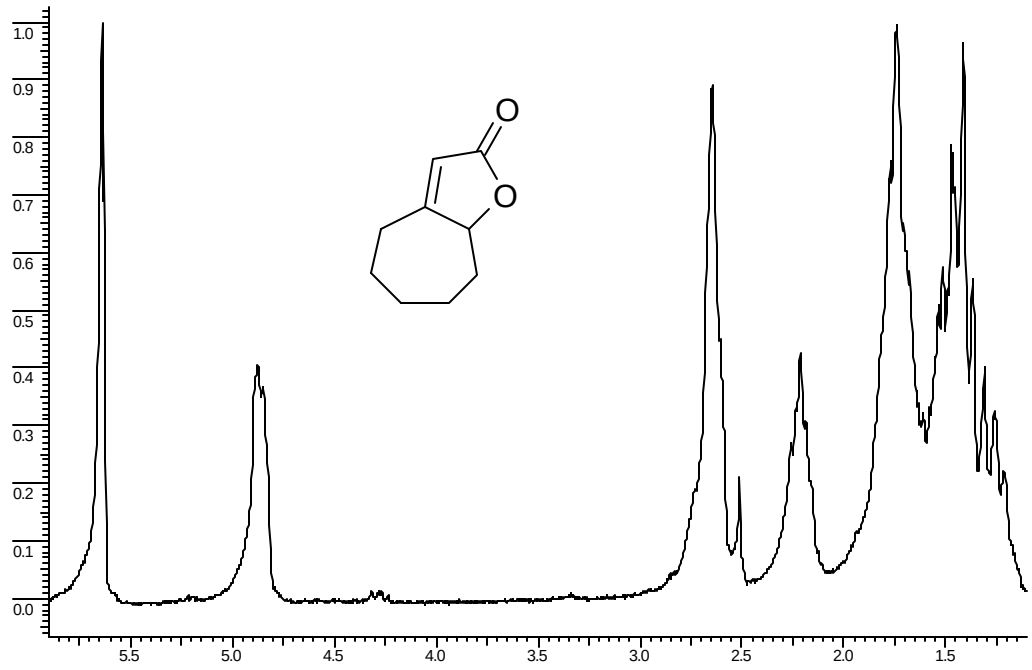
^{1}H NMR of 2-Iodo-9-methyl-4-oxa tricyclo[4.2.1.0^{3,7}]nonane ($CDCl_3$ 200 MHz)



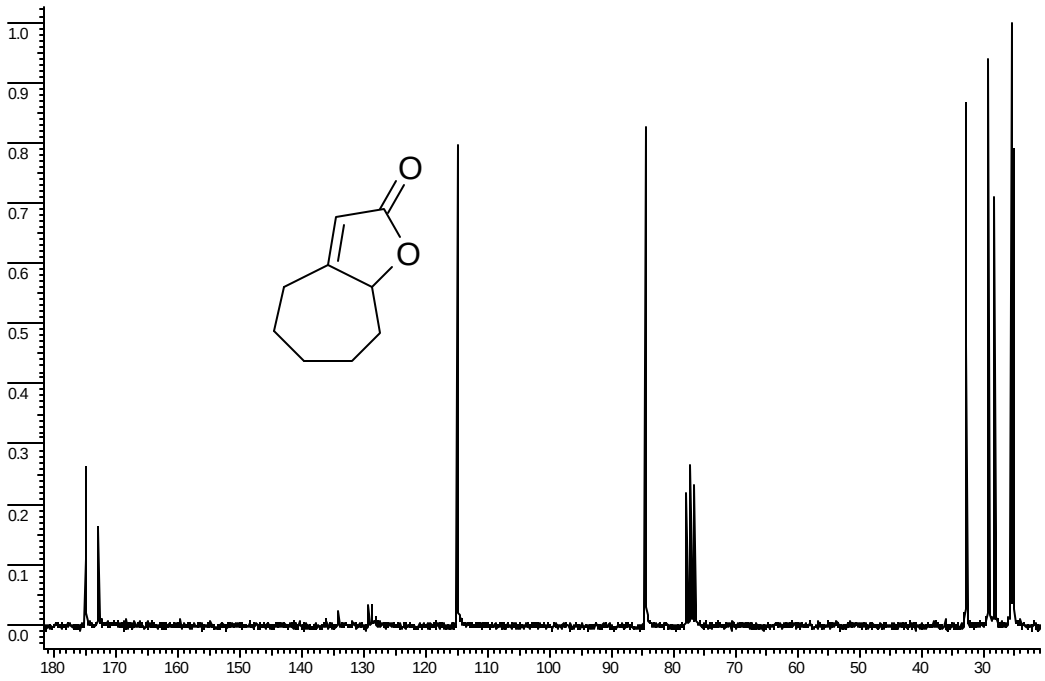
^{13}C NMR 2-Iodo-9-methyl-4-oxa tricyclo[4.2.1.0^{3,7}]nonane ($CDCl_3$ 200 MHz)



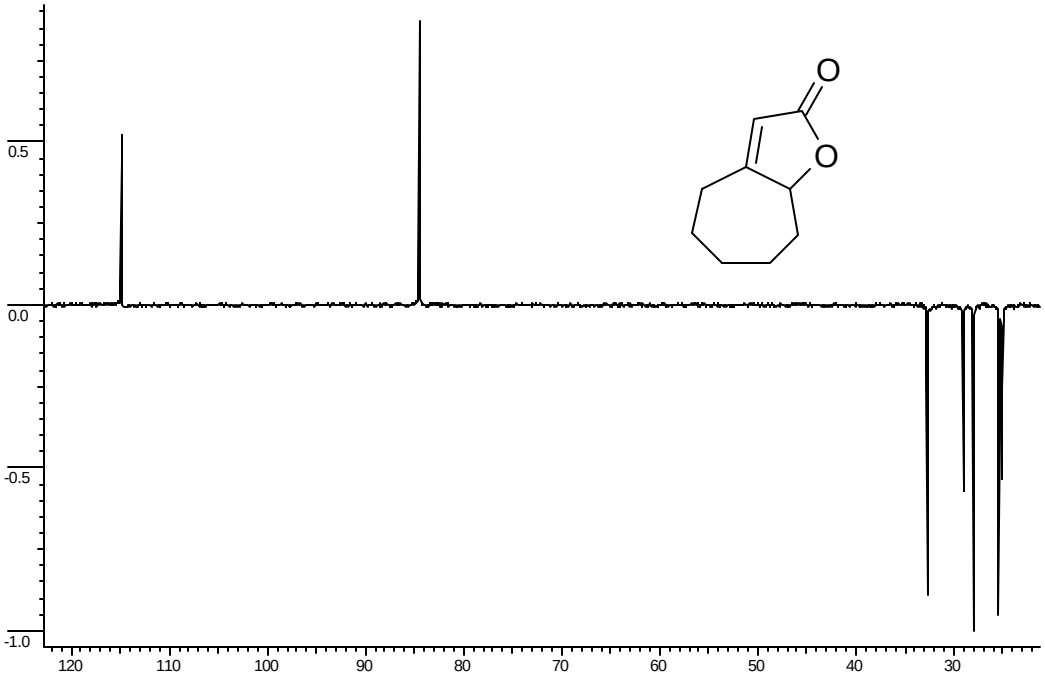
DEPT of 2-Iodo-9-methyl-4-oxa tricyclo[4.2.1.0^{3,7}]nonane ($CDCl_3$ 200 MHz)



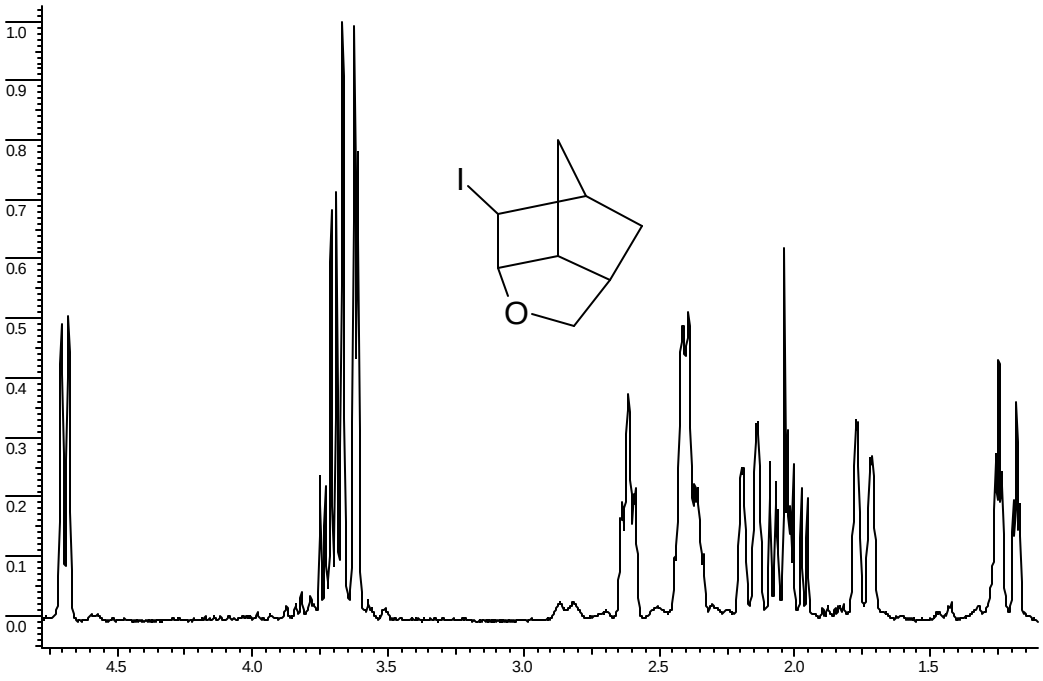
^{1}H NMR 4,5,6,7,8,8a-Hexahydro-cyclohepta[b]furan-2-one ($CDCl_3$ 200 MHz)



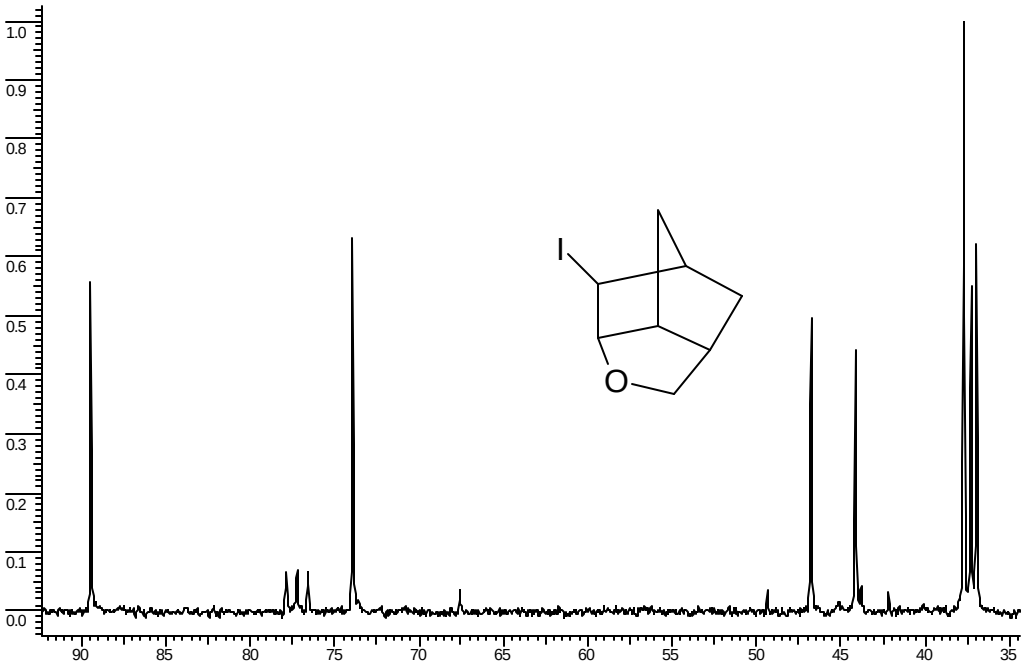
^{13}C NMR 4,5,6,7,8,8a-Hexahydro-cyclohepta[b]furan-2-one ($CDCl_3$ 200 MHz)



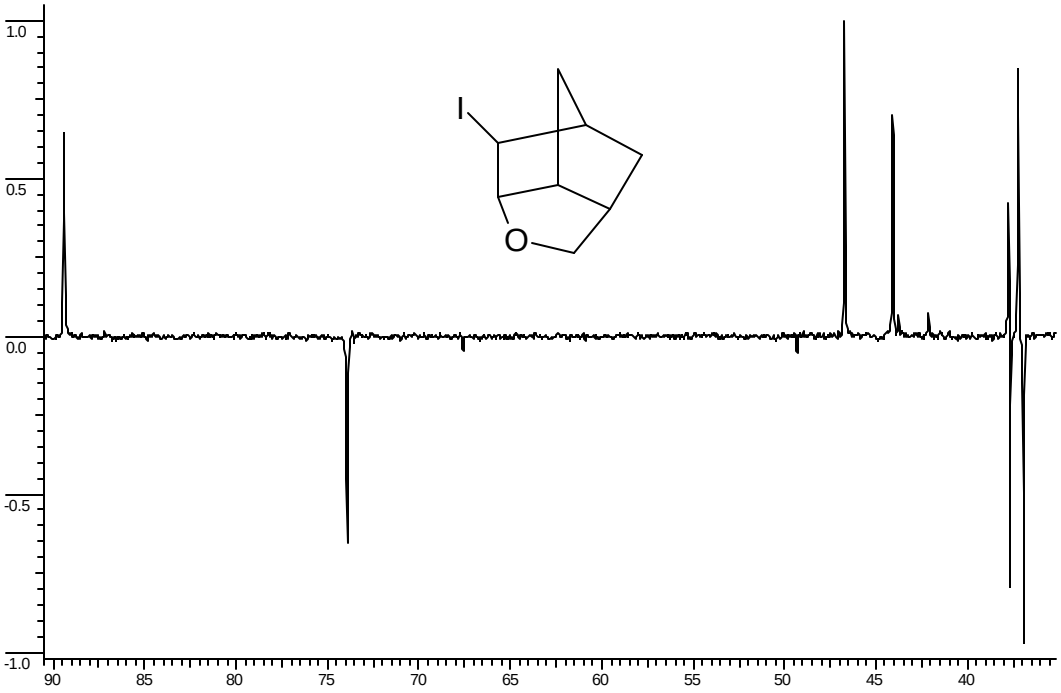
DEPT of 4,5,6,7,8,8a-Hexahydro-cyclohepta[b]furan-2-one ($CDCl_3$ 200 MHz)



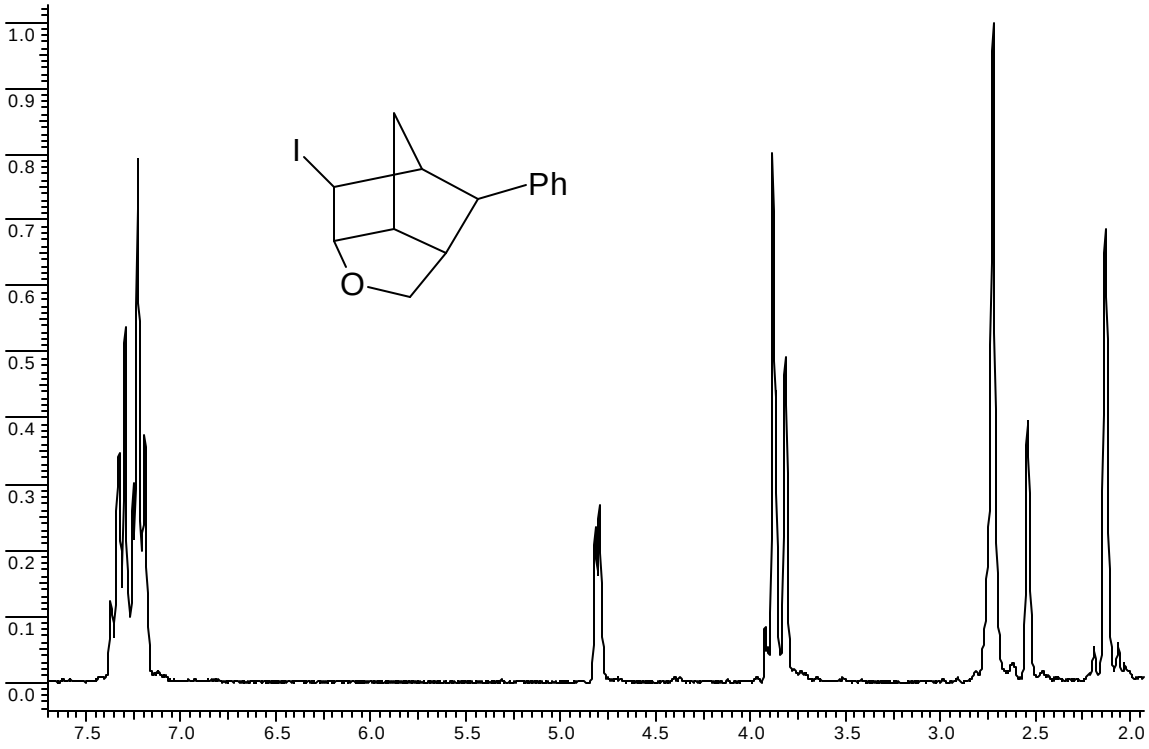
^{1}H NMR 2-Iodo-4-oxa tricyclo[4.2.1.0^{3,7}]nonane ($CDCl_3$ 200 MHz)



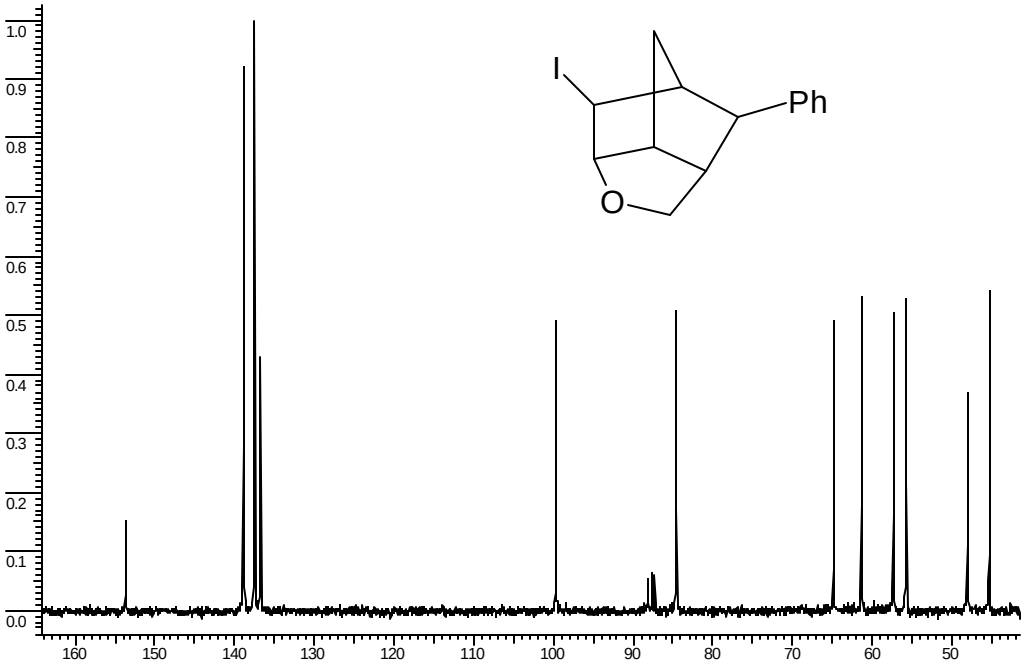
^{13}C NMR 2-Iodo-4-oxa tricyclo[4.2.1.0^{3,7}]nonane ($CDCl_3$ 200 MHz)



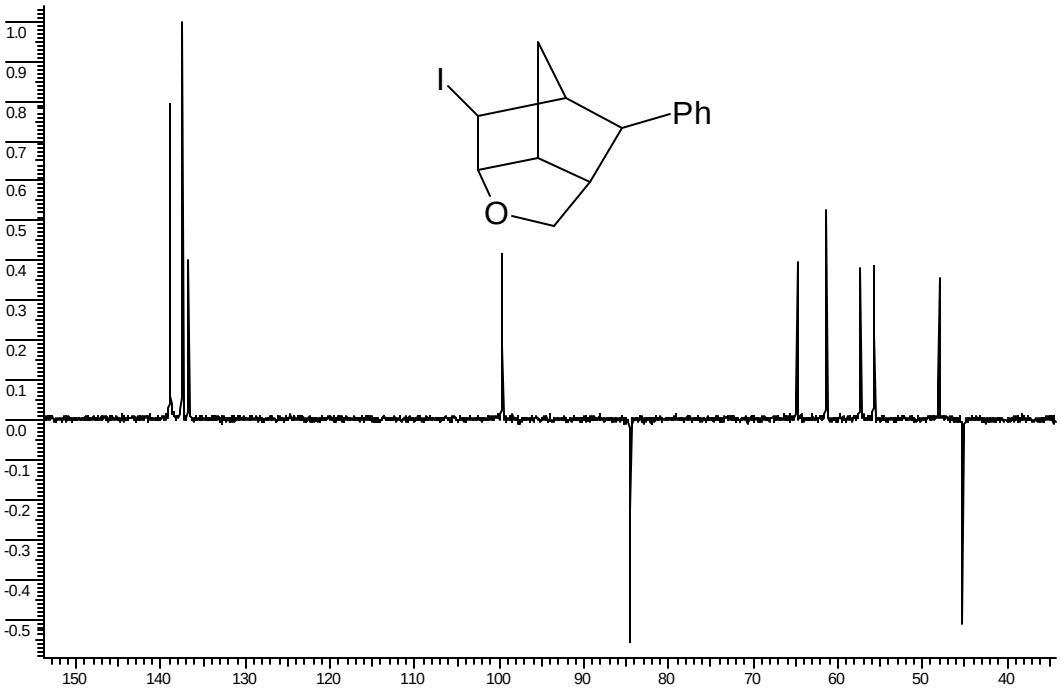
DEPT of 2-Iodo-4-oxa tricyclo[4.2.1.0^{3,7}]nonane ($CDCl_3$ 200 MHz)



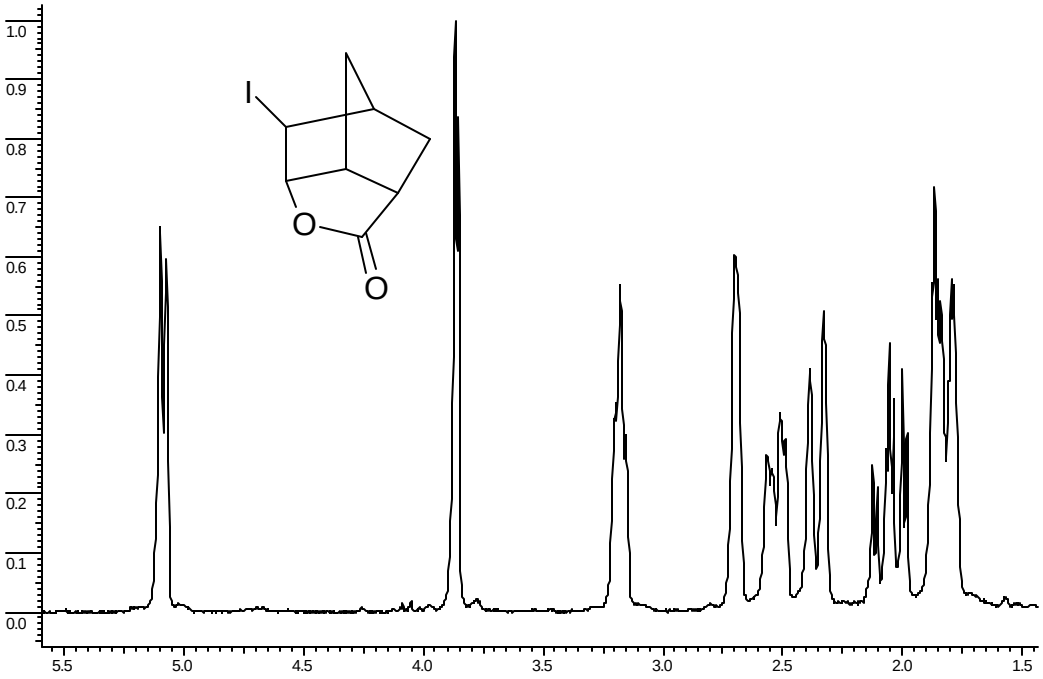
^{1}H NMR 2-Iodo-9-phenyl-4-oxa-tricyclo[4.2.1.0^{3,7}]nonane ($CDCl_3$ 200 MHz)



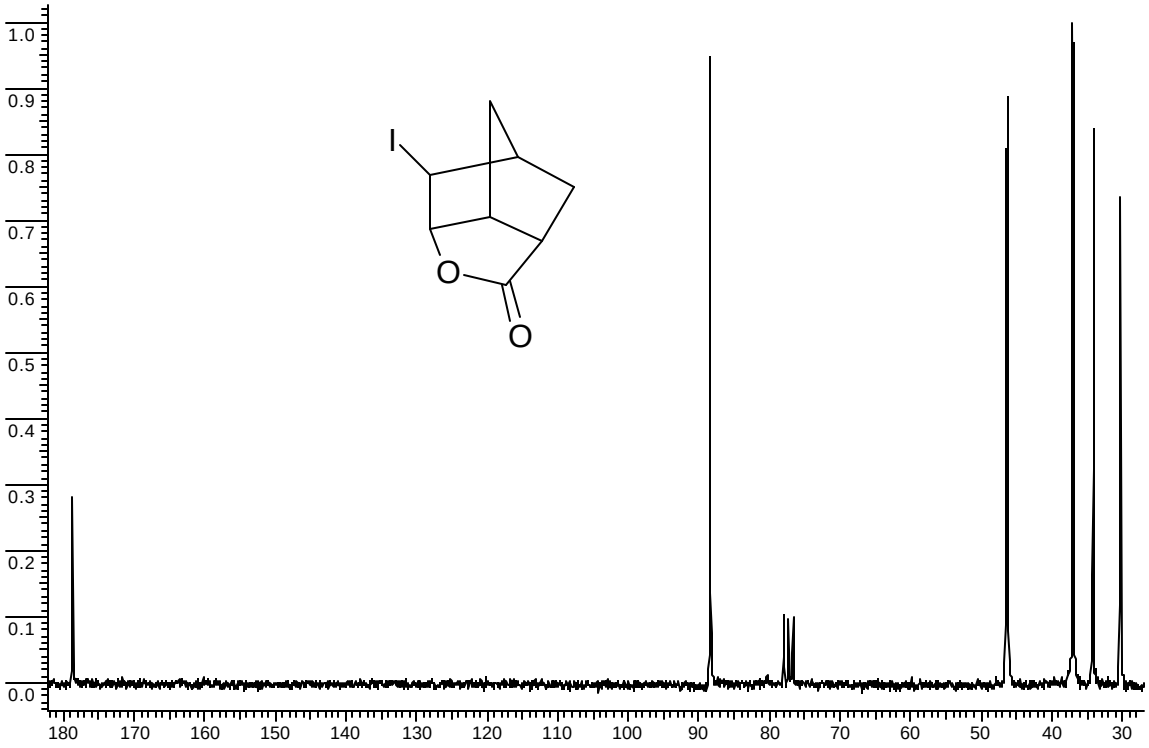
^{13}C NMR of 2-Iodo-9-phenyl-4-oxa-tricyclo[4.2.1.0^{3,7}]nonane ($CDCl_3$ 200 MHz)



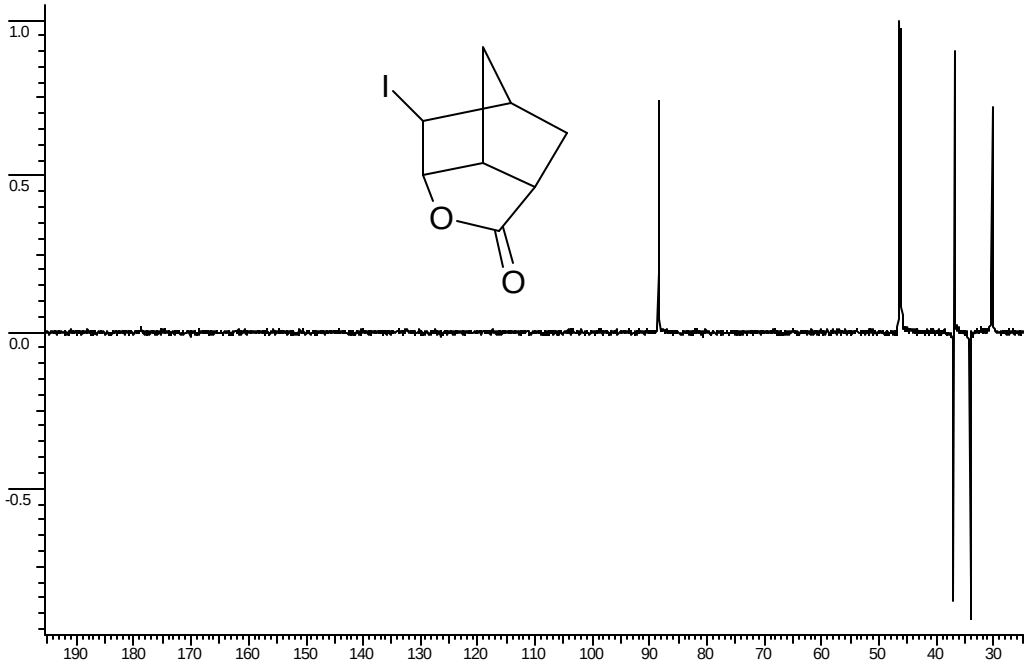
DEPT of 2-Iodo-9-phenyl-4-oxa-tricyclo[4.2.1.0^{3,7}]nonane ($CDCl_3$ 200 MHz)



^{1}H NMR 9-Iodo-5-oxa tricyclo[4.2.1.0^{3,7}]nonan-4-one ($CDCl_3$ 200 MHz)



^{13}C NMR of 9-Iodo-5-oxa tricyclo[4.2.1.0^{3,7}]nonan-4-one ($CDCl_3$ 200 MHz)

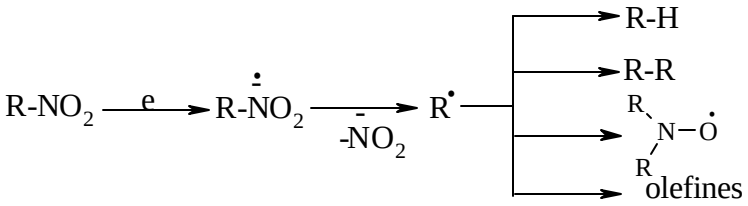


DEPT of 9-Iodo-5-oxa tricyclo[4.2.1.$0^{3,7}$]nonan-4-one ($CDCl_3$ 200 MHz)

Chapter 3:

Reductive cleavage of γ-nitro α, β-unsaturated esters mediated by Metals/MeOH

Nitro group is a versatile functionality that can be utilized for C-C bond formation in a variety of ways. It can be oxidatively cleaved to generate carbonyl compounds or can be reductively cleaved to furnish the hydrocarbon. The electrochemical and chemical reductive cleavage of tertiary nitro compounds leads to an unstable anion radical which eliminates the nitrite ion giving the corresponding free radical. The subsequent reaction of the free radical gives various compounds including denitrated products (R-H).



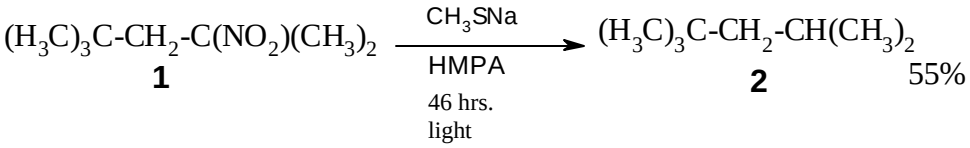
Denitration Reaction (Literature methods).

A vast amount of work has been devoted to the reductive cleavage of C-NO_2 bond using different reagents. Some of the important ones are as follows.

1. Sodium salt of methanethiol :

Kornblum, N.; Carlson,S. C.; Smith, R. G. *J. Am.Chem. Soc.*, **1979**, *101*, 647.

In 1979, Kornblum *et. al.*[1] discovered that the nitro group in tertiary nitro compounds is replaced by hydrogen on treatment with the sodium salt of methanethiol.



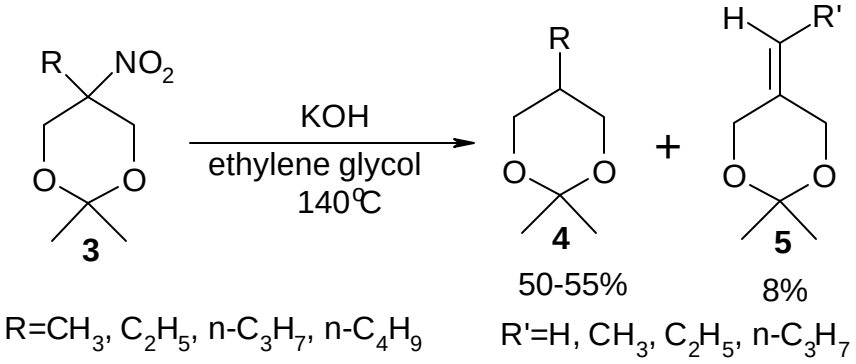
Limitation :

The method using sodium methanethiolate can be applied to various tertiary nitro compounds, but it has drawbacks due to the high nucleophilicity and the lack of hydrogen-donor ability of sodium methanethiolate.

2. KOH :

Krasuska, L.; Piotrowska, H.; Urbanski, T. *Tetrahedron Letters*, **1979**, *14*, 1243.

This reaction involves the cleavage of C-N bond of 5-nitro 1, 3-dioxanes and replacing the tertiary nitro group by hydrogen atom to yield 1, 3-dioxanes.[2]



Limitation :

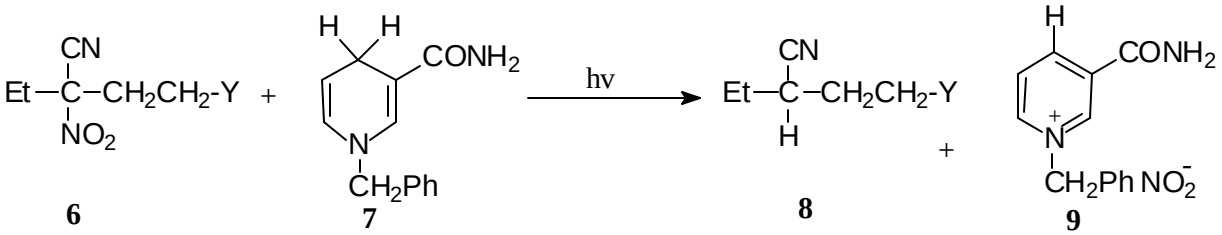
KOH is a strong base rather than a reducing agent.

3. 1-Benzyl-1, 4-dihydronicotinamide :

Ono, N.; Tamura, R.; Kaji, A. *J. Am. Chem. Soc*., **1980**, *102*, 4017

Ono *et. al*[3]. have reported light mediated reductive removal of aliphatic tertiary

nitro group with 3 eq. of 1-benzyl-1, 4-dihydronicotinamide (BNAH) at room temperature and N_2 atmosphere.



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

Y = COMe, CN, COOMe

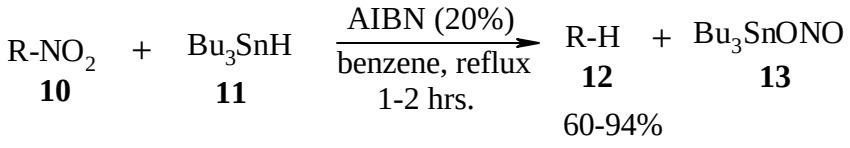
Limitation ;

The compound which can be denitrated with BNAH are limited to those that are activated by a cyano, an ester or a keto group.

4. Bu_3SnH :

Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron letters*, **1981**, *22*, 1705.

In this study it was demonstrated that the nitro group in tertiary or secondary aliphatic nitro compound can be replaced by hydrogen on treatment with tributyl tin hydride.[4]



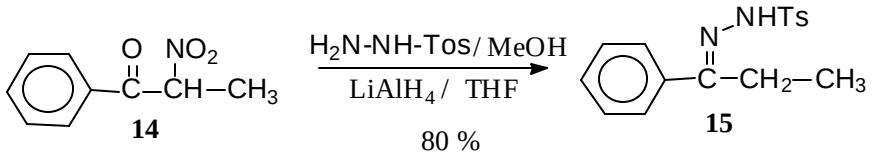
Limitation :

Use of Bu_3SnH is hazardous and toxic which creates waste disposal problem.

5. Lithium Aluminium Hydride :

Rosini, G.; Ballini, R. *Synthesis*, **1983**, 137.

This method consists of the conversion of á-nitro ketones into the corresponding tosyl hydrazones followed by treatment with LAH in THF at 0-10º C to furnish therespective



denitrated products in 65-91% yield.[5]

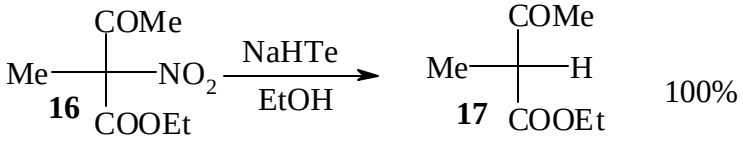
Limitation :

Lithium aluminium hydride reduces the nitro group to the amino group in most cases.

6. Sodium hydrogen telluride :

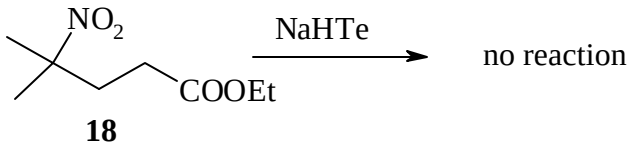
Suzuki, H.; Takaoka, K.; Osuka, A. *Bull.Chem. Soc. Jpn*., **1985**, *58*, 1067

NaHTe is a useful reagent for replacement of a class of tertiary nitro by hydrogen.[6]



Limitation :

Sodium Hydrogen telluride has wider applicability than BNAH, but it has limitations, namely the need of an activating group for smooth denitration. Moreover, simple nitroalkanes are inert to sodium hydrogen telluride *e.g.*

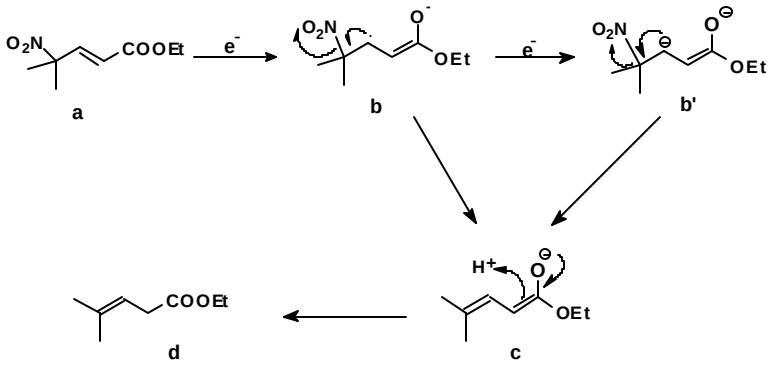


The reluctance of nitro compounds towards NaHTe might be ascribed to the failure of the initial electron transfer from NaHTe to these compounds.

Therefore, nitro group situated at ã position with respect to ketone, ester, and nitrile were quantitatively recovered after prolonged treatment with NaHTe even at refluxing conditions in ethanol.

Present work:

In view of the above limitations it was decided to explore a new mild method of reductive removal of nitro group employing Al, Mg or Zn in methanol as the reducing agent.

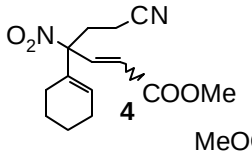
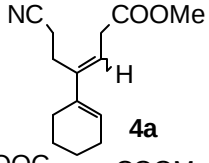
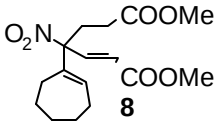
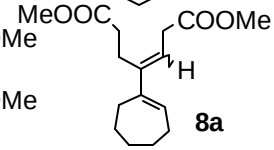
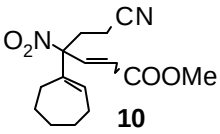
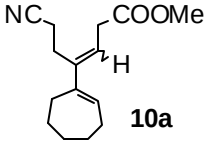
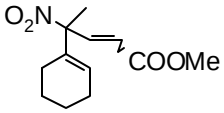
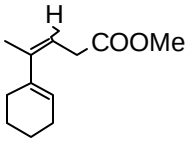
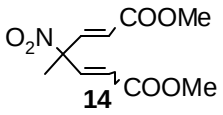
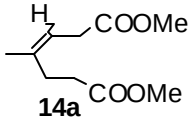
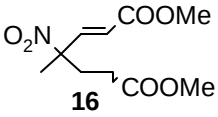
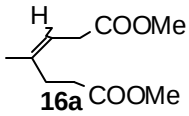
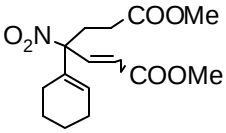
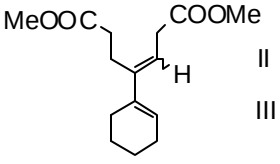


Scheme-1

As a logical extension it was surmised (**scheme-1**) that γ-nitro-α,β-unsaturated compounds when subjected to the treatment of appropriate metal/MeOH would lead to the formation of β, γ-unsaturated esters by addition of one electron across the double bond which would generate radical anion **b** which either can eliminate to **c** or accept another electron to form **b'** which by elimination of nitro group would lead to **c**. In order to test the efficacy of our hypothesis we synthesized a variety of γ-nitro-α,β-unsaturated esters (**1-8**) by the Michael addition[7] of nitro compounds to the corresponding activated acetylenes in the presence of base. These were then subjected to the treatment with metals/MeOH. Earlier[8] studies from our group has shown that magnesium in methanol of γ-nitro-α,β-unsaturated esters brings about reductive denitration to furnish β, γ-unsaturated esters. In order to explore other metals and decide the geometry of the newly created double bond, it was decided to explore other metals. **Table 1** shows that a wide variety of γ-nitro α,β-unsaturated ester were reductively cleaved using different metals in MeOH. The ratio of E:Z isomers of compound **6a** was determined to be 3:2 from spectral

Table 1

Reductive cleavage of γ-nitro α,β-unsaturated esters mediated by using different metals in MeOH.

entry	substrate	product	method	yield
1.	 **4**	 **4a**	II III	27% 40%
2.	 **8**	 **8a**	II III	37% 38%
3.	 **10**	 **10a**	II III	33% 33%
4.	 **12**	 **12a**	II III	33% 46%
5.	 **14**	 **14a**	II III	26% 47%
6.	 **16**	 **16a**	I II III	40% 35% 22%
7.	 **18**	 **18a**	II III	39% 30%

:

Methods : Al (10 eq.); MeOH, II, Mg (10 eq.); MeOH, III, Zn (10 eq.); MeOH.

analysis (^{1}H NMR, ^{13}C NMR) .[8] The methyl on the double bond in E isomers appeared at 1.56 ppm while for the Z isomer it appeared at 1.65 ppm. Similarly the ^{13}C NMR analysis

of the methyl of E isomer resonated at 15.75 ppm while that of Z isomer appeared at 22.37 ppm. This was in accordance with the literature reported values.[9] The geometry of the double bond was also confirmed by NOE experiments by irradiation of the Me and olefinic proton where an enhancement was observed for Z isomer.

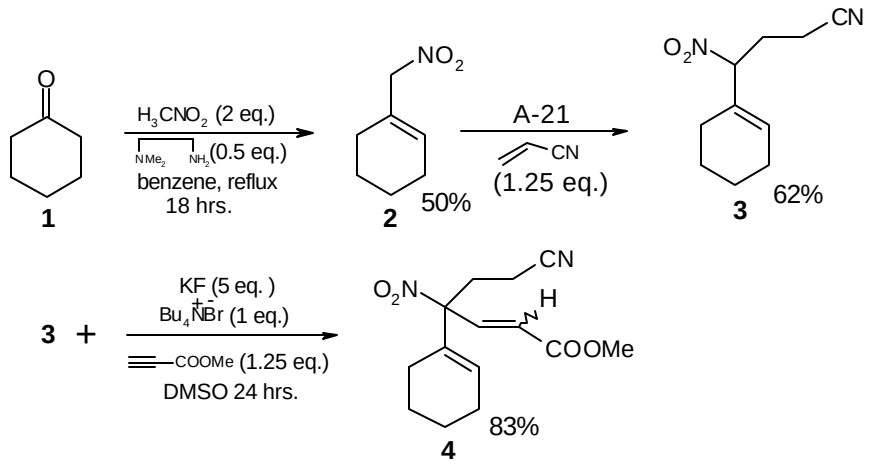
Effect of the geometry of double bond on the product stereochemistry : In order to study the effect of the geometry of the double bond on the product geometry, careful chromatography of 16 furnished E isomer in pure form. When pure E isomer was subjected to the treatment of Mg/MeOH the reaction conditions a mixture of β, γ-unsaturated ester 16a was obtained in the ratio E:Z=3:2. This study indicates that irrespective of the geometry of the double bond in the starting nitro olefin, same product distribution is observed.

From the table 1 it is apparent that of the three different metals tried (*i.e*. Mg, Al & Zn), the use of zinc proved to be slightly advantageous (entries 1, 4 & 5). The yields obtained by our method are moderate, due to formation of polar intractable compounds whose structure could not be ascertained. However, the â, ã-unsaturated esters formed in the reaction could be readily separated by column chromatography as it was relatively non-polar. The ease of operation, mild conditions employed, and easy availability of the metals make our method an attractive alternative to the existing methods,[1-6] which employ expensive and/or harsh conditions. Although there is no drastic change if one metal is substituted by another one, but by proper choice of reagents and conditions, it has a potential of developing into a synthetically attractive method.

In conclusion, a mild method for the elimination of γ-nitro α,β-unsaturated ester has been developed, by treating compounds having tertiary allylic nitro functionality tethered to α, β-unsaturated esters employing different metals in MeOH.

Preparation of substrates :

4-(Cyclohex-1-ene) 4-nitro 6-cyano methyl pent-2-enoate 4:



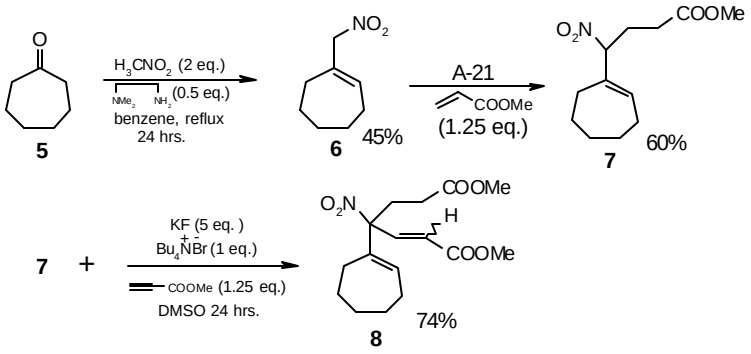
Scheme 2

According to the reported procedure,[9] condensation of cyclohexanone **1** with nitromethane in the presence of N, N-dimethyl ethylenediamine as the base furnished 1-(1-nitromethyl) cyclohexene **2** in 50% yield. Michael addition of 1-(1-nitromethyl) cyclohexene **2** to acrylonitrile in the presence of A-21 without any solvent was carried out at 0ºC to furnish 4-(cyclohex-1-ene) 4-nitro butyronitrile **3** in 62% yield. Second Michael addition of product **3** to methyl propiolate with potassium fluoride as base and tetrabutyl ammonium bromide as phase transfer catalyst in dimethyl sulphoxide as the solvent furnished 4-(cyclohex-1-ene) 4-nitro 6-cyano methyl pent-2-enoate **4** in 83% yield.

4-(Cyclohept-1-ene) 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate 8:

1-(Cyclohept-1-ene) nitromethane **6** was prepared by condensation of cycloheptanone **5** with nitroethane employing N, N-dimethyl ethylenediamine as base, in 45% yield.

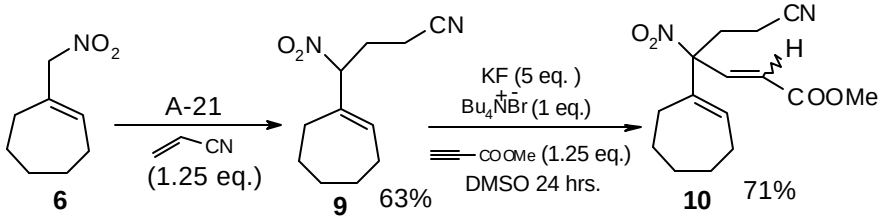
Michael addition of compound **6** to methyl acrylate using Amberlyst-21 furnished 4-(cyclohept-1-ene) 4-nitro 2-butenoate **7** in 60% yield.



Scheme 3

Second Michael addition of product **7** to methyl propiolate under phase transfer conditions was carried out to get 4-(cyclohept-1-ene) 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate **8** as viscous oil in 74% yield.

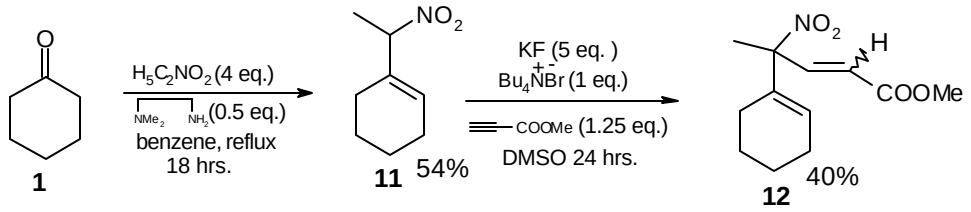
4-(Cyclohept-1-ene) 6-cyano methyl hex-3-enoate 10:



Scheme 4

Michael addition of compound **6** to acrylonitrile on the surface of A-21 at 0ºC furnished 4(cyclohept-1-ene) 4-nitrobutyronitrile **9** in 63% yield. Second Michael addition of product **9** to methyl propiolate under phase transfer conditions was carried out to get 4-(cyclohept-1-ene) 6-cyano 4-nitro methyl hex-2-enoate **10** as viscous oil in 71% yield.

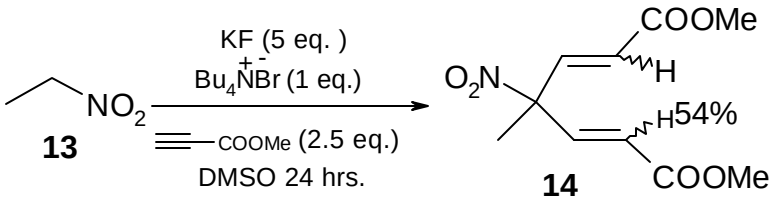
4-(Cyclohex-1-ene) 4-nitro methyl pent-2-enoate 12 :



Scheme 5

Condensation of compound **1** with nitroethane in the presence of base furnished of 1-(1-nitroethyl) cyclohexene **11** in 54% yield. Michael addition of compound **11** to methyl propiolate in the presence of KF and phase transfer catalyst in dimethyl sulphoxide furnished 4-(cyclohex-1-ene) 4-nitro methyl pent-2-enoate **12** as viscous oil in 40% yield.

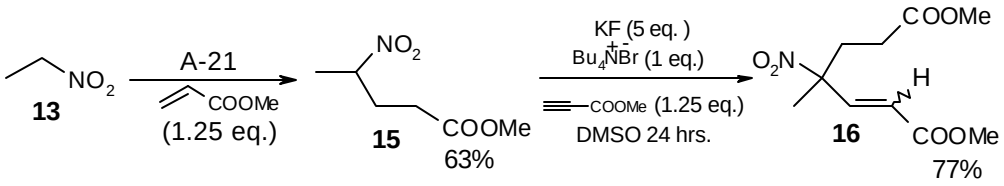
4-Methyl 4-nitro dimethyl hepta-2,5-diene-1,7-dicarboxylate 14:



Scheme 6

4-methyl 4-nitro dimethyl hepta-2,5-diene-1,7-dicarboxylate **14** was formed by the Michael addition of nitroethane **13** (2.5 eq.) with potassium fluoride as base (5 eq.) and tetrabutyl ammonium bromide as phase transfer catalyst (1 eq.) in dimethyl sulphoxide as the solvent to furnish compound **14** as viscous oil in 54% yield.

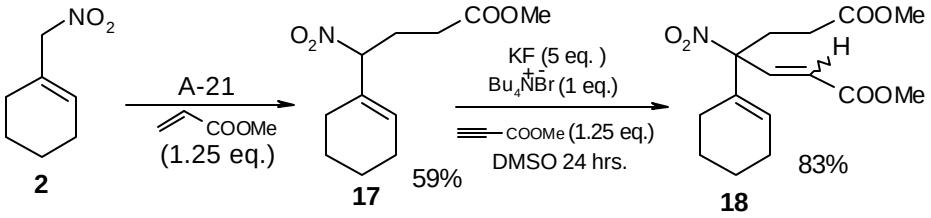
4-Methyl 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate 16:



Scheme 7

Nitroethane on Michael addition to ethyl acrylate with Amberlyst-21 furnished methyl 4-nitro pentanoate in 45% yield, which on further Michael addition with methyl propiolate in the presence of base furnished 4-methyl 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate as viscous oil in 77% yield.

4-(Cyclohex-1-ene) 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate 18:



Scheme 8

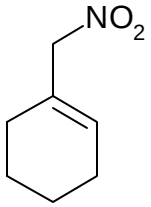
4-(Cyclo hex-1-ene) 4-nitro butanoate **17** was obtained by Michael addition of ethyl acrylate to

1-(1-nitromethyl) cyclohexene 2 on the surface of Amberlyst-21 at 0ºC. The compound **17** on further Michael addition reaction with methyl propiolate in the presence of base and phase transfer catalyst furnished 4-(cyclohex-1-ene)-4-nitro dimethyl hept-2-ene-1,7-dicarboxylate **18** as a viscous oil in 83 % yield.

All the compounds synthesized were characterized by the spectral (IR, ^{1}H NMR, ^{13}C and Mass) analyses.

Experimental :

1-(1-Nitromethyl) Cyclohexene 2:

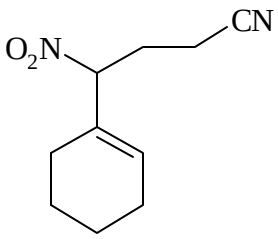


In a round bottom flask fitted with a Dean-Stark trap were placed, 2.5g (25.5 mmol) of cyclohexanone **1**, 6.22g (102 mmol) of the nitromethane and 1.12g (12.8 mmol) of N, N-dimethylethylene diamine as the catalyst in 100 ml. of dry benzene. The reaction mixture was refluxed for 6 hrs. After completion of reaction, the mixture was cooled, washed with 20 ml. of 2N HCl and finally with 20 ml. of water, the organic layer was separated and water layer was extracted with 2x25 ml of ethyl acetate. The organic layer was then dried with anhydrous Na_2SO_4, filtered and then concentrated on rotary evaporator and the residue thus obtained on column purification using 2% EtOAc-pet.ether as eluent furnished 2.0g of 1-(1-nitro methyl) cyclohexene **2** as viscous oil in 50% yield.

IR (neat) cm^{-1} : 1667, 1620, 1520, 1250.

^1H NMR (200 MHz) 1.5-1.8 (br m, 4H); 1.9-2.35 (m, 4H); 4.75 (s, 2H); 5.9 (br s, 1H, olefinic).

4-(Cyclohex-1-ene) 4-nitro butyronitrile 3:

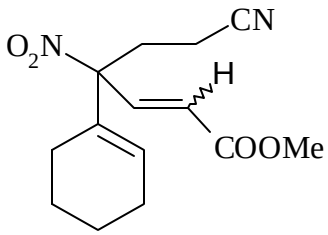


To a 2g (12.6 mmol) of 1-(1-nitromethyl) cyclohexene, was added 5g of Amberlyst-21 followed by the dropwise addition of 0.83g (15.8 mmol) of acrylonitrile at 0ºC. The mixture was stirred for 15 min. and kept for 24 hrs. at room temperature. After completion of reaction (TLC) 25 ml. of dichloromethane was added, the mixture was then filtered and washed with 2x10 ml. portions of dichloromethane. The solution was then dried with anhydrous Na_2SO_4, filtered and then concentrated on rotary evaporator to furnish a residue which on column purification (SiO_2) furnished 1.5g of 4-(cyclohex-1-ene) 4-nitro butyronitrile **3** as viscous oil in 62% yield.

IR (neat) cm^{-1} : 2249, 1730, 1680, 1632, 1549, 1436, 1275, 1164.

^1H NMR (200 MHz) : ä 1.45-1.85 (m,4H); 1.9-2.0 (m, 2H); 2.05-2.3 (m, 3H); 2.3-2.6 (m, 3H); 4.9 (t, 1H J=8Hz); 6.0 (br, s, 1H olefinic).

4-(Cyclohex-1-ene)4-nitro 6-cyano methyl hex-2-enoate 4:



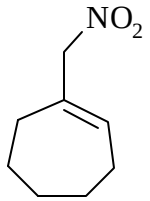
To a stirred solution of 1g (5.2 mmol) of 4-(cyclohex-1-ene) 4-nitro butyronitrile in 25 ml. DMSO, was added 1.49g (26 mmol) of KF and 1.66g (5.2 mmol) of tetrabutyl ammonium bromide. The reaction mixture was stirred for 1 hr. at room temperature. To this, 0.65g (7.8 mmol) of methyl propiolate was added dropwise and the reaction mixture was stirred further for 24 hrs. at room temperature. At the end of the reaction, 100 ml. of water was added. Extraction with ethyl acetate (3x50 ml.), drying with anhydrous sodium sulphate, concentration and on column purification of the residue furnished 1.2g of 4-(cyclohex-1-ene) 4-nitro 6-cyano methyl pent-2-enoate **4** as viscous oil in 83% yield.

IR (neat) cm^{-1} : 2249, 1764, 1712, 1620.

^{1}H NMR (200 MHz) : ä 1.2-1.9 (m, 4H); 2.05 (m, 2H); 2.2-2.6 (m, 6H); 3.8 (s, 3H, -$COOCH_3$); 5.9 (d, 1H, J=18 Hz olefinic); 6.15 (m, 1H olefinic); 7.4 (d, 1H J=16 Hz, olefinic).

^{13}C NMR (50 MHz) : 21.6 (t), 22.5 (t), 24.9 (t), 25.4 (t), 29.2 (t), 29.6 (t), 30.9 (t), 51.7 (q), 97.4 (s), 123.4 (d), 129.4 (t), 133.8 (s), 142.8 (d), 165.4 (s), 172 (s).

1-(Cyclohept-1-ene) nitromethane 6:

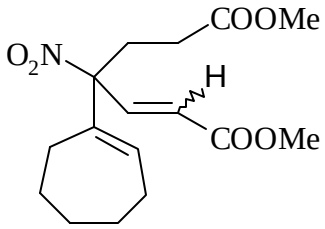


A solution of 2g (17.9 mmol) of cycloheptanone, 4.36g (71.6 mmol) of nitromethane and 0.79g (8.95 mmol) of N, N-dimethyl ethylenediamine as a base in 25 ml. of benzene was refluxed for 12 hrs. After completion of the reaction, usual work up and column purification furnished 1.25g of 1-(cyclohept-1-ene) nitromethane **6** as viscous oil in 45% yield.

IR (neat) cm^{-1} : 1712, 1642.

^{1}H NMR (200 MHz) : ä 1.55 (m, 4H); 1.8 (m, 2H); 2.2 (m, 4H); 4.8 (s, 2H); 6.05 (t, 1H olefinic).

4-(Cyclohept-1-ene) 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate 8:

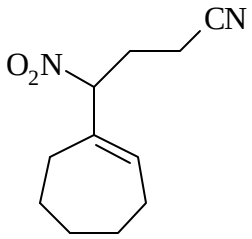


To a solution of 0.50 gm (2.1 mmol) of 4 (cyclohept-1-ene) 4-nitro 2-butenoate in 25 ml DMSO was added 0.60 gm KF (10.5 mmol) and 0.67 gm (2.1 mmol) of nBu_4NBr and stirred at RT for 1 hr. To the reaction mixture at RT, 0.26 gm (3 mmol) of methyl propiolate was added dropwise. Reaction mixture was stirred at room temperature for 24 hrs. After completion of reaction (TLC), usual work-up and column chromatography (SiO_2) furnished 0.5 gm (74% yield) of 4-(cyclohept-1-ene) 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate **8** as viscous oil.

IR (neat) cm^{-1} : 1712, 1642, 1555, 1520 1374, 1280.

^1H NMR (200 MHz) : ä 1.3-1.6 (m, 4H), 1.6-1.9 (m, 3H), 2.0-2.1 (m, 2H), 2.15-2.4 (m, 4H), 2.6-2.8 (m, 1H), 3.65 (s, 3H –COOMe), 3.75 (s, 3H $–COOCH_3$), 5.7-5.9 (d, 1H, J=16Hz, olefinic), 6.15 (t, 1H, J=8Hz, olefinic), 7.35-7.55 (d, 1H, J=16Hz, olefinic).

4(Cyclohep-1-ene) 4-nitrobutyronitrile 9:



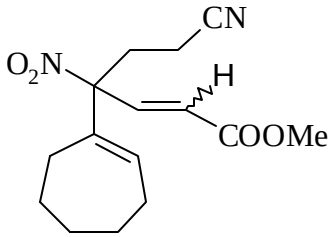
To a 1g (6.5 mmol) of 1-(cyclohept-1-ene) nitro methane, was added to 3g of Amberlyst-21 and 0.51g (9.67 mmol) of acrylonitrile dropwise at 0ºC. The mixture was stirred for 10-15 minutes, which was then kept without stirring for 24 hrs. at room temperature. Extraction of the compound using 3x25 ml.of dichloromethane drying with sodium sulphate, concentration on rotary evaporator and column purification furnished 0.85g of 4 (cyclohep-1-ene) 4-nitrobutyronitrile **9** as viscous oil in 63%.

IR (neat) cm^{-1} : 1642, 1712, 1555, 1373, 1279.

^1H NMR (200 MHz) : ä 1.35-1.7 (m, 4H); 1.7-1.95 (m, 2H); 2-2.3 (m, 4H); 2.3-2.6 (m,

3H); 4.9 (t, 1H J=8Hz); 6.15 (t, 1H J=7.5 Hz).

4-(Cyclohept-1-ene) 6-cyano methyl hex-3-enoate 10:



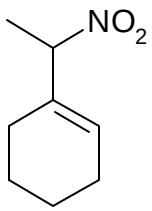
To a stirred solution of 0.5g (2.4 mmol) of 4-(cyclohex-1-ene) 4-nitro butyronitrile in 15 ml. DMSO, was added 0.7g (12 mmol) of KF and 0.77g (2.4 mmol) of tetrabutyl ammonium bromide. The reaction mixture was stirred for 1 hr. at room temperature. To this, 0.3g (3.6 mmol) of methyl propiolate was added dropwise and the reaction micture was stirred further for 24 hrs. at room temperature. At the end of the reaction, 100 ml. of water was added. Extraction with ethyl acetate (3x50 ml.), concentration and on column purification of the residue furnished 0.5g of 4-(cyclohept-1-ene) 6-cyano 4-nitro methyl hex-2-enoate **10** as viscous oil in 71% yield.

IR (neat) cm^{-1} : 2359, 1721, 1549, 1215.

^{1}H NMR (200 MHz) : ä 1.35 (m, 4H); 1.75 (m, 2H); 2.05 (m, 2H); 2.3 (m, 4H); 2.45 (m, 2H); 2.65 (m, 1H); 3.75 (s, 3H); 4.85 (d, 1H J=16 Hz); 6.15 (t, 1H J=8Hz) 7.35-7.55 (d, 1H, J=16Hz, olefinic).

$^{13}CNMR$ (50 MHz): 13.3 (t), 25.9 (t), 26.4 (t), 28.5 (t), 29.7 (t), 30.4 (t), 31.8 (t), 32.1 (t), 52.1 (q), 97.7 (s), 118 (s), 124.6 (d), 134.7 (d), 139.2 (s), 141.6 (s), 165.2 (s).

1-(1-Nitroethyl)cyclohexene 11:



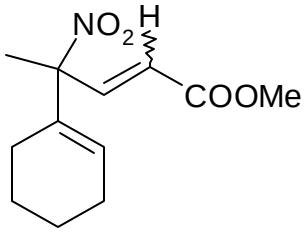
In a round bottom flask fitted with a Dean-Stark apparatus, 2g (20.4 mmol) of cyclohexanone **1** with 6.12g (81.6 mmol) of nitroethane **13** using 0.90g (10.2 mmol) of N,N-dimethylethylenediamine as the catalyst in 100 ml benzene, was refluxed for 18 hrs. After completion of reaction (TLC), benzene was evaporated under reduced pressure to furnish a residue. Column chromatography (SiO_2) of the residue using 2% EtOAc-pet.ether furnished 1.70g of 1-(1-nitroethyl)cyclohexene **11** as viscous oil in 54% yield.

IR (neat) cm^{-1} : 2900, 1540, 1440, 1380, 1350

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.60 (d, J=7.3Hz, 3H, CH_3) 1.75-1.45 (br m, 4H), 2.15-1.95 (br m, 4H), 4.95 (q, 1H), 5.90 (br s, 1H, olefinic).

Mass (m/e): 109, 107, 93, 91, 81, 79, 77, 67.

4-(Cyclohex-1-ene) 4-nitro methyl pent-2-enoate 12 :



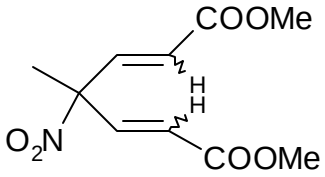
0.50g (3.22 mmol) of 1-(1-nitroethyl)cyclohexene **11** was stirred at RT with 0.94g (16.1 mmol) of KF and 1.03g (3.22 mmol) of tetrabutyl ammonium bromide in 25 ml DMSO for 1 hr. To this, 0.41g (4.83 mmol) of methyl propiolate was added dropwise and the reaction mixture was stirred at RT for 24 hrs. After completion of the reaction (TLC), the reaction mixture was poured into 100 ml of water. Extraction with ethyl acetate (3 x 50 ml), drying with anhydrous sodium sulphate and concentration under reduced pressure furnished a residue. Column chromatography (SiO_2) of the residue using 2% EtOAc-pet.ether as the eluent furnished 0.31g of 4-(cyclohex-1-ene) 4-nitro methyl pent-2-enoate **12** as viscous oil in 40% yield.

IR (neat) cm^{-1} : 2900, 1720, 1630, 1530, 1425, 1370, 1280, 1020, 980.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.75-1.50 (m, 4H) 1.85 (s, 3H, $\underline{CH_3}$), 2.0-1.85 (br m, 2H),. 2.05-2.50 (br m, 2H), 3.75 (s, 3H, COO$\underline{CH_3}$), 5.95 (m, 1H, olefinic), 5.95 (d, 1H, J=17 Hz, olefinic), 7.42 (d, 1H, J=17 Hz, olefinic).

Mass (m/e): 193, 177, 162, 149, 133, 117, 105, 91, 79, 77, 67, 59, 55.

4-Methyl 4-nitro dimethyl hepta-2,5-diene-1,7-dicarboxylate 14:

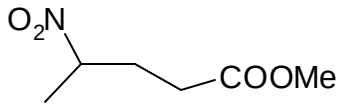


To a solution of 0.50 g (6.66 mmol) of nitroethane **13** in 25 ml DMSO was added 1.93 g KF (33.3 mmol) and 2.13g (6.66 mmol) of nBu_4NBr and stirred at RT for 1 hr. To the reaction mixture at RT, 1.40 gm (16.6 mmol) of methyl propiolate was added dropwise. Reaction mixture was stirred at room temperature for 24 hrs. After completion of reaction (TLC), usual work-up and column chromatography (SiO_2) furnished 0.87 gm of 4-methyl 4-nitro dimethyl hepta-2,5-diene-1,7-dicarboxylate **14** as viscous oil in 54% yield. Product obtained was a mixture of (E,E), (E,Z) and (Z,Z) stereoisomerically allylic nitro compounds with the (E,E) isomer being the major one.

IR (neat) cm^{-1} **:** 2920, 1720, 1650, 1550, 1435, 1380, 1190, 980

^{1}H-NMR (200 MHz, $CDCl_3$) δ: (Major E,E isomer) 1.91 (s, 3H, $\underline{CH_3}$), 3.79 (s, 6H, -COO$\underline{CH_3}$), 6.05 (d, J=15Hz, 2H, olefinic), 7.19 (d, J=15Hz, 2H, olefinic). In addition, there were peaks at 1.99 δ (s, 3H, CH_3) for (E,Z isomer), 3.69 δ (s, 6H, -$COOCH_3$) (Z,Z), 3.77 (s, 6H, $COOCH_3$) (E,Z) isomer and 5.95-6.04 (m, olefinic), 7.10-7.50 (m, olefinic) (for E,Z and Z,Z) isomer.

4-Nitro methyl butanoate 15:

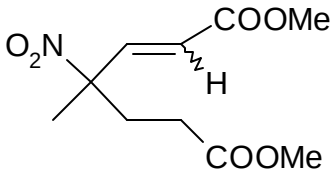


2 gm (26.7 mmol) of nitroethane **13** was stirred on the surface of 5g of Amberlyst-21 for 30 minutes under N_2 atmosphere at room temperature. The reaction was cooled to 0°C and 2.29 gm (26.7 mmol) of methyl acrylate was added dropwise with vigorous stirring. Reaction was kept for 24 hrs. at room temperature. After completion of reaction (TLC), washing A-21 with dichloromethane and concentration under reduced pressure furnished a residue. Column chromatography (SiO_2) of the residue furnished 2.7g of 4-nitro methyl heptanoate **15** as viscous oil in 63% yield.

IR (neat) cm^{-1} : 2840, 1740, 1540, 1370, 1170

^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.53 (d, J=8Hz, 3H), 2.0-2.48 (m, 4H), 3.70 (s, 3H, $COO\underline{CH_3}$), 4.60 (m, 1H).

4-Methyl 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate 16:



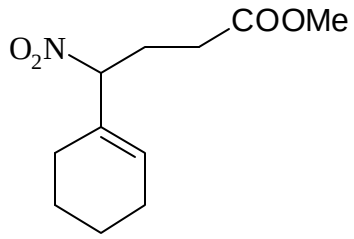
0.50g (3.10 mmol) of 4-nitro methyl heptanoate **15** was stirred at room temperature with 0.90g 15.5 mmol) of KF and 1.0g (3.10 mmol) of nBu_4NBr in 25 ml DMSO for 30 minutes. To the reaction mixture, 0.39g (4.66 mmol) of methyl propiolate was added dropwise and the reaction mixture was stirred at RT for 24 hrs. After completion of reaction (TLC), usual work-up and column chromatography (SiO_2) furnished 0.59 gm of

4-methyl 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate **16** was obtained as viscous oil in 77% yield.

IR (neat) cm^{-1} : 2900, 1750, 1720, 1620, 1540, 1370, 1160.

^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.71 (s, 3H, CH_3), 2.20-2.51 (m, 4H), 3.66 (s, 3H, $COO\underline{CH_3}$), 3.72 (s, 3H, $COO\underline{CH_3}$), 6.95 (d, J=16Hz, 1H, olefinic), 7.10 (d, J=16Hz, 1H, olefinic).

4-(Cyclo hex-1-ene) 4-nitro butanoate 17:

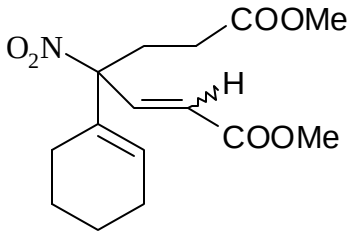


2 gm (14 mmol) of 1-(1-nitro methyl) cyclohexene **2** was stirred on the surface of 5g of the resin Amberlyst-21 for 30 minutes under N_2 atmosphere at RT. The reaction was cooled to 0°C and 1.21g (14 mmol) of methyl acrylate was added dropwise with vigorous stirring. Reaction was kept for 24 hrs. at room temperature. After completion of reaction (TLC), the resin was washed with dichloromethane which on filtration and concentration on reduced pressure furnished a residue. Column chromatography (SiO_2) of the residue furnished 1.9g of 4-(cyclo hex-1-ene) 4-nitro butanoate **17** as viscous oil in 59%.

IR (neat) cm^{-1} : 1735, 1667, 1620, 1600, 1520.

^{1}H NMR (200 MHz) :1.45-1.8 (m, 4H), 1.95-2.3 (m, 6H), 2.3-2.5 (m, 2H), 3.65 (s, 3H-COOMe), 4.9 (t, 1H J=8 Mz >CH-NO_2), 5.95 (t, 1H, J=3 Mz olefinic).

4-(Cyclohex-1-ene) 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate 18:



To a stirred solution of 1g (4.4 mmol) of 4-(cyclo hex-1-ene) 4-nitro butanoate **17** in 25 ml. DMSO, was added 1.28g (22 mmol) of KF and 1.41g (4.4 mmol) of tetrabutyl ammonium bromide. The reaction mixture was stirred for 1 hr. at room temperature. To this, 0.56g (6.6 mmol) of methyl propiolate was added dropwise and the reaction mixture was stirred further for 24 hrs. at room temperature. At the end of the reaction, 100 ml. of water was added. Extraction with ethyl acetate (3x50 ml.), drying with anhydrous Na_2SO_4, filtration and concentration on rotary evaporator and finally on column purification of the residue furnished 1.14g of 4-(cyclohex-1-ene) 4-nitro dimethyl hept-2-ene-1,7-dicarboxylate **18** as viscous oil in 83% yield.

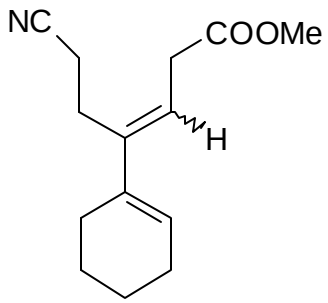
IR (neat) cm^{-1} : 1735, 1715, 1667, 1631, 1520, 1216, 1160.

^1H NMR (200 MHz) :1.45-1.65 (m, 4H), 1.7-1.9 (m, 2H), 2.05-2.2 (m, 2H), 2.2-2.4 (m, 2H), 2.55-2.8 (m, 2H), 3.65 (s, 3H-$COOCH_3$), 3.75 (s, 3H-$COOCH_3$), 5.75-5.9 (d, 1H, J=16Hz, olefinic), 5.95 (t, 1H, J=8Hz, olefinic), 7.3-7.45 (d, 1H, J=16Hz, olefinic).

General Procedure for the preparation of denitrated product: To a solution of 1mmol of γ-nitro α,β-unsaturated ester (**1-8**) in 15 ml of dry methanol at room temperature under nitrogen atmosphere, 5-10 eq.(as mentioned above) of freshly activated metal (metals were activated by washing it with dilute hydrochloric acid, water, and acetone and drying it at 100°C in oven for overnight) in form of turnings or powder was added. The reaction mixture was stirred at room temperature for 12 hrs. After

completion of reaction (TLC), acidic workup and column chromatography furnished the denitrated β, γ-unsatuarted ester in about 22-47% yield.

4-(Cyclohex-1-ene) 6-cyano methyl hex-3-enoate 4a:

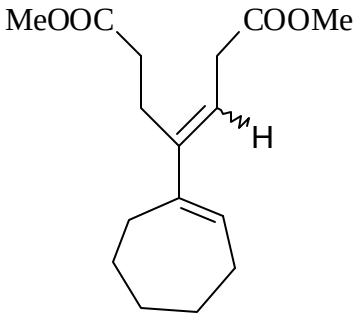


IR (neat) cm^{-1} : 2248, 1716, 1635, 1541, 1436, 1174.

^1H NMR (200 MHz) : ä 1.4-1.8 (m, 6H), 2-2.25 (m, 4H), 2.35 (m, 2H), 3.25 (d, J=8Hz 2H), 3.75 (s, 3H $–COOCH_3$), 5.8 (br m, 1H olefinic), 5.85 (t, 1H J=8Hz olefinic).

Mass (m/e): 233, 217, 175, 91, 69, 55.

4-(Cyclohept-1-ene) dimethyl hept-3-ene-1,7-dicarboxylate 8a:

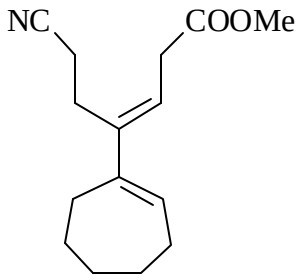


IR (neat) cm^{-1} : 1735, 1667, 1620.

^{1}H-NMR (200 MHz, $CDCl_3$) δ :1.4-1.6 (m, 4H), 1.6-1.85 (m, 3H), 2.2-2.45 (m, 5H), 2.5-2.6 (m, 2H), 3.15 (d, 2H >CH-CH_2-COOMe), 3.65 (s, 3H –$COOCH_3$), 3.7 (s, 3H –$COOCH_3$), 5.55 (t, 1H J=8Hz olefinic), 5.85 (t, 1H J=8Hz olefinic).

^{13}C NMR (50 MHz) : 24 (t), 26.6 (t), 28.3 (t), 29.5 (t), 30.5 (t), 32.2 (t), 32.8(t), 33 (t), 51.1 (q), 51.4 (q), 116.8 (d), 128.8 (d), 144.2 (s), 144.8 (s), 171.8 (s), 173 (s).

4-(Cyclohept-1-ene) 6-cyano methyl hex-3-enoate 10a:



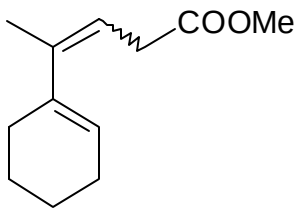
IR (neat) cm^{-1} : 2250, 1764, 1697, 1549, 1091.

^{1}H NMR (200 MHz) : ä 1.35 (m, 4H); 1.45 (m, 4H); 1.8 (m, 2H); 2.3 (m, 4H); 3.15 (d, 2H); 3.65 (s, 3H –$COOCH_3$); 5.65 (t, 1H J=6Hz olefinic); 5.9 (t, 1H J=6Hz olefinic).

^{13}C NMR (50 MHz) : 16.2 (t), 26(t), 26.2 (t), 27.8 (t), 28 (t), 32 (t), 32.2 (t), 34 (t), 51 (q), 54 (t), 118 (d), 133 (d), 142 (s), 150 (s), 172 (s).

Mass (m/e): 247, 188, 176, 66.

4-(Cyclohex-1-ene) methyl pent-3-enoate 12a:

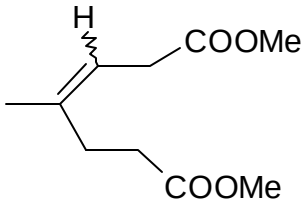


IR (neat) cm^{-1} : 2880, 1740, 1630, 1410, 1275, 1040.

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.75-1.45 (br m, 4H), 1.80 (s, 3H, CH_3), 2.25-2.10 (br m, 4H), 3.20 (d, 2H, J=8Hz, CH_2), 3.72 (s, 3H, -CO$\underline{O}CH_3$), 5.65 (t, 1H, J=8 Hz olefinic) 5.85 (br m, 1H, olefinic),.

Mass (m/e): 194, 179, 135, 120, 111, 79, 82, 54.

4-Methyl dimethyl hept-3-ene-1,7-dicarboxylate 14a:



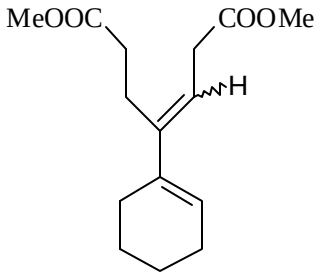
IR (neat) cm^{-1} : 2860, 1750-1730, 1640, 1150, 930.

^{1}H-NMR (200 MHz, $CDCl_3$) δ : 1.56 (s, 3H, -C$\underline{C}H_3$= for E isomer), 1.65 (s, 3H, -C$\underline{C}H_3$= for Z isomer), 2.28 (m, 4H), 2.94 (d, 2H J=8 Hz for E isomer), 2.98 (d, 2H J=8 Hz for Z isomer), 3.57 (s, 3H, -COO$\underline{C}H_3$), 3.58 (s, 3H, -COO$\underline{C}H_3$), 5.25 (m, 1H, olefinic).

^{13}C-NMR (50 MHz, $CDCl_3$) δ : 15.75 (q), 22.37 (q), 26.70 (t), 32.07 (t), 32.88 (t), 33.91 (t), 33.7 (t), 51.5 (q), 51.7 (q), 116 (d), 117 (d), 137 (s), 172.2 (s), 173.4 (s).

Mass (m/e) : 169, 153, 141, 135, 128, 125, 113, 99, 97, 85, 81, 71, 59, 55.

4-(Cyclohex-1-ene) dimethyl hept-3-ene-1,7-dicarboxylate 18a:



IR (neat) cm^{-1} : 1735, 1712,

^{1}H-NMR (200 MHz, $CDCl_3$) δ :1.3-1.75 (m, 4H), 1.8-2.2 (m, 4H), 2.25-2.45 (m, 2H), 2.45-2.7 (m, 2H), 3.2 (d, 2H J=5.4Hz), 3.7 (s, 3H –$COOCH_3$), 3.72 (s, 3H-$COOCH_3$), 5.6 (t, 1H J=8Hz olefinic), 5.8 (br s, 1H olefinic).

^{13}C NMR (50 MHz) : 23 (t), 23.5 (t), 26 (t), 26.5(t), 33.4 (t), 33.8 (t), 51.5 (q), 51.7 (q), 117 (d), 124 (d), 136 (s), 142 (s), 172 (s), 173 (s).

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