TOTAL SYNTHESIS OF α-LIPOIC ACID AND DEVELOPMENT OF USEFUL SYNTHETIC METHODOLOGIES

A thesis submitted to
The University of Pune
for the degree of

DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

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APRIL 2004

CERTIFICATE

Certified that the work incorporated in this thesis entitled "**Total Synthesis of α-Lipoic acid and Development of Useful Synthetic Methodologies**" submitted by **Mr. Ramesh Ratan Kale** was carried out by him under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

April, 2004
Pune

Dr. Subhash P. Chavan
Research supervisor

DECLARATION

I hereby declare that the work incorporated in the thesis entitled ***"Total Synthesis of α-Lipoic acid and Development of Useful Synthetic Methodologies"*** submitted for Ph. D. degree to the University of Pune has been carried out at NCL under the supervision of Dr. Subhash P. Chavan and the work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

Date : April, 2004 Ramesh Ratan Kale

Place : Organic Chemistry : Technology
National chemical laboratory
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DEDICATED

TO

MY FAMILY MEMBERS

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Words fall short to thank my family members for their never-ending encouragement, support and help in all respects without which this work wouldn't have been possible.

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April 2004 *Ramesh*

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
B. P.	Boiling point
BMS	Borane dimethyl sulfide complex
DMSO	Dimethyl sulfoxide
DCM	Dicholoromethane
DIBAL	Diisobutylaluminum hydride
DMF	*N*, *N*-dimethyl formamide
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram
h	Hour
mg	Milligram
ml	Millilitre
Me	Methyl
M. P	Melting point
NBS	N-Bromosuccinamide
NaH	Sodium hydride
NMR	Nuclear magnetic resonance
Ph	Phenyl
PTC	Phase transfer catalyst
pTSA	*p*-Toluene sulphonic acid
$TBHSO_4$	Tetrabutyl ammonium hydrogensulfate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

GENERAL REMARKS

1. All the melting points and boiling points are uncorrected and the temperature is expressed in degree Celsius.
2. The compound numbers, scheme numbers and reference numbers given in each section refers to that particular section only.
3. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80^{o}C.
4. Organic layers were dried over anhydrous sodium sulphate (Na_2SO_4).
5. Progress of the reaction was monitored by TLC and was visualized by UV absorption by fluorescence quenching or iodine staining or by both.
6. In most of the cases where chromatographic purification was done, 60-120 mesh SiO_2 was used as a stationary phase and in some cases flash silica was used for flash column chromatography.
7. The IR spectra were recorded on Perkin-Elmer infrared spectrophotometer model 683B or 1605 FTIR and IR absorbance is expressed in cm^{-1}.
8. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 200, MSL 300 and DRX 500 instrument. ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million from internal standard (tetramethylsilane) on δ scale.
9. Mass spectras were recorded at an ionization energy 70eV on Finnigan MAT-1020 automated GC/MS instrument and mass values are expressed as m/e. Some of the mass spectras were recorded on API Q STAR PULSAR instrument (ESI Technique).
10. The high-resolution mass spectra (HRMS) were recorded on a Micromass Q-Tof Micro with lock spray source (ESI^{+} mode).

THESIS ABSTRACT

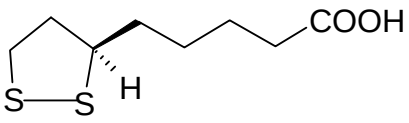
The thesis entitled "**Total Synthesis of α-Lipoic acid and Development of Useful Synthetic Methodologies**" is divided into two chapters. The first chapter deals with the total synthesis of α-lipoic acid, which includes the simple and practical synthesis of α-lipoic acid and also the butenolide approach for the synthesis of α-lipoic acid. Second chapter deals with the development of some useful synthetic methodologies like highly regioselective decomposition of tosylhydrazones to olefins using NaOH as a base**,** a facile deprotection of dithioacetals by $FeCl_3$/KI and a simple and efficient method for transesterification of β-ketoesters catalysed by iodine.

Chapter 1: Total Synthesis of α-Lipoic acid

This chapter is divided into three sections. The first section deals with the introduction and literature survey of α-lipoic acid. The second section deals with the simple and practical synthesis of α-lipoic acid using readily available thioglycolic acid. The third section deals with the total synthesis of α-lipoic acid using butenolide approach in which the synthesis of optically active α-lipoic acid has been described with the aid of menthol as a chiral auxillary.

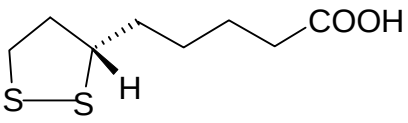
Section 1: α-Lipoic acid: A review:-

This section is devoted to the introduction of α-lipoic acid, a highly useful naturally occurring biologically active compound.[1] It also covers the biological, pharmacological and industrial importance of α-lipoic acid. The large number of literature reports[2] reflect the importance of this molecule from a synthetic point of view.



(R)-(+)- α-Lipoic acid

1a

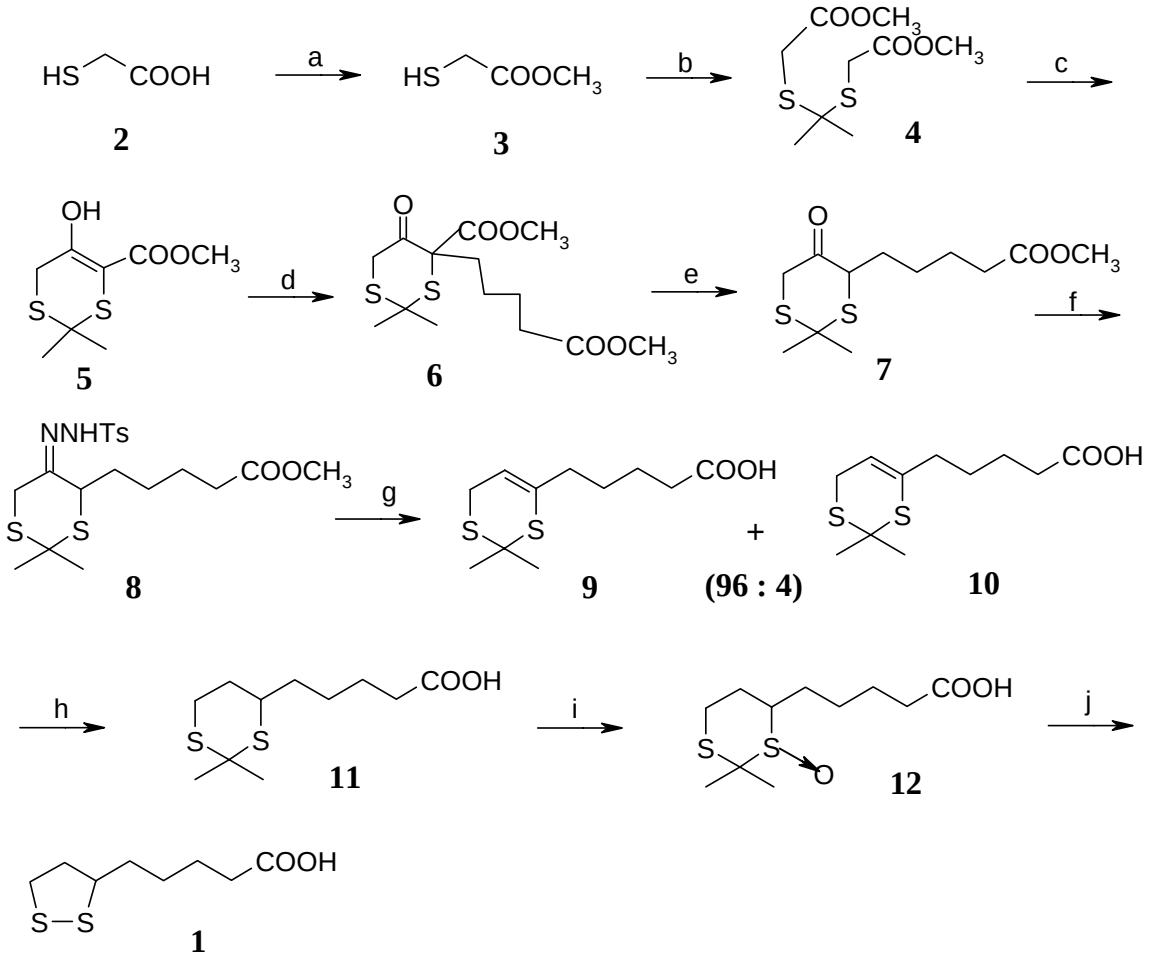


(S)-(-)- α-Lipoic acid

1b

Section 2: **A simple and practical synthesis of α-lipoic acid:-**

This section deals with synthesis of α-Lipoic acid starting from readily available starting material thioglycolic acid **2**. The methyl ester of thioglycolic acid was converted into cyclic β-ketoester (**5**) which is a key intermediate of this route.



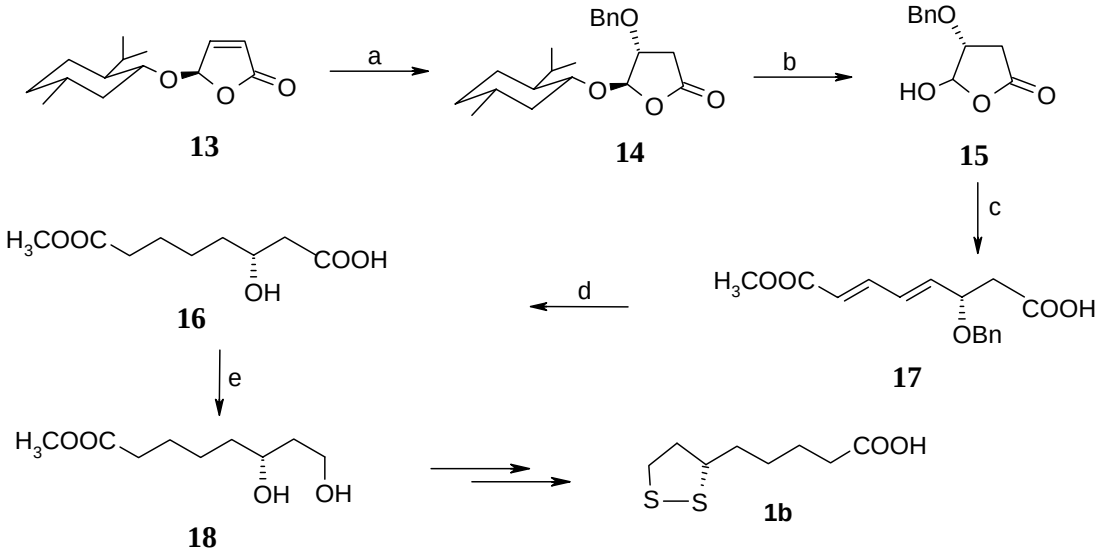
Reagents and conditions: a) MeOH, H_2SO_4 (cat.), reflux, 3 h, 70 %; b) acetone, $BF_3.Et_2O$ (cat.), 0 ^oC to rt, 6 h, 88 %; c) NaH, THF, 60 ^oC, 3 h, 86 %; d) Methyl 5-bromovalerate, K_2CO_3, Bu_4NHSO_4, THF, RT, 22 h, 70 %; e) DMSO, NaCl, H_2O, 135-140 ^oC, 7 h., 81 %; f) $TsNHNH_2$, MeOH, RT, 2 h, 92 %; g) NaOH, isopropyl alcohol, reflux, 2 h, 84 %; h) Et_3SiH (1 equiv.), TFA, 0 ^oC-RT, 2 h, 73 %; i) $NaIO_4$, MeOH, 0 ^oC, 2 h, 68 %; j) aq. HCl (1:1), benzene, 50 ^oC, 7 h, 69 %.

Scheme 1

The C-alkylation of **5** under phase transfer conditions followed by decarboxylation using Krapcho's protocol furnished ketone **7**. The reduction of ketone **7** to methylene was tried by different reduction methods. The Wolff-Kishner reduction and Clemensen's reduction failed to give desired product. Then ketone **7** was converted into its tosylhydrazone **8**. Reductive cleavage of tosylhydrazone **8** using $NaBH_4$/AcOH, catecholborane was also found to be unsuccessful.

However, on treatment with NaOH in refluxing isopropyl alcohol tosylhydrazone **8** underwent highly regioselective decomposition to give a mixture of highly substituted olefin **9** along with minor amount of less substituted olefin **10** (**9 : 10 = 96 : 4**). The reduction of mixture of olefins by ionic hydrogenation (Et_3SiH / TFA) resulted in the formation of desired product **11**. The dithiane acid **11** was then coverted into sulfoxide **12**, which finally furnished α-lipoic acid **1** on treament with aq. HCl in benzene, a biphase reaction. Thus a simple and practical synthesis of (±) α-Lipoic acid is achieved.

Section 3: Butenolide approach for the synthesis of α-Lipoic acid:-



Reagents and conditions: a. BnOH, Na (catalytic), DMF, RT, 24 h, 84 %; b. 2N HCl, acetone, RT, 72 h, 78 %; c. Ph_3P=CH-CH=CH-$COOCH_3$, CH_3CN, reflux, 2h, 41 %; d. H_2, Pd-C, 1 atm, RT, 6 h, 92 %; e. BMS, THF, RT, 2 h, 87 %.

Scheme 2

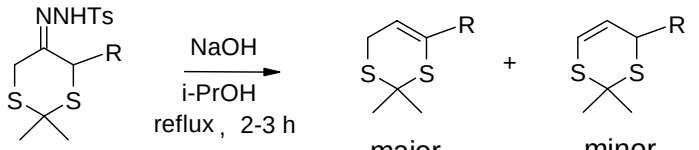
In this section we have described the use of 5-menthyloxy-2 (*5H*)-furanone **13** as a chiral precursor for the asymmetric synthesis of (S)-(-)-α-lipoic acid. The chiral auxillary menthol is recovered during the hydrolysis of **14.** The wittig reaction on hydroxy compound **15** is the key step of this synthetic route. The diol **18** was synthesized with 51 % ee. The diol **18** is a known intermediate which could be converted into lipoic acid by known method.[14] This constitutes a formal synthesis of lipoic acid.

Chapter 2: **Development of Useful Synthetic Methodologies**

This chapter is divided into three sections. First section describes highly regioselective decomposition of tosylhydrazones using NaOH as a base**,** second section describes a facile deprotection of dithioacetals by $FeCl_3$/KI and the third one deals with a simple and efficient method for transesterification of β-ketoesters catalysed by iodine.

Section 1: **Highly Regioselective Decomposition of Tosylhydrazones to Olefins Using NaOH as a Base**

The well-known Shapiro reaction involves the transformation of tosylhydrazones of aldehydes and ketones into olefins on treatment with organolithium compounds (usually MeLi). The yields of olefins are good without any side reactions and wherever choice is possible, predominantly the less substituted olefins are formed. The other bases like LiH, Na in ethylene glycol (Bamford-Stevens reaction), NaH have also been used for the decomposition of tosylhydrazones, but in these cases side reactions are common.



8a-8e **9a-9e** **10a-10e**

R = n-Bu, Bn, Allyl, n-Methyl valerate, Ethyl.

Scheme 3

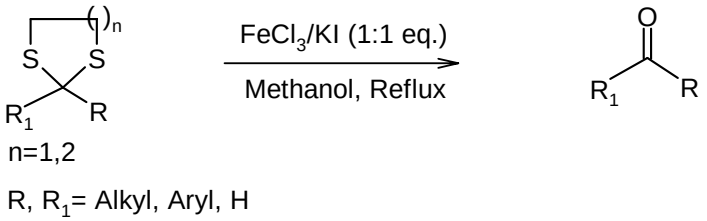
During our approach towards the synthesis of α-lipoic acid, it has been found that tosylhydrazones **8a-8e** on treatment with NaOH in isopropyl alcohol at reflux

temperature resulted in the formation of more substituted olefins **9a-9e** along with minor amount of less substituted olefins **10a-10e**.

In conclusion, the present protocol describes highly regioselective decomposition of tosylhydrazones containing sulphur atom to yield more highly substituted olefins as major products along with minor amount of less substituted olefins under mild conditions as compared to literature reports. This methodology has been extended towards the synthesis of (±)α-lipoic acid.

Section 2: **A Facile Deprotection of dithioacetals by $FeCl_3$/KI**

Dithioacetals are frequently used to protect carbonyl compounds in the course of total syntheses and hence several systems have been developed for their deprotection. Although there are a variety of methods reported for their preparation, there are not enough general and efficient methods for their deprotection. Our interest in developing methods for deprotection of dithioacetals encouraged us to investigate the reaction with one equivalent of $FeCl_3$/KI. It was surmised that $FeCl_3$/KI combination could serve as an excellent reagent as the source of iodonium ion/ iodine. These in turn would react with dithioacetal thereby making it a better leaving group, thus helping in regeneration of carbonyl compounds.



n=1,2

R, R_1= Alkyl, Aryl, H

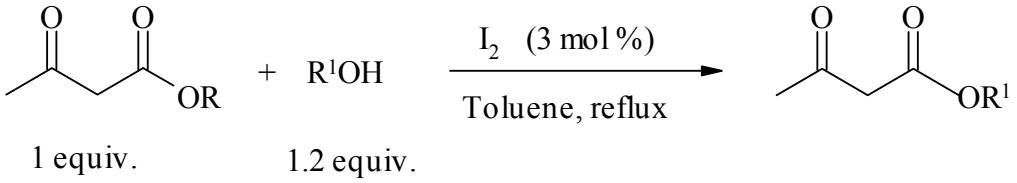
Scheme 4

We have described a facile protocol for the deprotection of thioacetals employing $FeCl_3$/KI combination as an efficient reagent. The present protocol is efficient, nonhazardous, and therefore should find widespread utility in organic synthesis.

Section 3:- **Transesterification of β-Ketoesters Catalysed by Iodine.**

The transesterification of β-ketoesters has been found to be very useful tool in organic synthesis having wide applications in academic as well as industrial research.

Facile reaction on the two electrophilic carbonyls and the two nucleophilic carbons have made β-ketoesters popular synthons. Many biologically active systems are accessible from β-ketoesters of different alcohols. In this section we have reported the use of iodine as an efficient catalyst for the transesterification β-ketoesters (Scheme 5).



Scheme 5

The noteworthy feature of our protocol is that in most of the cases only 1.2 equivalents of alcohol are sufficient for efficient conversions. Only in case of volatile alcohols like isopropanol, n-propanol and propargyl alcohol 2 equivalents of alcohol are required to obtain good yields of the corresponding ester. The other important feature of this protocol is that transesterification of β-ketoesters by various alcohols like benzyl, allylic, propargyl alcohols has been effectively catalysed by iodine giving products with moderate to high yields with comparatively less reaction time.

In conclusion, the present protocol describes a simple and efficient method for the transesterification of β-ketoesters by different alcohols catalysed by iodine. The ready availability of iodine alongwith efficiency, simplicity and superiority over the existing methods should make this protocol an attractive addition to the arsenal of synthetic chemists.

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CHAPTER I

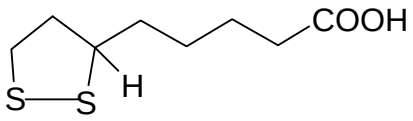
SECTION 1

Synthesis of α-Lipoic acid: A Review

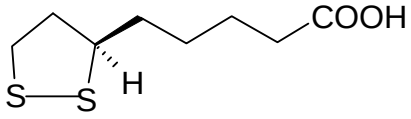
1.1.1 Introduction

α-Lipoic acid is an important protein-bound coenzyme and growth factor found in plant and animal tissues as well as in microorganisms.[1, 2] It is recognized as a vital cofactor for the multienzyme complexes which catalyse the oxidative decarboxylation of α-ketoacids such as pyruvate, α-ketoglutarate etc.[3] It also plays an important role as a protein-bound transacylating cofactor for α-ketoacid dehydrogenase enzyme complexes. It is known to assume crucial role in photosynthesis[4] as well as in tricarboxylic acid cycle.

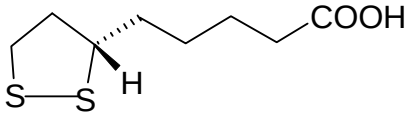
α-Lipoic acid was first isolated from processed liver by Reed *et al*[5] in 1951 and was characterized as the cyclic disulfide 5-[3-(1,2-dithiolanyl)]-pentanoic acid.[6] The biological activity of α-lipoic acid is confined only to the naturally occurring *R*-isomer.[7] The activity of *S*-isomer is essentially zero. However, (±)-α-lipoic acid is equally important for pharmaceutical use and moreover, the racemic mixture can be utilized without resolving, as the *S*-isomer has no significant side effects.



α-Lipoic acid (**1**)



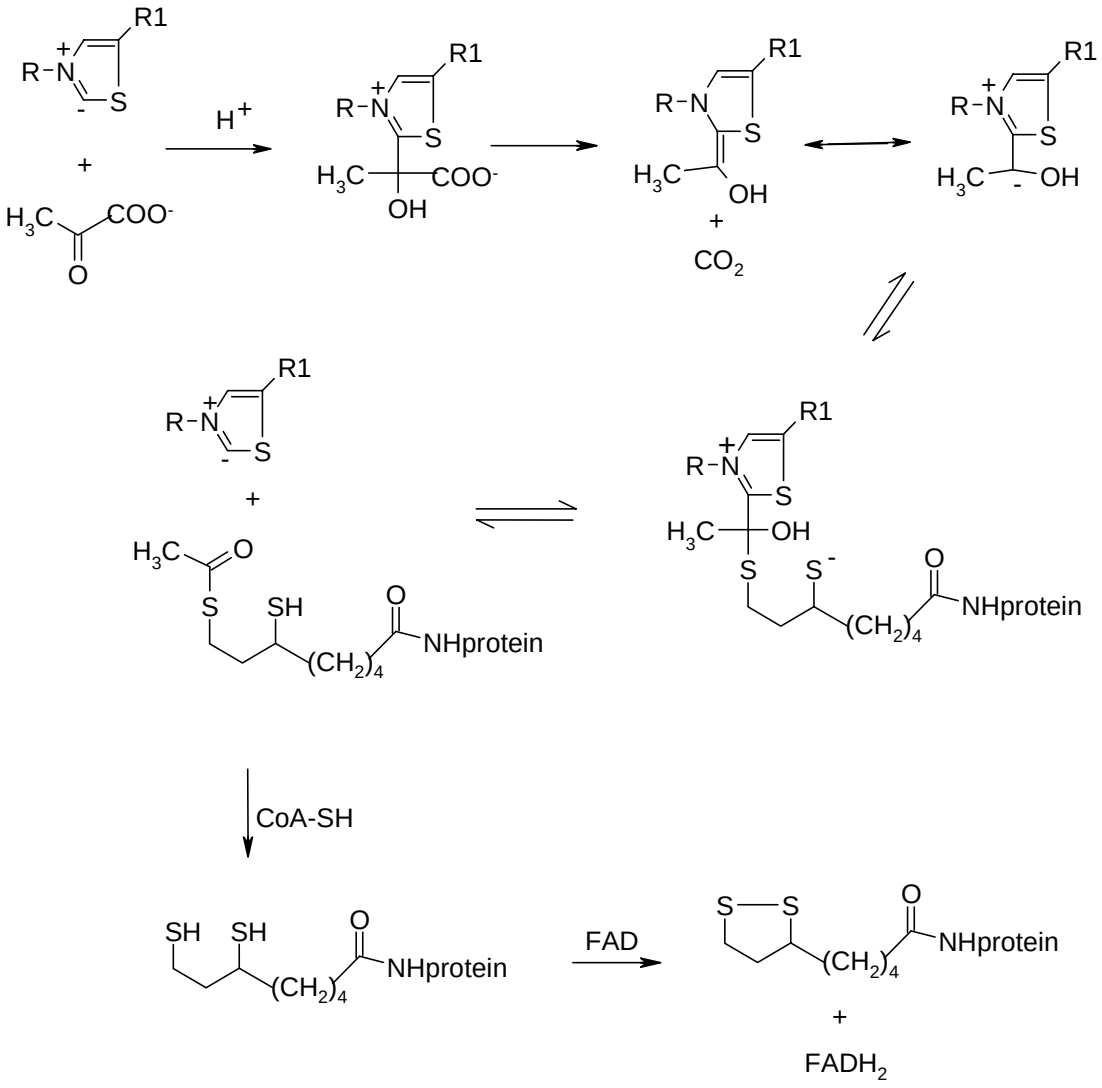
(*R*)-(+)- α-Lipoic acid (**1a**)



(*S*)-(-)- α-Lipoic acid (**1b**)

1.1.2 Mode of Biological Action of α-Lipoic Acid

The complete oxidation of pyruvate during aerobic glycolysis takes place by tricarboxylic acid (TCA) cycle. Pyruvate undergoes oxidative decarboxylation before it enters TCA cycle.



Scheme 1

The coenzymes required for the overall oxidative decarboxylation of pyruvate are thiamine pyrophosphate (TPP), nicotinamide adenine dinucleotide (NAD), α-lipoic acid,

coenzyme A and flavin adenine dinucleotide (FAD).[8] The stages involved in this complex process are shown in scheme 1.

Thiamine pyrophosphate interacts with lipoic acid to form an addition complex which subsequently gets cleaved to form acyl lipoic acid complex and TPP is regenerated. The acetyl group, now present as a thioester, is then transferred from acyl lipoic acid to coenzyme-A to form acyl-CoA by the acetyl-transfer enzyme system. Finally, the reduced lipoic acid moiety is reoxidised by the interaction with FAD and the cycle is completed. The acyl-CoA then enters the TCA cycle. FAD is regenerated by interaction with NAD^+ in the electron transport system.

The hydrophobic interaction and the metal ion coordinating ability[3b] of the molecule which helps the free passage of the compound in various tissues are the factors which are responsible for the high biological activity of lipoic acid. α-Lipoic acid offers metal ions two different binding sites, the carboxylate group and the disulfide linkage. The carboxylate group dominates the coordinating properties of this ligand towards metal ions but a disulfide-metal ion interaction is still possible, and under sterically favoured conditions, may become very important. This could be true under enzymic conditions when the carbonyl group is no longer free but in the form of amide-linked to the protein. Further, the lipoyl moiety is ideally suited to undergo hydrophobic ligand-ligand interaction in the mixed ligand complexes due to the presence of valeric acid side chain.

1.1.3 Biological and Pharmacological Importance of α-Lipoic acid

α-Lipoic acid has been shown to have significant physiological as well as pharmacological properties.[3] It shows protective and curative effects in heavy metal poisoning (e.g. Pb, Hg, As, Se) in animal tissues.[7, 9] It is also found to be very effective in the treatment of severe liver disorders caused by *Amanitta phalloides.*[10] It acts as a radioprotective agent which protects against ionizing radiation induced damge to DNA and its components.[11] It shows cytoprotective effects on the gastric mucosa against ethanol aggression.[12] One of the most important applications of lipoic acid is its ability to control diabetes.[13] Recently it has also been reported that lipoic acid and its derivatives show inhibitory effect against HIV replication[14] and also act as antitumor agents.[15]

Apart from the above pharmacological importance, α-lipoic acid also finds its use in cosmetic preparations. α-Lipoic acid and its derivatives are used in skin lotions, ointments and creams as skin-whitening cosmetics.[16] Also, α-lipoic acid and its derivatives are used in hair tonics to control dandruff and stimulate hair growth.[17]

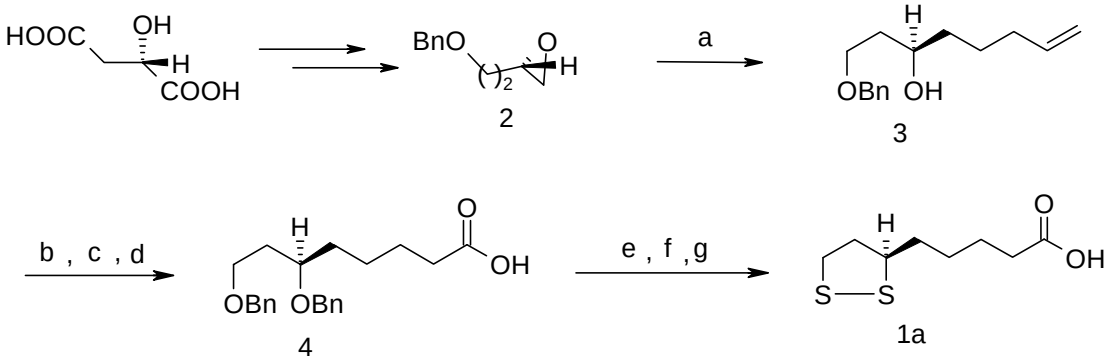
1.1.4 α-Lipoic acid: A Review of Literature

After the isolation of α-lipoic acid in 1951, its valuable biological activity and pharmocological importance soon triggered off a burst of efforts towards its synthesis. A number of syntheses of (±)-α-lipoic acid and optically active lipoic acid have been reported in the literature and are well reviewed up to 1990 by Yadav *et al*.[18] Some of these reports are described below. [19-31]

Golding's Syntheses (1983[19a], 1988[19b])[19]

The first synthesis of optically active ∝-lipoic acid was reported by Golding *et al*[19a] (scheme 2). The opening of the epoxide obtained from malic acid with but-3-enyl magnesium chloride catalyzed by lithium chlorocuprate to give compound **3** is the crucial step of this synthesis.

J. Chem. Soc. Chem. Commun. **1983**, 1051



Reagents and conditions: a) CH_2=$CHCH_2CH_2MgCl$, Li_2CuCl_4 (catalytic), THF; b) $PhCH_2Br$, NaH, THF; c) $HBSia_2$, THF, alkaline H_2O_2; d) PDC, DMF; e) i. MeOH-HCl; ii. Pd/C, H_2; f) i. $MeSO_2Cl$, Et_3N; ii. Na_2S, S, DMF; g) aq. NaOH.

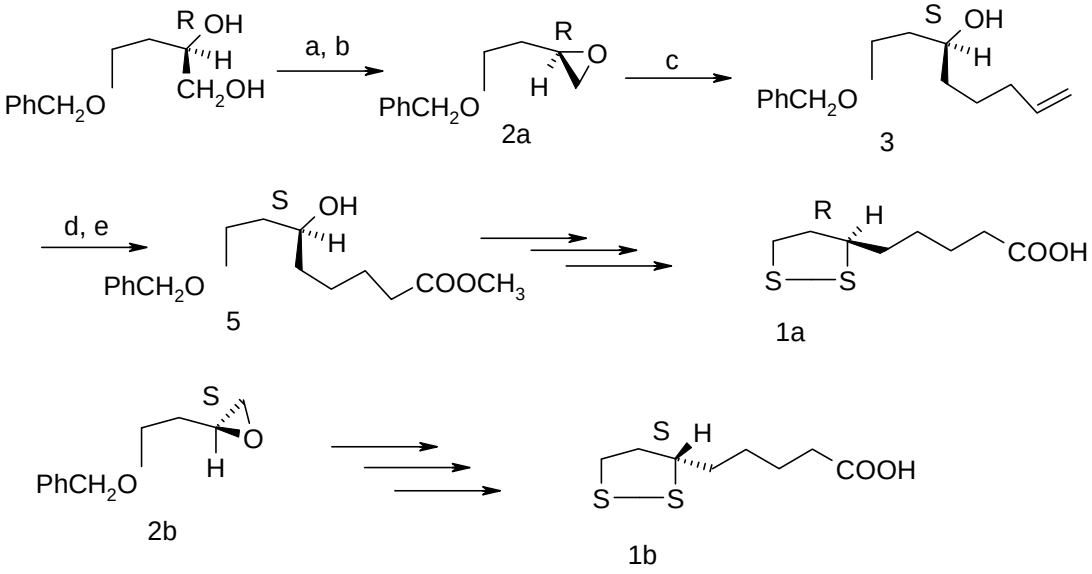
Scheme 2

The protection of free hydroxy of compound **3** followed by hydroboration and oxidation to acid using PDC resulted in the formation of dibenzyl acid **4**. This acid was esterified and the ester was then debenzylated to get diol ester. This diol was later mesylated and the dimesylated compound was treated with sodium sulphide, sulphur in DMF to furnish methyl lipoate in good yields. Methyl lipoate thus obtained was then

hydrolyzed using aqueous NaOH in THF to get lipoic acid **1a**. The overall yield of the reaction sequence was 25 %.

Later in 1988 Golding[19b] synthesised the *R*-isomer starting from *S*-malic acid, which involved the inversion in configuration at oxirane intermediate (scheme 3). The (*R*)-oxirane **2a** was cleaved with but-3-enylmagnesium bromide (cuprate catalysis) to get (*S*)-1-(phenylmethoxy) oct-7-en-3-ol (**3**). Olefin **3** was converted into methyl-(*S*)-6,8-dihydroxyoctanoate (**5)**. This key intermediate **5** was subjected to usual reactions to get (*R*)-lipoic acid **1a**. In a similar fashion (*S*)-oxirane **2b** was converted into (*S*)-lipoic acid **1b**.

J. Chem. Soc. Perkin Trans.1 **1988**, 9.



Reagents and conditions: a) PhCHO, H^+; b) NBS, ClF_2CCCl_2F and then NaOH, $HOCH_2CH_2OH$; c) CH_2=$CHCH_2CH_2MgBr$, Li_2CuCl, THF; d) $HB[Pr^iC(Me)H^-]_2$, THF, aq. HO_2^- and then PCC, DMF; e) MeOH-HCl.

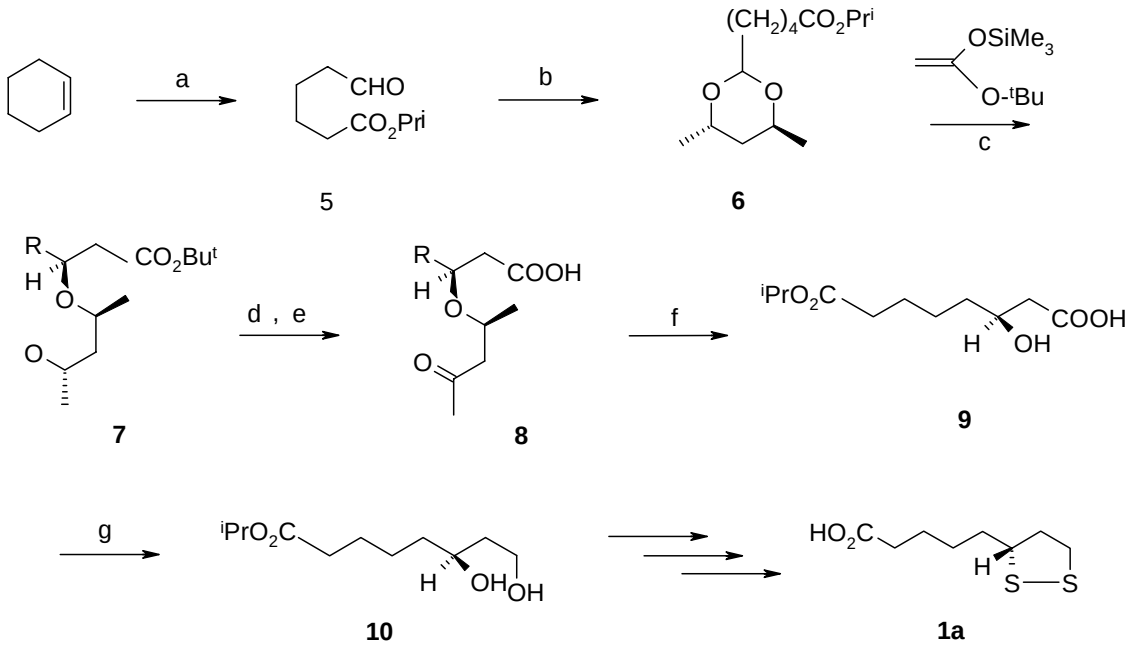
Scheme 3

Elliott's Synthesis (1985)[20]

Elliot *et al*[20] synthesized (*R*) - (+) Lipoic acid via chiral acetal templates (scheme 4). This strategy involves the $TiCl_4$ catalysed coupling of chiral acetal **6** with 1-t-butyldimethylsilyloxyethene to generate the β-alkoxy carboxylate **7** in which the new

asymmetric center is formed with excellent diastereoselection. The hydrolysis of ester **7** followed by oxidation with Jones reagent gives **8**. The chiral auxiliary is removed by treating **8** with piperidinium acetate in boiling benzene to afford β-hydroxy acid **9**, which is converted to the diol **10** by hydroboration.

Tetrahedron Lett. **1985**, *26*, 2535.



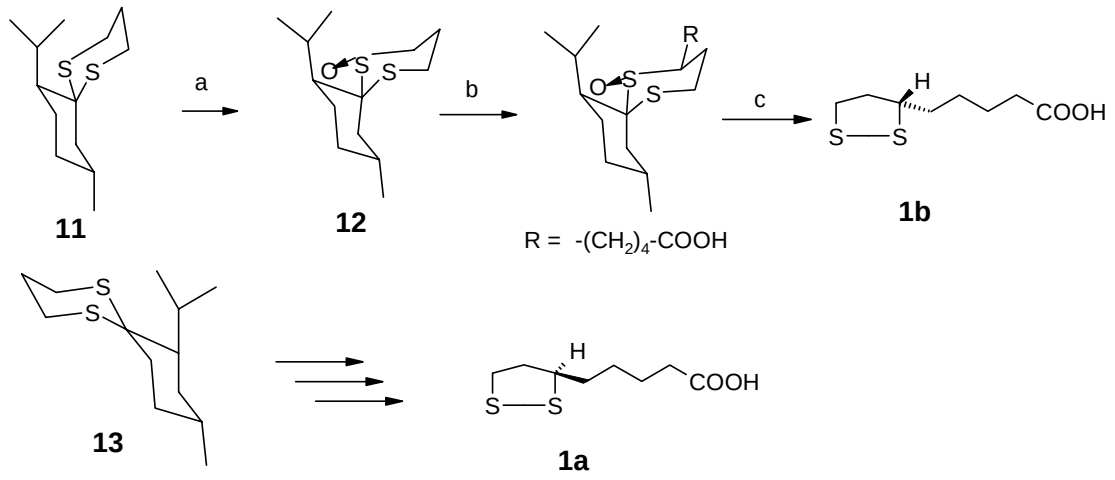
Reagents and conditions: a) O_3, ^{i}PrOH, -78^{o}C, Ac_2O, Et_3N; b) (2S, 4S)-pentan-2,4-diol/*p*-TSA, benzene; c) $TiCl_4$, DCM, -78^{o}C, 93 %; d) TFA, H_2O, ; e) Jones' oxidation, 98 %; f) Piperidinium acetate, benzene reflux, 97 %; g) BH_3/THF, then 4M aq. KOH, 82 %.

Scheme 4

Ravindranathan's Synthesis (1987)[21]

Ravindranathan *et al*[21] reported a very short, elegant and efficient route for (*R*)-(+)-lipoic acid (Scheme 5**).** The strategy involves the formation of 1,3-dithiane from 1,3-propanedithiol and a ketone, which could subsequently lead to racemic or optically active 1,2-dithiolanes, depending on the choice of the ketone. Dithiane **11** derived from 1-menthone on oxidation afforded **12** as a single regio isomer. Stereoselective alkylation of **12** followed by hydrolytic cyclization afforded (*S*)-(-)-lipoic acid **1b**. In the similar manner dithiane derivative **13** derived form d-menthone afforded (*R*)-(+)-lipoic acid **1a**.

Tetrahedron Lett. **1987**, *28*, 5313.



Reagents and conditions: a) $NaIO_4$, MeOH, -5 ^oC, 80 %; b) LDA, TMEDA, $Br(CH_2)_4CO_2H$, THF, 65-75 %; c) aq. HCl, C_6H_6, 65 %.

Scheme 5

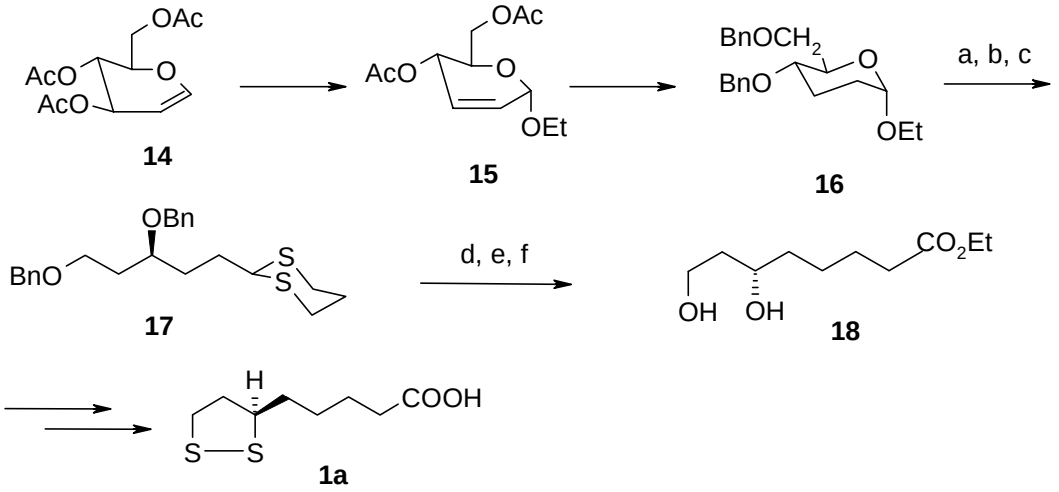
Rama Rao's Syntheses (1986,[22a] 1987,[22b] 1987,[22c] 1987 [22d])[22]

Rama Rao *et al*[22] have reported four different routes for the synthesis of α-lipoic acid.

The first synthesis[22a] starts with 3,4,6-tri-O-acetyl-D-glucal (**14)**, which is derived from D-glucose (scheme 6). The tri-O-acetyl-D-glucal **14** was converted into 4,6-di-O-benzyl derivative by known methods. The key step of the synthesis was the treatment of compound **16** with propanedithiol to furnish dithiane **17**. Two carbon Wittig olefination followed by hydrogenation using Raney nickel furnished 1,3-dihydroxy ester which was then converted to lipoic acid in three steps.

In the second synthesis[22b] (Scheme 7) tri-O-acetyl-D-glucal **14** was opened with mercuric sulphate followed by protection using acetic anhydride and pyridine to furnish compound **19**. Two carbon wittig olefination of **19** followed by hydrogenation using Raney nickel furnished the triacetate ethylester **20**.

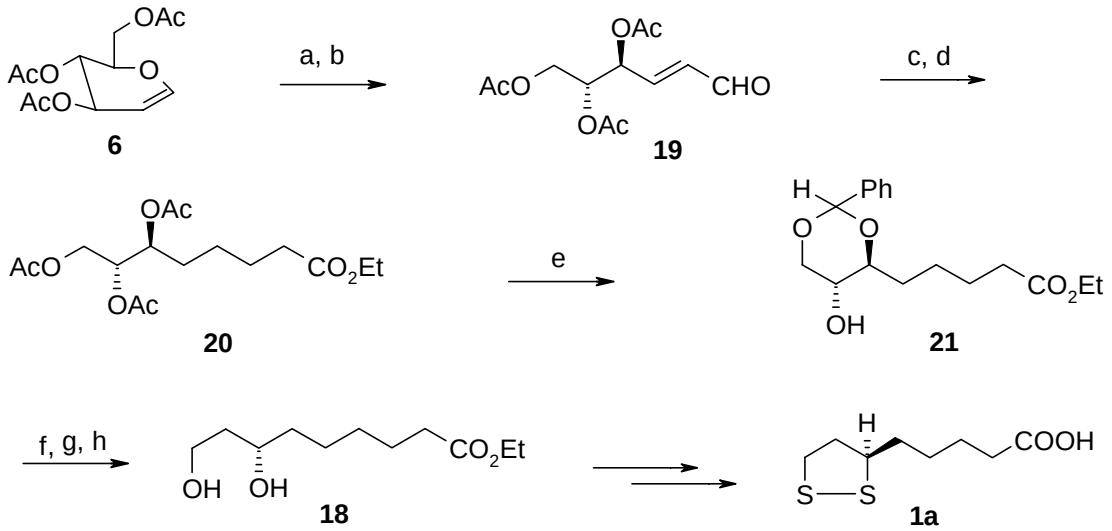
Carbohydr. Res. **1986**, *148*, 51.



Reagents and conditions: a) 1,3-propanedithiol, $BF_3.Et_2O$, DCM, 80 %; b) NaH, CS_2, MeI, 85 %; c) nBu_3SnH, AIBN, 96 %; d) HgO, $BF_3.Et_2O$; e) Ph_3P=CHCOOEt, 83 %; f) H_2, Raney Ni, 90 %.

Scheme 6

Synth. Commun. **1987**, *17*, 1095.

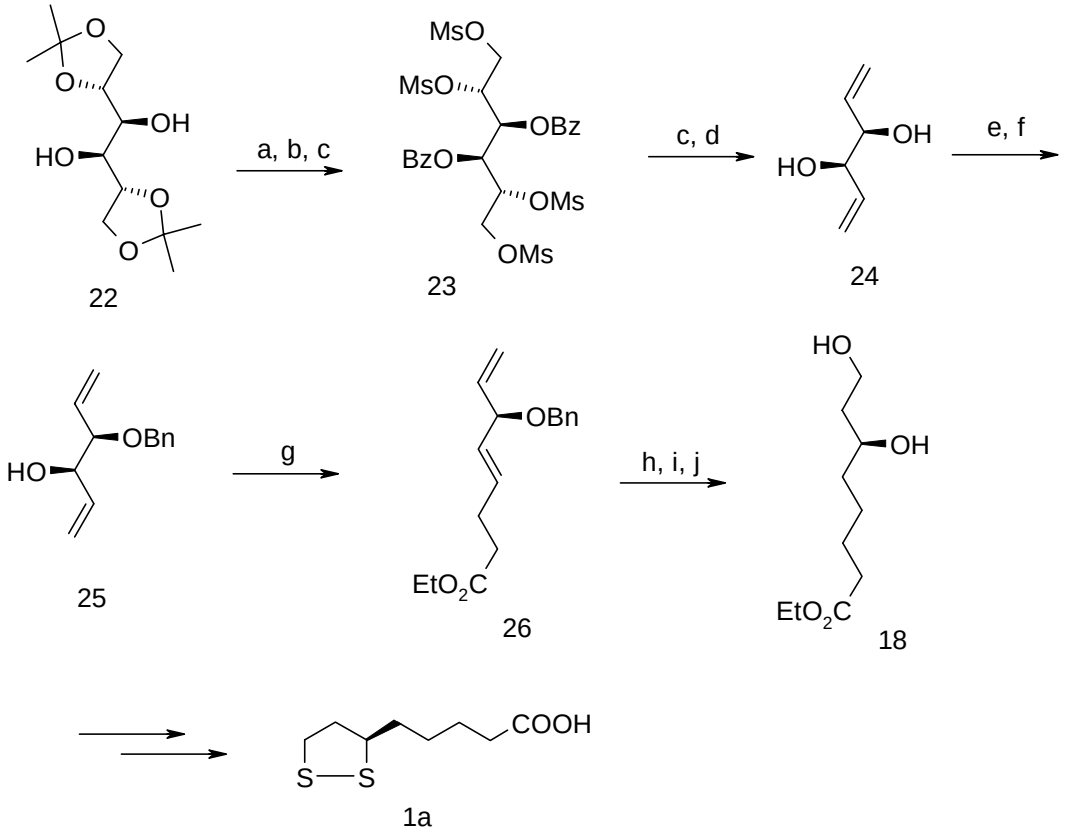


Reagents and conditions: a) $HgSO_4$, H^+, dioxane; b) Ac_2O, pyridine; c) Ph_3P=CHCOOEt; d) H_2, Raney Ni, 88 % (2 steps); e) i) NaOEt, EtOH; ii) $PhCH(OMe)_2$ / H^+, 75 %; f) Thiocarbonyldiimidazole, THF, 85%; g) nBu_3SnH, 70 %; h) H_2, Pd/C, 70%.

Scheme 7

Compound **20** has the same number of carbons as that of lipoic acid. Functional group transformations involved deprotection of three acetates and selective protection of the triol with benzaldehyde dimethylacetal to give only dioxane. Deoxygenation of free hydroxyl was accomplished *via* xanthate. The diol ester **18** thus obtained is a known intermediate for the synthesis of lipoic acid.

The third synthesis[22c] (Scheme 8**)** involved the use of mannitol diacetonide **22**, which was treated with benzoyl chloride to protect two free hydroxyl groups.
Tetrahedron Lett. **1987**, *28*, 2183



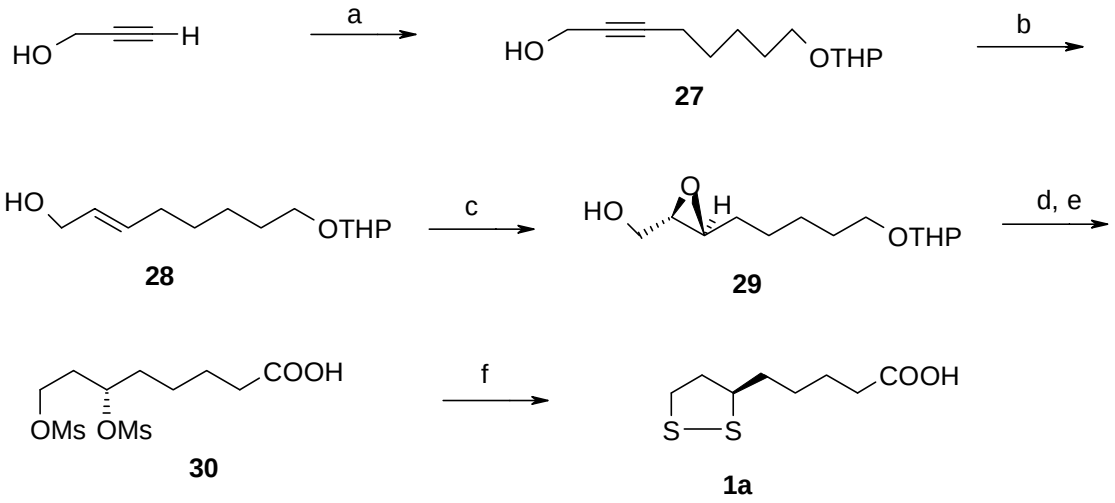
Reagents and conditions: a) PhCOCl / Py; b) 50 % aq. AcOH; c) CH_3SO_2Cl; d) NaI, Zn, DMF, Heat; e) NaOMe; f) Bu_2SnO, $PhCH_3$, reflux; g) 1.2 eq. $PhCH_2Br$, DMF, 100^oC; h) $CH_3CH(OEt)_3$, CH_3CH_2COOH (cat) 145^oC; i) 9-BBN, OH^-/H_2O_2, j) H_2, Pd/C.

Scheme 8

The acetonides were cleaved and the resultant hydroxyls were treated with mesyl chloride to furnish compound **23**, which was then treated with sodium iodide and zinc followed by sodium methoxide to furnish (3*R*, 4*R*)-1,2-divinyl-glycol **24**. The divinyl glycol **24** was then selectively benzylated to furnish compound **25**. Two carbon homologation on **25** was achieved *via* Clasien ester rearrangement to give compound **26**. In a sequence of three steps involving hydroboration, oxidation and reduction of the double bond using palladium charcoal the diol-ester **18** was obtained, which is a known intermediate in the synthesis of lipoic acid.

In the fourth synthesis,[22d] (Scheme 9) Rama Rao *et al* started with propargyl alcohol, which was alkylated to furnish the eight carbon skeleton required for lipoic acid. Compound **27** thus obtained was then partially reduced to give the allylic alcohol **28**. Asymmetric epoxidation was achieved on **28** using Sharpless's epoxidation protocol. The epoxide **29** was then opened regioselectively and mesylated to give the dimesyl compound **30**, which was then treated with sodium sulphide, sulfur in DMF to furnish lipoic acid.

Synth. Commun. **1987**, *17*, 1339



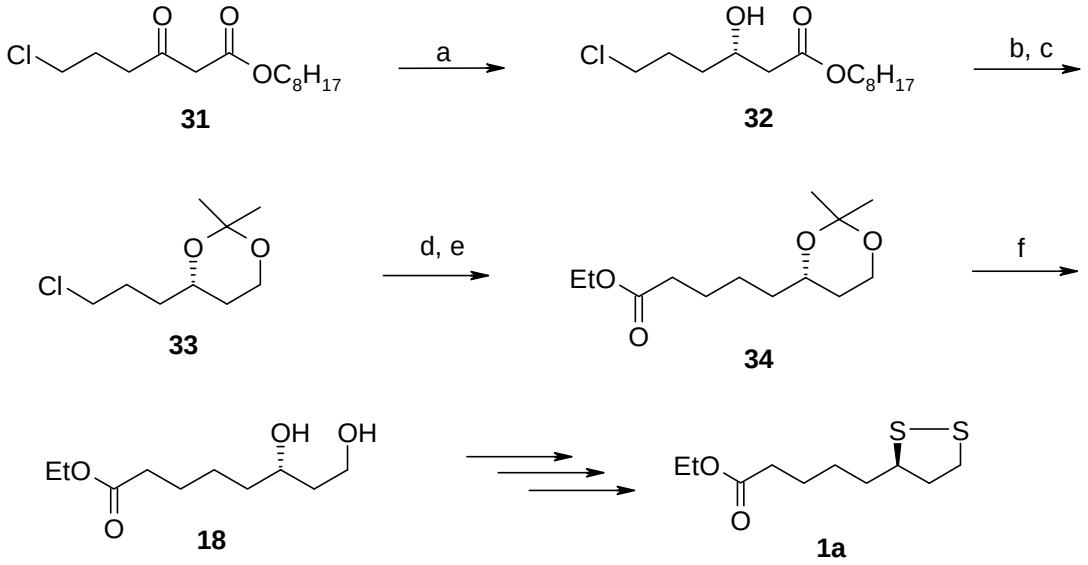
Reagents and conditions: a) Li/Liq. NH_3, $Br(CH_2)_5OTHP$; b) LAH, THF; c) $Ti(OP^iPr)_4$, (+) DIPT, TBHP, DCM d) Red-Al; e) $MeSO_2Cl$; f) Na_2S, S, DMF.

Scheme 9

Gopalan's Synthesis (1990)[23]

The enantioselective reduction of β-ketoesters using Baker's yeast is the highlight of this synthesis (Scheme 10).[23] Octyl-6-chloro-3-oxohexanoate (**31**) was reduced using Baker's yeast to give alcohol **32** which was further reduced to 1,3-diol using Lithium borohydride. The 1,3-diol thus obtained was then protected as acetonide to give compound **33**. The two-carbon homologation was achieved by alkylation with diethylmalonate to furnish the acetonide **34**. Cleavage of the acetonide **34** in acidic conditions gave the diol-ester **18**, which was then converted to lipoic acid by standard protocol.

J. Chem. Soc. Perkin. Trans. 1, **1900**, 1897.



Reagents and conditions: a) Baker's yeast, 62 %, 90 % ee; b) $LiBH_4$, THF, 80 %; c) $Me_2C(OMe)_2$, *p*-TSA, DCM, 60 %; d) $CH_2(COOEt)_2$, NaH, DMF, 75°C, 43 %; e) NaCN, DMSO, 165°C, 43 %; f) H^+, EtOH, 98 %.

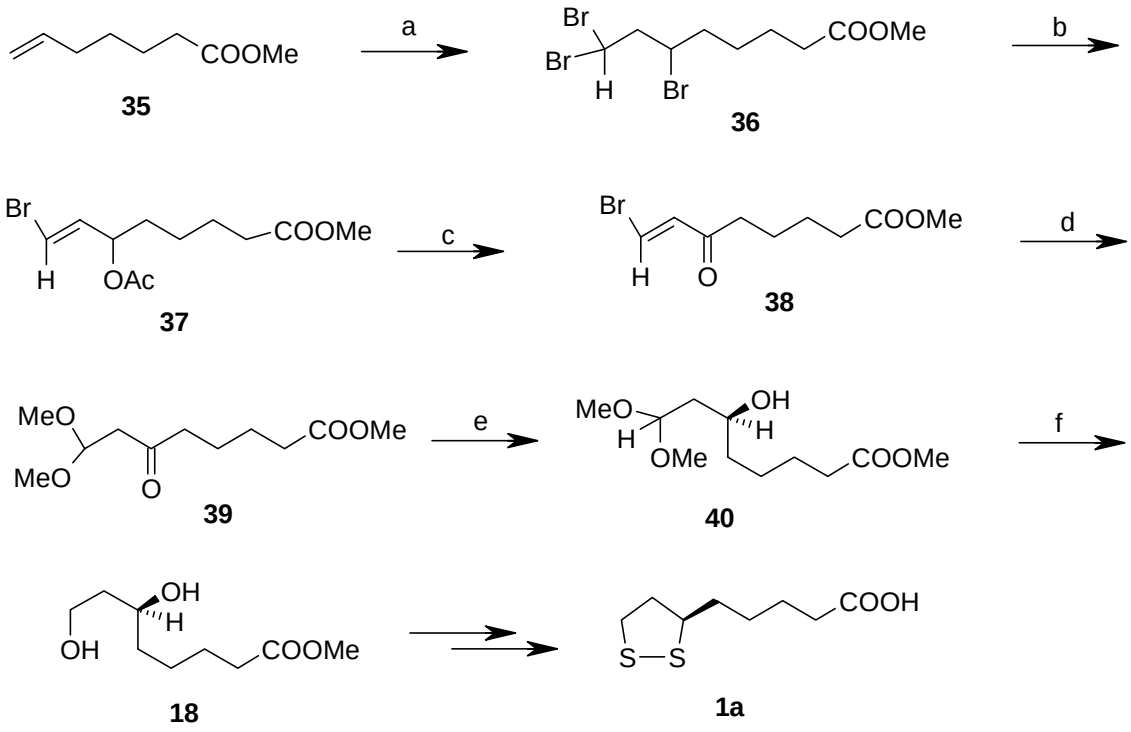
Scheme 10

Bhalerao's Synthesis (1990)[24]

This synthesis involved the copper catalysed bromoform addition to alkene **35** to give methyl-6, 8, 8-tribromo-octanoate (**36)**, which on treatment with potassium acetate and 18-crown-6 in DMF gave compound **37**. Hydrolysis, oxidation followed by treatment

with triton B furnished methyl 8, 8-dimethoxy-6-oxo-octanoate (**39)**. This ketoacetal **39** was then enantioselectively reduced by Baker's yeast to give compound **40**, which on treatment with H_3PO_4 in acetone followed by $NaBH_4$ reduction resulted in the formation of diol **18**. The diol **18** could be converted into lipoic acid by usual way (scheme 11).

J. Chem. Soc. Chem. Commun. **1990**, 729.



Reagents and conditions: a) Cu, $CHBr_3$, 80 %; b) KOAc, (2 equiv.), 18-crown-6, DMF, 85 %; c) K_2CO_3, MeOH then PCC, 68 %; d) Triton B / MeOH; e) Immobilized Baker's yeast, pH = 4.5-5, 60 % for 2 steps; f) H_3PO_4, acetone, then $NaBH_4$, 80 %.

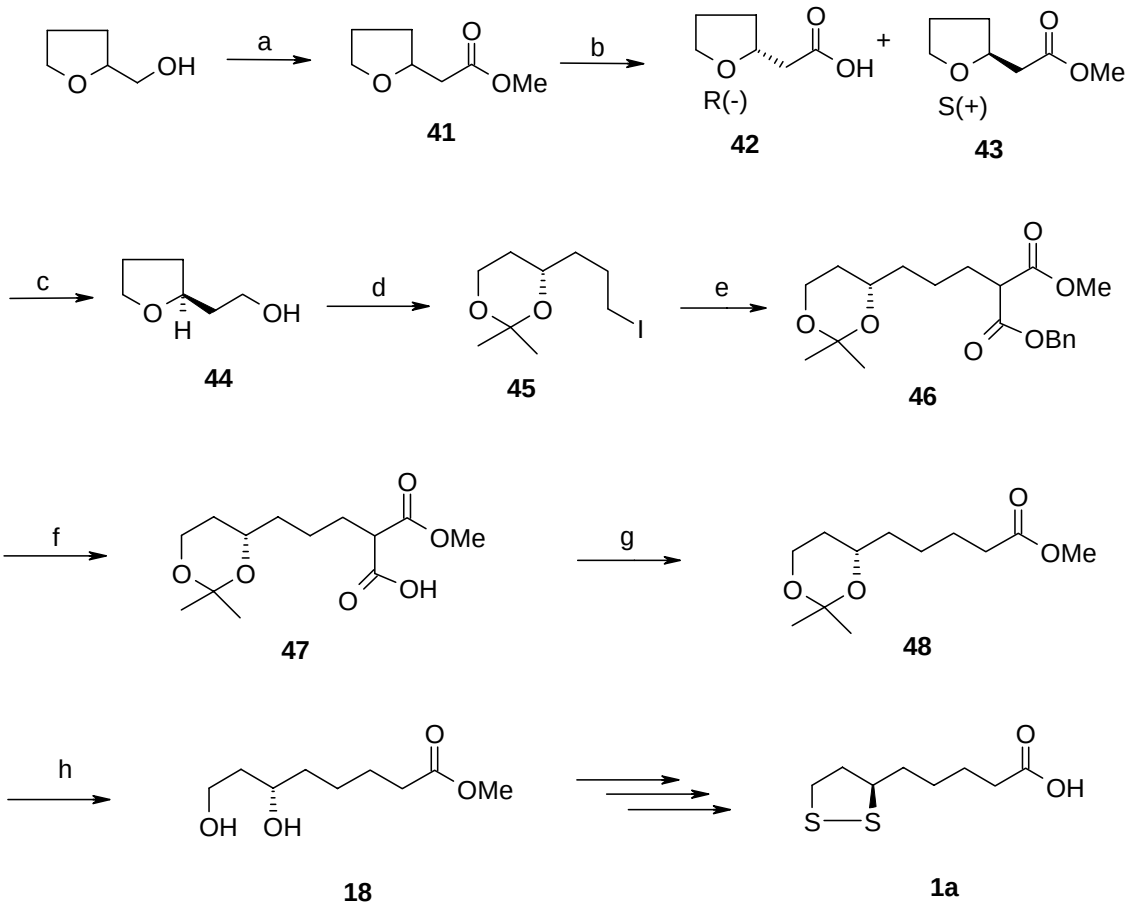
Scheme 11

Iyengar Synthesis (1996)[25]

The selective hydrolysis of methyl 2-(tetrahydro-2-furyl)acetate (**41)** using enzyme is the key feature of this synthesis (Scheme 12).[25] Lipase was used to selectively hydrolyse the ester **41**. The *S* (+) isomer did not under go hydrolysis. The *S* (+) isomer **43** was then reduced using LAH to give compound **44**. Regioselective opening of **44** with

TMSCl, sodium iodide in acetone gave iodoacetonide **45**. The iodoacetonide **45** was then alkylated with benzylmethylmalonate to give compound **46**. Debenzylation, decarboxylation followed by hydrolysis in acidic condition furnished diol-ester **18**, which was then converted into lipoic acid in usual way.

Synthesis, **1996**, 594.



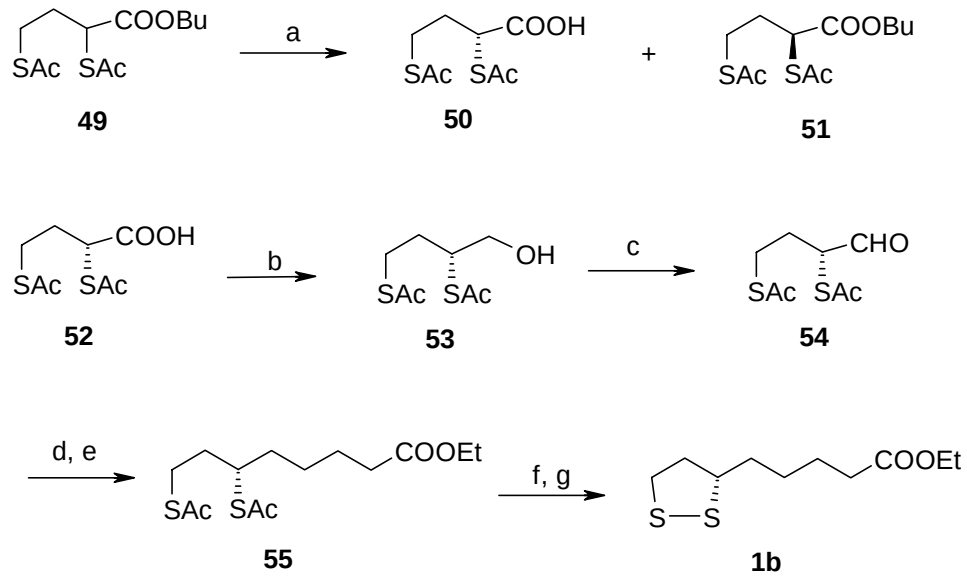
Reagents and conditions: a) i) p-TsCl, KOH, 93 %; ii) KCN, 74 %; iii) KOH, 93 %; iv) MeOH / H^+, 97 %; b) Lipase/phosphate buffer; c) LAH, ether, 84 %; d) TMSCl, NaI, acetone; e) Benzyl methyl malonate, NaH, THF, 25 %; f) Pd-C/H_2, 98 %; g) 160^{o}C, 95 %; h) MeOH, H^+, 98 %.

Scheme 12

Fadanavis's Synthesis (1998)[26]

Fadnavis *et al*[26] synthesized both enantiomers of lipoic acid by lipase catalysed regio- and stereospecific hydrolysis of n-butyl ester of 2,4-dithioacetyl butanoic acid (**49)** (scheme 13). The compound **49** was hydrolysed by lipase from *Candida rugosa* to give 2,4-dithioacetyl butyric acid (**50)** and 2-thio-4-thioacetyl butyrate (**51)** with high enantiomeric excess. The reduction of compound **50** using BH_3.DMS followed by PCC oxidation resulted in the formation of aldehyde **54**. Wittig olefination by using triphenylphosphonium salt of ethyl-4-bromo butyrate and subsequent hydrogenation by using Willkinson's catalyst gave ethyl ester **55**. The hydrolysis of **55** with wheat germ lipase followed by treament with oxidative enzyme mushroom tyrosinase gave (*S*)-lipoic acid **1b**. Simillarly (*R*)- lipoic acid **1a** was obtained by starting with **51**.

Tetrahedron Asymmetry, **1998**, *9*, 4109.



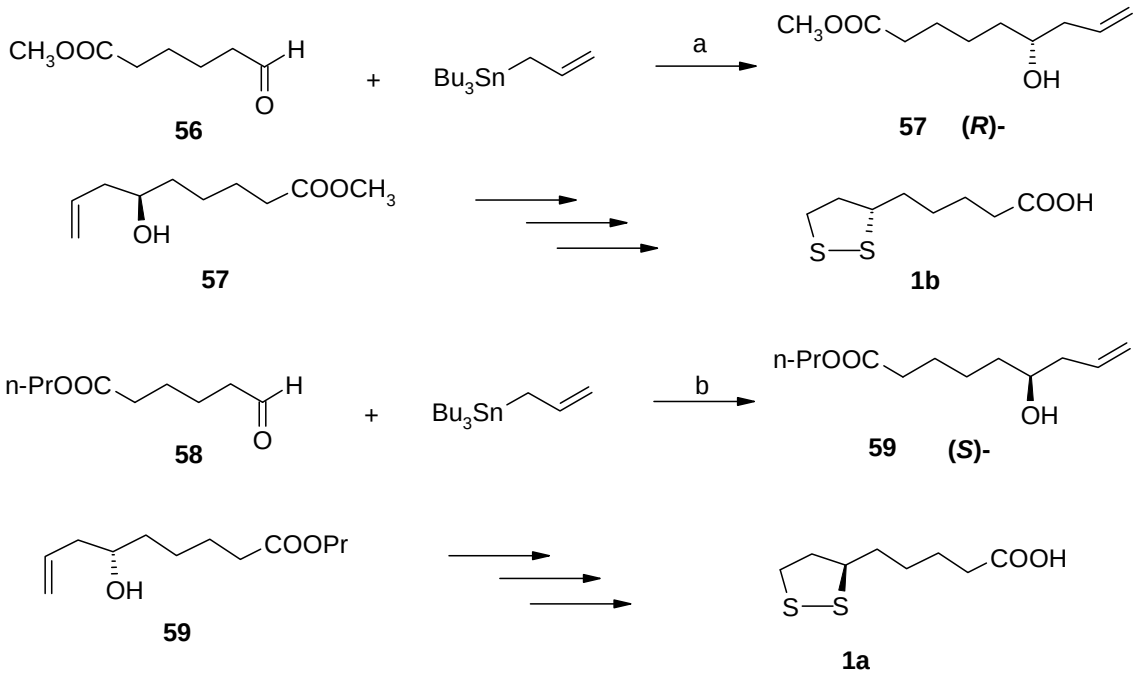
Reagents and conditions: a) Candida rugosa lipase, Phosphate buffer, pH = 7.5; b)BH_3.DMS, 0^oC; c) PCC; d) $Br^-PPh_3^+(CH_2)_3COOEt$, NaHMDS, -78 ^oC; e) $(PPh_3)_3RhCl$, H_2; f) wheat germ lipase, pH = 7.0; g) mushroom tyrosinase.

Scheme 13

Zimmer's Synthesis (2000)[27]

Zimmer *et al*[27] synthesized (*S*)- and (*R*)- configured 6-hydroxy-8-nonene-carboxylates **57** and **59** enantioselectively by allylation of alkoxycarbonyl substituted aldehydes with allyltrimethylstannane and BINOL / $Ti(OiPr)_4$ as the catalyst. These are the precursors for lipoic acid (scheme 14). The homoallyl alcohols **57** and **59** could be converted into lipoic acid by known method.

Tetrahedron Asymmetry, **2000**, *11*, 879.



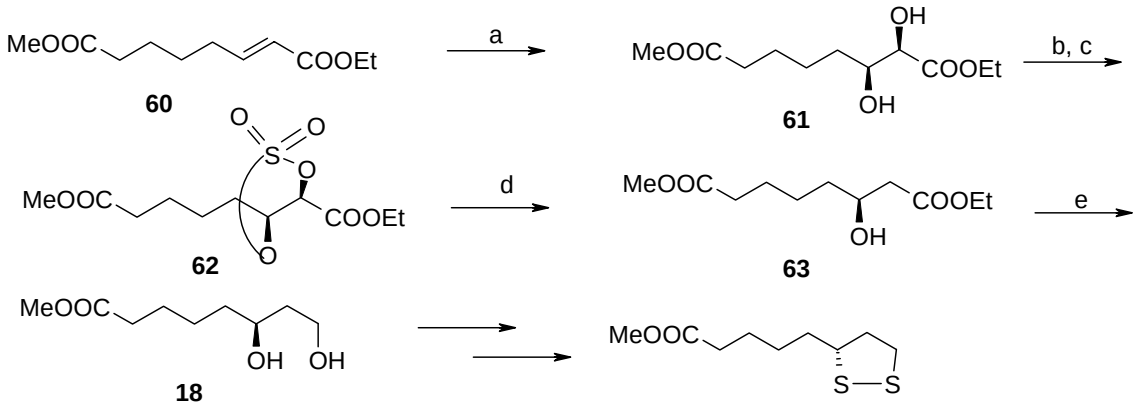
Reagents and conditions: a) (S)-BINOL (0.2 equiv.) / $Ti(OiPr)_4$ (0.2 equiv.), DCM, 2 days, 73%, 98 % ee; b) (R)-BINOL (0.2 equiv.) / $Ti(OiPr)_4$ (0.1 equiv.), DCM, 6 days, 89 %, 98 % ee.

Scheme 14

Sudalai's Synthesis (2001)[28]

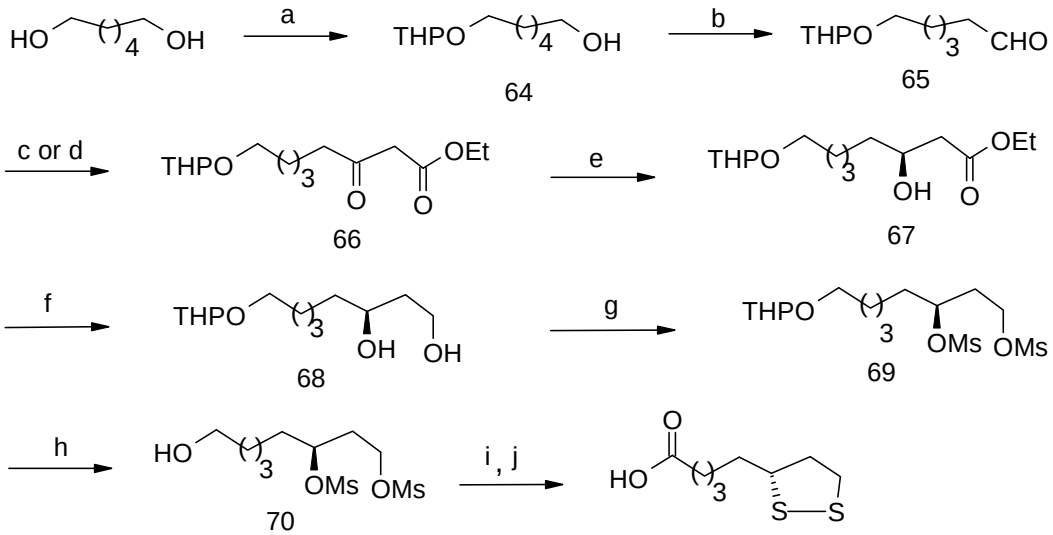
Sudalai *et al*[28] synthesized β-hydroxy esters **63** and **67** using OsO_4 catalysed asymmetric dihydroxylation and Ru-catalysed asymmetric hydrogenation respectively, as the key steps in the reaction sequence. These esters **63** and **67** are the precursors for lipoic acid. Thus this method delineates the formal synthesis of lipoic acid **(**Scheme 15 and 16**).**

Tetrahedron Lett. **2001**, *42*, 4891.



Reagents and conditions: a) OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, RT, 95 %; b) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 92 %; c) $RuCl_3$ (cat.), $NaIO_4$, 85 %; d) $NaBH_4$, DMAC, 20 % H_2SO_4, 63 %; e) $NaBH_4$, Et_3N, MeOH:DMF (2:1), AcOH, 0°C, 5h.

Scheme 15

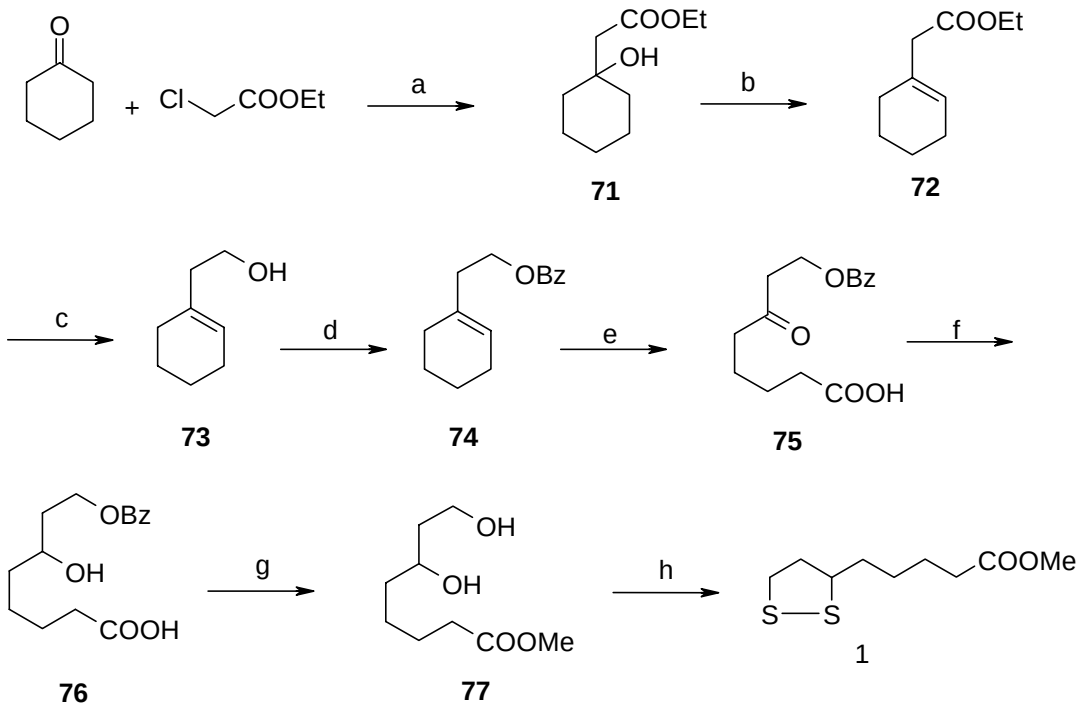


Reagents and conditions: a) DHP (0.5 mol), ether, PTSA, RT, 10h; b) $(COCl)_2$ DMSO, CH_2Cl_2, TEA, 75 %; c) N_2CHCO_2Et, CH_2Cl_2, $SnCl_2$, 1h, 85 %; d) Zn, $BrCH_2CO_2Et$, benzene, 4h then PCC, CH_3CO_2Na, CH_2Cl_2, 4h, 65 %; e) CH_3OH, H_2 (400psi), (S)-BINAP-Ru(II), 6h, 90 %; f) $NaBH_4$, $CuSO_4$, EtOH, 7 h; g) $MeSO_2Cl$, TEA, CH_2Cl_2, 0°C, 6h; h) PTSA, MeOH, 10h; i) PCC, CH_2Cl_2, 3h and Ag_2O, NaOH, 1h, 62 %; j) KOH, $Na_2S.9H_2O$, DMF, HCl, 28h, 45 %.

Scheme 16

Chavan's synthesis (2002)

Recently in our group, the synthesis of lipoic acid has been achieved by using modified Reformatsky reaction (scheme 17).[29] The elimination of the alcohol to furnish only the β, γ-unsaturated ester is another feature of this synthesis. Reformatsky reaction with chloroester was carried out on cyclohexanone to furnish alcohol **71**, which was then set for elimination using thionyl chloride and pyridine. The β, γ-ester thus obtained was then reduced using DIBAL-H. The alcohol **73** formed, was then protected using benzoyl chloride to give benzoate ester **74**, which was then subjected to ozonolysis followed by Jones oxidation to furnish ketoacid **75**. The reduction of ketoacid **75**, followed by esterification, furnished diol ester **77.** The diol ester **77** was then converted into methyl lipoate by known protocol.



Reagents and conditions:- a) Zinc, benzene-ether (1:1), reflux, 65 %; b) $SOCl_2$, pyridine, DCM, 86 %; c) DIBAL-H, DCM, -78 ^oC, 65 % ; d) BzCl, Et_3N, DCM, 92 %; e) i. O_3, DCM; ii. Jones reagent, 85 %; f) NaBH4, MeOH, 90 %; g) i. CH_2N_2, ether; ii. NaOMe, MeOH, 91 %; h) $MeSO_2Cl$, Et_3N, ii Na_2S, S, DMF, 60 % for 2 steps.

Scheme 17

1.1.5 References

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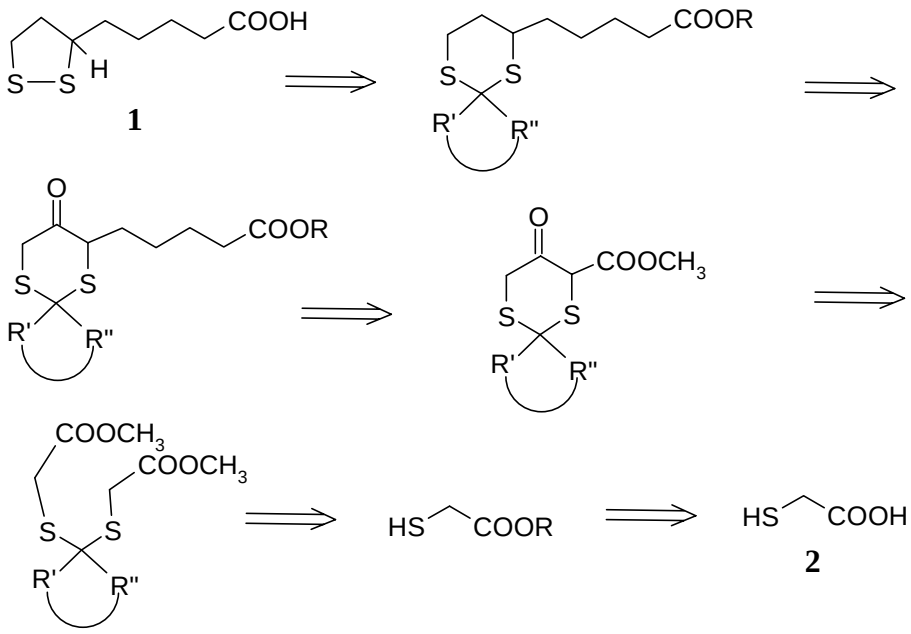
CHAPTER-1

SECTION-2

A Simple and Practical Synthesis of α-Lipoic acid

1.2.1 Present Work

From the literature survey of ∝-lipoic acid, it is evident that a large number of syntheses of this pharmaceutically and industrially important and biologically active molecule have been reported. However, the most of the synthetic routes involve the insertion of sulfur in the later stages of the synthetic sequence and free sulfur is used for this purpose. But the removal of this free sulfur impurity from the product becomes difficult. In order to avoid this problem, we thought of using the starting material which itself would contain sulfur and thus the sulfur would be inserted at the early stages of the synthetic sequence. With this perspective, following retrosynthetic analysis was proposed (Scheme 1).

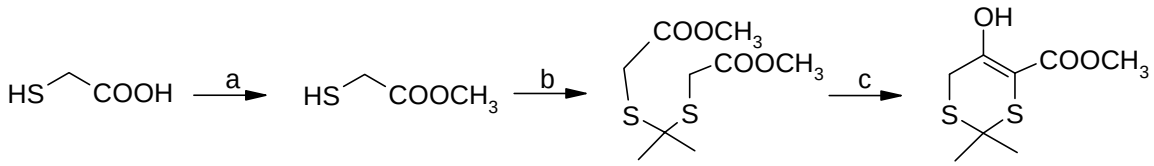


Scheme 1

The retrosynthetic analysis revealed a simple and practical synthetic route for ∝-lipoic acid starting from cheap and readily available thioglycolic acid **2**.

1.2.2 Results and Discussion

Methyl thioglycolate **3** was prepared from thioglycolic acid **2** by refluxing in methanol in presence of catalytic amount of H_2SO_4 in 70 % yields.[1] The ester **3** on acetonoide protection[2] gave 88 % of diester **4** which was then subjected to Dieckmann condensation[3] by using NaH in dry THF at 60 ^oC to give cyclic β- ketoester **5** in 86 % yield. The ^1H NMR spectrum of **5** displayed a singlet at δ 12.60. The downfield chemical shift showed that the β- ketoester was present in the enolic form (scheme 2).



2 **3** **4** **5**

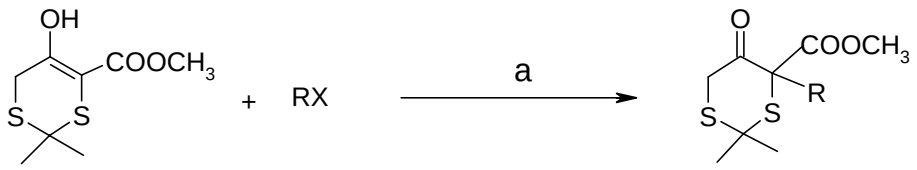
Reagents and conditions: a) MeOH, H_2SO_4 (cat.), reflux, 3 h, 70 %; b) acetone, $BF_3.Et_2O$ (cat.), 0 ^oC to rt, 6 h, 88 %; c) NaH, THF, 60 ^oC, 3 h, 86 %.

Scheme 2

The C-alkylation of β-ketoester **5** was supposed to be the crucial step of this synthesis. For this purpose various alkylating reagents were used under different conditions of phase transfer catalysis.[4]

Initially alkylation of **5** with n-butyl bromide was attempted under different conditions. The alkylation of **5** with n-butyl bromide in the presence of catalytic amount of phase transfer catalyst Et_3BnNCl in acetone at reflux temperature resulted in the formation of O-alkylated product **7a** as the major one along with 10 % of desired C-alkylated product **6a**. When the same reaction was carried out in presence of 0.5 equivalents of Bu_4NHSO_4 in THF at room temperature the C-alkyated product was obtained in 29 % yield. The ratio C-alkylation/O-alkylation was found to be increased when the amount of phase transfer catalyst was increased upto equimolar quantities (table 1).

After trying this reaction using different conditions of phase transfer catalysis, we could obtain the desired product **6a** in 71 % yields along with 12 % of O-alkylated product **7a** when the β-ketoester **5** was treated with 2.2 equivalents of K_2CO_3, 1.2 equivalents of Bu_4NHSO_4 as a phase transfer catalyst and n-butyl bromide in THF at room temperature for 24 h. The product **6a** was characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. After arriving at the proper conditions for alkylation, we have carried out alkylation of β-ketoester **5** with different alkylating agents (scheme 3).

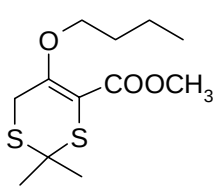


5 **RX** **6a - 6e**

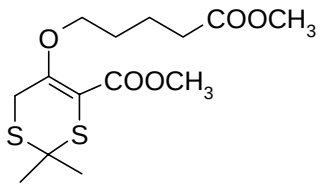
n-Butyl bromide	R = n-butyl	**6a**
Benzyl bromide	R = benzyl	**6b**
CH_3OOC-$(CH_2)_4$-Br	R = -$(CH_2)_4$-$COOCH_3$	**6c**
Allyl bromide	R = allyl	**6d**
Ethyl iodide	R = ethyl	**6e**

Reagents and conditions: a) K_2CO_3, Bu_4NHSO_4, THF, RT, 5-24 h.

Scheme 3



7a



7c

It has been observed that as expected only 0.25 equivalents of phase transfer catalyst was sufficient for alkylation of **5** using active alkylating agents like BnBr, allyl

bromide and ethyl iodide. However, for n-butyl bromide and methyl 5-bromovalerate (entries 2 and 4 in table 1), 1.2 equivalents of PTC were required for efficient reaction.

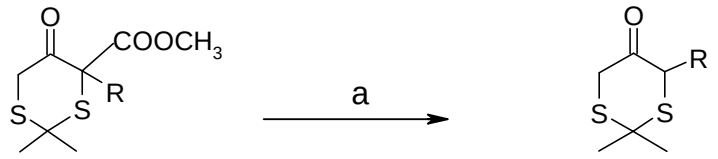
Table 1: Alkylation of β- ketoester **5** under phase transfer conditions

Sr. No.	RX	Phase Transfer Catalyst (equiv.)	Time h	C-alkylated		O-alkylated	
				Product	Yield[a] (%)	Product	Yield[a] (%)
1	n-BuBr	Et_3BnNCl (0.1)	5	6a	10[b]	7a	68
2	n-BuBr	Bu_4NHSO_4 (0.5)	19	6a	29	7a	42
3	n-BuBr	Bu_4NHSO_4 (1.0)	24	6a	57	7a	30
4	n-BuBr	Bu_4NHSO_4 (1.2)	24	6a	71	7a	12
5	BnBr	Bu_4NHSO_4 (0.25)	5	6b	62	7b	-
6	Methyl 5-bromovalerate	Bu_4NHSO_4 (1.2)	22	6c	70	7c	19
7	Allyl Bromide	Bu_4NHSO_4 (0.25)	5	6d	88	7d	-
8	Ethyl iodide	Bu_4NHSO_4 (0.25)	5.5	6e	84	7e	-

a. Yields refer to the isolated products.

b. Reaction is carried out in acetone at reflux temperature.

The next target was to achieve the decarboxylation of alkylated products **6**. The alkylated product **6a** was subjected to decarboxylation using Krapcho's protocol[5] (scheme 4). The compound **6a** on treatment with 2 equivalents of NaCl in wet DMSO at 135-140 ^oC for 7 h resulted in the formation of ketone **8a** in 90 % yield. The product **8a** was characterized by IR, ^1H NMR, ^{13}C NMR and mass spectroscopy. The disappearance of carbonyl frequency at 1732 cm^{-1} in IR spectrum reflected the absence of ester functionality in the product. The doublet of doublet at 3.97 (J = 7.3 Hz, 5.4 Hz) in ^1H NMR spectrum reflected the appearance of proton attached to tertiary carbon, which was bearing an ester group in the starting compound.



6a – 6e **8a – 8e**

R = n-butyl **8a**

R = benzyl **8b**

R = $-(CH_2)_4-COOCH_3$ **8c**

R = allyl **8d**

R = ethyl **8e**

Reagents and conditions: a) DMSO, NaCl, H_2O, 135-140 ^oC, 5-8 h.

Scheme 4

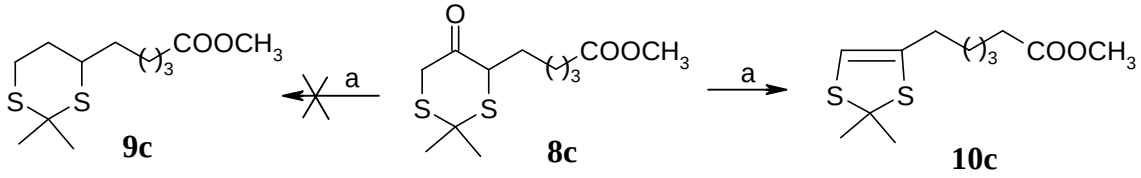
Table 2: Decarboxylation of alkylated ketoester **6**

C-alkylated ketoester	Reaction conditions	Time / h	Product	Isolated Yields (%)
6a	DMSO / NaCl	7	8a	90
6b	DMSO / NaCl	8	8b	49
6c	DMSO / NaCl	7	8c	81
6d	DMSO / NaCl	5	8d	48
6e	DMSO / NaCl	5	8e	69

The reduction of ketone functionality in compound **8** was attempted using different literature methods.

The ketone **8c** was subjected to Clemmensen's reduction[3, 6] using zinc dust, $HgCl_2$ and conc. HCl in toluene at room temperature (scheme 5). But instead of getting the desired deoxygenated product **9c**, we got some different product. The product formed was characterized by IR, ^1H NMR, ^{13}C NMR, heteronuclear correlation spectrum and mass spectroscopy. The ^1H NMR spectrum of the product showed a singlet at δ 5.60 integrating for one proton, which reflected the presence of one olefinic proton. The presence of a doublet at δ 110.3 and a singlet at δ 135.1 in ^{13}C NMR spectrum indicated

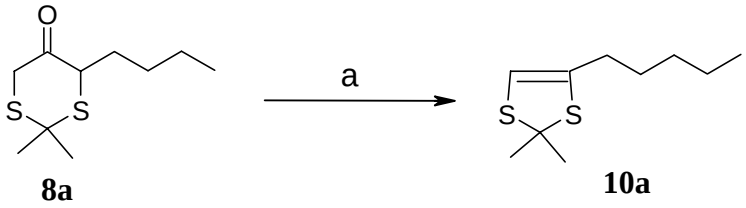
the presence of two olefinic carbons in the product. Also the singlet at δ 65.5 in ^{13}C NMR spectrum showed the presence of quaternary carbon (S-C-S). The mass spectrum showed peak at m/z = 260. From these spectral observations, we have tentatively assigned structure **10c** to the product. (Mole. Wt. of the product **10c** is 260). Thus a ring contraction from six membered ring to a five membered ring has been observed which is an important feature of this transformation (scheme 5).



Reagents and conditions: a) Zn dust, $HgCl_2$, conc. HCl, toluene, RT, 3 h, 90 %.

Scheme 5

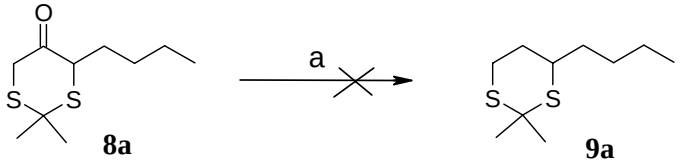
When the ketone **8a** was subjected to the same reaction, product **10a** was formed in 92 % yield (scheme 6).



Reagents and conditions: a) Zn dust, $HgCl_2$, conc. HCl, toluene, RT, 3 h, 92 %.

Scheme 6

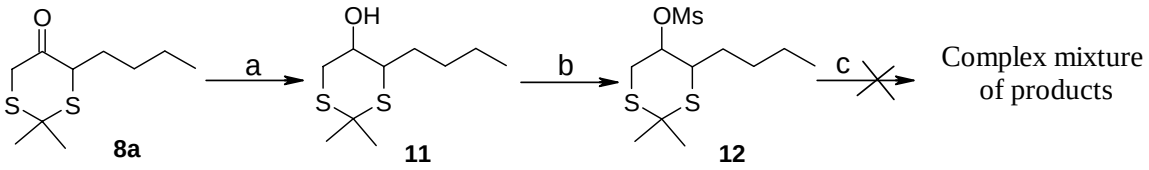
The Wolff Kishner reduction[7] of ketone **8a** also failed to furnish the desired deoxygenated product **9a** (scheme 7).



Reagents and conditions: a) NH_2NH_2, KOH, Diethylene glycol, reflux, 12 h.

Scheme 7

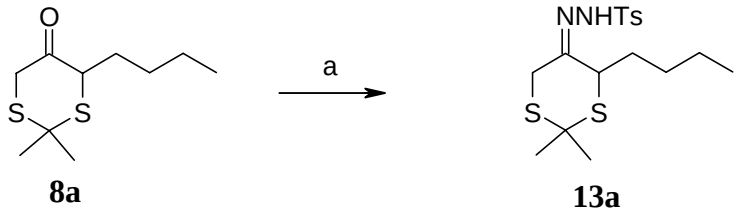
The ketone **8a** was then converted into its alcohol **11**, which was mesylated to give compound **12**. However, the compound **12** on treatment with LAH resulted in the formation of complex mixture of products (scheme 8).



Reagents and conditions: a) $NaBH_4$, MeOH, 0 ^oC-RT, 2 h; b) MsCl, Et_3N, DMAP, DCM, RT; c) LAH, THF, 0 ^oC-RT, 5 h.

Scheme 8

Then we thought of using a mild and well known protocol, which included deoxygenation of ketones via tosylhydrazones.[8] For this purpose, the ketone **8a** was converted into its tosylhydrazone by treating it with tosylhydrazine in methanol at room temperature to yield 92 % of tosylhydrazone **13a** as a white solid (scheme 9).

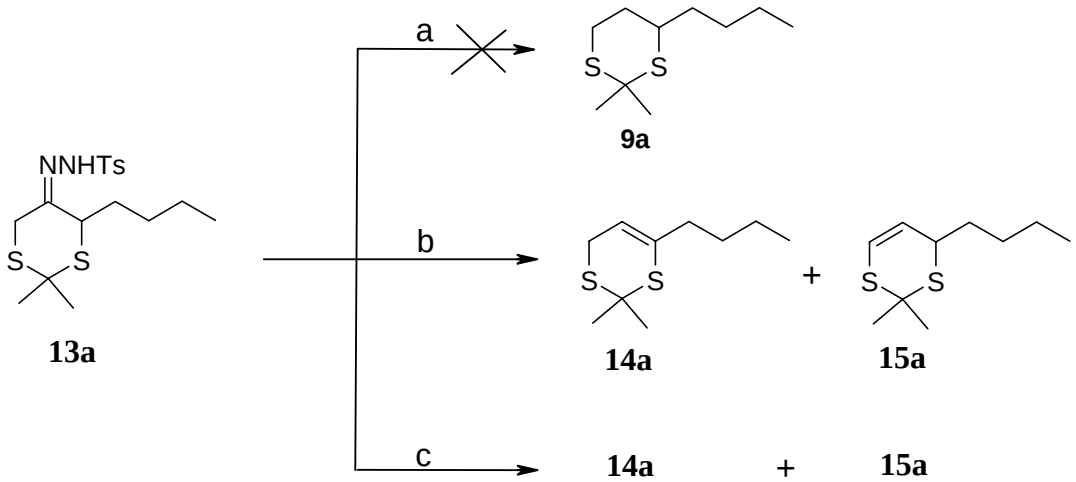


Reagents and conditions: a) $TsNHNH_2$, MeOH, RT, 2 h, 92 %.

Scheme 9

The tosylhydrazone **13a** was treated with $NaBH_4$ in methanol[8] at room temperature, which did not furnish the desired deoxygenated product **9a** (scheme 10). The tosylhydrazone **13a** was then treated with excess of $NaBH_4$ in isopropyl alcohol at reflux temperature for 2 h, which surprisingly resulted in the decomposition of **13a** in regioselective manner producing a mixture of olefins **14a** and **15a** (scheme 10). As $NaBH_4$ is alkaline, it was thought that this formation of olefins must have occurred due to the NaOH present in $NaBH_4$. In order to establish this on firmer grounds, the same

experiment was repeated using 2 equivalents of NaOH instead of $NaBH_4$ and as expected we could end up with the same result (scheme 10).



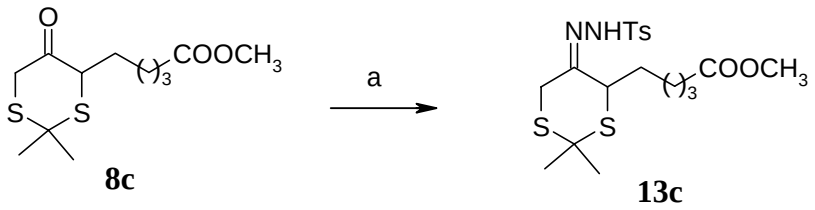
Reagents and conditions: a) $NaBH_4$, MeOH, RT-50 ^oC, 1 h: b) $NaBH_4$, Isopropyl alcohol, reflux, 2 h, 86 %; c) NaOH (2 equiv.), Isopropyl alcohol, reflux, 2 h, 88 %.

Scheme 10

The product formed was characterized by IR, ^1H NMR, ^{13}C NMR and mass spectroscopy. The ^1H NMR spectrum of the product displayed a triplet in olefinic region at δ 5.74 integrating for one proton. This indicated the presence of more substituted olefin **14a**. However, two very small peaks δ 5.82 (doublet) and δ 6.28 (doublet of doublet) also appeared in the olefinic region which indicated that the other regioisomer (less substituted olefin) **15a** was also present in the minor amount alongwith the more substituted olefin **14a**. The ratio of two regioisomers was determined from the ratio of integrations for olefinic protons. The ratio of integrations for signals at δ 5.74 and δ 5.82 revealed the presence of two regioisomers in the ratio **14a : 15a** = 87 : 13, more substituted olefin **14a** being the major one. The presence of doublet at δ 110.9 along with very small peaks at δ 121.5 and δ 122.2 corresponding to two doubets in the ^{13}C NMR spectrum confirmed the presence of two regioisomers in the product as predicted by ^1H

NMR spectrum. (This result has been explored as a useful synthetic methodology in ***Chapter-2, Section-1*** of this thesis).

The ketone **8c** was then converted into its tosylhydrazone **13c** by treatment with $TsNHNH_2$ in methanol at room temperature for 3 h in 87 % yield (scheme 11).

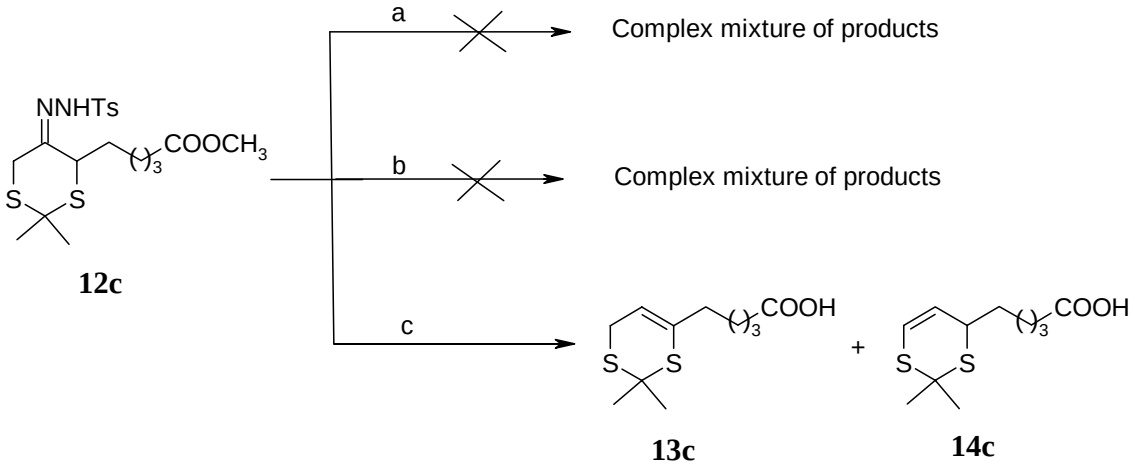


8c **13c**

Reagents and conditions: a) $TsNHNH_2$, MeOH, RT, 3 h, 87 %.

Scheme 11

The tosylhydrazone **13c** was then treated with sodium borohydride in acetic acid[9] as well as with catecholborane[10] in chloroform, but in both the cases complex mixture of products was formed (scheme 12).



12c **13c** **14c**

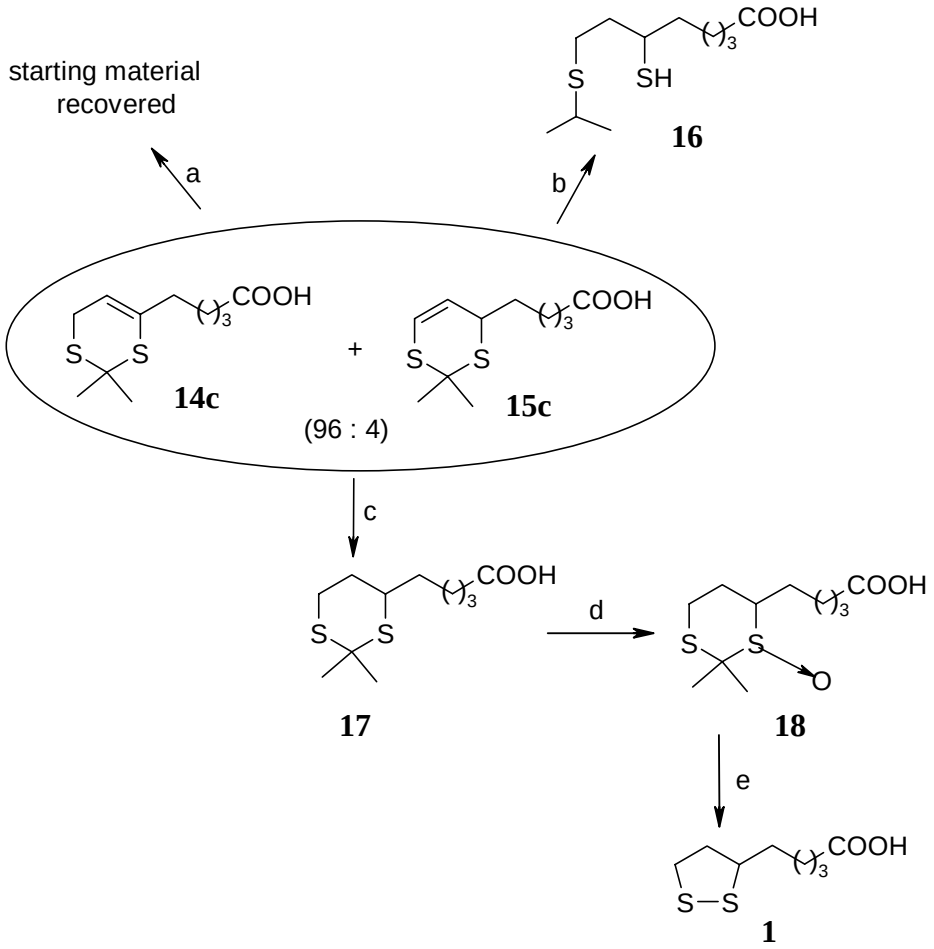
Reagents and conditions: a) $NaBH_4$, AcOH, RT to 70 ^oC; b) catecholborane, $CHCl_3$, -10 ^oC-RT; c) NaOH (2 equiv.), Isopropyl alcohol, reflux, 2-3 h, 84 %.

Scheme 12

However, the tosylhydrazone **13c** on treatment with NaOH in isopropyl alcohol at reflux temperature resulted in the formation of mixture of olefins **14c** and **15c** in a highly regioselective manner. The product formed was characterized by IR, ^1H NMR ^{13}C NMR

and mass spectroscopy. The ratio of two products was determined by ^{1}H NMR and it was found to be **14c** : **15c** = 96 : 4, more substituted olefin **14c** being the major one (scheme 12).

The mixture of olefins **14c** and **15c** was then subjected to catalytic hydrogenation using 10 % Pd-C in methanol at 250 psi pressure and 50 ^oC temperature for 12 h. This reaction failed completely, with the recovery of starting material, possibly due to poisoning of the catalyst by sulfur. Then we thought of using a more suitable protocol for hydrogenation of sulfur containing heterocycles, i. e. ionic hydrogenation.[11]

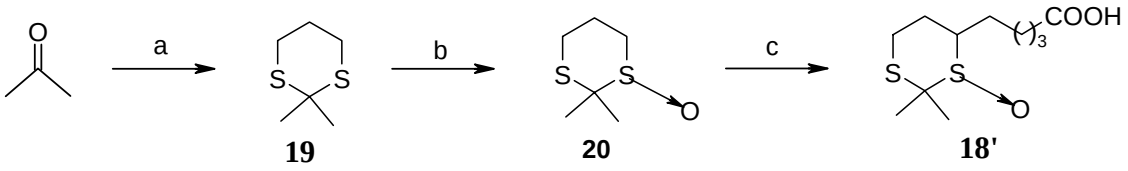


Reagents and conditions: a) H_2 / Pd-C, MeOH, 250 psi, 50 ^oC, 12 h; b) Et_3SiH (4 equiv.), TFA, RT, 12 h, 68 %; c) Et_3SiH (1 equiv.), TFA, 0 ^oC-RT, 2 h, 73 %; d) $NaIO_4$, MeOH, 0 ^oC, 2 h, 68 %; e) aq. HCl (1:1), benzene, 50 ^oC, 7 h, 69 %.

Scheme 13

Accordingly, the mixture of olefins **14c** and **15c** on treatment with 4 equivalents of triethylsilane in trifluoroacetic acid at room temperature for 12 h resulted in the formation of ring opened acid **16** in 68 % yields. However, when the same reaction was carried out using 1 equivalent of triethylsilane in TFA for 1 h, the desired product **17** was obtained in 73 % yield. The dithiane acid **17** was then oxidized to monosulfoxide **18** by treatment with aqueous solution of $NaIO_4$ in methanol at 0 ^oC for 2 h.[2] The IR spectrum of the product **18** displayed the characteristic S-O stretching band at 1024 cm^{-1}. The mass spectrum (ESI technique, m/z = 265.04, M+1) also confirmed the formation of monosulfoxide. The study of ^1H NMR and ^{13}C NMR spectra of the sulfoxide revealed that the sulfoxide was formed by the oxidation of sulfur attached to more substituted carbon giving the product **18**, which was unexpected due to steric reasons. To confirm this observed regioselectivity of sulfoxide formation, the similar sulfoxide **18'** was prepared by known literature method (scheme 14)[2].

The ^1H NMR and ^{13}C NMR spectra of sulfoxide **18'** prepared by literature method indicated that it was a mixture of two isomers and it was found that the sulfoxide **18** was identical with one of the isomers present in the compound **18'**. Finally sulfoxide **18** was converted into lipoic acid by treament with aqueous HCl (1:1) in benzene at 50 ^oC for 7 h (scheme 13).[2]



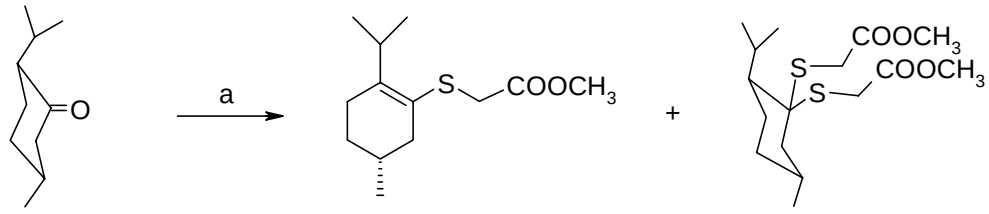
19 **20** **18'**

Reagents and conditions: a) 1,3-propanedithiol, $BF_3.Et_2O$ (cat.), 0 ^oC to RT, 8 h, 78 %; b) $NaIO_4$, MeOH, 0 ^oC, 2 h, 75 %; c) Bromovaleric acid, LDA-TMEDA, THF, -78 ^oC, 5 h, 38 %.

Scheme 14

Initially the thinking behind this proposed scheme was to synthesize optically active lipoic acid by using menthone as a chiral auxiliary. For this purpose asymmetric

ketone *l*-menthone **21** was treated with 2 equivalents of methylthioglycolate **3** and 0.25 equivalents of $BF_3.Et_2O$ at 0 ^oC for 8 h and then at room temprature for further 2 h. The mixture of two products was formed which were characterized by ^1H NMR and ^{13}C NMR spectra.



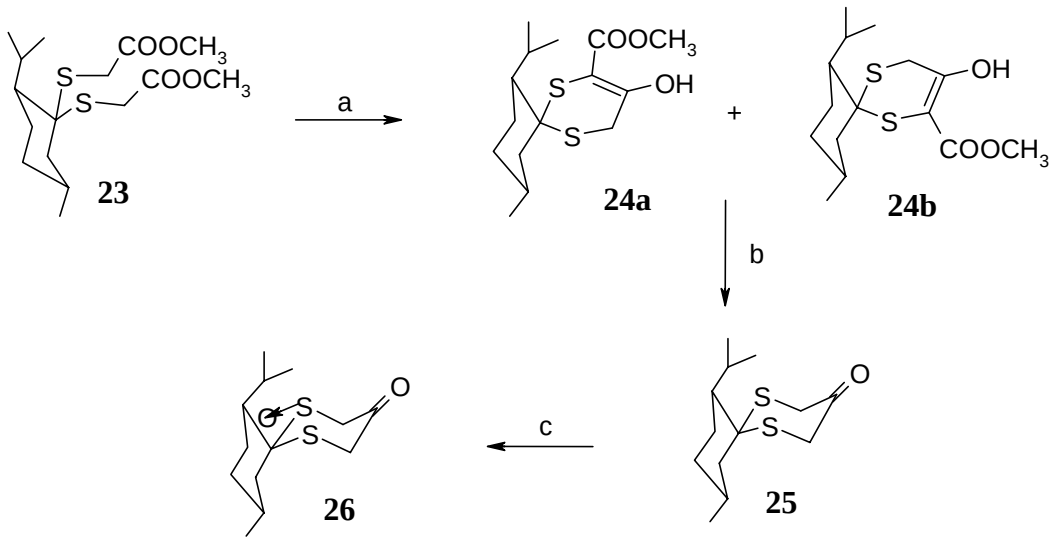
21 **22** (35 %) **23** (48 %)

Reagents and conditions: a) $BF_3.Et_2O$ (cat.), 0 ^oC to RT, 10 h.

Scheme 15

The faster moving spot on TLC after purification furnished 35 % of the product. This product displayed a singlet at δ 3.67 integrating for three protons in ^1H NMR spectrum which indicated that the product contained only one OCH_3 group and the spectrum revealed the formation of olefin ester **22**. The presence of two singlets at δ 146.7 and δ 120.9 in the ^{13}C NMR spectrum indicated the presence of two olefinic carbons and thus confirmed the formation of olefin ester **22**. The slower moving spot was isolated in 48 % yield which showed a singlet at δ 3.72 integrating for six protons in ^1H NMR spectrum. This indicated that the product contained two OCH_3 groups and the spectrum revealed the formation of desired diester **23**. The presence of two singlets at δ 170.0 and δ 169.8 in the ^{13}C NMR spectrum indicated the presence of two ester groups and thus confirmed the formation of desired diester **23** (Scheme 15).

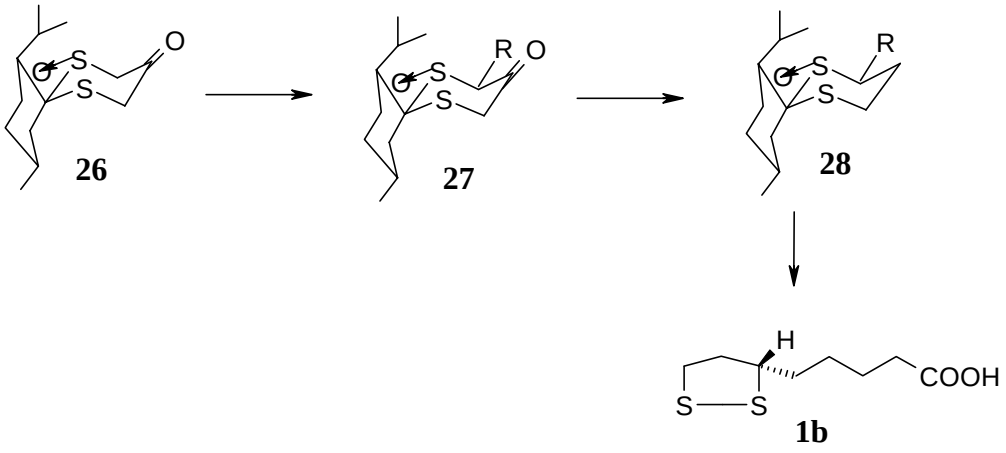
The diester **23** on Dieckmann condensation using NaH in THF at 60 ^oC resulted in the formation of regioisomeric mixture of β- ketoesters **24a** and **24b** in 78 % yield (Scheme 16). The ^1H NMR spectrum of the product displayed two singlets at δ 12.50 and δ12.55 which showed that two regioisomers of β- ketoesters were present and also it reflected the enolic form of ketoesters. The mixture of β- ketoesters **24a** and **24b** was then subjected to decarboxylation using Krapcho's protocol to furnish ketone **25** in 68 % yield. The ketone **25** was then oxidized to monosulfoxide **26** by treatment with aqueous solution of $NaIO_4$ in methanol at 0 ^oC for 6 h.



Reagents and conditions: a) NaH, THF, 60 ^{o}C, 3 h, 78 %; b) NaCl, H_2O, DMSO, 120 ^{o}C, 68 %; c) $NaIO_4$, MeOH, 0 ^{o}C, 6 h, 72 %.

Scheme 16

We thought of alkylating this sulfoxide **26,** which was expected to be stereoselective and the deoxygenation of ketone **27** followed by hydrolysis of sulfoxide **28** to give lipoic acid was the proposed route for the asymmetric synthesis of lipoic acid (Scheme 17).



Scheme 17

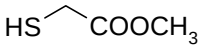
But as we failed to deoxygenate ketone **8a or 8c** without destroying the chiral center, we did not proceed further to achieve asymmetric synthesis of lipoic acid using this route.

1.2.3 Conclusion

We have demonstrated a simple and practical route for the synthesis of α-lipoic acid starting from cheap and easily available thioglycolic acid. This synthetic route involves a simple reaction sequence like C-alkylation using mild base like K_2CO_3, decarboxylation using Krapcho's protocol, highly regioselective decomposition of tosylhydrazones using mild conditions as compared to literature methods. As this protocol resulted in the formation of more substituted olefin as the major product, it could be extended towards the asymmetric synthesis of α-lipoic acid.

1.2.4 Experimental

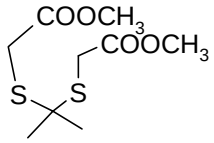
i) Methyl thioglycolate (3)



Procedure: - Thioglycolic acid (150 g, 1.627 mol) was taken in dry methanol (250 ml), conc. H_2SO_4 (8 ml) was added to it and refluxed for 3 h. The reaction mixture was cooled to room temperature, barium carbonate was added to it and the mixture was filtered. After evaporation of methanol under vacuum, the liquid was distilled under reduced pressure to give 121.0 g of methyl thioglycolate.

Molecular Formula	:	$C_3H_6O_2S$
Yield	:	70 %
B. P.	:	38 ^oC / 10 mm Hg. (lit. B. P. = 49 ^oC / 15 mm Hg).
^1H NMR ($CDCl_3$, 200 MHz)	:	δ = 3.61 (s, 3H), 3.14 (d, *J* = 8.3 Hz, 2H), 1.91 (t, *J* = 8.3 Hz, 1H).

ii) Diester (4)



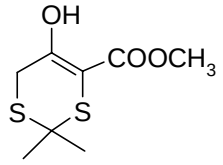
Procedure: - Methyl thioglycolate (10.61 g, 0.1 mol) was taken in dry acetone (25 ml), and to this solution $BF_3.Et_2O$ (2.5 ml) was added at 0 ^oC. The resulting reaction mixture was stirred at room temperature for 6 h. Excess acetone was then removed under vacuum and water was added to the residue and extracted twice with ether. The combined extracts were dried over anhydrous Na_2S0_4, filtered and concentrated under vacuum, which resulted in pure product (22.19 g, 88 %).

Molecular Formula	:	$C_9H_{16}O_4S_2$
Yield	:	88 %
IR ($CHCl_3$, cm^{-1})	:	2944, 1730, 1701, 1429, 1369, 1282, 1120, 989.
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 3 .70 (s, 6H), 3.38 (s, 4H), 1.59 (s, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ = 170.7 (s), 57.0 (s), 52.3 (q), 32.6 (t), 30.0 (q).

Mass : m/z = 252 (2), 221 (2), 202 (1), 179 (1), 147 (100), 132 (2), 115 (47), 106 (5), 87 (36), 74 (5), 59 (13).

iii) Methyl 5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylate (5)



Procedure: - Sodium hydride (2.59 g, 0.104 mol) was placed in 500 ml two neck round bottom flask fitted with reflux condenser and washed twice with dry pet ether, anhydrous THF (100 ml) was added to it and heated up to 60 ^{o}C. Then diester **3** (13 g, 0.0516 mol) in anhydrous THF (100 ml) was added slowly over 30 minutes and stirred for additional 3h. (Yellow colour was developed.) The reaction mixture was cooled to room temperature and dry methanol (20 ml) was syringed into the reaction mixture to destroy excess of NaH. Then acetic acid-water (30 ml, 1:1) was added to it and MeOH was removed under vacuum. The residue was extracted with ether. The organic layer was dried over anhydrous Na_2SO_4, filtered and after the evaporation of solvent the crude product was purified by column chromatography (PE : EA = 99.5 : 0.5) to give 9.8 g of pure β-ketoester as a white solid.

Molecular Formula : $C_8H_{12}O_3S_2$

Yield : 86 %.

M. P. : 49 ^{o}C (white solid)

IR ($CHCl_3$, cm^{-1}) : 3194, 3168, 3099, 2959, 2907, 2850, 1653, 1571, 1434, 1311, 1203, 1141, 1062, 775.

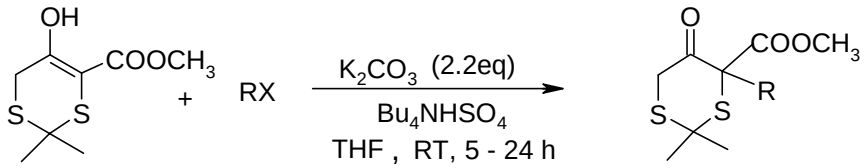
^{1}H NMR ($CDCl_3$, 200 MHz) : δ = 12.60 (s, 1H), 3.84 (s, 3H), 3.46 (s, 2H), 1.70 (s, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ = 174.4 (s), 171.0 (s), 95.8 (s), 55.8 (s), 52.0 (q), 32.0 (t), 31.9 (q).

Mass : m/z = 220 (34), 188 (20), 170 (18), 160 (28), 146 (21),

127 (60), 114 (82), 103 (21), 86 (100), 74 (90), 69 (15), 59 (43).

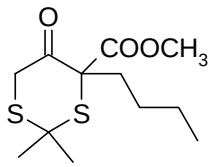
iv) Preparation of C-alkylated Products (6a-6e)



RX = n-BuBr, BnBr, Methyl 5-bromovalerate, Allyl Bromide, Ethyl iodide.

General Procedure:-Tetrabutyl ammonium hydrogen sulphate (9.23 g, 0.0272 mol) was added to the stirred solution of K_2CO_3 (6.9 g, 0.05 mol) in 30ml THF. To this was added solution of β-ketoester (5.0 g, 0.0227 mol) in 20 ml of THF and the resulting solution was stirred for one hour, alkyl halide RX (0.034 mol) was added to the reaction mixture and it was further stirred at room temperature. The reaction was monitored by TLC. After the completion of the reaction, THF was removed under vacuum, water was added to the residue and extracted twice with ether. Ether layer was dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and the crude product was then purified by column chromatography. (Note: In case of alkylation using allyl bromide, BnBr and ethyl iodide only 0.25 equivalents of phase transfer catalyst are required.)

a) Methyl 4-butyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6a)



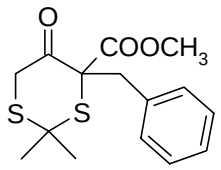
Molecular Formula	:	$C_{12}H_{20}O_3S_2$
Yield	:	71 %.
B. P.	:	Viscous liquid.
IR (neat, cm^{-1})	:	2949, 2862, 1732, 1710, 1440, 1371, 1217, 1121, 1005.
^1H NMR ($CDCl_3 + CCl_4$, 200 MHz)	:	δ = 3.82 (d, *J* = 18.6 Hz, 1H), 3.81 (s, 3H), 3.35 (d, *J* = 18.6 Hz, 1H), 1.78 (s, 3H), 1.69 (s, 3H), 1.62-1.85 (m,

2H), 1.23-1.35 (m, 4H), 0.89 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz) : δ = 197.3 (s), 170.1 (s), 61.8 (s), 53.0 (q), 50.5 (s), 36.6 (t), 32.7 (q), 32.2 (q), 26.7 (t), 22.9 (t), 13.8 (q).

Mass (EI) : m/z = 276 (75), 261 (2), 243 (5), 212 (25), 202 (17), 187 (12), 170 (29), 154(80), 139 (23), 127 (35), 115 (28), 101 (42), 95 (11), 87 (28), 73 (100), 67 (6), 59 (24).

b) Methyl 4-benzyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6b)



Molecular Formula : $C_{15}H_{18}O_3S_2$

Yield : 62 %

M. P. : 114 ^{o}C (White solid).

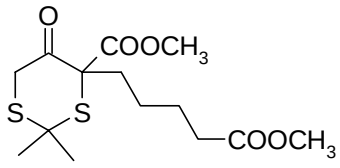
IR ($CHCl_3$, cm^{-1}) : 3019, 2953, 1746,1712, 758.

^{1}H NMR ($CDCl_3 + CCl_4$, 200 MHz) : δ: 7.14-7.31 (m, 5H), 3.85 (d, *J* = 18.1 Hz, 1H), 3.39 (d, *J* = 14.2 Hz, 1H), 3.38 (d, *J* = 18.1 Hz, 1H), 2.94 (d, *J* = 14.2 Hz, 1H), 1.74 (s, 3H), 1.71 (s, 3H).

^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz) : δ = 196.8 (s), 169.1 (s), 134.6 (s), 130.4 (d), 127.7 (d), 127.0 (d), 62.9 (s), 52.4 (q), 50.6 (s), 38.4 (t), 36.6 (t), 32.6 (q), 31.9 (q).

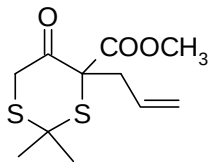
MS (ESI, Solv.: $CH_3CN + H_2O + CH_3COONH_4$) : m/z = 328.04 ($M + NH_4^+$), 311.04 (M + 1).

c) Methyl 4 - (4-methoxycarbonyl - butyl) - 2, 2 – dimethyl – 5 – oxo - (1,3) dithiane–4-carboxylate (6c)



Molecular Formula	:	$C_{14}H_{22}O_5S_2$
Yield	:	70 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	3021, 2953, 2925, 1748, 1713, 1439, 1160, 765.
^1H NMR ($CDCl_3$+CCl_4, 200MHz)	:	δ = 3.76 (d, *J* = 18.6 Hz, 1H), 3.75 (s, 3H), 3.60 (s, 3H), 3.30 (d, *J* = 18.6 Hz, 1H), 2.24 (t, *J* = 7.3 Hz, 2H), 1.64-1.85 (m, 5H), 1.72 (s, 3H), 1.64 (s, 3H), 1.17-1.27 (m, 2H).
^{13}C NMR ($CDCl_3$+CCl_4, 125MHz)	:	δ = 197.1 (s), 173.5 (s), 170.0 (s), 61.7 (s), 53.1 (q), 51.4 (q), 50.6 (s), 36.6 (t), 33.6 (t), 32.7 (q), 32.6 (t), 32.2 (q), 25.0 (t), 24.2 (t).
Mass (EI)	:	m/z = 334 (26), 303 (6), 270 (15), 260 (10), 237 (2), 228 (18), 212 (14), 197 (27), 180 (36), 169 (23), 159 (27), 155 (39), 141 (32), 127 (81), 123 (68), 115 (100), 99 (94), 87 (51), 73 (76), 59 (25).
HRMS (ESI^+ mode)	:	Calculated mass = 357.0806($C_{14}H_{22}O_5NaS_2$ $[M + Na]^+$) Mass found = 357.0811

d) Methyl 4-allyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6d)

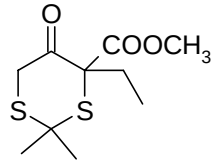


Molecular Formula	:	$C_{11}H_{16}O_3S_2$
Yield	:	88 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	3020, 2955, 2921, 1747, 1712, 1434, 994.
^1H NMR ($CDCl_3$+CCl_4, 200MHz)	:	δ = 5.54-5.74 (m, 1H), 4.97 (dd, *J* = 11.2 Hz, 2.4 Hz, 2H), 3.72 (d, *J* = 18.6 Hz, 1H), 3.67 (s, 3H), 3.29 (d, *J* = 18.6 Hz, 1H), 2.57 (dd, *J* = 6.8, 14.2 Hz, 1H), 2.35 (dd, *J* = 6.8, 14.2 Hz, 1H), 1.68 (s, 3H), 1.60 (s, 3H).
^{13}C NMR	:	δ = 196.8 (s), 169.3 (s), 131.4 (d), 118.8 (t), 61.5 (s), 52.8

($CDCl_3$+ CCl_4, 50 MHz) (q), 50.3 (s), 37.3 (t), 36.2 (t), 32.4 (q), 31.9 (q).

MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4) : m/z = 261.05 (M+1).

e) Methyl 4-ethyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6e)



Molecular Formula : $C_{10}H_{16}O_3S_2$

Yield : 84 %

B. P. : Viscous liquid.

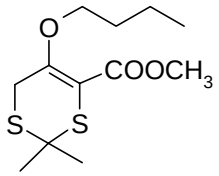
IR (Neat, cm^{-1}) : 2955, 1749, 1712, 1456, 999.

^1H NMR ($CDCl_3$+CCl_4, 500 MHz) : δ = 3.75 (s, 3H), 3.74 (d, *J* = 18.3 Hz, 1H), 3.3 (d, *J* = 18.3 Hz, 1H), 1.92-1.98 (m, 1H), 1.72(s, 3H), 1.64 (s, 3H), 1.6-1.7 (m, 1H), 0.88 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$+CCl_4, 125 MHz) : δ = 197.0 (s), 169.7 (s), 62.0 (s), 52.8 (q), 50.3 (s), 36.4 (t), 32.5 (q), 32.0 (q), 26.2 (t), 9.2 (q).

MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4) : m/z = 266.03 ($M + NH_4^+$), 249.03 (M+1).

f) Methyl-5-butoxy-2,2-dimethyl-*6H*-(1,3)-dithiine-4-carboxylate (7a)

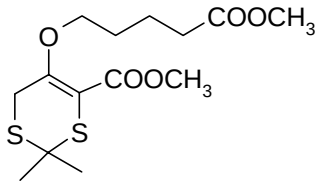


Molecular Formula : $C_{12}H_{20}O_3S_2$

B. P. : Viscous liquid

^1H NMR ($CDCl_3$, 200 MHz) : δ = 4.03 (t, *J* = 6.6 Hz, 2H), 3.76 (s, 3H), 3.49 (s, 2H), 1.40-1.78 (m, 6H), 1.70 (s, 6H), 0.96 (t, *J* = 7.3 Hz, 3H).

f) Methyl-5 (4-methoxy carbonyl-butoxy)-2,2-dimethyl-*6H*-(1,3)-dithiine-4-carboxylate (7c)

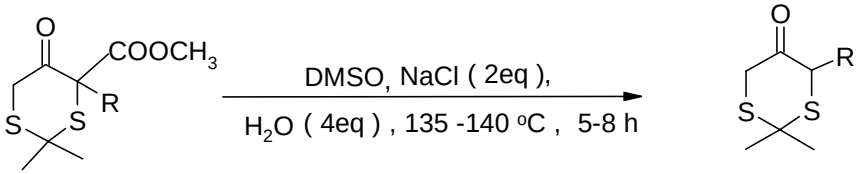


Molecular Formula : $C_{14}H_{22}O_5S_2$

B. P. : Viscous liquid

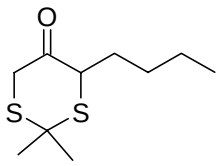
^{1}H NMR (CDCl$_3$, 200 MHz) : δ = 3.95 (t, *J* = 6.5 Hz, 2H), 3.67 (s, 3H), 3.57 (s, 3H), 3.39 (s, 2H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.62-1.75 (m, 4H), 1.60 (s, 6H).

v) Preparation of ketones 8a-8e



General Procedure:-A solution of alkylated β-ketoester **6** (2 mmol), NaCl (4 mmol) and water (8 mmol) in DMSO (10 ml) was heated to 135-140 ^{o}C for 5-8 h. The reaction mixture was then cooled, poured into water (25 ml) and extracted with ether (2x10ml). The combined extracts were washed with water and brine solution. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum and the product was purified by column chromatography.

a) 4-Butyl-2,2-dimethyl- (1,3) dithian-5-one (8a)

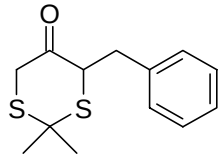


Molecular Formula : $C_{10}H_{18}OS_2$

Yield : 90 %.

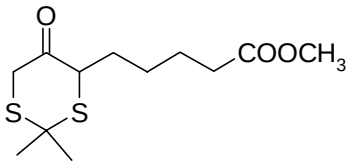
B. P.	:	Viscous liquid.
IR (Neat, cm^{-1})	:	3020, 1712.
^1H NMR ($CDCl_3$, 200 MHz)	:	δ = 3.97 (dd, *J* = 7.3 Hz, 5.4 Hz, 1H), 3.64 (d, *J* = 16.1 Hz, 1H), 3.21 (d, *J* = 16.1 Hz, 1H), 1.71-1.93 (m, 1H), 1.84 (s, 3H), 1.67 (s, 3H), 1.23-1.46 (m, 5H), 0.89 (t, *J* = 6.4 Hz, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz)	:	δ = 204.4 (s), 50.0 (s), 47.2 (d), 37.0 (t), 32.5 (q), 31.6 (q), 29.0 (t), 27.0 (t), 22.3 (t), 13.7 (q).

b) 4-Benzyl-2,2-dimethyl- (1,3) dithian-5-one (8b)



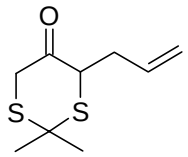
Molecular Formula	:	$C_{13}H_{16}OS_2$
Yield	:	49 %.
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	3025, 2921, 1711, 1453, 759.
^1H NMR ($CDCl_3 + CCl_4$, 200 MHz)	:	δ = 7.17-7.36 (m, 5H), 4.33 (dd, *J* = 7.3 Hz, 6.3 Hz, 1H), 3.64 (d, *J* =16.1 Hz, 1H), 3.32 (dd, *J* = 14.2 Hz, 6.3 Hz, 1H), 3.29 (d, *J* = 16.1 Hz, 1H), 2.68 (dd, *J* = 14.2 Hz, 7.3 Hz, 1H), 1.83 (s, 3H), 1.69 (s, 3H).
^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz)	:	δ = 203.6 (s), 138.0 (s), 129.0 (d), 128.2 (d), 126.6 (d), 50.42 (s), 48.6 (d), 37.1 (t), 33.3 (t), 32.4 (q), 31.6 (q).
MS (ESI, Solv.: $CH_3CN + H_2O + CH_3COONH_4$)	:	m/z = 253.05 (M+1).

c) Methyl 5-[2,2-dimethyl- 5-oxo-(1,3) dithian-4-yl]-pentanoate (8c)



Molecular Formula	:	$C_{12}H_{20}O_3S_2$
Yield	:	81 %.
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	3020,1732, 1711, 772, 744.
^1H NMR ($CDCl_3 + CCl_4$, 200 MHz)	:	δ = 3.98 (dd, *J* = 6.8 Hz, 5.9 Hz, 1H), 3.64 (s, 3H), 3.63 (d, *J* = 16.6 Hz, 1H), 3.25 (d, *J* = 16.6 Hz, 1H), 2.29 (t, *J* = 7.3 Hz, 2H), 1.76-1.92 (m, 1H), 1.84 (s, 3H), 1.56-1.71 (m, 2H), 1.66 (s, 3H), 1.34-1.49 (m, 3H).
^{13}C NMR ($CDCl_3 + CCl_4$, 125 MHz)	:	δ = 204.0 (s), 173.6 (s), 51.4 (q), 50.4 (s), 47.1 (d), 37.1 (t), 33.7 (t), 32.8 (q), 31.9 (q), 27.2 (t), 26.6 (t), 24.7 (t).
Mass (EI)	:	m/z = 276 (57), 262 (3), 243 (13), 225 (6), 211 (8), 202 (11), 179 (8), 170 (100), 153 (24), 142 (28), 127 (36), 111 (16), 93 (21), 73 (68), 56 (11).
HRMS (ESI^+ mode)	:	Calculated mass = 299.0752 ($C_{12}H_{20}O_3NaS_2$ $[M + Na]^+$) Mass found = 299.0742

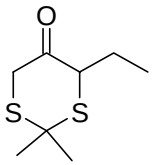
d) 4-Allyl-2,2-dimethyl- (1,3) dithian-5-one (8d)



Molecular Formula	:	$C_9H_{14}OS_2$
Yield	:	48 %.
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	3019, 2979, 1711, 1640, 922, 757.
^1H NMR ($CDCl_3 + CCl_4$, 500 MHz)	:	δ = 5.68-5.89 (m, 1H), 5.05-5.13 (m, 2H), 4.07 (dd, *J* = 6.4 Hz, 7.2 Hz, 1H), 3.67 (d, *J* = 16.1 Hz, 1H), 3.27 (d, *J* = 16.1 Hz, 1H), 2.58-2.71 (m, 1H), 2.17-2.27 (m, 1H), 1.87 (s, 3H), 1.69 (s, 3H).
^{13}C NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 203.6 (s), 134.2 (d), 117.8 (t), 50.4 (s), 46.9 (d), 37.1 (t), 32.7 (q), 32.6 (q), 31.8 (t).

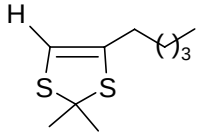
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4) : m/z = 203.05 (M+1).

e) 4-Ethyl-2,2-dimethyl- (1,3) dithian-5-one (8e)



Molecular Formula	:	$C_{12}H_{20}O_3S_2$
Yield	:	69 %.
B. P.	:	Viscous liquid.
IR (Neat, cm^{-1})	:	2953, 1713.
^1H NMR ($CDCl_3$ +CCl_4, 500 MHz)	:	δ = 3.90 (dd, *J* = 7.3 Hz, 5.9 Hz, 1H), 3.58 (d, *J* = 16.1 Hz, 1H), 3.25 (d, *J* = 16.1 Hz, 1H), 1.78-1.94 (m, 1H), 1.83 (s, 3H), 1.63 (s, 3H), 1.38-1.51 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR ($CDCl_3$+CCl_4, 125 MHz)	:	δ = 203.8 (s), 50.1 (s), 49.0 (d), 37.0 (t), 32.7 (q), 31.9 (q), 21.0 (t), 11.6 (q).
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4)	:	m/z = 208.05 (M + NH_4^+), 191.05 (M+1).

vi) 2,2-dimethyl-pentyl-[1,3]-dithiole (10a)

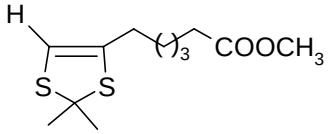


Procedure:- The fine zinc powder (1.00 g) was shaken with a solution of $HgCl_2$ (500 mg) and conc. HCl (1 ml) in water (10 ml) for 15 minutes. The amalgam was washed several times with water and then to it was added a solution of ketone **8a** (218 mg, 1.00 mmol) in toluene (5 ml) and conc. HCl (8 ml). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was washed with water, toluene was

removed under vacuum and the residue was purified by column chromatography (Pet. Ether: EtOAc = 98 : 2) to furnish 186 mg of pure product.

Molecular Formula	:	CHOS
Yield	:	92 %.
B. P.	:	Viscous liquid.
^{1}H NMR ($CDCl_3$ +CCl_4, 500 MHz)	:	δ = 5.60 (s), 2.17-2.30 (m, 2H), 1.79 (s, 6H), 1.25-1.57 (m, 6H), 0.93 (t, *J* = 7.3 Hz, 3H).

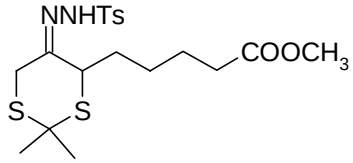
vii) Methyl 6-(2,2-dimethyl-[1,3]-dithiol-4-yl-hexanoate (10c)



Procedure:- The fine zinc powder (1.00 g) was shaken with a solution of $HgCl_2$ (500 mg) and conc. HCl (1 ml) in water (10 ml) for 15 minutes. The amalgam was washed several times with water and then to it was added a solution of ketone **8c** (276 mg, 1.00 mmol) in toluene (5 ml) and conc. HCl (8 ml). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was washed with water, toluene was removed under vacuum and the residue was purified by column chromatography (Pet. Ether: EtOAc = 98 : 2) to furnish 234 mg of pure product.

Molecular Formula	:	$C_{12}H_{20}O_2S_2$
Yield	:	90 %.
B. P.	:	Viscous liquid.
IR (Neat, cm^{-1})	:	3021, 2997, 2949, 2936, 1732, 756.
^{1}H NMR ($CDCl_3$ +CCl_4, 500 MHz)	:	δ = 5.60 (s), 3.66 (s), 2.22-2.35 (m, 4H), 1.80 (s, 6H), 1.32-1.68 (m, 6H).
^{13}C NMR ($CDCl_3$+CCl_4, 125 MHz)	:	δ = 173.5 (s), 135.1 (s), 110.3 (d), 65.5 (s), 51.1(q), 33.5 (t) 31.2 (q), 28.4 (t), 28.1(t), 24.2 (t).
MS (EI)	:	m/z = 260 (M^+)

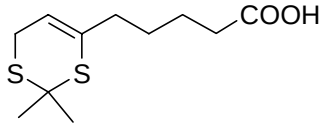
viii) Methyl 5- [5-(*p*-toluenesulfonyl) hydrazono-2, 2- dimethyl-(1, 3)dithian-4-yl] - pentanoate (13c)



Procedure: The mixture of ketone **8c** (276 mg, 1 mmol) and tosylhydrazine (279 mg, 1.5 mmol) in methanol (10 ml) was stirred at room temperature. The reaction was monitored by TLC, and after the completion of the reaction, methanol was removed under vacuum and the residue was purified by column chromatography to yield 386 mg of pure tosylhydrazone as a white solid (87 % yields).

Molecular Formula	:	$C_{19}H_{28}O_4N_2S_3$
Yield	:	87 %.
M. P.	:	120 ^oC (White solid).
IR ($CHCl_3$, cm^{-1})	:	3020, 2400, 1731, 757.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 8.53 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 3.74 (dd, *J* = 7.8 Hz, 6.4 Hz, 1H), 3.61 (s, 1H), 3.56 (d, *J* = 15.6 Hz, 1H), 3.21 (d, *J* = 15.6 Hz, 1H), 2.37 (s, 3H), 2.19 (t, *J* = 7.8 Hz, 2H), 1.76-1.84 (m, 1H), 1.68 (s, 3H), 1.46 (s, 3H), 1.20-1.61 (m, 5H).
^{13}C NMR ($CDCl_3$+CCl_4, 50MHz)	:	δ = 173.6 (s), 155.7 (s), 143.9 (s), 135.4 (s), 129.3 (d), 128.1 (d), 51.2 (q), 49.7 (s), 45.1 (d), 33.6 (t), 32.2 (q), 31.0 (q), 28.9 (t), 26.1 (t), 25.6 (t), 24.4 (t), 21.3 (q).
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4)	:	m/z = 445.04 (M+1).
HRMS (ESI^+ mode)	:	Calculated mass = 445.1289($C_{19}H_{29}N_2O_4S_3$ $[M + H]^+$) Mass found = 445.1271.

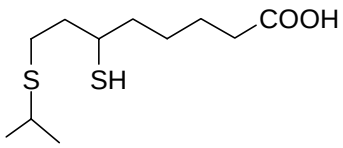
ix) 5-(2,2-dimethyl-*6H*-[1,3]dithiin-4-yl)-pentanoic acid (14c)



Procedure:- The mixture of tosylhydrazone **13c** (200 mg, 0.450 mmol) and NaOH (2 equivalents) in isopropyl alcohol (10 ml) was refluxed for 2-3 h. The reaction was monitored by TLC and after the completion of the reaction, isopropyl alcohol was removed under vacuum and water was added to the reaction mixture. Then aqueous layer was washed with ether and then acidified with dilute HCl. Finally the aqueous layer was extracted with ether (3 x 15 ml). The ether layer was dried over anhydrous sodium sulfate, filtered and ether was removed under vacuum. The residue was purified by column chromatography to give 93 mg of pure product.

Molecular Formula	:	$C_{11}H_{18}O_2S_2$
Yield	:	84 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	2985, 1709, 1216, 1167.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 10.06 (bs, 1H), 5.75 (t, *J* = 4.4 Hz, 1H), 3.44 (d, *J* = 4.4 Hz, 2H), 2.34 (t, *J* = 7.3 Hz, 2H), 2.20 (t, *J* = 6.4 Hz, 2H), 1.67 (s, 6H), 1.42-1.74 (m, 4H).
^{13}C NMR ($CDCl_3 + CCl_4$, 50MHz)	:	δ = 179.2 (s), 136.5 (s), 111.4 (d), 47.3 (s), 38.2 (t), 33.8 (t), 31.0 (q), 28.3 (t), 26.4 (t), 23.7 (t).
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	:	m/z = 245.05 (M-1).

x) 8-Isopropylsulfanyl-6-mercapto-octanoic acid (16)

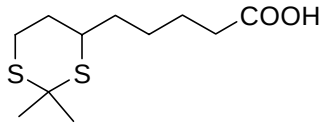


Procedure: To a mixture of olefin acids **14c and 15c** (39 mg, 0.159 mmol) and triethylsilane (74 mg, 0.636 mmol), trifluoroacetic acid (0.8 ml) was added slowly at room temperature and the reaction mixture was stirred overnight. Then the reaction

mixture was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (Pet. Ether : E tOAc = 94 : 6) to yield 27 mg of the product.

Molecular Formula	:	$C_{11}H_{22}O_2S_2$
Yield	:	68 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	2927, 2865, 1709, 1443, 1155, 757.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 2.86-2.95 (m, 1H), 2.58-2.77 (m, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 1.84-1.95 (m, 1H), 1.44-1.82 (m, 8H), 1.31 (d, *J* = 6.6 Hz, 1H), 1.27 (d, *J* = 8.0 Hz, 6H).
^{13}C NMR ($CDCl_3 + CCl_4$, 50MHz)	:	δ = 179.8 (s), 39.9 (d), 38.9 (t), 38.7 (t), 35.0 (d), 33.9 (d), 28.1 (t), 26.6 (t), 24.4 (t), 23.5 (q).
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	:	m/z = 268.04 ($M + NH_4^+$).

xi) 5-(2,2-Dimethyl-[1,3]dithian-4-yl)-pentanoic acid (17)

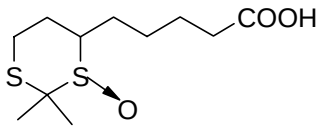


Procedure: To a mixture of olefin acids **14c and 15c** (116 mg, 0.472 mmol) and triethylsilane (60 mg, 0.472 mmol), trifluoroacetic acid (1 ml) was added slowly at 0 ^oC and the reaction mixture was stirred for 1 h at 0 ^oC and another 1 h at room temperature. Then the reaction mixture was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (Pet. Ether : EtOAc = 93 : 7) to yield 86 mg of the product.

Molecular Formula	:	$C_{11}H_{20}O_2S_2$
Yield	:	73 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	2926, 1709, 1419, 1116, 935.

^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 2.94-3.15 (m, 2H), 2.69-2.80 (m, 1H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.10-2.20 (m, 1H), 1.79 (s, 3H), 1.58 (s, 3H), 1.40-1.71 (m, 8H).
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz)	:	δ = 179.8 (s), 47.2 (s), 40.0 (d), 35.3 (t), 33.6 (t), 32.6 (t), 31.2 (q), 30.6 (q), 27.4 (t), 25.4 (t), 24.2 (t).
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	:	m/z = 266.04 ($M + NH_4^+$), 249.04 (M+1).

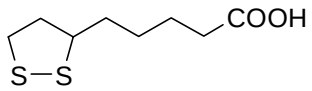
xii) 5-(2,2-Dimethyl-3-oxo-[1,3]dithian-4-yl)-pentanoic acid (18)



Procedure: A solution of $NaIO_4$ (69 mg, 0.323 mmol) in 5 ml water was added dropwise to a solution of dithiane acid **17** (80 mg, 0.323 mmol) in methanol (25 ml) at -5 ^oC. The resulting white slurry was stirred at 0 ^oC for 2 h. The precipitated sodium iodide was removed by filtration. The methanol was removed under vacuum and the residue was extracted with $CHCl_3$ (3x10ml). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and solvent was removed under vacuum. The residue was then purified by column chromatography (Pet. Ether / EtOAc: 25:75) to yield 50 mg of the product.

Molecular Formula	:	$C_{11}H_{20}O_3S_2$
Yield	:	68 %
M. P.	:	128 ^oC (White solid).
IR ($CHCl_3$, cm^{-1})	:	3018, 2934, 1711, 1024.
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 2.62-2.91 (m, 2H), 2.23-2.52 (m, 4H), 1.93-2.17 (m, 2H), 1.66 (s, 3H), 1.56 (s, 3H), 1.40-1.71 (m, 5H).
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz)	:	δ = 177.5 (s), 57.9 (s), 57.0 (d), 34.6 (t), 33.6 (t), 29.2 (t), 25.9 (q), 25.5 (t), 25.3 (t), 24.6 (t), 16.4 (q).
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	:	m/z: 265.04 (M+1).

xiii) α-Lipoic acid (1)



Procedure: The sulfoxide **18** (50 mg, 0.189 mmol) was taken in benzene (10 ml) and to this was added aqueous HCl (1 ml, 1:1) and the reaction mixture was vigorously stirred at 50 ^{o}C for 7 h until the reaction was complete. The benzene layer was separated and aqueous layer was extracted twice with benzene. The combined extracts were washed with brine and dried over anhydrous sodium sulfate and filtered. The solvent was removed under vacuum at room temperature and the residue was purified by column chromatography (Pet. Ether : EtOAc = 80 : 20) to give 27 mg of the product.

Molecular Formula	:	$C_8H_{14}O_2S_2$
Yield	:	69 %
^{1}H NMR	:	δ = 3.48-3.60 (m, 1H), 3.04-3.22 (m, 2H), 2.42-2.55 (m,
($CDCl_3$ + CCl_4, 200MHz)		1H), 2.37 (t, *J* = 6.8 Hz, 2H), 1.30-1.98 (m, 7H).
^{13}C NMR	:	δ = 180.0 (s), 56.1 (d), 40.0 (t), 38.3 (t), 34.4 (t), 33.7 (t),
($CDCl_3$ + CCl_4, 50MHz)		28.5 (t), 24.2 (t).

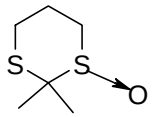
xiv) 2,2-Dimethyl-[1,3]dithiane (19)

Procedure:- To a solution of 1, 3-propanedithiol (2.16 g, 20 mmol) in acetone (20 ml) was added $BF_3.OEt_2$ (0.5 ml) slowly at 0 ^{o}C and the reaction mixture was stirred for 8 h and then brought to room temperature. Then excess acetone was removed under vacuum and the residue was treated with 5 % of aq. NaOH and extracted twice with ether. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by column chromatography to give 2.3 g of dithiane **19**.

Molecular Formula	:	$C_6H_{12}S_2$
Yield	:	78 %

^{1}H NMR : δ = 2.76-2.96 (m, 4H), 1.85-2.10 (m, 2H), 1.65 (s, 6H).
($CDCl_3$ + CCl_4, 200MHz)

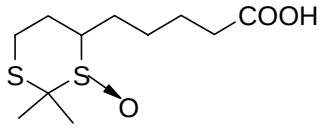
xv) 2,2-Dimethyl-[1,3]dithiane 1-oxide (20)



Procedure:- A solution of $NaIO_4$ (1.445 g, 6.757 mmol) in water (20 ml) was added dropwise to a solution of dithiane **19** (1.00 g, 6.757 mmol) in methanol (60 ml) at 0 ^{o}C. The resulting white slurry was stirred at 0 ^{o}C for 2 h. The precipitated sodium iodate was removed by filtration and methanol was removed under vacuum. The residue was extracted twice with chloroform and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography (Pet. Ether : EtOAc = 15 : 85) to give 0.831 g of pure sulfoxide.

Molecular Formula : $C_6H_{12}OS_2$
Yield : 75 %
B. P. : Viscous liquid.
IR ($CHCl_3$, cm^{-1}) : 2923, 1035.
^{1}H NMR : δ = 2.83-3.04 (m, 2H), 2.53-2.72 (m, 2H), 2.25-2.38 (m, 2H), 1.57 (s, 3H), 1.51 (s, 3H).
($CDCl_3$ + CCl_4, 200MHz)
^{13}C NMR : δ = 57.3 (s), 46.4 (t), 28.3 (t), 25.4 (q), 25.3 (t), 16.3 (q).
($CDCl_3$ + CCl_4, 50MHz)

xvi) 5-(2,2-Dimethyl-3-oxo-[1,3]dithian-4-yl)-pentanoic acid (18')



(Mixture of two isomers)

Procedure:-The solution of sulfoxide **20** (150 mg, 0.915 mmol) in THF (2 ml) was added dropwise to a solution of LDA-TMEDA (2.2 equiv.) in THF (4 ml) at –78 ^{o}C. The

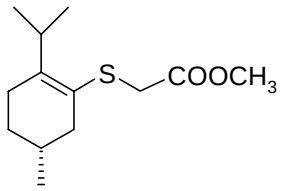
mixture was stirred for 0.5 h at –78 ^{o}C and then a solution of 5-bromovaleric acid (182 mg, 1.006 mmol) in THF (2 ml) was added dropwise and the reaction mixture was allowed to stir at –78 ^{o}C for 5 h. It was then warmed up to 0 ^{o}C and then quenched with aqueous HCl (1:1). THF was removed under vacuum and the aqueous layer was extracted several times with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The product was purified by column chromatography ((Pet. Ether : EtOAc = 20 : 80) to give 91 mg of compound sulfoxide **18'**.

Molecular Formula	:	$C_{11}H_{20}O_3S_2$
Yield	:	38 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	3400, 2930, 1720, 1033.
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 9.38 (bs, 1H), 2.62-2.97 (m, 2H), 2.22-2.51 (m, 4H), 1.90-2.18 (m, 2H), 1.35-1.75 (m, 11H).
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz)	:	δ = 177.0 (s), 58.5 (s), 57.9 (s), 57.0 (d), 51.7 (d), 34.6 (t), 33.6 (t), 29.1 (t), 26.0 (q), 25.9 (q), 25.5 (t), 25.4 (t), 24.6 (t), 24.3 (t), 22.6(q), 20.7 (t), 16.4 (q). (Mixture of two isomers)

xvii) Olefin ester 22 and Diester 23

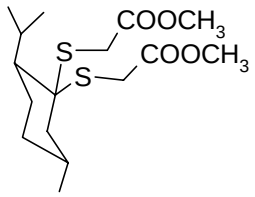
Procedure: - Methyl thioglycolate **3** (21.22 g, 0.2 mol) and menthone **21** (15.4 g, 0.1 mol) was taken in dry DCM (50 ml), and to this solution $BF_3.Et_2O$ (3.17 ml, 0.025 mol) was added at –5 ^{o}C. The resulting reaction mixture was stirred at –5 ^{o}C for 8 h and then at room temperature for 2 h. DCM was then removed under vacuum and water was added to the residue and extracted twice with ether. The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified to give product **22** in 35 % yield and product **23** in 48 % yield.

a) Olefin ester (22)



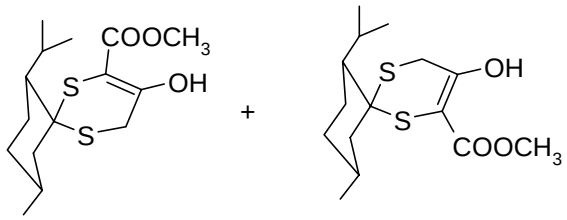
Molecular Formula	:	$C_{13}H_{22}O_2S$
Yield	:	35 %
B. P.	:	Viscous liquid.
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 3.67 (3, 3H), 3.30-3.50 (m, 1H), 3.29 (s, 2H), 2.30-2.43 (m, 1H), 1.58-2.26 (m, 5H), 0.81-1.05 (m, 10H).
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz)	:	δ = 169.3 (s), 146.7 (s), 120.9 (s), 51.1 (q), 38.7 (t), 32.8 (t), 30.7 (d), 30.2 (t), 29.1 (d), 24.0 (t), 20.7 (q), 20.3 (q), 19.7 (q).

b) Diester 23



Molecular Formula	:	$C_{16}H_{28}O_4S_2$
Yield	:	48 %
B. P.	:	Viscous liquid.
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 3.72 (s, 6H), 3.25-3.52 (m, 4H), 2.33-2.47 (m, 1H), 1.30-2.07 (m, 7H), 0.77-1.21 (m, 8H).
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz)	:	δ = 170.0 (s), 169.8 (s), 67.2 (s), 51.8 (q), 51.5 (q), 45.6 (t), 34.3 (t), 31.2 (t), 30.5 (t), 28.1 (d), 26.1 (d), 23.9 (d), 22.2 (t), 20.9 (q), 18.2 (q).

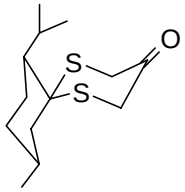
xviii) β-Ketoester (24a + 24b)



Procedure: The compound **24** was prepared from diester **23** by using the procedure as described for the preparation of methyl 5-hydroxy-2,2-dimethyl-6H-(1,3) dithiine-4-carboxylate **(5)**.

Molecular Formula	:	$C_{15}H_{24}O_3S_2$
Yield	:	78 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	3440, 3019, 2957, 1712, 1642, 1585, 1443, 1246, 1035, 756.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 12.55 (s, 1H), 12.50 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.66 (d, *J* = 14.2 Hz, 1H), 3.51 (d, *J* = 13.7 Hz, 1H), 3.25 (d, *J* = 14.2 Hz, 1H), 3.18 (d, *J* = 13.7 Hz, 1H), 2.45-2.65 (m, 1H), 2.22-2.41 (m, 1H), 1.90-2.06 (m, 1H), 1.14-1.80 (m, 6H), 0.79-1.12 (m, 10H). (Mixture of two regioisomers)
^{13}C NMR ($CDCl_3$, 50MHz)	:	δ = 170.6 (s), 170.4 (s), 127.0 (s), 67.6 (s), 52.0 (q), 46.1 (t), 34.6 (t), 31.6 (t), 31.0 (t), 28.4 (d), 26.5 (d), 24.2 (d), 22.5 (t), 21.2 (q), 18.4 (q)

xix) Ketone 25

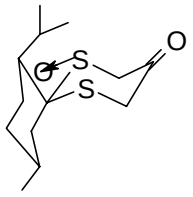


Procedure: A solution of β-ketoester **24** (774 mg, 3 mmol), NaCl (351 mg, 6 mmol) and water (0.212 ml, 12 mmol) in DMSO (10 ml) was heated to 120 ^oC for 8 h. The reaction

mixture was then cooled, poured into water (25 ml) and extracted with ether (2x10ml). The combined extracts were washed with water and brine solution. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum and the product was purified by column chromatography.

Molecular Formula	:	$C_{13}H_{22}OS_2$
Yield	:	68 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	3019, 2928, 1712, 1456, 1386, 757.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 3.25-3.63 (m, 4H), 2.33-2.56 9m, 2H), 1.72-1.89 (m, 2H), 1.36-1.72 (m, 4H), 0.86-1.03 (m, 10H).
^{13}C NMR ($CDCl_3 + CCl_4$, 50MHz)	:	δ = 201.8 (s), 60.9 (s), 54.0 (d), 51.2 (t), 36.9 (t), 36.1(t), 34.8 (t), 29.6 (d), 27.5 (d), 24.8 (q), 23.7 (t), 21.9 (q), 18.4 (q).

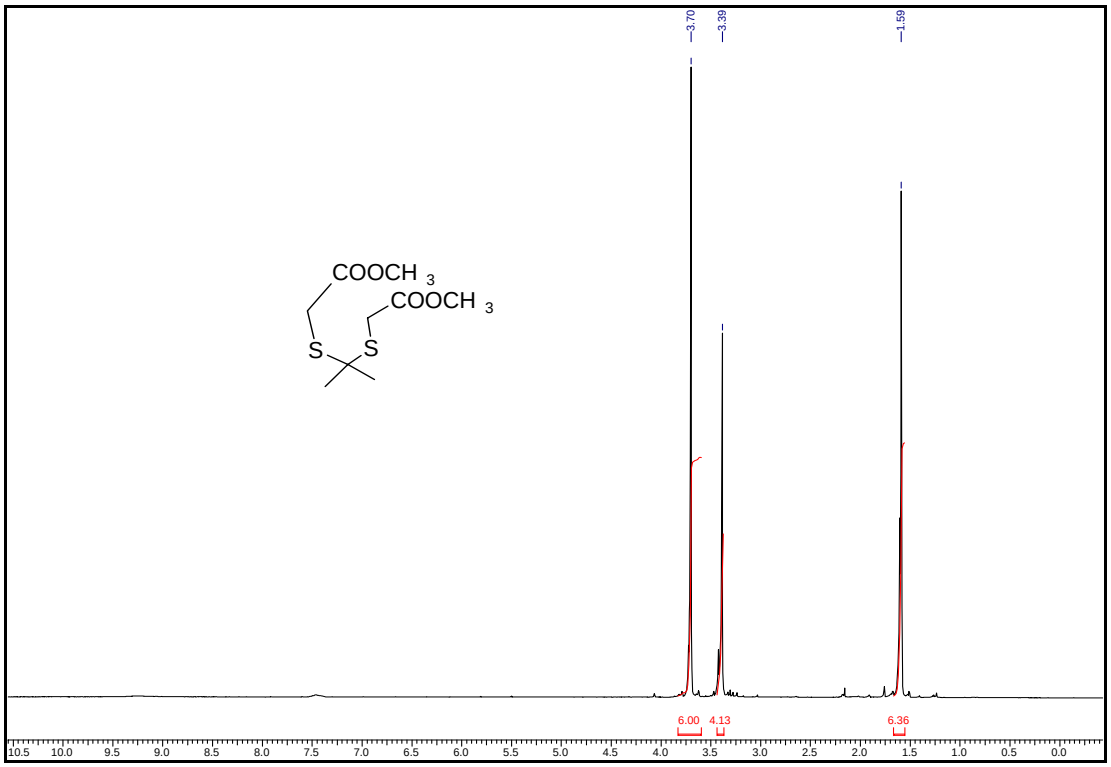
xx) Sulfoxide 26



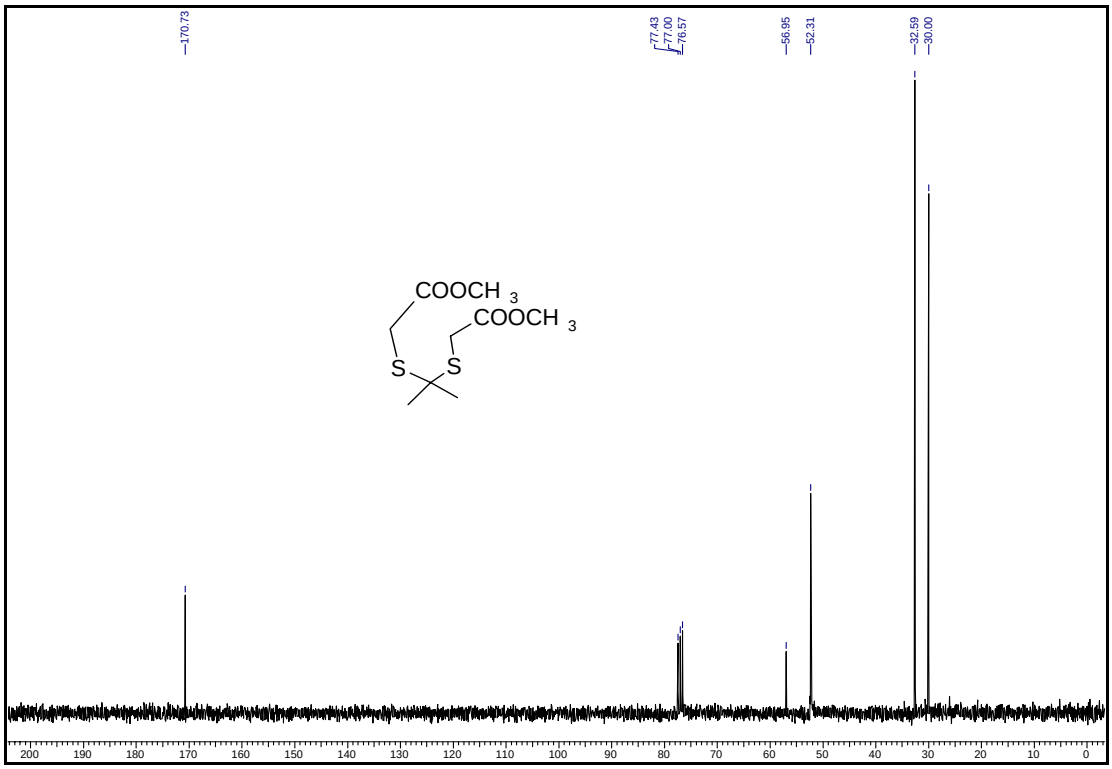
Procedure: A solution of $NaIO_4$ (415 mg, 1.94 mmol) in water (10 ml) was added dropwise to a solution of ketone **25** (500 mg, 1.94 mmol) in methanol (40 ml) at 0 ^oC. The resulting white slurry was stirred at 0 ^oC for 6 h. The precipitated sodium iodate was removed by filtration and methanol was removed under vacuum. The residue was extracted twice with chloroform and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography (Pet. Ether : EtOAc = 25 : 75) to give 382 mg of pure sulfoxide **26**.

Molecular Formula	:	$C_{13}H_{22}O_2S_2$
Yield	:	72 %
^1H NMR	:	δ = 3.84 (dd, *J* = 11.7 & 2.0 Hz, 1H), 3.64 (d, *J* = 11.7

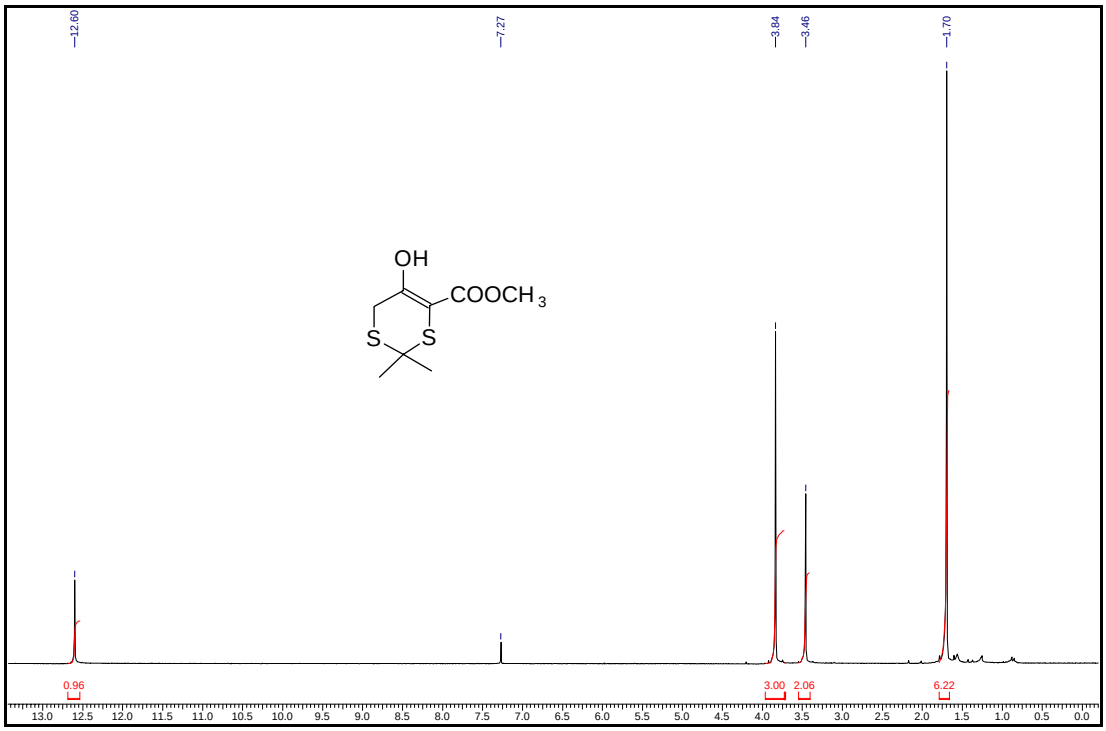
($CDCl_3$ + CCl_4, 200MHz)		Hz, 1H), 3.32 (d, *J* = 14.2 Hz, 1H), 2.86-2.93 (m, 1H), 2.28-2.42 (m, 1H), 1.53-2.12 (m, 7H), 0.91-1.10 (m, 7H), 0.87 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR	:	δ = 189.7 (s), 70.1 (s), 57.3 (t), 44.6 (d), 34.4 (t), 34.1 (t),
($CDCl_3$ + CCl_4, 50MHz)		29.5 (t), 27.4 (d), 25.4 (d), 24.2 (q), 22.0 (t), 21.8 (q), 19.6 (q).



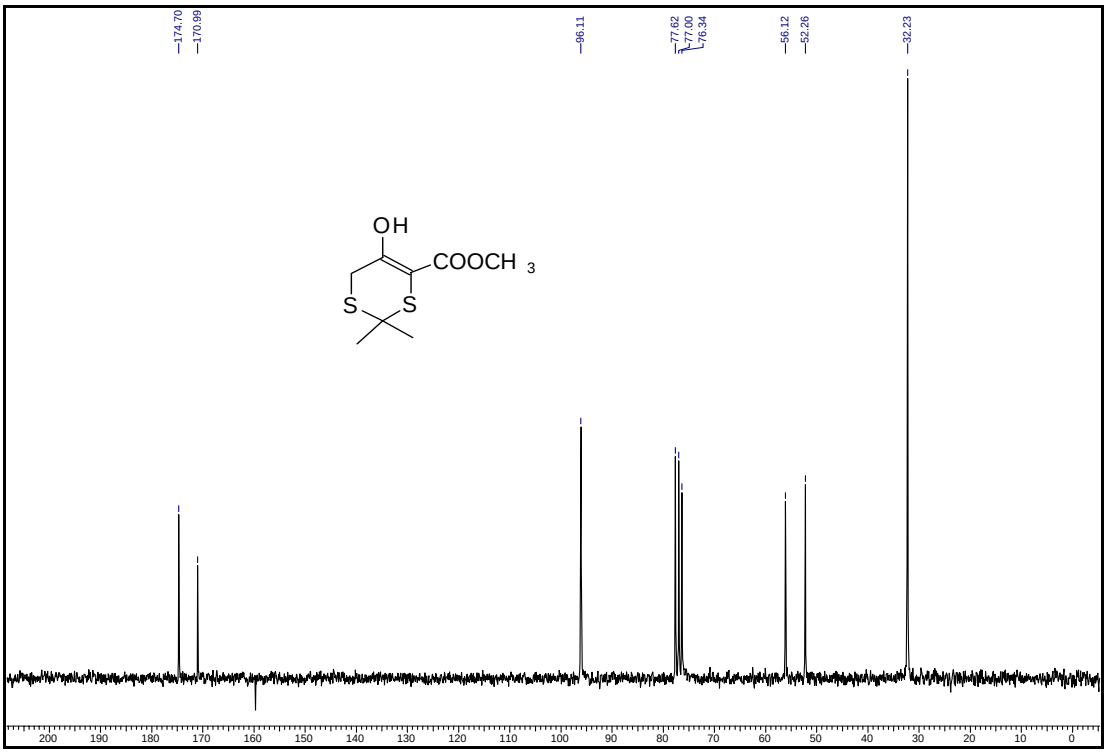
^{1}H NMR spectrum of diester 4 ($CDCl_3$ + CCl_4, 200 MHz)



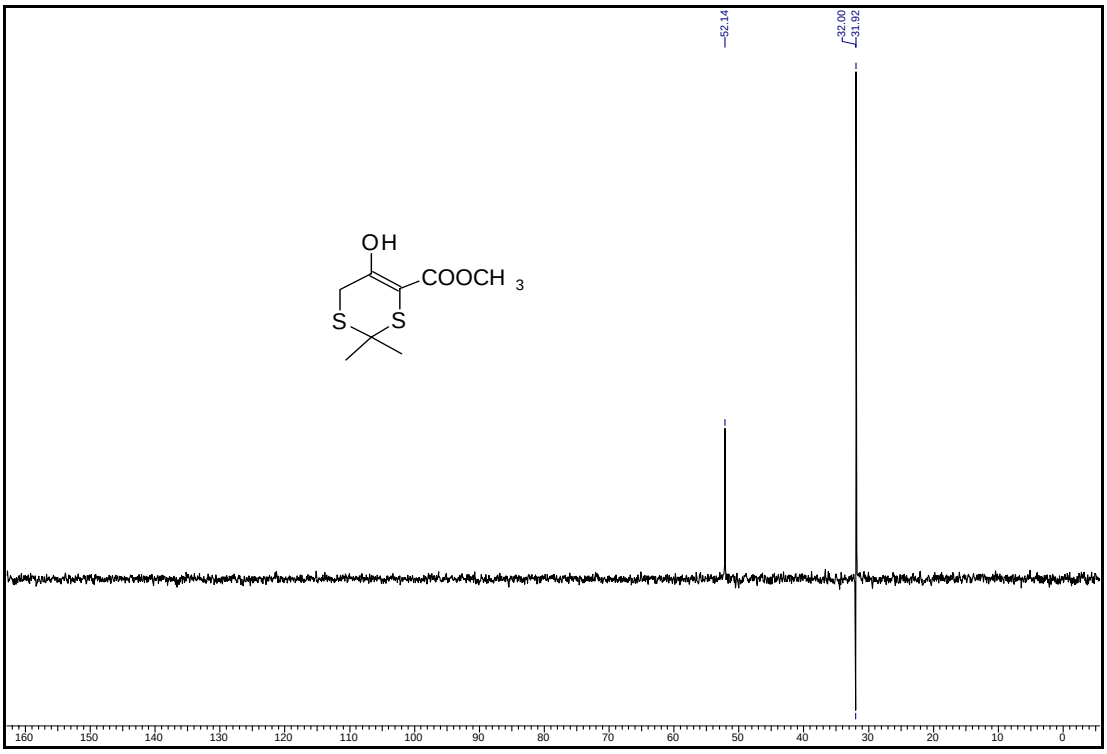
^{13}C NMR spectrum of diester 4 ($CDCl_3$ + CCl_4, 50 MHz)



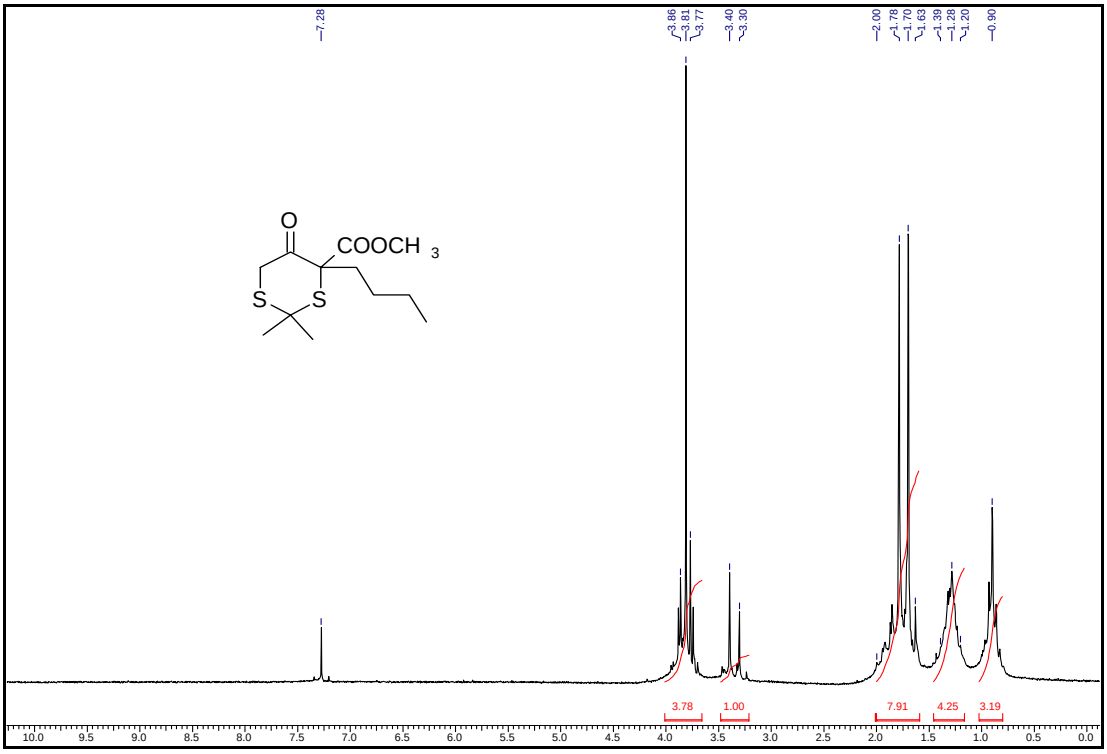
^{1}H NMR spectrum of methyl 5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylate (5) ($CDCl_3$, 200 MHz)



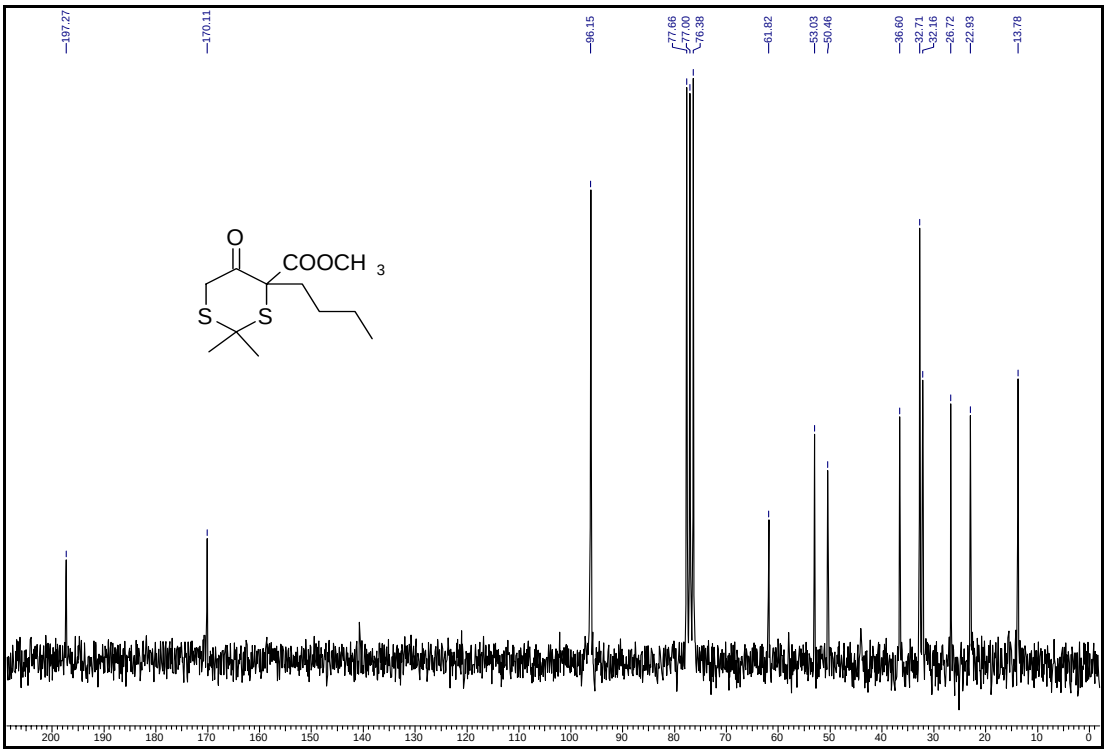
^{13}C NMR spectrum of methyl 5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylate (5) ($CDCl_3$, 50 MHz)



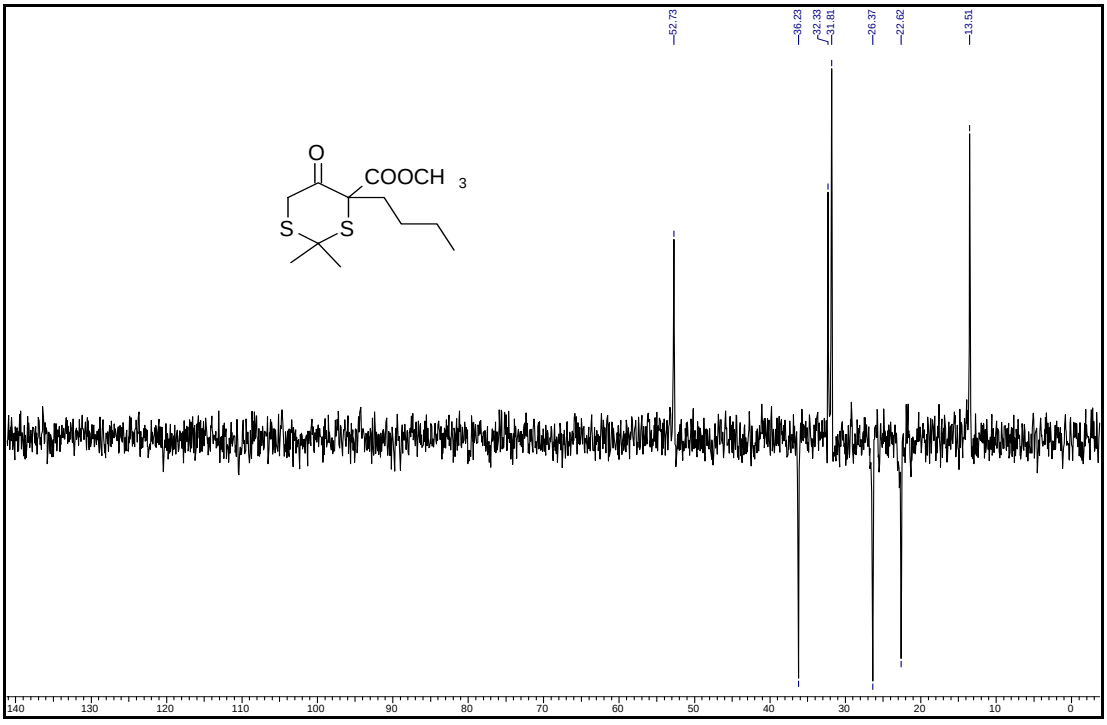
DEPT spectrum of methyl 5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylate (5) ($CDCl_3$, 50 MHz)



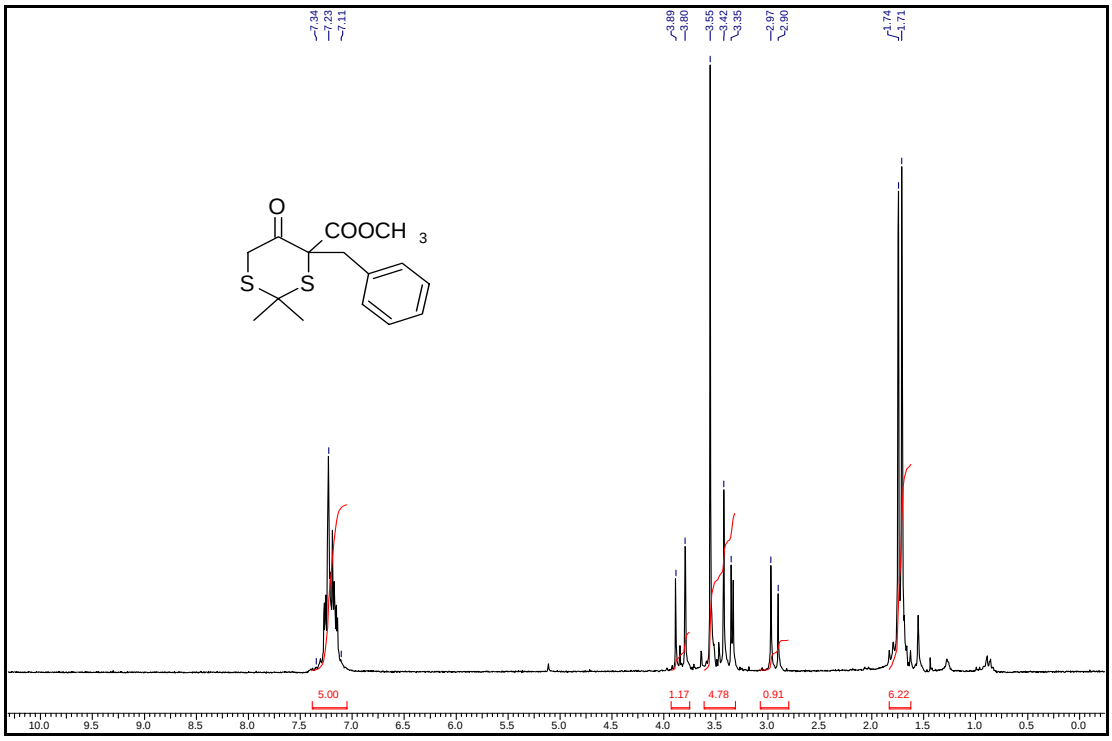
^{1}H NMR spectrum of methyl 4-butyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6a) ($CDCl_3$ + CCl_4, 200 MHz)



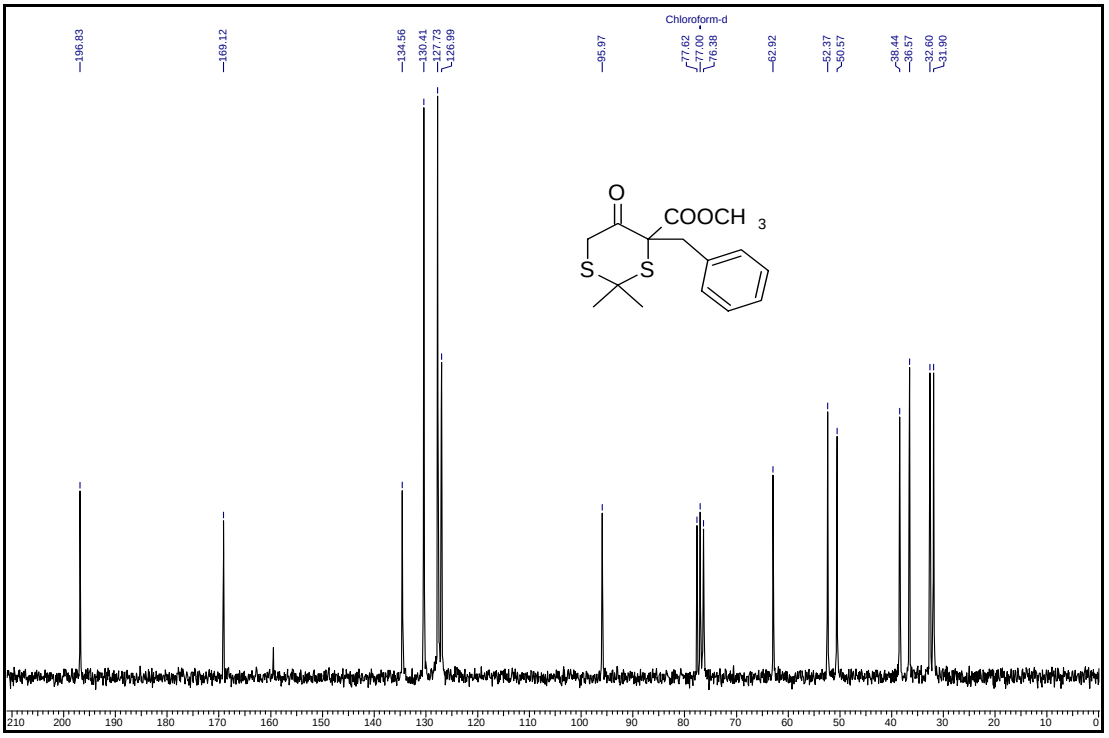
^{13}C NMR spectrum of methyl 4-butyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6a) ($CDCl_3$ + CCl_4, 50 MHz)



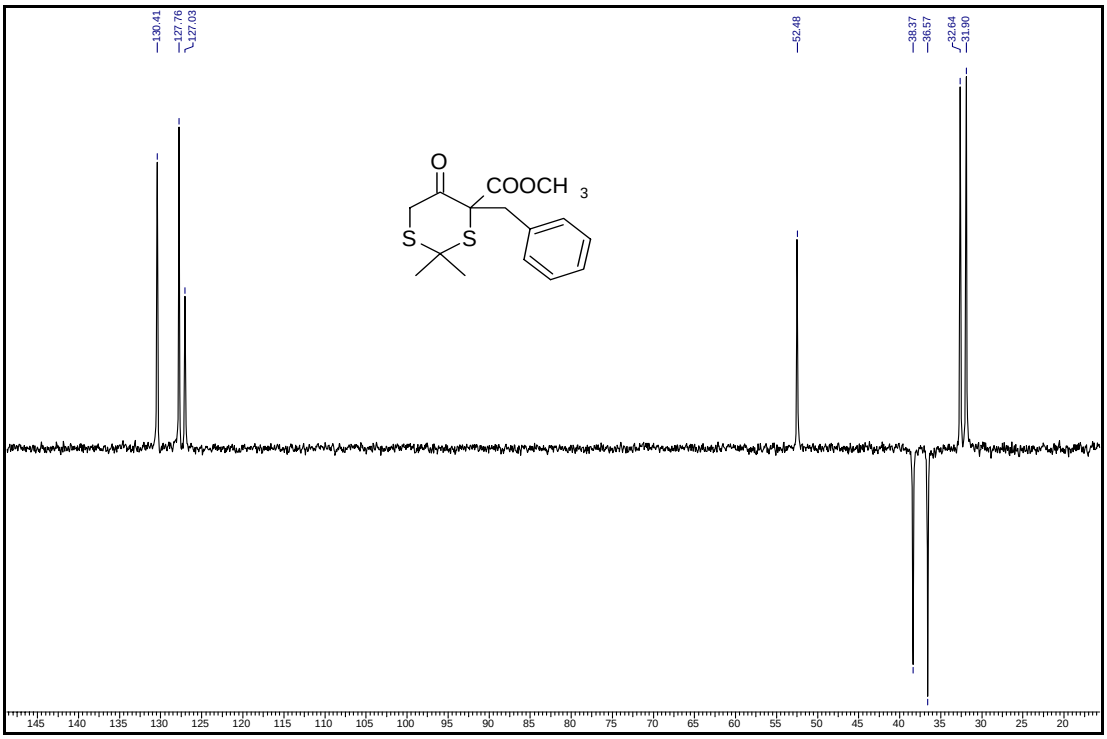
DEPT spectrum of methyl 4-butyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6a) ($CDCl_3$ + CCl_4, 50 MHz)



^{1}H NMR spectrum of methyl 4-benzyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6b) ($CDCl_3$ + CCl_4, 200 MHz)

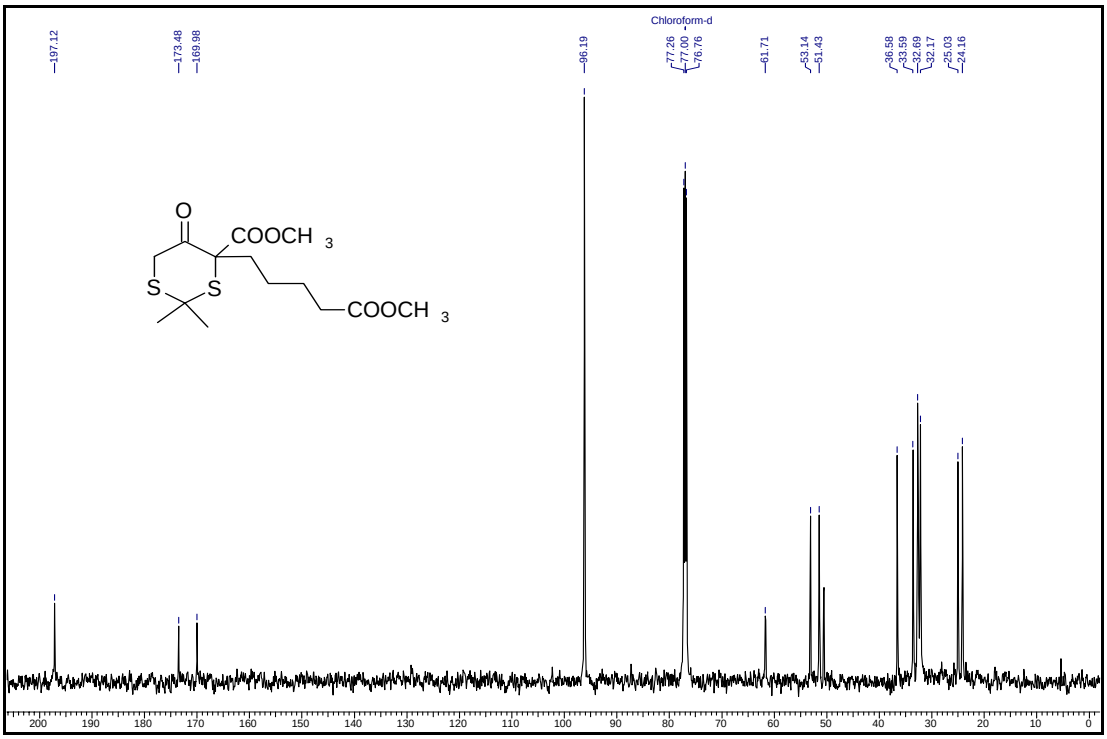


^{13}C NMR spectrum of methyl 4-benzyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4 - carboxylate (6b) ($CDCl_3$ + CCl_4, 50 MHz)

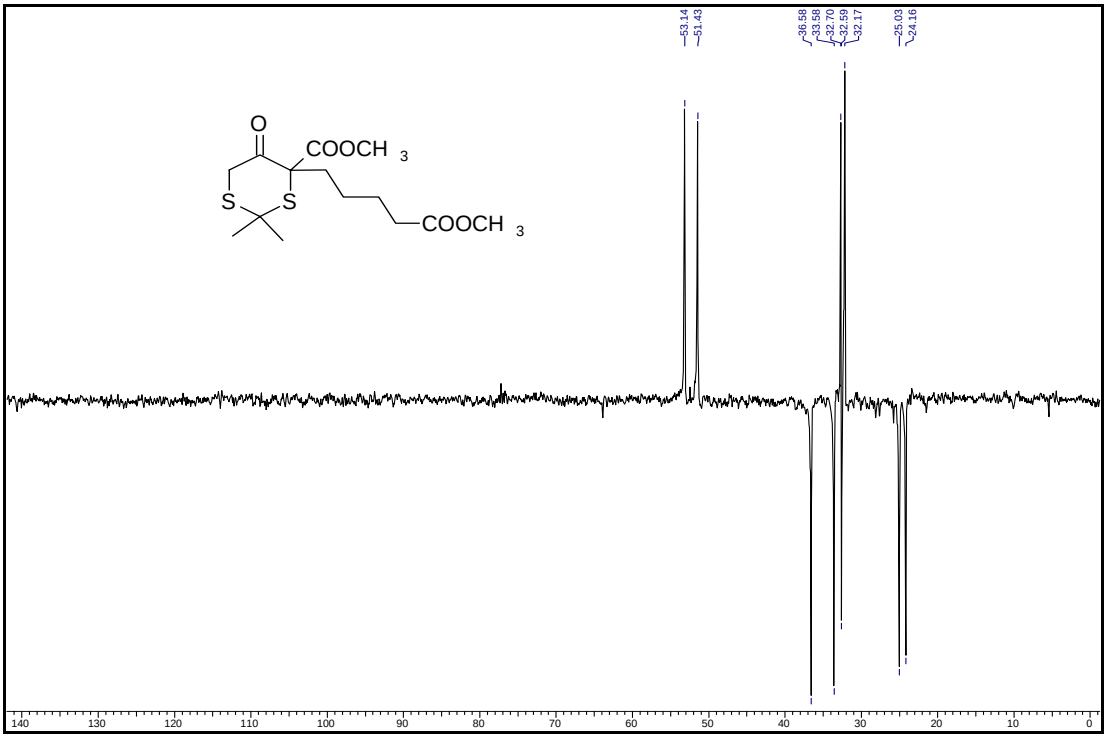


DEPT spectrum of methyl 4-benzyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6b) ($CDCl_3$ + CCl_4, 50 MHz)

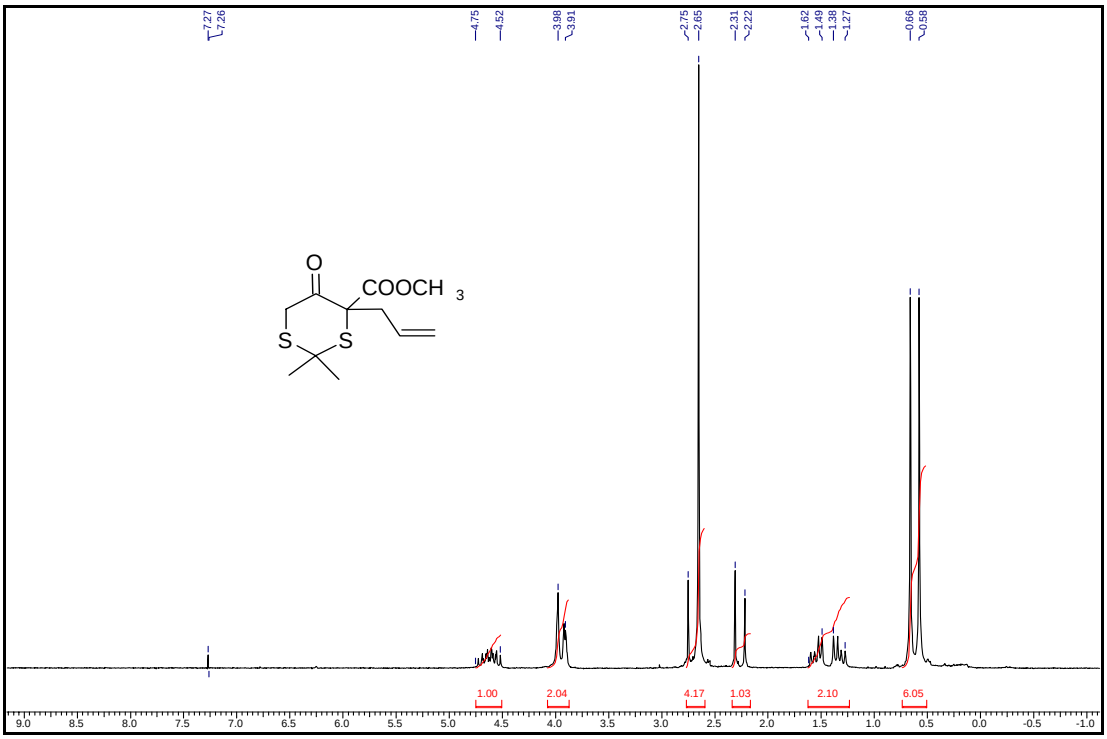
^{1}H NMR spectrum of methyl 4 -(4-methoxycarbonyl-butyl) -2, 2–dimethyl – 5 –oxo- (1,3) dithiane- 4 carboxylate (6c) ($CDCl_3$ + CCl_4, 200 MHz)



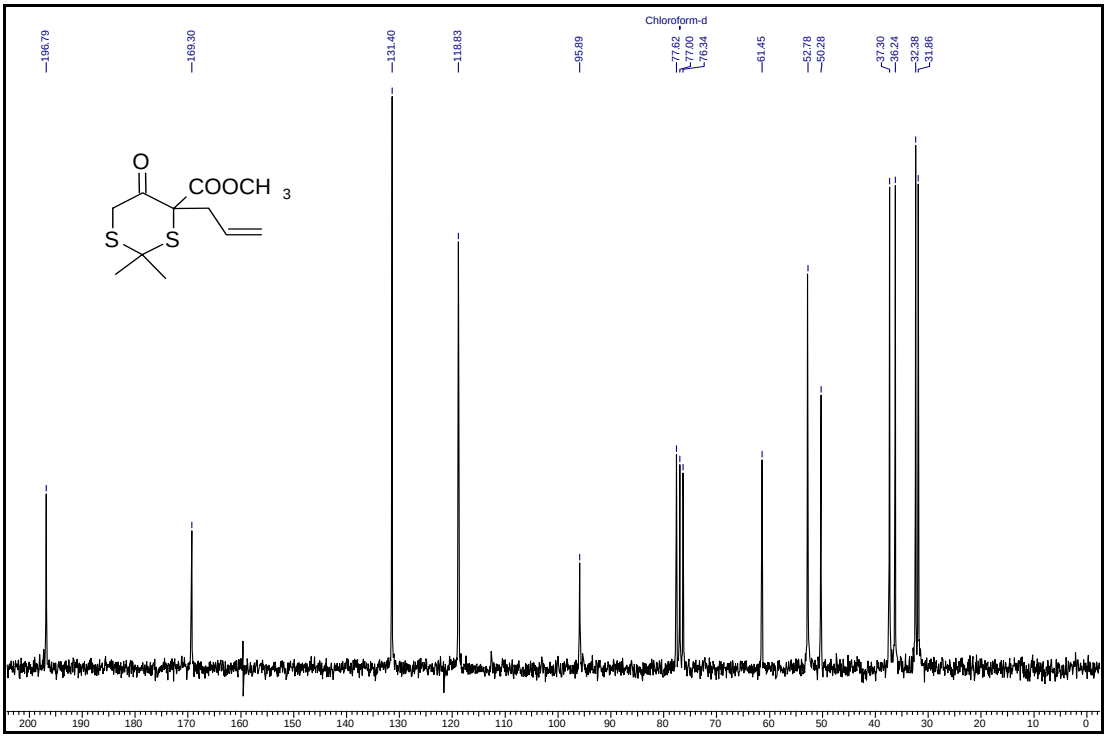
^{13}C NMR spectrum of methyl 4 -(4-methoxycarbonyl-butyl) -2, 2–dimethyl – 5 –oxo- (1,3) dithiane- 4 carboxylate (6c) ($CDCl_3$ + CCl_4, 50 MHz)



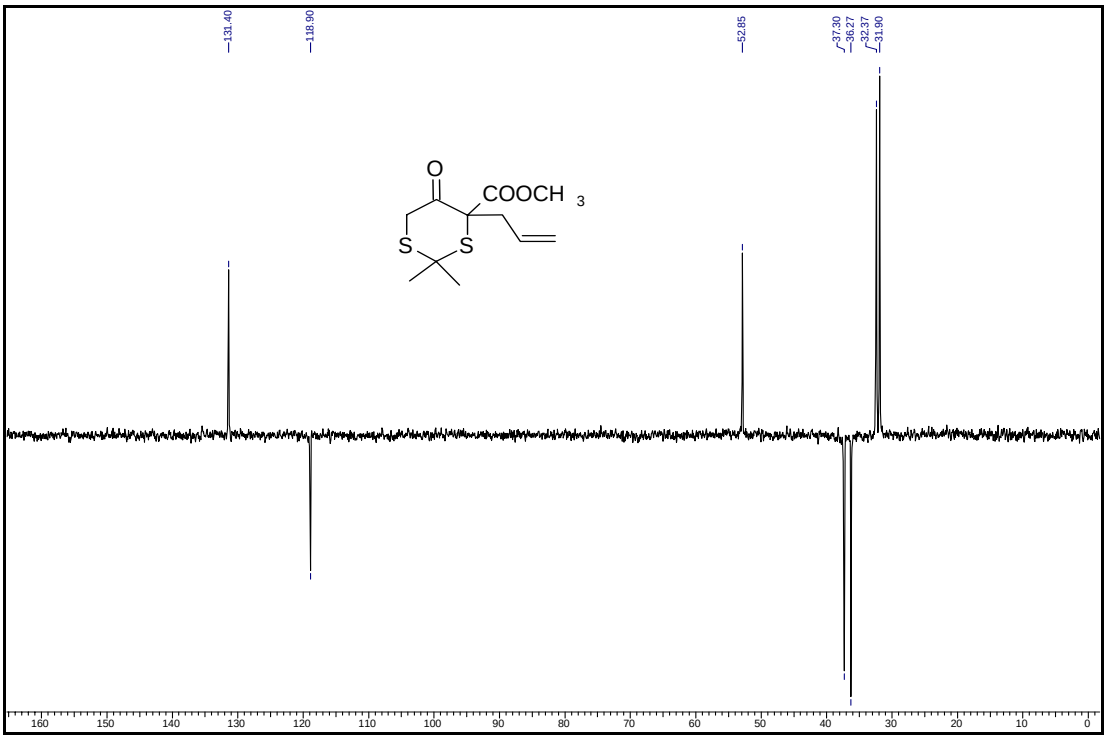
DEPT spectrum of methyl 4 -(4-methoxycarbonyl-butyl) -2, 2–dimethyl – 5 –oxo- (1,3) dithiane- 4 carboxylate (6c) ($CDCl_3$ + CCl_4, 50 MHz)



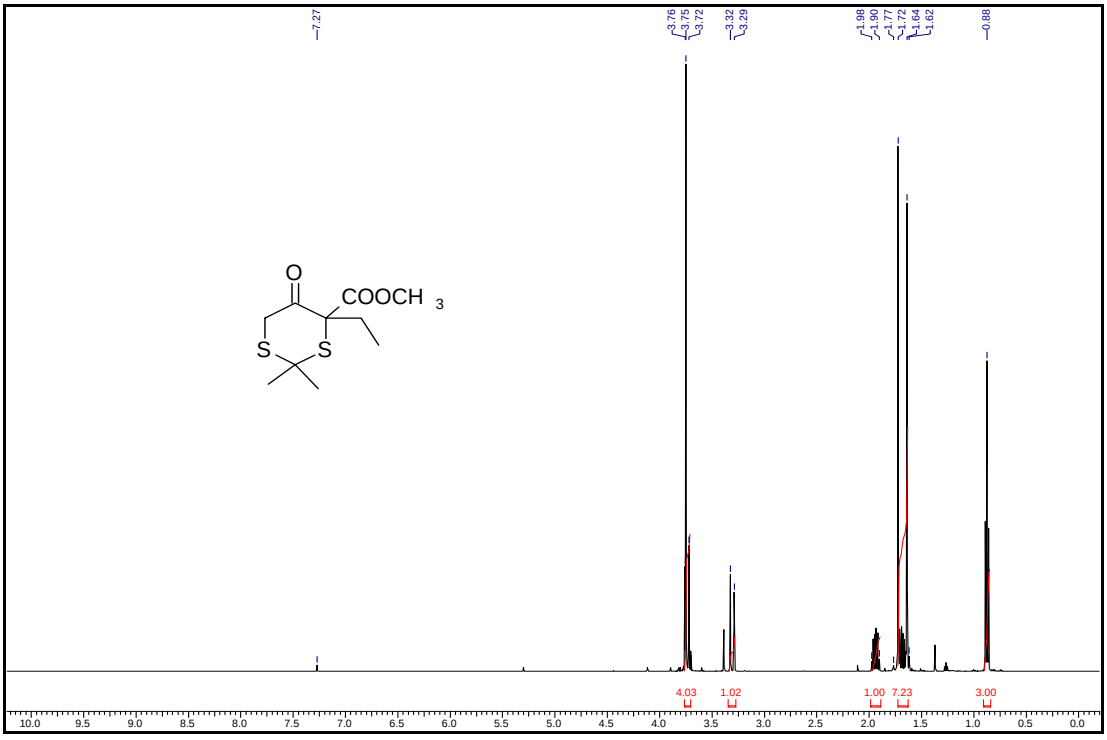
^{1}H NMR spectrum of methyl 4-allyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6d) ($CDCl_3$ + CCl_4, 200 MHz)



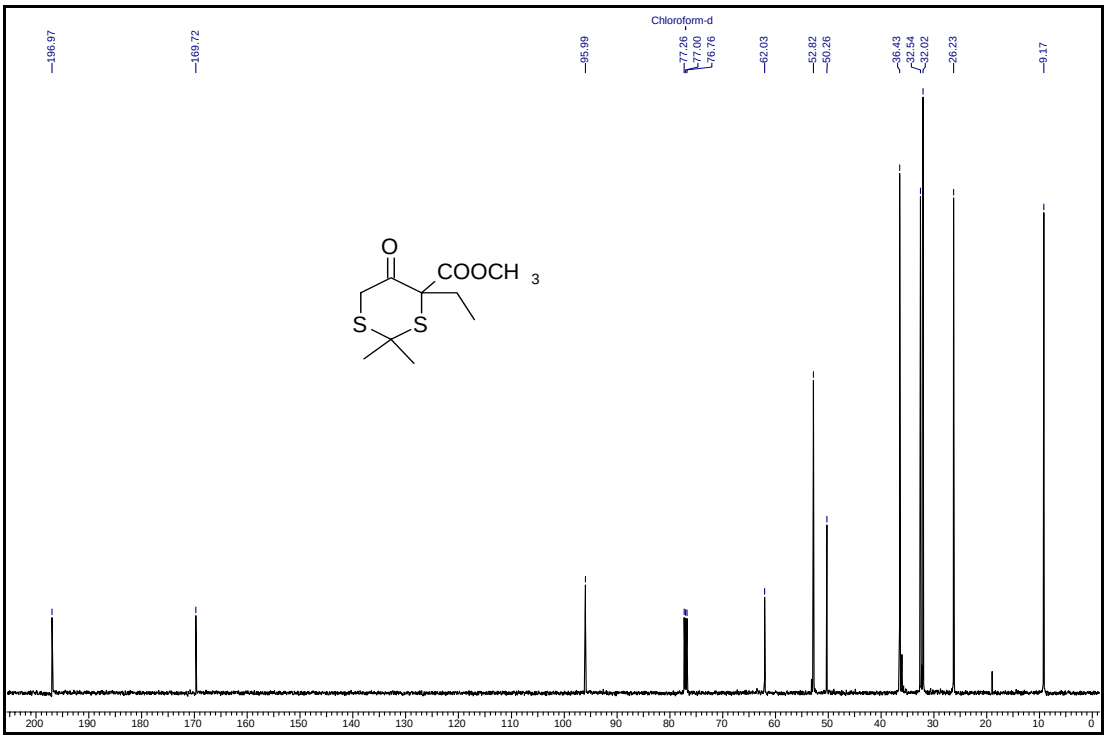
^{13}C NMR spectrum of methyl 4-allyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6d) ($CDCl_3$ + CCl_4, 50 MHz)



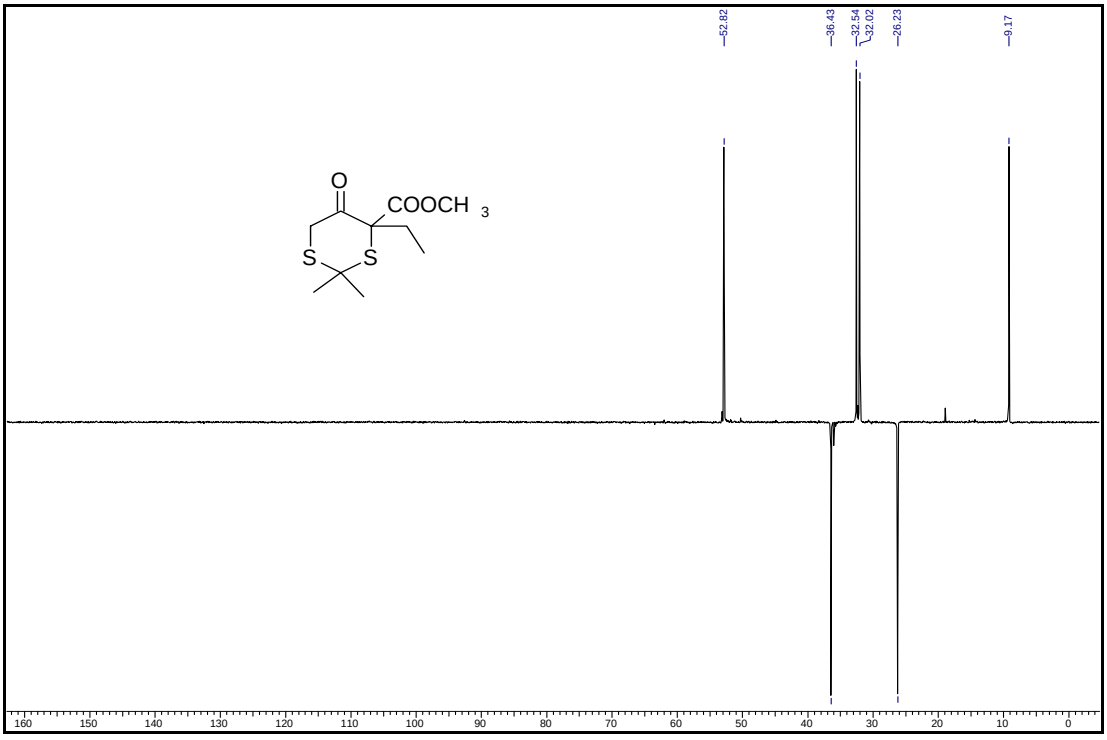
DEPT spectrum of methyl 4-allyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6d) ($CDCl_3$ + CCl_4, 50 MHz)



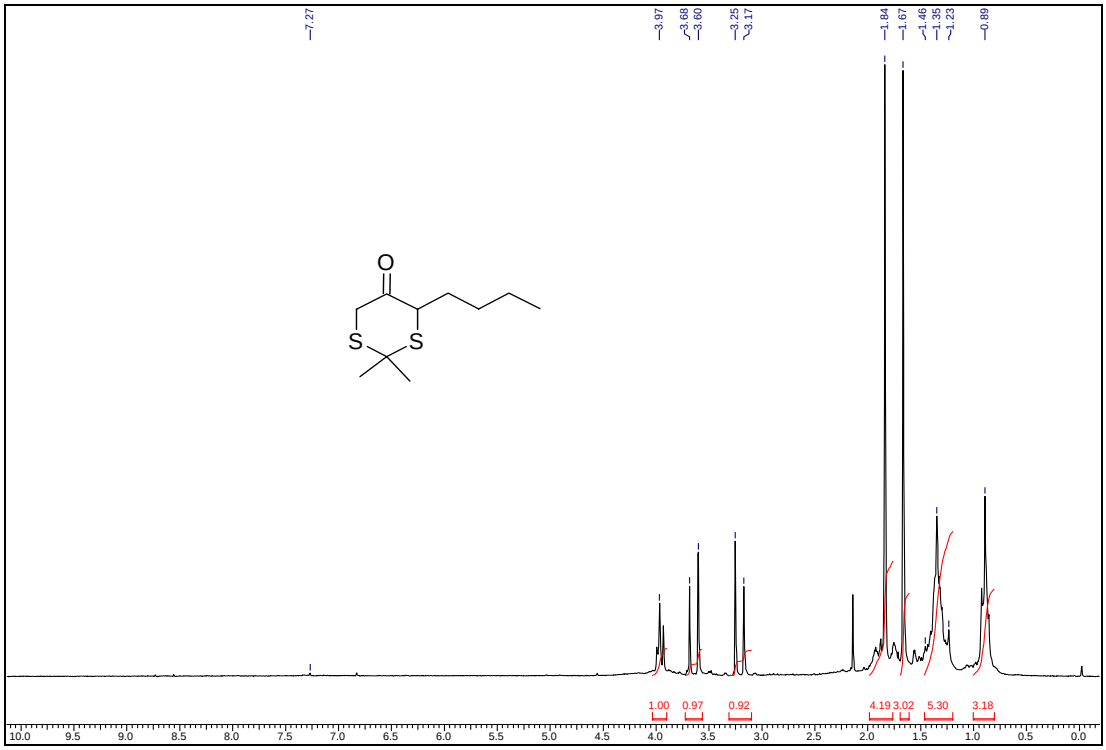
^{1}H NMR spectrum of methyl 4-ethyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6e) ($CDCl_3$ + CCl_4, 200 MHz)



^{13}C NMR spectrum of methyl 4-ethyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6e) ($CDCl_3$ + CCl_4, 500 MHz)

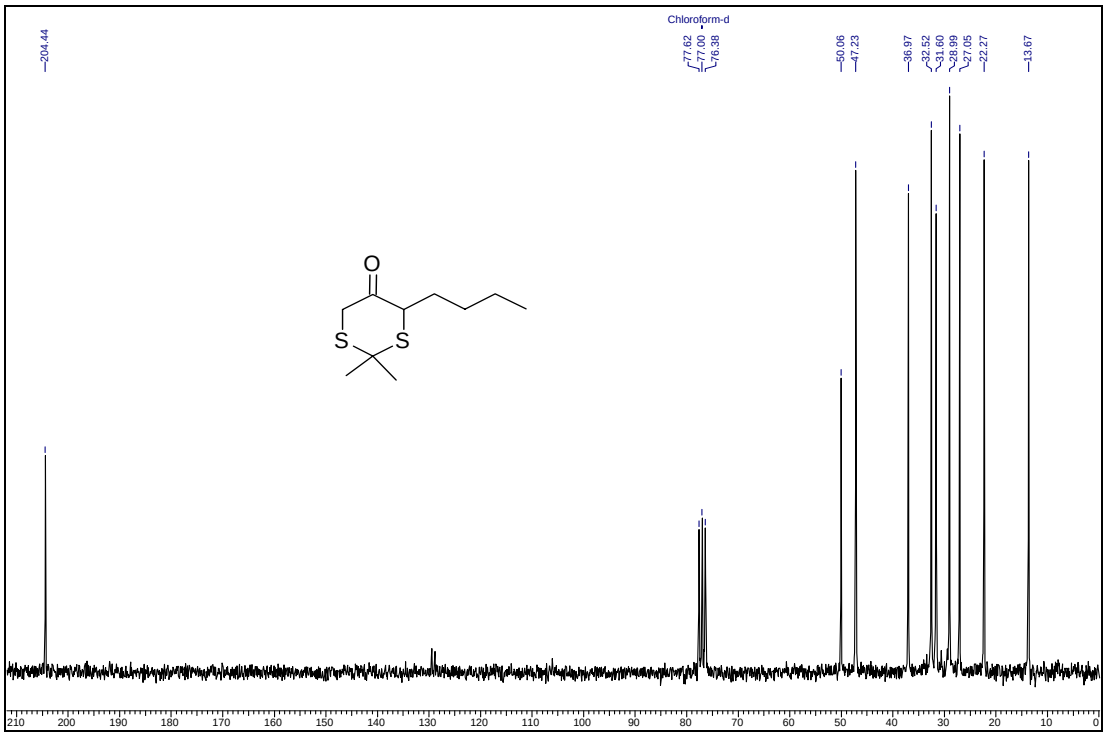


DEPT spectrum of methyl 4-ethyl-2,2-dimethyl-5-oxo-(1,3) dithiane-4-carboxylate (6e) ($CDCl_3$ + CCl_4, 500 MHz)



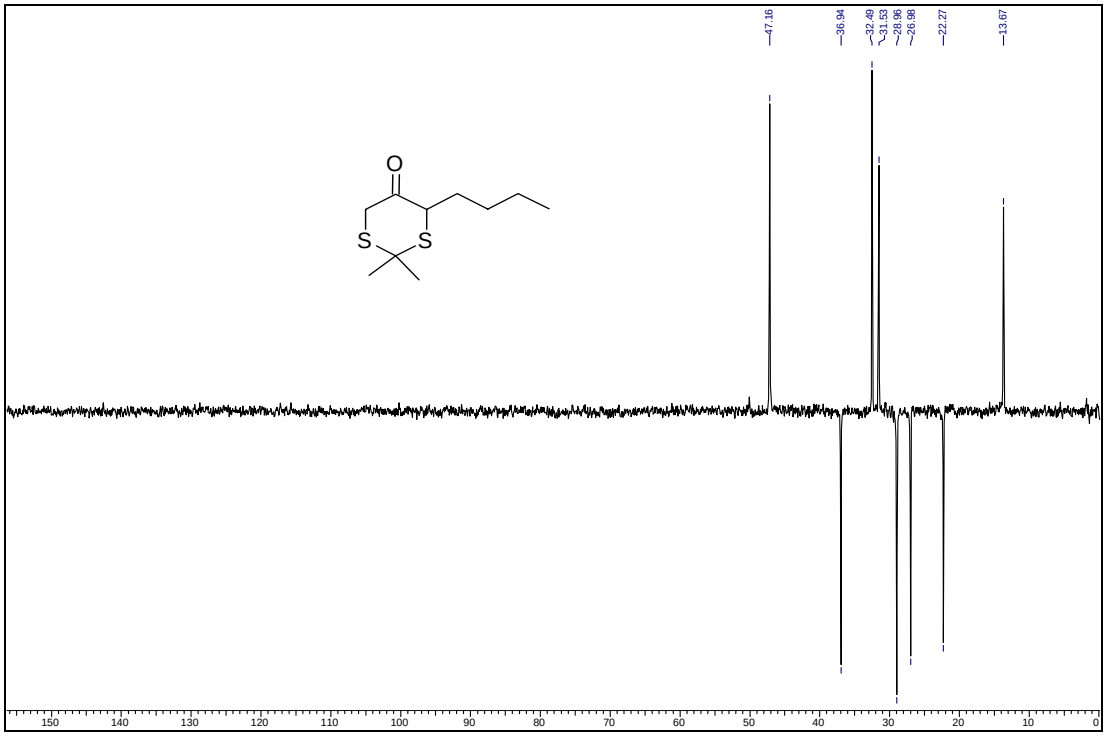
^{1}H NMR spectrum of 4-butyl-2,2-dimethyl- (1,3) dithian-5-one (8a)

($CDCl_3$ + CCl_4, 200 MHz)



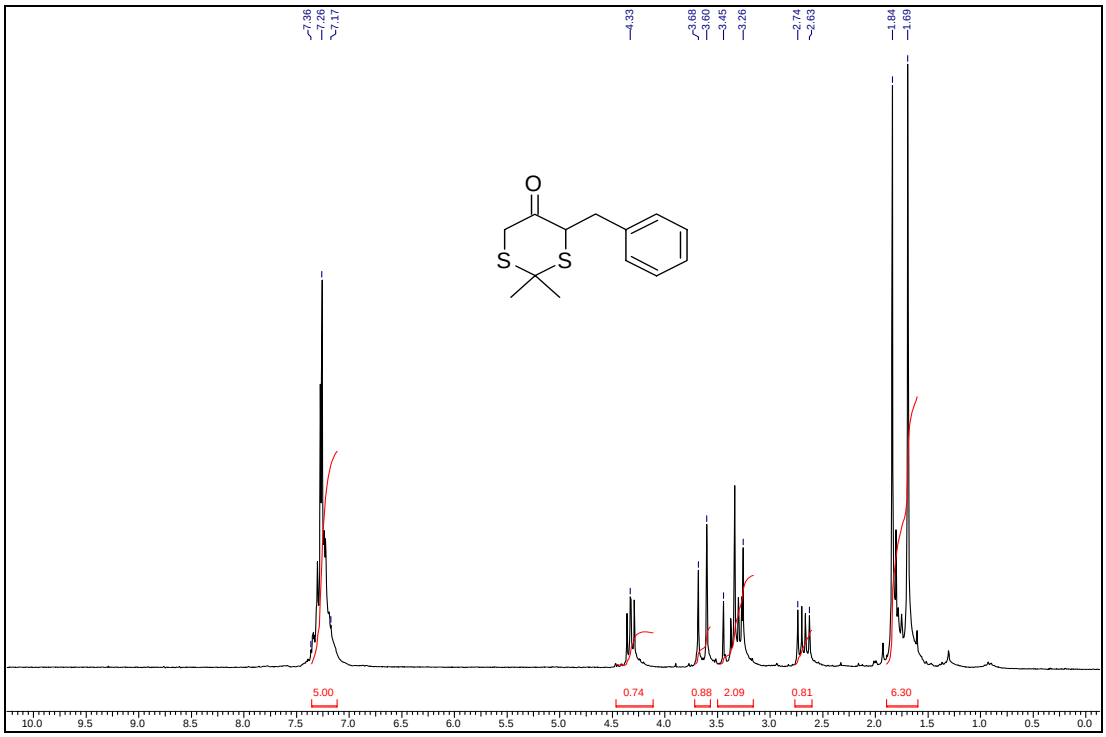
^{13}C NMR spectrum of 4-butyl-2,2-dimethyl- (1,3) dithian-5-one (8a)

($CDCl_3$ + CCl_4, 50 MHz)



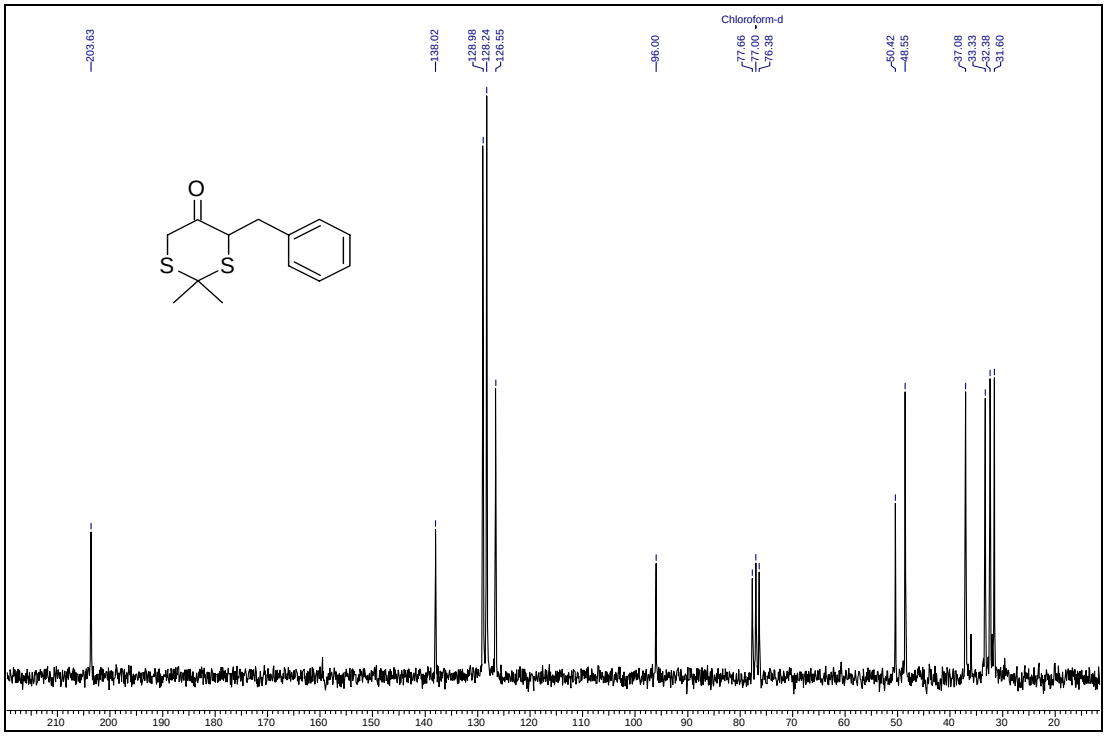
DEPT spectrum of 4-butyl-2,2-dimethyl- (1,3) dithian-5-one (8a)

($CDCl_3$ + CCl_4, 50 MHz)



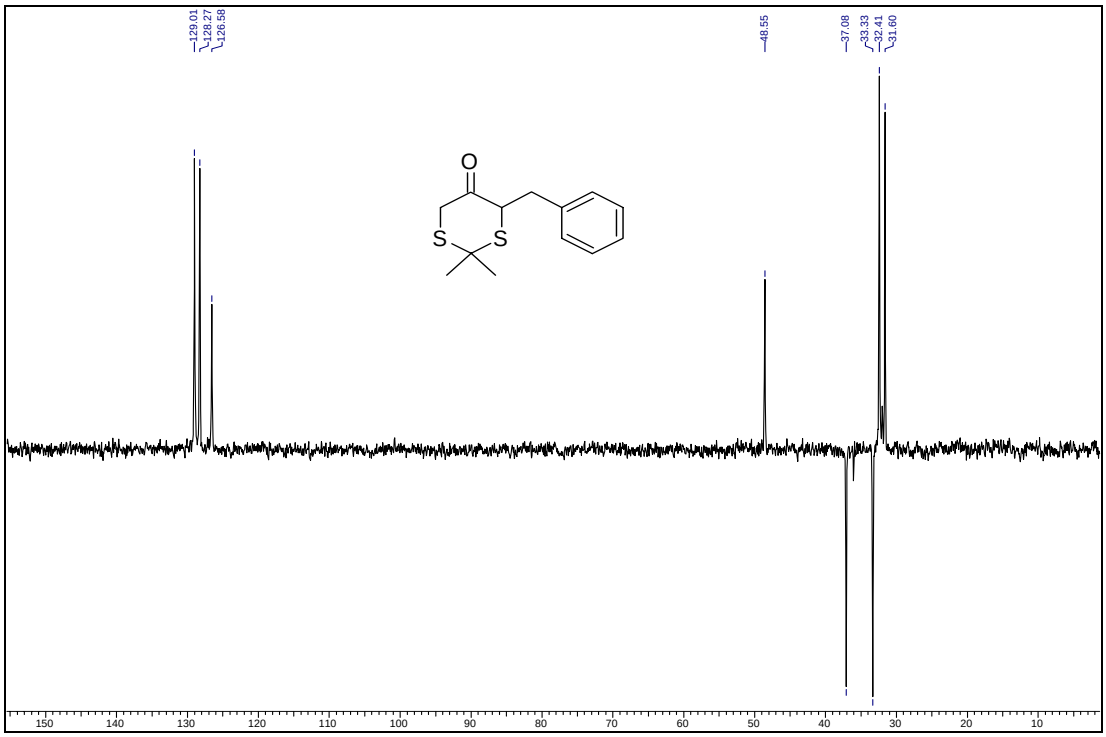
^{1}H NMR spectrum of 4-benzyl-2,2-dimethyl- (1,3) dithian-5-one (8b)

($CDCl_3$ + CCl_4, 200 MHz)



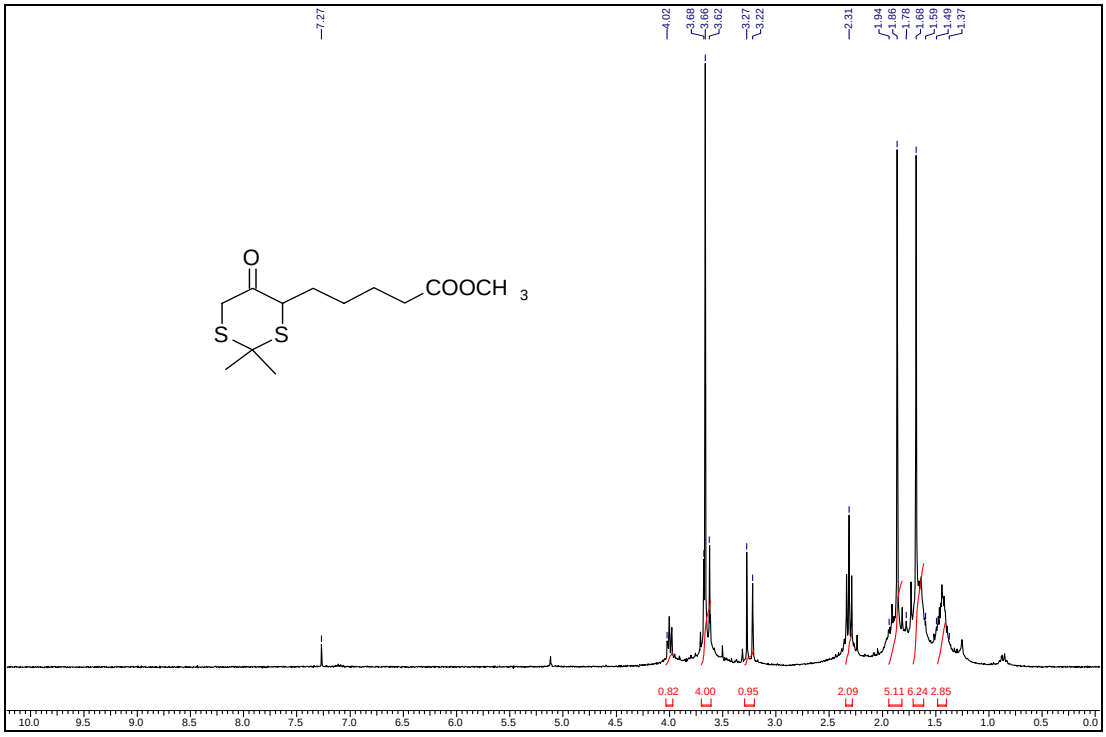
^{13}C NMR spectrum of 4-benzyl-2,2-dimethyl- (1,3) dithian-5-one (8b)

($CDCl_3$ + CCl_4, 50 MHz)

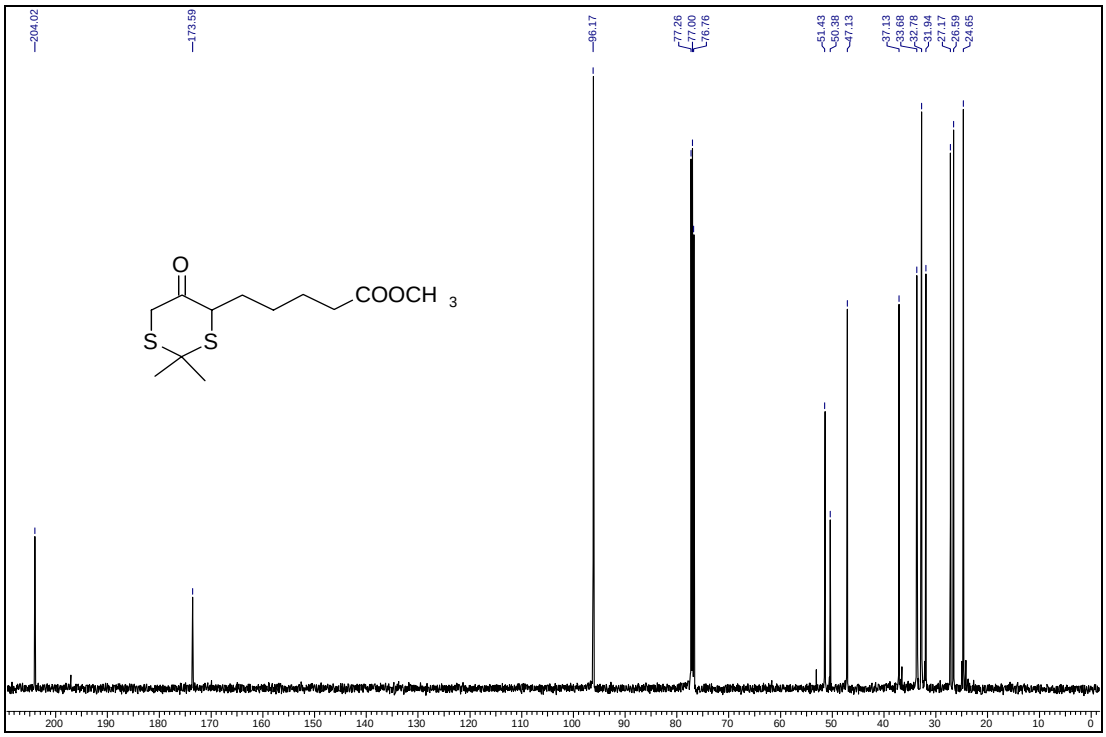


DEPT spectrum of 4-benzyl-2,2-dimethyl- (1,3) dithian-5-one (8b)

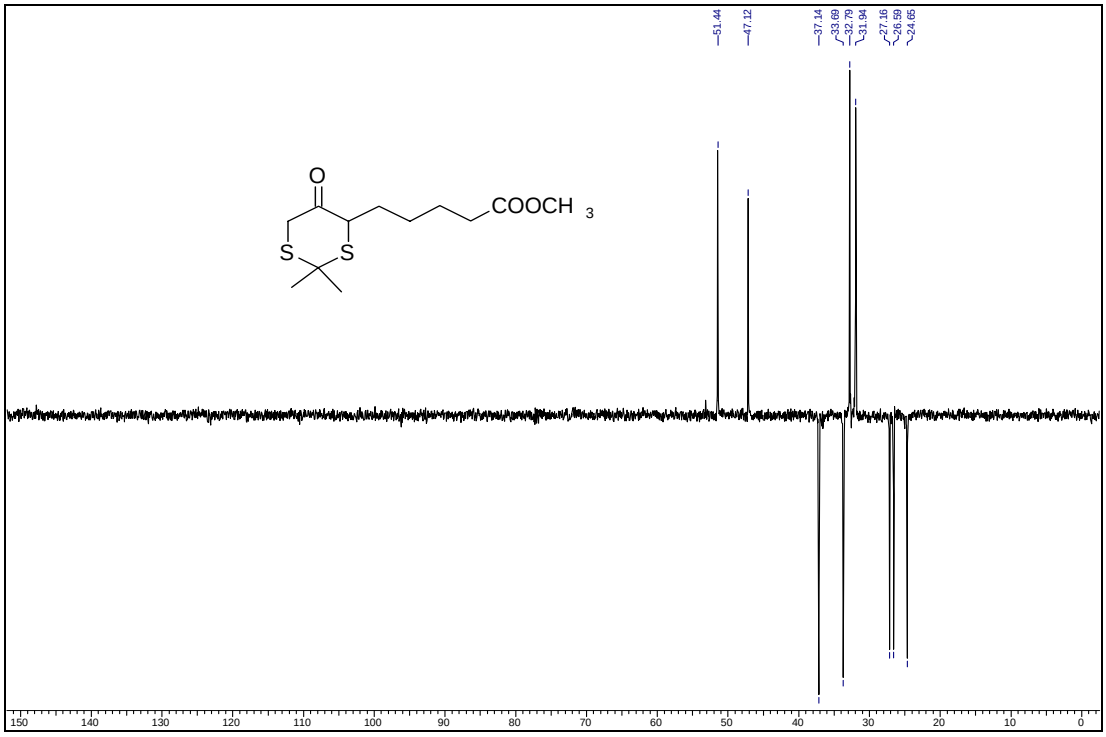
($CDCl_3$ + CCl_4, 50 MHz)



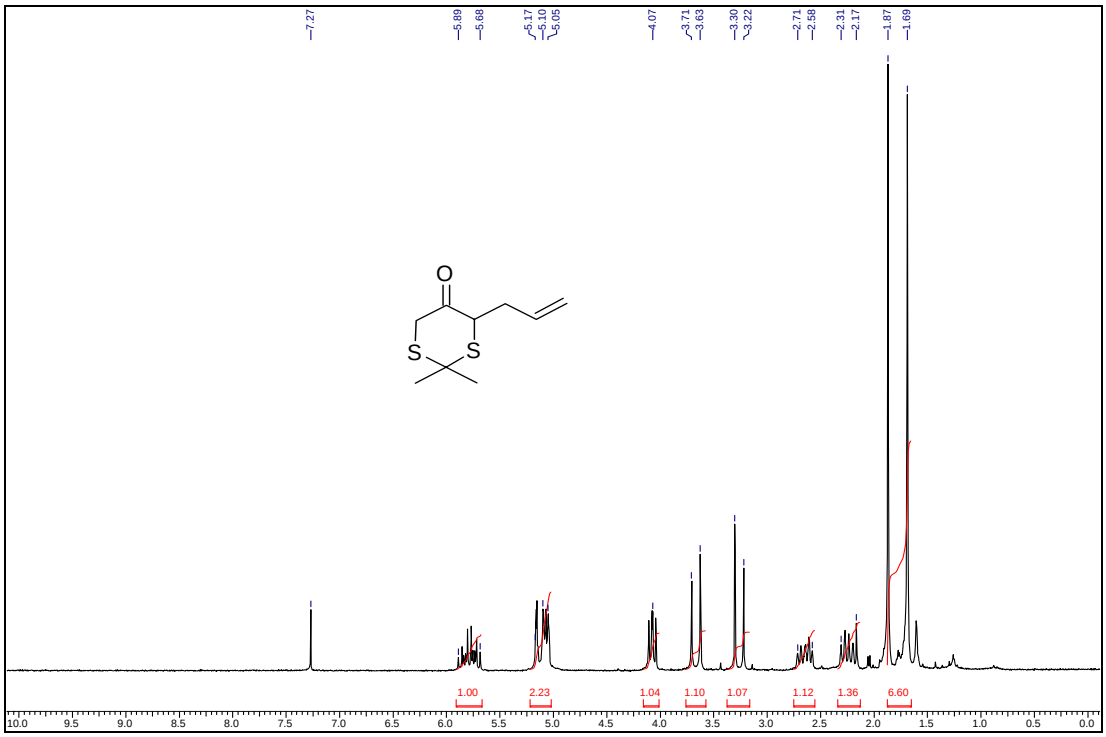
^{1}H NMR spectrum of methyl 5-[2,2-dimethyl- 5-oxo-(1,3) dithian-4-yl]-pentanoate (8c) ($CDCl_3$ + CCl_4, 200 MHz)



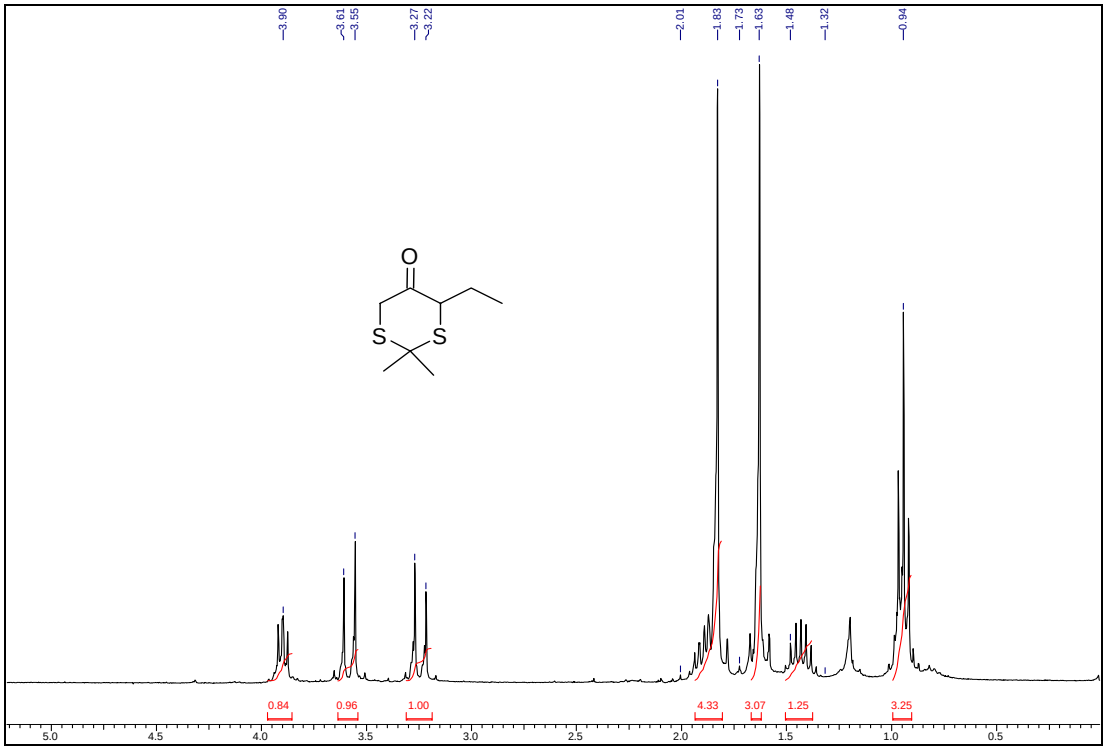
^{13}C NMR spectrum of methyl 5-[2,2-dimethyl- 5-oxo-(1,3) dithian-4-yl]-pentanoate (8c) ($CDCl_3$ + CCl_4, 50 MHz)



DEPT spectrum of methyl 5-[2,2-dimethyl- 5-oxo-(1,3) dithian-4-yl]-pentanoate (8c) ($CDCl_3$ + CCl_4, 50 MHz)

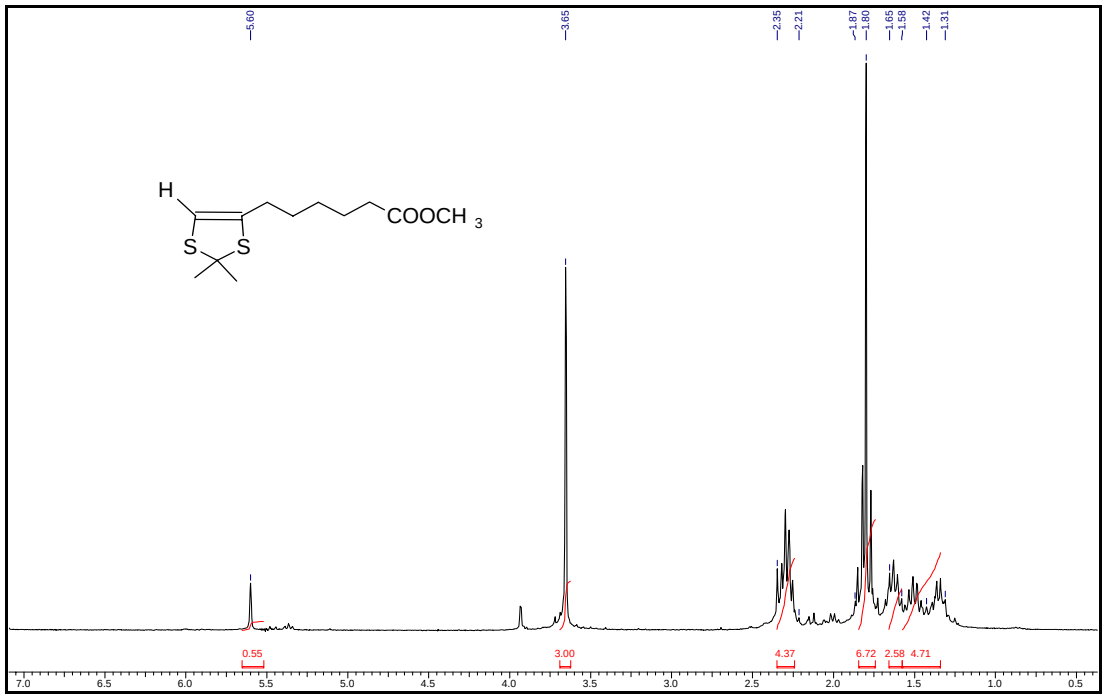


^{1}H NMR spectrum of 4-allyl-2,2-dimethyl- (1,3) dithian-5-one (8d) ($CDCl_3$ + CCl_4, 200 MHz)

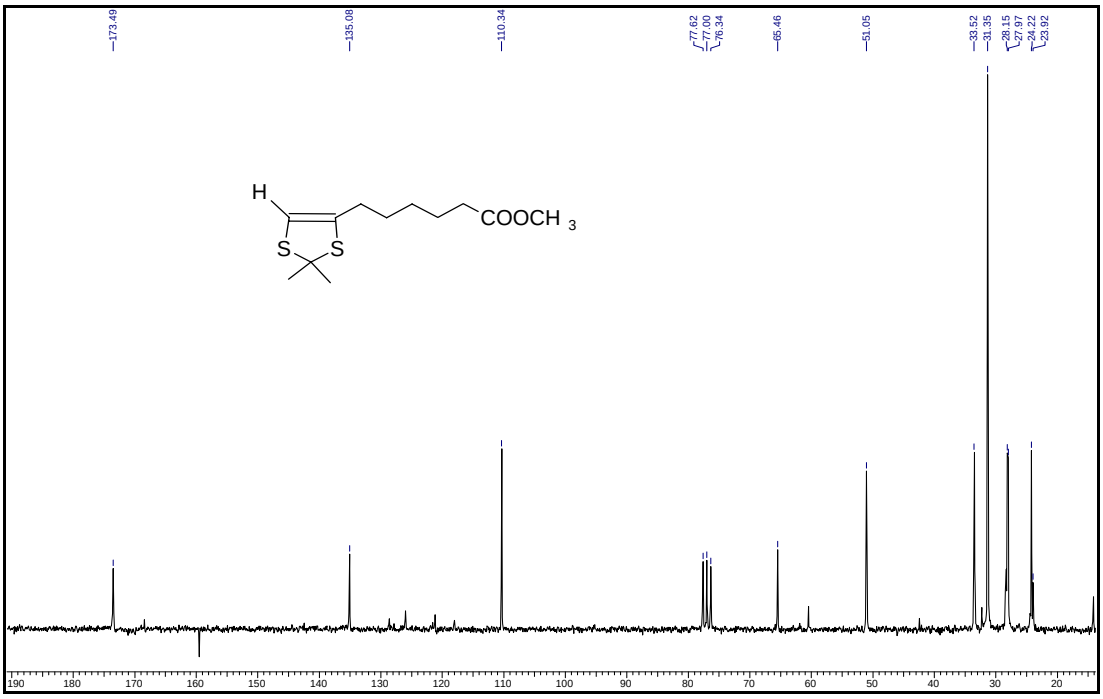


^{1}H NMR spectrum of 4-ethyl-2,2-dimethyl- (1,3) dithian-5-one (8e)

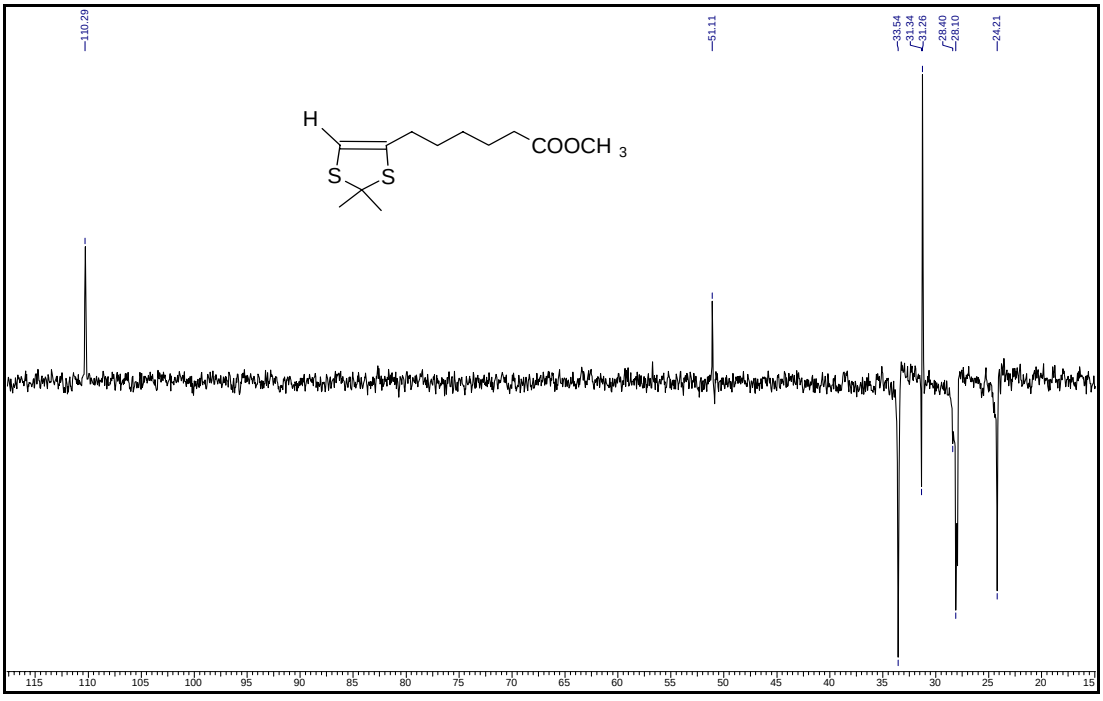
($CDCl_3$ + CCl_4, 500 MHz)



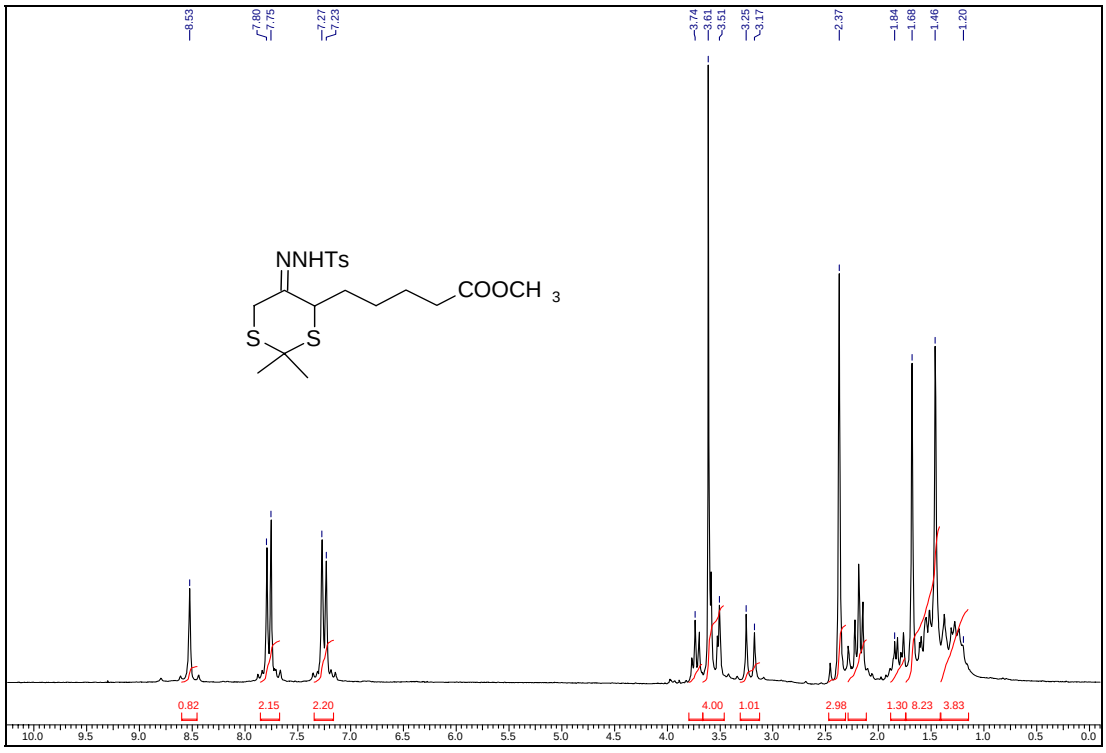
^{1}H NMR spectrum of methyl 6-(2,2-dimethyl-[1,3]-dithiol-4-yl-hexanoate (10c) ($CDCl_3$ + CCl_4, 200 MHz)



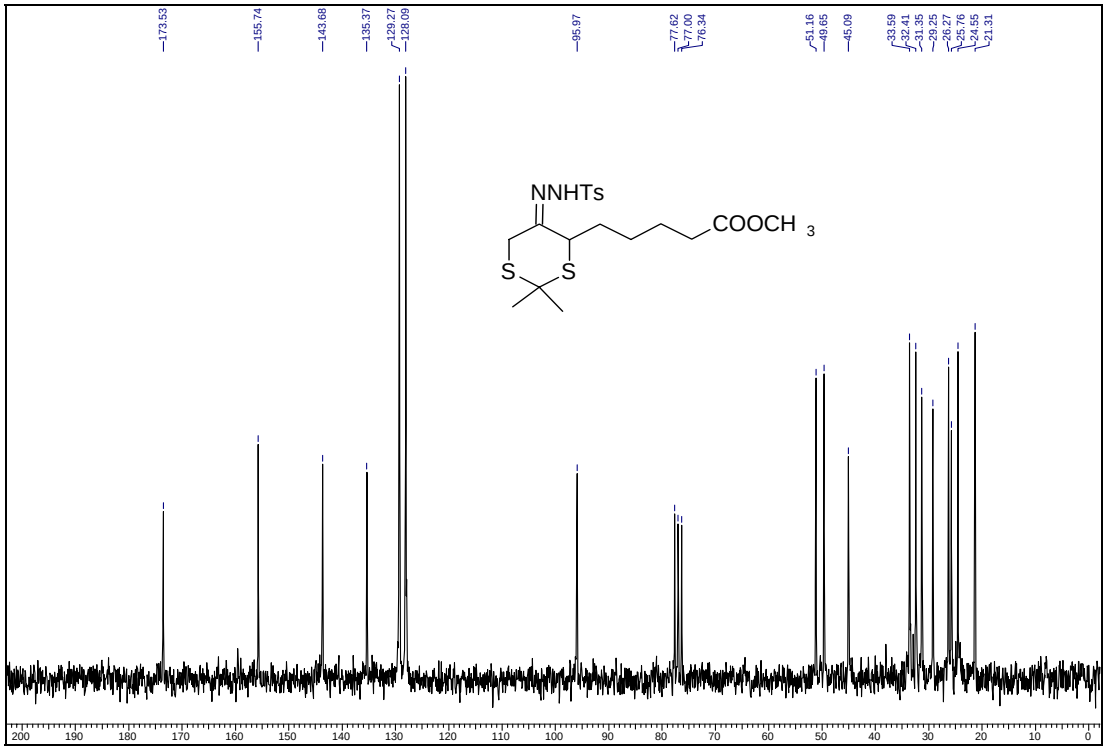
^{13}C NMR spectrum of methyl 6-(2,2-dimethyl-[1,3]-dithiol-4-yl-hexanoate (10c) ($CDCl_3$ + CCl_4, 125 MHz)



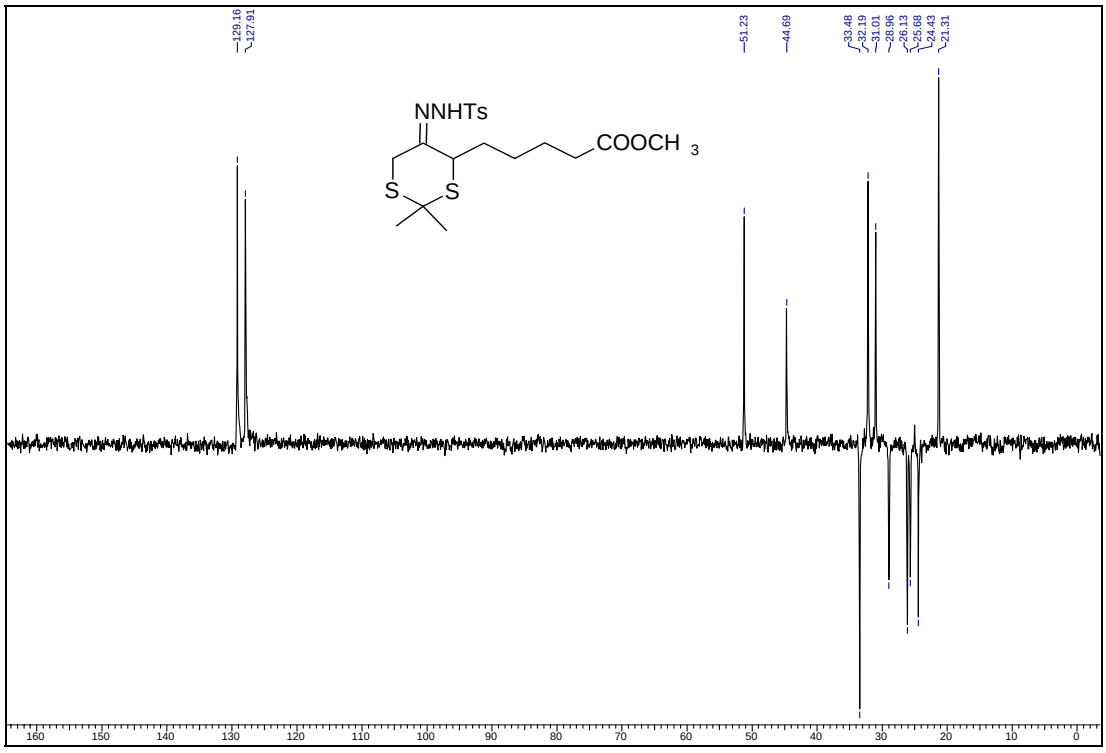
DEPT NMR spectrum of methyl 6-(2,2-dimethyl-[1,3]-dithiol-4-yl-hexanoate (10c) ($CDCl_3$ + CCl_4, 125 MHz)



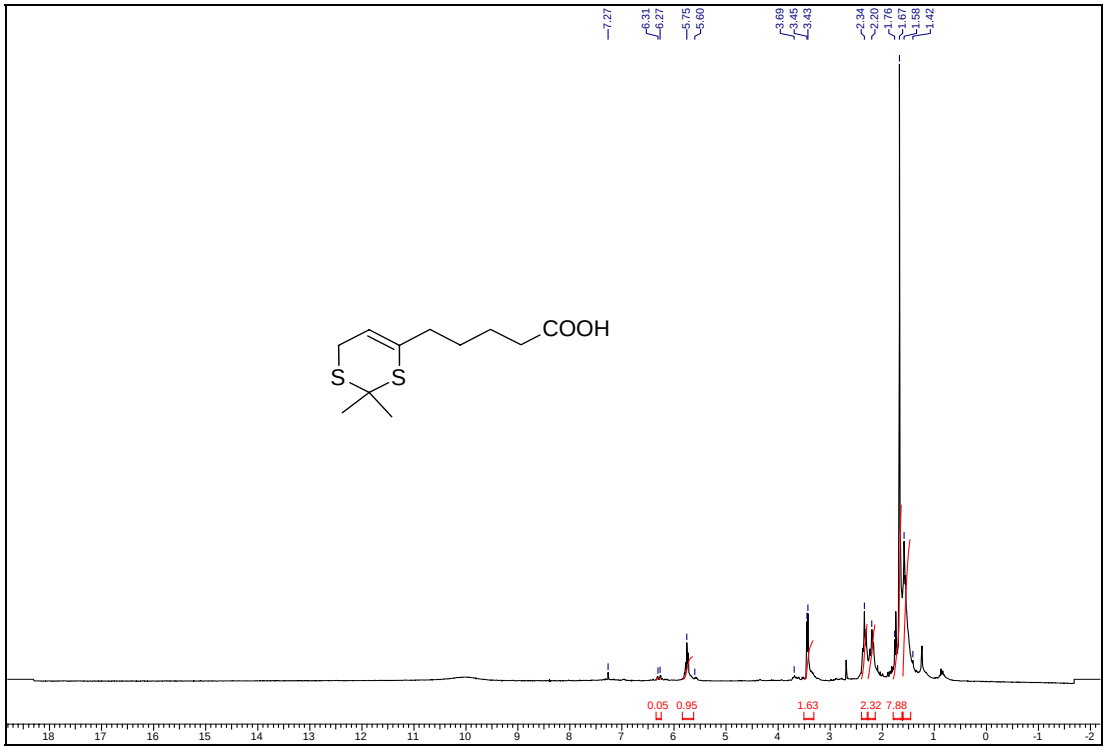
^{1}H NMR spectrum of methyl 5- [5-(*p*-toluenesulfonyl) hydrazono-2, 2-dimethyl-(1, 3)dithian-4-yl] - pentanoate (13c) ($CDCl_3$ + CCl_4, 200 MHz)



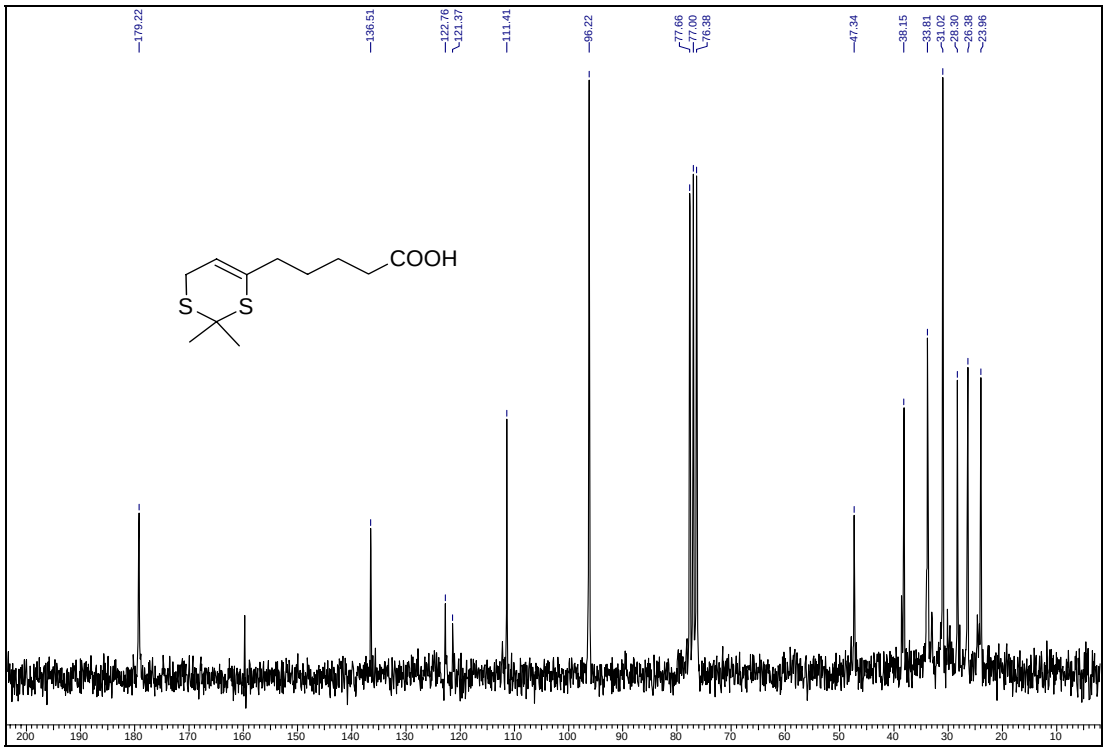
^{13}C NMR spectrum of methyl 5- [5-(*p*-toluenesulfonyl) hydrazono-2, 2-dimethyl-(1, 3)dithian-4-yl] - pentanoate (13c) ($CDCl_3$ + CCl_4, 50 MHz)



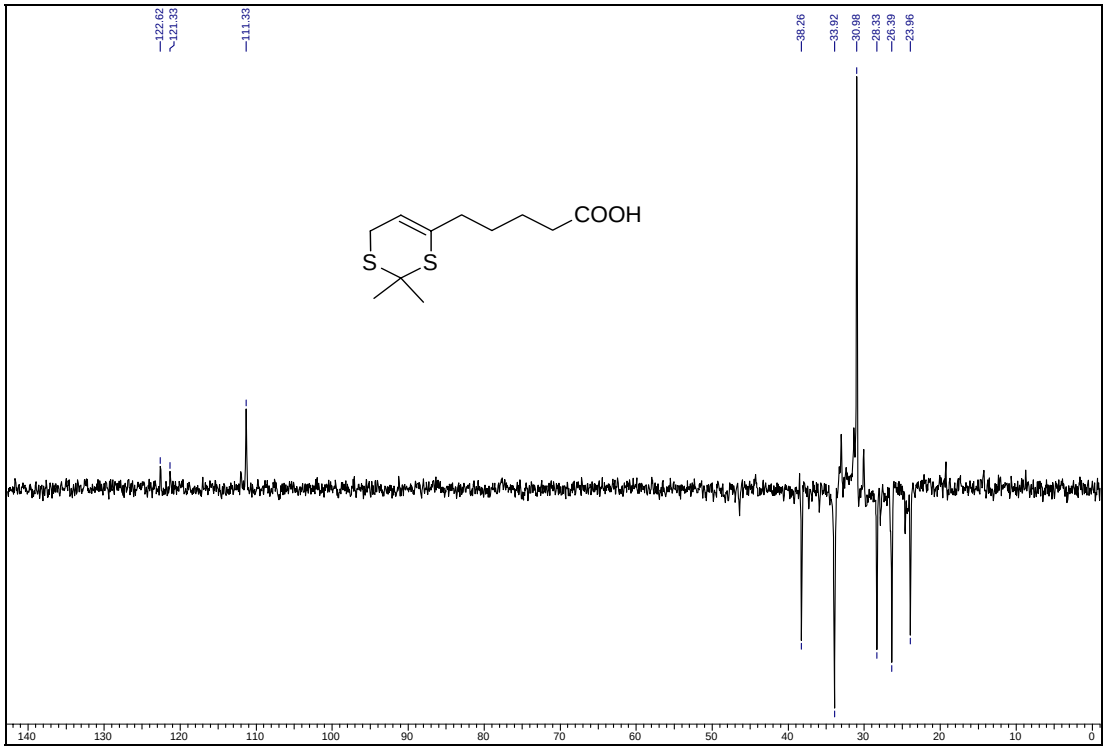
DEPT spectrum of methyl 5- [5-(*p*-toluenesulfonyl) hydrazono-2, 2-dimethyl-(1, 3)dithian-4-yl] - pentanoate (13c) ($CDCl_3$ + CCl_4, 50 MHz)



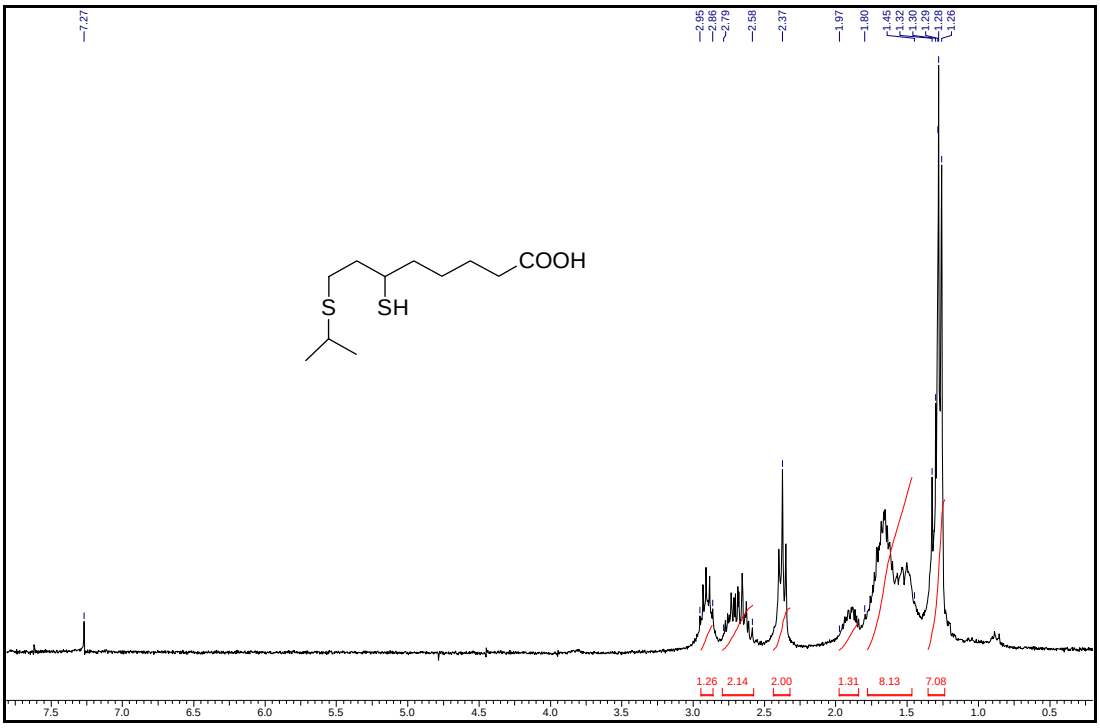
^{1}H NMR spectrum of 5-(2,2-dimethyl-*6H*-[1,3]dithiin-4-yl)-pentanoic acid (14c) ($CDCl_3$ + CCl_4, 200 MHz)



^{13}C NMR spectrum of 5-(2,2-dimethyl-*6H*-[1,3]dithiin-4-yl)-pentanoic acid (14c) ($CDCl_3$ + CCl_4, 50 MHz)

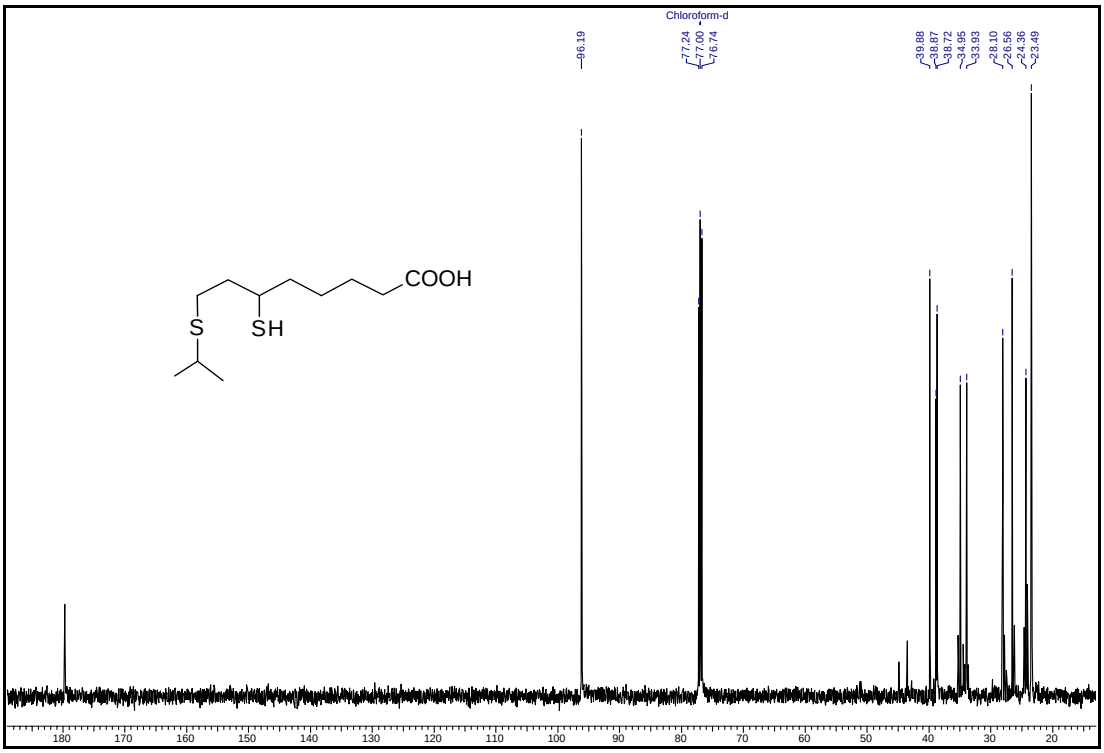


DEPT spectrum of 5-(2,2-dimethyl-*6H*-[1,3]dithiin-4-yl)-pentanoic acid (14c) ($CDCl_3$ + CCl_4, 50 MHz)



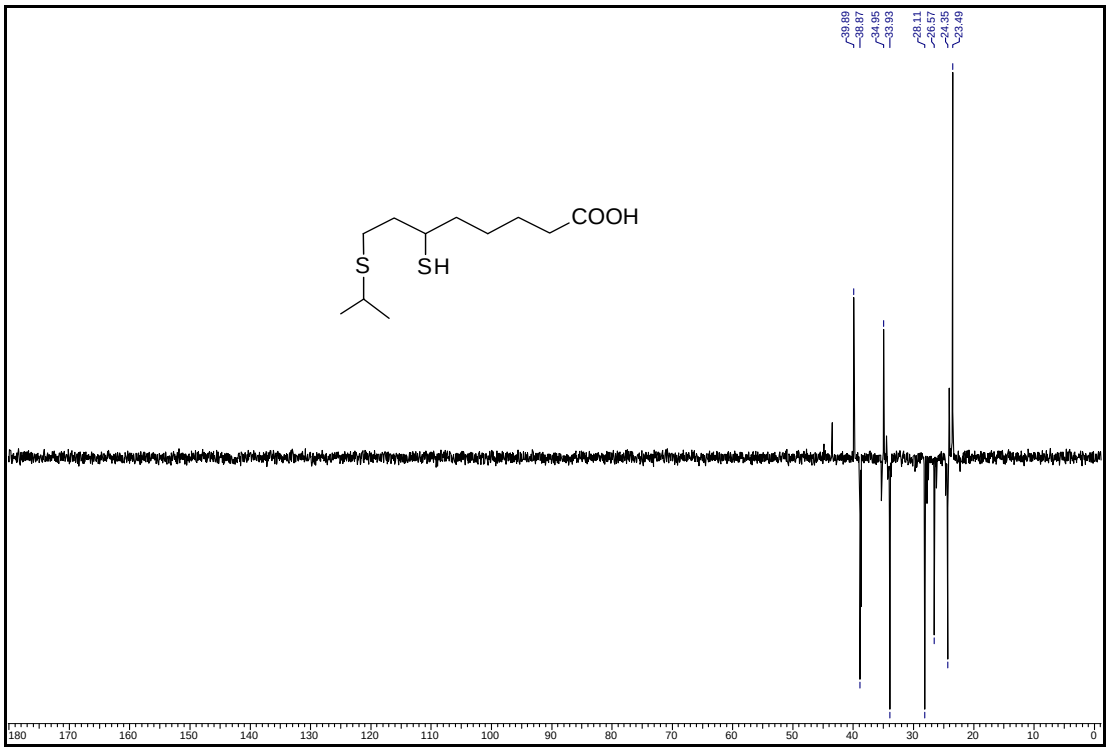
^{1}H NMR spectrum of 8-isopropylsulfanyl-6-mercapto-octanoic acid (16)

($CDCl_3$ + CCl_4, 200 MHz)

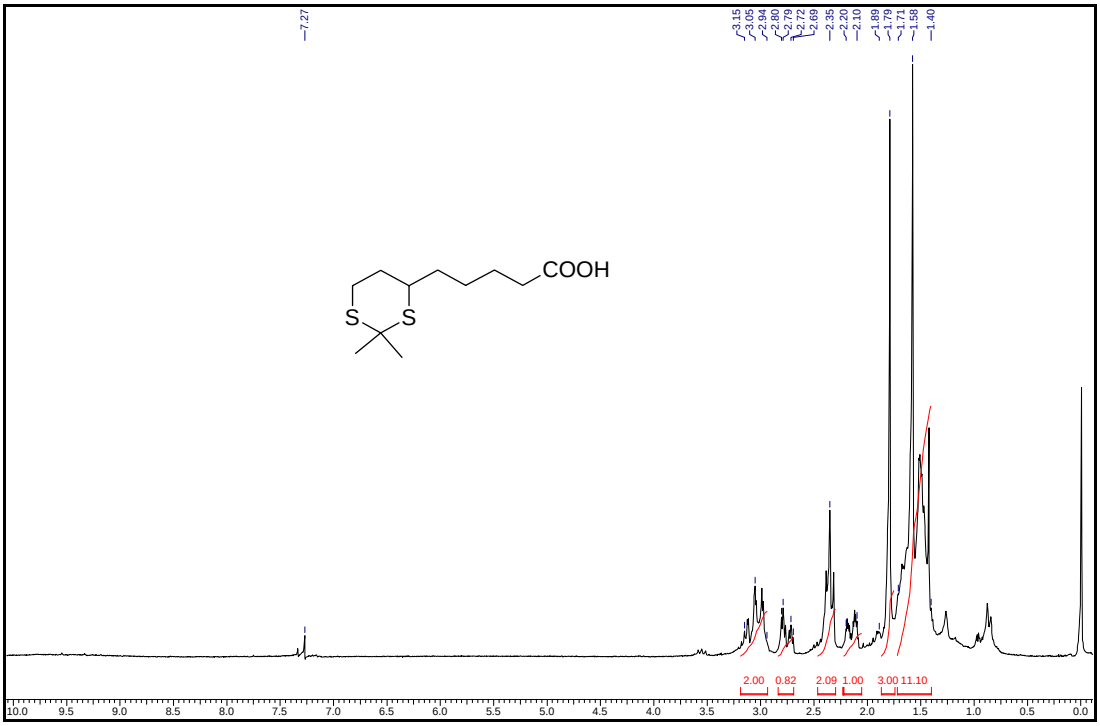


^{13}C NMR spectrum of 8-isopropylsulfanyl-6-mercapto-octanoic acid (16)

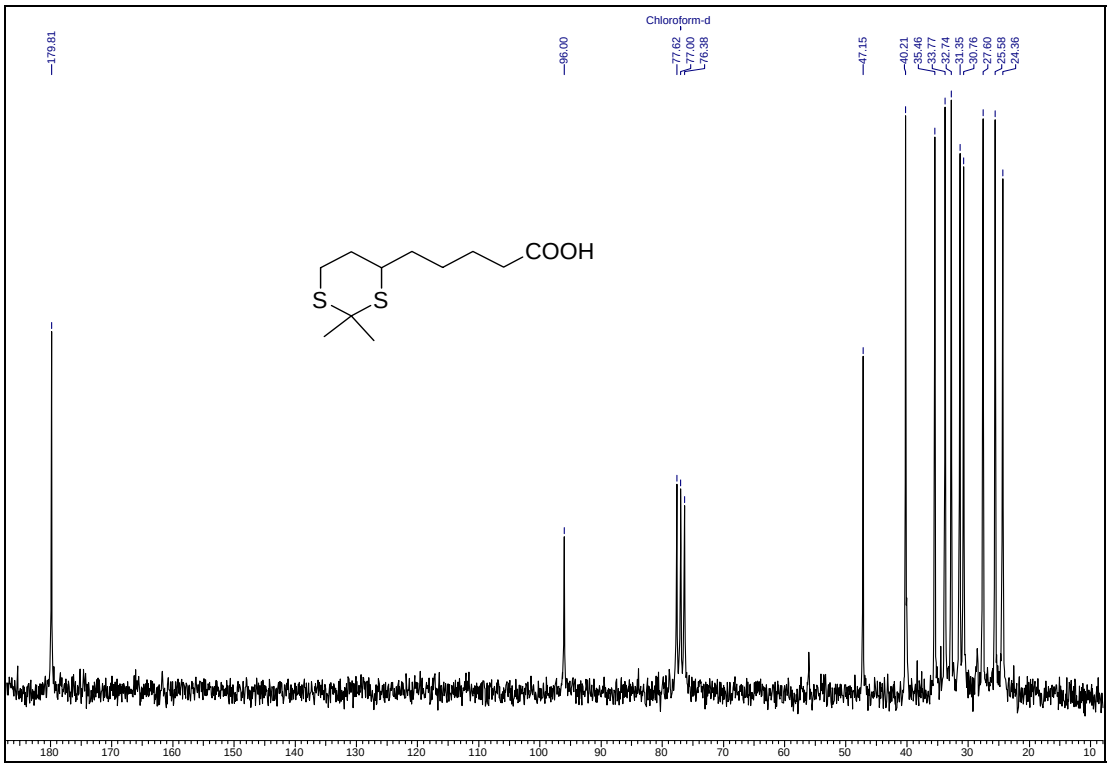
($CDCl_3$ + CCl_4, 50 MHz)



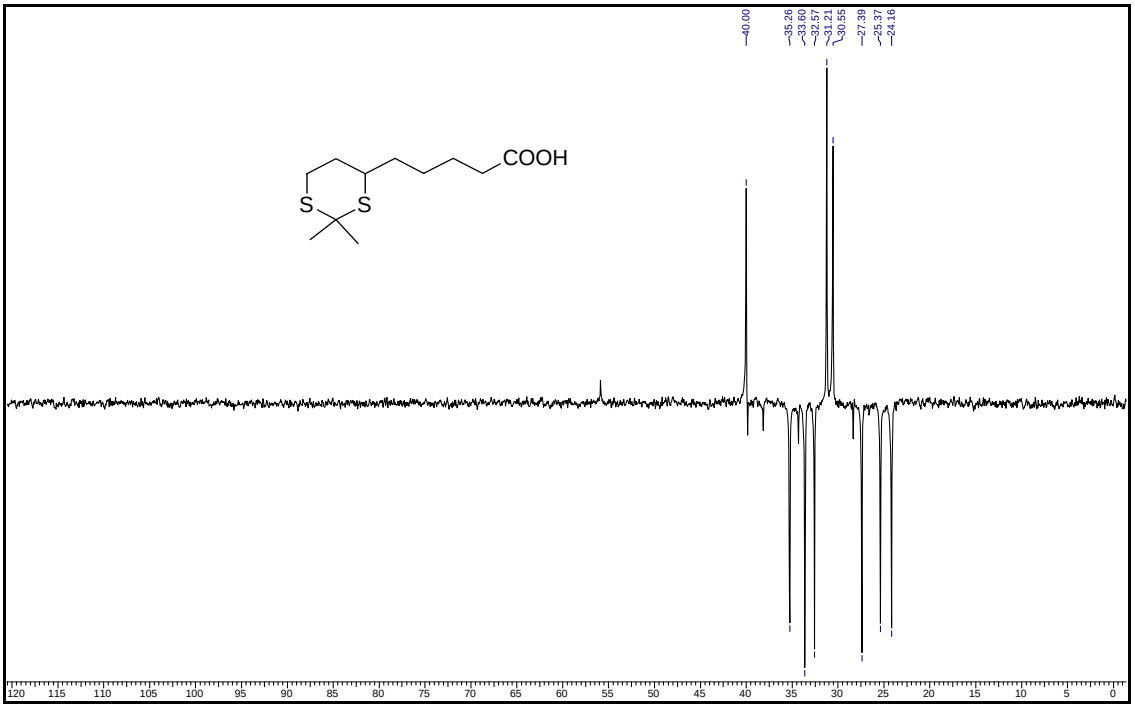
DEPT spectrum of 8-isopropylsulfanyl-6-mercapto-octanoic acid (16) ($CDCl_3$ + CCl_4, 50 MHz)



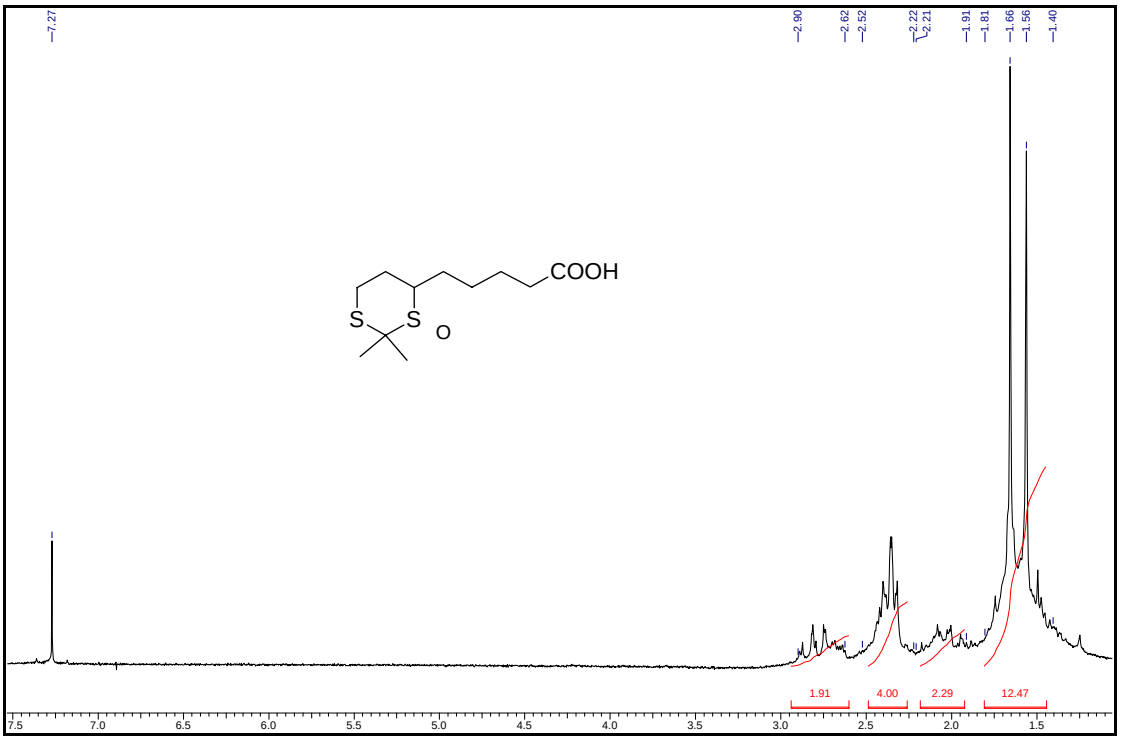
^{13}C NMR spectrum of 5-(2,2-dimethyl-[1,3]dithian-4-yl)-pentanoic acid (17) ($CDCl_3$ + CCl_4, 50 MHz)



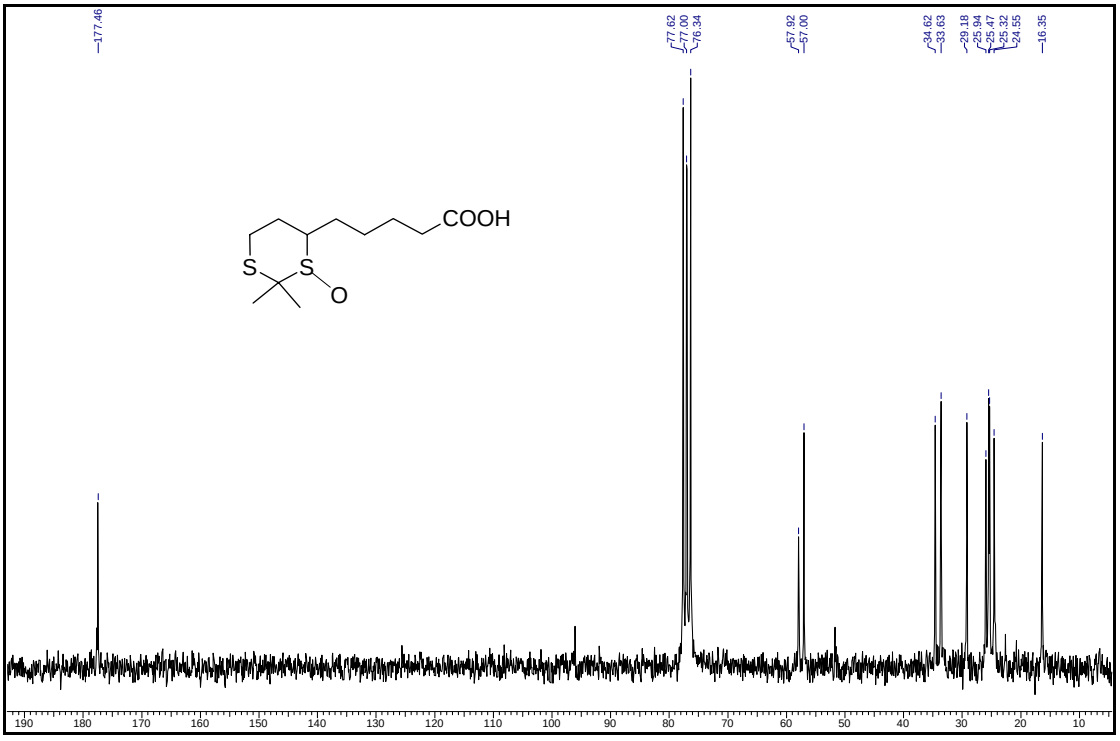
^{13}C NMR spectrum of 5-(2,2-dimethyl-[1,3]dithian-4-yl)-pentanoic acid (17) ($CDCl_3$ + CCl_4, 50 MHz)



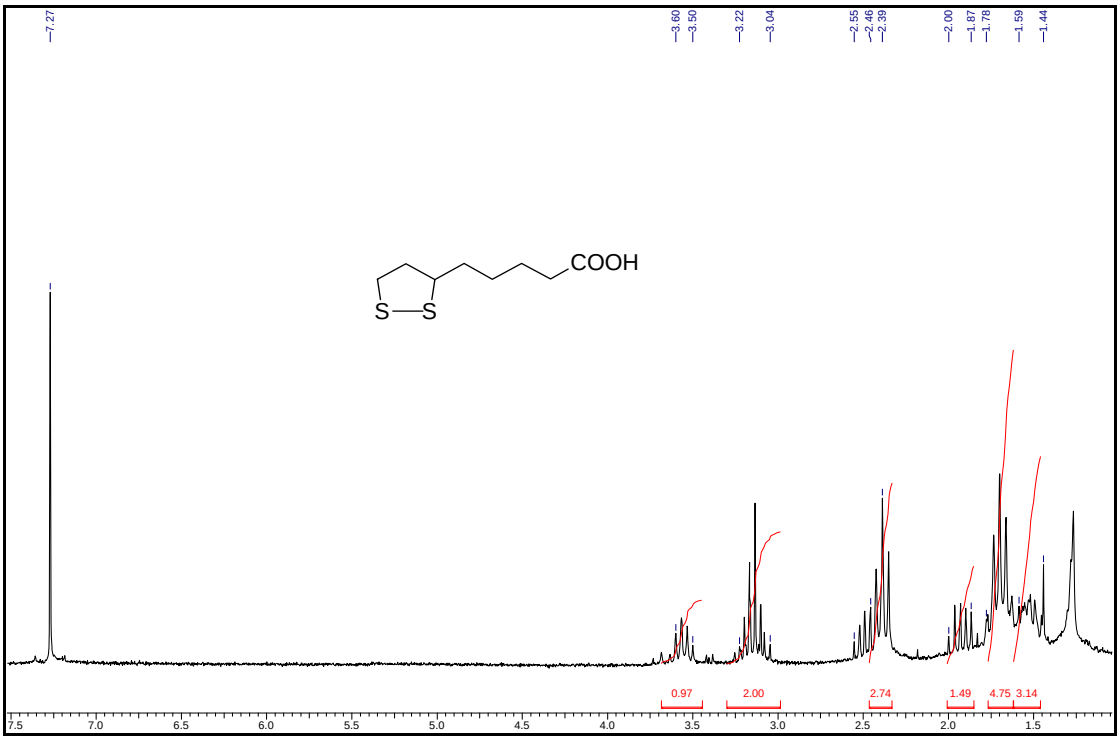
DEPT spectrum of 5-(2,2-dimethyl-[1,3]dithian-4-yl)-pentanoic acid (17) ($CDCl_3$ + CCl_4, 50 MHz)



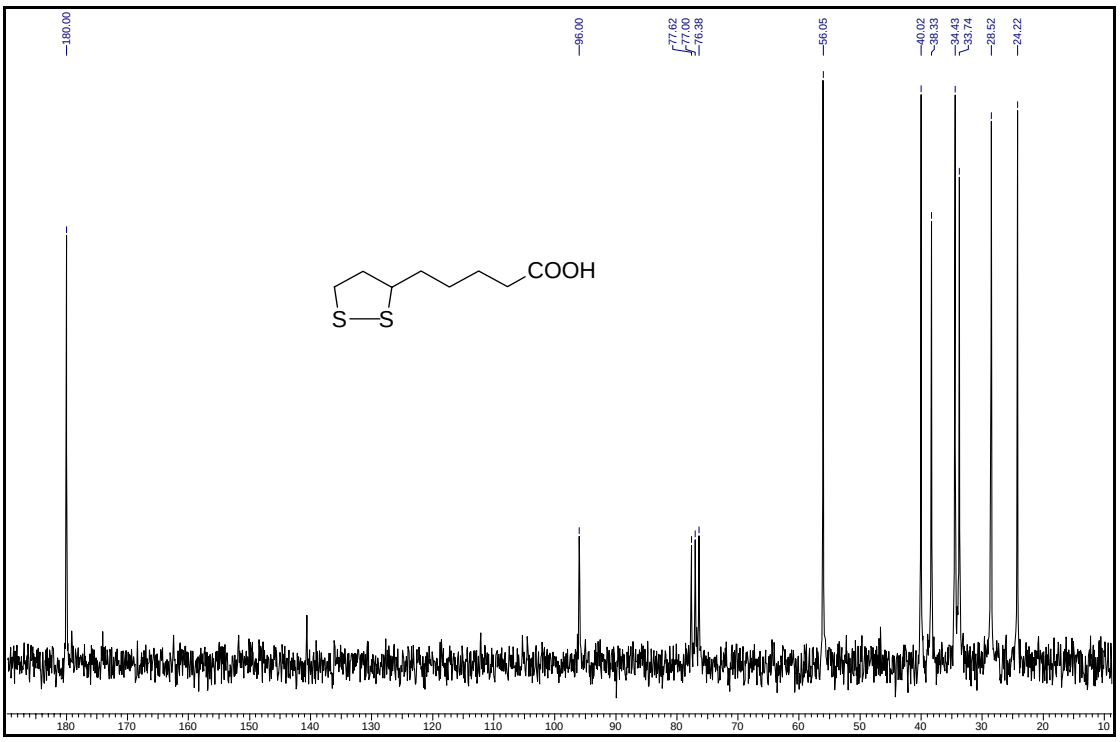
^{1}H NMR spectrum of 5-(2,2-dimethyl-3-oxo-[1,3]dithian-4-yl)-pentanoic acid (18) ($CDCl_3$ + CCl_4, 200 MHz)



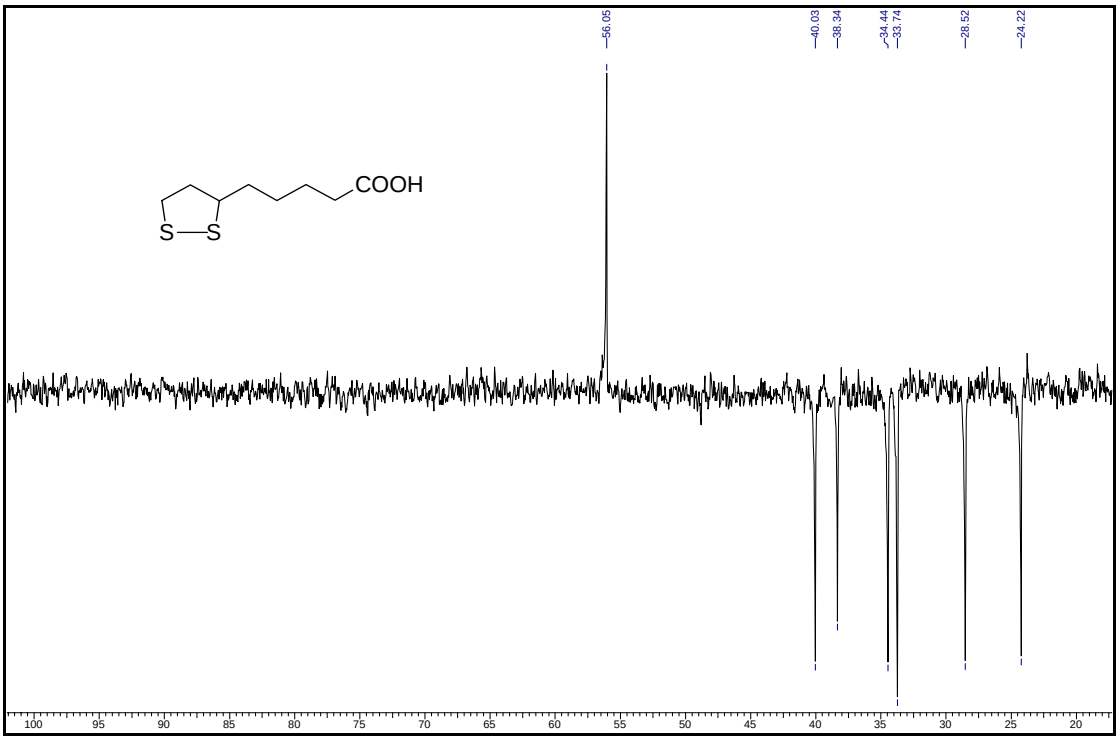
^{13}C NMR spectrum of 5-(2,2-dimethyl-3-oxo-[1,3]dithian-4-yl)-pentanoic acid (18) ($CDCl_3$ + CCl_4, 50 MHz)



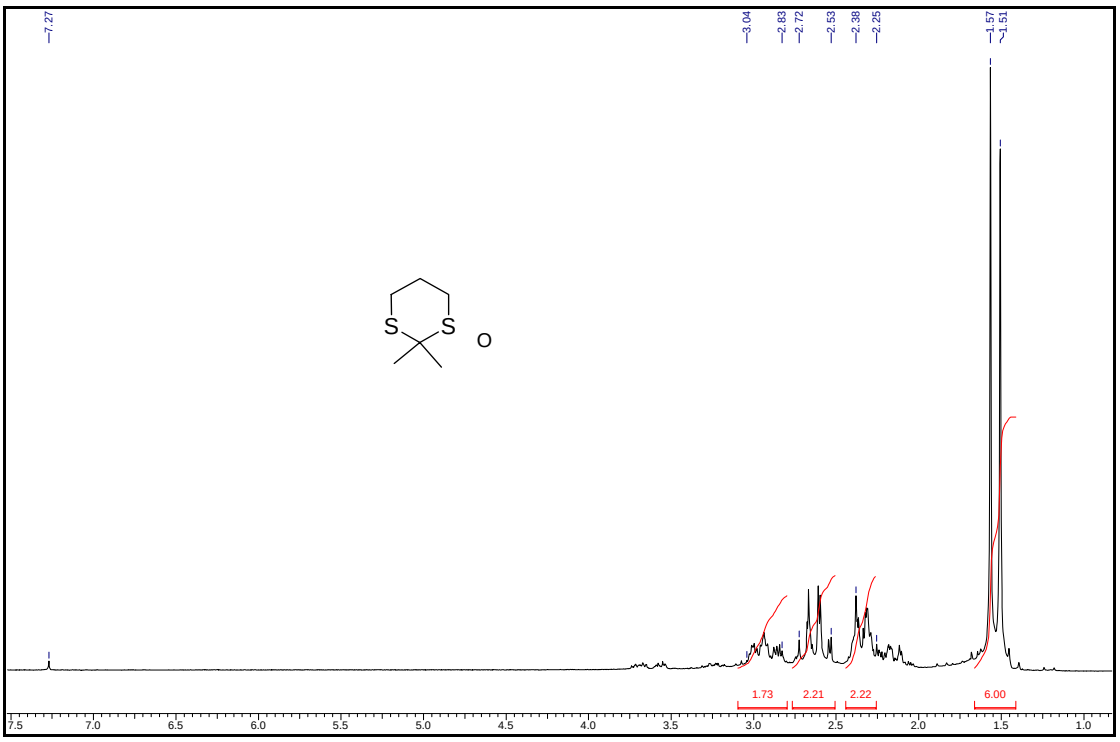
^{1}H NMR spectrum of α-lipoic acid (1) ($CDCl_3$ + CCl_4, 200 MHz)



^{13}C NMR spectrum of α-lipoic acid (1) ($CDCl_3$ + CCl_4, 50 MHz)

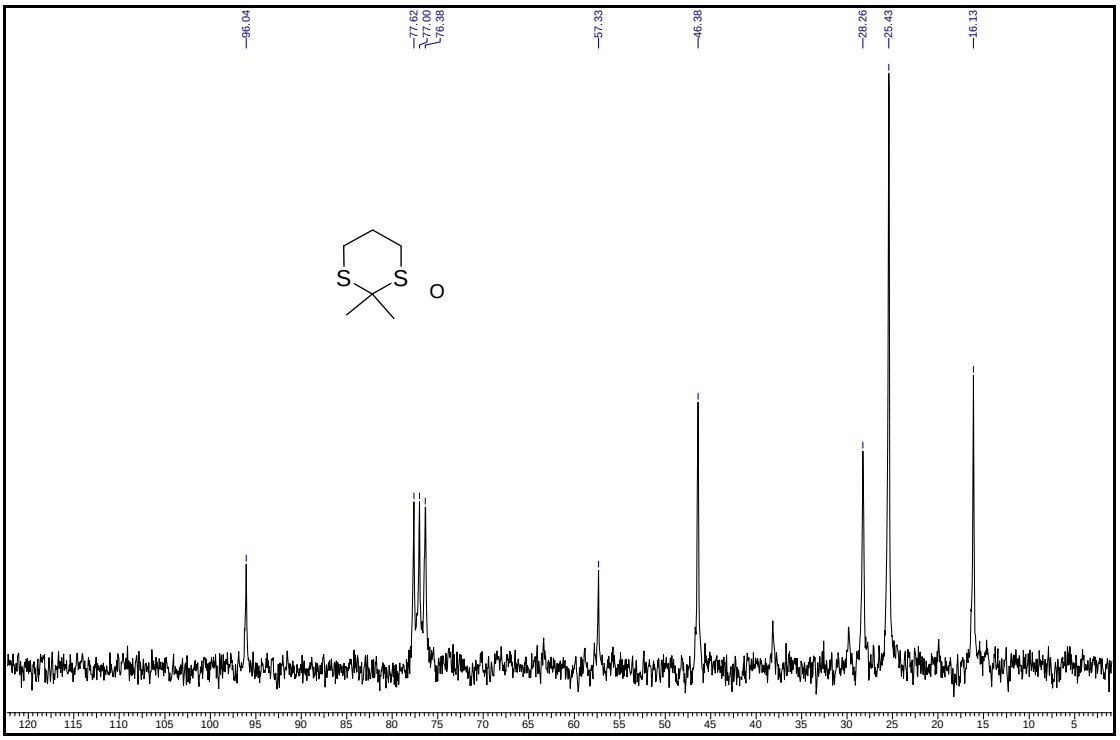


DEPT NMR spectrum of α-lipoic acid (1) ($CDCl_3$ + CCl_4, 50 MHz)



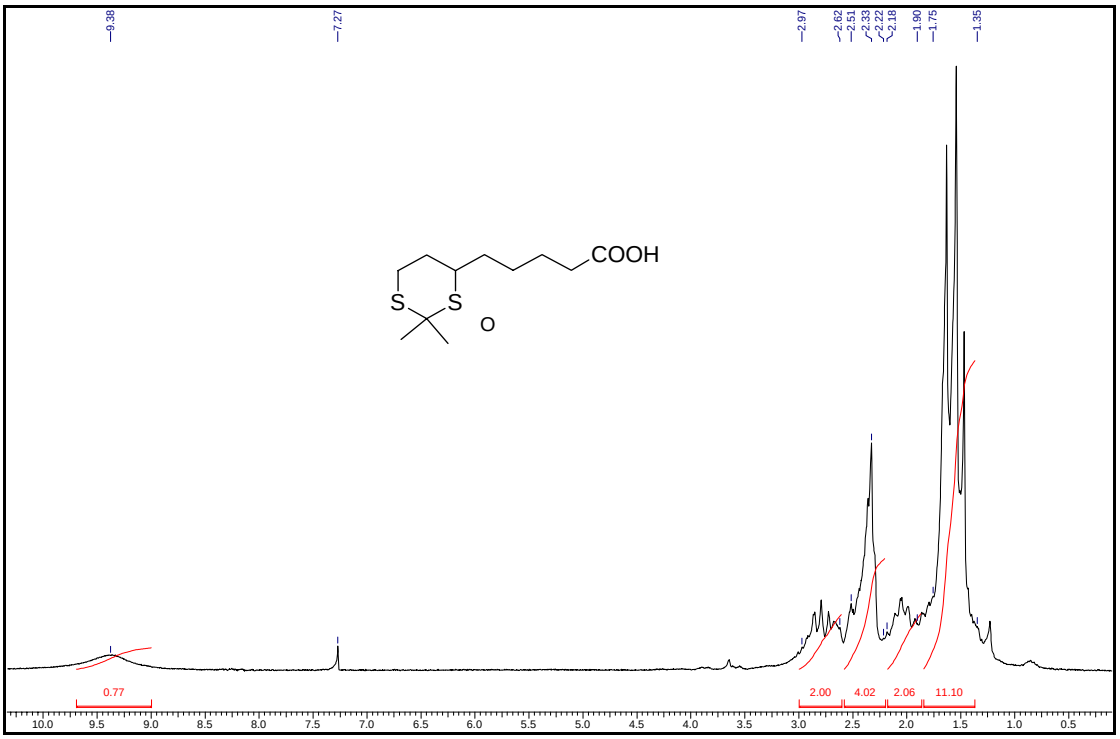
^{1}H NMR spectrum of 2,2-dimethyl-[1,3]dithiane 1-oxide (20)

($CDCl_3$ + CCl_4, 200 MHz)



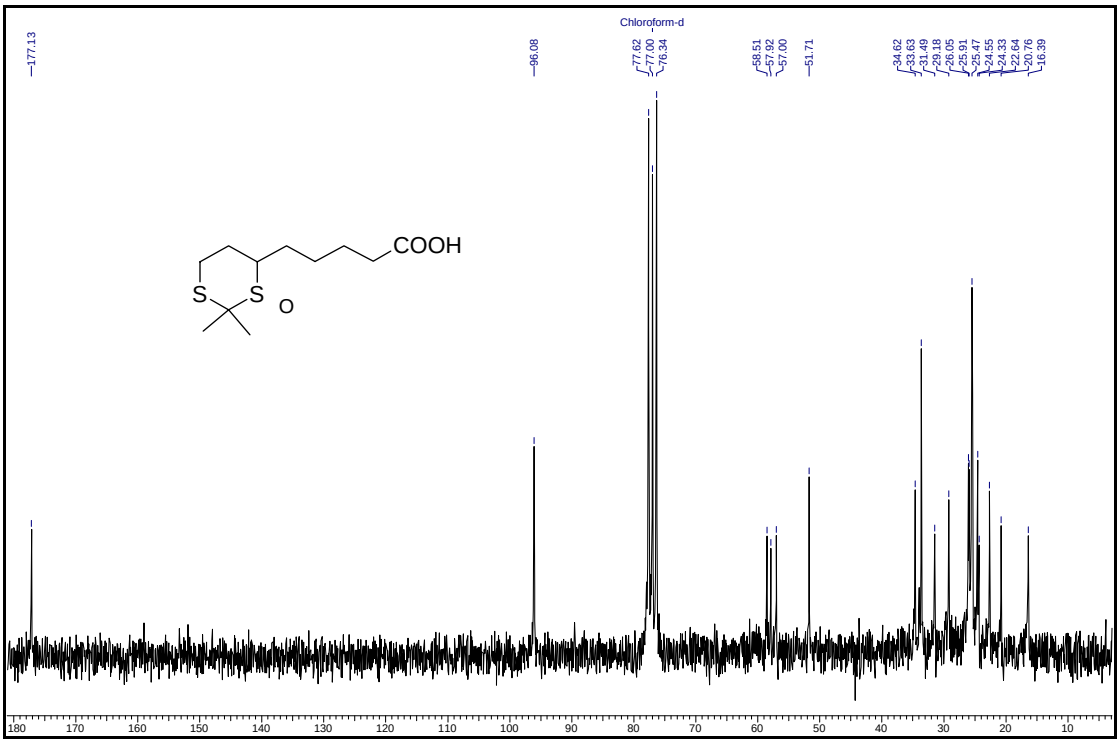
^{13}C NMR spectrum of 2,2-dimethyl-[1,3]dithiane 1-oxide (20)

($CDCl_3$ + CCl_4, 50 MHz)

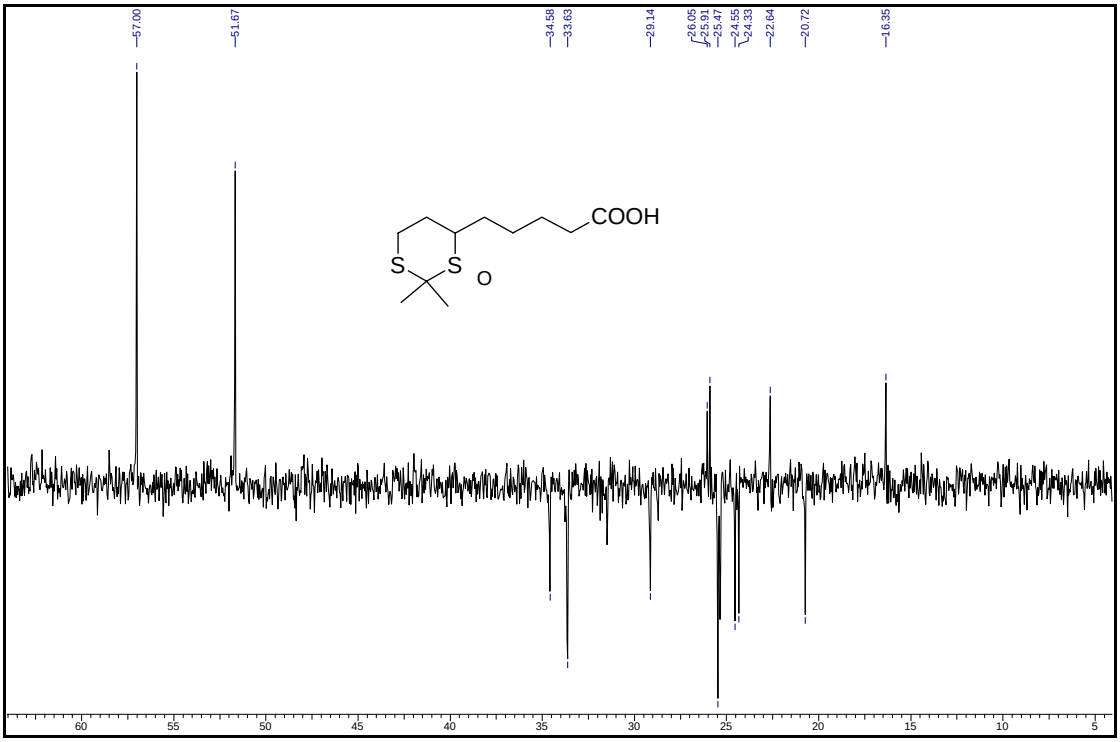


^{1}H NMR spectrum of 5-(2,2-dimethyl-3-oxo-[1,3]dithian-4-yl)-pentanoic acid

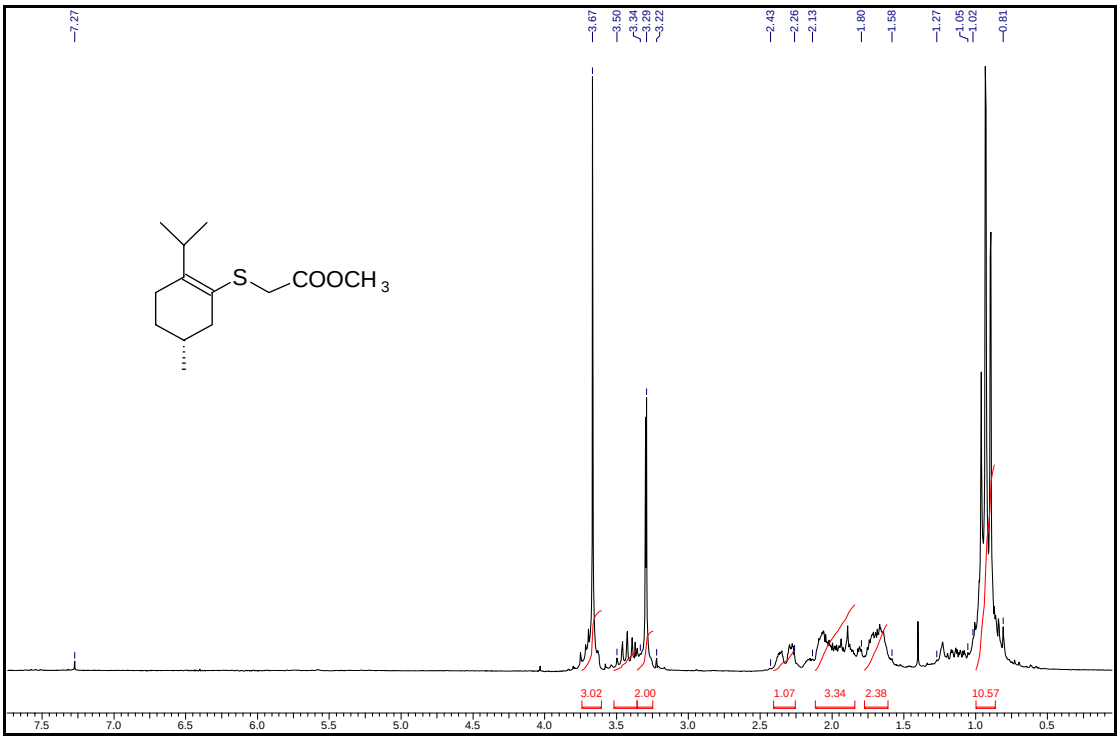
(18') ($CDCl_3$ + CCl_4, 200 MHz)



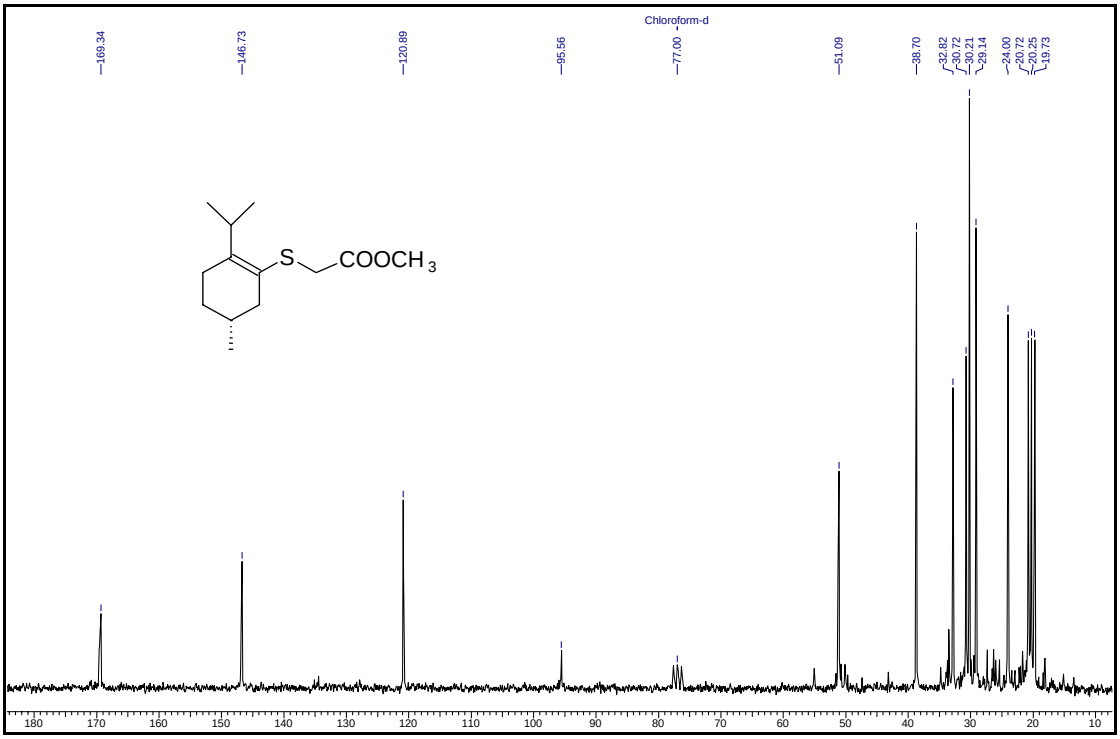
^{13}C NMR spectrum of 5-(2,2-dimethyl-3-oxo-[1,3]dithian-4-yl)-pentanoic acid (18') ($CDCl_3$ + CCl_4, 50 MHz)



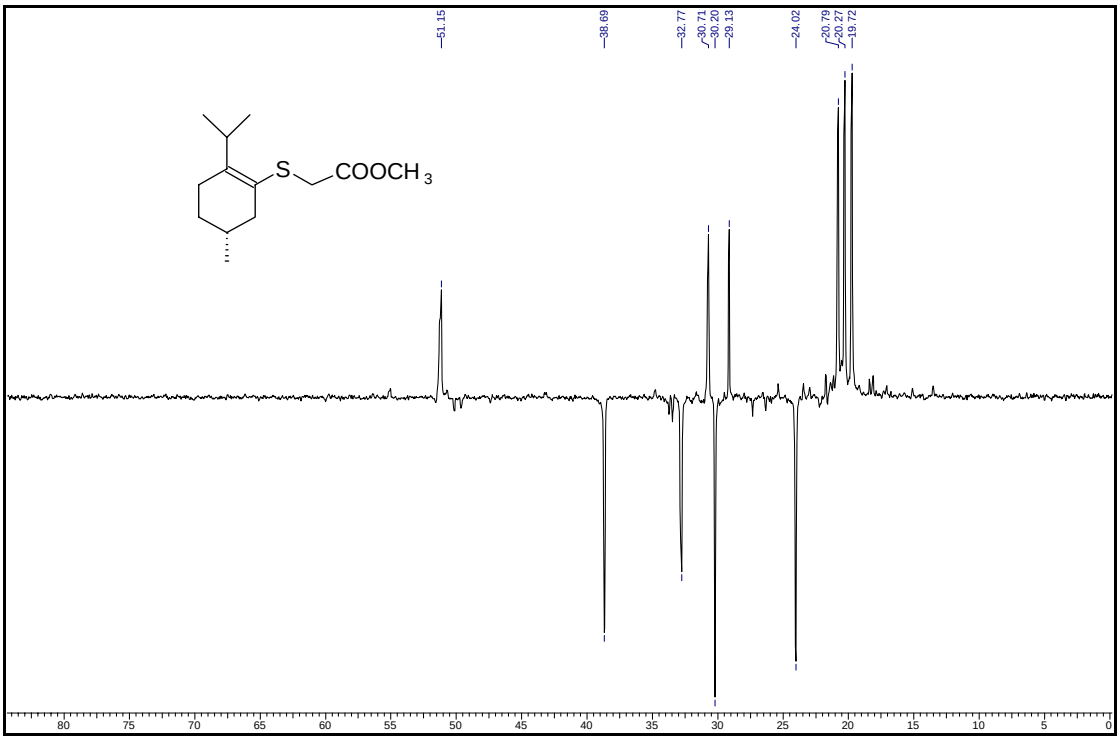
DEPT NMR spectrum of 5-(2,2-dimethyl-3-oxo-[1,3]dithian-4-yl)-pentanoic acid (18') ($CDCl_3$ + CCl_4, 200 MHz)



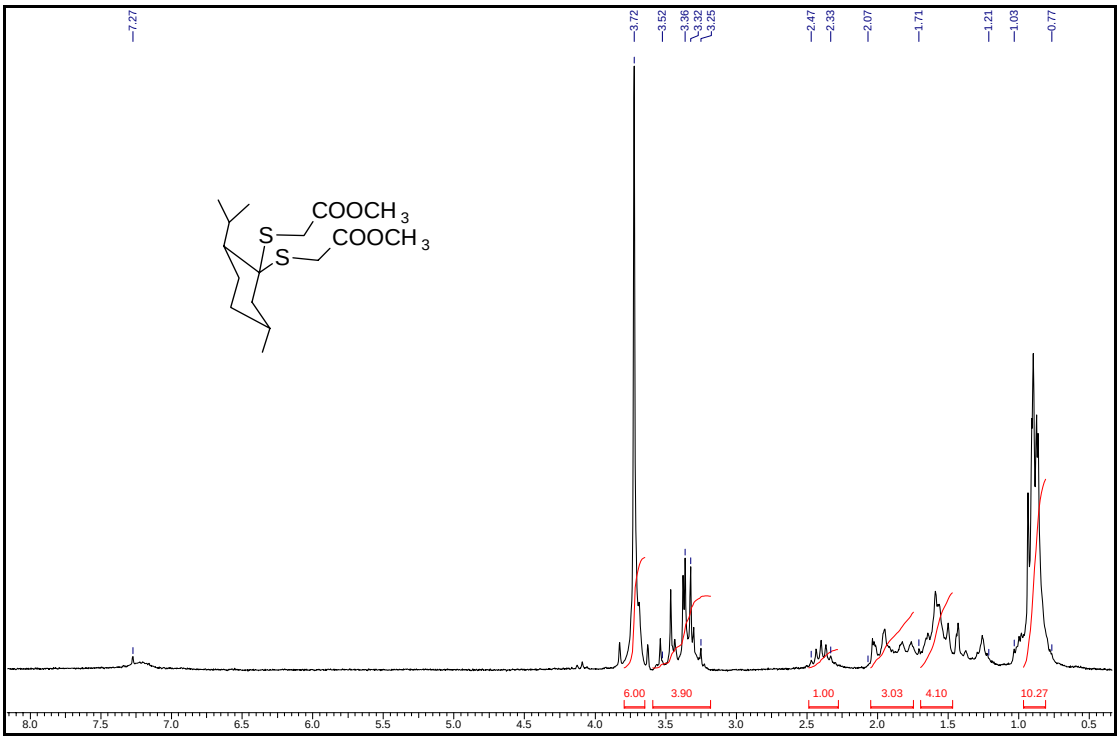
^{1}H NMR spectrum of olefin ester 22 ($CDCl_3$ + CCl_4, 200 MHz)



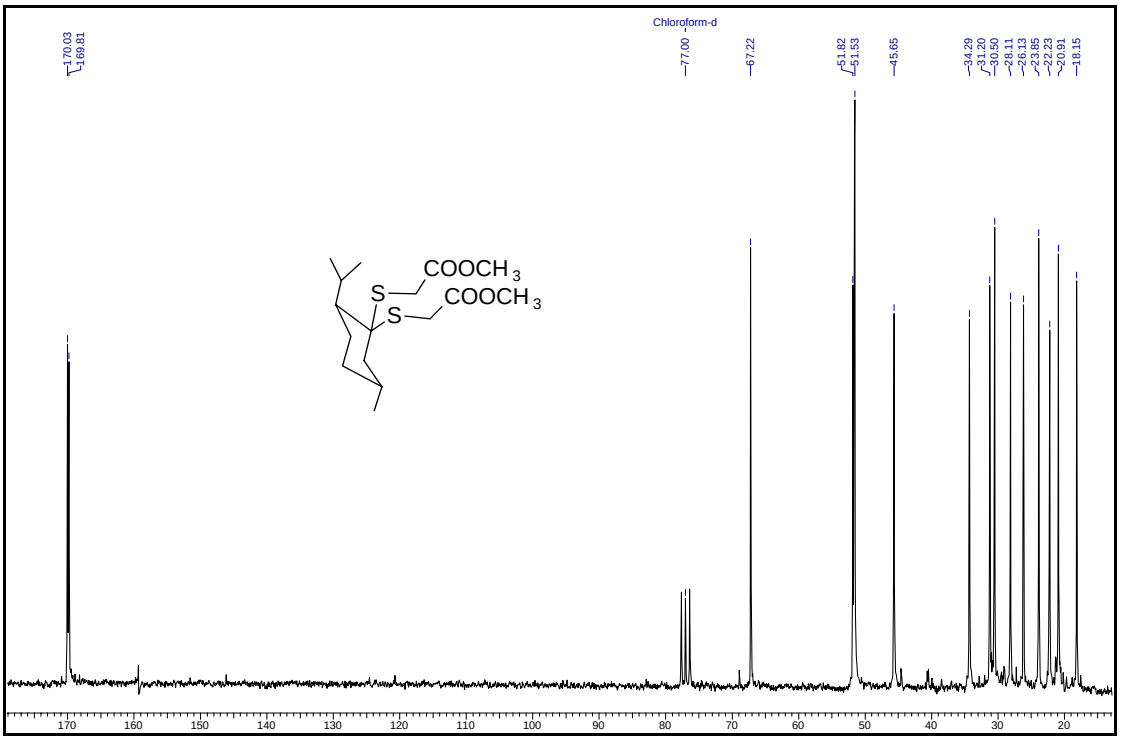
^{13}C NMR spectrum of olefin ester 22 ($CDCl_3$ + CCl_4, 50 MHz)



DEPT NMR spectrum of olefin ester 22 ($CDCl_3$ + CCl_4, 50 MHz)

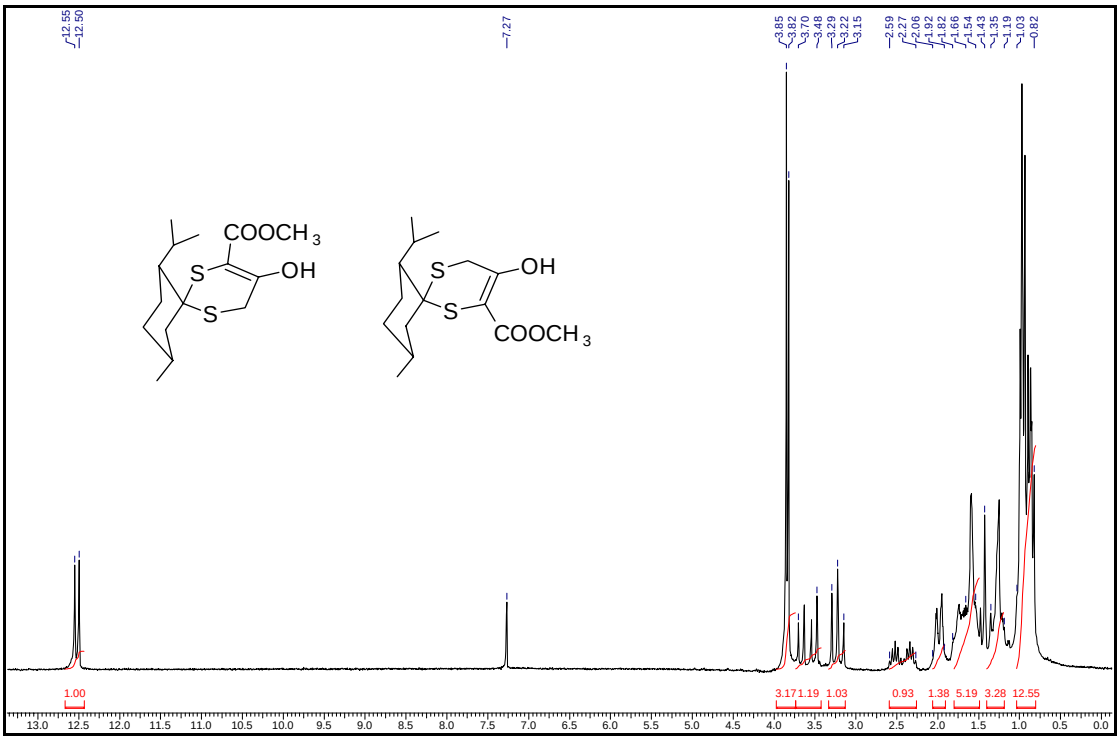


^{1}H NMR spectrum of diester 23 ($CDCl_3$ + CCl_4, 200 MHz)

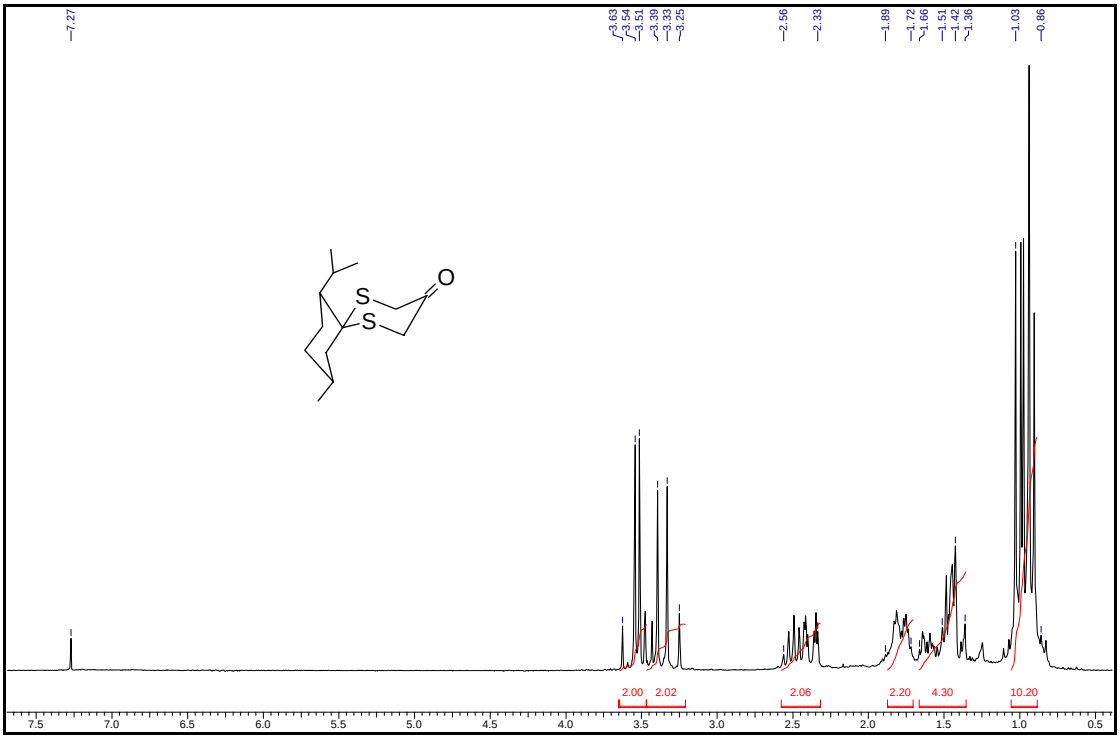


^{13}C NMR spectrum of diester 23 ($CDCl_3$ + CCl_4, 50 MHz)

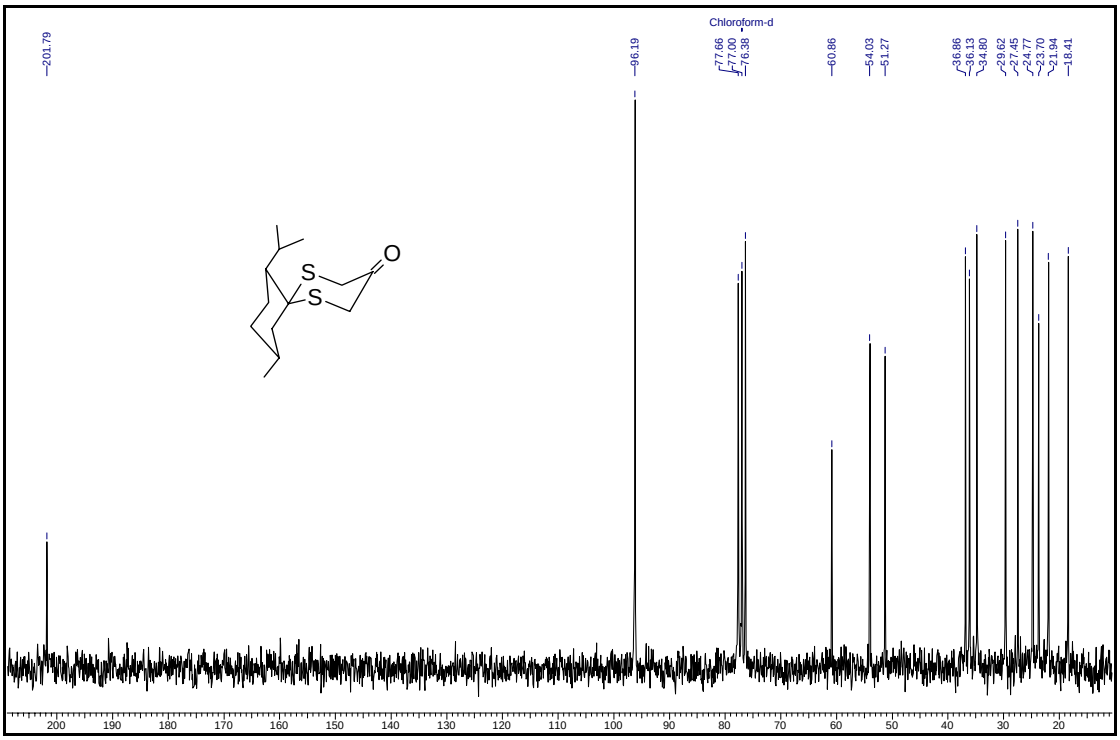
DEPT NMR spectrum of diester 23 ($CDCl_3$ + CCl_4, 200 MHz)



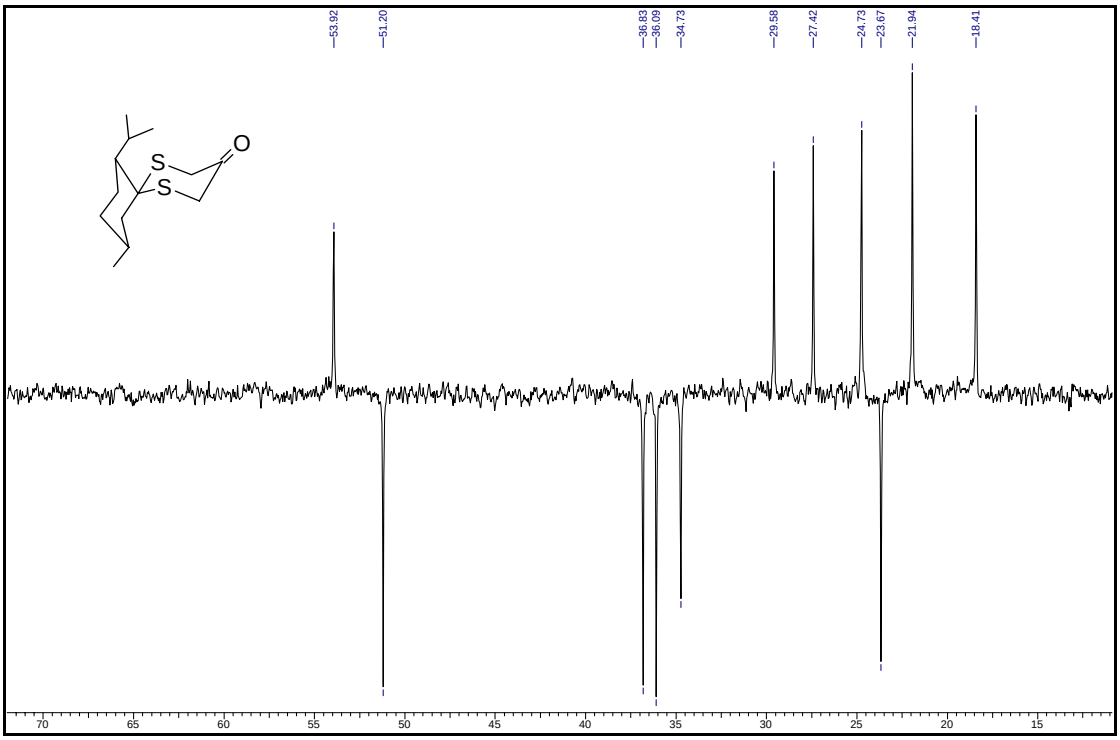
^{1}H NMR spectrum of β-Ketoester (24a + 24b) ($CDCl_3$ + CCl_4, 200 MHz)



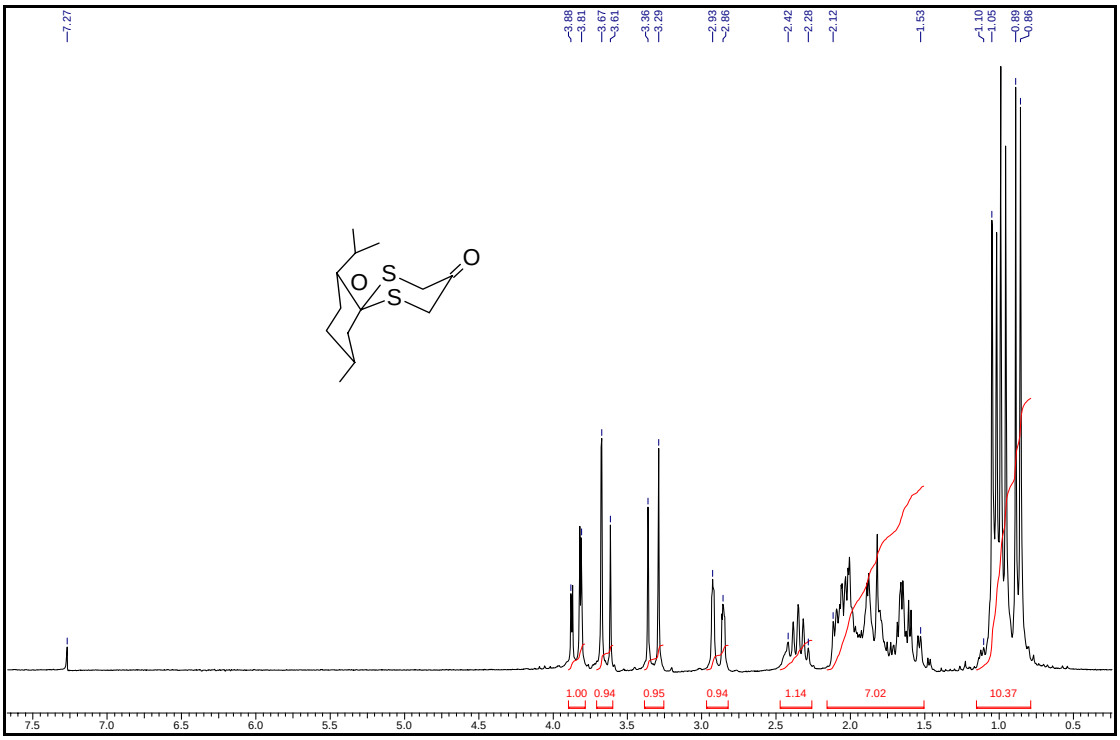
^{1}H NMR spectrum of ketone 25 ($CDCl_3$ + CCl_4, 200 MHz)



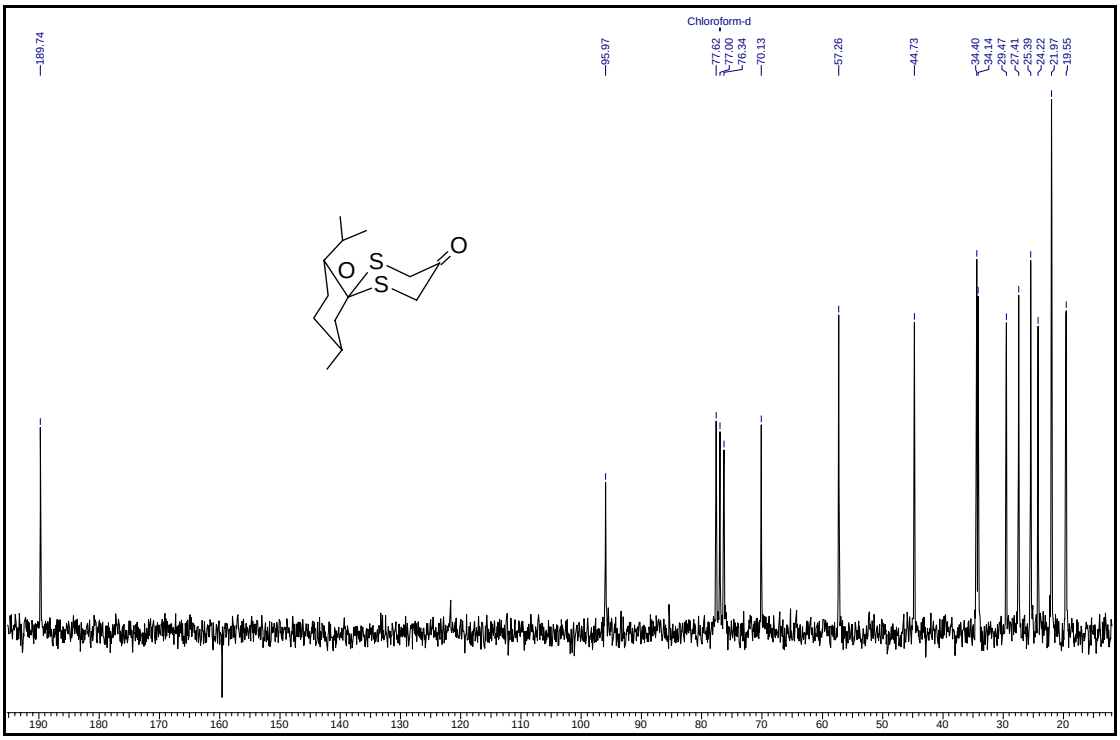
^{13}C NMR spectrum of ketone 25 ($CDCl_3$ + CCl_4, 50 MHz)



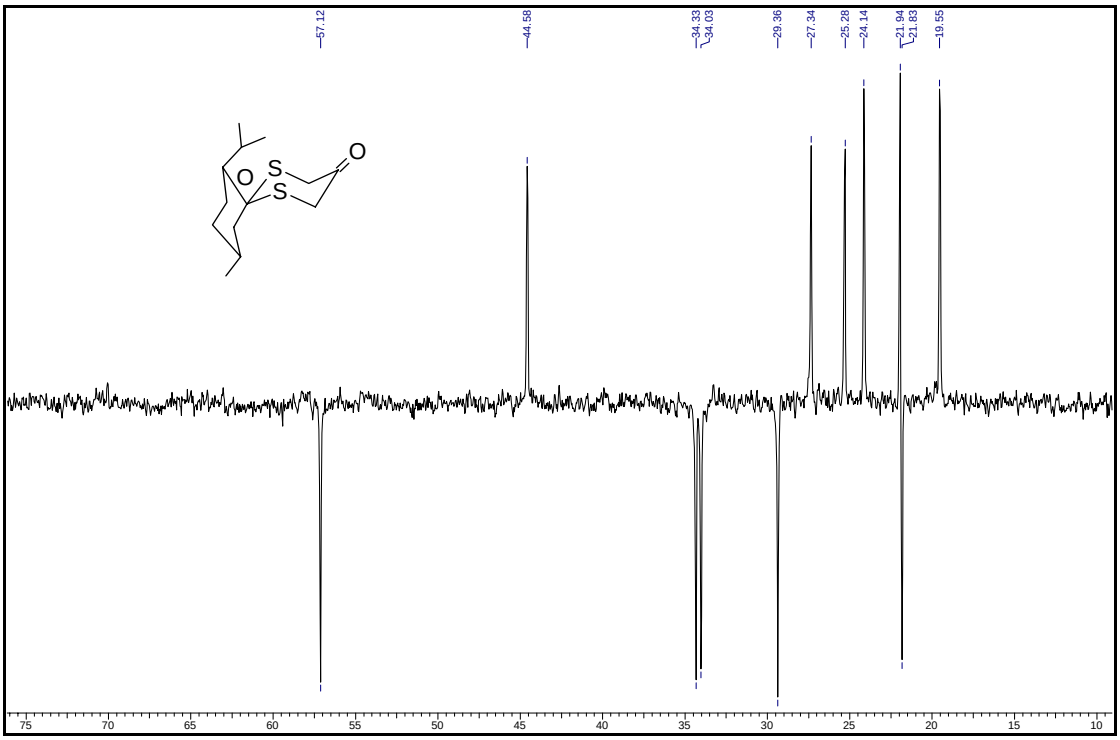
DEPT NMR spectrum of ketone 25 ($CDCl_3$ + CCl_4, 50 MHz)



^{1}H NMR spectrum of sulfoxide 26 ($CDCl_3$ + CCl_4, 200 MHz)



^{13}C NMR spectrum of sulfoxide 26 ($CDCl_3$ + CCl_4, 50 MHz)



DEPT NMR spectrum of sulfoxide 26 ($CDCl_3$ + CCl_4, 50 MHz)

1.2.4 References

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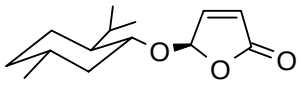
CHAPTER-1

SECTION-3

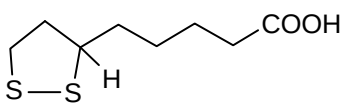
Butenolide approach for the synthesis of α-Lipoic acid

1.3.1 Present work

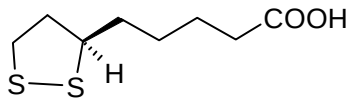
The synthesis and properties of γ-substituted butenolides have recently attracted much attention owing to the unique carbon skeleton of 2(*5H*)-furanone which is widely present in a variety of biologically active natural products[1] and their utility as valuable synthetic intermediates.[2] Among the various asymmetric transformations studied, chiral auxiliary based methods have afforded very good results.[3] Feringa and coworkers[4] have reported the γ-(l-menthyloxy) butenolide **1a** as a chiral synthon which has been efficiently utilized in organic synthesis.



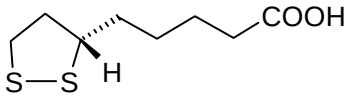
1a



α-Lipoic acid (**2**)

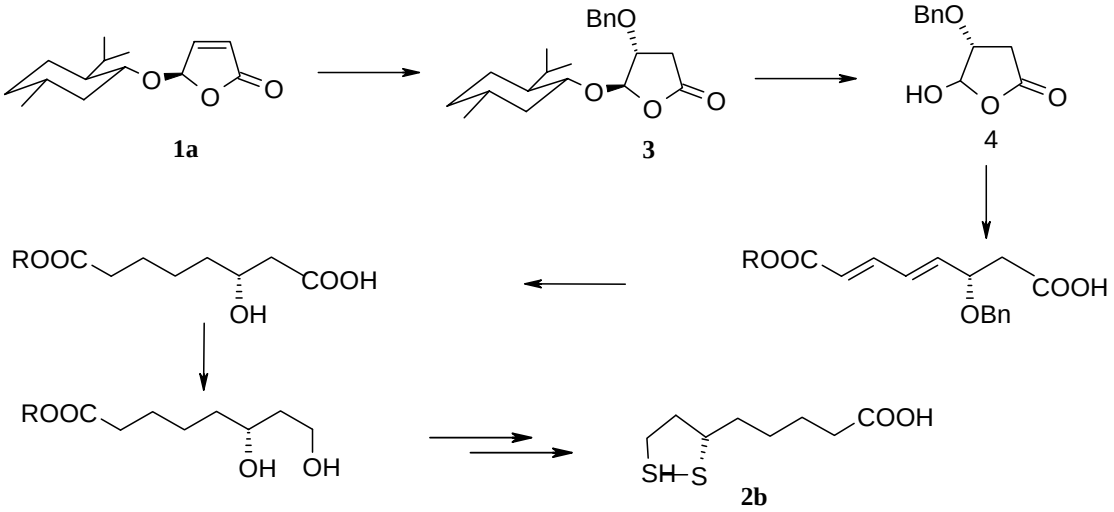


(*R*)-(+)- α-Lipoic acid (**2a**)



(*S*)-(-)- α-Lipoic acid (**2b**)

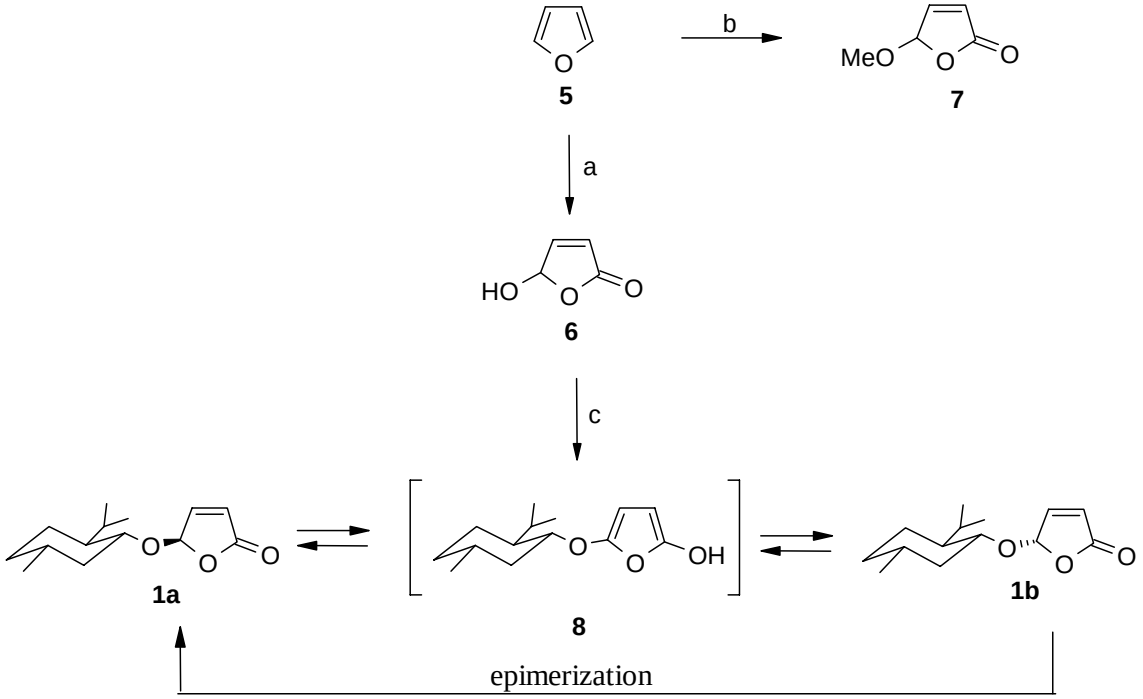
After achieving a simple and practical synthesis of (±) ∝-lipoic acid **2**, we planned a different synthetic route for the asymmetric synthesis of ∝-lipoic acid using butenolide approach (scheme 1).



Scheme 1

1.3.2 Results and Discussion

The chiral precursor, 5-menthyloxy-2(*5H*)-furanone **1a** was prepared from furan in two steps by known method.[5] Furan **5** on treatment with catalytic amount of titanium silicate zeolite catalyst (TS-1) and H_2O_2 in acetonitrile at 0 ^oC to room temperature underwent singlet oxidation to furnish 5-hydroxy-2(*5H*)-furanone **6** in 76 % yield. When the same reaction was carried out in methanol as a solvent, 5-methoxy-2(*5H*)-furanone **7** was formed in 68 % yield.



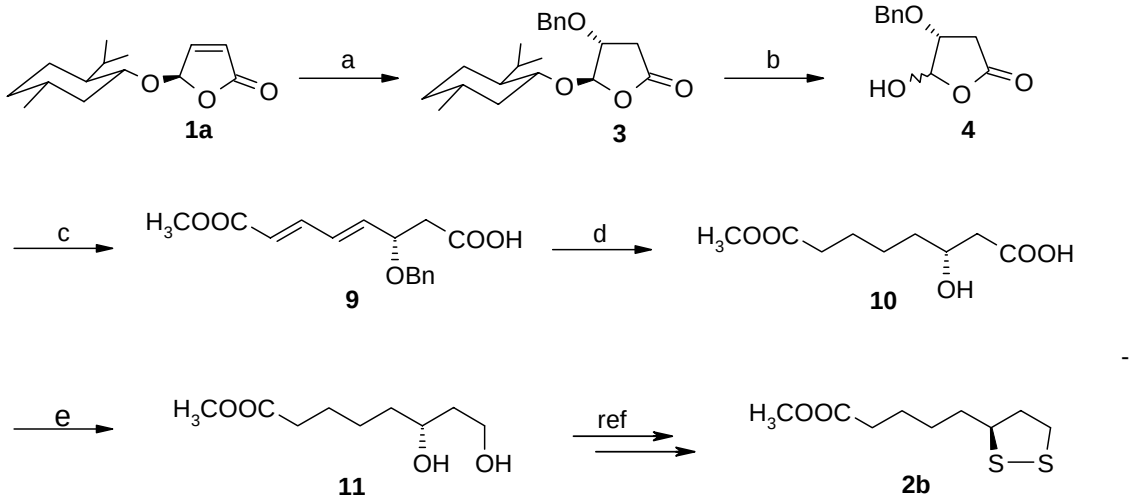
Reagents and conditions:- a) TS-I, H_2O_2, acetonitrile, 0 ^oC-RT, 8 h, 76 %; b) TS-I, H_2O_2, MeOH, 0 ^oC-RT, 8 h, 68 %; c) *l*-menthol, *p*-TSA, benzene, reflux, 12 h, 86 % (**1a+1b**).

Scheme 2

The hydroxy butenolide **6** was then refluxed with menthol in benzene in the presence of catalytic amount of p-TSA with azeotropic removal of water formed during the reaction to yield 86 % of the product containing a mixture of diastereomers **1a** and **1b** (ratio 60 : 40).[6] The diastereomeric ratio was determined from the ^1H NMR spectrum of

the product by integration of the signals of the acetal protons of **1a** and **1b** (singlets at δ 6.08 and δ 5.95 respectively).[7] The major diastereomer **1a** was obtained in enantiomerically pure form by recrystallization from light petroleum ether (bp 40-60 ^{o}C). After two crystallizations, enantiomerically pure **1a** was obtained as a white crystalline solid in 45 % yield. The crystallization process is accompanied by a remarkable "second order asymmetric transformation"[8] of **1** in solution. This "crystallization induced epimerization" is essentially driven by the continuous removal of the major crystalline isomer **1a** from the solution. The epimerization probably takes place via enolization of **1b** and **1a** to the unstable 5-*l*-menthyloxy)-2-hydroxyfuran intermediate **8**, which has lost his stereogenic center at C_5 (scheme 2). After repeated crystallizations we could obtain additional 12 % of enantiomerically pure **1a**. Thus pure **1a** was obtained in overall 57 % yield.

The diastereomer **1a** was then subjected to 1,4-addition with benzyl alcohol by known method using catalytic sodium in dry DMF at room temperature to furnish (4*R*, 5*R*)-(-)-4-benzyloxy-5-[(1*R*, 2*S*, 5*R*)-menthyloxy]-γ-butyrolactone (**3**) in 84 % yield (scheme 3).[9]

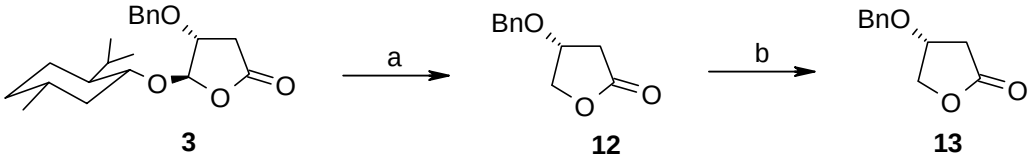


Reagents and conditions: a. BnOH, Na (catalytic), DMF, RT, 24 h, 84 %; b. 2N HCl, acetone, RT, 72 h, 78 %; c. Ph_3P=CH-CH=CH-$COOCH_3$, CH_3CN, reflux, 2h, 41 %; d. H_2, Pd-C, 1atm, RT, 6 h, 92 %; e. BMS, THF, RT, 2 h, 87 %.

Scheme 3

The product **3** was characterized by IR, ^{1}H NMR, ^{13}C NMR, melting point and optical rotation. The IR, ^{1}H NMR and ^{13}C NMR spectra were found in accordance with the reported values and also reflected the presence of only one diastereomer in the product. But unfortunately, the observed optical rotation $\{[\alpha]_{577}^{25} = -114$ (c=1, hexane)$\}$ of compound **3** was substantially less than the reported rotation $\{[\alpha]_{577}^{25} = -230$ (c=1, hexane)$\}$. This forced us to confirm the optical purity of **3** by some different means.

Accordingly, compound **3** was subjected to reduction with $NaBH_4$ in methanol which furnished 4-benzyloxy-dihydro-furan-2-one (**12**) in 57 % yield (scheme 4).



3 **12** **13**

Reagents and conditions:- a. $NaBH_4$, 0 ^{o}C-RT, 4 h, 57 %; b. H_2, Pd-C, 1atm, RT, 12 h, 42 %;

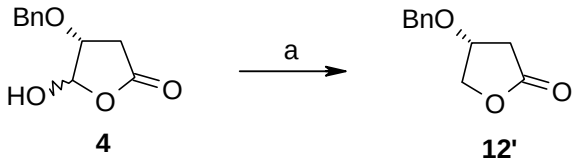
Scheme 4

The lactone **12** was characterized by ^{1}H NMR, ^{13}C NMR, and optical rotation. The observed rotation for lactone **12** was $[\alpha]_D^{22} = +28.3$ (c = 1, $CHCl_3$). The lactone **12** on catalytic hydrogenation using Pd-C gave 42 % of hydroxy lactone **13** with recovery of starting material **12** in 35 % yield**.** The observed rotation for hydroxy lactone **13** $\{[\alpha]_D^{22} = +91.4$ (c = 0.9, EtOH)$\}$ indicated that the lactone **13** was formed in almost optically pure form {lit. $[\alpha]_D = +94.0$, (c = 1.5, EtOH)}.[10] This proved that compound **3** should be present in optically pure form.

The compound **3** was then hydrolysed by stirring it with 2N HCl in acetone at room temperature for 72 h to furnish 4-benzyloxy-5-hydroxy-dihydro-furan-2-one (**4**) in 78 % yield. In this reaction chiral auxiliary *viz.*menthol was recovered in 75 % yield. The compound **4** was then subjected to Wittig olefination by heating it with the stable ylide obtained from 4-bromocrotonate[11] and triphenyl phospine in acetonitrile for 2 h to furnish 41 % of olefin acid, i.e. 6-benzyloxy-octa-2,4-dienedioic acid-1 methyl ester (**9**).[12] The olefin acid **9** on catalytic hydrogenation using Pd-C gave 92 % of saturated acid **10.** Finally the acid functionality in compound **10** was selectively reduced in the presence of

ester by using borane dimethyl sulfide complex[13] in THF to furnish 87 % of diol **11**. However, the observed rotation of diol **11** indicated that the diol was formed only with 51 % ee. { $[\alpha]_D^{25}$ = -1.99 (c = 1.1, $CHCl_3$), lit.[16] $[\alpha]_D^{25}$ = -3.9, (c = 2.3, $CHCl_3$)} (scheme 3).

This observation reflected that at some stage of the present synthetic route, racemization has occurred to some extent. To investigate this problem, we reduced compound **4** with $NaBH_4$ in methanol to furnish lactone **12'** in 40 % yield (scheme 5).



4 **12'**

Reagents and conditions:- a) $NaBH_4$, 0 ^oC-RT, 3 h, 40 %.

Scheme 3

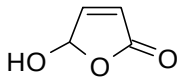
The observed rotation of this lactone **12'** {+17.2 (c = 1, $CHCl_3$)} indicated that the lactone **12'** was formed with only 61 % ee. {$[\alpha]_D$ = +28.3, (c = 1.0, $CHCl_3$) for lactone **12**}. This proved that during hydrolysis of compound **3**, the epimerization has occurred to some extent leading to the decrease in ee of the final product. The diol **11** is a known intermediate which could be converted into lipoic acid by known method.[14] This constitutes a formal synthesis of lipoic acid.

1.3.3 Conclusion

The synthesis of (6*S*)-(-)-methyl-6,8-dihydroxy octanoate (**11)** has been achieved with 51 % ee using chiral butenolide approach. The chiral auxiliary alcohol menthol has been recovered with 75 % yield. This diol **11** could be converted into (*S*)-(-)- α-Lipoic acid by known method. Thus it provides a simple synthetic route for the synthesis of (*S*)-(-)- α-Lipoic acid with moderate enantiomeric excess. However by proper choice of reagents and conditions where there is no epimerization, this protocol would be of immense potential value.

1.3.4 Experimental

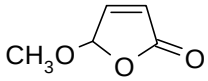
1) 5-Hydroxy 2 (*5H*)-furanone (6)



Procedure: To a cooled solution (0 ^{o}C) of furan **5** (25 g, 0.368 mol) in acetonitrile (250 ml), was added TS-I catalyst (5 g) and stirred for 10 min at 0 ^{o}C. Then 30 % H_2O_2 (70 ml, 0.618 mol, 1.68 equiv.) was added dropwise and the mixture was stirred for 8 h and allowed to attain room temperature gradually. The catalyst was filtered off, the filtrate was concentrated at room temperature under reduced pressure, extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered, solvent was removed under vacuum and the residue was purified by column chromatography (Pet. Ether : EtOAc = 60 : 40) to yield 5-Hydroxy 2 (5*H*)-furanone (**6**) as a white solid (28 g, 76 %).

Molecular Formula	:	$C_4H_4O_3$
Yield	:	76 %
M. P.	:	57-58.5 ^{o}C (lit.[15] Mp = 58.0-59.0 ^{o}C)
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 7.34 (d, J=5.4 Hz, 1H), 6.26 (s, 1H), 6.22 (d, J=5.4 Hz, 1H), 4.88 (bs, 1H).

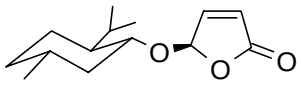
2) 5-methoxy 2 (*5H*)-furanone (7)



Procedure: To a cooled solution (0 ^{o}C) of furan (20 g, 0.294 mol) in methanol (200 ml) was added TS-I catalyst (4 g) and stirred for 10 min at 0 ^{o}C. Then 30 % H_2O_2 (56 ml 0.470 mol) was added dropwise and the mixture was stirred for 8 h and allowed to warm at room temperature. The catalyst was filtered off, the filtrate was concentrated at room temperature under reduced pressure, extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered, solvent was removed under vacuum and the residue was distilled under reduced pressure to give 5-methoxy 2 (5*H*)-furanone as a colourless liquid (23 g, 68 %).

Molecular Formula	:	$C_5H_6O_3$
Yield	:	68 %
B. P.	:	70 ^oC at 2 mm of Hg, (lit bp = 70-72 ^oC at 2 mm of Hg).
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 7.20 (dd, *J* = 5.9 Hz, 1.5 Hz, 1H), 6.24 (dd, *J* = 5.9 Hz, 1.0 Hz, 1H), 5.84 (dd, *J* = 1.5 Hz, 1.0 Hz, 1H), 3.58 (s, 3H).

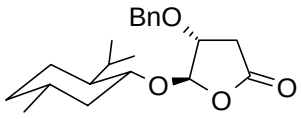
3) (5R)-5 (*l*-Menthyloxy)-2 (5*H*)-furanone (1a)



Procedure: The mixture of 5-hydroxy 2 (5*H*)-furanone (**6**) (20 g, 0.2 mol), menthol (29.6 g, 0.19 mol) and catalytic amount of *p*-TSA (190 mg, 1 mmol) was taken in benzene and refluxed for 20 h with azeotropic removal of water. The reaction mixture was cooled to room temperature and washed with water and brine. The solvent was removed under vacuum and the residue was purified by column chromatography (Pet. Ether : EtOAc = 99 : 1) to yield mixture of diastereomers in the ratio 60:40 in 86 % yield. After repeated recrstallizations from light petroleum ether at –23 ^oC, diastereomerically pure **1a** was obtained in 52 % yield.

Molecular Formula	:	$C_{14}H_{22}O_3$
Yield	:	86 % (60 : 40 mixture, 52 % enantiomerically pure **1a**)
M. P.	:	70.2 ^oC (lit.[7] Mp = 70.5-70.7 ^oC)
$[\alpha]_D^{25}$	:	-135.8 (c=1, ab. ethanol). {lit.[7] $[\alpha]_D$ = -136.4, (c=1, ab. ethanol)}.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 7.15 (dd, *J* = 1.0 Hz, 5.8 Hz, 1H), 6.20 (dd, *J* = 1.0 Hz, 5.8 Hz, 1H), 6.08 (s, 1H), 3.65 (dt, *J* = 4.4 Hz, 10.3 Hz, 1H), 2.02-2.18 (m, 2H), 1.63-1.72 (m, 2H), 1.18-1.41 (m, 2H), 0.85-1.15 (m, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 7.3 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR ($CDCl_3 + CCl_4$, 50MHz)	:	138.4 (s), 136.4 (s), 129.0 (d0, 128.3 (d), 126.5, (d), 112.9 (d), 47.6 (s), 44.4 (t), 30.9 (q), 26.5 (t).

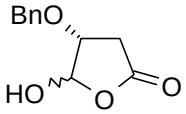
4. (4*R*, 5*R*)-(-)-4-Benzyloxy-5-[(1R, 2S, 5R)-menthyloxy]-γ-butyrolactone (3)



Procedure: To a stirred solution of benzyl alcohol (2 ml) in DMF (5 ml) was added a catalytic amount of metallic sodium (10 mg, 0.42 mmol). As soon as the sodium disappeared, (5*R*)-5 (*l*-menthyloxy)-2 (5*H*)-furanone (**1a**) (1.0 g, 4.2 mmol) was added and the resulting red solution was stirred at room temperature for 24 h.. Then the reaction mixture was dissolved in ether and washed with water, brine and dried over anhydrous sodium sulfate. The ether layer was then filtered and the removal of the solvent afforded the crude product which was purified by column chromatography (Pet. Ether : EtOAc = 98.5 : 1.5). The product was recrystallized from hexane to yield 1.220 g of (4*R*, 5*R*)-(-)-4-benzyloxy-5-[(1*R*, 2*S*, 5*R*)-menthyloxy]-γ-butyrolactone (**3**) as a white solid.

Molecular Formula	:	$C_{21}H_{30}O_4$
Yield	:	84 %
M. P.	:	86 ^oC (lit.[9] mp: 86-87 ^oC) (white solid)
$[\alpha]_{577}^{25}$	:	-114 (c=1, hexane). {lit.[9] $[\alpha]_{578}^{20}$ = -230, (c=1, hexane)
IR ($CHCl_3$, cm^{-1})	:	3021, 2956, 2926, 2870, 1789, 1115, 756.
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 7.24-7.43 (m, 5H), 5.57 (s, 1H), 4.58 (s, 2H), 4.04 (dd, *J* = 5.9 Hz, 1.8 Hz, 1H), 3.53 (dt, *J* = 10.7 Hz, 4.4 Hz, 1H), 2.79 (dd, *J* = 18.0 Hz, 5.9 Hz, 1H), 2.51 (dd, *J* = 18.0 Hz, 1.8 Hz, 1H), 1.91-2.10 (m, 2H), 1.62-1.80 (m, 2H), 1.13-1.52 (m, 2H), 0.76-0.98 (m, 12H).
^{13}C NMR ($CDCl_3$, 50MHz)	:	δ = 174.1 (s), 137.0 (s), 128.4 (d), 127.9 (d), 127.6 (d), 102.6 (d), 78.4 (d), 76.6 (d), 71.5 (t), 47.6 (d), 39.5 (t), 34.1 (t), 31.2 (d), 25.4 (d), 23.0 (t), 22.1 (q), 20.7 (q), 15.5 (q).

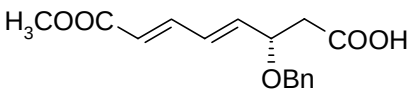
5. 4-Benzyloxy-5-hydroxy-dihydro-furan-2-one (4)



Procedure: To a mixture of (*4R, 5R*)-(-)-4-benzyloxy-5-[(*1R, 2S, 5R*)-menthyloxy]-γ-butyrolactone (**3**) (1.00 g, 2.88 mmol) in acetone (10 ml) was added HCl (2 N, 1 ml) slowly at 0 ^{o}C and stirred at room temperature for 72 h. Then water (2 ml) was added to the reaction mixture and acetone was removed under vacuum at room temperature. The residue was extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The organic solvent was removed under vacuum at room temperature and the residue was purified by column chromatography (Pet. Ether : Ethyl acetate = 60 : 40) to furnish pure product (479 mg, 78 % yield).

Molecular Formula	:	$C_{11}H_{12}O_4$
Yield	:	78 %
B. P.	:	Viscous liquid.
$[\alpha]_D^{25}$	:	-9.29 (c=1.02, acetone)
IR (neat, cm^{-1})	:	3385, 2934, 1785, 1365, 1118, 1078, 973.
^{1}H NMR ($CDCl_3$, 200MHz)	:	δ = 7.34 (m, 5H), 5.80 (s, 1H), 4.57 (d, *J* = 2.4 Hz, 2H), 5.15 (bs, 1H), 4.10 (dd, *J* = 2.0 Hz, 5.9 Hz, 1H), 2.91 (dd, *J* = 5.9 Hz, 18.1 Hz, 1H), 2.56 (dd, *J* = 2.0 Hz, 18.1 Hz, 1H).
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz)	:	δ = 176.1 (s), 136.8 (s), 128.3 (d), 127.8 (d), 127.6 (d), 101.8 (d), 78.7 (d), 71.2 (t), 34.1 (t).
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	:	m/z = 226.04 ($M + NH_4^+$)

6. **6-Benzyloxy-octa-2,4-dienedioic acid-1 methyl ester (9)**

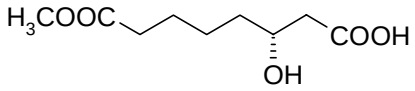


Procedure: The mixture of compound (100 mg, 0.481 mmol) and ylide (260 mg, 0.721 mmol) in acetonitrile (5 ml) was refluxed for 2 h. The reaction was monitered by TLC

and after the completion of the reaction, solvent was removed under vacuum and the residue was purified by flash column chromatography (Pet. Ether : Ethyl Acetate = 75 : 25) to yield the pure product (41 %).

Molecular Formula	:	$C_{16}H_{18}O_5$
Yield	:	41 %
B. P.	:	Viscous liquid.
$[\alpha]_D^{25}$	:	+1.98 (c = 1.00, $CHCl_3$)
IR (neat, cm^{-1})	:	3400, 3021, 1715, 1438, 757.
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 7.23-7.37 (m, 6H), 6.42 (dd, *J* = 15.6 Hz, 10.7 Hz, 1H), 5.90-6.12 (m, 2H), 4.40-4.57 (m, 3H), 3.77 (s, 3H), 2.53-2.62 (m, 2H).
^{13}C NMR ($CDCl_3$ + CCl_4 , 50MHz)	:	δ = 175.5 (s), 167.2 (s), 143.3 (d), 140.4 (d), 137.5 (s), 130.5 (d), 128.4 (d), 127.8 (d), 122.2 (d), 106.8 (d), 75.2 (d), 71.2 (t), 51.6 (q), 40.5 (t).
MS (ESI, Solv.: MeOH + H_2O + CH_3COONH_4)	:	m/z = (308.04, M + NH_4^+)

7. **3-Hydroxy octanedioic acid-8-methyl ester (10)**

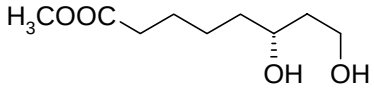


Procedure :- The olefin acid **9** (120 mg, 0.414 mmol) was taken in methanol (15 ml) and catalytic amount of Pd-C (10 %) was added to it and the reaction was stirred at room temperature under hydrogen atmosphere (1 atm pressure) for 6 h. Then the reaction mixture was filtered and methanol was removed under vacuum. The residue was then purified by flash column chromatography (Pet. Ether : Ethyl Acetate = 80 : 20) to yield the pure product (77 mg).

Molecular Formula	:	$C_9H_{16}O_5$
Yield	:	92 %
B. P.	:	Viscous liquid.
$[\alpha]_D^{25}$	:	-3.76 (c = 0.85, $CHCl_3$)

^{1}H NMR (CDCl$_3$, 200MHz)	:	δ = 6.80 (bs, 1H), 4.00-4.04 (m, 1H), 3.65 (s, 3H), 2.47 (t, *J* = 8.3 Hz, 2H), 2.31 (t, *J* = 6.8 Hz, 2H), 1.30-1.76 (m, 6H).

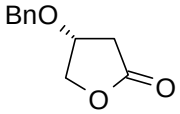
8. (6*S*)-(-)-Methyl-6,8-dihydroxy octanoate (11)



Procedure:- To a solution of acid **10** (60 mg, 0.317 mmol) in THF (4 ml), borane dimethyl sulfide complex (0.120 ml, 1.27 mmol) in THF (2 ml) was added slowly at 0 ^{o}C and then stirred at room temperature for 2 h. The reaction was quenched with saturated ammonium chloride and THF was removed under vacuum. The residue was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was then purified by flash column chromatography (Pet Ether. : Ethyl Acetate. = 85 : 15) to yield the pure product.

Molecular Formula	:	$C_9H_{18}O_4$
Yield	:	87 %
B. P.	:	Viscous liquid.
$[\alpha]_D^{25}$	:	-1.99 (c = 1.1, $CHCl_3$), {lit.^{16} $[\alpha]_D^{25}$ = -3.9, (c = 2.3, $CHCl_3$)}
^{1}H NMR (CDCl$_3$, 200MHz)	:	δ = 3.75-3.95 (m, 2H), 3.66 (s, 3H), 2.91-3.12 (m, 1H), 2.32 (t, *J* = 7.3 Hz, 2H), 1.35-1.79 (m, 8H).

9. **4-benzyloxy-dihydro-furan-2-one (12)**



Procedure:-

A. From (*4R, 5R*)-(-)-4-Benzyloxy-5-[(*1R, 2S, 5R*)-menthyloxy]-γ- butyrolactone (3)

To a solution of (*4R, 5R*)-(-)-4-benzyloxy-5-[(*1R, 2S, 5R*)-menthyloxy]-γ-butyrolactone (**3**) (450 mg, 1.297 mmol) in methanol (10 ml) was added $NaBH_4$ (240 mg, 5 equiv.) slowly at 0 oC and the reaction mixture was stirred for 4 h and then it was

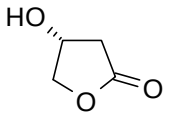
brought to room temperature slowly. The reaction was quenched with dil HCl (2N) and methanol was removed under vacuum. The residue was extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by flash column chromatography (Pet. Ether. : EtOAc = 80 : 20) to yield the pure product (141 mg).

B. From 4-benzyloxy-5-hydroxy-dihydro-furan-2-one (4)

To a solution of 4-benzyloxy-5-hydroxy-dihydro-furan-2-one (**4**) (75 mg, 0.361 mmol) in methanol (10 ml) was added $NaBH_4$ (54 mg, 1.44 mmol, 4 equiv.) slowly at 0 ^oC and the reaction mixture was stirred for 3 h and then it was brought to room temperature slowly. The reaction was quenched with dil HCl (2N) and methanol was removed under vacuum. The residue was extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under vacuum and the residue was purified by flash column chromatography (Pet. Ether : EtOAc = 80 : 20) to yield the pure product (28 mg).

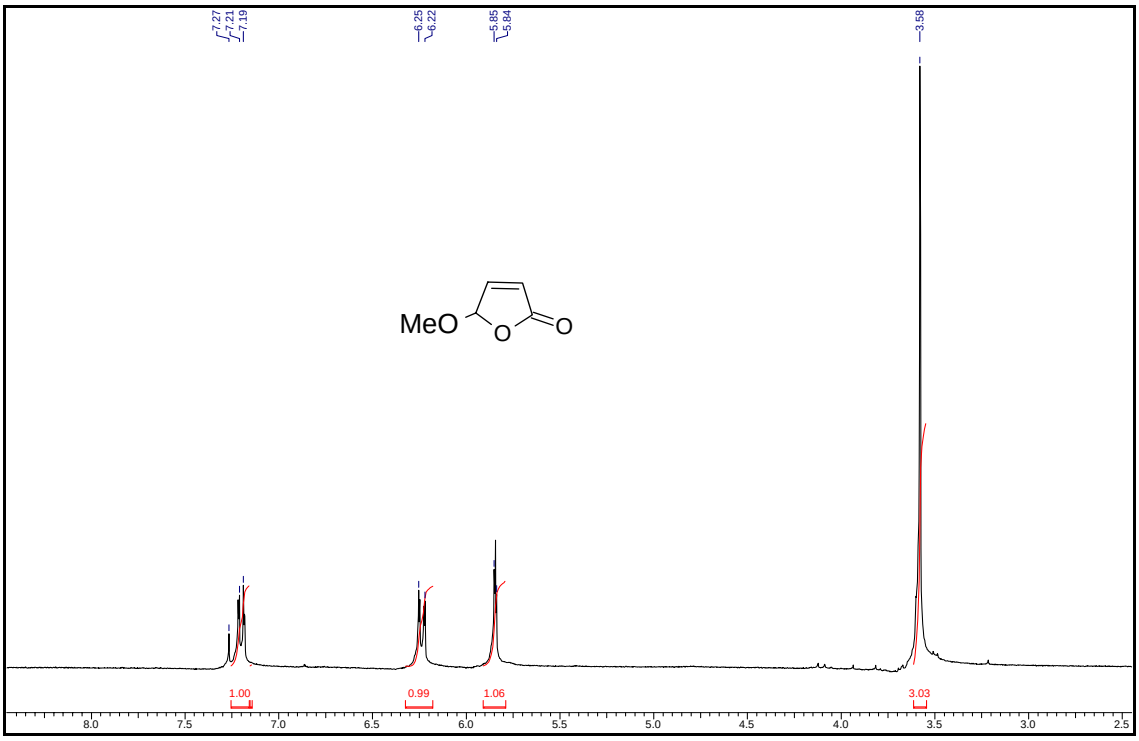
Molecular Formula	:	$C_{11}H_{12}O_3$
Yield	:	57 % by Method A
		40 % by Method B
$[\alpha]_D^{25}$	:	+28.3 (c = 1, $CHCl_3$) by Method A (Compound **12**)
		+17.2 (c = 1, $CHCl_3$) by Method B (Compound **12'**)
		{lit.[10] $[\alpha]_D$ = 29.0, (c = 1, $CHCl_3$).
^1H NMR	:	δ = 7.23-7.46 (m, 5H), 4.55 (d , *J* = 2.7 Hz, 2H), 4.32-
($CDCl_3$, 200MHz)		4.42 (m, 3H), 2.60-2.69 (m, 2H).
^{13}C NMR	:	δ = 175.3 (s), 136.9 (s), 128.4 (d), 127.9 (d), 127.5 (d),
($CDCl_3$ + CCl_4 , 50MHz)		73.7 (d), 72.8 (t), 70.9 (t), 34.7 (t).

10. **4-Hydroxy-dihydro-furan-2-one (13)**

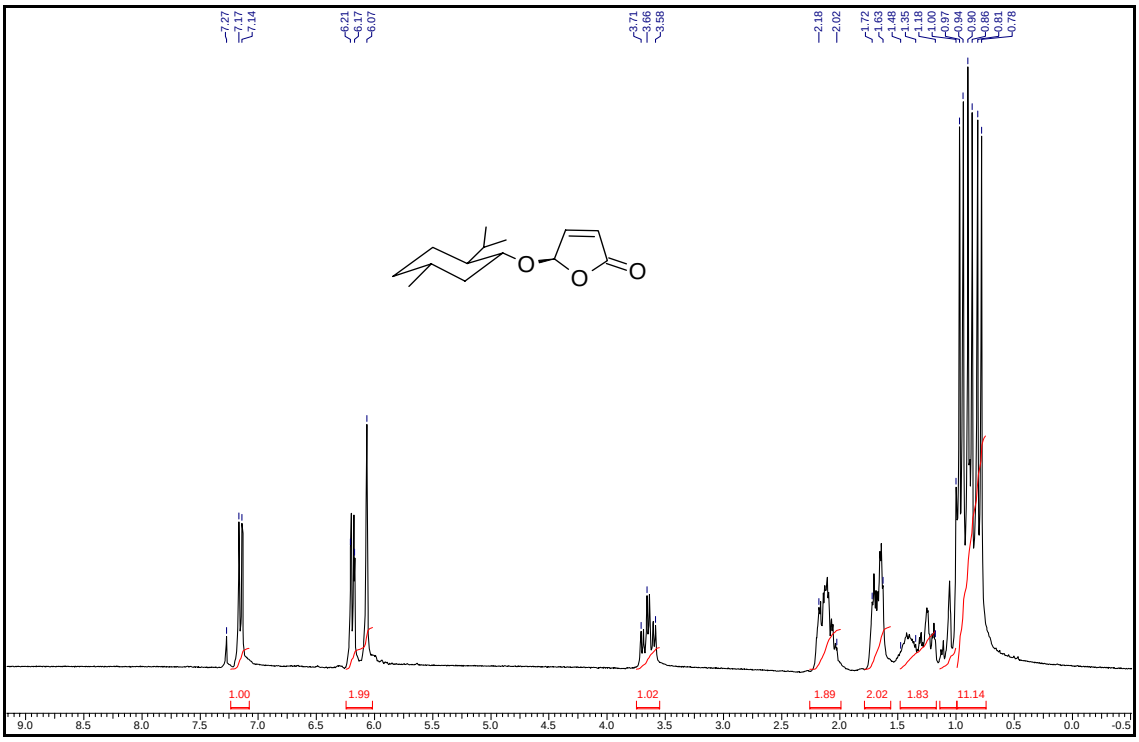


Procedure:- The lactone **12** (60 mg, 0.313 mmol) was taken in methanol (15 ml) and catalytic amount of Pd-C (10 %) was added to it and the reaction was stirred at room temperature under hydrogen atmosphere (1 atm pressure) for 12 h. Then the reaction mixture was filtered and methanol was removed under vacuum. The residue was then purified by flash column chromatography (Pet. Ether : Ethyl Acetate = 80 : 20) to yield the pure product (13 mg).

Molecular Formula	:	$C_4H_6O_3$
Yield	:	42 %
$[\alpha]_D^{25}$	:	+91.4 (c = 0.9, EtOH)
		{lit. $[\alpha]_D$ = +94.0, (c = 1.5, EtOH)}[10]
^{1}H NMR	:	δ = 4.64-4.73 (m, 1H), 4.25-4.47 (m, 2H), 2.76 (dd, *J* =
($CDCl_3$, 200MHz)		17.6 Hz, 5.9 Hz, 1H), 2.51 (dd, *J* = 17.6 Hz, 2.4 Hz, 1H).

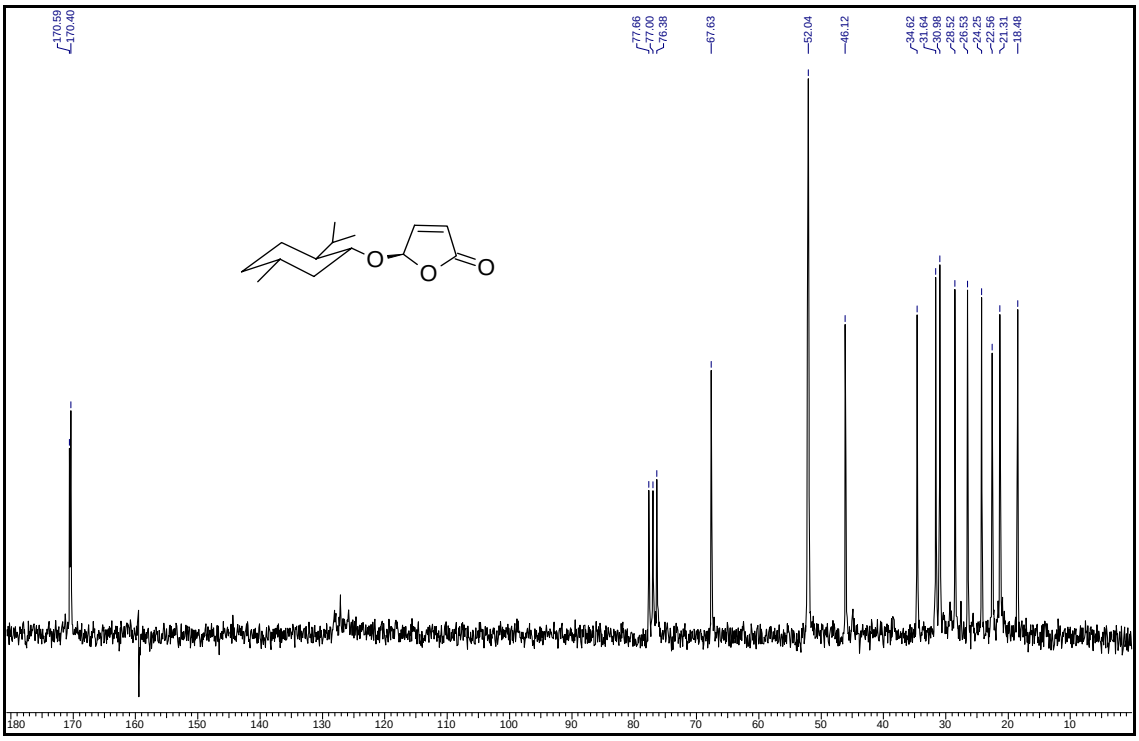


^{1}H NMR spectrum of 5-methoxy 2 (*5H*)-furanone (7) ($CDCl_3$, 200 MHz)



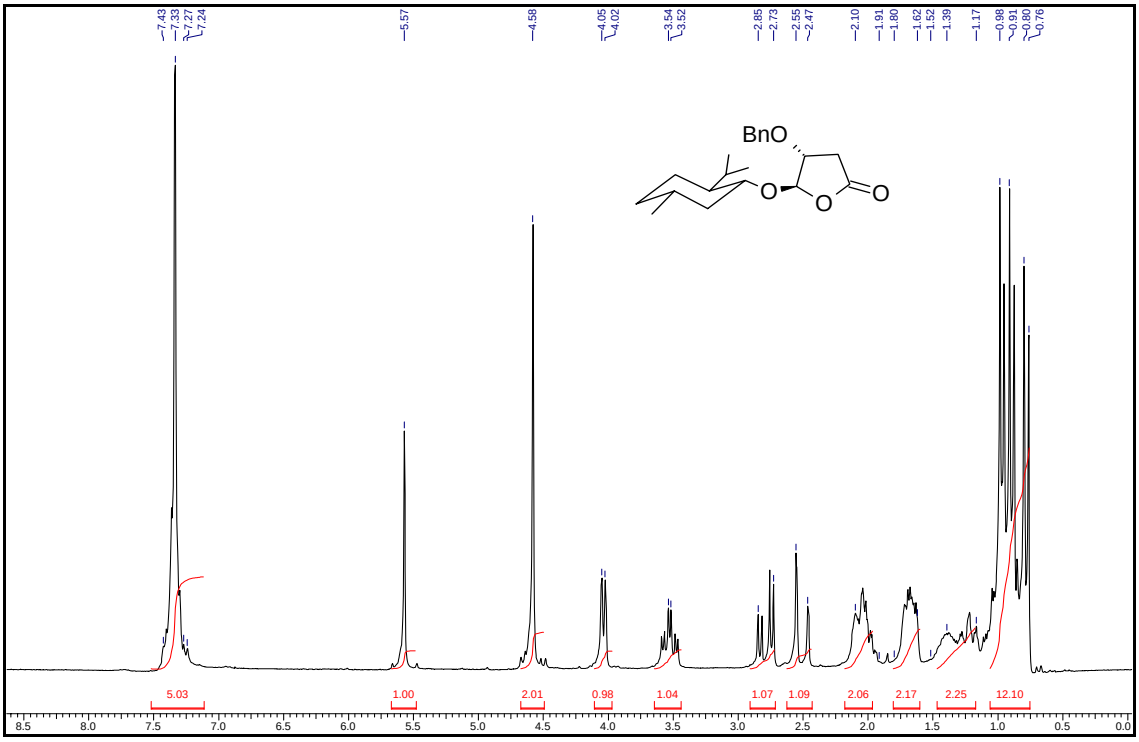
^{1}H NMR spectrum of (*5R*)-5 (*l*-menthyloxy)-2 (*5H*)-furanone (1a)

($CDCl_3$ + CCl_4, 200MHz)

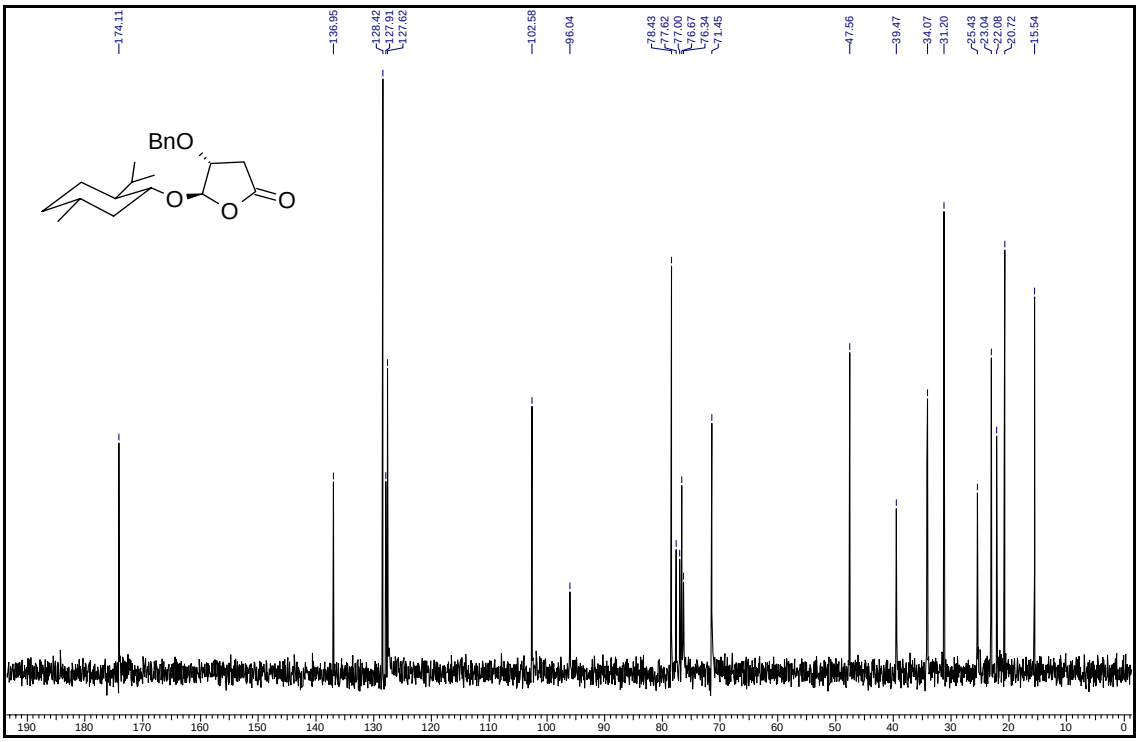


^{13}C NMR spectrum of (*5R*)-5 (*l*-menthyloxy)-2 (*5H*)-furanone (1a)

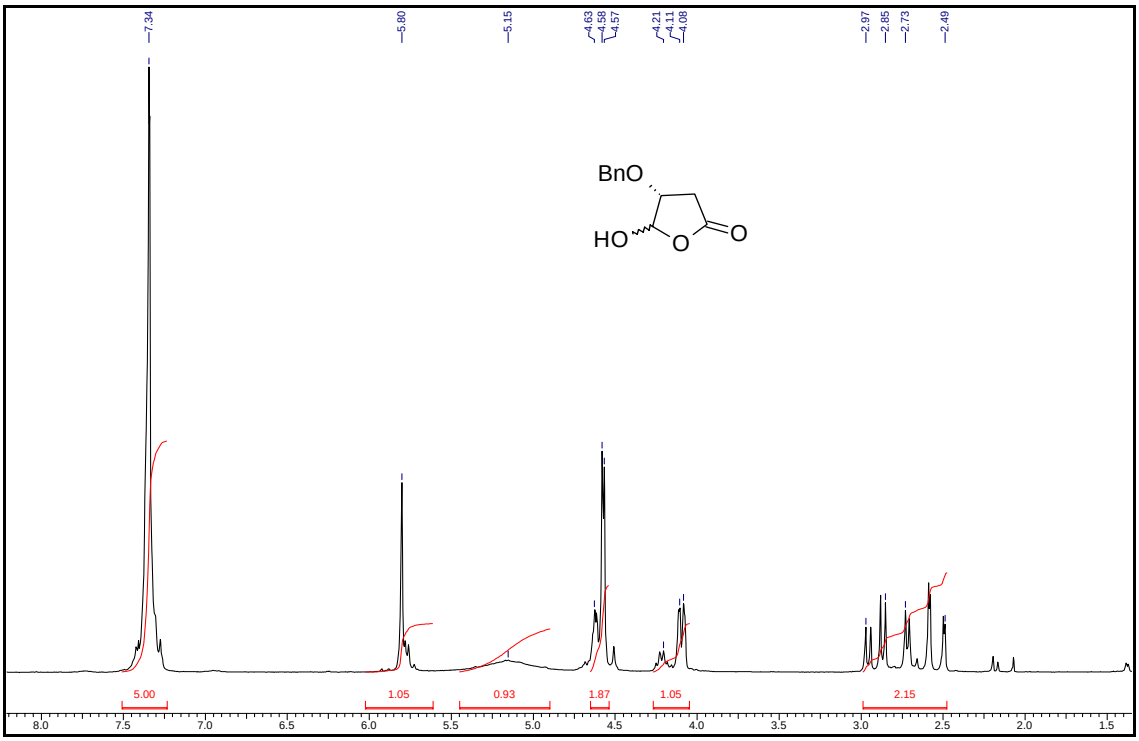
($CDCl_3$ + CCl_4, 50MHz)



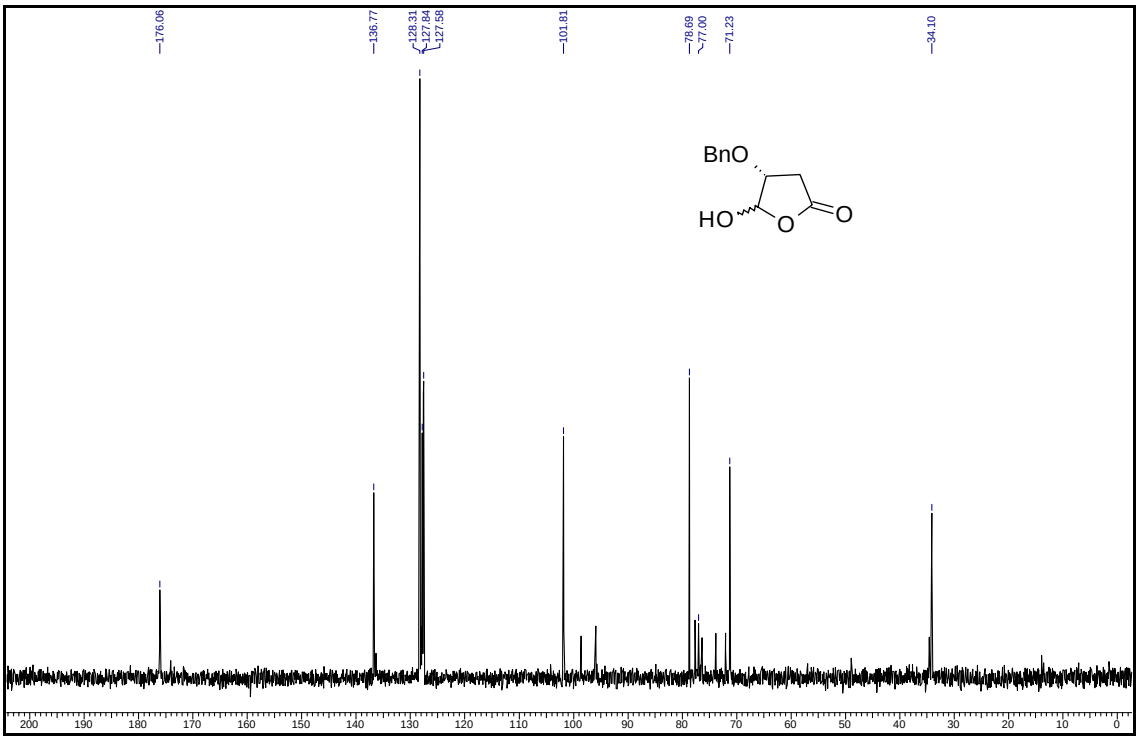
^{1}H NMR spectrum of (*4R, 5R*)-(-)-4-benzyloxy-5-[(*1R, 2S, 5R*)-menthyloxy]-γ-butyrolactone (3) ($CDCl_3$ + CCl_4, 200MHz)



^{13}C NMR spectrum of (*4R, 5R*)-(-)-4-benzyloxy-5-[(*1R, 2S, 5R*)-menthyloxy]-γ-butyrolactone (3) ($CDCl_3$ + CCl_4, 50MHz)

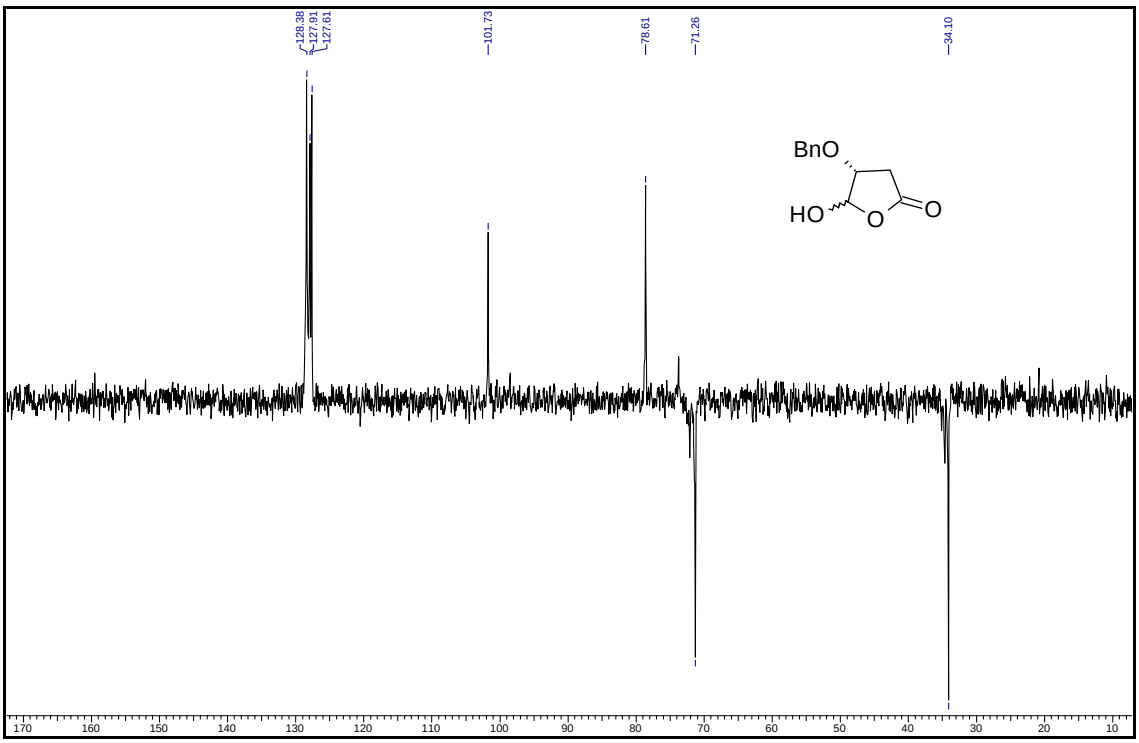


^{1}H NMR spectrum of 4-benzyloxy-5-hydroxy-dihydro-furan-2-one (4) ($CDCl_3$ + CCl_4, 200MHz)



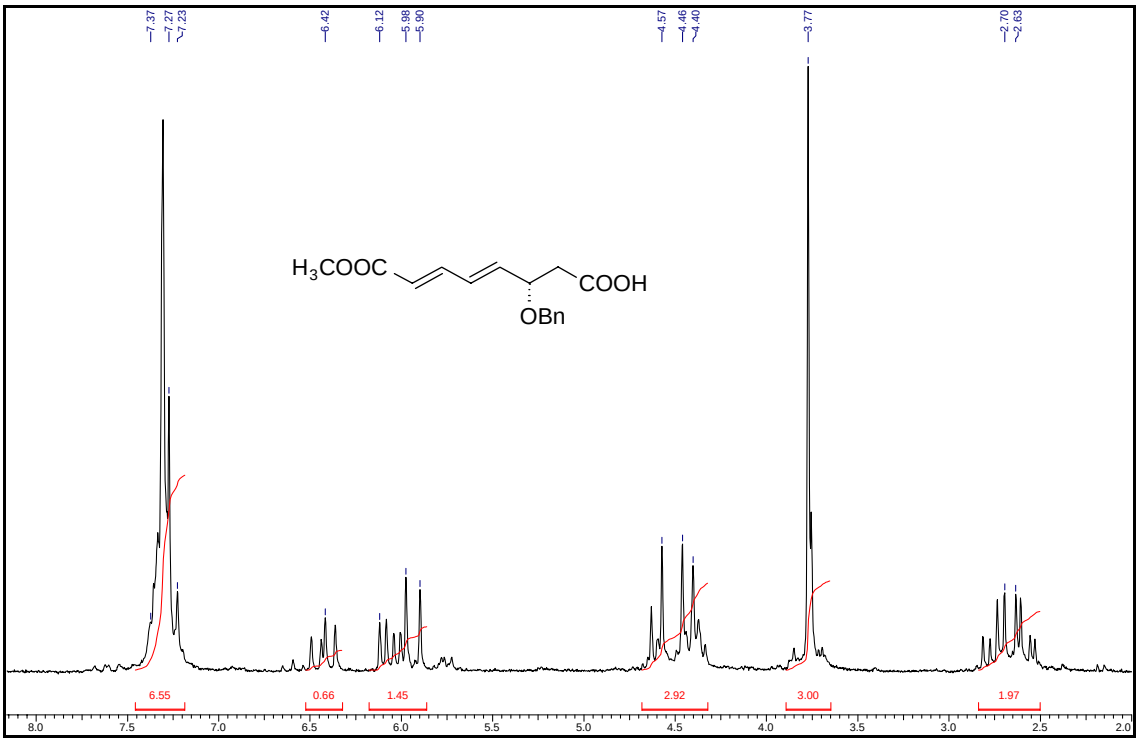
^{13}C NMR spectrum of 4-benzyloxy-5-hydroxy-dihydro-furan-2-one (4)

($CDCl_3$ + CCl_4, 50MHz)



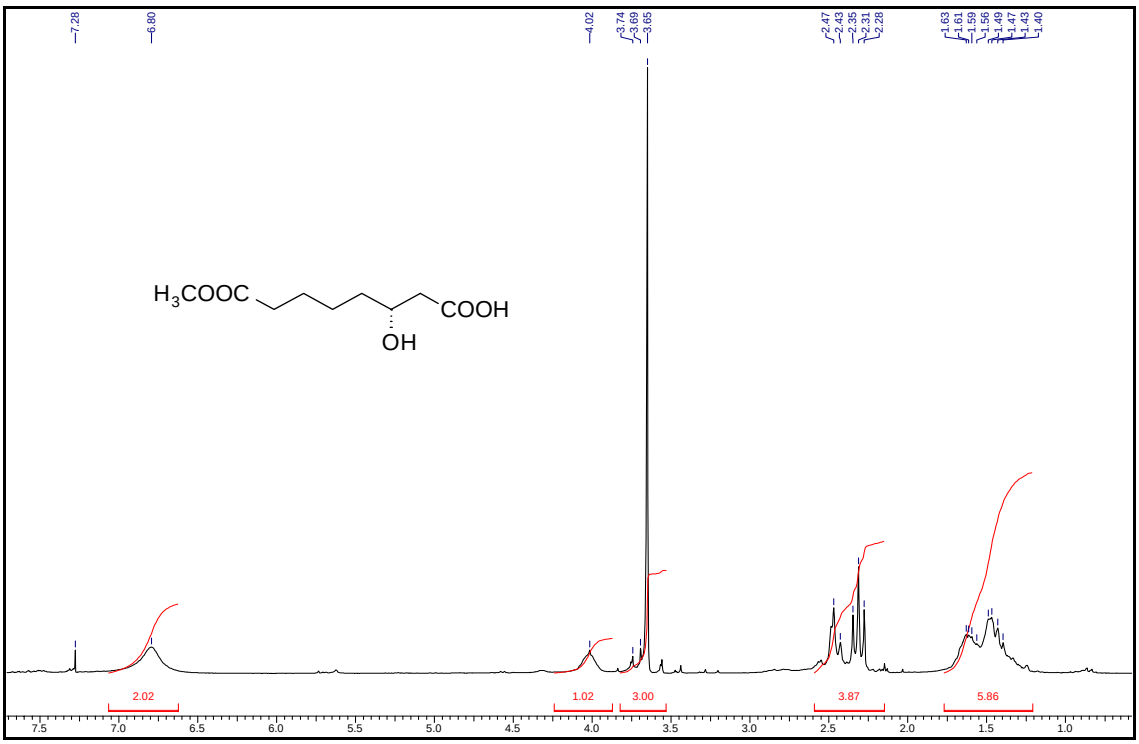
DEPT spectrum of 4-benzyloxy-5-hydroxy-dihydro-furan-2-one (1)

($CDCl_3$ + CCl_4, 50MHz)



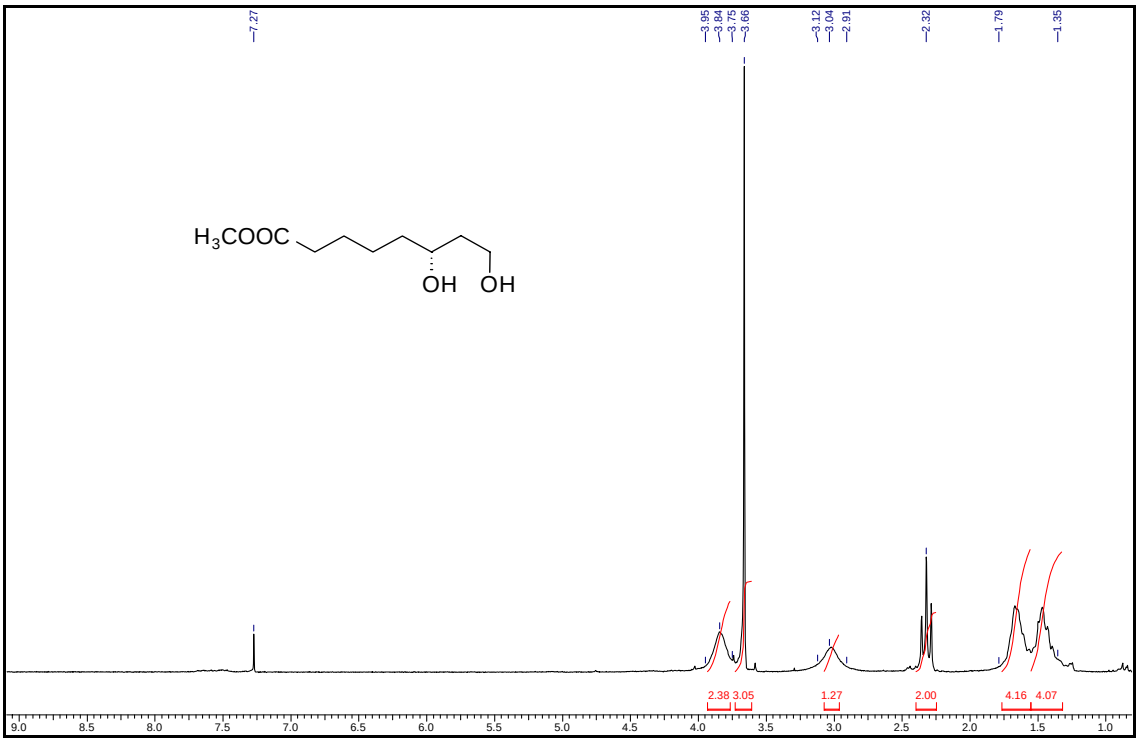
^{1}H NMR spectrum of 6-benzyloxy-octa-2,4-dienedioic acid-1 methyl ester (9)

($CDCl_3$ + CCl_4, 200 MHz)



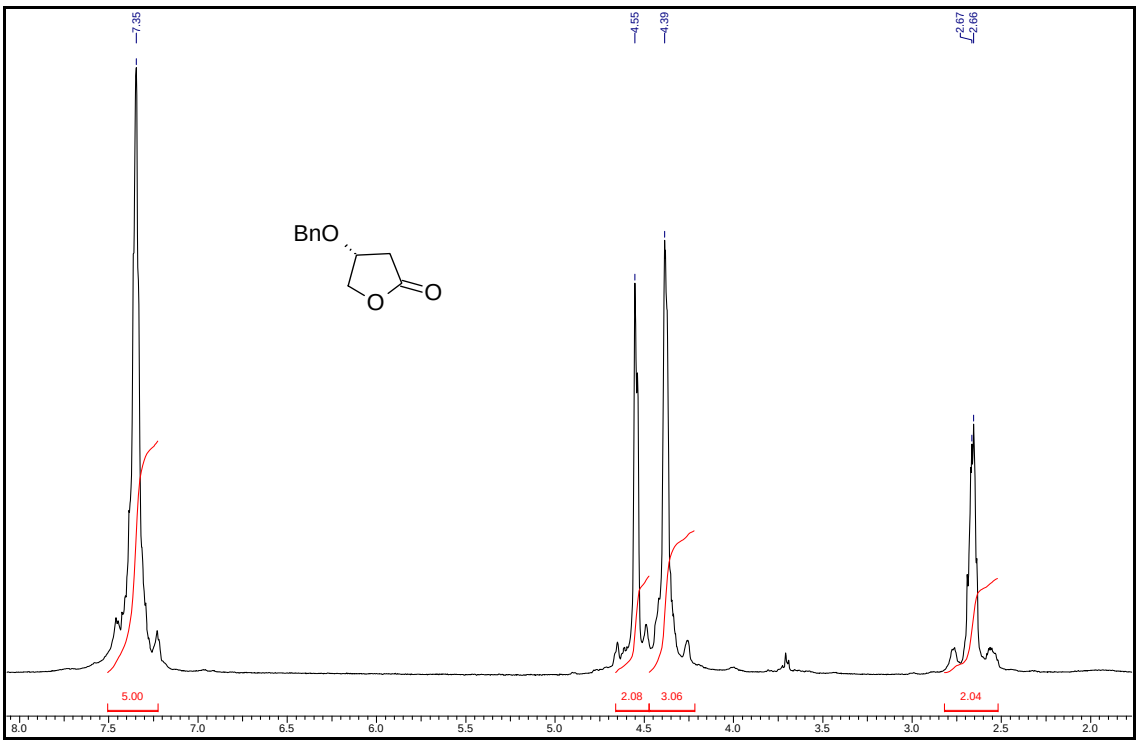
^{1}H NMR spectrum of 3-hydroxy octanedioic acid-8-methyl ester (10)

($CDCl_3$ + CCl_4, 200 MHz)



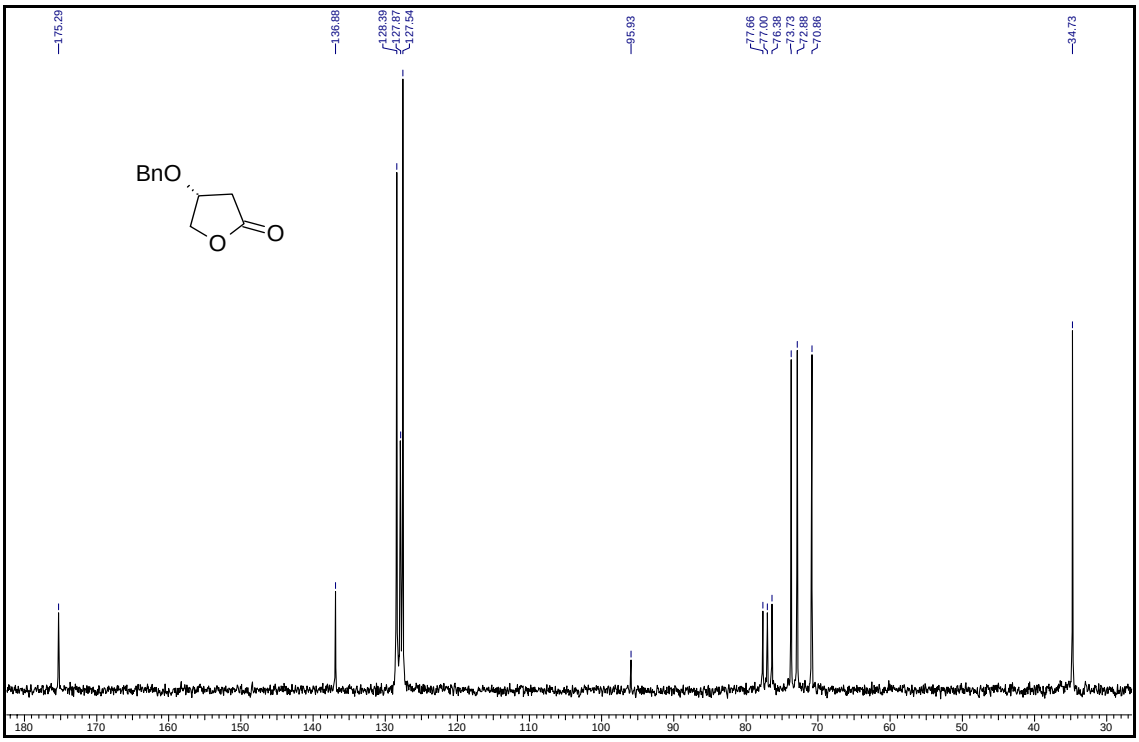
^{1}H NMR spectrum of methyl 6,8-dihydroxy octanoate (11)

($CDCl_3$ + CCl_4, 200 MHz)



^{1}H NMR spectrum of 4-benzyloxy-dihydro-furan-2-one (12)

($CDCl_3$ + CCl_4, 200MHz)



^{13}C NMR spectrum of 4-benzyloxy-dihydro-furan-2-one (12)

($CDCl_3$ + CCl_4, 50 MHz)

1.3.4 References

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CHAPTER-2

SECTION 1

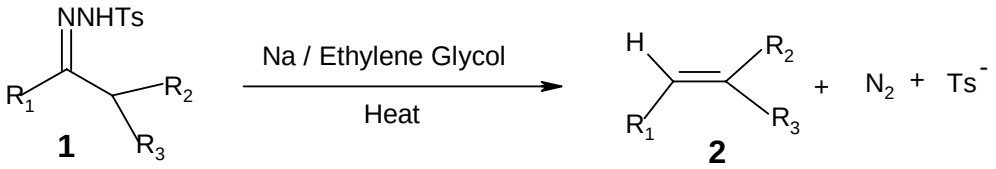
Highly Regioselective Decomposition of Tosylhydrazones Using NaOH as a Base

2.1.1 Introduction

In 1898 Curtius and Lorenzen[1] reported that benzene sulfonyl chloride reacted with hydrazine that cleanly condensed with benzaldehyde or acetone forming the crystalline (phenylsulfonyl) hydrazone derivatives. These workers noted the acidity of these substances associated with *N*-H proton adjacent to the electron withdrawing phenyl sulfonyl group and their instability. These compounds on heating underwent decomposition to give readily expelled benzene sulfinic acid and nitrogen. These observations were first applied in a useful synthetic procedure by Bamford and Stevens after 54 years.[2]

Bamford–Stevens Reaction

Ketones condense readily with (4-tolylsulfonyl) hydrazine to give the invariably crystalline (4-tolylsulfonyl) hydrazones commonly known as tosylhydarzones. These derivatives contain an array of acidic functionality. In 1952, Bamford and Stevens observed that tosylhydrazones of aliphatic ketones **1** furnished alkenes **2** on treatment with sodium salt of ethylene glycol in boiling ethylene glycol. In addition to the alkene, molecular nitrogen and *p*-toluenesulfinate anion were produced (scheme 1).



R_1, R_2, R_3 = alkyl or H; Ts = *p*-CH_3-$C_6H_4SO_2$

Scheme 1

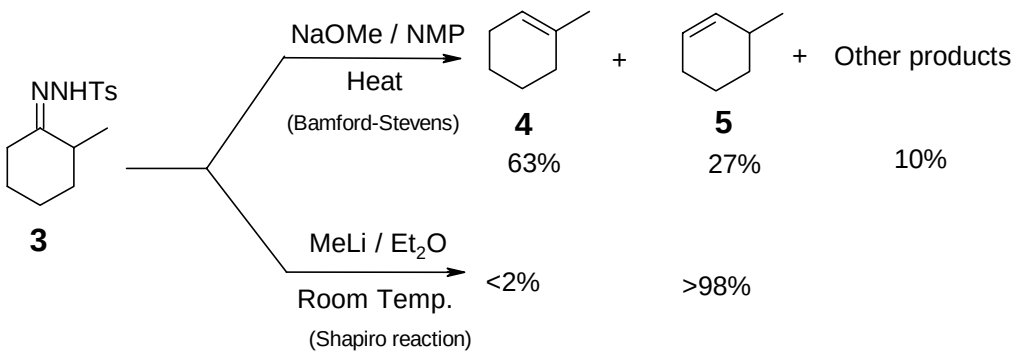
The protic reaction is defined as the reaction of a tosylhydrazone with strong base in a protic solvent i.e. the original Bamford–Stevens conditions. The solvent most commonly employed is ethylene glycol (EG), but higher boiling glycols like diethylene glycol (DEG) have also been used. The base is prepared by dissolving metallic sodium in

the solvent before the tosylhydrazone is added or commercial sodium methoxide may be added to the tosylhydrazone dissolved or suspended in the solvent.

The aprotic reaction employs a solvent of little or no proton donating ability. Diglyme (diethylene glycol dimethyl ether) is typical, but other high boiling ethers such as diethyl carbitol (diethylene glycol diethyl ether DEC), hydrocarbons (e.g. decalin) and *N,N*-disubstituted amides (e.g. *N*-methylpyrrolidene, NMP) have been used with success. Even acetamide is a reliable "aprotic" solvent. In the reactions employing acetamide as the solvent, it is convenient to prepare the base *in situ* by the dissolution of the metallic sodium, as is done with ethylene glycol. The most common base employed in the aprotic reaction is sodium methoxide, but other alkoxides as well as sodium and lithium hydride have been used ocassionally. Lithium aluminum hydride[3] and sodium amide[4] have been tested and found to be less satisfactory.

Shapiro Reaction

A different course is followed when a tosylhydrazone bearing a α-hydrogen atom is allowed to react with alkyl lithium reagent. In such reactions an unrearranged, less substituted alkene is almost always exclusive product.[5] To illustrate the utility of this reaction and to contrast it with the protic and aprotic Bamford and Stevens reaction, the following example is shown (scheme 2). 2-Methyl cyclohexanone tosylhydarzone **3** yields the more substituted alkene, 1-methyl cyclohexene **4** as the major product upon treatment with sodium methoxide in *N*- methyl pyrrolidene[6] whereas the less substituted alkene, 3-methyl cyclohexene **5**, is the dominant product with methyl lithium in ether.[7]



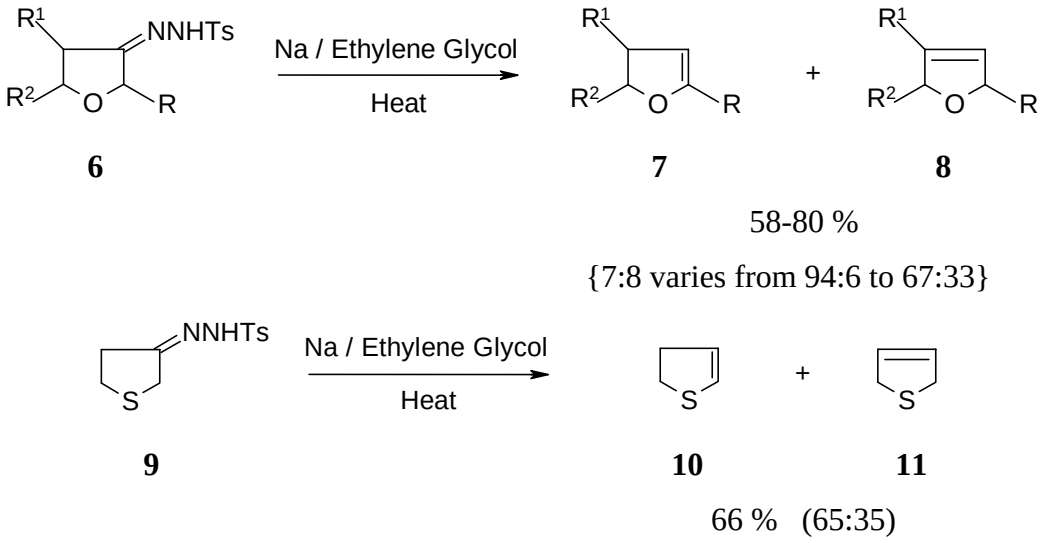
Scheme 2

Both the protic Bamford–Stevens reaction and ketone reduction followed by dehydration of the corresponding alcohol involve two steps from ketone to olefin. Although the yield of alkene from tosylhydrazone is often poor, in some cases it is still the more convenient and hence preferred route.

There are few other reports wherein tosylhydrazones are decomposed to give olefins.

1. Gianturco *et al*[8] reported an excellent procedure for the synthesis of 2, 3-dihydrofurans using Bamford-Stevens reaction (scheme 3). The tosylhydrazones of tetrahydrofuran-3-ones **6** on treatment with sodium in ethylene glycol at 140-170 ^{o}C resulted in the formation of 2, 3-dihydrofurans **7** along with some amount of 2, 5-dihydrofurans **8** in 58-80 % yields. The reaction proceeded with good yields also when applied to the tosylhydrazones of tetrahydrothiophen-3-one **9**.

Tetrahedron Lett., **1965,** *6,* 1847**.**



6 **7** **8**

58-80 %

{7:8 varies from 94:6 to 67:33}

9 **10** **11**

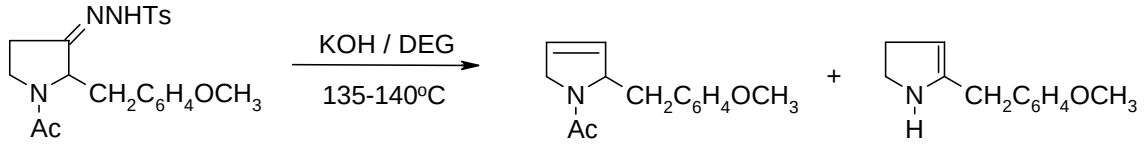
66 % (65:35)

Scheme 3

2. During their approach towards the total synthesis of Anisomycin, Oida *et al*[9] observed that tosylhydrazone **12** on treatment with KOH in diethylene glycol at 135-140^{o}C gave 1-acetyl-2-(*p*-methoxyphenylmethyl)-3-pyrroline **13** in 55 % yield along with 2-(*p*-

methoxyphenylmethyl)-2-pyrroline **14** (30 %). Formation of **13** and **14** suggested that the olefins were formed without selectivity (scheme 4).

Chem. Pharm. Bull. (Tokyo), **1969,** *17*,1405**.**

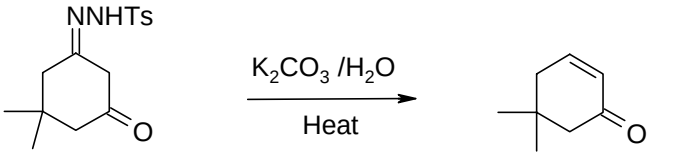


12 **13** (55 %) **14** (30 %)

Scheme 4

3. Hiegel *et al*[10] have found that cyclic 1,3-diketones could be converted into cyclic 2-enones **16** through treatment of their monotosylhydrazones **15** with weak base like K_2CO_3 (scheme 5). Since cyclic 1,3-diketones have sufficiently acidic α protons, they would be expected to undergo such reaction.

J. Org. Chem., **1973,** *38*, 3637**.**

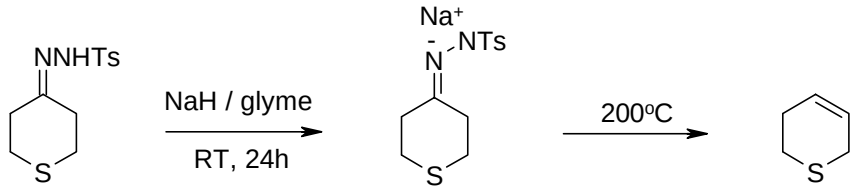


15 **16** (53 %)

Scheme 5

3. Johnson *et al*[11] pyrolised the sodium salts of alkyl sulfide tosylhydrazones **17** at several temperatures (scheme 6). The sodium salts of tosylhydrazones **18** were obtained by adding 1 equivalent of NaH to 1 equivalent of tosylhydrazone in freshly distilled glyme and stirred for 24h. The dried salts were used for pyrolysis. The pyrolysis resulted in the formation of olefins **19** in low to moderate yields.

J. Org. Chem., **1973,** *38*, 2967.

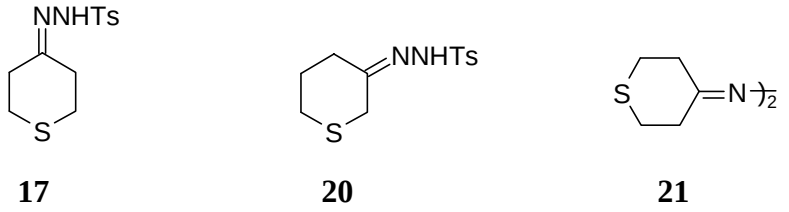


17 **18** **19** (70 %, GC yield)

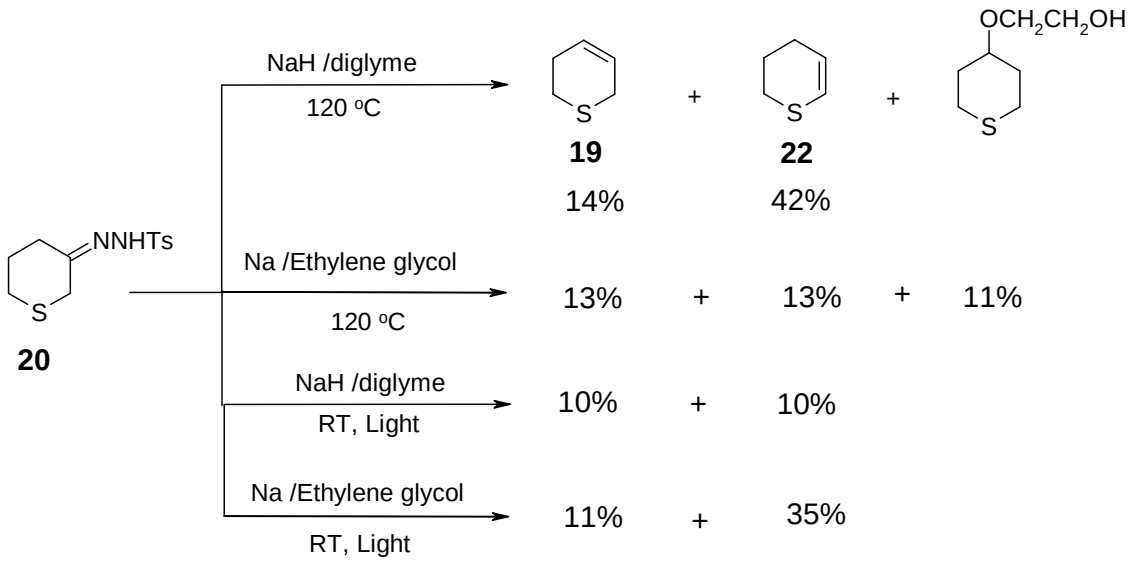
Scheme 6

4. The thermal and the photolytic decomposition of tosylhydrazones of tetrahydro-*4H*-thio-pyran-4-one **17** and dihydro-*2H*-thiopyran-(*4H*)-one **20** were studied by Ogata *et al*[12] (scheme 7).

Nippon Kagaku Kaishi, **1987**, *7*, 1370.



17 **20** **21**



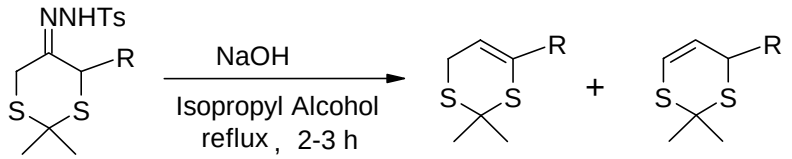
20

Scheme 7

In the case of **20**, α, β-unsaturated olefin **22** predominated over β, γ -unsaturated one **19** in the thermal decomposition in the presence of sodium hydride in diglyme and the photolytic decomposition in the presence of sodium in ethylene glycol. On the other hand, in case of **17**, the corresponding azine **21** was the major product in the thermal decomposition in the presence of sodium methoxide in ethylene glycol and the photolytic decomposition in the presence of NaH in diglyme.

2.1.2 Present Work

During our approach towards the synthesis of lipoic acid, as described in the *Chapter-1, Section-2* of this thesis, it has been found that tosylhydrazones **23** on treatment with NaOH in isopropyl alcohol at reflux temperature resulted in the formation of more substituted olefins **24** along with minor amount of less substituted olefins **25** (scheme 8).

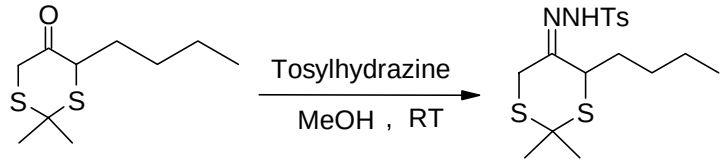


23 **24 (major)** **25 (minor)**

Scheme 8

2.1.3 Results and Discussion

The starting materials i.e. tosylhydrazones were prepared by known method.[13] In a typical experiment, mixture of 4-butyl-2, 2-dimethyl- (1,3) dithian-5-one (**26)** and excess of tosylhydrazine in methanol were stirred at room temperature to furnish [4-butyl-2, 2-dimethyl-(1,3)-dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (**23a)** as a white solid in 92 % yield (scheme 9). The preparation of ketone 26 has been described in *Chapter-1, Section-2* of this thesis.



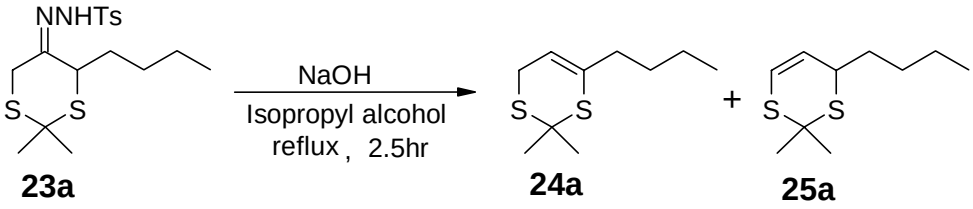
26 **23a**

Scheme 9

The product **23a** was characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The disappearance of carbonyl functionality was confirmed by the absence

of peak at 1712 cm^{-1} in the IR spectrum of the product. The singlet at δ 8.21 and two doublets at δ 7.84 and 7.30 appeared in the ^{1}H NMR spectrum of the product which revealed the presence of *N*-H and aromatic protons. The absence of signal at δ 204.4 in ^{13}C NMR spectrum of the product also confirmed the absence of carbonyl functionality in the product. The mass spectrum [ESI technique, m/z = 387.05 (M+1)] gave additional evidence for the formation of tosylhydrazone **23a**.

The tosylhydrazones prepared in this way were used as starting materials for the present protocol. In a typical experiment, [4-butyl-2, 2-dimethyl-(1,3) dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine **23a** was refluxed with excess of NaOH (2 equivalents) in isopropyl alcohol for 2.5 h (scheme 10).



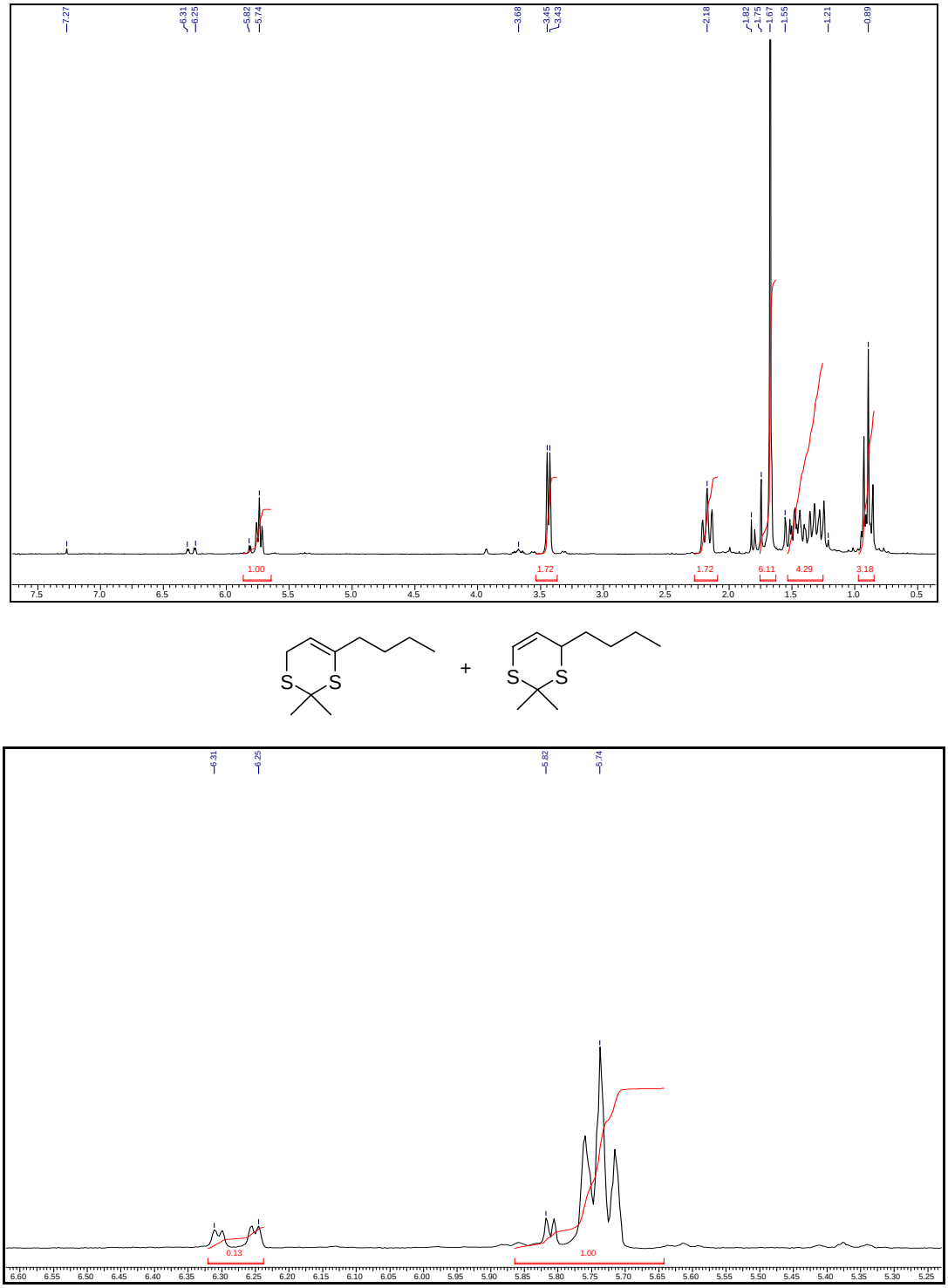
23a **24a** **25a**

88 % (87:13)

Scheme 10

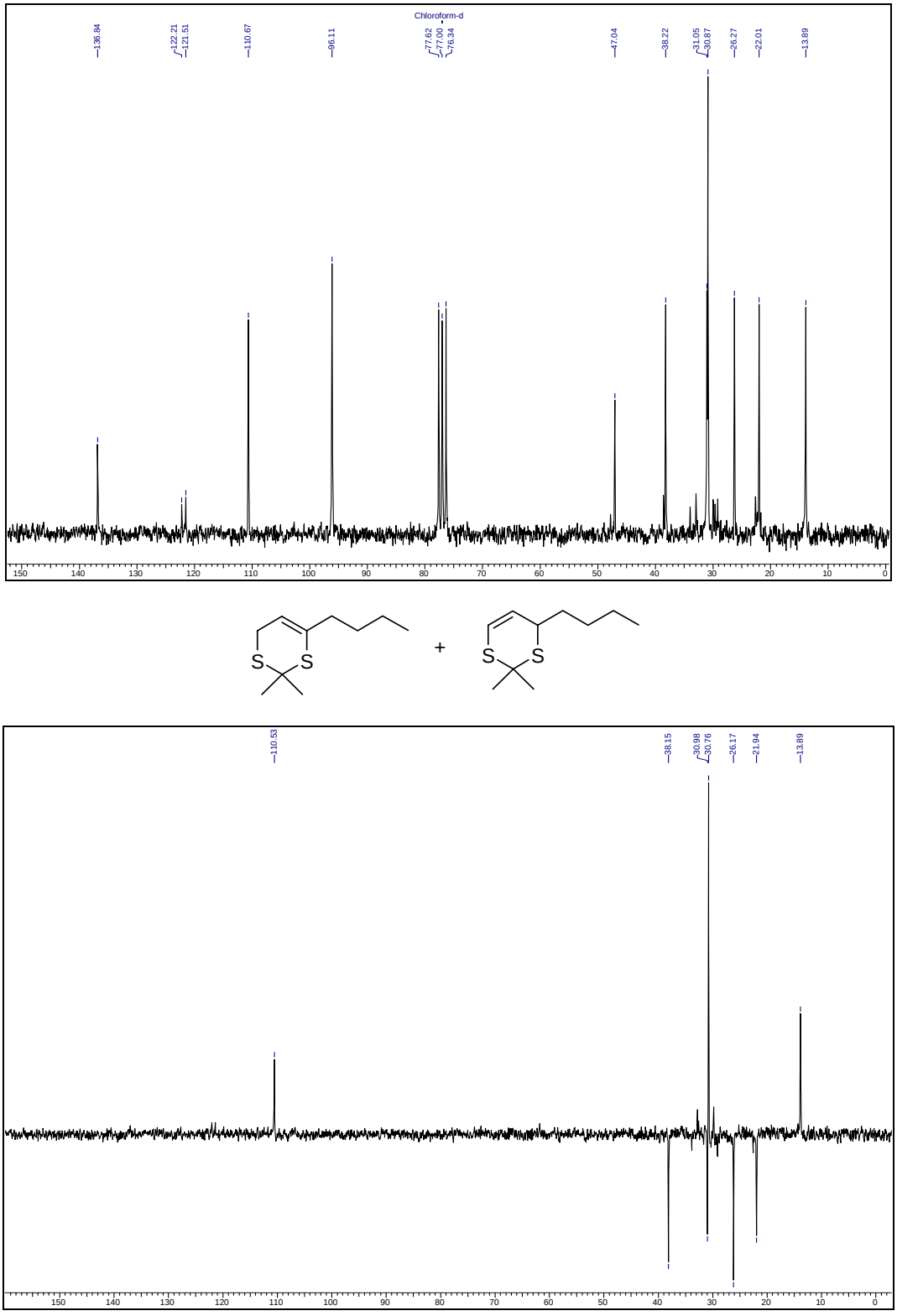
The product thus formed was purified by column chromatography and characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The ^{1}H NMR spectrum of the product displayed a triplet in olefinic region at δ 5.74 integrating for one proton. This indicated the presence of more substituted olefin **24a**. However, two very small peaks δ 5.82 (doublet) and δ 6.28 (doublet of doublet) also appeared in the olefinic region which indicated that the other regioisomer (less substituted olefin) **25a** was also present in the minor amount alongwith the more substituted olefin **24a**. The ratio of two regioisomers was determined from the ratio of integrations for olefinic protons. The ratio of integrations for signals at δ 5.74 and δ 5.82 revealed the presence of two regioisomers in the ratio **24a : 25a** = 87 : 13, more substituted olefin **24a** being the major one (figure 1). The presence of doublet at δ 110.9 along with very small peaks at δ 121.5 and δ 122.2

corresponding to two doubets in the ^{13}C NMR spectrum confirmed the presence of two regioisomers in the product as predicted by ^{1}H NMR spectrum (figure 2).



^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz) spectrum of compounds (24a + 25a)

Figure 1

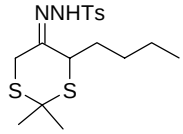
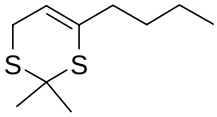
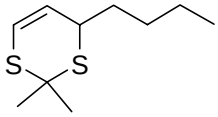
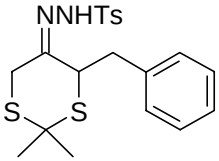
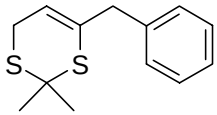
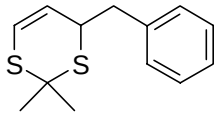
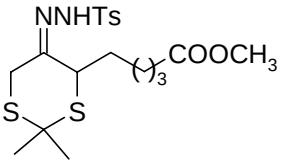
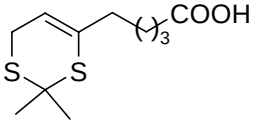
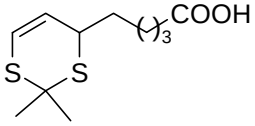
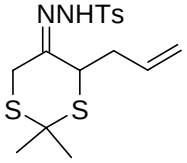
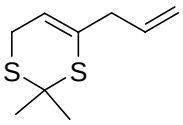
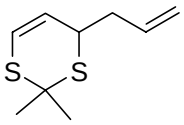
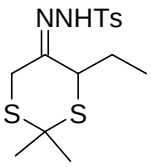
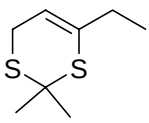
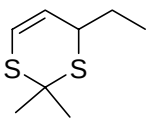


^{13}C NMR and DEPT ($CDCl_3$ + CCl_4, 50MHz) spectrum of compounds (24a + 25a)

Figure 2

In order to establish the generality of this protocol different tosylhydrazones were treated with NaOH under similar conditions and the results are summarized in table 1. It was observed that the tosylhydrazones were decomposed to olefins with excellent regioselectivity in moderate to high yields.

Table 1:- Decomposition of tosylhydrazones to olefins using NaOH as a base*:*

Sr. No.	Tosylhydrazones **23**	Products **24**	**25**	Isolated % Yields (**24:25**)
1	 **23a**	 **24a**	 **25a**	88 (87:13)
2	 **23b**	 **24b**	 **25b**	80 (93:7)
3	 **23c**	 **24c**	 **25c**	84 (96:4)
4	 **23d**	 **24d**	 **25d**	53 (86:14)
5	 **23e**	 **24e**	 **25e**	71 (89:11)

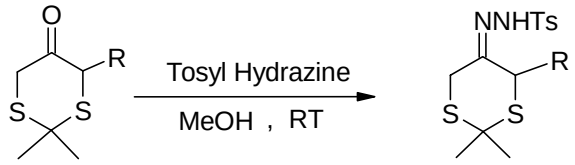
2.1.4 Conclusion

The different tosylhydrazones of cyclic ketones containing sulfur atom are decomposed regioselectively to give olefins using NaOH as a base in refluxing isopropyl alcohol. This protocol is highly regioselective producing more substituted olefins as the major products along with very small amount of less substituted olefins. The yields are moderate to high for this protocol. Moreover, mild reaction conditions are required for this protocol as compared to the literature methods.

This protocol has been successfully applied for the synthesis of (±) α-lipoic acid and could be extended towards the asymmetric synthesis of optically active α-lipoic acid.

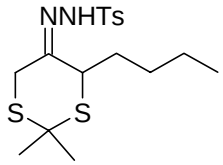
2.1.5 Experimental

A) Preparation of Tosylhydrazones[13]



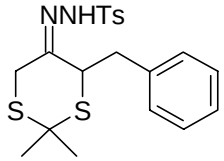
General Procedure:- The mixture of ketone (1 mmol) and tosylhydrazine (1.5 mmol) in methanol (10 ml) was stirred at room temperature. The reaction was monitored by TLC, and after the completion of the reaction, methanol was removed under vacuum and the residue was purified by column chromatography to yield pure tosylhydrazone.

1. [4-Butyl-2,2-dimethyl-(1,3)-dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23a)



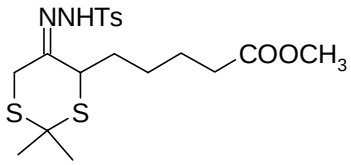
Molecular Formula	:	$C_{17}H_{26}O_2N_2S_3$
Yield	:	92 %
M. P.	:	148 ^oC (White solid).
IR ($CHCl_3$, cm^{-1})	:	3020, 1599, 759.
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 8.21 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 3.79 (dd, *J* = 6.8, 6.3 Hz, 1H), 3.57 (d, *J* = 15.6 Hz, 1H), 3.23 (d, *J* = 15.6 Hz, 1H), 2.42 (s, 3H), 1.78-1.98 (m, 1H), 1.70 (s, 3H), 1.51 (s, 3H), 1.37-1.61 (m, 1H), 1.16-1.34 (m, 4H), 0.85 (t, *J* = 6.4 Hz, 3H).
^{13}CNMR ($CDCl_3$, 50MHz)	:	δ = 156.8 (s), 144.1 (s), 135.2 (s), 129.5 (d), 128.3 (d), 50.0 (s), 45.8 (d), 32.6 (q), 31.5 (q), 29.6 (t), 29.0 (t), 25.7 (t), 22.5 (t), 21.3 (q), 13.7 (q).
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4)	:	m/z = 387.05 (M+1).

2. [4-Benzyl-2,2-dimethyl-(1,3) dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23b)



Molecular Formula	:	$C_{20}H_{24}O_2N_2S_3$
Yield	:	94 %.
M. P.	:	156 ^oC (White solid).
IR ($CHCl_3$, cm^{-1})	:	3020, 2401, 1599, 1167, 755.
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 8.42 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.16-7.26 (m, 5H), 4.13 (dd, *J* = 7.3, 5.4 Hz, 1H), 3.63 (d, *J* = 15.6 Hz, 1H), 3.40 (dd, *J* = 14.2, 5.4 Hz, 1H), 3.30 (d, *J* = 15.6 Hz, 1H), 2.66 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.46 (s, 3H), 1.69 (s, 3H), 1.52 (s, 3H).
^{13}CNMR ($CDCl_3$, 50MHz)	:	δ = 156.1 (s), 144.2 (s), 138.4 (s), 135.3 (s), 129.5 (d), 129.2 (d), 128.6 (d), 128.2 (d), 126.5 (d), 50.2 (s), 47.0 (d), 35.7 (t), 32.3 (q), 31.3 (q), 25.9 (t), 21.5 (q).
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4)	:	m/z = 421.04 (M+1).

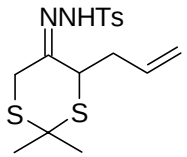
3. 5-[5-(*p*-toluenesulfonyl)hydrazono-2,2-dimethyl-(1,3)dithian-4-yl]-pentanoic acid methyl ester (23c)



Molecular Formula	:	$C_{19}H_{28}O_4N_2S_3$
Yield	:	87 %.
M. P.	:	120 ^oC (White solid).
IR ($CHCl_3$, cm^{-1})	:	3020, 2400, 1731, 757.
^1H NMR	:	δ = 8.53 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3

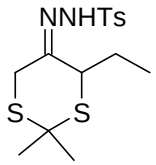
($CDCl_3$ + CCl_4, 200MHz)		Hz, 2H), 3.74 (dd, *J* = 7.8 Hz, 6.4 Hz, 1H), 3.61 (s, 3H), 3.56 (d, *J* = 15.6 Hz, 1H), 3.21 (d, *J* = 15.6 Hz, 1H), 2.37 (s, 3H), 2.19 (t, *J* = 7.8 Hz, 2H), 1.76-1.84 (m, 1H), 1.68 (s, 3H), 1.46 (s, 3H), 1.20-1.61 (m, 5H).
^{13}CNMR	:	δ = 173.6 (s), 155.7 (s), 143.9 (s), 135.4 (s), 129.3 (d),
($CDCl_3$+CCl_4, 50MHz)		128.1 (d), 51.2 (q), 49.7 (s), 45.1 (d), 33.6 (t), 32.2 (q), 31.0 (q), 28.9 (t), 26.1 (t), 25.6 (t), 24.4 (t), 21.3 (q).
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4)	:	m/z = 445.04 (M+1).

4. [4-Allyl-2,2-dimethyl-(1,3) dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23d)



Molecular Formula	:	$C_{16}H_{22}O_2N_2S_3$
Yield	:	83 %
M. P.	:	172 ^{o}C (White solid).
IR ($CHCl_3$, cm^{-1})	:	3019, 2400, 1216, 758.
^{1}H NMR	:	δ = 8.43 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3
($CDCl_3$ + CCl_4, 200MHz)		Hz, 2H), 5.58-5.78 (m, 1H), 5.01 (dd, *J* = 18.7, 8.3 Hz, 2H), 3.86 (dd, *J* = 7.3, 6.4 Hz, 1H), 3.59 (d, *J* = 16.1 Hz, 1H), 3.25 (d, *J* = 16.1 Hz, 1H), 2.53-2.71 (m, 1H), 2.44 (s, 3H), 2.15-2.30 (m, 1H), 1.74 (s, 3H), 1.52 (s, 3H).
^{13}C NMR	:	δ = 155.6 (s), 143.9 (s), 135.5 (s), 134.8 (d), 129.5 (d),
($CDCl_3$ + CCl_4, 50MHz)		128.4 (d), 117.0 (t), 50.0 (s), 45.3 (d), 34.1 (t), 32.6 (q), 31.5 (q), 26.0 (t), 21.6 (q).
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4)	:	m/z = 371.04 (M+1).

5. [4-Ethyl-2,2-dimethyl-(1,3) dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23e)



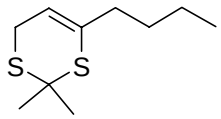
Molecular Formula	:	$C_{15}H_{22}O_2N_2S_3$
Yield	:	82 %
M. P.	:	120 ^oC (White solid).
IR (Nujol, cm^{-1})	:	3209, 2924, 1460, 1377.
^1H NMR ($CDCl_3 + CCl_4$, 500MHz)	:	δ = 8.04 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 3.73 (dd, *J* = 7.2, 6.8 Hz, 1H), 3.56 (d, *J* = 15.1 Hz, 1H), 3.24 (d, *J* = 15.1 Hz, 1H), 2.44 (s, 3H), 1.93-1.99 (m, 1H), 1.71 (s, 3H), 1.53 (s, 3H), 1.45-1.53 (m, 1H), 0.93 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR ($CDCl_3 + CCl_4$, 500MHz)	:	δ = 156.1 (s), 143.9 (s), 135.2 (s), 129.4 (d), 128.2 (d), 49.9 (s), 47.3 (d), 32.6 (q), 31.5 (q), 25.8 (t), 23.1 (t), 21.6 (q), 11.7 (q).
MS (ESI, Solv.: $CH_3CN + H_2O + CH_3COONH_4$)	:	m/z = 359.03 (M+1).

B) Decomposition of Tosylhydrazones to Olefins:-

General Procedure: - A mixture of tosylhydrazone (1 mmol) and NaOH (2 mmol) in isopropyl alcohol (10 ml) was refluxed for 2-3 h. The reaction was monitored by TLC, and after the completion of the reaction, isopropyl alcohol was removed under vacuum and the residue was extracted with ether. The ether layer was dried over anhydrous Na_2SO_4 and filtered. Then ether was removed under vacuum and the residue was purified by column chromatography.

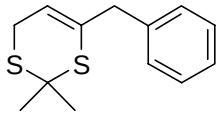
(The modified workup procedure for entry 3 in table 1 is given in *chapter 1*, *section 2*.)

1. 6-Butyl-2,2-dimethyl-*4H*-[1,3]dithiine (24a)



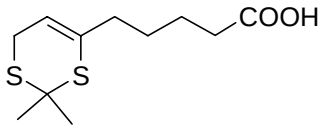
Molecular Formula	:	$C_{10}H_{18}S_2$
Yield	:	88 %
B. P.	:	Viscous liquid.
IR (neat, cm^{-1})	:	2959, 2928, 2871, 1459, 1362, 1216, 1111, 758.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 5.74 (t, *J* = 4.4 Hz, 1H), 3.44 (d, *J* = 4.4 Hz, 2H), 2.18 (t, *J* = 6.8 Hz, 2H), 1.67 (s, 6H), 1.21-1.55 (m, 4H), 0.89 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR ($CDCl_3 + CCl_4$, 50MHz)	:	δ = 137.0 (s), 110.9 (d), 47.3 (s), 38.4 (t), 31.3 (t), 31.1 (q), 26.5 (t), 22.2 (t), 14.1 (q).
Mass (EI)	:	m/z = 202 (12), 169 (18), 159 (12), 145 (13), 139 (3), 128 (83), 113 (34), 99 (72), 95 (76), 86 (100), 74 (56), 65 (26), 59 (48).

2. **6-Benzyl-2,2-dimethyl-*4H*-[1,3]dithiine (24b)**



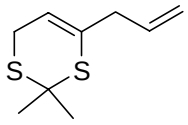
Molecular Formula	:	$C_{13}H_{16}S_2$
Yield	:	80 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	3020, 1620, 757.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 7.22-7.34 (m, 5H), 5.82 (t, *J* = 3.4 Hz, 1H), 3.52 (s, 2H), 3.50 (d, *J* = 3.4 Hz, 2H), 1.70 (s, 6H).
^{13}C NMR ($CDCl_3 + CCl_4$, 50MHz)	:	δ = 138.4 (s), 136.4 (s), 129.0 (d), 128.3 (d), 126.5, (d), 112.9 (d), 47.6 (s), 44.4 (t), 30.9 (q), 26.5 (t).
MS (ESI, Solv.: $CH_3CN + H_2O + CH_3COONH_4$)	:	m/z = 253.05 ($M+NH_3$), 235.05 (M-1).

3. 5-(2,2-dimethyl-*6H*-[1,3]dithiin-4-yl)-pentanoic acid (24c)



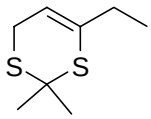
Molecular Formula	:	$C_{11}H_{18}O_2S_2$
Yield	:	84 %
B. P.	:	Viscous liquid.
IR ($CHCl_3$, cm^{-1})	:	2985, 1709, 1216, 1167.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 10.06 (bs, 1H), 5.75 (t, *J* = 4.4 Hz, 1H), 3.44 (d, *J* = 4.4 Hz, 2H), 2.34 (t, *J* = 7.3 Hz, 2H), 2.20 (t, *J* = 6.4 Hz, 2H), 1.67 (s, 6H), 1.42-1.74 (m, 4H).
^{13}C NMR ($CDCl_3 + CCl_4$, 50MHz)	:	δ = 179.2 (s), 136.5 (s), 111.4 (d), 47.3 (s), 38.2 (t), 33.8 (t), 31.0 (q), 28.3 (t), 26.4 (t), 23.7 (t).
MS (ESI, Solv.: $CH_3CN + H_2O + CH_3COONH_4$)	:	m/z = 263.05 ($M+NH_3$), 245.05 (M-1).

4. 6-Allyl-2,2-dimethyl-*4H*-[1,3]dithiine (24d)

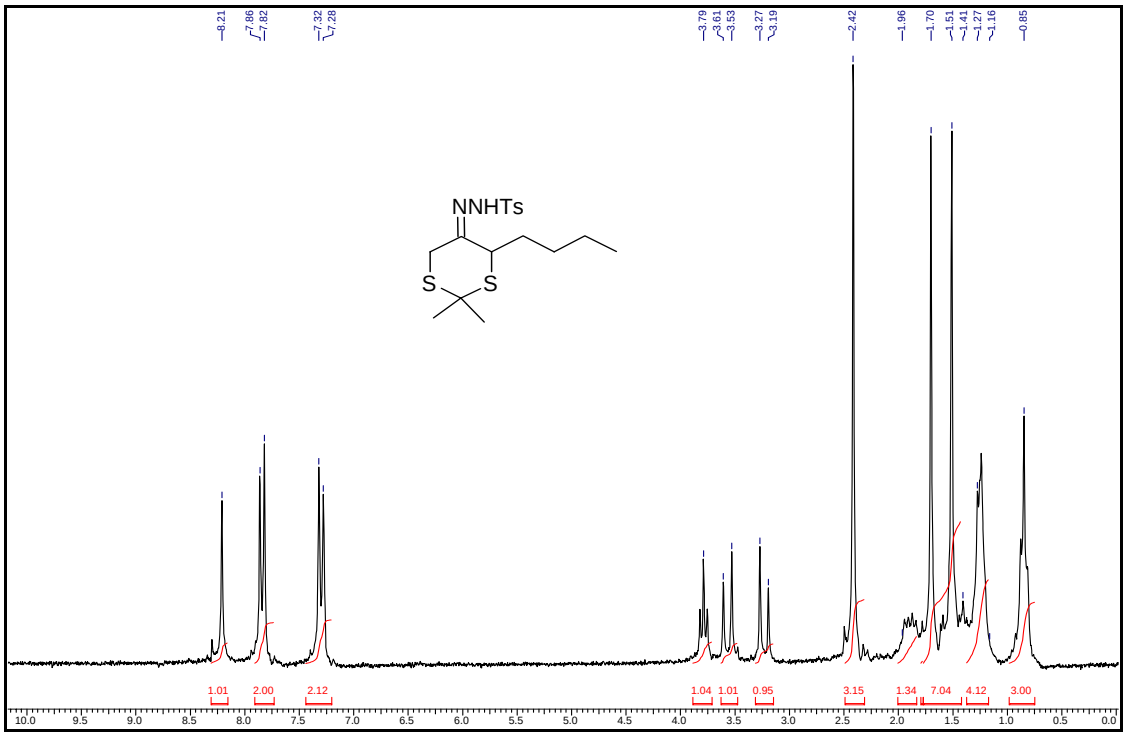


Molecular Formula	:	$C_9H_{14}S_2$
Yield	:	53 %
B. P.	:	Viscous liquid
IR ($CHCl_3$, cm^{-1})	:	2985, 1734, 1374, 1265, 1247, 1046, 909.
^1H NMR ($CDCl_3 + CCl_4$, 200MHz)	:	δ = 5.73-5.91 (m, 2H), 5.07-5.16 (m, 2H), 3.46 (d, *J* = 4.9 Hz, 2H), 2.92 (d, *J* = 6.8 Hz, 2H), 1.69 (s, 6H).
^{13}C NMR ($CDCl_3 + CCl_4$, 500MHz)	:	δ = 134.1 (d), 132.7 (s), 118.1 (t), 111.8 (d), 49.6 (s), 35.8 (t), 31.4 (q), 28.2 (t).
MS (ESI, Solv.: $CH_3CN + H_2O + CH_3COONH_4$)	:	m/z = 203.05.05 ($M+NH_3$).

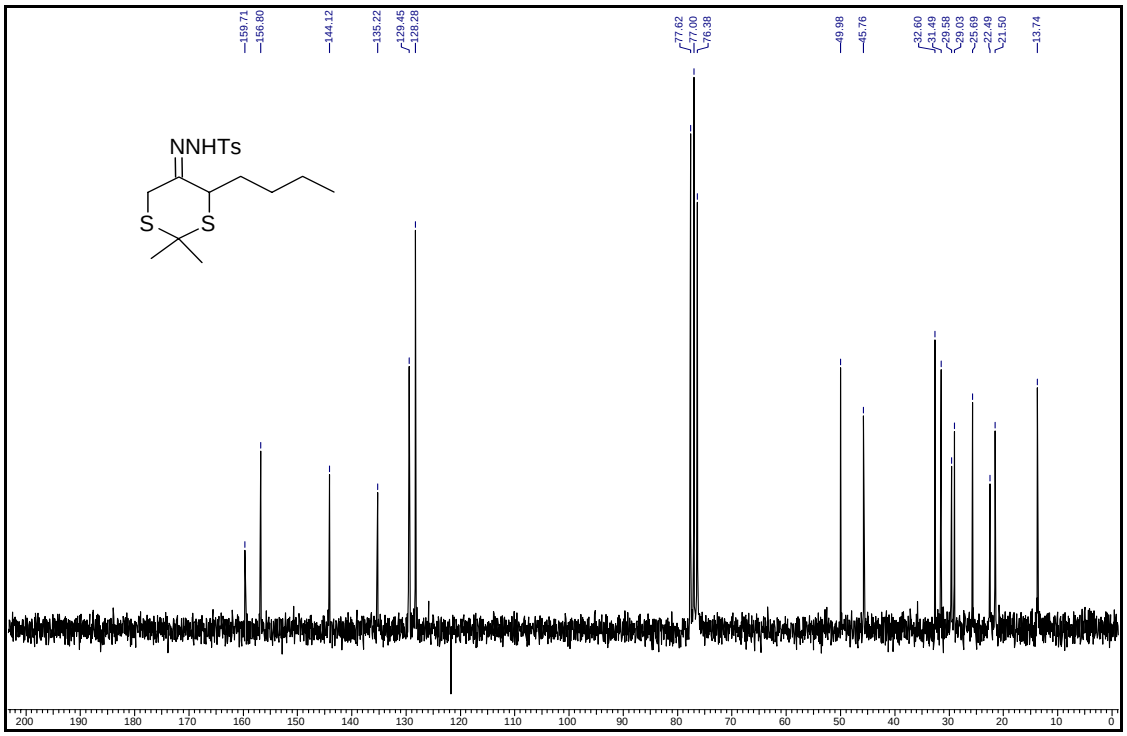
5. 6-Ethyl-2,2-dimethyl-*4H*-[1,3]dithiine (**24e**)



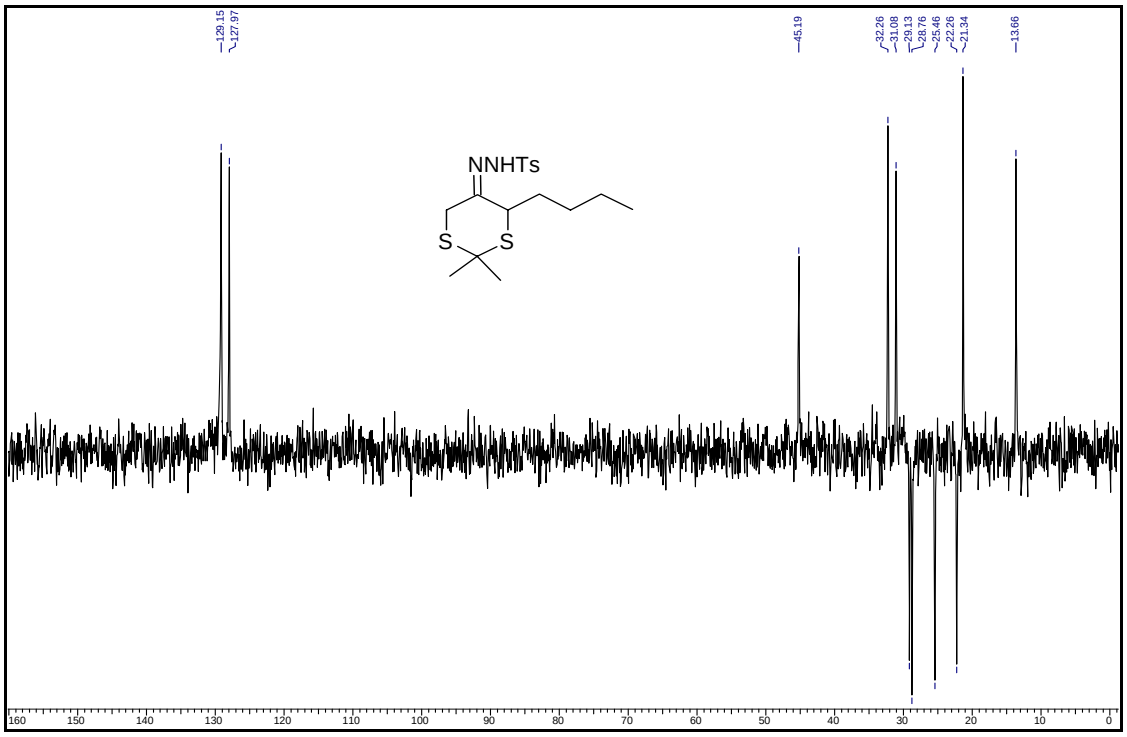
Molecular Formula	:	$C_8H_{14}S_2$
Yield	:	71 %
B. P.	:	Viscous liquid
IR ($CHCl_3$, cm^{-1})	:	3019, 2926, 1458, 758.
^1H NMR ($CDCl_3$ + CCl_4, 500MHz)	:	δ = 5.77 (t, *J* = 4.4 Hz, 1H), 3.45 (d, *J* = 4.4 Hz, 2H), 2.22 (q, *J* = 7.6 Hz, 2H), 1.70 (s, 6H), 1.12 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR ($CDCl_3$ + CCl_4, 500MHz)	:	δ = 138.5 (s), 109.9 (d), 47.1 (s), 31.6 (t), 31.0 (q), 26.3 (t), 13.8 (q).
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4)	:	m/z = 191.05 ($M+NH_3$), 173.05 (M-1).



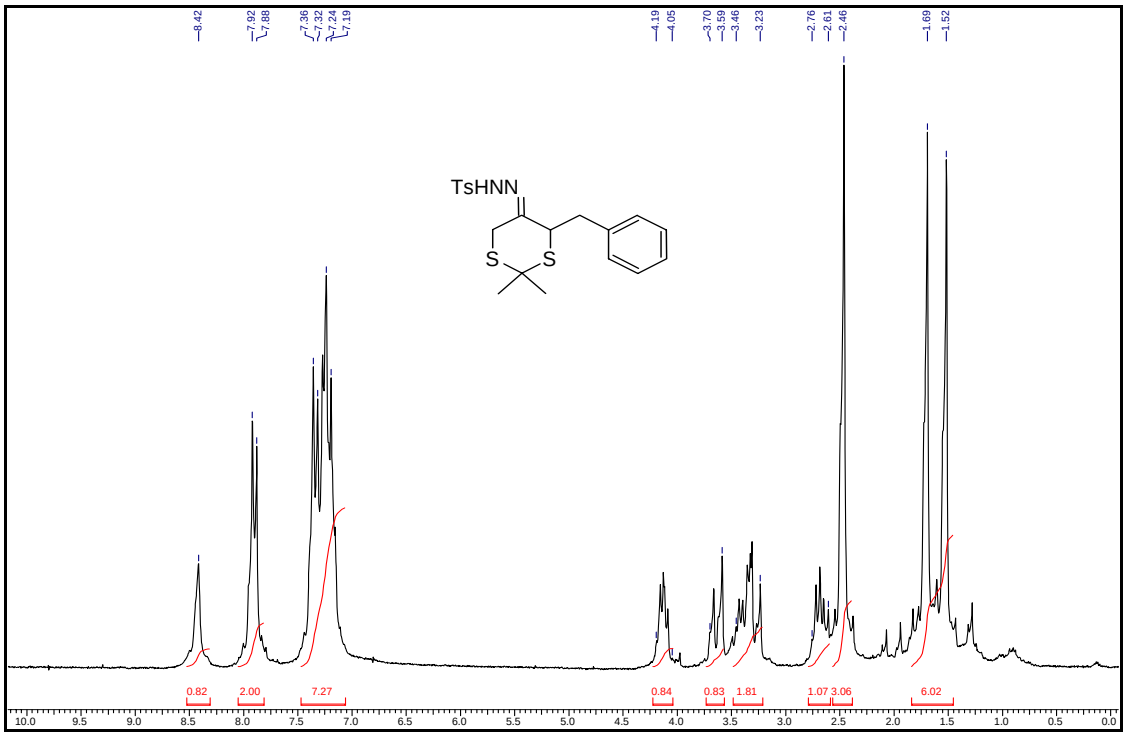
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz) spectrum of [4-butyl-2,2-dimethyl-(1,3)-dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23a)



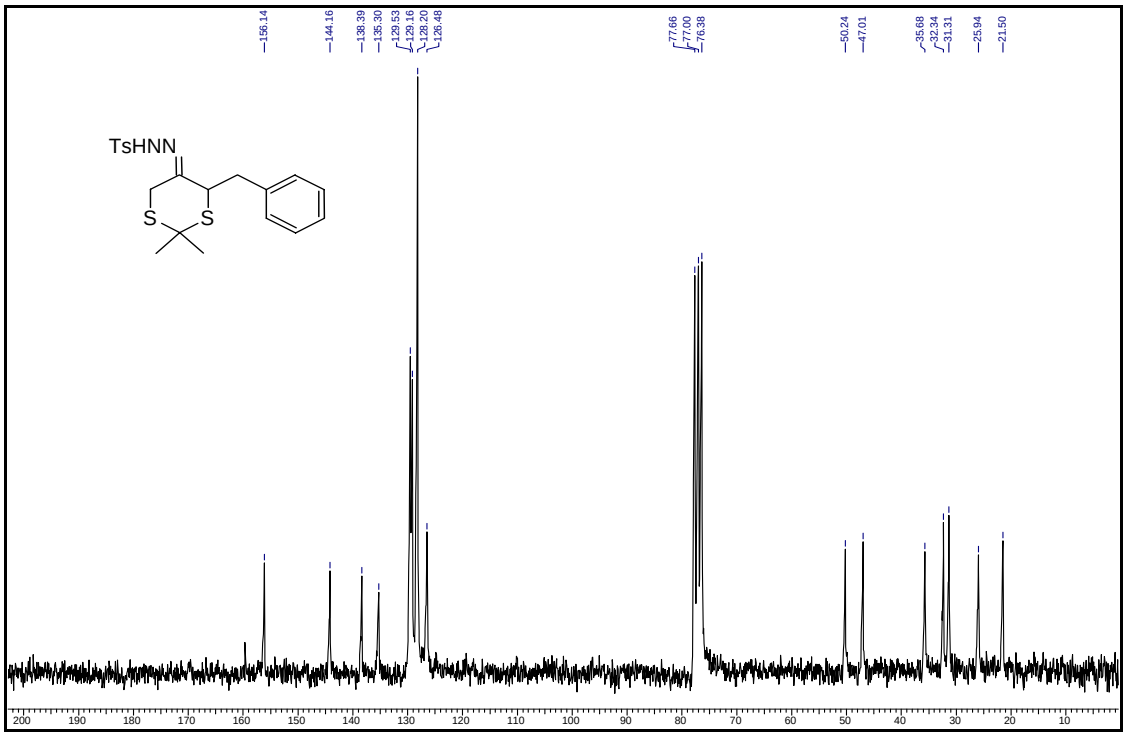
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz) spectrum of [4-butyl-2,2-dimethyl-(1,3)-dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23a)



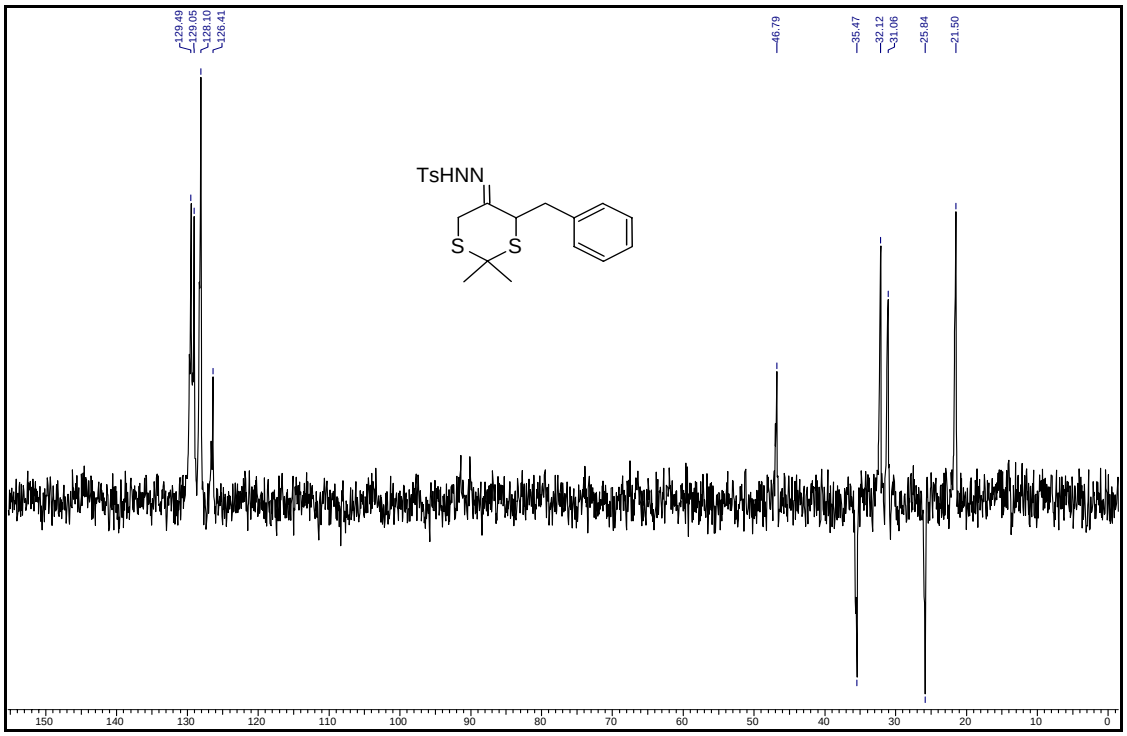
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz) spectrum of [4-butyl-2,2-dimethyl-(1,3)-dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23a)



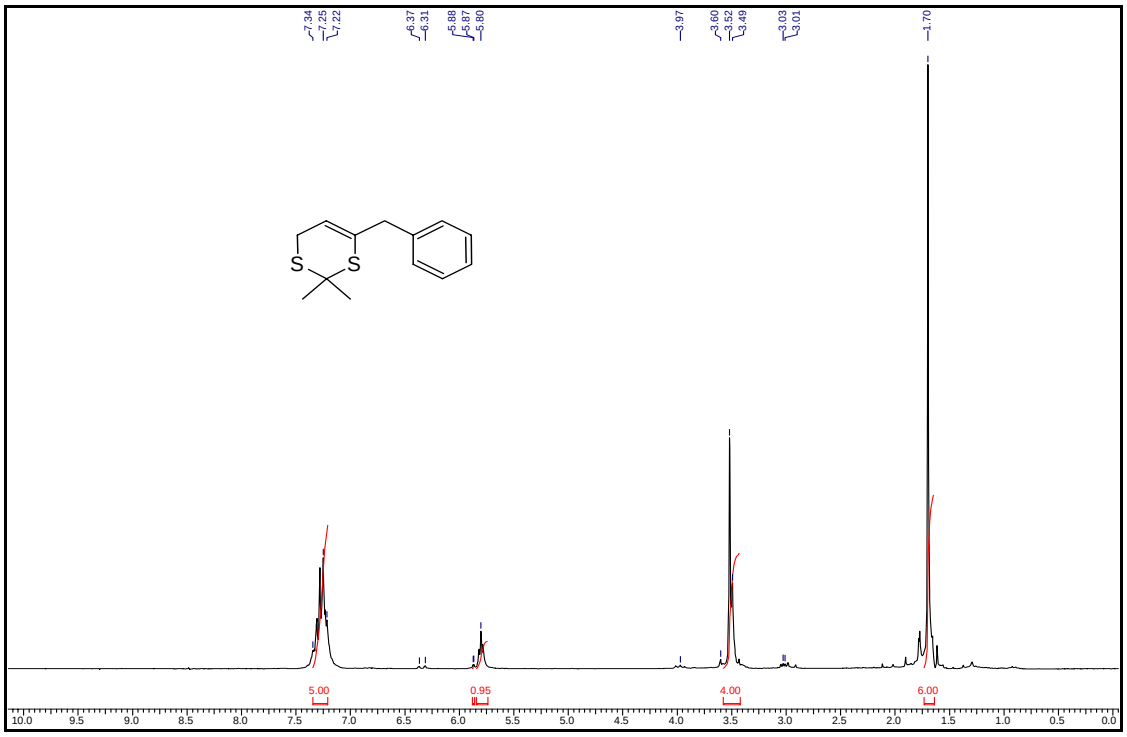
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz) spectrum of [4-benzyl-2,2-dimethyl-(1,3) dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23b)



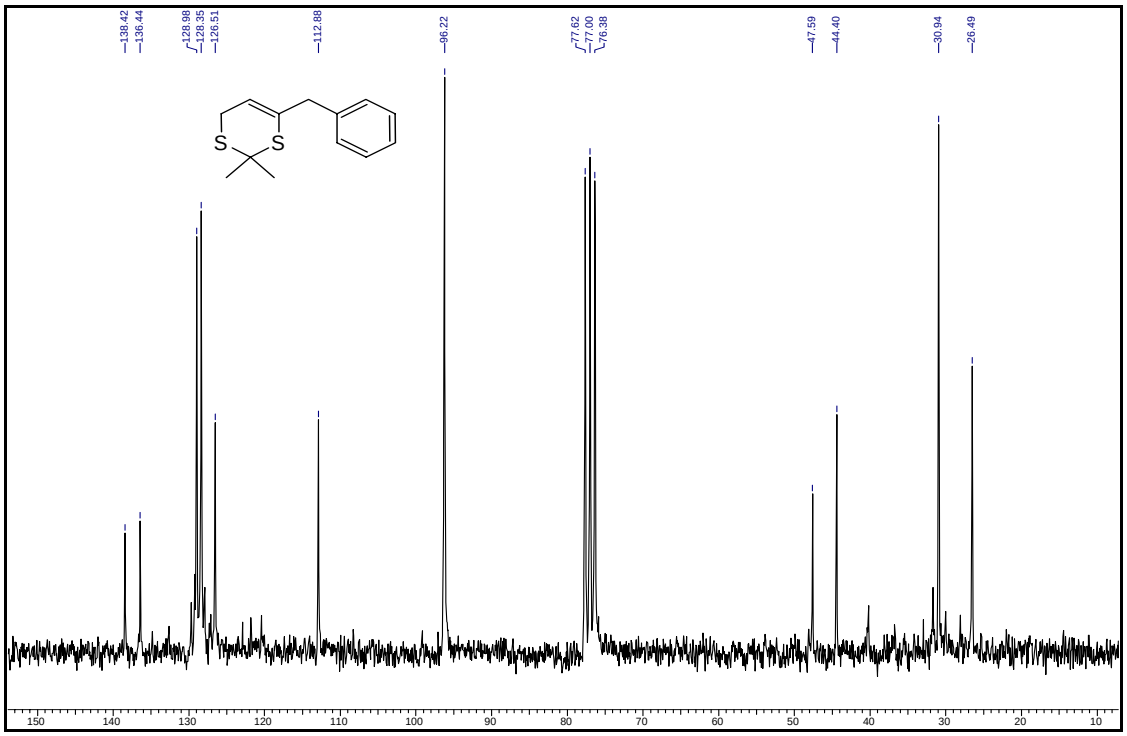
^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz) spectrum of [4-benzyl-2,2-dimethyl-(1,3) dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23b)



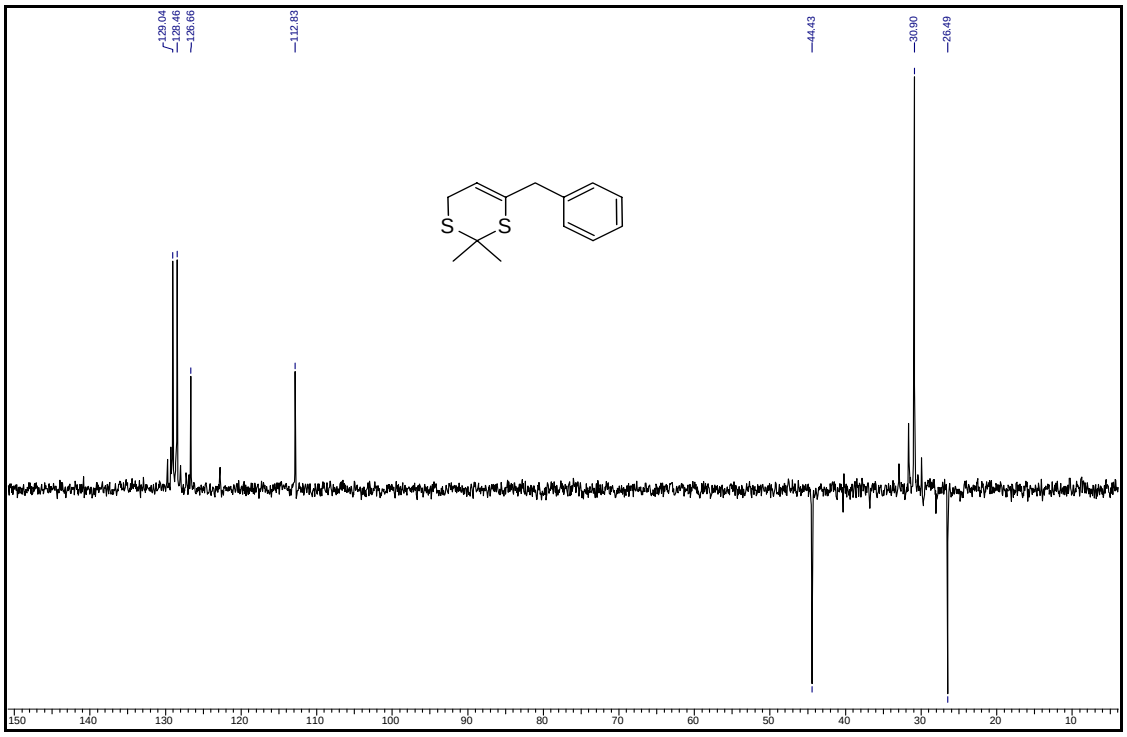
DEPT NMR ($CDCl_3$ + CCl_4, 50MHz) spectrum of [4-benzyl-2,2-dimethyl-(1,3) dithian-5-ylidene]-*p*-toluenesulfonyl hydrazine (23b)



^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz) spectrum of 6-benzyl-2,2-dimethyl-*4H*-[1,3] dithiine (24b)



^{13}C NMR ($CDCl_3$ + CCl_4, 50MHz) spectrum of 6-benzyl-2,2-dimethyl-*4H*-[1,3] dithiine (24b)



DEPT NMR ($CDCl_3$ + CCl_4, 50MHz) spectrum of 6-benzyl-2,2-dimethyl-*4H*-[1,3] dithiine (**24b**)

2.1.6 References

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CHAPTER-2

SECTION 2

A Facile Deprotection of dithioacetals by $FeCl_3$ / KI

2.2.1 Introduction

For the last hundred years, great efforts have been made by the researchers to develop new protecting groups for the organic functionalities and hence deprotection methods have also been devised after Fischer's pioneering work in the field of carbohydrate[1] and peptide chemistry.[2] It is extremely difficult to realize the synthetic target without the use of protecting groups in the field of organic chemistry.

During the past decades, the highly selective construction of polyfunctional molecules e.g. nucleotides, oligosaccharides, peptides and complex natural products like alkaloids, macrolides and prostaglandins has been achieved. These achievements were only possible through the extensive use of protecting groups, which in numerous cases had to be newly designed to overcome the emerging difficulties in the experimental realization of the synthetic plans. Today, therefore protecting group chemistry is the most important than ever.[3]

Protection for Carbonyl Groups

During a synthetic sequence, a carbonyl group may have to be protected against attack by various reagents such as nucleophiles like organometallic reagents, acidic, basic or hydride reducing agents and some oxidants.[3] The most useful protecting groups are the acyclic and cyclic acetals or thioacetals. The other stable protecting groups include cyanohydrins, hydrazones, oximes and semicarbazones etc. However, they are less common as protective groups because of the greater difficulty involved in their removal.

Cyclic and acyclic acetals and thioacetals are stable to aqueous and nonaqueous bases, nucleophiles including organometallic reagents and to hydride reduction. Oxygen acetals are stable to neutral and basic catalytic reduction, oxidants and heavy metal ions. At the same time, they are readily cleaved by acid hydrolysis. In contrast, thioacetals are very labile to the neutral and basic catalytic reduction, oxidation and are cleaved by heavy metal ions like Hg (II), Ag (I), Ce (IV) or Cu (II) salts. However, they are resistant to acid hydrolysis.

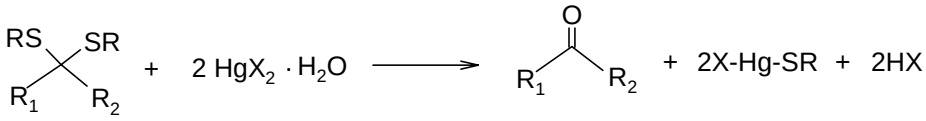
Apart from the use as protecting groups, thioacetals have gained prominence in organic transformations because of their use as acyl anion equivalents.[4] Synthetic chemists have used this protocol widely to metallate thioacetals and later unmask the carbonyl compound, in chain extension reactions. This marked reversal of the reactivity of carbonyl group was developed and introduced by Corey and Seebach[5] and was termed as "Umpolung of the reactivity".

2.2.2 Deprotection of thioacetals: A review

A protecting group must satisfy the requirements for being a good protecting group that it must react selectively to give protected substrate in good yield that is stable to the projected reactions and it must be selectively removed in good yield by readily available, non-toxic reagents. The formation of thioacetal is very facile and high yielding step in the presence of acidic or Lewis acid catalysis. However, at the same time, the deprotection of thioacetal is always a difficult task for the synthetic chemists. Several methods have been reported right from E. Fischer's pioneering work on thioacetals.[6] All these methods, upto 1977, are reviewed by Seebach and Grobel[7] and from 1977 to 1989 by Page *et al.*[8] Some of the literature reports are described below.

1. Transition metal induced hydrolysis: A number of groups have contributed tremendously in this work and produced a well-known procedure[9] for the hydrolysis of thioacetals. The driving force in this reaction is the formation of a stable heavy metal thiolate which undergoes easy hydrolysis (scheme 1), particularly using Hg (II) salts.

Eliel, *et. al*. *J. Org. Chem*. **1972**, *37*, 505.



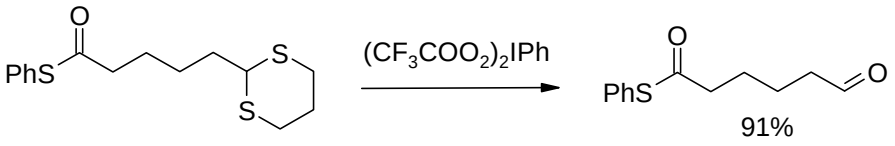
Scheme 1

The disadvantage of this procedure is that it renders the reaction mixture strongly acidic. This was overcome either by using additives like $CaCO_3$[10] and $BaCO_3$[11] or by the use of HgO / 35% HBF_4 instead of $HgCl_2$ / additives. However sensitive functionalities cannot servive under these conditions. Above all, the toxic nature of Hg (II) salts that too in stoichiometric quantities makes this protocol less attractive due to the waste disposal problems especially on a large scale.

2. The use of *bis*(trifluoroacetoxy)iodobenzene in aq. MeOH for the thioacetal deprotection by Stork *et al*[12] allows sufficiently mild hydrolytic conditions so that various

functional groups such as esters, nitriles, alcohols, halides, alkenes, amines and thioesters are unaffected (scheme 2). Because of the generation of trifluoroacetic acid in the reaction medium, this protocol is very harsh to acid sensitive functionalities.

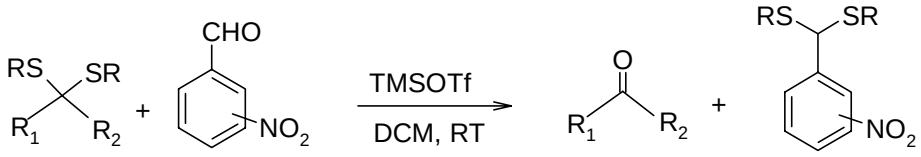
Stork *et. al*, *Tetrahedron Lett*. **1989**, *30*, 287.



Scheme 2

3. From our group[13] a transthioacetalization protocol has been developed for the deprotection of dithioacetals under anhydrous conditions. Thioacetals are converted efficiently under mild conditions to the corresponding carbonyl compounds in good to excellent yields by treatment with reactive aldehyde like nitrobenzaldehyde in the presence of TMSOTf as the catalyst (Scheme 3).

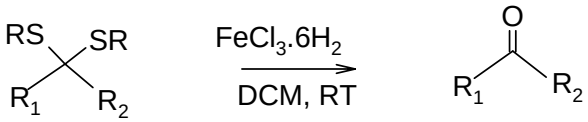
Ravindranathan *et. al*, *J. Chem. Soc*. *Chem.Commun*. **1991**, 1750.



Scheme 3

3. Another very mild method has been reported for the deprotection of thioacetals by Kamal *et al*[14] (scheme 4).

Kamal *et. al*, *Synlett,* **2000**, 1476

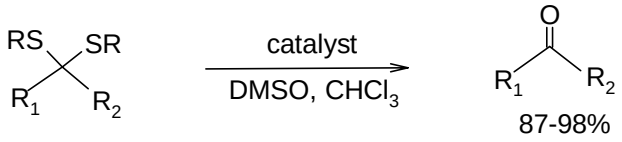


Scheme 4

This involves use of $FeCl_3.6H_2O$ to deprotect thioacetals which requires less reaction time as well. However it requires 3-6 equivalents of $FeCl_3.6H_2O$ for the reaction.

4. Iranpoor *et al*[15] have developed a chemoselective protocol for the deprotection of thioacetals and thioketals in presence of their O-O analogs (scheme 5). It describes the use of catalysts like NBS, TABCO or Br_2 along with DMSO in $CHCl_3$ for the deprotection and the yields are excellent. However this protocol is not applicable to the thioketals containing enolizable hydrogen.

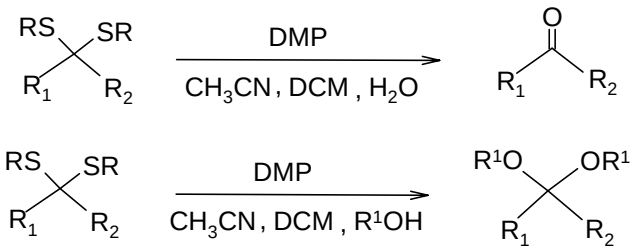
Iranpoor *et. al*, *Tetrahedron Lett*. **2003**, *44*, 4769.



Scheme 5

5. Most recently Panek *et al*[16] have developed a useful procedure for the removal of thioacetals and thioketals using Dess-Martin Periodinane (DMP) reagent (scheme 6).

Panek and cowarkers, *Org. Lett*. **2003**, *5*, 575.

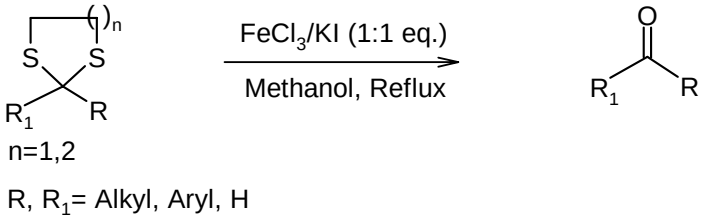


Scheme 6

This method offers chemoselective removal of thioacetals and thioketals on the substrate containing different functional groups including nitriles, esters, lactones, aldehydes, olefins, primary TBDPS ethers and secondary TBS ethers. Moreover, thioacetals can directly be converted to acetals under anhydrous conditions using this protocol. However, this protocol requires use of DMP which itself requires multistep preparation procedure.

2.2.3 Present work

In connection with our interest in exploring the utility of $FeCl_3$ our group has recently demonstrated the unique efficiency of $FeCl_3$ to function both as a Lewis acid[17] in catalyzing ionic Diels-Alder reactions as well as an oxidising agent[18] in effecting iodoetherification and iodolactonisation. The reports from our group for deprotection of oxathioacetals[19, 20] and dithioacetals[13] encouraged us to investigate the reaction of dithioacetals with $FeCl_3$/KI. It was surmised that $FeCl_3$/KI combination could serve as an excellent reagent as the source of iodonium ion/ iodine. These in turn would react with dithioacetal thereby making it a better leaving group, thus helping in regeneration of carbonyl compounds. We found that the dithioacetals were efficiently deprotected in the presence of $FeCl_3$ and KI in refluxing methanol (Scheme 5).



n=1,2

R, R_1= Alkyl, Aryl, H

Scheme 5

2.2.4 Results and discussion

The starting materials, dithioacetals were prepared by using known protocol. A mixture of carbonyl compound, dithiol and ferric chloride adsorbed on silica in DCM is stirred at room temperature to yield dithioacetal of the corresponding carbonyl compound. All thioacetals were characterized by IR, ^{1}H NMR and comparision with authentic samples.[21-26]

The dithioacetals on treatment with $FeCl_3$ (1eq) and KI (1eq) in refluxing methanol furnished the corresponding carbonyl compounds in good to excellent yields. The reaction product is isolated by a simple aqueous workup. It is interesting to note that the reaction does not proceed with either $FeCl_3$ (1eq) or KI (1eq) alone. After considerable trials it was concluded that combination of $FeCl_3$ and KI in the ratio 1:1 is required for clean transformation.

In a typical experimental procedure, a mixture of 2-(4-methoxyphenyl)-1,3-dithiolane (1 mmol), $FeCl_3$ (1 mmol) and KI (1 mmol) was refluxed in methanol for three hours to give anisaldehyde in 90% yield. The product was characterized by IR, ^{1}H NMR .The IR spectrum showed the presence of carbonyl absorption peak at 2739 cm^{-1} and ^{1}H NMR spectrum showed the singlet at δ 9.90 which confirmed the presence of aldehyde group in the product.

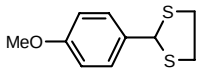
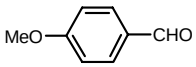
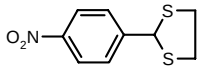
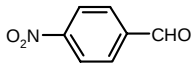
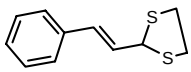
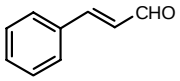
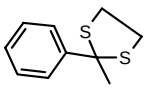
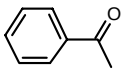
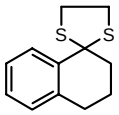
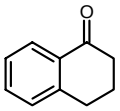
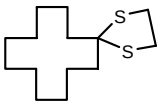
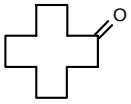
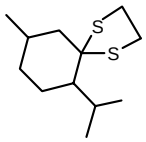
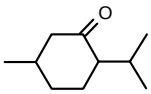
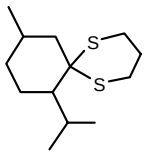
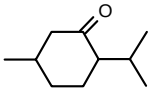
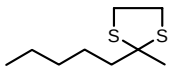
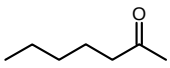
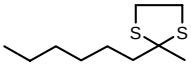
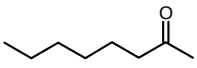
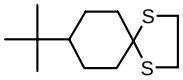
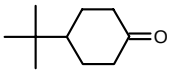
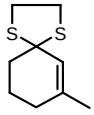
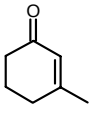
A wide variety of dithiolanes derived from ketones and aldehydes were shown to undergo facile deprotection under these conditions (table 1). Both dithiolanes as well as dithiane (entries 7 and 8 respectively) were deprotected with equal ease.

2.2.5 Conclusion

The deprotection of 1,3-dithiolanes and 1,3-dithianes was achieved efficiently by using $FeCl_3$ and KI in refluxing methanol. The present protocol is efficient, nonhazardous, and therefore should find widespread utility in organic synthesis.

We have also demonstrated that $FeCl_3$ which is known to catalyse thioacetal formation in catalytic amounts, when used in stoichiometric quantities alongwith KI brings about facile deprotection of thioacetals to parent carbonyl compounds.

Table 1: Deprotection of dithioacetals by $FeCl_3$/KI

Entry	Dithioacetal	Product	Time (h)	Isolated Yield (%)
1			3	90
2			4	91
3			3	90
4			3	91
5			3	91
6			11	87[a]
7			7	89
8			6	89
9			5.5	90
10			7	91
11			6	92
12			4	78

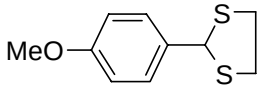
[a]based on recovery of the starting material.

2.2.6 Experimental

Preparation of Dithioacetals

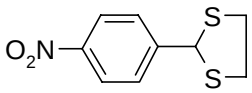
General Procedure: A mixture of p-methoxy benzaldehyde (400 mg, 2.94 mmol), ethanedithiol (303 mg, 3.23 mmol) and $FeCl_3$ adsorbed on silica (2 g) was stirred at room temperature in DCM. Progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was filtered, washed with 5% NaOH and subsequently with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporation of the solvent under reduced pressure followed by purification by column chromatography furnished 2-(4-methoxyphenyl)-1, 3-dithiolane (486mg, 78 %).

1. 2-(4-methoxyphenyl)-1, 3-dithiolane



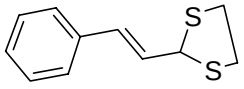
Molecular Formula	:	$C_{10}H_{12}OS_2$
M. P.	:	58-59.5 ^oC (lit.[22] mp : 60-61 ^oC)
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 7.41 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 5.56 (s, 1H), 3.79 (s, 3H), 3.30-3.40 (m, 4H).

2. 2-(4-nitrophenyl)-1, 3-dithiolane



Molecular Formula	:	$C_9H_9NO_2S_2$
M. P.	:	67-68 ^oC (lit.[23] mp: 67-69 ^oC)
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 8.15 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.9 Hz, 2H), 5.60 (s, 1H), 3.35-3.60 (m, 4H).

3. 2-styryl-1, 3-dithiolane

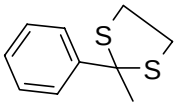


Molecular Formula	:	$C_{11}H_{12}S_2$

M. P. : 57-58 °C (lit. [22] mp: 59-59.5 °C)

^{1}H NMR ($CDCl_3$, 200MHz) : δ = 7.2 (m, 5H), 6.40 (d, *J* = 15.3 Hz, 1H), 6.1 (dd, *J* = 15.3 Hz, 7.6 Hz, 1H), 5.2 (d, *J* = 7.6 Hz, 1H), 3.11-3.15 (m, 4H).

4. 2-methyl-2-phenyl-1, 3-dithiolane

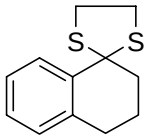


Molecular Formula : $C_9H_9NO_2S_2$

IR ($CHCl_3$, cm^{-1}) : 3056, 2975, 2928, 1500, 1450, 1383, 1285, 1075, 1040, 840, 780.

^{1}H NMR ($CDCl_3$, 200MHz) : δ = 7.83 (m, 2H), 7.37 (m, 3H), 3.40 (bs, 4H), 2.1 (s, 3H).

5. 3', 4'-Dihydro spiro-[1, 3-dithiolane-2, 1' (2' II)-naphthalene]



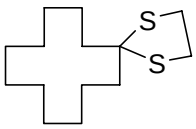
Molecular Formula : $C_{12}H_{14}S_2$

M. P. : 64.5 °C (lit. [13] mp : 66 °C)

IR ($CHCl_3$, cm^{-1}) : 2940, 2872, 1460, 1375, 1392, 1170, 1080, 950, 850, 759.

^{1}H NMR ($CDCl_3$, 200MHz) : δ: 7.67 (m, 1H), 6.84-7.24 (m, 3H), 3.37-3.71 (m, 4H), 2.65-2.69 (m, 2H), 2.19-2.22 (m, 2H), 1.78-1.82 (m, 2H).

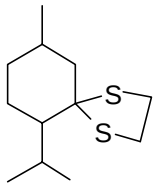
6. 1,4-Dithiaspiro[4.11]hexadecane



Molecular Formula : $C_{14}H_{26}S_2$

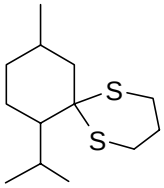
M. P.	:	84-84.8 ^oC (lit. [24] mp : 85-86 ^oC)
IR ($CHCl_3$, cm^{-1})	:	3020, 1385, 1084, 759, 669.
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 3.29 (bs, 4H), 1.98-2.06 (m, 4H), 1.36 (bs, 18H).
^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz)	:	δ = 71.0 (s), 38.9 (t, 2 x CH_2), 38.6 (t, 2 x CH_2), 26.4 (t, 2 x CH_2), 25.9 (t), 22.6 (t, 4 x CH_2), 22.4 (t, 2 x CH_2).

7. 2-menthyl-1, 3-dithiolane



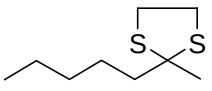
Molecular Formula	:	$C_{12}H_{22}S_2$
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 3.05-3.31 (m, 4H), 2.25-2.50 (m, 1H), 2.01-2.40 (m, 1H), 1.10-1.85 (m, 6H), 0.82-1.05 (m, 10H).

8. 2-menthyl-1,3-dithiane



Molecular Formula	:	$C_{13}H_{24}S_2$
M. P.	:	39.5-40 ^oC (lit. mp : 41-42 ^oC)
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 2.77-3.01 (m, 4H), 2.02-2.40 (m, 2H), 1.60-1.90 (m, 3H), 1.15-1.55 (m, 5H), 0.80-1.10 (m, 10H).

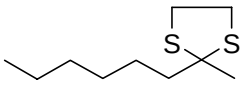
9. 2-methyl-2-pentyl-1, 3-dithiolane



Molecular Formula	:	$C_9H_{18}S_2$

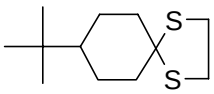
M. P. / B. P.	:	Viscous liquid
IR ($CHCl_3$, cm^{-1})	:	2938, 2887, 1450, 1375, 1277, 1042.
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 3.22 (bs, 4H), 1.70 (t, *J* = 8.4 Hz, 2H), 1.60 (s, 3H), 1.12-1.30 (m, 6H), 0.75 (t, *J* = 6.8 Hz, 3H).

10. 2-methyl-2-hexyl-1, 3-dithiolane



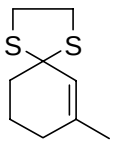
Molecular Formula	:	$C_{10}H_{20}S_2$
M. P. / B. P.	:	Viscous liquid
IR ($CHCl_3$, cm^{-1})	:	2958, 2920, 2857, 1456, 1375, 1339, 1063, 759.
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 3.21 (bs, 4H), 1.90 (t, *J* = 8.8 Hz, 2H), 1.72 (s, 3H), 1.14-1.52 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H).
^{13}C NMR ($CDCl_3$ + CCl_4, 50 MHz)	:	δ = 66.8 (s), 45.8 (t), 39.7 (t, 2 x SCH_2), 32.3 (q), 31.7 (t), 29.4 (t), 27.3 (t), 22.6 (t), 14.1 (t).

11. 2-(4-t-butyl cyclohexyl)-1, 3-dithiolane



Molecular Formula	:	$C_9H_9NO_2S_2$
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 3.23-3.34 (m, 4H), 2.14-2.23 (m, 2H), 1.74-1.96 (m, 4H), 1.18-1.41 (m, 2H), 0.98-1.07 (m, 1H), 0,87 (s, 9H).

12. 2-(3-methyl-2-cyclohexenyl)-1, 3-dithiolane



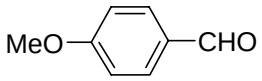
Molecular Formula	:	$C_9H_{14}S_2$
^1H NMR	:	δ = 5.55 (s, 1H), 3.24-3.41 (m, 4H), 2.09-2.14 (m, 2H),

($CDCl_3$, 200MHz) 1.76-1.90 (m, 4H), 1.67 (s, 3H).

Deprotection of dithioacetals

General Procedure: A mixture of 2-(4-methoxyphenyl)-1,3-dithiolane (212 mg, 1 mmol), $FeCl_3$ (162 mg, 1 mmol) and KI (166 mg, 1 mmol) was refluxed in methanol. Progress of the reaction was monitored by TLC. After the completion of the reaction, methanol was removed under reduced pressure and residue was extracted in ether. The ether extract was dried over anhydrous Na_2SO_4 and the organic layer was filtered. Evaporation of the solvent under reduced pressure furnished pure anisaldehyde (122 mg, 90 %).

1. *p*-methoxy benzaldehyde



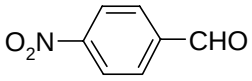
Molecular Formula : $C_8H_8O_2$

Yield : 90 %

IR ($CHCl_3$, cm^{-1}) : 2958, 2834, 2740, 1689, 1600, 1498, 1502, 1550, 1300, 1151, 1009.

^1H NMR ($CDCl_3$, 200MHz) : δ = 9.90 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 3H), 7.01 (d, *J* = 8.7 Hz, 2H).

2. *p*-nitro benzaldehyde



Molecular Formula : $C_7H_5NO_3$

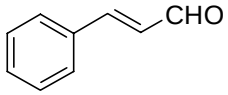
Yield : 91 %

M. P. : 106 ^oC (lit. [27] mp: 106-106.5 ^oC)

IR ($CHCl_3$, cm^{-1}) : 3020, 2850, 1710, 1600, 1520, 1450, 1352, 1200, 1100, 850, 820, 740.

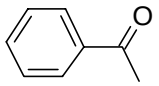
^1H NMR ($CDCl_3$, 200MHz) : δ = 10.17 (s, 1H), 8.39 (d, *J* = 8.7 Hz, 2H), 8.07 (d, *J* = 8.7 Hz, 2H).

3. Cinnamaldehyde



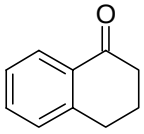
Molecular Formula	:	C_9H_8O
Yield	:	90 %
IR ($CHCl_3$, cm^{-1})	:	3010, 1800. 2719, 1670, 1608, 1440, 1120, 960.
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 9.72 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 16.1 Hz, 1H), 7.33 (m, 5H), 6.75 (dd, *J* = 16.1 Hz, 7.8 Hz, 1H).

4. **Acetophenone**



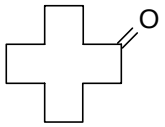
Molecular Formula	:	C_8H_8O
Yield	:	91 %
IR (Neat, cm^{-1})	:	30658, 2990, 1770, 1675, 1650, 1570, 1449, 1150, 1079, 1050, 880, 820, 740.
^1H NMR ($CDCl_3$, 200 MHz)	:	δ = 7.7 (m, 2H), 7.20 (m, 3H), 2.5 (s, 3H).

5. **α-Tetralone**



Molecular Formula	:	$C_{10}H_{10}O$
Yield	:	91 %
IR (Neat, cm^{-1})	:	3050, 3030, 2930, 2880, 1678, 1599, 1460, 1311, 1100, 1025, 900.
^1H NMR ($CDCl_3$ + CCl_4, 200 MHz)	:	δ = 8.00 (m, 1H), 7.3 (m, 3H) , 2.84 (m, 2H) , 2.51 (t, 2H) , 2.00 (m, 2H).

6. **Dodecanone**



Molecular Formula : $C_{12}H_{22}O$

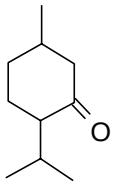
Yield : 87 %

M. P. : 58.5-60 ^oC (lit. mp: 59-61 ^oC)

^1H NMR : δ = 2.42 - 2.48 (m, 4H), 1.67-1.73 (m, 4H), 1.29 (m, 14H).

($CDCl_3$ + CCl_4, 200 MHz)

7. **Menthone**



Molecular Formula : $C_{10}H_{18}O$

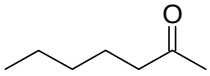
Yield : 89 %

IR ($CHCl_3$, cm^{-1}) : 2957, 2872, 1709, 1458, 1368, 757.

^1H NMR : δ = 1.6-2.40 (m, 7H), 1.32 (m, 1H), 0.6-1.10 (m, 10H).

($CDCl_3$ + CCl_4, 200 MHz)

9. 2-Heptanone



Molecular Formula : $C_7H_{14}O$

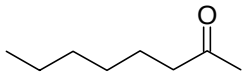
Yield : 90 %

IR (Neat, cm^{-1}) : 2920, 2848, 1709, 1470, 1418, 1170, 1120.

^1H NMR : δ = 2.41 (t, *J* = 7.1 Hz 2H), 2.12 (s, 3H), 1.58 (m, 2H), 1.30 (m, 4H), 0.80 (t, *J* = 6.8 Hz, 3H).

($CDCl_3$ + CCl_4, 200MHz)

10. **2-Octanone**



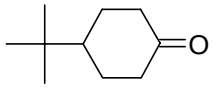
Molecular Formula : $C_8H_{16}O$

Yield : 91 %

IR (Neat, cm^{-1}) : 2958, 2922, 1711, 1466, 1162, 1099.

^1H NMR ($CDCl_3 + CCl_4$, 200 MHz) : δ = 2.25 (t, *J* = 7.3 Hz, 2H), 1.96 (s, 3H), 1.39 (m, 2H), 1.03-1.30 (m, 6H), 0.73 (t, *J* = 6.8 Hz, 3H).

10. 4-t-butyl cyclohexanone



Molecular Formula : $C_{10}H_{18}O$

Yield : 92 %

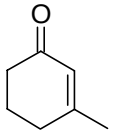
M. P. : 49 ^oC (lit. [28] mp: 49-50 ^oC)

IR ($CHCl_3$, cm^{-1}) : 3016, 2958, 2870, 1717, 1479, 1367, 1163, 757.

^1H NMR ($CDCl_3 + CCl_4$, 200 MHz) : δ = 2.21-2.40 (m, 4H), 2.01-2.13 (m, 2H), 1.36-1.46 (m, 3H), 0.90 (s, 9H).

^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz) : δ = 211.2 (s), 46.5 (d), 40.9 (t), 32.2 (s), 27.8 (q), 27.7 (t).

11. 3-methyl-2-cyclohexen-1-one

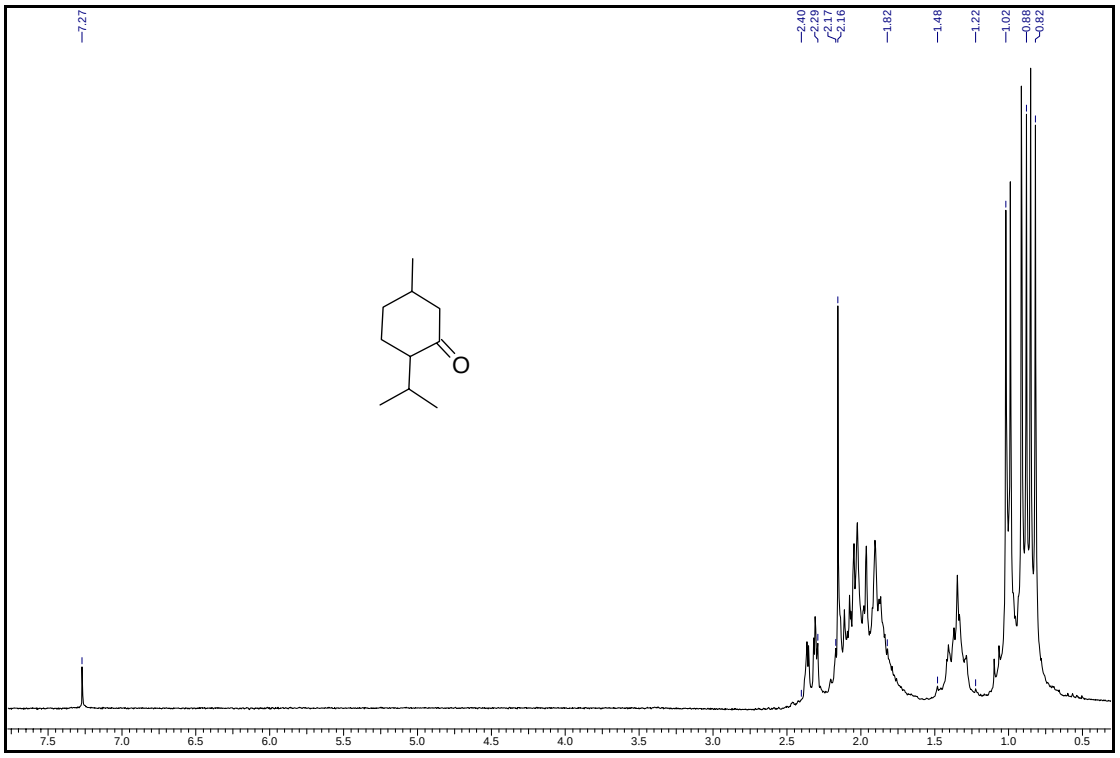


Molecular Formula : $C_7H_{10}O$

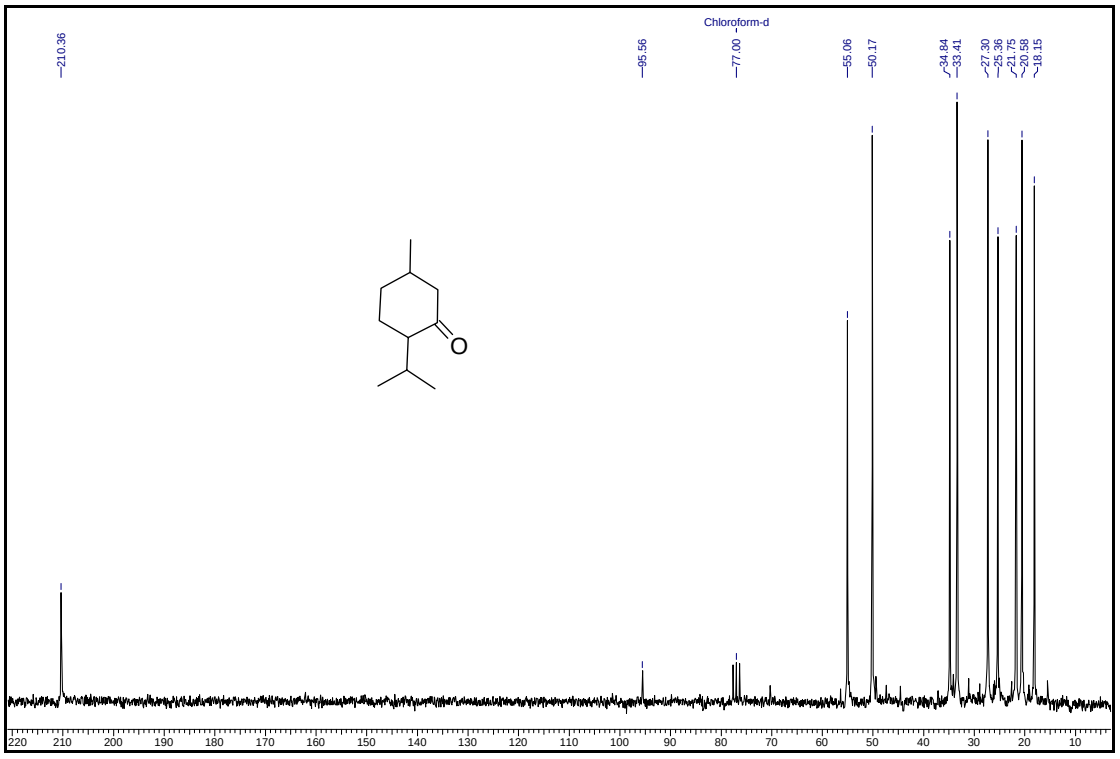
Yield : 78 %

IR ($CHCl_3$, cm^{-1}) : 2941, 1666, 1631, 1429, 1379, 1193, 885, 756.

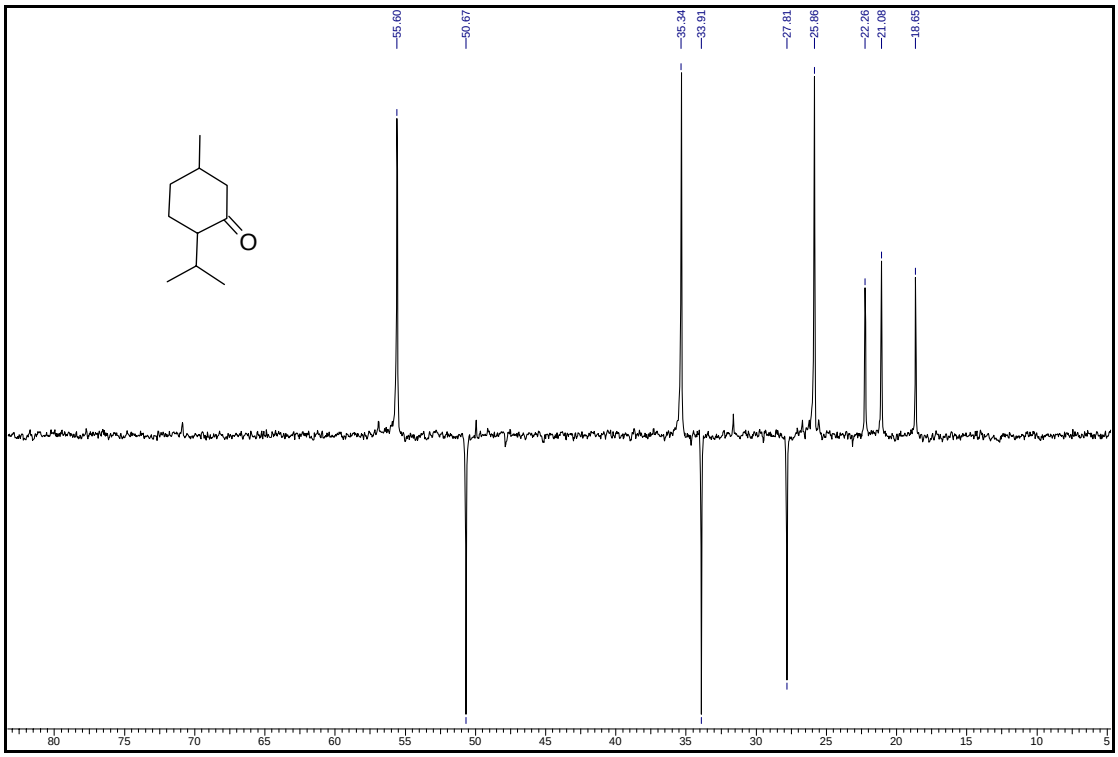
^1H NMR ($CDCl_3 + CCl_4$, 200 MHz) : δ = 5.76 (s, 1H), 2.20 (m, 4H), 1.91 (m, 2H), 1.88 (s, 3H).



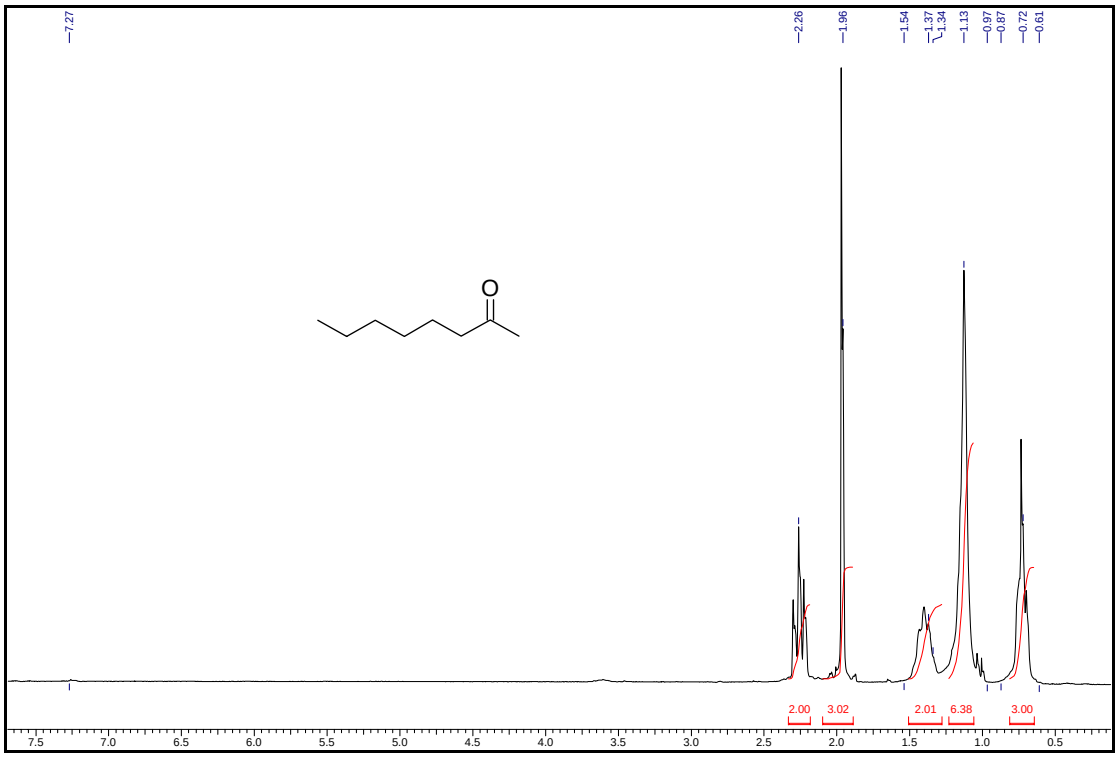
^{1}H NMR spectrum of menthone ($CDCl_3$ + CCl_4, 200 MHz)



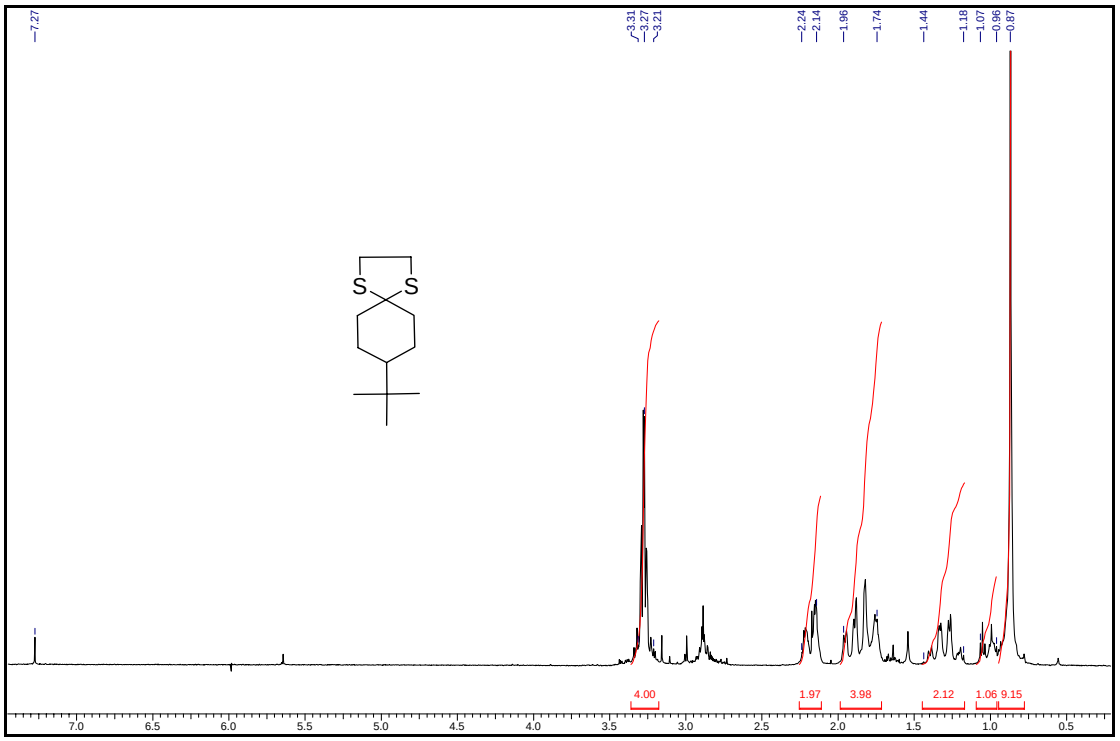
^{13}C NMR spectrum of menthone ($CDCl_3$ + CCl_4, 50 MHz)



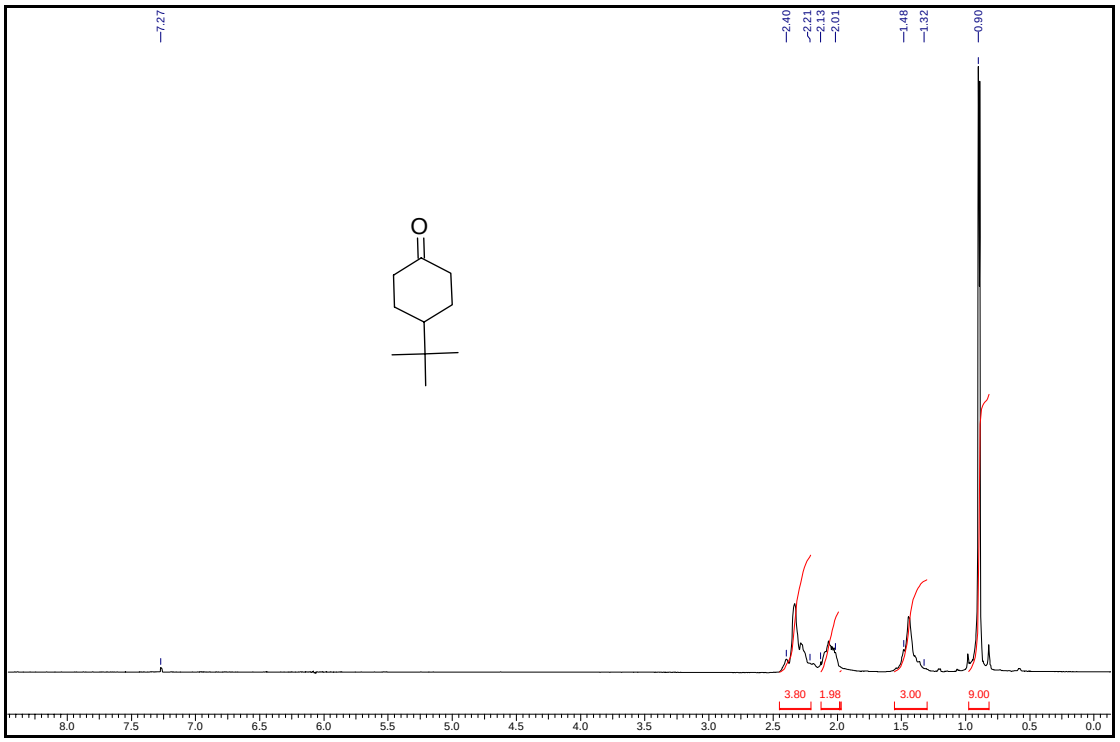
DEPT NMR spectrum of menthone ($CDCl_3$ + CCl_4, 50 MHz)



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



^{1}H NMR spectrum of 2-(4-t-butyl cyclohexyl)-1, 3-dithiolane ($CDCl_3$ + CCl_4, 200 MHz)



^{1}H NMR spectrum of 4-t-butyl cyclohexanone ($CDCl_3$ + CCl_4, 200 MHz)

2.2.7 References:

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CHAPTER-2

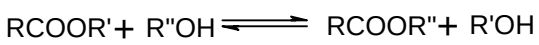
SECTION 3

Transesterification of β-Ketoesters Catalysed by Iodine

2.3.1 Introduction

Transesterification is one of the classic organic reactions that have enjoyed numerous laboratory uses and industrial applications. Organic chemists make use of this reaction quite often as a convenient means to prepare esters. Transesterification on some occasions, becomes more advantageous than the ester synthesis from carboxylic acid and alcohol when the parent carboxylic acids are labile and difficult to isolate or they have poor solubility in organic solvent where as the esters are commonly soluble in most of the organic solvents. Apart from the laboratory utilization, transesterification is widely used in paint industry for curing of alkylated resins, also for polymerizations *i.e.* ring opening of lactones.[1]

Transesterification is a process where an ester is transformed into another through interchange of the alkoxy moiety (Scheme 1).



Scheme 1

Since the reaction is an equilibrium process, the transformation occurs essentially by simply mixing the two components. However, it has long been known that the reaction is accelerated by acid and base catalysts.

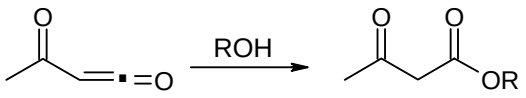
2.1.2 Transesterification of β-ketoesters

β-ketoesters are proven to be the valuable tools in the synthesis of a wide variety of molecular systems due to the presence of both nucleophilic as well as electrophilic sites. Their structural unit is composed of two different electrophilc carbonyls and two nucleophilic carbons, which can react selectively under suitable conditions. These highly important synthons have been prepared by variety of ways of which transesterification has received a great deal of attention.

1) Synthesis of β-ketoesters via C_1-O_1 bond formation had been conventionally done by the alcoholysis of acetyl ketene in presence of a suitable catalyst.[2] Though diketenes are

highly toxic and lachrymatory, it still remains most common and easy mode of preparation of β-ketoesters due to their high reactivity and low cost. The other disadvantage of using diketene is that it undergoes decomposition liberating CO_2, also self-condensation in both acidic and basic medium and thereby making it unattractive as a starting material for the preparation of β-ketoesters[3] (scheme 2).

Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241

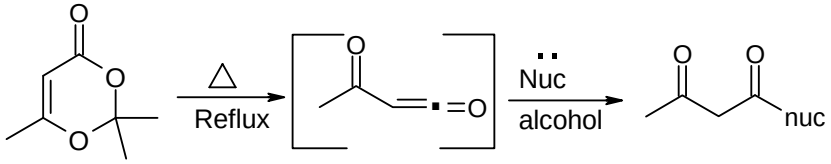


1 **2**

Scheme 2

2) Clemens[4] has reviewed acetoacetylation of alcohols by reaction with diketene in presence of acidic as well as basic catalysts as an alternative to diketene by the use of 2,2,6-trimethyl-*4H*, 1,3-dioxin-4-one as acylating agent of alcohol (scheme 3).

Clemens *et. al. J. Org. Chem.*, **1985**, *50*, 2431

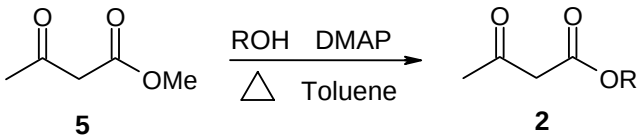


3 **4**

Scheme 3

3) Taber *et al*[5] have introduced a procedure for transesterification by use of DMAP as a catalyst (Scheme 4).

Taber *et. al J. Org. Chem*. **1985**, *50*, 3618



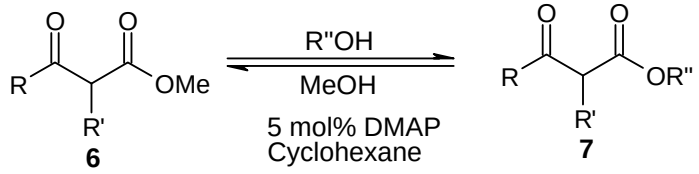
5 **2**

Scheme 4

This protocol gives valuable results though with some limitations, for instance, the reactions of non-enolisable β-ketoesters and tertiary alcohols failed to proceed under these conditions. Use of large amounts of DMAP (25 %) is another disadvantage of this protocol.

4) A modification of the above protocol has been suggested recently by Christoffers *et. al*[6] (scheme 5).

Christoffers *et. al*, *Eur. J. Org. Chem*. **2000**, *8*, 1633

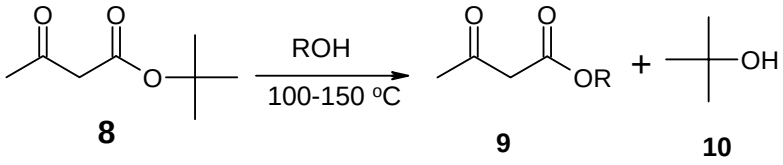


Scheme 5

The modification suggests the simultaneous removal of methanol generated during the course of the reaction. In this case only very high boiling alcohols have been used and the duration of the reaction is very long (overnight reactions). The yields obtained by this modification are comparable to the parent protocol.

5) Witzeman *et al* [7] have reported a convenient method for the transesterification of *tert*-butyl acetoacetates. Although the reaction procceds in excellent yields without the catalyst, this reaction however is limited to the use of *tert*-butyl acetoacetate only which in turn is very difficult to obtain and hence lacks generality (scheme 6).

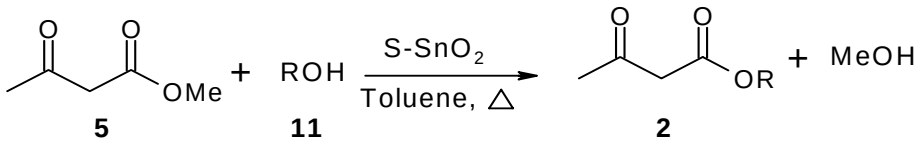
Witzeman *et. al. J. Org. Chem*. **1991**, *56*, 1713



Scheme 6

6) From our group the utility of S-SnO_2 was first time demonstrated as heterogenous catalyst for the transesterification of β-ketoesters.[8] The reaction conditions involving only simple toluene reflux and simultaneous distillation of the lower boiling alcohol. The yields are good to excellent in some cases. The other important feature of this methodology is that *tert*-butyl esters can also be accessed using this protocol. The recovery and reusability of the catalyst is the salient feature of this reaction (Scheme 7).

Chavan *et. al. Tetrahedron Lett*. **1996**, *37*, 233.

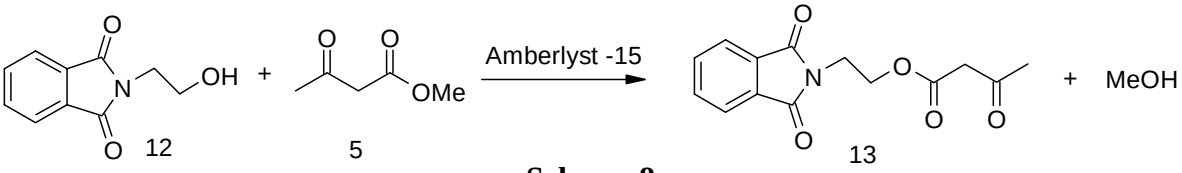


5 **11** **2**

Scheme 7

7) Use of Amberlyst –15 as an efficient heterogeneous catalyst for transesterification was also reported from our group.[9] The conditions remaining the same as that of previous scheme (scheme 8) involving the simultaneous distillation of lower boiling alcohol. The transesterification could even be performed on allyl alcohols, which is usually very difficult. The commercial availability of resin Amberlist-15 makes this an attractive choice for transesterification reaction.

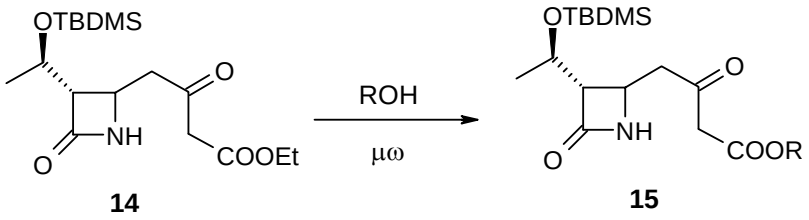
Chavan *et. al, Syn. Comm*. **2001**, *31*, 289.



Scheme 8

8) Recently Martelli *et. al*[10] have reported the use of microwaves for transesterification of β-ketoesters. (scheme 9).

Martelli and coworkers, *Syn. Comm.* **2000**, *30*, 1725.



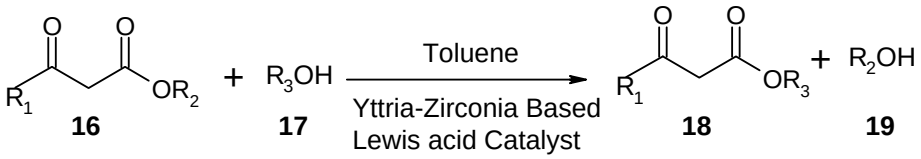
14 **15**

Scheme 9

The yields obtained are good to excellent in some cases. The disadvantage of this protocol is that only enolizable β-ketoesters furnished the transesterified products.

9) Yttria-Zirconia based catalyst has also been demonstrated as an effective catalyst to effect the transesterification of β-ketoesters (scheme 10).[11] Wide variety of alcohols have been used. The procedure has been extended to a wide variety of nucleophiles such as thiols and amines.

Kumar *et al. Synlett* **2000**, 251.

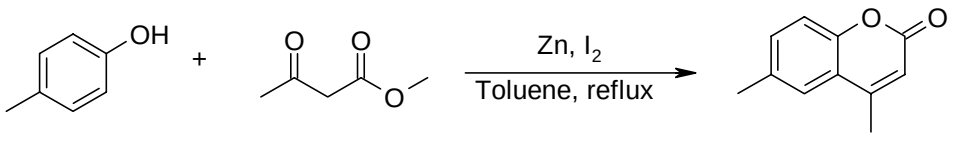


16 **17** **18** **19**

Scheme 10

10) Most recently our group has reported the transesterification of β-ketoesters using zinc and catalytic iodine (scheme 11).[12]

Chavan *et. al*. *Tetrahedron Lett*. **2002**, *43*, 8583



20 **21** **22**

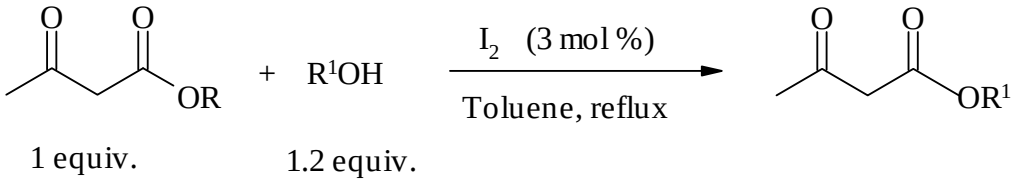
Scheme 11

The important feature of this protocol is that it describes transesterification of β-ketoesters not only with various aliphatic alcohols but also with phenols to furnish coumarins.

There are few other methods reported for the transesterification of β-ketoesters.[12]

2.3.2 Present work:

As mentioned earlier, β-ketoesters are very important synthons for various natural product syntheses and can be transformed easily into chiral building blocks.[14] Although the reactions are equilibrium driven reactions, most of the reactions utilize excess of reagent. A number of methods have been reported to effect transesterification of β-ketoesters.[12] Recent report on use of iodine[13] for transesterification of esters shows that iodine acts as an efficient catalyst to effect the transesterification. It has limitations as benzyl alcohol fails to undergo transesterification with normal esters. Additionally iodine catalysed protocol involves use of excess alcohol to push the equilibrium driven reaction in the desired direction, requiring long periods of time. Recently our group has demonstarted that zinc can be activated by iodine[14] and this reagent was shown to effect transesterification with normal alcohols as well as phenols to furnish coumarins. These finding prompted us to explore the transesterification of β-ketoesters using iodine as a catalyst, which could be a cheap and easily available commercial alternative for reported catalysts (scheme 12).



Scheme 12

2.3.3 Results and discussion

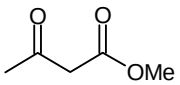
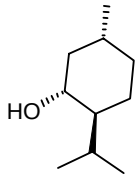
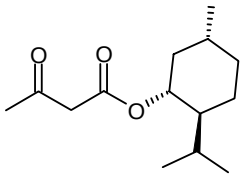
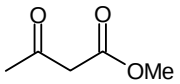
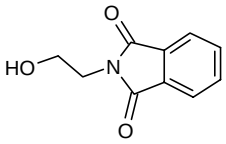
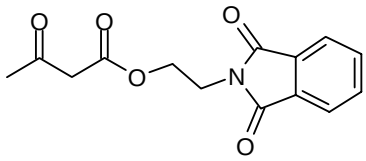
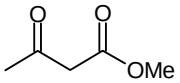
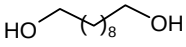
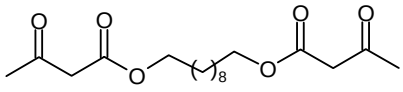
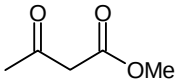
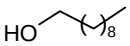
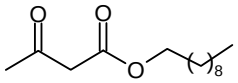
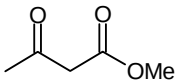
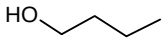
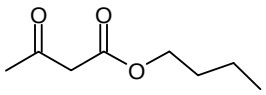
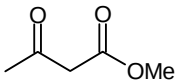
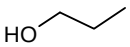
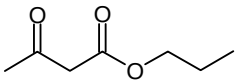
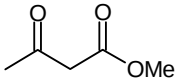
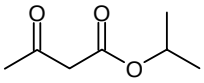
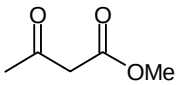
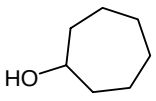
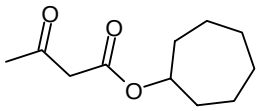
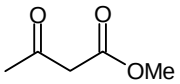
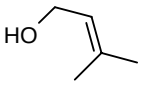
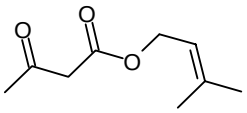
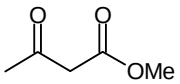
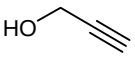
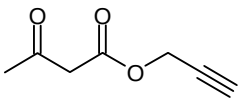
A wide variety of alcohols have been used to transesterify different β-ketoesters like methyl acetoacetate, ethyl acetoacetate, ethyl cyclopentanone-2-carboxylate and 5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylic acid methyl ester (entry 14 in table 1) using iodine in catalytic (3mol %) amounts to yield the corresponding transesterified products in moderate to excellent yields. The reaction was pushed in the forward direction by simultaneous distillation of low boiling alcohol (methanol or ethanol).

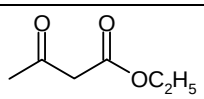
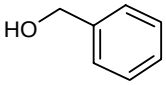
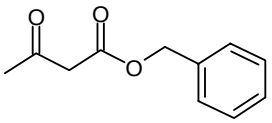
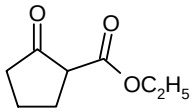
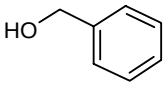
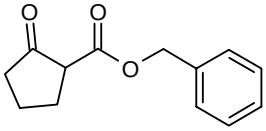
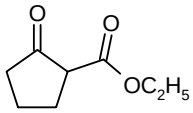
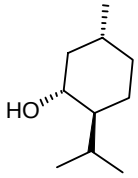
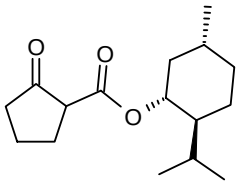
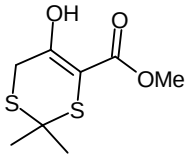
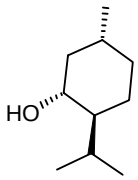
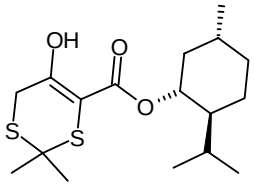
In a typical experimental procedure, ethyl acetoacetate (1 equiv.), benzyl alcohol (1.2 equiv.), iodine (3 mol %) in toluene (10 ml) were placed in 50 ml round bottom flask fitted with a distillation condenser. The reaction mixture was heated to reflux temperature for 5h to give transesterified product in 83 % yield. The transesterified product was characterized by IR and ^{1}H-NMR spectroscopy. The ^{1}H NMR spectrum displayed the presence of a singlet at 5.18 δ corresponding to benzylic protons and a singlet at 3.50 δ corresponding to –OC-CH_2. The disappearance of the –OCH_2CH_3 group from ethyl acetoacetate confirmed the formation of transesterified product.

The results of this protocol are summarized in table 1. The noteworthy feature of our protocol is that β-ketoesters like ethyl acetoacetate and ethyl cyclopentanone-2-carboxylate underwent transesterification by benzyl alcohol to furnish the transesterified products in good yields (83% and 88% respectively). In most of the cases only 1.2 equivalents of alcohols are sufficient for efficient conversions. However in case of volatile alcohols like 2-propanol, 1-propanol and propargyl alcohol 2 equivalents of alcohol is required to obtain good yields of the corresponding ester.

The other important feature of this protocol is that transesterification of β-ketoesters by various alcohols like benzyl, allylic, propargyl alcohols has been effectively catalysed by iodine giving products with moderate to high yields with comparatively less reaction time. Although several aliphatic esters underwent smooth transesterification, phenols did not undergo transesterification reaction with either methyl acetoacetate or ethyl acetoacetate.

Table 1: Iodine catalysed transesterification of β-ketoesters.[a]

Sr. No.	β-ketoester	Alcohol[b]	Product	Time h	% Yields
1				4	96
2				6.5	87
3				7	79[c]
4				5	86
5				5	81
6				7	65[d]
7				7	63[d]
8				5	89
9				4	74
10				6.5	80[d]

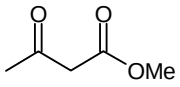
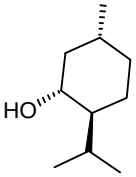
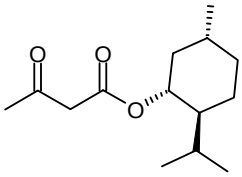
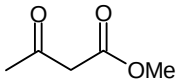
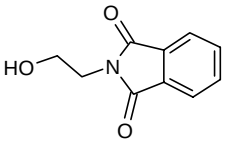
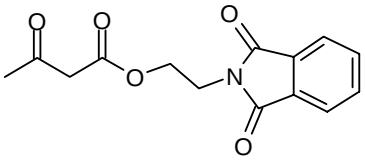
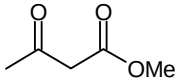
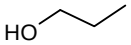
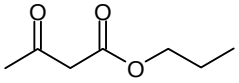
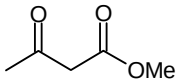
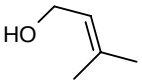
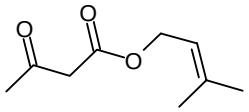
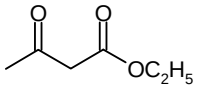
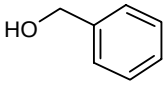
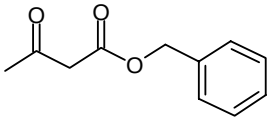
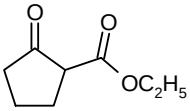
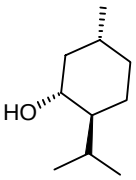
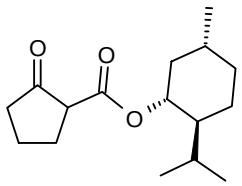
11				5	83
12				5	88
13				4.5	92
14				4	96

a. 3 mol % of iodine is used. b. 1.2 equivalents of alcohol is used. c. 0.5 equivalents of alcohol is used. d. 2 equivalents of alcohol is used. e. All the compounds were characterized by physical and spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR, Mass etc.) and comparision with authentic samples. f. Yields are of isolated products.

In order to ascertain the role of iodine as a catalyst in enhancing the rate of the reaction, some examples of transesterification were conducted in the absence of iodine (table 2). From table 2 it is clear that the time required for the reaction by employing iodine as the catalyst is considerably reduced.

Phenols did not undergo transesterification with β-ketoesters when subjected to iodine as the catalyst and formation of coumarins was not observed as was the case with zinc and iodine in the successful synthesis of coumarins.[12]

Table 2: Transesterification of β-ketoesters in the absence of catalyst.

Sr. No.	β-ketoester	Alcohol[a]	Product	Time h	% Yields
1				15	93
2				18	92
3				21	61[b]
4				8.5	71
5				13	85
6				16	94

a. 1.2 equivalents of alcohol used. b. 3 equivalents of alcohol used.

2.3.4 Conclusion

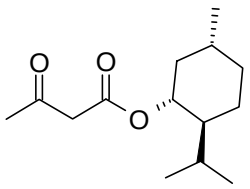
The present protocol describes a simple and efficient method for the transesterification of β-ketoesters by different alcohols catalysed by iodine**.** The use of different β-ketoesters such as methyl acetoacetate, ethyl acetoacetate (entry 11), ethyl cyclopentanone-2-carboxylate (entries 12 and 13) and 5-hydroxy-2,2-dimethyl-6*H*-(1,3) dithiine-4-carboxylic acid methyl ester (entry 14) and various types of alcohols makes this protocol a more generalized one.

Mild conditions, ease of work-up and efficiency are the main features of this protocol. The reaction time for the present protocol is less as compared to most of the literature reports. Most of the reagents reported for transesterification are toxic, expensive or difficult to prepare. The ready availability of iodine along with efficiency, simplicity and superiority over the existing methods should make this protocol an attractive addition to the arsenal of synthetic chemists.

2.3.5 Experimental

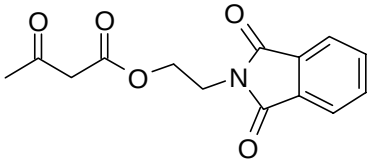
Typical procedure:- In a typical experimental procedure, methyl acetoacetate (1.004 g, 8.655 mmol, 1 equiv.), menthol (1.620 g, 10.386 mmol, 1.2 equiv.), iodine (66 mg, 0.26 mmol, 3 mol %) in toluene (10 ml) were taken in 50 ml round bottom flask fitted with distillation condenser. The reaction mixture was heated to 115-120 ^{o}C (oil bath temperature) for 4h. The reaction was monitored by TLC and after completion of the reaction, the reaction mixture was cooled, washed with sodium thiosulphate solution and subsequently with water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography to give the transesterified product (1.988 g, 96 %).

Menthyl 3-oxobutanoate[9]



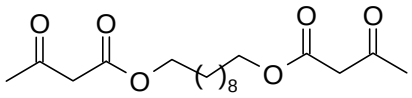
Molecular Formula	:	$C_{14}H_{24}O_3$
Yield	:	96 %
IR ($CHCl_3$, cm^{-1})	:	2926, 2871, 1339, 1739,1717, 1648, 1456, 1313, 1149, 1026.
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 4.75 (dt, *J* = 4.4, 10.7 Hz, 1H), 3.45 (s, 2H), 2.25 (s, 3H), 1.9-2.1 (m, 2H), 1.65-1.75 (m, 2H), 1.4 – 1.5 (m, 2H), 0.9-1.2 (m, 9H), 0.85 (d, *J* = 6 Hz, 3H).
$[\alpha]_D^{25}$	:	-72.00, (c=10.24, benzene). {lit.[10] $[\alpha]_D^{20}$ = -69.3, (c=10, benzene)}.

N-(2-Pthalimidoethyl)-3-oxobutanoate [9]



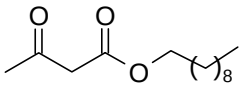
Molecular Formula	:	$C_{14}H_{13}O_5N$
Yield	:	87 %
M. P.	:	87-88 ^{0}C (lit.[9] mp = 88-89 ^{0}C).
IR ($CHCl_3$, cm^{-1})	:	3022, 1775, 1746, 1717, 1616, 1469, 1429, 1395, 1035, 759.
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 7.85 (dd, *J* = 2.9, 8.3 Hz 2H), 7.75 (dd, *J* = 2.9, 8.3 Hz, 2H), 4.38 (t, *J* = 4.9 Hz, 2H), 3.97 (t, *J* = 4.9 Hz, 2H), 3.42 (s, 2H), 2.25 (s, 3H).
MS (ESI, Solv.: CH_3CN + H_2O + CH_3COONH_4)	:	m/z = 293.02 (M + NH_4^+), 276.02 (M + 1).

Decane-1, 10-diyl Bis(3-oxobutanoate)[11]



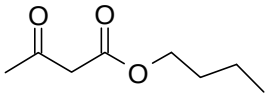
Molecular Formula	:	$C_{18}H_{30}O_6$
Yield	:	79 %
IR ($CHCl_3$, cm^{-1})	:	3021, 2932, 1740, 1716, 1317, 1152, 1037, 759.
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 4.09 (t, *J* = 6.4 Hz, 4H), 3.40 (s, 4H), 2.24 (s, 6H), 1.50-1.65 (m, 4H), 1.10-1.40 (m, 12H).

Decyl 3-oxobutanoate[9]



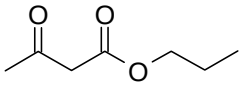
Molecular Formula	:	$C_{14}H_{26}O_3$
Yield	:	86 %
IR ($CHCl_3$, cm^{-1})	:	3024, 2928, 2857, 1742, 1717, 1652, 1467, 1316, 1236, 1152, 1037, 759.
^{1}H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 4.06 (t, *J* = 6.4 Hz, 2H), 3.37 (s, 2H), 2.21 (s, 3H), 1.51-1.61 (m, 2H), 1.14-1.40 (m, 14H), 0.82 (t, *J* = 6.4 Hz, 3H).

Butyl 3-oxobutanoate[9]



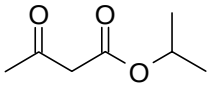
Molecular Formula	:	$C_8H_{14}O_3$
Yield	:	81 %
IR ($CHCl_3$, cm^{-1})	:	2962, 2936, 2876, 1742, 1719, 1650, 1412, 1317, 1152, 1063, 1033, 757.
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 4.11 (t, *J* = 6.8 Hz, 2H), 3.42 (s, 2H), 2.24 (s, 3H), 1.60 (tt, *J* = 2.6, 6.8 Hz, 2H), 1.35 (tq, *J* = 7.3, 6.8 Hz, 2H), 0.91 (t, *J* = 6.8 Hz, 3H).

Propyl 3-oxobutanoate[9]



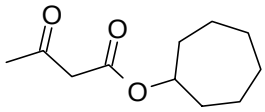
Molecular Formula	:	$C_7H_{12}O_3$
Yield	:	65 %
IR ($CHCl_3$, cm^{-1})	:	3022, 2970, 2930, 1740, 1716, 1395, 1086, 758.
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 4.06 (t, *J* = 6.8 Hz, 2H), 3.42 (s, 2H), 2.24 (s, 3H), 1.65 (tq, *J* = 6.8, 7.3 Hz, 2H), 0.93 (t, *J* = 6.8 Hz, 3H).

Isopropyl 3-Oxobutanoate[15]



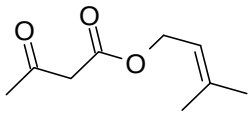
Molecular Formula	:	$C_8H_{12}O_3$
Yield	:	63 %
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 4.99 (m, 1H), 3.33 (s, 2H), 2.19 (s, 3H), 1.20 (d, *J* = 6.4 Hz, 6H).

Cycloheptyl 3-oxobutanoate[9]



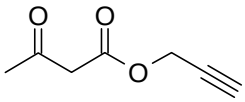
Molecular Formula	:	$C_{11}H_{18}O_3$
Yield	:	89 %
IR ($CHCl_3$, cm^{-1})	:	3021, 2933, 1744, 1713, 1408, 763, 669.
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 4.97 (m, 1H), 3.39 (s, 2H), 2.25 (s, 3H), 1.86-1.98 (m, 2H), 1.42-1.73 (m, 10H).

Prenyl 3-oxobutanoate[15]



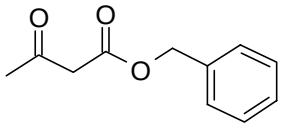
Molecular Formula	:	$C_9H_{14}O_3$
Yield	:	74 %
IR ($CHCl_3$, cm^{-1})	:	2975, 2935, 1739, 1718, 1676, 1648, 1447, 1380, 1361, 1337, 1151, 1029, 957.
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 5.29 (t, *J* = 7.3 Hz, 1H), 4.57 (d, *J* = 7.3 Hz, 2H), 3.38 (s, 2H), 2.21 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H).

Propargyl 3-oxobutanoate[15]



Molecular Formula	:	$C_7H_8O_3$
Yield	:	80 %
^1H NMR ($CDCl_3$ + CCl_4, 200MHz)	:	δ = 4.70 (d, *J* = 2.4 Hz, 2H), 3.46 (s, 2H), 2.48 (t, *J* = 2.4 Hz, 1H), 2.24 (s, 3H).

Benzyl 3-oxobutanoate[9]



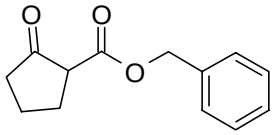
Molecular Formula : $C_{11}H_{12}O_3$

Yield : 83 %

^{1}H NMR : δ = 7.36 (s, 5H), 5.18 (s, 2H), 3.50 (s, 2H), 2.25 (s, 3H).

($CDCl_3$ + CCl_4, 200MHz)

Benzyl 2-oxacyclopentane-1-carboxylate [6]



Molecular Formula : $C_{13}H_{14}O_3$

Yield : 88 %

IR ($CHCl_3$, cm^{-1}) : 2962, 1750, 1729, 1456, 1157, 1111, 1028, 751, 698.

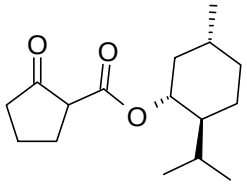
^{1}H NMR : δ = 7.32 (s, 5H), 5.14 (s, 2H), 3.16 (t, *J* = 8.8 Hz, 1H),

($CDCl_3$ + CCl_4, 200MHz) 2.25-2.33 (m, 4H), 2.15 (m, 1H), 1.87 (m, 1H).

^{13}C NMR : δ = 211.3 (s), 168.9 (s), 135.5 (s), 128.3 (d), 128.0 (d),

($CDCl_3$ + CCl_4, 50MHz) 127.8 (d), 66.7 (t), 54.4 (d), 37.7 (t), 27.2 (t).

(-)-Menthyl 2-oxacyclopentane-1-carboxylate [6]



Molecular Formula : $C_{16}H_{25}O_3$

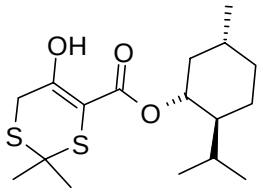
Yield : 92 %

IR ($CHCl_3$, cm^{-1}) : 2925, 2856, 1755, 1714, 1456, 1377, 1300, 1183, 1038.

^{1}H NMR : δ = 4.75 (m, 1H), 3.11 (m, 1H), 2.14-2.43 (m, 4H), 1.75-

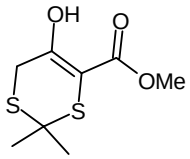
($CDCl_3$ + CCl_4, 200MHz)		2.14 (m, 4H), 1.55-1.75 (m, 2H), 1.23-1.55 (m, 3H), 0.65-1.05 (m, 11H).
^{13}C NMR	:	(Mixture of two diasteriomers, partly doubled signals) δ
($CDCl_3$ + CCl_4, 50MHz)		= 211.1 (s), 168.5 (s), 74.6 (d), 54.6 (d), 54.3 (d), 46.6 (d), 40.4 (t), 37.4 (t), 33.9 (t), 31.0 (d), 27.7 (t), 26.9 (t), 25.8 (t), 25.3 (t), 23.1 (t), 22.8 (t), 21.7 (q), 20.7 (q), 15.9 (q), 15.6 (q).

Menthyl-5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylate

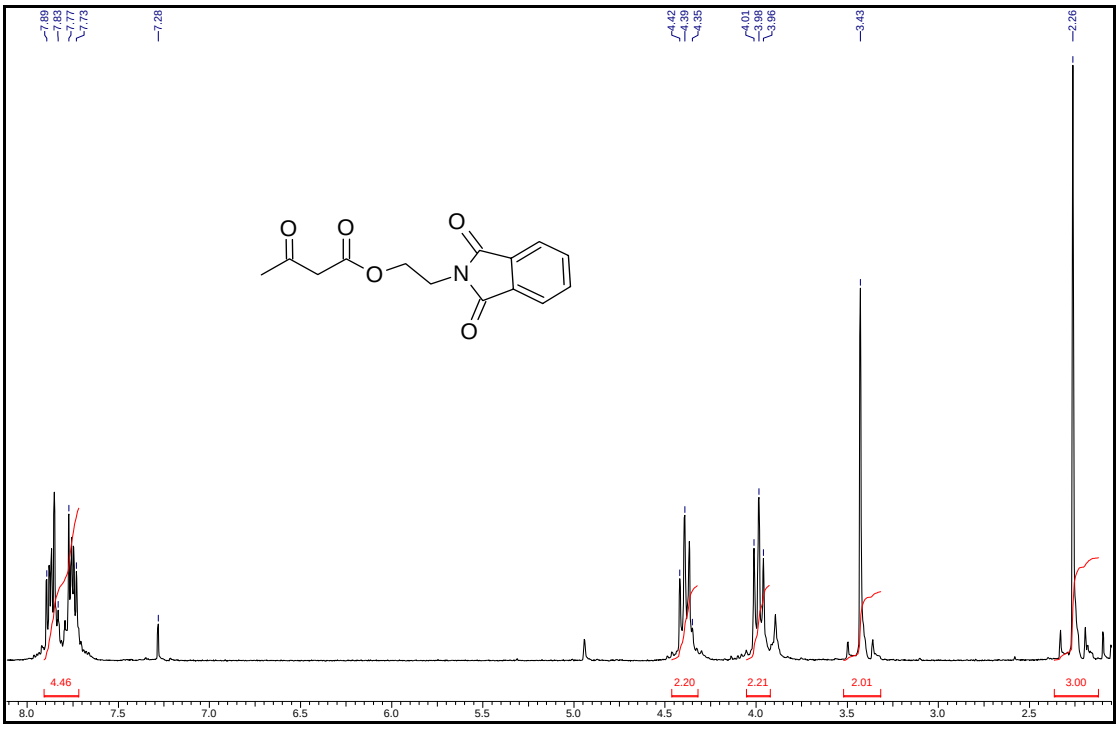


Molecular Formula	:	$C_{17}H_{28}O_3S_2$
Yield	:	96 %
$[\alpha]_D^{25}$	:	-76.30 (c = 2.2, benzene).
IR ($CHCl_3$, cm^{-1})	:	2958, 2925, 2871, 1717, 1632, 1587, 758.
^1H NMR	:	δ = 12.81 (s, 1H), 4.78 (dt, *J* = 3.9, 10.4 Hz, 1H), 3.45 (d,
($CDCl_3$ + CCl_4, 200MHz)		*J* = 8.6 Hz, 2H), 1.79-2.08 (m, 2H), 1.70 (s, 3H), 1.66 (s, 3H), 1.47-1.60 (m, 2H), 1.07-1.27 (m, 2H), 0.89-0.95 (m, 9H), 0.76 (d, *J* = 7.4, 3H).
^{13}C NMR	:	δ = 174.3 (s), 170.0 (s), 95.8 (s), 75.30 (d), 55.9 (s), 46.4
($CDCl_3$ + CCl_4, 200MHz)		(d), 40.4 (t), 33.9 (t), 32.1 (q), 31.8 (t), 31.1 (d), 26.0 (d), 23.2 (t), 21.7 (q), 20.4 (q), 16.1 (q).
MS (ESI, Solv.: CH_3CN +	:	m/z = 362.05 ($M + NH_4^+$), 345.05 (M + 1)
H_2O + CH_3COONH_4)		

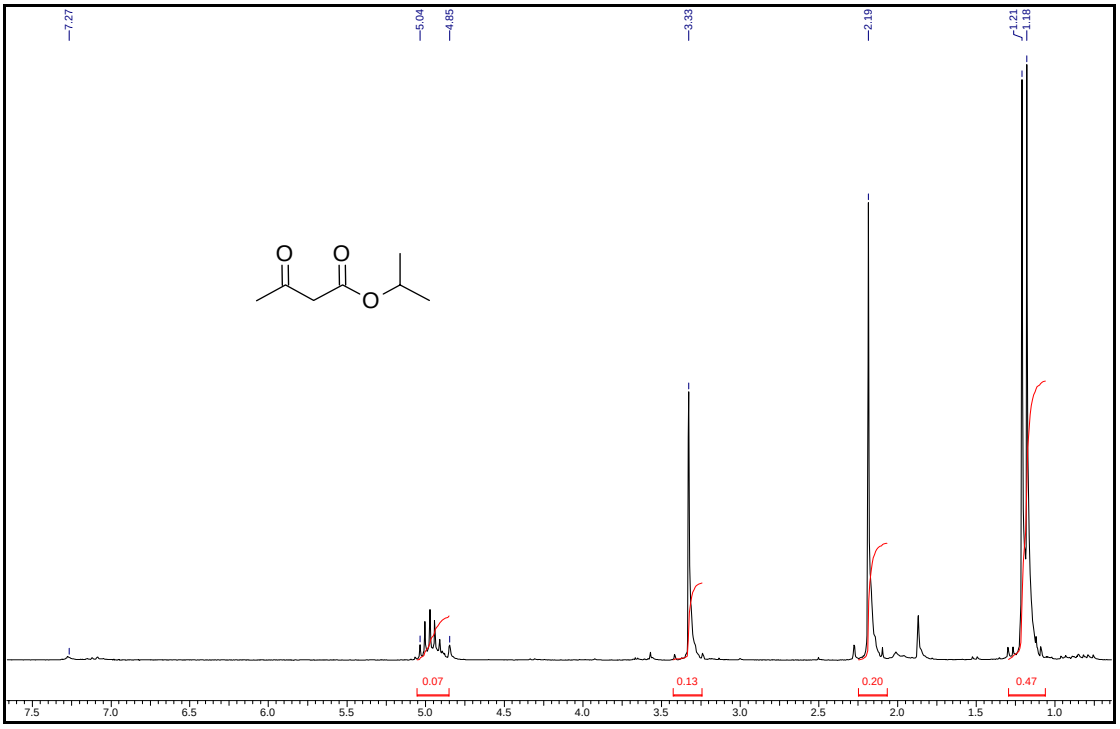
Methyl-5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylate [16]



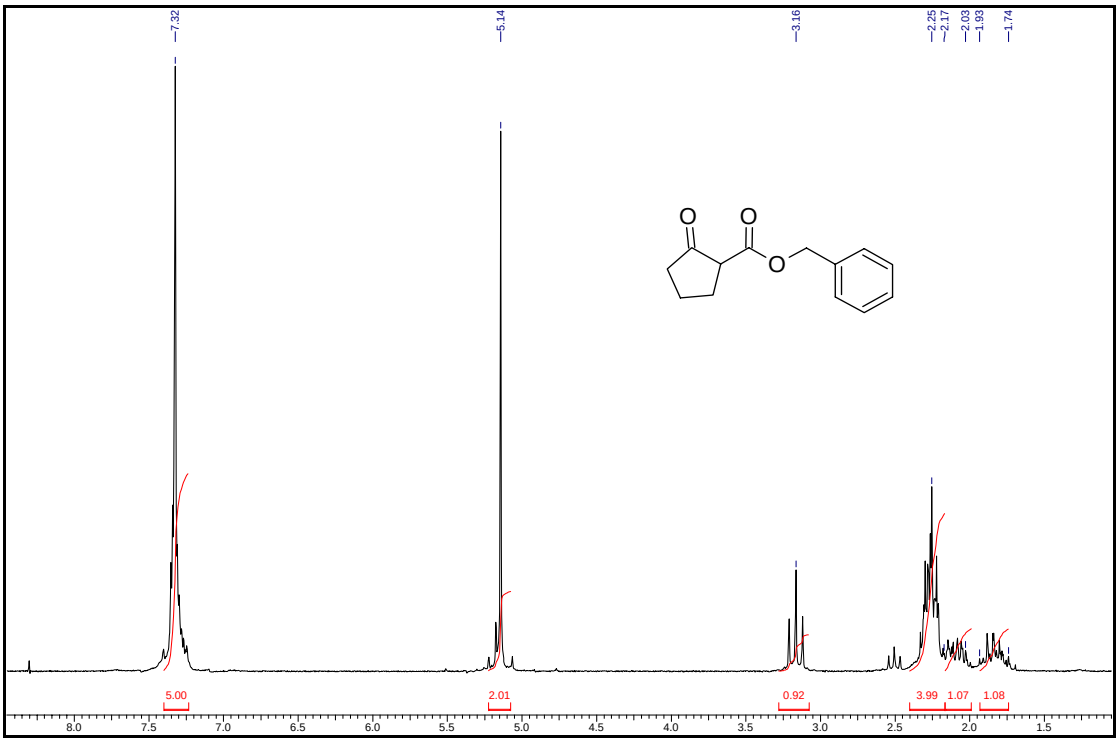
Molecular Formula	:	$C_8H_{12}O_3S_2$
Yield	:	86 %
M. P.	:	49 ^oC (pale yellow solid)
IR ($CHCl_3$, cm^{-1})	:	3194, 3168, 3099, 2959, 2907, 2850, 1653, 1571, 1434, 1311, 1203, 1141, 1062, 775.
^1H NMR ($CDCl_3$, 200MHz)	:	δ = 12.60 (s, 1H), 3.84 (s, 3H), 3.46 (s, 2H), 1.70 (s, 6H).
^{13}C NMR ($CDCl_3$, 50MHz)	:	δ = 31.9 (q), 32.0 (t), 52.0 (q), 55.8 (s), 95.8 (s), 171.0 (s), 174.4 (s).
Mass (EI)	:	m/z = 220 (34), 188 (20), 170 (18), 160 (28), 146 (21), 127 (60), 114 (82), 103 (21), 86 (100), 74 (90), 69 (15), 59 (43).



^{1}H NMR spectrum of *N*-(2-Pthalimidoethyl)-3-oxobutanoate ($CDCl_3$ + CCl_4, 200 MHz)

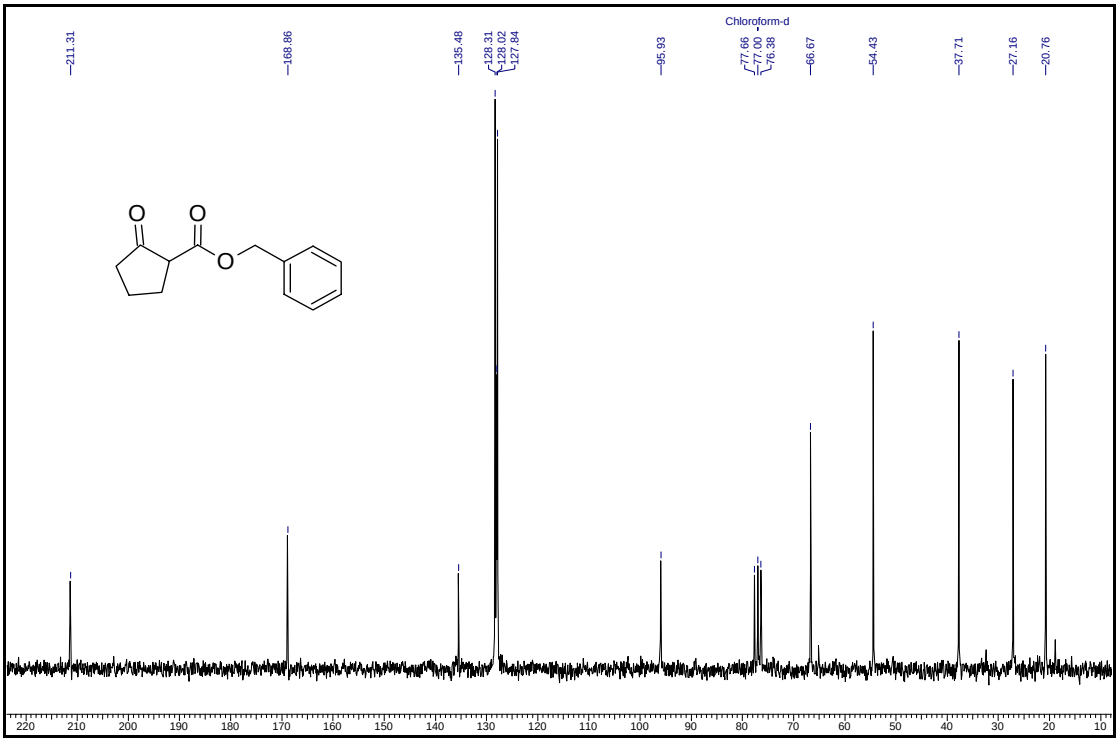


^{1}H NMR spectrum of isopropyl 3-oxobutanoate ($CDCl_3$ + CCl_4, 200 MHz)



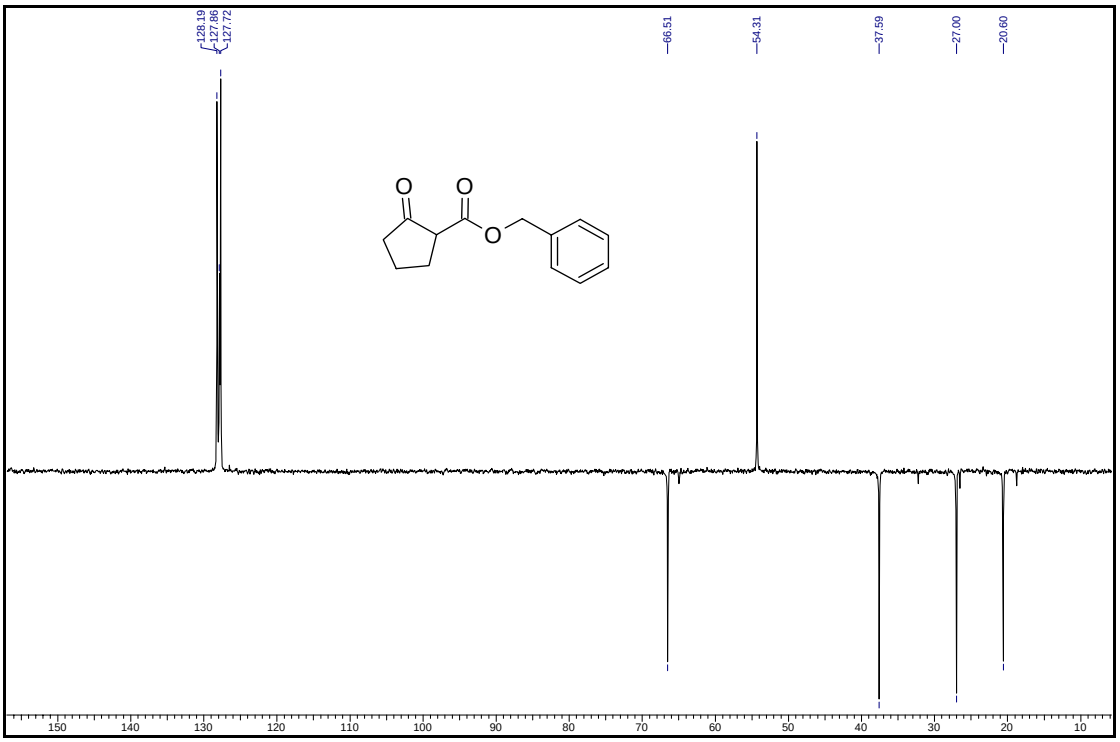
^{1}H NMR spectrum of benzyl 2-oxacyclopentane-1-carboxylate

($CDCl_3$ + CCl_4, 200 MHz)

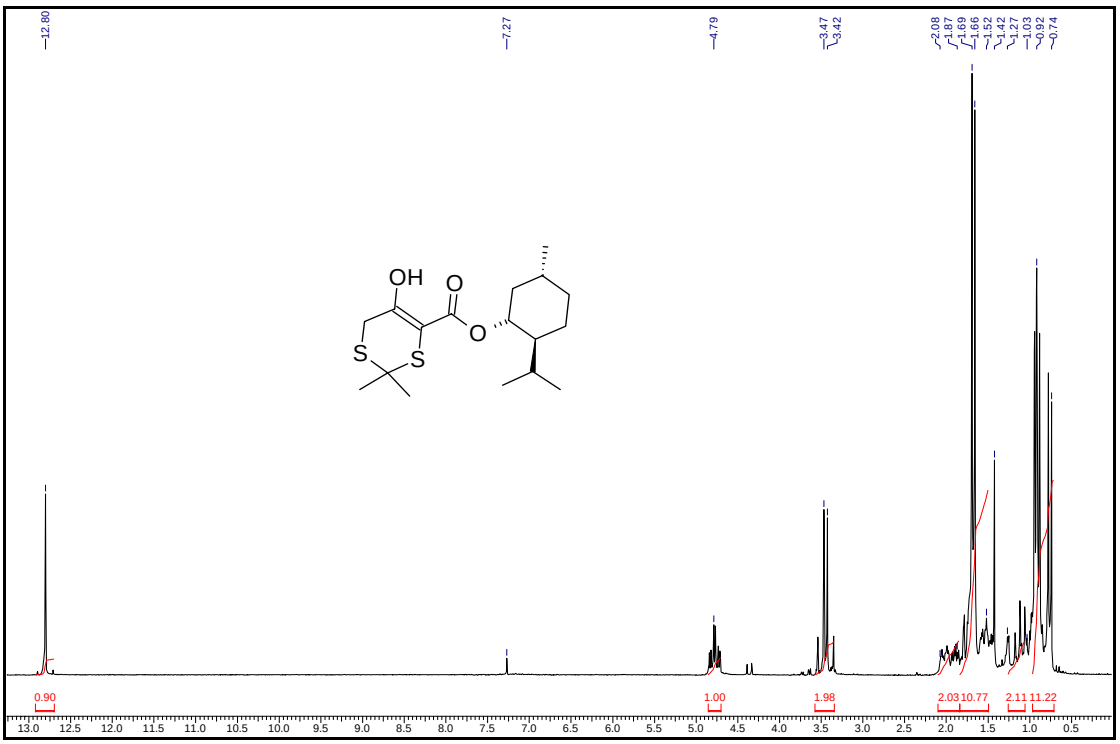


^{13}C NMR spectrum of benzyl 2-oxacyclopentane-1-carboxylate

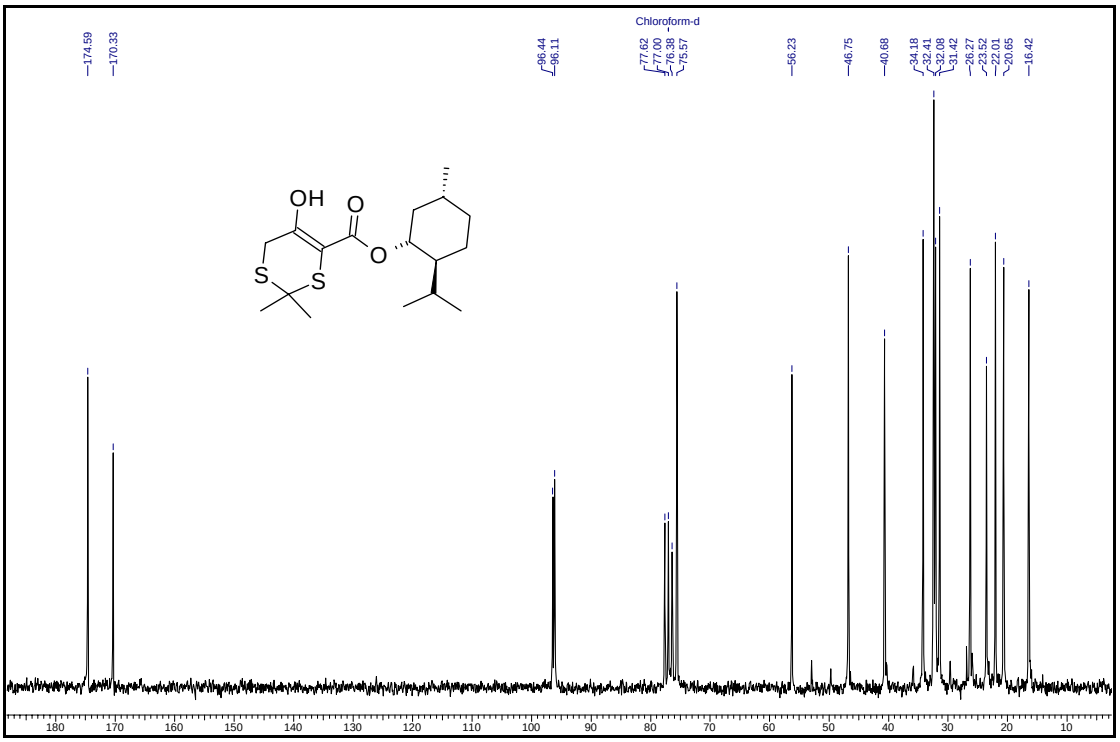
($CDCl_3$ + CCl_4, 50 MHz)



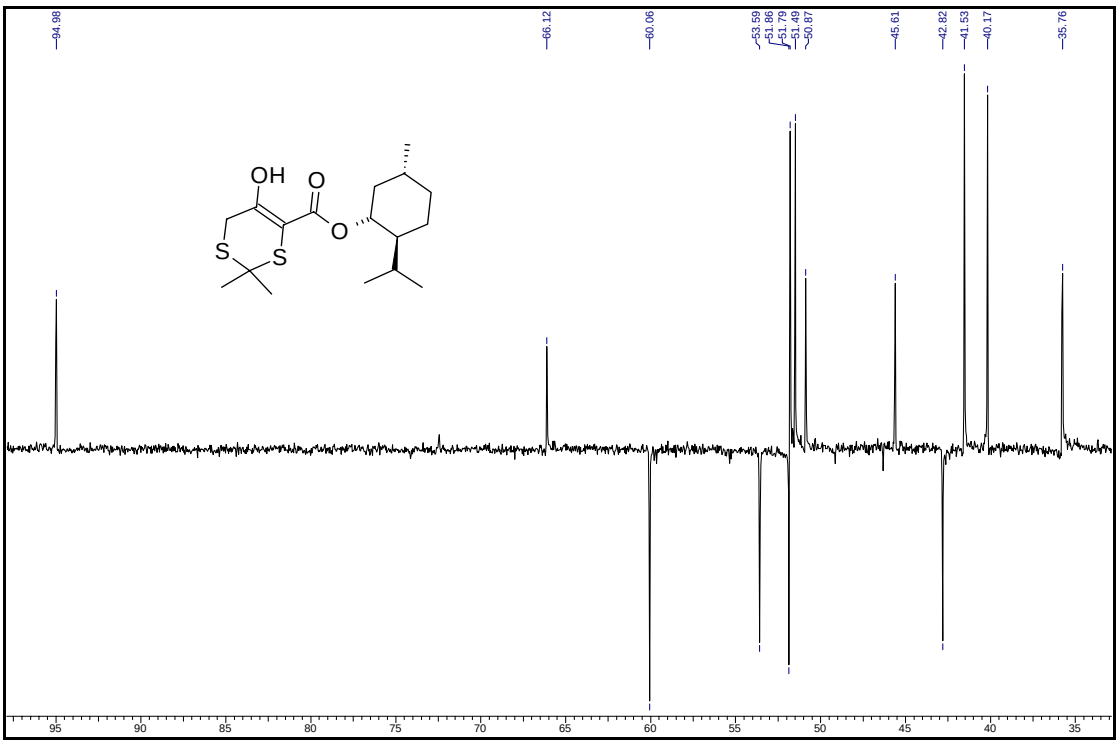
DEPT NMR spectrum of benzyl 2-oxacyclopentane-1-carboxylate ($CDCl_3$ + CCl_4, 50 MHz)



^{1}H NMR spectrum of menthyl-5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylate ($CDCl_3$ + CCl_4, 200 MHz)



^{13}C NMR spectrum of menthyl-5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylate ($CDCl_3$ + CCl_4, 50 MHz)



DEPT NMR spectrum of menthyl-5-hydroxy-2,2-dimethyl-*6H*-(1,3) dithiine-4-carboxylate ($CDCl_3$ + CCl_4, 50 MHz)

2.3.6 References

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