NEW SYNTHETIC METHODOLOGIES FOR THIO- AND DETHIO-ACETALIZATION OF CARBONYL COMPOUNDS, AND DESILYLATION OF *TERT*-BUTYLDIMETHYLSILYL ETHERS

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

by

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to the

DEPARTMENT OF CHEMISTRY
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April, 2004

Dedicated to my late father

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI
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CERTIFICATE-I

This is to certify that Mr. Ejabul Mondal has satisfactorily completed all the courses required for the Ph. D. degree programme.
These courses include:

CH 603	Supra Molecules: Concept and Applications
CH 611	Bio Inorganic Chemistry
CH 627	New Reagents in Organic Synthesis
CH 630	A Molecular Approach to Physical Chemistry

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This is to certify that Mr. Ejabul Mondal has been working in my research group since March 30, 1999. At the beginning, he joined as a Junior Research Fellow in the CSIR project and later on, he has been registered as a self-sponsored Ph. D student on January 4, 2002 in the Department of Chemistry. Subsequently, he has been converted as regular registered Ph. D. student from August 15, 2002. I am forwarding his thesis entitled "NEW SYNTHETIC METHODOLOGIES FOR THIO- AND DETHIOACETALIZATION OF CARBONYL COMPOUNDS, AND DESILYLA-TION OF *TERT*-BUTYLDIMETHYL SILYL ETHERS" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

(Dr. A. T. Khan)

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor Abu T. Khan.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

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Ejabul Mondal

SUMMARY

This dissertation describes the successful efforts on the development of new synthetic methodologies in protection-deprotection chemistry for thio- and dethioacetalization of carbonyl compounds and desilylation of *tert*-butyldimethylsilyl ethers to the hydroxyl compounds.

The thesis contains mainly three chapters. Each chapter is subdivided into two parts viz. **Part I** and **Part II**.

In each of the Chapter**, Part I** describes a review of literature of the present work and its significance. Similarly, in each chapter of the **Part II** is subdivided into sections, which give an account of the work carried out by the candidate.

Chapter I, Part I briefs the usefulness and importance of dithioacetals in organic synthesis as well as a survey of their preparations from the corresponding carbonyl compounds. In addition, it also highlights reasons for choosing the present research problem for investigation.

In **Chapter I, Part II** consists of three sections viz., **Section A**, **Section B** and **Section C,** respectively**.** Each section describes a new synthetic protocol for thioacetalization of carbonyl compounds

Section A gives a description of a new method for chemoselective thioacetalization of aldehydic compounds by using nickel(II) chloride as an efficient and useful catalyst.

By applying this methodology, various aromatic and aliphatic aldehydes are smoothly converted into the corresponding acyclic and cyclic dithioacetals **25**, **34**, **66**, **98, 99**, **100, 101-120** in good to high yields depending upon the substrates and thiol or dithiols used as indicated in the Table 1. A large number of other protecting groups such as acetyl (for example, **108** and **109**), benzoyl (**110**), benzyl (**107**), allyl (**106**), TBS ether (**105**), esters (**120**) are stable during the reaction conditions. Moreover, a chemoselective thioacetlization of an aldehyde group in presence of a keto group in the same molecule, for substrate **129**, is possible by our method. However, thioketalisation of ketones are unsuccessful even after prolonged reaction times. All the protected compounds are fully characterized by IR, ^{1}H NMR ^{13}C NMR and by elemental analyses, all are in full agreement with the expected products.

Section B gives an account of a simple and practical synthetic protocol for thioacetalization of carbonyl compounds by using acetyl chloride under solvent free-conditions.

When a mixture of aldehyde or ketone (10 mmol) and dithiol (10 mmol) or thiol (22 mmol) was treated with a catalytic amount of acetyl chloride (72 μL, 1 mmol or 144 μL, 2 mmol for a ketone) at room temperature, it smoothly converted to the corresponding dithioacetal derivatives in good yields. The final products can be obtained either by direct recrystallisation or by distillation under reduced pressure depending upon the nature of the products. By applying this methodology, both cyclic as well as acyclic dithioacetals of various aldehydes and ketones were prepared in very good yields on reaction with the respective thiols or dithiols. It is important to mention that hydroxyl aldehydes can be easily protected to the desired dithioacetals (**29** and **114**) without acetylating the hydroxyl groups under the reaction conditions. More interestingly, highly acid sensitive substrates such as an ester aldehyde and 2-furaldehyde were also converted to the corresponding dithioacetals (**120** and **134**) in fairly good yields as mentioned in the Table 2. By applying our protocol, dithioacetalization of D-arabinose and a highly hindered ketone such as benzophenone can be protected to the corresponding dithioacetal derivatives **135** and **136**, respectively in fairly high yield and shorter time. The protected dithioacetals are characterized by usual spectroscopic techniques.

Section C elaborates an exceptionally simple and convenient synthetic protocol for thioacetalization of the carbonyl compounds by employing bromodimethylsulfonium bromide ($Me_2S^+BrBr^-$) as a new pre-catalyst under solvent-free conditions.

When a mixture of carbonyl compounds (1 mmol) and thiol (2.2 mmol) or dithiol (1.1 mmol) was subjected with a catalytic amount of bromodimethylsulfonium bromide (0.05 mmol for aldehyde and 0.15 mmol for ketone) at room temperature, it converted readily to the corresponding dithioacetals. After completion of the reaction, the reaction mixture was passed directly through a silica gel column in a non-aqueous work up to obtain the pure product. By applying this methodology, various aldehydes and ketones are smoothly converted into the corresponding dithioacetals. The potentiality of the present method is that various dithioacetals can be obtained in large scale from the corresponding carbonyl compounds by using bromodimethylsulfonium bromide. The successful results are discussed in the Table 3 in **Chapter I**, **Part II** in **section C**. Moreover, this method is chemoselective for aldehyde group protection instead of ketonic group present in the same molecule. It is noteworthy to mention that no bromination takes place during experimental conditions and the reaction can also be performed in the presence of a large number of other protecting groups.

Chapter II is divided again into two parts as usual **Part I** and **Part II.**

Chapter II, Part I provides a brief review on the cleavage of various dithioacetals into the corresponding carbonyl compounds by using various reagents and their drawbacks. This part also emphasizes reasons for taking up the research problem for our present study.

Chapter II, **Part II** is divided into four sections such as **Section A**, **Section B**, **Section C**, and **Section D**, respectively.

Section A tells about an expedient and efficient method for the cleavage of dithioacetals to the corresponding carbonyl compounds by employing organic ammonium tribromides (OATB), namely by using cetyltrimethylammonium tribromide (CetTMATB) and tetrabutylammonium tribromide (TBATB) as new reagents.

Various dithianes and acyclic diethyl dithioacetals **34**, **38**, **111**, **132**, **135**, **184**, **185**, **186**, **187** and **188** are hydrolyzed to the corresponding carbonyl compounds **65**, **85**, **162**, **189**, **190**, **191**, **192**, **193**, and **194** as mentioned in the Table 4, on treatment with either CetTMATB or TBATB. The products are compared with the authentic compound by co-IR, mix melting point as well as characterized by ^{1}H NMR and elemental analyses. Interestingly, no aromatic ring brominations or any other brominations are observed by this procedure.

Section B describes a new method for deprotection of dithioacetals by oxidation of ammonium bromide promoted by $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$-$H_2O_2$.

We have noticed that a 1: 3: 0.2: 10: 0.1 substrate to ammonium bromide to ammonium heptamolypdate to hydrogen peroxide to perchloric acid stoichiometry was found to be optimal (ostensibly to speed conversions to products with high yields and CH_2Cl_2/H_2O 1:1, 4 mL of solvent per mmol of substrate) to provide good yields. By applying this procedure, various protected compounds are cleaved chemoselectively into the parent carbonyl compounds in good yields (60-88%) within a short time as shown in the Table 4.

Section C describes a useful and environmentally benign synthetic protocol for dethioacetalization by employing vanadium pentoxide catalyzed oxidation of ammonium bromide by hydrogen peroxide

We observe that (1: 1: 0.1: 10) substrate / ammonium bromide / vanadium pentoxide / hydrogen peroxide in CH_2Cl_2-H_2O solvent (5:1, 6 mL per mmol of substrate) gives the best result for deprotection of dithioacetals to the parent carbonyl compounds. By following the above typical procedure, various protected compounds are chemoselectively deprotected to the parent carbonyl compounds within a short period as mentioned in the Table 6. The deprotected products are characterized by recording IR and compared with the authentic sample spectra as well as ^{1}H NMR and elemental analysis. In this method, we have tried

deprotection of dithioacetals by using a combination of V_2O_5 and H_2O_2 without involvement of ammonium bromide. We have noticed that no deprotection was observed without adding ammonium bromide. From this observation, it is quite clear that bromonium ion is responsible for hydrolysis.

In Chapter II, Section D we describe a highly efficient procedure for regeneration carbonyl groups from their corresponding dithioacetals using sodium nitrite and acetyl chloride.

In **Chapter II** of the **Part II** in **Section A**, **Section B** and **Section C**, we had already shown that the electrophile Br^+ ion, is a good reactive species for hydrolysis of dithioacetals. We intended to find out whether other electrophile, such as NO^+, could be used for regeneration of carbonyl compounds from their corresponding dithioacetals. We had found that acetyl chloride and sodium nitrite is a good combination for *in situ* generation of NO^+ ion. By using this combination, we have developed another methodology for dethioacetalization. This methodology is compatible with the other protecting groups such as acetyl, benzyl, benzoyl, TBS ether, allyl and it also provides good yield for enolizable ketones. The successful results are mentioned in the Table 7.

As like earlier**, Chapter III** is divided into two parts **Part I** and **Part II**, respectively.

Chapter III, Part I contains a brief review on the deprotection of TBS ethers to the parent hydroxyl compounds and also highlights their importance in organic synthesis.

Part II describes about a highly efficient and useful synthetic protocol for the cleavage of *tert*-butyldimethylsilyl (TBS) ethers using a catalytic amount of acetyl chloride in dry methanol. *Tert*-butyldimethylsilyl ether of 1-octanol (**48**) was deprotected to the corresponding alcohol by employing 0.15 equivalent amount of acetyl chloride in dry methanol at 0-5°C. A large number of other protecting groups such as acetyl (**53**), benzoyl (**54**), benzyl (**55**), ester (**56**), allyl (**57**), thioketal (**58**) are stable under the reaction conditions. This method is also applicable for substrates containing double or triple bonds (**60** and **61**) for selective deprotection without any chlorination. Another advantages of the method is that a highly acid sensitive TBS ether **59** and a TBS ether containing a thio group at the anomeric position such as **67** can also be deprotected without any difficulty during the experimental conditions as mentioned in the Table 1 in Chapter III. All the products are characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis and their characterization data are included in the experimental part of the **Section A** in the **Chapter III** of the **Part II**.

CONTENTS

CHAPTER II

GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam, from March 30, 1999 to December, 2004 as a research scholar.

The analytical samples were routinely dried *in vacuo* at 50 ^{o}C for 8 hours. Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Buechi R-114V instrument. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent and spots were detected by staining with iodine vapour or under UV light or charring 15% Conc. H_2SO_4 in MeOH or MOSTAIN solution [by dissolving 20 g ammonium heptamolybdate and 0.4 g cerium(IV) sulphate in 400 mL 10% H_2SO_4 solution]. ^{1}H-Nuclear Magnetic Resonance spectra and ^{13}C-Nuclear Magnetic Resonance spectra were recorded on Varian (60 MHz), Bruker (300 MHz), and Jeol (400 MHz), instruments using tetramethyl silane (TMS) as an internal standard and $CDCl_3$ as solvent. The chemical shift values were expressed in δ scale and their multiplications were described using the following symbols: s-singlet, d-doublet, t-triplet, q-quartet, quin-quintet, *m*-multiplet, br-broad, brs-broad singlet.

The infrared spectra were recorded in KBr pellets or in liquid film on a Perkin Elmer 1330 and Nicolet Impact 410 instruments, respectively. Melting points were determined on a sulphuric acid bath or Buechi B-545 instrument and were uncorrected. Department of Chemistry, IIT-Guwahati, using Perkin Elmer CHNS/O-2400 instrument. All the solvents and reagents employed were purified using recommended procedures in literature.

Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
Bn	benzyl
Bu	butyl
Bz	benzoyl
CH_2Cl_2	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethyl formamide
DMSO	dimethyl sulfoxide
m-CPBA	*m*-chloroperbenzoic acid
Lev	levulinoyl
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
OATB	organic ammonium tribromide
PCC	pyridiniumchloro chromate
PMB	p-methoxyphenylmethyl
py	pyridine
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TDS	thexyldimethylsilyl
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSCl	trimethylchlorosilane
TMSOTf	trifluoromethanesulfonate
Tr	trityl
Ts	*p*-toluenesulfonyl
TBATB	tetrabutylammonium tribromide
CetTMATB	cetyltrimethylammonium tribromide

CHAPTER I

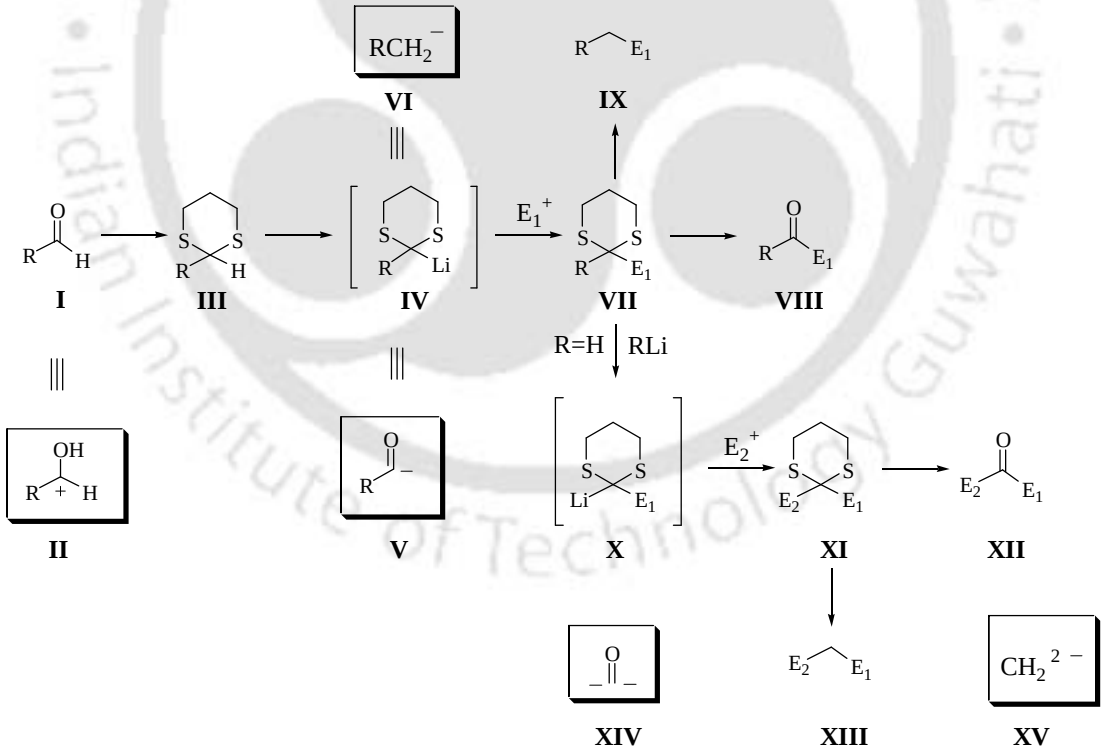
PART I

LITERATUE SURVEY ON THE USEFULNESS AND IMPORTANCE OF DITHIO-ACETALS IN THE ORGANIC SYNTHESIS AS WELL AS THEIR PREPARATIONS

REVIEW OF LITERATURE

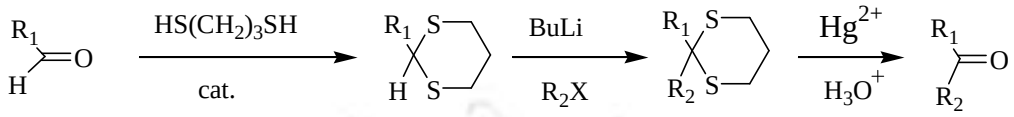
Introduction

The thioacetalization of aldehydes or ketones is an important organic transformation due to their useful applications. Due to their inherent stability under acidic and basic reaction conditions as compared to *O,O*-acetals or ketals, they serve as stable protecting groups in organic synthesis.[1] The normal reactivity of a carbonyl compound (**I**) at the carbonyl carbon is electropositive in nature. Therefore, the carbonyl carbon is usually susceptible to nucleophilic attack, which is well documented. On the other hand, the reactivity of the carbonyl center can be reversed as a nucleophile by converting it into the derivatives of dithioacetals. The temporary reversal of the characteristic pattern of reactivity of a functional group is described by the term umpolung, which was first introduced by Corey and Seebach.[2] The various synthons **V** and **VI**, which act as masked methylene functions and acyl carbanion equivalent can be substituted by using various 1,3-dithiane derivative **III** as represented in the scheme 1.



Scheme 1

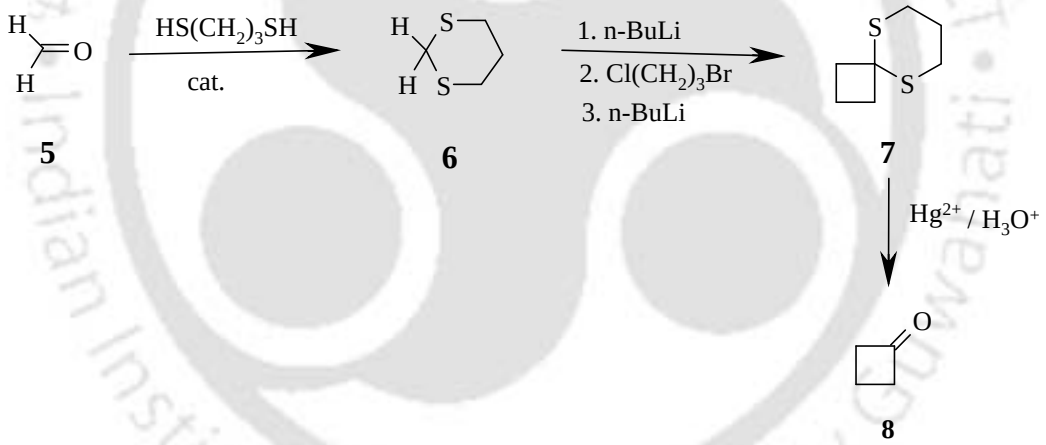
An acyl carbanion equivalent, which is usually generated from the corresponding dithioacetals can be used directly for the preparation of an unsymmetrical ketone,[3] which is an important synthetic protocol for the conversion of aldehydic compound to the ketonic compound as shown in scheme 2.



1 **2** **3** **4**

Scheme 2

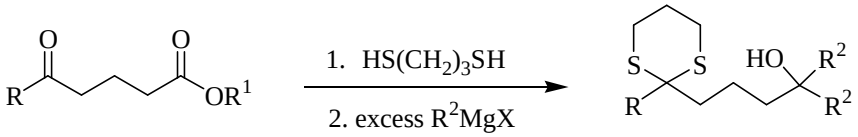
By extending the same sequence of reactions, it is also possible to prepare cyclic ketones from 1,3-dithiane (**6**), which is conventionally difficult to prepare, as shown in the scheme 3.



5 **6** **7** **8**

Scheme 3

The protection of carbonyl group as a dithioacetal is used for functional group manipulation[4] as represented in the scheme 4.

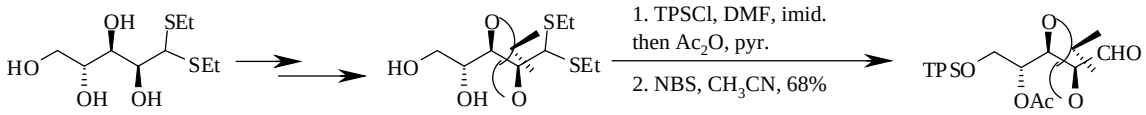


9 **10**

Where, R = alkyl / aryl
R^1 = alkyl, R^2 = alkyl / aryl

Scheme 4

Moreover, acyclic dithioacetal particularly diethyldithioacetal is frequently employed as a stable protecting group in carbohydrate chemistry to easily access open chain aldosugars as building blocks,[5] as shown in scheme 5.

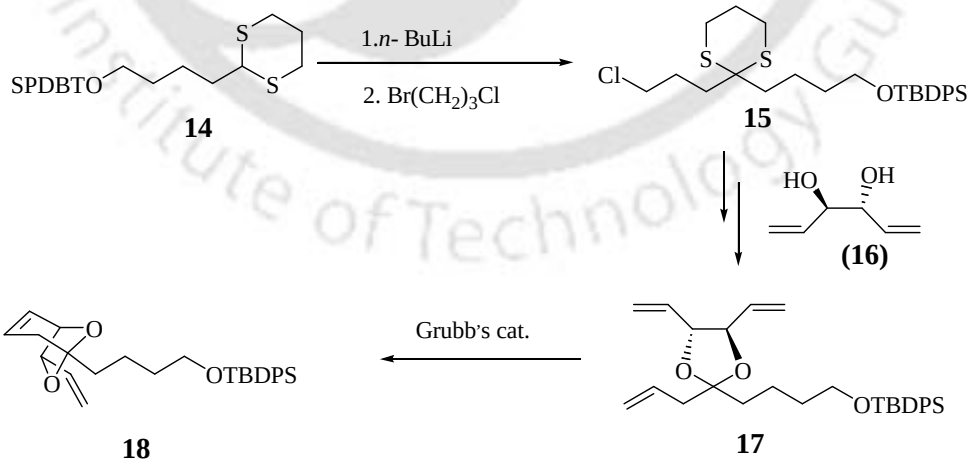


11 **12** **13**

Scheme 5

Among various dithioacetals particularly 1,3-dithiane derivatives are enormously used as building blocks in organic synthesis, which has also been reviewed recently.[6] A few applications of various dithioacetal derivatives are given below, which can be prepared easily from the reaction of aldehydic compounds with 1,3-propanedithiol in the presence of a suitable catalyst.

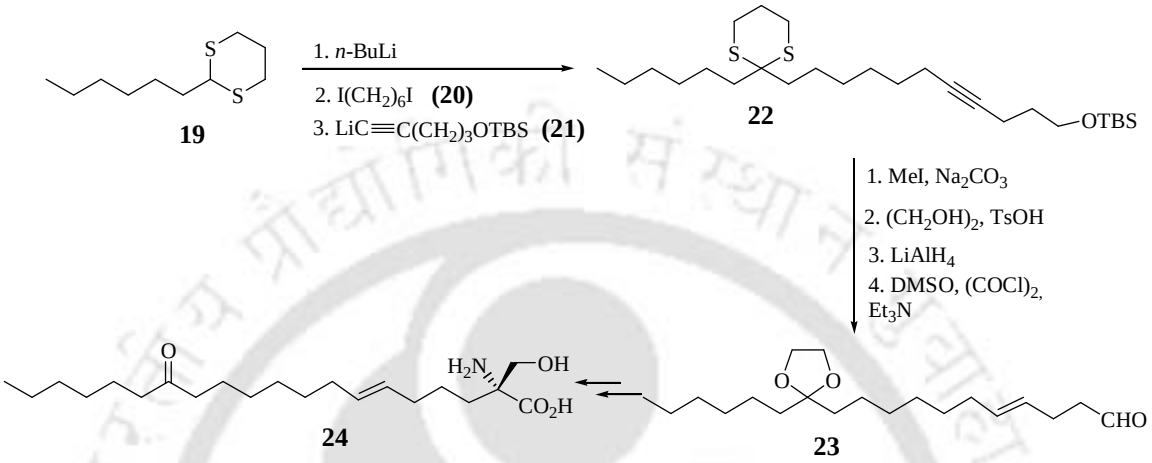
Burke *et al*. reported the synthesis of the bicyclic acetal **18**, a precursor of several polyfunctionalized 1,7-dioxaspiro[5.5]undecane spiroacetal systems via acid-catalyzed rearrangement.[7] The 1,3-dithiane derivative **14** was used as a starting material for the construction of bicyclic acetal **18** as represented in scheme 6.



14 **15** **(16)** **17** **18**

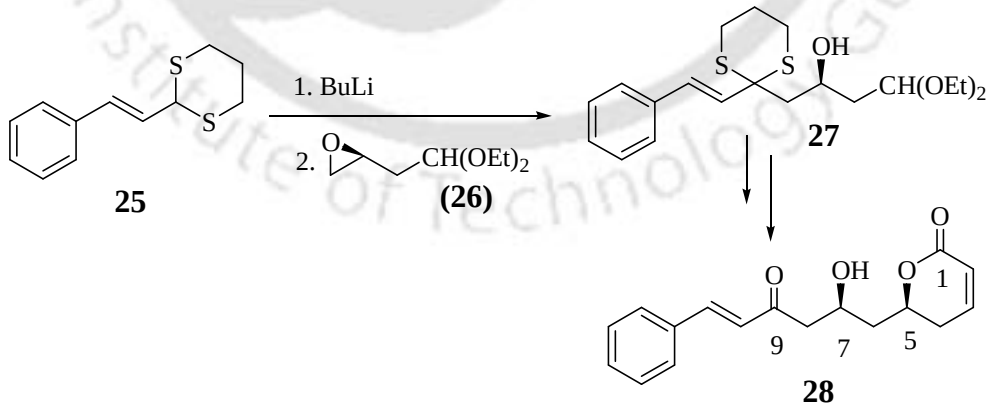
Scheme 6

Hatakeyama *et al*. have accomplished the enantioselective synthesis of (-)-mycestericin E (**24**),[8] a potent immunosuppressant, which was isolated from the culture broth of the fungus *Mycelia sterilia* ATCC 20349.[9] The required long chain precursor **23** was prepared from the 1,3-dithiane derivative of heptanal **19**, as depicted in the scheme 7.



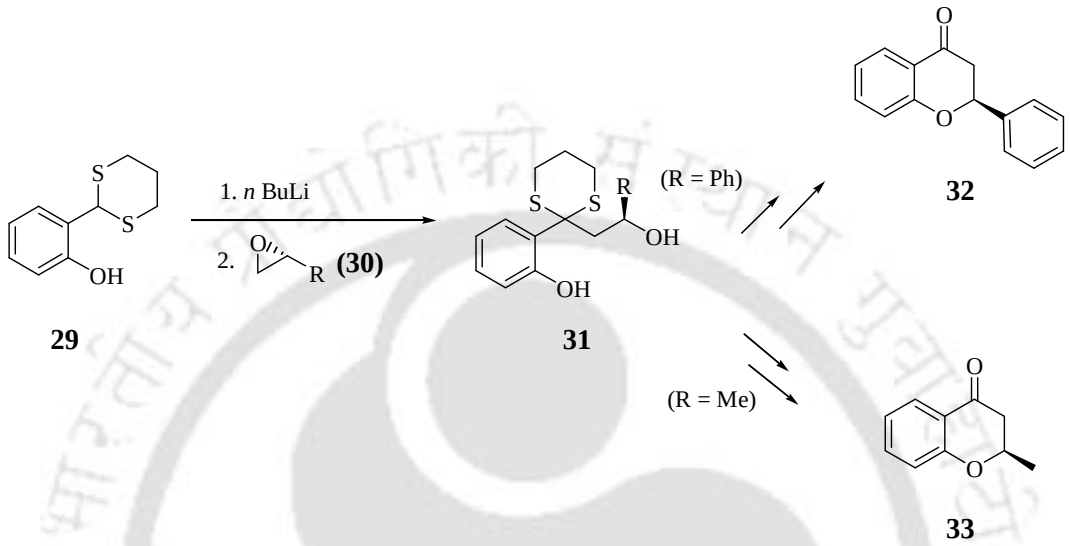
Scheme 7

Jiang and Chen recently reported the synthesis of Kurzilactone (**28**),[10] which was isolated from the leaves of the Malaysian plant *Cryptocarya kurzii* starting from the dithiane derivative **25.** The key building block **27** for the synthesis of kurzilactone was obtained through the coupling of the acyl anion equivalent **25,** which was generated *in situ***,** with the epoxide **26**, as represented in the scheme 8.[11]



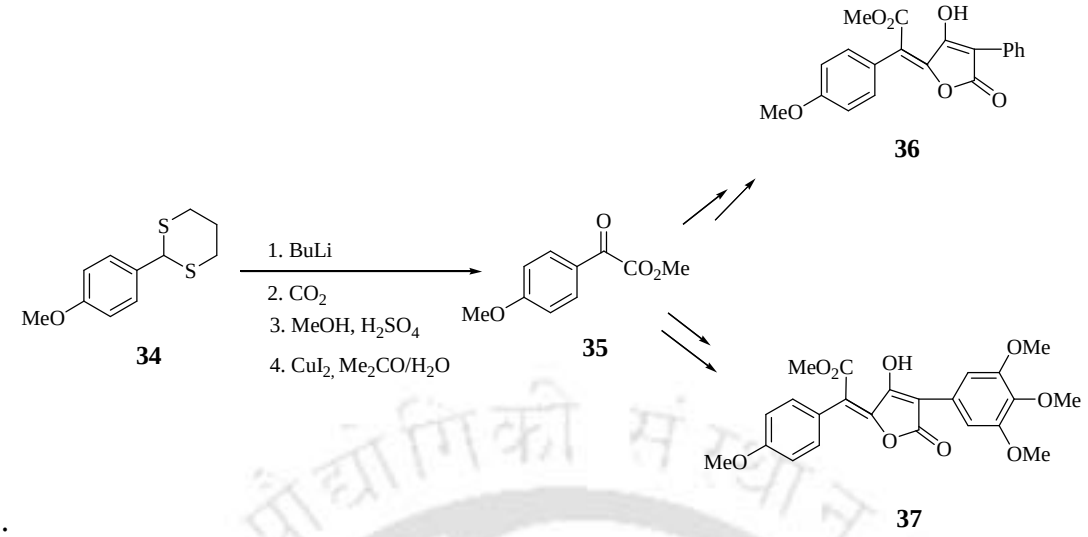
Scheme 8

Noda and Watanabe have demonstrated[12] a general and efficient synthesis of the optically active flavanone (**32**) and 2-methylchromanone (**33**) in high enantiomeric purity from the readily available starting material such as 1,3-dithiane derivative of salicylaldehyde **29**, as represented in scheme 9.



Scheme 9

Later on, Pattenden and Knight have also demonstrated[13] the utility of the dithioacetal derivative **34** for the synthesis of *O*-methylisopinastric acid (**36**) and permethylated gomphidic acid (**37**) as shown in scheme 10. The compound **34** was prepared from the thioacetalization of 4-methoxybenzaldehyde with 1,3-propanedithiol. The key intermediate **35** was obtained from compound **34** by successive metallation, carboxylation and esterification, followed by the final removal of the dithiane group. The compound **36** and **37** have long been recognized as the pigments responsible for the striking yellow and orange colors of the lichens.



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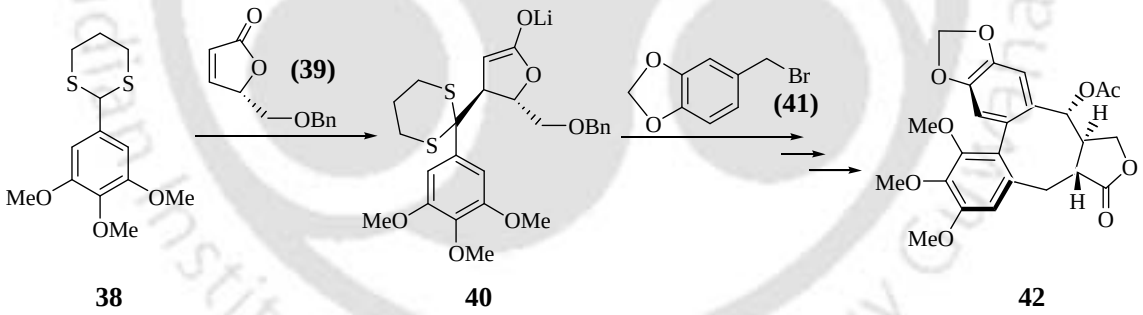
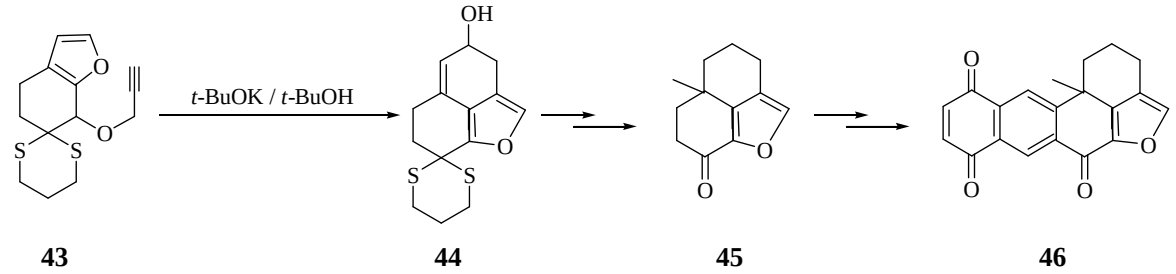
Scheme 10

Koga *et al*. have elegantly shown the synthesis of the natural lignan (-)- steganacin (**42**),[14] a benzocyclooctadiene lactone**,** which exhibits an antileukemic activity. The key starting material **40** was derived from the valuable starting material of 1,3-dithiane derivative of 3,4,5-trimethoxybenzaldehyde **40**, as represented in scheme 11.



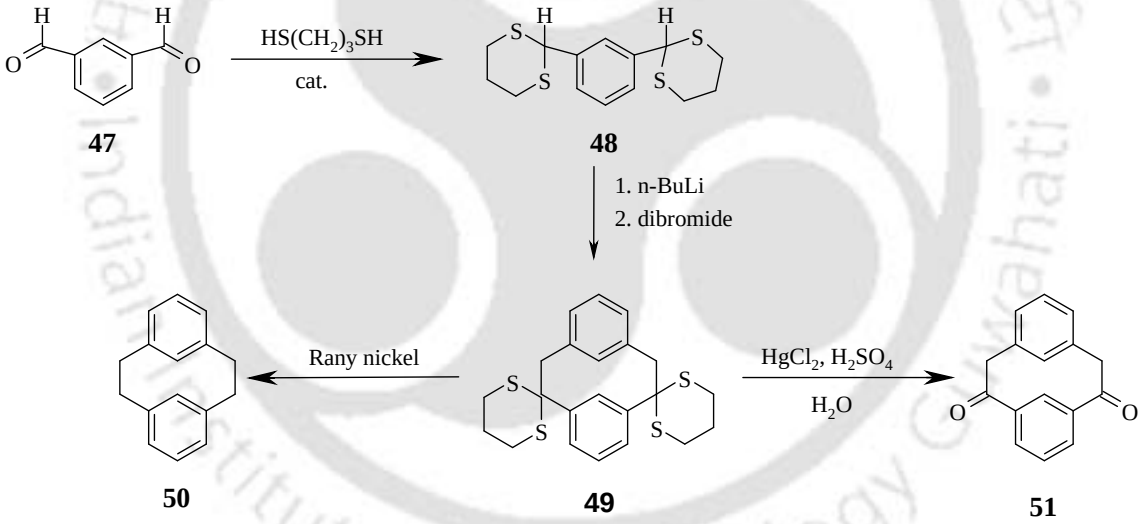
Scheme 11

Kanematsu *et al*. have reported a formal synthesis of the natural product such as fused furan xestoquinone (**46**),[15] a powerful cardiotonic constituent, which was isolated from the marine sponge *Xestospongia sapra*.[16] The first total synthesis of the compound **46** was also achieved by Harada and his co-workers.[17] The tricyclic furan derivative **45** is the key intermediate, which was actually prepared from the dithiane derivative **43,** [18] as mentioned in the scheme12.



Scheme 12

The other useful application of the dithioacetal chemistry is the conversion of carbonyl compounds to the corresponding hydrocarbons, which provide an alternative synthetic route for the transformation of carbonyl compounds to the hydrocarbon.[19] By using a dithioacetal derivative **48**, synthesis of a fascinating non-natural product cyclophane (**50)** can be easily accomplished[20] as shown in the scheme 13.



Scheme 13

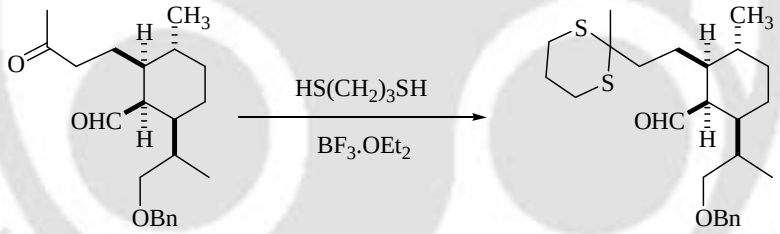
It is quite clear from the above few representative examples that various dithioacetal derivatives, which are eventually prepared from the reaction of aldehydes with thiols and dithiols, can serve as valuable building blocks for non-natural and natural product synthesis.

Next, we were interested to find out what are the methods available in the literature for their preparations. After going through the literature, we had noticed that a large number

of methods have been developed over the years for their preparation from the corresponding carbonyl compounds by involving various catalysts. A brief literature review on thioacetalization of carbonyl compounds based on their merits and demerits are discussed below.

H. Zinner first reported[21] the utility of the thioacetalization reaction in the carbohydrate chemistry to prepare open-chain aldosugars by protecting aldehyde functionality as diethyl dithioacetal using a strong protic acid HCl as catalyst. However, the method has some draw backs such as it requires an excess amount of catalyst, provides low yield, requires longer reaction time and highly acid sensitive protecting groups might not survive during reaction conditions.

Fieser reported[22] the thioacetalization of carbonyl compounds by employing $BF_3{\cdot}OEt_2$ as catalyst. This method was extensively used for the preparation of dithioacetals from the corresponding carbonyl compounds. Conventionally, aldehyde group can be selectively protected in presence of a ketonic group. Sometimes, the keto group can also be protected over aldehydic group by tuning the reaction conditions due to presence of a large steric factor in the molecule as mentioned in scheme 14.[23]



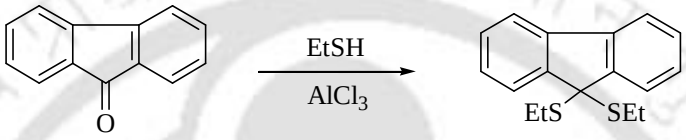
52 **53**

Scheme 14

Although this method is superior compared to the HCl method, still it has some limitations such as use of stoichiometric amount of the catalyst which makes the method inconvenient for acid sensitive functional groups for example TBS ether group.[24]

The application of dithioacetals was limited earlier until they used extensively as acyl carbanion equivalent for carbon carbon bond forming reaction. Hence, emphasis on new methods for protection of carbonyl group as dithioacetal was less earlier. Recently, a number of new methods have been developed for natural and non-natural product synthesis starting from dithioacetals derivatives. This has strengthened the efforts of Organic Chemist to develop new synthetic methodology for thioacetalization.

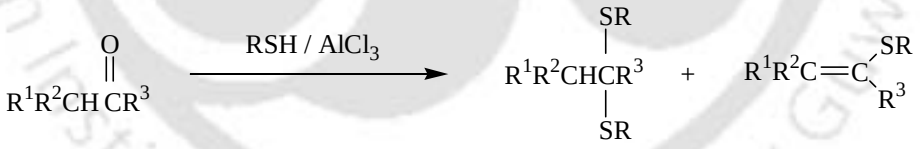
Ong and Chan have reported the dithioacetalization of carbonyl compounds by using Me_3SiCl as a catalyst.[25] Later on, Evans *et al.* have also shown[26] the thioacetalization of carbonyl compounds by employing thiosilanes ($RSSiMe_3$) in combination with Lewis acid ZnI_2. Further, Ong demonstrated[27] a new method for thioacetalization of carbonyl compounds using $AlCl_3$ as efficient catalyst. By using this method, an aromatic ketone fluorenone (**54)** was converted to the corresponding diethyldithioacetal **55** within a short period of 5 min in quantitative yield, on treatment with ethanethiol in the presence of stoichiometric amount of $AlCl_3$ as shown in Scheme 15.



54 **55**

Scheme 15

However, this method has serious drawbacks such as difficult in accessing acyclic dithioacetals in case of a highly enolizable ketone. In this case only the elimination product vinyl sulfide **58** was formed instead of the expected dithioacetals as shown in scheme 16.



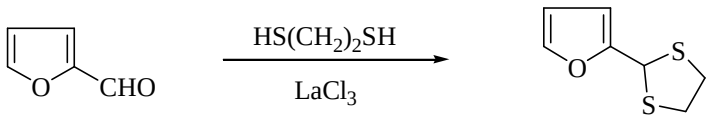
56 **57** **58**

Scheme 16

In addition, use of excess catalyst and work-up procedure are also the disadvantages of this method.

Later on, two new methods have been developed for thioacetalization using Lewis acid $TiCl_4$[28] and $SiCl_4$[29] respectively. However, both the methods have some inherent drawbacks such as they are expensive as well as hygroscopic in nature.

Garlaschelli and Vidari have developed[30] the thioacetalization of carbonyl compounds by using anhydrous $LaCl_3$ as catalyst, shown in scheme 17.

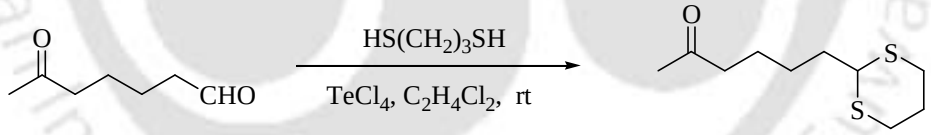


59 **60**

Scheme 17

Unfortunately, this method fails to provide dithioacetal derivatives for camphor, acetophenone and benzophenone even after a long reaction time. The main drawbacks of this method are $LaCl_3$ is highly expensive, the reaction requires excess amount of catalyst and longer reaction times.

Hiroyuki Tani and his group have demonstrated[31] the dithioacetalization of carbonyl compounds by using small amount of tellurium tetrachloride as a mild Lewis acid catalyst as represented in scheme 18. The advantages of this method are that no vinyl sulfide **58** is formed from the enolizable carbonyl compounds and no aqueous work-up is required. But the disadvantage of this procedure is that aromatic ketone does not provide dithioacetal derivative under the same reaction conditions.



61 **62**

Scheme 18

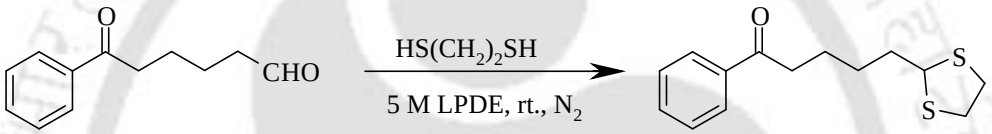
Kumar *et al.* have reported[32] thioacetalization of carbonyl compounds using H-Y Zeolites (Si/Al = 2.43) as a new catalyst. The disadvantage of this procedure is that the reaction is to be carried out under refluxing conditions.

Villemin *et al.* have demonstrated[33] the dithioacetalization of carbonyl compounds by employing clay KSF in refluxing condition. The present method offers several advantages over the classical methods using acids such as it exhibits strong acidic property, no corrosive action and easy work-up procedure. Here, clay acts as a solid Bronsted acid catalyst. In addition, it is useful for chemoselective protection of aromatic

aldehyde in the presence of an aliphatic aldehyde and an aromatic ketone. Unfortunately, use of excess reagent and longer reaction times are the limitations of this method.

Zhang *et al*. have ulitized[34] SmI_3 as the catalyst for dithioacetalization of carbonyl compounds.

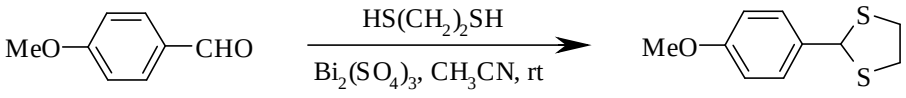
Sankararaman *et al*. have reported[35] the chemoselective dithioacetalization of carbonyl compounds by employing lithium perchlorate in diethyl ether medium as depicted in scheme 19. This method that works under neutral reaction condition and shows chemoselective protection of aldehydic group instead of a ketonic group present in the molecule. However, it fails to give dithioacetal derivatives from 4-methoxybenz-aldehyde and acetophenone. Moreover, the reaction has to be performed under inert atmospheric conditions.



63 **64**

Scheme 19

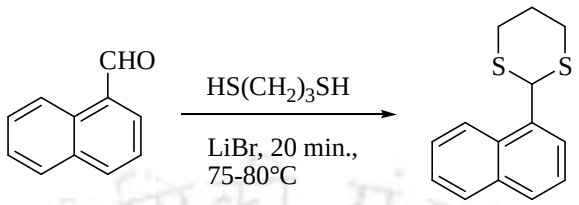
Suzuki *et al*.[36] have investigated that various bismuth(III) salts can be used as efficient catalyst for chemoselective thioacetalization of aldehydic compounds as shown in scheme 20. The present method is applicable for aromatic, aliphatic aldehydes and ketones. Even a highly acid sensitive substrate furfuraldehyde was smoothly converted to corresponding dithioacetal without accompanying any self-condensation product or ring cleavage. The difficulty of the procedure is that it takes longer time to complete and it also requires air to carry out the reaction.



65 **66**

Scheme 20

Firouzabadi and Iranpoor *et al*. have introduced[37] lithium bromide as an efficient catalyst for highly chemoselective dithioacetalizations of aromatic and α, β- unsaturated aldehydes in the presence of other structurally different aldehydes and ketones under solvent-free conditions as shown in scheme 21.



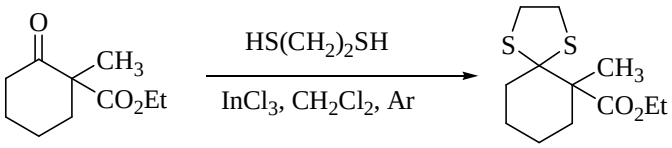
67 **68**

Scheme 21

Though this method is very useful for acid sensitive substrates, but it does not provide dithioacetal derivatives for aliphatic aldehydes and ketones under the same reaction conditions even after a prolonged reaction time. In addition, LiBr is hygroscopic which puts some additional restriction for its use.

Later on, Yadav *et al*. have used[38] lithium tetrafluroborate as the catalyst for chemoselective conversion of carbonyl compounds to dithioacetal derivatives. This method has no additional advantages over LiBr, only $LiBF_4$ is a mild Lewis acid and the counterion BF_4^- is non-nucleophilc and non-oxidizing. However, they have not investigated a substrate containing TBS ethers group, which may not servive under the experimental conditions. Moreover, the reagent lithium tetrafluoroborate is difficult to use because it is moisture-sensitive, irritant and relatively expensive.

Muthusamy *et al.* have reported[39] the use of indium(III) trichloride as mild Lewis acid catalyst for efficient synthesis of 1,3-dithiolane derivatives as well as chemoselective protection of various carbonyl compounds as represented in scheme 22. They have also studied the chemoselectivity between an aldehydic group and a ketonic group both intra- and intermolecularly.

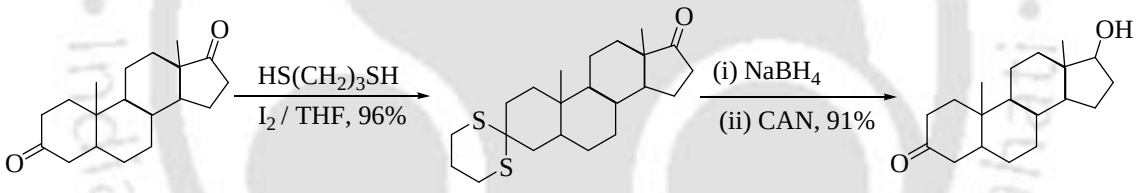


69 **70**

Scheme 22

Although this method is superior due to its chemoselectivity, but it requires expensive indium(III) trichoride as catalyst and argon atmosphere to carry out the reaction.

More recently, Banik *et al*. have reported[40] a facile and convenient iodine-catalyzed thioketalization for various carbonyl compounds. The advantage of this method is that a six membered cyclic ketone can be chemoselectively protected in the presence of a five membered ketone as shown in scheme 23. They have also achieved a selective protection of an aliphatic ketone such as 2- methyl cyclopentanone in presence of an aromatic ketone e.g. acetophenone.



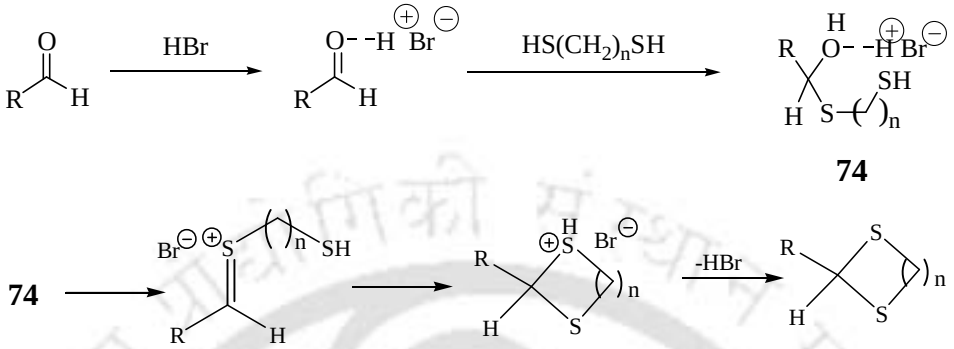
71 **72** **73**

Scheme 23

They proposed that *in situ* generated hydroiodic acid is the actual catalyst involved in the reaction. However, they have not studied whether the substrates containing acid sensitive groups are survived under this reaction conditions or not. The main disadvantage of this procedure is the involvement of a highly expensive dry solvent THF.

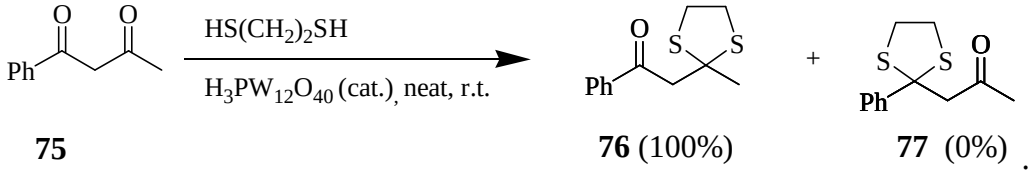
Kamal and Chouhan have demonstrated[41] a mild and chemoselective procedure for the conversion of aldehydes to the corresponding 1,3-dithiolanes and 1,3-dithianes derivatives using catalytic amount of NBS in dichloromethane under almost neutral reaction conditions. They have proposed that NBS first reacts with the dithiol to

generate HBr, which may activate the carbonyl group for further reaction with dithiol to produce hemithioacetal type intermidiate (**74**), which loses water molecule to afford dithioacetal derivative as shown in scheme 24.



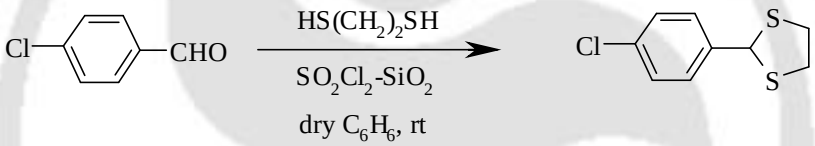
Scheme 24

Firouzabadi *et al.* have reported[42] another method for thioacetalizations of carbonyl compounds by employing trichloroisocyanuric acid as mild catalyst, which is cheap and commercially available reagent and used primarily as a disinfectant and deodorant. This method also serves as chemoselective protection of aldehyde group instead of ketonic group present in a mixture. The same group has also demonstrated[43] the usefulness of tungstophosphoric acid in its solid state as catalyst for the thioacetalization reactions. Among the different heteropoly acids (HPAS) as mentioned in their report $H_3PW_{12}O_{40}$ is the most effective one. It has been observed that aromatic and aliphatic aldehydes are smoothly thioacetalized in presence of 0.01 mol% -0.03 mol% of tungstophosphoric acid at room temperature. Under this reaction conditions aliphatic ketones are more reactive than aromatic ketones which encourage them to study chemoseletivity as shown in the scheme 25.



Scheme 25

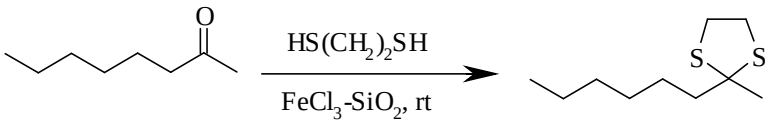
Hojo *et al*. have reported[44] the solid supported thioacetalization of carbonyl compounds by using a solid supported SO_2Cl_2-SiO_2 as catalyst shown in scheme 26. Aromatic, aliphatic and α,β-unsaturated aldehydes are smoothly converted to the corresponding thioacetals by employing the above catalyst at room temperature. On the other hand, ketones are less reactive under similar reaction conditions and it does not provide dithioacetals even at refluxing temperature. However, they have overcome the difficulties by using a large excess amount of reagent and by refluxing the reaction mixture. They have also shown for the first time the chemoselectivity between an aldehyde group and a keto group present in a molecule by using a solid supported catalyst. However, the method has some drawback as it fails to give acyclic dithioacetal under similar conditions.



78 **79**

Scheme 26

Patney [45] has shown that anhydrous iron(III) chloride dispersed on silica gel can be used as an efficient catalyst for rapid conversion of a wide variety of carbonyl compounds into their respective dithioacetals at room temperature in high yields as given in scheme 27. The high reactivity of the catalyst is clearly manifested as the less reactive aromatic ketones also react very fast at room temperature. The efficiency of the anhy. iron(III) chloride reagent may presumably be attributed to its strong affinity for carbonyl oxygen thereby facilitating the substitution of the hemithioacetal intermediate and its remarkable ability to act as water scavenger. Interestingly, the main drawback is that the catalyst is toxic and hygroscopic in nature, which is inconvenient to use.



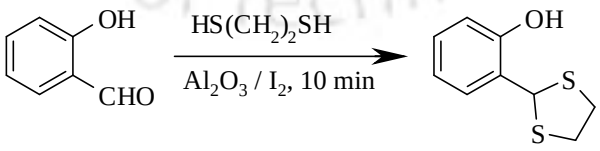
80 **81**

Scheme 27

Subsequently, Patney also reported[46] thioacetalization of carbonyl compounds by employing $CoBr_2$ impregnated silica gel as catalyst. This method has no additional advantages over the previous one. However, α,β-unsaturated ketone does not provide the desired dithioacetals under the reaction conditions, which is one of the drawback.

Further, Patney and Morgan have demonstrated[47] $ZrCl_4$-SiO_2 mediated thioacetalization of carbonyl compounds. However, this method also failed to protect α,β-unsaturated ketone. The main drawback is that it takes much longer reaction time as compared to the earlier two methods. Two more methods have been developed for thioacetalization of carbonyl compounds by using solid supported reagents such as $TaCl_5$-SiO_2[48] and $Cu(OTf)_2$-SiO_2.[49] The later method works under solvent-free condition, but $Cu(OTf)_2$ is highly expensive as compared to $TaCl_5$.

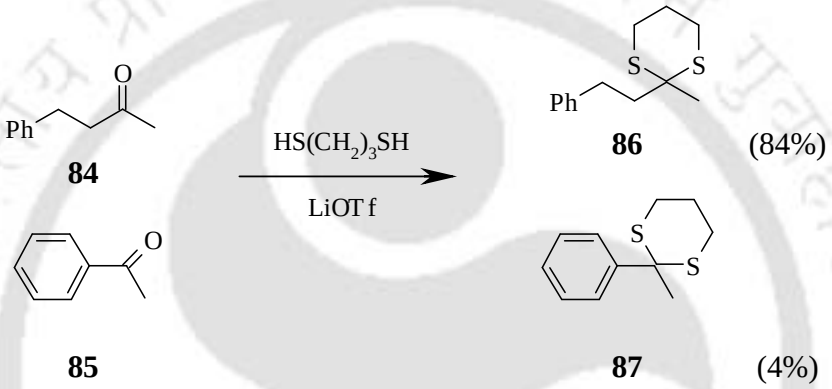
Recently, Sarmah *et al*. have reported[50] dithioactalization using iodine supported on neutral alumina under solvent-free conditions as represented in scheme 28. They have claimed iodine that is the real catalyst for thioacetalization because in absence of iodine reaction does not proceed. Interestingly, by using only iodine[40] as catalyst the reaction takes much longer time as compared to the solid supported catalyst. The advantage of this procedure is that α,β-unsaturated ketones can be protected easily as compared to the other solid supported reagents.



82 **83**

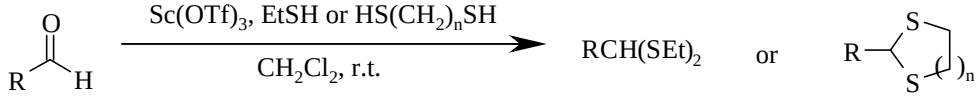
Scheme 28

Corey *et al.* have shown[51] the useful application of metal triflate such as $Zn(OTf)_2$ as a catalyst for the preparation of dithioacetals from carbonyl compounds. However, it is expensive, corrosive and hygroscopic, which are the disadvantages of this procedure. Similarly, $Mg(OTf)_2$ can also be utilized[52] for dithioacetalization of carbonyl compound. Likewise, Firouzabadi *et al.* have also demonstrated[53] chemoselective dithioacetalization of carbonyl compounds by employing LiOTf as catalyst under solvent-free conditions. The advantage of this method is that one of the ketonic substrate can be protected chemoselectively in the presence of other ketone intermolecularly as shown in scheme 29.



Scheme 29

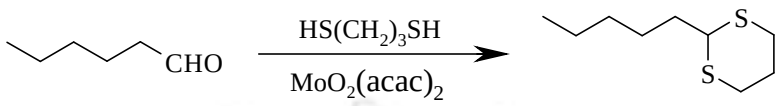
On the otherhand, the disadvantage is that the reagent LiOTf is also hygroscopic and expensive. Very recently, Kamal and Chouhan have reported[54] the useful application of scandium triflate as recyclable catalyst for thioacetalization of carbonyl compounds, as represented in scheme 30. The advantage of the method is that ketone is not reactive under the reaction condition. Therefore, they have explored that the catalyst can be used exclusively for chemoselective protection of various aldehydes. The catalyst is highly expensive which is one of the drawbacks.



88 **89** **90**

Scheme 30

Recently, Roy *et al.* have shown[55] that molybdenyl acetylacetonate mediated thioacetalization of carbonyl compounds. This method has shown first time that metal acetylacetonate can be used for thioacetalization of carbonyl compounds. The disadvantage is that it takes relatively longer reaction time as shown in scheme 31.



91 **92**

Scheme 31

Over the years, some more methods have been developed which have not been included for discussion.

With this literature background on the usefulness of dithioacetal derivatives and their preparations, our aims are:

i) To find out better synthetic methodologies for the preparation of various dithioacetals from the corresponding carbonyl compounds by involving a more efficient and economically cheaper new catalyst.

ii) To investigate whether the aldehydic compound can be protected chemoselectivity in presence of a ketonic compound.

iii) To study the compatibility of other protecting groups during finding out a better methodology.

iv) To find out a better methodology whether it works under environmentally benign reaction conditions.

PART II

(SECTION A)

NEW SYNTHETIC METHOD FOR CHEMOSELECTIVE THIOACETALIZATION OF ALDEHYDIC COMPOUNDS BY EMPLOYING NICKEL(II) CHLORIDE AS A CATALYST

RESULTS AND DISCUSSION

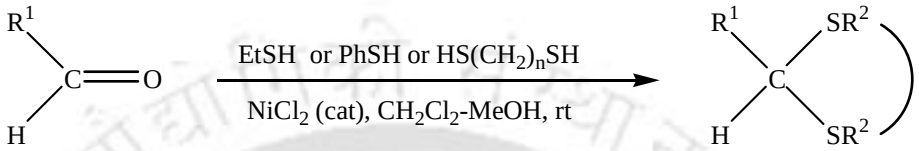
Results and Discussion

The importance and usefulness of dithioacetals have been discussed in the previous chapter. It appears to us that there is a further scope to develop a new methodology by using a less expensive catalyst.

The protection of carbonyl functionality as dithioacetals[1] is a common practice in multi-step synthesis of natural[6] and non-natural[20] products due to their inherent stability under both acidic and basic conditions. In addition, they are also utilized as masked acyl anions[3] or masked methylene functions[56] in carbon-carbon bond forming reactions. They are conventionally prepared by the condensation of carbonyl compounds with monothiols or dithiols using a Lewis acid $BF_3.OEt_2$[22] as catalysts. Unfortunately, this procedure has certain disadvantages such as require stoichiometric amount of catalyst and also provide relatively low yields. Other Lewis acids such as $(CH_3)_3SiCl$,[25] $AlCl_3$,[27] $TiCl_4$,[28] $SiCl_4$,[29] $LaCl_3$,[30] WCl_6,[57] and 5M $LiClO_4$[35] have also been used for their preparations. Their drawbacks are already highlighted in the introduction chapter. Recently, some solid supported reagents have been reported for thioacetalization of various carbonyl compounds by using $SOCl_2$-SiO_2,[44] $CoBr_2$-SiO_2,[46] $ZrCl_4$-SiO_2,[47] $TaCl_5$-SiO_2,[48] and $Cu(OTf)_2$-SiO_2.[49] Very recently some new methods have also been developed for protection of carbonyl compounds as dithioacetals by employing LiBr,[37] $LiBF_4$,[38] $InCl_3$,[39] molecular I_2,[40] NBS,[41] and $Sc(OTf)_3$.[54] Interestingly, only a few methods are well known in the literature for the chemoselective protection of aldehydic compounds[35, 37-54] in the presence of ketones. Some of the methods as mentioned above are also associated with some problems such as relatively harsh conditions,[44] difficult to access acyclic dithioacetals,[44] require inert atmosphere to carry out the reaction[35, 39-41] and also involvement of more expensive reagents[39, 46-49, 54] and incompatibility with other protecting groups like TBS ether[24, 58-60] and failure to protect deactivated aromatic substrate.[54] For our ongoing research project, we had to prepare various dithioacetals and dithioketals as our starting materials. Therefore, there is still a scope to find out better alternatives for the preparation of dithioacetals due to their wide applicability in organic synthesis. Consequently, what is needed a methodology, which might work under mild conditions and economically cheaper reaction conditions. As our ongoing research programme to develop a new synthetic methodology,[61] we have conceived that nickel(II) chloride,

which act as a mild Lewis acid,[62] might be useful catalyst for thioacetalization of carbonyl compounds, although raney nickel is well known for desulfurization of dithioacetals.

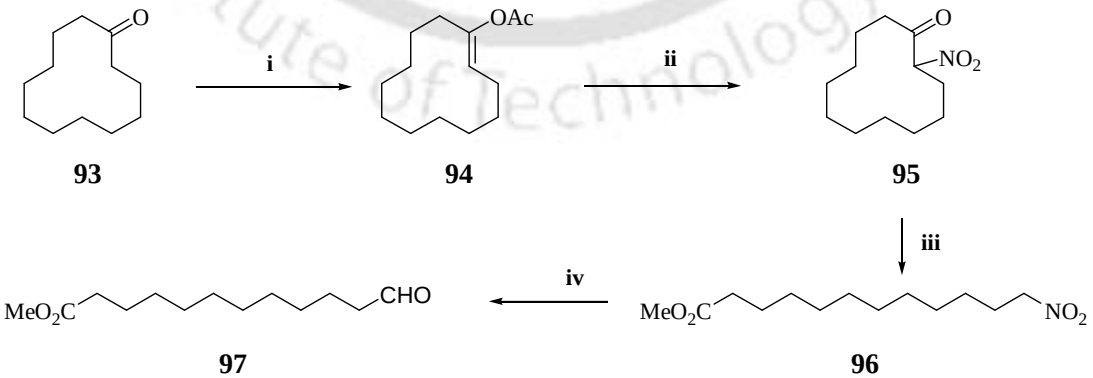
In this chapter, we wish to discuss a simple and easy method for chemoselective thioacetalization of various aromatic and aliphatic aldehydic compounds using nickel(II) chloride as a new catalyst, depicted in scheme 32.



R^1 = aryl, alkyl, alkenyl
R^2 = Et, Ph, -$(CH_2)_n$- n = 2, 3

Scheme 32

For our requirement, we have prepared the starting materials 4-*tert*-butyldimethylsilyloxy benzaldehyde and 4-allyloxybenzaldehyde, the precursor of the products **105** and **106**, were prepared from 4-hydroxybenzaldehyde by silylation[63] and allylation[64] following standard reaction procedures. Similarly, 4-benzoyloxybenzaldehyde was prepared by benzoylation from 4-hydroxybenzaldehyde using a literature procedure.[65] The substrate ester aldehyde **97**, the precursor of compound **120**, was prepared from cyclododecanone (**93**) using four steps sequence by the following literature procedure[66-68] as shown in scheme 33.



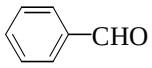
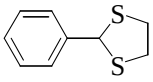
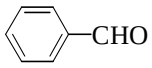
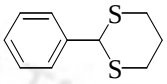
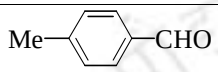
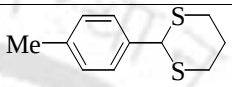
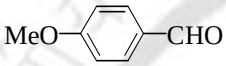
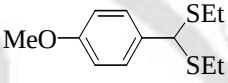
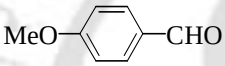
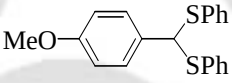
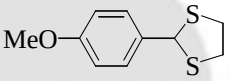
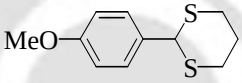
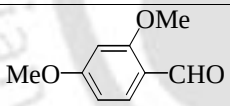
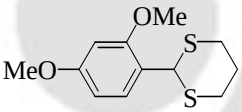
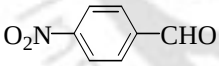
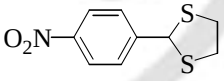
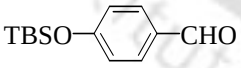
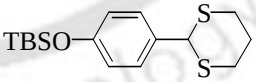
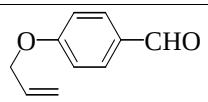
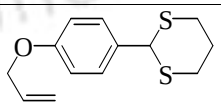
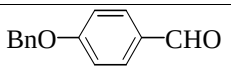
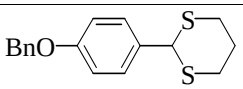
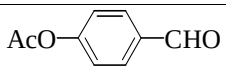
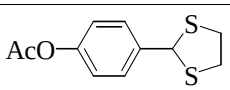
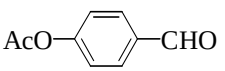
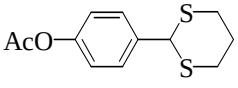
Scheme 33

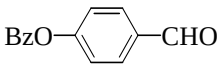
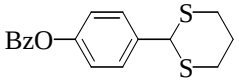
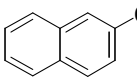
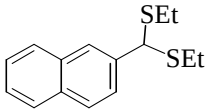
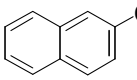
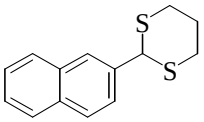
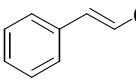
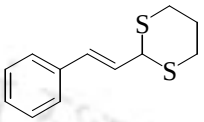
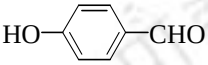
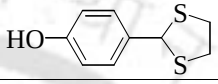
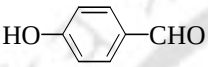
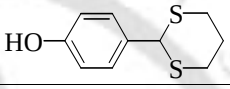
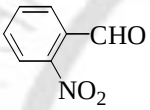
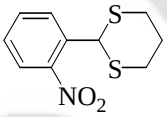
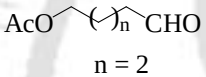
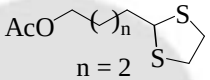
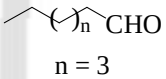
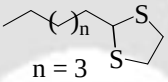
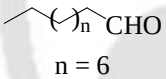
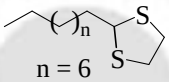
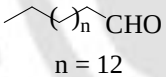
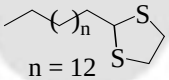
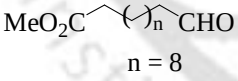
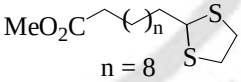
Reagents and reaction conditions: i) Ac_2O, p-TSA, reflux, 8 h, 65%; ii) Ac_2O, CH_2Cl_2, conc. HNO_3 / H_2SO_4, 0°C- rt; 80%; iii) $KF{\cdot}2H_2O$ / MeOH, reflux, 2.5 h, 85%; iv) (a) alc. KOH, (b) $KMnO_4$, $MgSO_4$, H_2O, 0°C, 15 min- 2 h, 75%.

Firstly, we have attempted the reaction of benzaldehyde (1 mmol) with 1,2-ethanedithiol (1.1 mmol) in the presence of nickel(II) chloride (0.1 mmol) at room temperature in CH_2Cl_2-MeOH (5:1, 3 mL) afforded the desired 1,3-dithiolane derivative of benzaldehyde (**98**) in 96% yield (run 1). The structure of the product **98** was confirmed by recording IR, ^{1}H NMR spectrum and elemental analysis, which were full agreement with the expected values. In the IR spectrum, it shows the disappearance of carbonyl band at ~1700 cm^{-1}, which indicates the carbonyl group has been reacted. Moreover, in the ^{1}H NMR spectrum the following signals were appeared at 3.39 (m, 4H, SCH_2-), 5.55 (s, 1H, ArCH-) and 7.30-7.40 (m, 5H, ArH). The disappearance of the aldehydic proton at ~δ 9.80 and appearance of the two new signals at δ 3.39 and 5.55 is clearly pointed out the formation of 1,3-dithiolane derivative of benzaldehyde (**98**). Similarly, 1,3-dithiane derivative of benzaldehyde (**99**) was obtained from benzaldehyde (run 2), on treatment with 1,3-propanedithiol by following the identical procedure. The protected compound **99** was again confirmed by spectroscopic data such as IR, ^{1}H NMR, ^{13}C NMR and elemental analysis as well as melting point. In the IR spectrum, it exhibits the frequency values 3037, 2940, 2894, 2827, 1593, 1491, 1429, 1281, 1183, 1066, 912, 728, 697 cm^{-1}. From the disappearance of carbonyl frequency in the IR spectrum clearly indicates the formation of dithioacetal of benzaldehyde. On the other hand, ^{1}H NMR spectrum gives the signals at δ 1.85-1.96 (m, 1H, $SCH_2CHaHbCH_2S$), 2.09-2.16 (m, 1H, $SCH_2CHaHbCH_2S$), 2.85-2.90 (m, 2H, SCH_2), 2.99-3.07 (m, 2H, SCH_2), 5.16 (S, 1H, ArCH), 7.24-7.35 (m, 3H, ArH), 7.45-7.47 (m, 2H, ArH). The following five new signals at δ 1.85-1.96, 2.09-2.16, 2.85-2.90, 2.99-3.07 and 5.16 as well as disappearance of the signal at ~δ 9.80 is also clearly demonstrated the formation of 1,3-dithiane derivative of benzaldehyde. Again, in the ^{13}C NMR spectrum, it shows carbon values at δ 24.96, 31.95 (2C), 51.34, 127.61 (2C), 128.29, 128.59 (2C), 138.99. The disappearance of the carbonyl carbon also indicates the formation of dithiane derivative of benzaldehyde. After getting these products in hand, we have further encouraged to study thio-acetalization reaction.

By following the above typical reaction procedure as mentioned in the experimental section, 4-methoxybenzaldehyde was converted to the corresponding acyclic dithioacetals **101** and **102**, on reaction with ethane thiol and thiophenol, respectively. It is important to mention that the formation of diphenyl dithioacetal derivative of 4-methoxybenzadehyde (**102**) is also possible by employing our methodology. The product diphenyl dithioacetal of 4-methoxybenzaldehyde (**102**) was also confirmed by recording spectra IR, ^{1}H NMR and ^{13}C NMR as shown in the Figures **1-3**, respectively. Likewise, various aromatic aldehydes (run 6-21) were converted smoothly to the corresponding cyclic dithioacetals **66, 25, 34,** and **103-115** in good yields, on reaction with dithiols depending upon aromatic aldehydes used in the presence of catalytic amount of nickel(II) chloride at room temperature. The dithioacetal derivatives of compound 4-*tert*-butyldimethylsilyloxybenzaldehyde (**105**) and 4-hydroxybenzaldehyde (**114**) were characterized on the basis of IR, ^{1}H NMR and ^{13}C NMR spectra as shown in figures **4-8**, respectively. The results are summarized in the table 1 and the products are fully characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and melting point. These were in full agreement with the expected values and most of them are incorporated in the experimental section. The results shown in the Table1 clearly indicates the scope and generality of the reaction with respect to different aromatic, aliphatic and alkenyl aldehydes. It is noteworthy to highlight that the conversion can be achieved in the presence of other protecting groups such as acetyl, benzyl, benzoyl, allyl, ester and TBS ether. We have also noticed that highly deactivated aromatic aldehydes (run 9 and 21) can be protected as dithioacetals (**104** and **115**) in good yields in longer reaction time. It is important to mention that diethyldithioacetals of 2-naphthaldehyde (**111**) was obtained from 2-naphthaldehyde (run 16) by using nickel(II) chloride catalyst in 85% yield in 3 h, which provides much better yield than the recently reported procedure.[54] Similarly, various aliphatic aldehydes were converted to the corresponding 1,3-dithiolanes derivatives **116-120** on treatment with 1,2-ethanedithiol using the same catalyst. The IR, ^{1}H NMR and ^{13}C NMR spectra of products **117** and **120** are given in figures **9-12** for confirmation of their structures. These results reflect again the efficacy of our procedure.

Table 1 Protection of various aldehydic compounds to the corresponding dithioacetals by employing 0.1 equivalent amount of anhydrous nickel chloride ($NiCl_2$)

Run	Substrate	Thiol used	Time min/ [h]	Product[a]	Pro-duct No.	Yield[b]/ %
1		C	[2.75]		**98**	96
2		D	[2.50]		**99**	94
3		D	[2.25]		**100**	92
4		A	[5.0]		**101**	87
5		B	[13]		**102**	90
6		C	[0.75]		**66**	90
7		D	[1.15]		**34**	89
8		D	12		**103**	96
9		C	[20]		**104**	82
10		D	[1]		**105**	87
11		D	[2.5]		**106**	79
12		D	[0.45]		**107**	90
13		C	[3.50]		**108**	76
14		D	[4.00]		**109**	77

15		D	[5.50]		**110**	79
16		A	[3.0]		**111**	85
17		D	[1.75]		**112**	97
18		D	40		**25**	83
19		C	8		**113**	96
20		D	30		**114**	93
21		D	[18]		**115**	84
22		C	[8]		**116**	84
23		C	[7.0]		**117**	80
24		C	[1.5]		**118**	89
25		C	[7.5]		**119**	85
26		C	10		**120**	75

[a] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. [b] Isolated yields after purification. Thiol used: A = Ethanethiol, B = Thiophenol, C = 1,2-Ethanedithiol, D = 1,3-Propanedithiol.

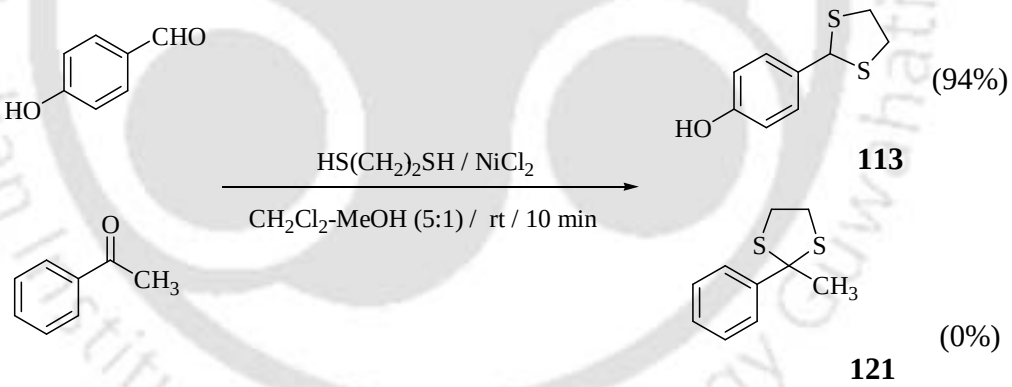
We found that electron rich aromatic aldehydes usually take much less time for the formation of the product. We have observed that nickel(II) chloride hexahydrate can also be used for similar reaction. However, it requires much longer reaction time than anhydrous nickel(II) chloride.

The formation of the product can be explained as follows. We believe that nickel(II) chloride acts as a Lewis acid, which activates the carbonyl group during the formation of product. Alternatively, the formation of dithioacetal might be catalyzed hydrochloric

acid, which is actually generated *in situ* in the reaction medium by the reaction of 1,2-ethanedithiol and nickel(II) chloride. We have also found in the literature[69] that reaction of 1,2-ethanedithiol and nickel(II) chloride gives polymeric compound [Ni(es)]*n* and hydrochloric acid.

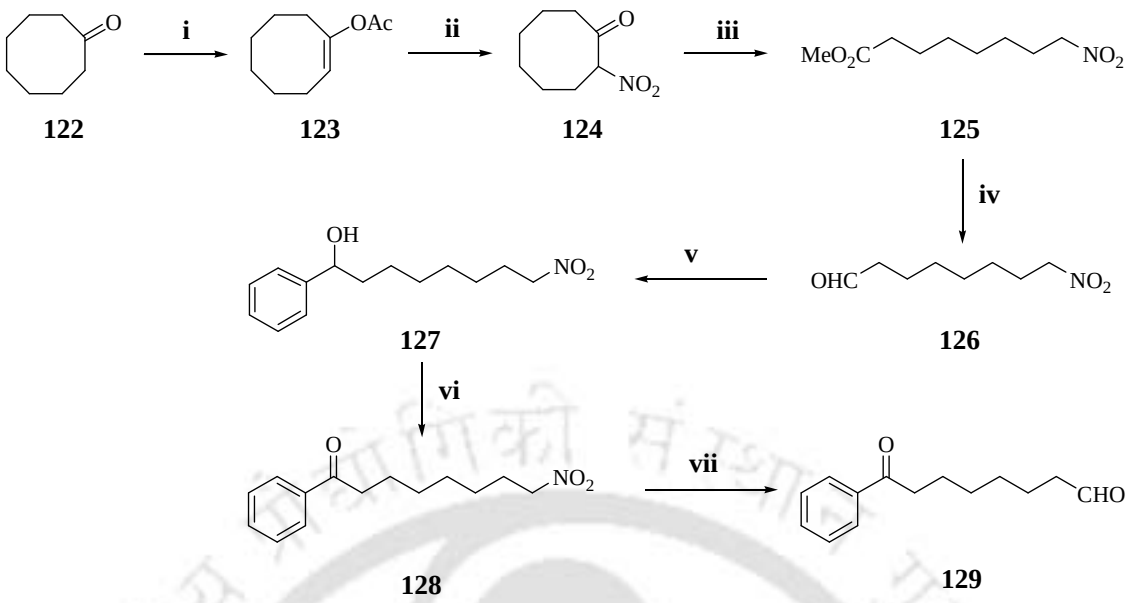
Next, we have turned our attention whether the same catalyst can be utilized for thioacetalization of ketones or not. We have observed the reaction of cyclohexanone and 1,2-ethanedithiol in the presence of catalytic amount nickel(II) chloride is very sluggish under identical conditions and the reaction does not complete even after a prolonged reaction time.

This result encourages us to extend the methodology for chemoselective protection of an aldehyde group in presence of a ketone. For instance, when an equimolar mixture of 4-hydroxybenzaldehyde and acetophenone was allowed to react with 1,2-ethanedithiol in the presence of catalytic amount of $NiCl_2$ under identical conditions then only 1,3-dithiolane derivative of 4-hydroxybenzaldehyde was obtained and unreacted aceto-phenone was recovered, as shown in scheme 34.



Scheme 34

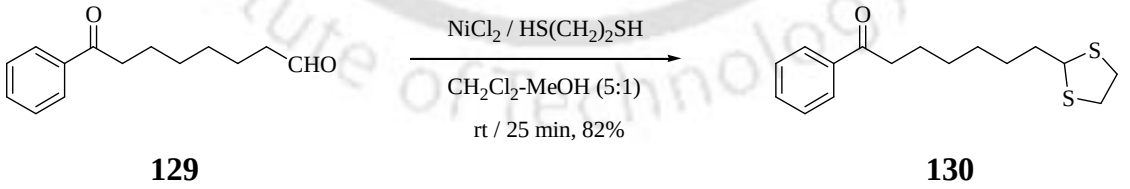
Next, we wanted to investigate whether an aldehydic group can be protected chemoselectively containing a keto group in the same molecule under identical conditions. For this study, we had to prepare keto-aldehyde **129** from cyclooctanone. The compound **129** was prepared by following literature procedures[66-68] as shown in the scheme 35.



Scheme 35

Reagents and reaction conditions: i) Ac_2O, p-TSA, reflux, 5 h, 75%; ii) Ac_2O, CH_2Cl_2, conc. HNO_3 / H_2SO_4; 70%; iii) $KF{\cdot}2H_2O$ / MeOH, reflux, 3 h, 85%; iv) DIBAL-H, CH_2Cl_2, -72°C, 2.5 h, 83%; v) PhMgBr, Et_2O, 60%; vi) PCC / CH_2Cl_2, 70%; vii) (a) alc. KOH, (b) $KMnO_4$, $MgSO_4$, H_2O, 15 min.-3 h, 70%.

Then, the keto-aldehyde **129** was chemoselectively protected the aldehydic group into the corresponding dithioacetals in good yield without affecting the keto group under identical reaction conditions, as shown in the scheme 36.



Scheme 36

In conclusion, we have achieved a very simple and convenient protocol for the protection of various aldehydic compounds chemoselectively to the corresponding acyclic as well as cyclic dithioacetals in the presence of wide range of other protecting groups using a

catalytic amount of less expensive catalyst $NiCl_2$. The present method is considered to be a useful and efficient one for transformation of the wide variety of aldehydic compounds into the corresponding dithioacetals without involving dry solvent and inert atmosphere. In addition, an aldehyde group can be protected chemoselectively in the presence of a keto group. Moreover, highly deactivated aromatic aldehydes can be converted to the corresponding dithioacetals without any difficulty. Due to its operational simplicity, good yields, high chemoselectivity, mild reaction conditions, non-aqueous work up and absence of concurrent side reaction this procedure is expected to be a practical use. The main drawback of the present method is that ketone does not provide dithioacetal derivatives under similar reaction conditions, which encourage us to further pursue thioacetalization of carbonyl compounds in the presence of other catalyst. We expect that other nickel salts can also be used for similar transformations and under investigation.

PART II

(SECTION A)

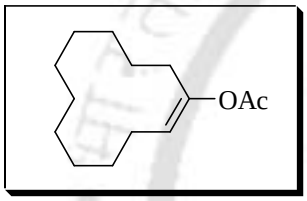
NEW SYNTHETIC METHOD FOR CHEMOSELECTIVE THIOACETALIZATION OF ALDEHYDIC COMPOUNDS BY EMPLOYING NICKEL(II) CHLORIDE AS A NEW CATALYST

EXPERIMENTALS

Experimental

Preparation of 1-Acetoxy cyclododecene (94)[66]

Cyclododecanone (2.5 g, 13.74 mmol) was added to a mixture of acetic anhydride (2.59 ml, 27.48 mmol) and *p*-toluenesulfonic acid (0.011 g, 0.058 mmol). The reaction mixture was heated to 175 °C at an oil bath and generated acetic acid was removed by distillation time to time. After 8 h, the reaction mixture was cooled to room temperature and extracted with dichloromethane. The organic extract was washed with 5% aqueous sodium carbonate solution (2 × 10 ml) and washed it with water (2 × 20 ml). The organic layer was dried over anhydrous magnesium sulfate and it was concentrated in rotavapor. The product 1-acetoxy cyclododecene (**94**) was obtained by distillation under reduced pressure.



Nature: Light yellow liquid

Yield: 65%

IR (Neat): cm^{-1} 1747, 1683

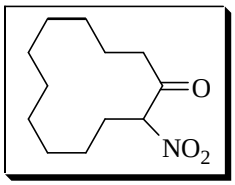
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (m, 12H $–CH_2$-), 1.31 (m, 4H, $-CH_2$-), 1.95 (m, 4H, $-CH_2$-), 2.08 (s, 3H, $-COCH_3$), 4.79 (t, 1H, *J* = 8.3 Hz, C*H*= $COCOCH_3$)

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{24}O_2$	C 74.95	C 74.83
224.34	H 10.78	H 10.85

2-Nitro cyclododecanone (95)[66]

To a mixture of 1-acetoxycyclododecene (2.0 g, 8.93 mmol) and acetic anhydride (2.68 ml) containing one drop of concentrated sulfuric acid in 10 ml of CH_2Cl_2 was added a mixture of glacial acetic acid (0.447 ml) and concentrated nitric acid (0.63 ml) over a period of 30 min at ice-bath temperature. The inner reaction temperature was maintained below 6 °C by external cooling. The resulting mixture was stirred at 0-5 °C for 1.5 h and kept for stirring at room temperature for another 3 h. Then, acetic acid was removed completely as much as possible under vaccum at 40 °C and the residue was extracted with diethyl ether (2 x 100 ml) and finally washed with water (2 × 30

ml). The ether solution was dried with magnesium sulfate and it was removed to give a light yellow solid residue, which was finally purified by passing through a silica gel column to obtain the desired pure 2-nitrocyclododecanone (**95**).



Nature: Light yellow solid

Yield: 80%

Melting point: 72 °C

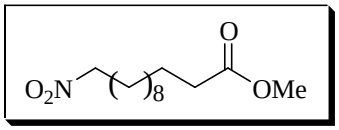
IR (KBr): cm^{-1} 1741, 1557, 1480, 1367, 1250

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (m, 14H, -CH_2-), 1.69 (m, 2H, -CH_2-), 2.69 (m, 2H, -CH_2-), 2.80 (m, 2H, -CH_2-), 5.17 (t, 1H, *J* = 5.6 Hz, -$CHNO_2$)

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{21}NO_3$	C 63.41	C 63.45
227.30	H 9.31	H 9.39
	N 6.16	S 6.17

Methyl 12-nitrododecanoate (96)[68]

To a solution of 2-nitro cyclododecanone (**95**) [1.0 g, 4.4 mmol] in 10 ml of absolute methanol was added potassium fluoride dihydrate (0.292 g, 3.11 mmol) at room temperature and kept for refluxing at an oil bath. After 3 h, the solvent was evaporated and water was added into it. The reaction mixture was extracted with diethyl ether (3 × 50 ml) and dried over Na_2SO_4. Concentration of the organic layer followed by purification of the crude residue through a silica gel column gave the desired compound **96** as an oily liquid. The compound was eluted with 10% ethylacetate / hexane mixture.



Nature: Oil

Yield: 85%

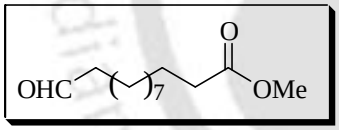
IR (Neat): cm^{-1} 1741, 1557, 1449, 1383, 1173

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18-1.45 (m, 14H, -CH_2-), 1.52-1.70 (m, 2H, -CH_2-), 1.95- 2.08 (m, 2H, -CH_2-), 2.30 (t, 2H, *J* = 7.4 Hz, -CH_2-), 3.65 (s, 3H, -CO_2CH_3), 4.38 (t, 2H, *J* = 7.2 Hz, -CH_2NO_2)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{25}NO_4$	C 60.21	C 60.32
259.34	H 9.72	H 9.56
	N 5.40	S 5.27

Methyl 12-Oxododecanoate (97)[68]

To a stirred solution of *w*-nitro ester **96** (0.516 g, 2 mmol) in 15 ml of methanol was added slowly a methanolic solution of 0.1 M KOH (28 ml, 2.8 mmol) at 0 °C temperature. After stirring for an additional 15 min, 30 ml of an aqueous solution of $KMnO_4$ (0.22 g, 1.4 mmol) and $MgSO_4$ (0.240 g, 2 mmol) was added dropwise with efficient stirring by maintaining the same temperature. The reaction mixture was stirred for an additional 2.5 h at 0 °C and then filtered it through a celite pad. The filtrate was dried over anhydrous $MgSO_4$. Removal of organic solvent and purification by silica gel column provided the desired ester aldehyde **97** in good yield.



Nature: Oil

Yield: 85%

IR (Neat): cm^{-1} 2720,1746, 1716

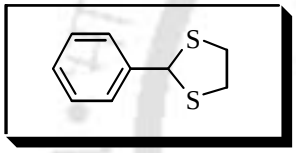
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (m, 12H, -CH_2-), 1.65 (m, 4H, -CH_2-), 2.26 (m, 2H, -CH_2-), 2.38 (m, 2H, -CH_2-), 3.62 (s, 3H, -CO_2CH_3), 9.72 (t, 1H, *J* = 1.8 Hz, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{24}O_3$	C 68.38	C 68.47
228.33	H 10.59	H 10.52

General procedure for thioacetalization of aldehydes:

To a mixture of an aldehyde (I mmol) and thiol (2.2 mmol) or dithiol (1.1) in 3 ml of CH_2Cl_2-MeOH (5:1) was added anhydrous nickel(II) chloride (0.013 g, 0.1mmol), which was actually prepared from $NiCl_2 \cdot 6H_2O$ by heating in an oven at 150 °C and cooling in a desicator at room temperature. After adding the catalyst, the reaction mixture was turned into black in the case of 1,2-ethanedithiol or dark brown for 1,3-propanedithiol. The reaction mixture was stirred at room temperature and monitored by TLC until the starting material was disappeared. After completing the reaction, it was concentrated *in vacuo* and the residue was passed through a silica gel column to obtain the desired product dithioacetals.

2-[phenyl]-1,3-dithiolane (98):



Nature: Liquid

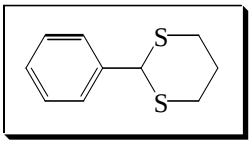
Yield: 96%

R_f: (Hexane/AcOEt = 9.5: 0.5)

^{1}H NMR (60 **MHz, $CDCl_3$):** δ 3.39 (m, 4H, -SCH_2-), 5.55 (s, 1H, ArCH-), 7.35 (m, 5H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_9H_{10}S_2$	C 59.30	C 59.47
182.31	H 5.53	H 5.47
	S 35.18	S 35.29

2-[phenyl]-1,3-dithiane (99):



Nature: White solid

Yield: 94%

R_f: 0.94 (Hexane/AcOEt = 9.5: 0.5)

Melting Point: 74 °C [Lit.[37] 71-72 °C]

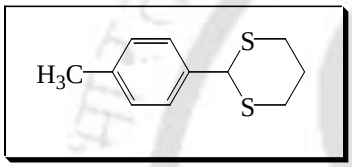
IR (KBr): cm^{-1} 3037, 2940, 2894, 2827, 1593, 1491, 1429, 1281, 1183, 1066, 912, 728, 697

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85-1.96 (m, 1H, -SCH_2CHaHbCH_2S-), 2.09-2.16 (m, 1H, - $SCH_2CHaHbCH_2S$-), 2.85-2.90 (m, 2H, SCH_2-), 2.99-3.07 (m, 2H, SCH_2-), 5.16 (s, 1H, ArCH-), 7.24-7.35 (m, 3H, ArH), 7.45-7.47 (m, 2H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.96, 31.95 (2C), 51.34, 127.61 (2C), 128.29, 128.59 (2C), 138.99

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}S_2$	C 61.17	C 61.32
196.34	H 6.16	H 6.14
	S 32.66	S 32.49

2-[4à-Methylphenyl]-1,3-dithiane (100):



Nature: White solid

Yield: 92%

R_f: 0.84 (Hexane/AcOEt = 9.9: 0.1)

Melting Point: 85 °C

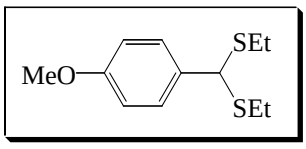
IR (KBr): cm^{-1} 3048, 2935, 2904, 1614, 1521, 1429, 1276, 1178, 1112, 1035, 753

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84-1.98 (m, 1H, -SCH_2CHCH_2S-), 2.11-2.19 (m, 1H, -SCH_2CHCH_2S-), 2.32 (s, 3H, -CH_3), 2.84-2.92 (m, 2H, -SCH_2-), 2.99-3.09 (m, 2H, -SCH_2-), 5.14 (s, 1H, ArCH-), 7.13 (d, 2H, *J* = 9.0 Hz, ArH), 7.32 (d, 2H, *J* = 9.0 Hz, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 25.1, 32.1 (2C), 51.1, 127.5 (2C), 129.3 (2C), 136.1, 138.2

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{14}S_2$	C 62.80	C 62.65
210.37	H 6.71	H 6.82
	S 30.48	S 30.32

4à-Methoxyphenyl diethyldithioacetal (101):



Nature: White solid

Yield: 87%

R_f: 0.94 (Hexane/AcOEt = 19:1)

Melting point: 43 °C

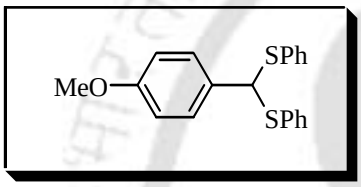
IR (KBr): cm^{-1} 2965, 2928, 1609, 1510, 1447, 1301, 1261, 1174, 1106,1025

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, 6H, *J* = 7.3 Hz, 2 x -SCH_2CH_3), 2.46-2.63 (m, 4H, 2 x -SCH_2CH_3), 3.80 (s, 3H, -OCH_3), 4.91 (s, 1H, ArCH-), 6.85 (d, 2H, *J* = 8.6 Hz, ArH), 7.37 (d, 2H, *J* = 8.5 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.24 (2C), 26.15 (2C), 51.69, 55.22, 113.75 (2C), 128.77 (2C), 132.37, 159.00

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{18}OS_2$	C 59.46	C 59.65
242.41	H 7.48	H 7.59
	S 26.46	S 26.22

4â-Methoxyphenyl diphenyldithioacetal (102):



Nature: White solid

Yield: 90%

R_f: 0.87 (Hexane/AcOEt = 9.8: 0.2)

Melting point: 80-82 °C

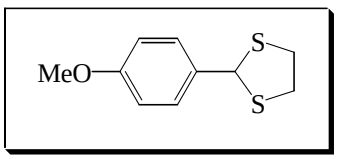
IR (KBr): cm^{-1} 3073, 3001, 2960, 2904, 2843, 1660, 1588, 1511, 1460, 1250, 1173, 1096, 1025, 846, 738, 687

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H, -OCH_3), 5.42 (s, 1H, ArCH-), 6.78 (d, 2H, *J* = 6.9 Hz, ArH), 7.21-7.35 (m, 12H, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 59.7, 113.8 (2C), 127.6 (3C), 128.8 (4C), 129.0 (2C), 131.6, 132.3 (4C), 134.7, 159.2

Elemental Analysis	**Calculated**	**Found**
$C_{20}H_{18}OS_2$	C 70.97	C 70.75
338.49	H 5.36	H 5.20
	S 18.95	S 18.82

2-[4â-Methoxyphenyl]-1,3-dithiolane (66):



Nature: White solid

Yield: 90%

R_f: 0.88 (Hexane/AcOEt = 9.5: 0.5)

Melting Point: 65 °C [Lit.[35] 60-61 °C]

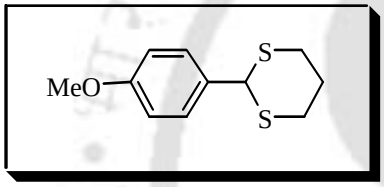
IR (KBr): cm^{-1} 2955, 2938, 2838, 1609, 1511, 1470, 1429, 1312, 1245, 1189, 1030, 840, 758

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28-3.35 (m, 2H, -SCH_2-), 3.43-3.51 (m, 2H, -SCH_2-), 3.77 (s, 3H, -OCH_3), 5.62 (S, 1H, ArCH-), 6.83 (d, 2H, *J* = 8.56 Hz, ArH), 7.44 (d, 2H, *J* = 8.76 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 40.09 (2C), 55.20, 55.94, 113.74 (2C), 129.04 (2C), 131.69, 159.25

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}OS_2$	C 56.57	C 56.70
212.33	H 5.70	H 5.58
	S 30.20	S 30.35

2- [4̀-Methoxyphenyl]-1,3-dithiane (34):



Nature: White solid

Yield: 89%

R_f: 0.82 (Hexane/AcOEt = 9.5: 0.5)

Melting Point: 121 °C [Lit.[37] 115-116 °C]

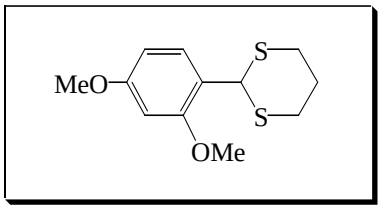
IR (KBr): cm^{-1} 2939, 2909, 1613, 1511, 1439, 1253, 1178, 1111,1040

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83-1.98 (m, 1H, -SCH_2C*Ha*HbCH_2S-), 2.11- 2.18 (m, 1H, -SCH_2CHa*Hb*CH_2S-), 2.85- 2.92 (m, 2H, -SCH_2-), 3.00-3.09 (m, 2H, -SCH_2), 3.78 (s, 3H, -OCH_3), 5.13 (s, 1H, ArCH-), 6.86 (d, 2H, *J* = 8.61 Hz, ArH), 7.38 (d, 2H, *J* = 8.58 Hz, ArH)

^{13}C NMR (63 MHz, $CDCl_3$): δ 24.05, 31.16, 49.71, 54.27, 113.05, 127.90, 130.29, 158.53

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{14}OS_2$	C 58.37	C 58.58
226.36	H 6.23	H 6.20
	S 28.33	S 28.25

2-[2à,4à-Dimethoxyphenyl]-1,3-dithiane (103):



Nature: White solid

Yield: 96%

R_f: 0.83 (Hexane/AcOEt = 9: 1)

Melting Point: 103 °C

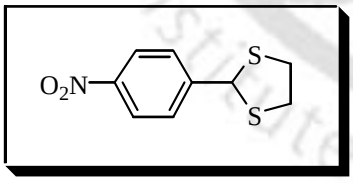
IR (Neat): cm^{-1} 2996, 2939, 2893, 2837, 1618, 1505, 1454, 1424, 1326, 1290, 1116, 1039, 992

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85-1.92 (m, 1H, -$SCH_2CHaHbCH_2S$-), 2.12-2.17 (m, 1H, - $SCH_2CHaHbCH_2S$-), 2.84-2.90 (m, 2H, -SCH_2-), 3.05-3.16 (m, 2H, -SCH_2), 3.78 (s, 3H, -OCH_3), 3.83 (s, 3H, -OCH_3), 5.61 (S, 1H, ArCH-), 6.42 (d, 1H, *J* = 2.4 Hz, ArH), 6.48 (dd, 1H, *J* = 2.4 Hz, *J* = 8.5 Hz, ArH), 7.48 (d, 1H, *J* = 8.5 Hz, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ 25.20, 32.41 (2C), 43.10, 55.30, 55.60, 98.50, 104.70, 119.80, 129.70, 156.40, 160.60

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{16}O_2S_2$	C 56.22	C 56.01
256.39	H 6.29	H 6.36
	S 25.01	S 25.14

2-[4à-Nitrophenyl]-1,3-dithiolane (104):



Nature: Yellow low melting solid

Yield: 82%

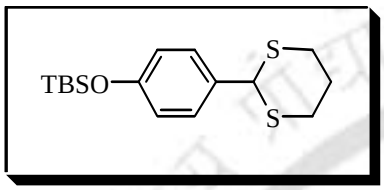
R_f: 0.85 (Hexane/AcOEt = 9: 1)

IR (Neat): cm^{-1} 2930, 2853, 1603, 1521, 1424, 1352, 1317, 1291, 1245, 1112, 1015, 984, 876, 830, 784

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.37-3.43 (m, 2H, -SCH_2-), 3.45-3.55 (□m, 2H, -SCH_2-), 5.65 (s, 1H, ArCH-), 7.66 (d, 2H, *J* = 8.6 Hz, ArH), 8.17 (d, 2H, *J* = 8.7 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_9H_9NO_2S_2$	C 47.56	C 47.29
227.31	H 3.99	H 3.95
	N 6.16	N 6.01
	S 28.21	S 28.01

2-[4-*tert*-Butyldimethylsilyloxyphenyl]-1,3-dithiane (105):



Nature: White crystalline solid

Yield: 87%

R_f: 0.62 (Hexane/EtOAc = 9.9: 0.1)

Melting Point: 82 °C

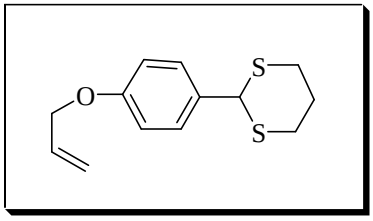
IR (KBr): cm^{-1} 2940, 2899, 2853, 1603, 1501, 1255, 1168, 912

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.19 (s, 6H, 2 × -$SiCH_3$), 0.97 (s, 9H, -$SiC(CH_3)_3$), 1.83-1.98 (m, 1H, -SCH_2*CH* CH_2S-), 2.10-2.19 (m, 1H, -SCH_2*CH* CH_2S-), 2.85- 2.92 (m, 2H, -SCH_2-), 2.99-3.10 (m, 2H, -SCH_2-), 5.12 (s, 1H, ArCH-), 6.78 (d, 2H, *J* = 8.4 Hz, ArH), 7.30 (d, 2H, *J* = 8.4 Hz, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ -4.5 (2C), 18.1, 25.0, 25.6 (3C), 32.1 (2C), 50.8, 120.1 (2C), 128.8 (2C), 131.8, 155.7

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{26}OS_2Si$	C 58.84	C 58.60
310.60	H 8.02	H 7.95
	S 19.63	S 19.70

2-[4â-Allyloxyphenyl]-1,3-dithiane (106):



Nature: White solid

Yield: 79%

R_f: 0.66 (Hexane /AcOEt = 9.9: 0.1)

Melting Point: 81 °C

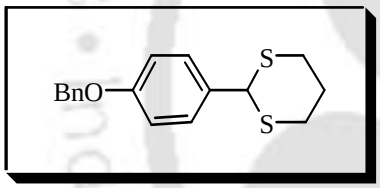
IR (KBr): cm^{-1} 2914, 1603, 1506, 1429, 1245, 1183, 1015, 779

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84-1.97 (m, 1H, -$SCH_2CHaHbCH_2S$-), 2.11-2.17 (m, 1H, -$SCH_2CHaHbCH_2S$), 2.86-2.91 (m, 2H, -SCH_2-), 3.00-3.14 (m, 2H, -SCH_2-), 4.50-4.52 (m, 2H, -$OCH_2CH=CH_2$), 5.13 (s, 1H, ArCH-), 5.27 (dd, 1H, *J* = 3.0 Hz, *J* = 10.6 Hz, -$OCH_2CH=CH_aH_b$), 5.39 (dd, 1H, *J* = 3.2 Hz, *J* = 17.1 Hz, -$OCH_2CH=CH_aH_b$), 5.98-6.08 (m, 1H, $OCH_2CH=CH_aH_b$), 6.87 (d, 2H, *J* = 8.8 Hz, ArH), 7.38 (d, 2H, *J* = 8.8 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.97, 32.10 (2C), 50.66, 68.81, 114.86 (2C), 118.26, 128.86 (2C), 131.34, 133.03, 158.49

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{16}OS_2$	C 61.86	C 61.69
252.40	H 6.39	H 6.32
	S 25.41	S 25.18

2-[4å-Benzyloxyphenyl]-1,3-dithiane (107):



Nature: White solid

Yield: 90%

R_f: 0.50 (Hexane /AcOEt = 9.8:0.2)

Melting Point: 78°C

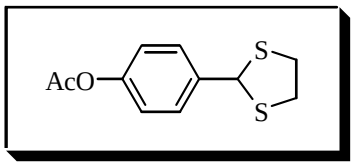
IR (KBr): cm^{-1} 2945, 2889, 1609, 1511, 1393, 1245, 1189, 1009, 748.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85-1.95 (m, 1H, -$SCH_2CHaHbCH_2S$-), 2.12-2.17 (m, 1H, -$SCH_2CHaHbCH_2S$-), 2.85-2.95 (m. 2H, -SCH_2-), 3.00-3.07(m. 2H, -SCH_2-), 5.04 (s, 2H, -OCH_2Ph), 5.12 (s, 1H, ArCH-), 6.92 (d, 2H, *J* = 8.52 Hz, ArH), 7.24-7.42 (m, 7H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.03, 32.13 (2C), 50.70, 69.98, 114.94 (2C), 127.42 (2C), 127.94, 128.54 (2C), 128.92 (2C), 131.53 (2C), 136.79

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{18}OS_2$	C 67.51	C 67.32
302.26	H 6.00	H 6.12
	S 21.20	S 21.25

2-[4à-Acetoxyphenyl]-1,3-dithiolane (108):



Nature: White solid

Yield: 76%

R_f: 0.78 (Hexane/AcOEt = 9:1)

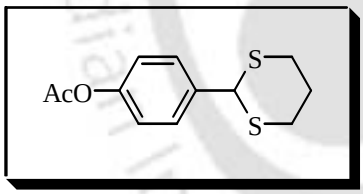
Melting Point: 102 °C

IR (KBr): cm^{-1} 2925, 1762, 1614, 1511, 1374, 1204, 1009, 912

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H, -$OCOCH_3$), 3.25-3.32 (m, 2H, -SCH_2-), 3.41-3.45 (m, 2H, -SCH_2-), 5.56 (s, 1H, ArCH-), 6.96 (d, 2H, *J* = 8.56 Hz , ArH), 7.47 (d, 2H, *J* = 8.52 Hz, ArH).

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{12}O_2S_2$	C 54.97	C 54.74
240.35	H 5.03	H 5.12
	S 26.68	S 26.53

2-[4à-Acetoxyphenyl]-1,3-dithiane (109):



Nature: White solid

Yield: 77%

R_f: 0.73 (Hexane/AcOEt = 9:1)

MeltingPoint: 108 °C

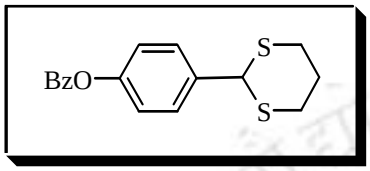
IR (KBr): cm^{-1} 2950, 2904, 2827, 1756, 1603, 1511, 1424, 1372, 1239, 1019, 922, 768

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87-1.97 (m, 1H, -SCH_2CHCH_2S-), 2.13-2.19 (m, 1H, -SCH_2CHCH_2S-), 2.28 (s, 3H, -$OCOCH_3$), 2.86-2.92 (m, 2H, -SCH_2-), 3.0-3.08 (m, 2H, -SCH_2-), 5.16 (s, 1H, ArH), 7.06 (d, 2H, *J* = 8.52 Hz, ArH), 7.48 (d, 2H, *J* = 8.52 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.07, 24.97, 31.96 (2C), 50.61, 121.74 (2C), 128.89 (2C), 136.61, 150.46, 169.19

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{14}O_2S_2$	C 56.66	C 56.54
254.37	H 5.55	H 5.39
	S 25.21	S 25.27

2-[4å-Benzoyloxyphenyl]-1,3-dithiane (110):



Nature: White solid

Yield: 79%

R_f: 0.36 (Hexane/EtOAc = 9:1)

Melting Point: 163-164 °C

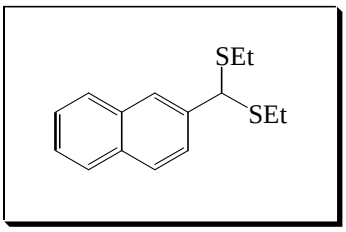
IR (KBr): cm^{-1} 3068, 2955, 2894, 1731, 1593, 1506, 1424, 1265, 1204, 1168, 1071, 1020, 886, 769, 707

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88-1.98 (m, 1H, -$SCH_2CHaHbCH_2S$-), 2.15-2.18 (m, 1H, -$SCH_2CHaHbCH_2S$-), 2.89-2.93 (m, 2H, -SCH_2-), 3.03-3.09 (m, 2H, -SCH_2-), 5.20 (s, 1H, ArCH-), 7.20 (d, 2H, *J* = 8.8 Hz, ArH), 7.51 (m, 2H, ArH), 7.53 (d, 2H, *J* = 8.5 Hz, ArH), 7.63 (m, 1H, ArH), 8.18 (m, 2H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.04, 32.03 (2C), 50.72, 121.95 (2C), 128.57 (2C), 129.03 (2C), 129.43, 130.17 (2C), 133.64, 136.74, 150.80, 164.95

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{16}O_2S_2$	C 64.53	C 64.35
316.44	H 5.10	H 5.03
	S 20.27	S 20.01

Diethyldithioacetal of 2-Naphthaldehyde (111):



Nature: Viscous liquid

Yield: 85%

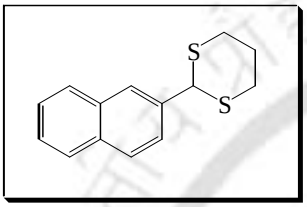
R_f: 0.93 (Hexane/EtOAc = 9.5: 0.5)

IR (Neat): cm^{-1} 2966, 2924, 1597, 1506, 1449, 1265, 1150,1051

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (t, 6H, *J* = 7.4 Hz, -CH_3), 2.45-2.70 (m, 4H, -S*C*$H_2$$CH_3$)**,** 5.09 (s, 1H, ArCH-), 7.48 (m, 2H, ArH), 7.63 (d, 1H, *J* = 8.8 Hz, ArH), 7.82 (m, 4H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{18}S_2$	C 68.65	C 68.57
262.44	H 6.91	H 6.72
	S 24.44	S 24.61

2-[Naphthyl]-1,3-dithiane (112):



Nature: White solid

Yield: 97%

R_f : 0.48 (Hexane/ EtOAc = 9.9: 0.1)

Melting Point: 111-113 °C

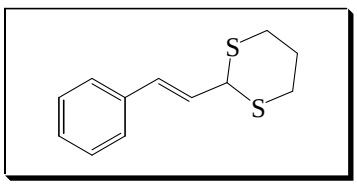
IR (KBr): cm^{-1} 2939, 2899, 2827, 1608, 1511, 1429, 1280, 1178, 901, 829, 778

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.93-2.03 (m, 1H, -SCH_2C*H*CH_2S-), 2.13-2.22 (m, 1H, -SCH_2C*H*CH_2S-), 2.89-2.96 (m, 2H, -SCH_2-), 3.04-3.13 (m, 2H, -SCH_2-), 5.32 (s, 1H, ArCH-), 7.48 (m, 2H, ArH), 7.58 (dd, 1H, *J* = 1.5 Hz, *J* = 8.7 Hz, ArH), 7.77-7.84 (m, 3H, ArH), 7.95 (bs, 1H, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 32.1 (2C), 51.5, 125.6, 126.3 (2C), 126.8, 127.6, 128.0, 128.4, 133.2, 133.3, 136.4

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{14}S_2$	C 68.24	C 68.35
246.40	H 5.73	H 5.63
	S 26.03	S 24.97

2-Styryl-1, 3-dithiane (25):



Nature: Viscous Liquid

Yield: 83%

R_f: 0.8 (Hexane/EtOAc = 9.8: 0.2)

Melting Point: 62 °C [Lit.[37] 62-63 °C]

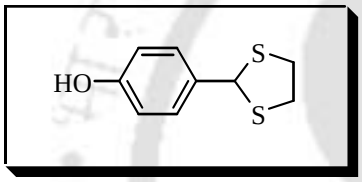
IR (KBr): cm^{-1} 3027, 2919, 2853, 1614, 1542, 1486, 1424, 1271, 1173, 1040, 963, 764, 697

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84-1.98 (m, 1H, -$SCH_2CHaHbCH_2S$-), 2.09-2.16 (m, 1H, -$SCH_2CHaCHbCH_2S$-), 2.85-3.13 (m, 4H, 2 x -SCH_2-), 4.81 (d, 1H, *J* = 7.6 Hz, ArCH-), 6.26 (dd, 1H, *J* = 7.8 Hz, *J* = 15.9 Hz, PhCH=*CH*CH-), 6.75 (d, 1H, *J* = 15.6 Hz, Ph*CH*=CHCH-), 7.22-7.32 (m, 3H, ArH), 7.36-7.47 (m, 2H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.18, 30.21 (2C), 47.66, 126.01, 126.65 (2C), 128.08, 128.57 (2C), 133.37, 136.06

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{14}S_2$	C 64.82	C 64.68
222.37	H 6.34	H 6.23
	S 28.84	S 28.59

2-[4å-Hydroxyphenyl]-1,3-dithiolane (113):



Nature: White solid

Yield: 96%

R_f: 0.47 (Hexane/EtOAc = 9:1)

Melting point: 117 °C

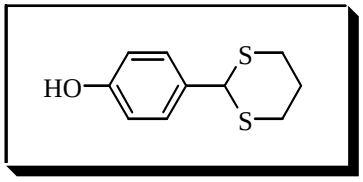
IR (KBr): cm^{-1} 3396, 2914, 1603, 1511, 1450, 1368, 1250, 1178, 1102, 851

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.31-3.37 (m, 2H, -SCH_2-), 3.45-3.52 (m, 2H, -SCH_2-), 5.23 (s, 1H, -OH), 5.62 (S, 1H, ArCH-), 6.75 (d, 2H, *J* = 7.8 Hz, ArH), 7.39 (d, 2H, *J* = 8.5 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 40.18 (2C), 56.03, 115.34 (2C), 129.40 (2C), 131.96, 155.30

Elemental Analysis	**Calculated**	**Found**
$C_9H_{10}OS_2$	C 54.51	C 54.65
198.31	H 5.08	H 5.25
	S 32.34	S 32.21

2-[4å-Hydroxyphenyl]-1,3-dithiane (114):



Nature: White solid

Yield: 93%

R_f: 0.36 (Hexane/EtOAc = 9:1)

Melting point: 156-158 °C

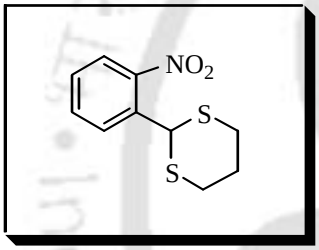
IR (KBr): cm^{-1} 3370, 2940, 2894, 2807, 1609, 1516, 1450, 1363, 1250, 1173, 1112, 851, 774

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85-1.96 (m, 1H, -SCH_2C*Ha*HbCH_2S-), 2.12-2.19 (m, 1H, -SCH_2CHa*Hb*CH_2S-), 2.86-2.92 (m, 2H, -SCH_2-), 3.01-3.08 (m, 2H, -SCH_2), 5.12 (S, 1H, ArCH-), 6.77 (d, 2H, *J* = 8.2 Hz, ArH), 7.31 (d, 2H, *J* = 8.3 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.06, 32.18 (2C), 50.74, 115.58 (2C), 129.18 (2C), 131.45, 155.61

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}OS_2$	C 56.56	C 56.34
212.34	H 5.70	H 5.63
	S 30.20	S 32.01

2-[2å-Nitrophenyl]-1,3-dithiane (115):



Nature: Low melting yellow solid

Yield: 84%

R_f: 0.39 (Hexane/AcOEt = 9:1)

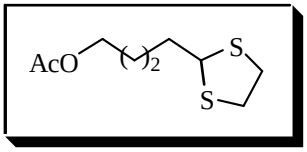
Melting Point: 132 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89-2.05 (m, 1H, -SCH_2C*Ha*HbCH_2S-), 2.22–2.27 (m, 1H, -SCH_2CHa*Hb*CH_2S-), 2.95-3.01 (m, 2H, -SCH_2-), 3.14-3.21 (m, 2H, -SCH_2), 5.94 (S, 1H, ArCH-), 7.49(t, 1H, *J* = 7.2 Hz, ArH), 7.67 (t, 1H, *J* = 6.8 Hz, ArH), 7.91-7.95 (m, 2H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.93, 32.18, 45.87, 124.65, 129.0, 130.66, 133.26, 133.40, 147.66

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{11}O_2NS_2$	C 47.04	C 47.14
255.34	H 4.34	H 4.29
	N 10.97	N 11.08
	S 25.12	S 25.28

2-[4-Acetoxy butane]-1, 3-dithiolane (116):



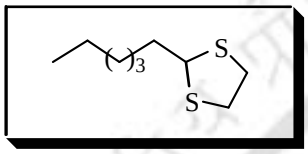
Nature: Liquid

Yield: 80%

R_f: 0.40 (Hexane/EtOAc = 9.5: 0.5)

IR (Neat): cm^{-1} 2930, 2858, 1737, 1455, 1271, 1199, 1091, 1035

2-Hexyl-1, 3-dithiolane (117):



Nature: Liquid

Yield: 80%

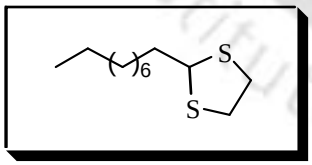
R_f: 0.40 (Hexane/EtOAc = 9.9: 0.1)

IR (Neat): cm^{-1} 2930, 2858, 1465, 1378, 1281, 1117, 861, 728

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 3H, *J* = 6.6 Hz, $-CH_3$), 1.25-1.42 (m, 8H, $-CH_2-$), 1.76-1.82 (m, 2H, $-CH_2CHS-$), 3.14-3.25 (m, 4H, 2x $-SCH_2-$), 4.44 (t, 1H, *J* = 7.08 Hz, -SCHS-)

Elemental Analysis	**Calculated**	**Found**
$C_9H_{18}S_2$	C 56.78	C 56.49
190.37	H 9.53	H 9.46
	S 33.69	S 33.51

2-Nonane-1,3-dithiolane (118):



Nature: Liquid

Yield: 80%

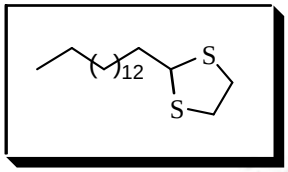
R_f: 0.75 (Hexane/EtOAc = 9.9: 0.1)

IR (Neat): cm^{-1} 2925, 2863, 1460, 1271, 1055, 963, 856

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 4.8 Hz, $-CH_3$), 1.26 (bs, 12H, $-CH_2-$), 1.70-1.77 (m, 2H, $-CH_2-$), 1.87-1.93 (m, 2H, $-CH_2CHS-$), 2.62-2.67 (m, 2H, 2× $-SCH_2-$), 2.70-2.87 (m, 2H, 2× $-SCH_2-$), 4.08 (t, 1H, -SCHS-)

Elemental Analysis	Calculated	Found
$C_{12}H_{24}S_2$	C 62.01	C 62.18
232.45	H 10.41	H 10.57
	S 27.59	S 27.68

2-Pentadecane-1,3-dithiolane (119):



Nature: Liquid

Yield: 80%

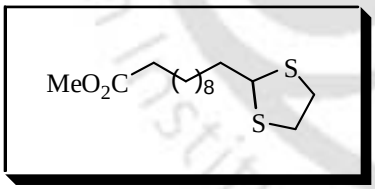
R_f: 0.75 (Hexane/EtOAc = 9.9: 0.1)

IR (Neat): cm^{-1} 2950, 2900, 1480, 1220

^{1}H NMR (60 MHz, $CDCl_3$): δ 0.75 (t, 3H, *J* = 6.5 Hz, $-CH_3$), 1.05-1.75 (m, 28H, $-CH_2-$), 2.95 (s, 4H, 2 × $-SCH_2-$), 4.15 (t, 1H, *J* = 6.0 Hz, -SCHS-)

Elemental Analysis	Calculated	Found
$C_{18}H_{36}S_2$	C 68.29	C 68.32
316.61	H 11.46	H 11.56
	S 20.26	S 20.10

2-[10å-Carboxymethyldecane]-1,3-dithiolane (120):



Nature: Liquid

Yield: 75%

R_f: 0.73 (Hexane/EtOAc = 9: 1)

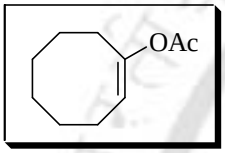
IR (KBr): cm^{-1} 2930, 2858, 1742, 1557, 1450, 1373, 1245, 1183, 1127,1066

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (bs, 16H, $-CH_2-$), 1.58-1.63 (m, 2H, $-CH_2-$), 2.30 (t, 2H, *J* = 7.56 Hz, $-CH_2-$), 3.31 (s, 2H, $-SCH_2-$), 3.49 (s, 2H, $-SCH_2-$), 3.67 (s, 3H, $-CO_2CH_3$), 4.38 (t, 1H, *J* = 7.03 Hz, -SCHS-).

Elemental Analysis	Calculated	Found
$C_{15}H_{28}O_2S_2$	C 62.15	C 62.00
328.54	H 8.60	H 8.55
	S 19.52	S 19.27

Preparation of 1-Acetoxy cyclooctene (123):

Cyclooctanone (5.0 g, 40 mmol) was dissolved into a solution of acetic anhydride (7.54 ml, 80 mmol) and *p*-toluenesulfonic acid (0.026 g, 0.135 mmol) in 50 ml round bottomed flask and kept for heating at 175 °C in an oil bath. After 3.5 h, the generated acetic acid was removed by distillation and extracted with dichloromethane (2 x 75 ml). The organic extract was washed with 5% aqueous sodium carbonate (2 × 15 ml), washed again with water (2× 30 ml) and dried over anhydrous magnesium sulfate. The organic extract was concentrated in rotavapour and the residual material was distilled off at 58-62 ^{o}C at 0.4 mm (lit. b.p. 60-62 ^{o}C/0.4 mm) to get the desired compound **123**. The product was obtained 5.04 g in 75% yield.

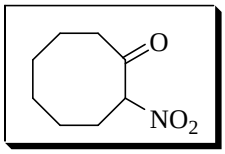


Nature: Liquid

Yield: 75%

2-Nitro cyclooctanone (124):

Into a solution of 1-acetoxycyclooctene **123** (4.0 g, 23.81 mmol) and acetic anhydride (7.15 ml) in 10 ml of CH_2Cl_2 was added one drop of concentrated sulfuric acid and kept for cooling at ice-bath temperature. Then, a mixture of glacial acetic acid (1.19 ml) and concentrated nitric acid (1.68 ml) was added to the above reaction mixture over a period of 30 min by keeping the same bath temperature. The resulting mixture was stirred at 0-5 °C for 1 h and then at room temperature for 2.5 h. Acetic acid was removed completely as much as possible under reduced pressure at 40 °C and finally it was extracted with diethyl ether (2 x 50 ml). The organic layer was washed with water (2 × 30 ml) and dried over magnesium sulfate. After concentration followed by purification through a silica gel column, the desired pure nitroketone **124** was obtained 2.85 g in70% yield.



Nature: Liquid

Yield: 70%

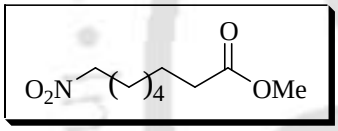
IR (KBr): cm^{-1} 1720, 1555, 1372

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00-3.00 (m, 12H, -CH_2-), 5.45 (t, 1H, *J* = 6.0 Hz, -$CHNO_2$)

Elemental Analysis	**Calculated**	**Found**
$C_8H_{13}NO_3$	C 56.12	C 55.97
	H 7.65	H 7.80
	N 8.16	N 8.06

Methyl 8-nitrooctanoate (125):

To a solution of 2.5 g (14.62 mmol) 2-nitro cyclooctanone (**124**) in 10 ml of absolute methanol was added potassium fluoride dihydrate (0.971 g, 10.33 mmol) and kept for refluxing in an oil bath. After 49 h, the solvent was removed and extracted with ether (3 × 50 ml), and finally dried over Na_2SO_4. The ether was removed in rotavapour and the residual material was passed through a silica gel column to furnish the desired compound **125** as an oily liquid. The compound was eluted in 10% ethyl acetate/ hexane mixture in 85% yield.



Nature: Liquid

Yield: 85%

IR (KBr): cm^{-1} 1735, 1550, 1372

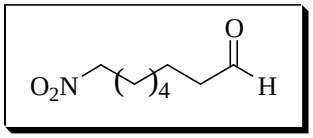
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20-2.20 (m, 10H, -CH_2-), 2.30 (t, 2H, *J* = 6.8 Hz -$COCH_2$-), 3.70 (s, 3H, -CO_2CH_3), 4.37 (t, 2H, *J* = 7.0 Hz, –CH_2NO_2)

Elemental Analysis	**Calculated**	**Found**
$C_9H_{17}NO_4$	C 53.19	C 53.08
203.24	H 8.43	H 8.50
	N 6.89	N 6.77

Preparation of 8-nito-1-octanal (126):

Into a three-jacked cooling flask methyl 8-nitrooctanate **125** (1.11 g, 5.46 mmol) was taken in anhydrous 25 ml of dichloromethane. Then, 4 ml of diisobutylaluminium hydride (DIBAL-H) was added slowly at –72 °C. After 1 h of stirring, the reaction mixture was quenched by addition a drop of methanol and the entire mixture was brought to the room temperature. The reaction mixture was diluted with 100 ml of CH_2Cl_2 and washed with 100 ml of cold water. The organic layer was dried over

anhydrous Na_2SO_4 and concentrated in rotavapour. The pure product 8-nito-1-octanal **126** was obtained 0.780 g in 83% yield as a colourless liquid after passing through a silica gel column.



Nature: Liquid

Yield: 83%

IR (KBr): cm^{-1} 1715, 1545

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (brs, 10H, -CH_2-), 2.19 (t, 2H, *J* = 6.0 Hz -$COCH_2$-), 4.37 (t, 2H, *J* = 7.0 Hz –CH_2NO_2-), 9.77 (t, 1H, *J* = 1.0 Hz, – CHO)

Elemental Analysis	**Calculated**	**Found**
$C_8H_{15}NO_3$	C 54.49	C 54.39
173.21	H 8.86	H 8.80
	N 8.10	N 8.20

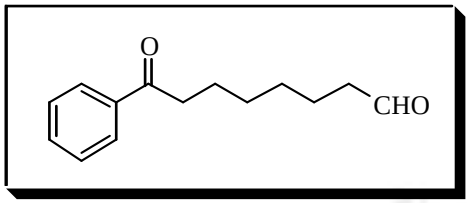
Preparation of Keto-aldehyde (129) from 8-nitooctan-1-al (126):

(A) Into a solution of 0.519 g (3 mmol) of 8-nitooctan-1-al **126** in 30 ml of dry diethyl ether was added a freshly prepared phenyl magnesium bromide (6.0 mmol) slowly at ice-bath temperature. The reaction mixture was stirred further for 30 min at 0 °C and it was brought to room temperature. The reaction was quenched by adding saturated solution of aqueous ammonium chloride, extracted with diethyl ether (3 x 30 ml) and dried over anhydrous Na_2SO_4. The organic solvent was removed and finally the residue was passed through a silica gel column to obtain 0.452 g of compound **127** in 60% yield. The Grignard addition product **127** was used in the next step without characterization**.**

(B) To a stirred solution of 0.374 g compound **127** (1.5 mmol) in 20 ml of anhydrous dichloromethane was added 0.483 g of pyridinium chlorochromate (2.25 mmol) in portion at room temperature. After 2 h of stirring, dry diethyl ether (50 ml) was added into it. Then, the entire solution was passed through a silica gel column to get the keto nitro compound **128** as 0.260 g in 70% yield.

(C) The compound **128** (0.250 g, 1 mmol) was taken in 15 ml of methanol and then added slowly a methanolic solution of 0.1 M KOH (14 ml, 1.4 mmol) at 0 °C temperature into it. After stirring for 20 min, 15 ml mixture of aqueous solution of $KMnO_4$ (0.11 g, 0.70 mmol) and $MgSO_4$ (0.120 g, 1 mmol) was added dropwise with efficient stirring at the same temperature. The reaction mixture was stirred for an

additional 3 h at 0 °C and then filtered it through a celite pad. The filtrate was dried over anhydrous $MgSO_4$. Removal of organic solvent and purification through a silica gel column provided 0.152 g the desired keto aldehyde **129** in 70% yield.



Nature: Colourless liquid

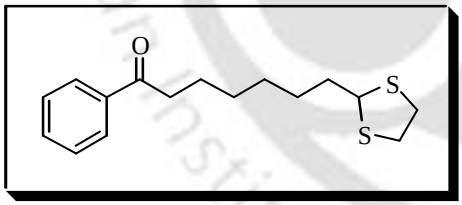
Yield: 70%

IR (Neat): cm^{-1} 2930, 2853, 1726, 1685, 1598, 1450, 1409, 1363, 1276, 1214, 1178, 1076, 1009, 753

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.33 (m, 6H, -CH_2-), 1.69-177 (m, 2H, -CH_2-), 2.42 (ddd, 2H, *J* = 2.0 Hz, *J* = 7.6 Hz, PhCOCH_2-), 2.96 (t, 2H *J* = 7.3 Hz, -*CH_2*CHO), 7.46 (t, 2H, *J* = 7.6 Hz, ArH), 7.54-7.57 ((m, 1H, ArH), 7.95 (d, 2H, *J* = 8.6 Hz, ArH), 9.76 (s, 1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{18}O_2$	C 77.03	C 77.23
218.29	H 8.31	H 8.25

Ketodithioacetal (130):



Nature: Colourless liquid

Yield: 82%

R_f: 0.65 (Hexane/EtOAc = 9.5: 0.5)

IR (Neat): cm^{-1} 2930, 2853, 1685, 1598, 1450, 1368, 1276, 1209, 1102, 1086, 1035, 974, 758

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18-1.30 (m, 8H, -CH_2-), 1.63-177 (m, 2H, -CH_2-), 2.77-2.83 (m, 2H, PhCOCH_2-), 2.87-2.94 (m, 2H, -SCH_2-), 3.11-3.21 (m, 2H, -SCH_2), 4.40 (t, 1H, *J* = 7.0 Hz, -CH_2*CH*S-), 7.39 (t, 2H, *J* = 7.6 Hz, ArH), 7.48 (t, 1H, *J* = 7.3 Hz, ArH), 7.89 (d, 2H, *J* = 7.3 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{22}OS_2$	C 65.26	C 65.01
294.48	H 7.53	H 7.45
	S 21.78	S 21.58

CHAPTER I

PART II

(SECTION B)

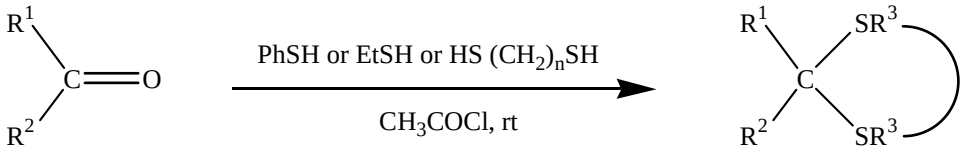
NEW SYNTHETIC PROTOCOL FOR THIOACETALIZATION OF CARBONYL COMPOUNDS BY USING CATALYTIC AMOUNT ACETYL CHLORIDE

RESULTS AND DISCUSSION

Results and Discussion

The methodology for thioacetalization of aldehydes developed by us using nickel(II) chloride as catalyst had some drawbacks such as difficult to prepare dithioketals from the corresponding ketones under identical reaction conditions. In addition, we have to use organic solvent in the reaction medium. Moreover, the nickel(II) chloride method takes relatively much longer reaction time although it is a suitable catalyst for chemoselective protection of aldehydic compounds. These drawbacks prompted us to investigate further whether these drawbacks can be minimized or eliminated by developing an alternative method.

In an endeavor to gradually change the current working practices to greener alternatives and to meet environmental demands,[70] there is a need for a solvent free and catalytically efficient alternative for protection of carbonyl compounds as dithioacetals. Recently, we are working to develop new synthetic methodologies for deprotection of carbonyl compounds as dithioacetals.[71] For our requirements, we had to prepare various dithioacetals from the corresponding carbonyl compounds as our key starting materials. Therefore, we are searching for more simplest and convenient way to access these compounds in large amounts in hand. Consequently, what is needed a methodology, which might undergo under mild, clean, operationally simple, environmentally friendly, highly efficient and economically much cheaper reaction conditions. From the literature, it is well known that acetyl chloride reacts with methanol to generate dry hydrochloric acid,[72] which can be exploited as catalyst for thioacetalization of carbonyl compounds. We conceived that acetyl chloride might also react with thiol or dithiol to generate dry HCl in the reaction medium, which can be ultimately utilized for thioacetalization reaction. In this chapter we would like to discuss a very mild, highly efficient and chemoselective synthetic protocol for transformation of the carbonyl compounds into the corresponding dithioacetals or dithioketals involving catalytic amount of acetyl chloride as shown in Scheme 37.



R^1 = aryl, alkyl, sugar residue
R^2 = H, alkyl, aryl; R^3 = Et, Ph, -$(CH_2)_n$-, n = 2, 3

Scheme 37

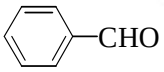
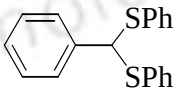
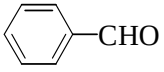
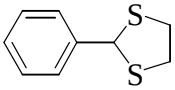
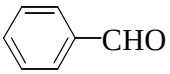
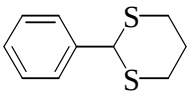
The most of the starting aldehydes and ketones were purchased. Some of them we had prepared by following literature procedure as discussed in the earlier chapter.

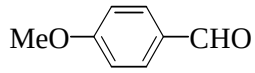
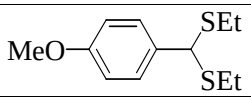
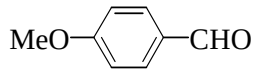
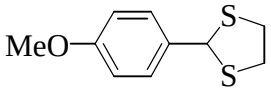
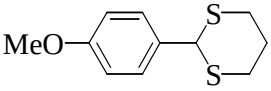
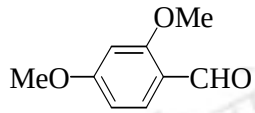
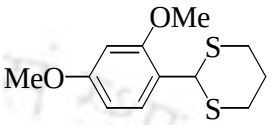
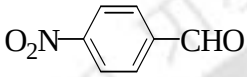
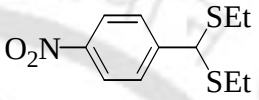
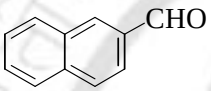
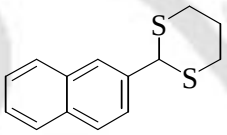
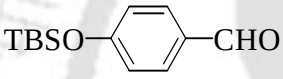
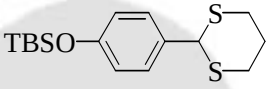
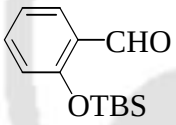
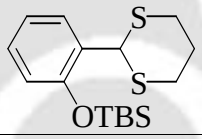
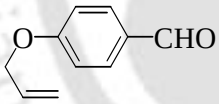
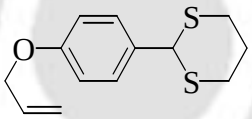
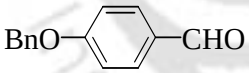
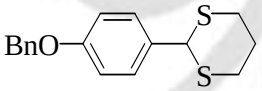
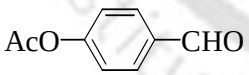
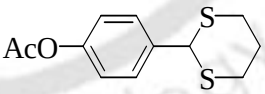
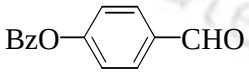
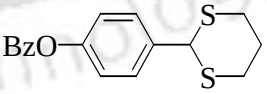
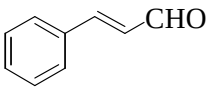
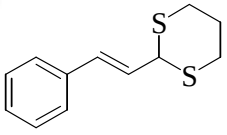
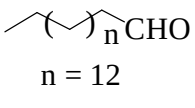
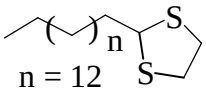
Then, we have attempted optimization the reaction conditions for protection of a wide variety of carbonyl compounds into the corresponding dithioacetals. The reaction of benzaldehyde (10 mmol) [run 1] with thiophenol (20 mmol) in the presence of catalytic amount of acetyl chloride (72 μL, 1 mmol) smoothly provided diphenyl dithioacetal derivative of benzaldehyde (**131**) in 98%yield. The product was obtained directly by recrystallisation without column purification. The compound **131** was confirmed by recording IR, ^{1}H NMR and melting point. In the IR spectrum, it shows frequency values 3063, 3027, 1588, 1491, 1440, 1173, 1081, 1025, 748 and 702 cm^{-1}. The disappearance of carbonyl band at ~1700 cm^{-1}clearly indicates the carbonyl group has been reacted. In addition, in the ^{1}H NMR spectrum the following signals appear for compound **131** at δ 5.43 (s, 1H, ArCH-) and 7.21-7.36 (m, 15H, ArH). The new signal comes at δ 5.43 as well as disappearance of the aldehydic signal at δ~9.80 clearly points out that aldehydic group has been affected. Moreover, in the ^{13}C NMR spectrum it shows the signals δ 60.35, 126.19, 127.73 (2C), 127.81 (2C), 127.99, 128.41 (2C), 128.78 (3C), 132.46 (3C), 133.71, 134.45 (2C), 139.57. The disappearance of the carbonyl carbon signal and appearance of the new signal at 60.35 clearly tell about that aldehydic group has reacted. Additionally, the melting point of the dithioacetal derivative **131** was 56 °C, which is comparable with the literature melting point [lit.[37] m.p. 51-52 °C]. Similarly, 1,3-dithiolane and 1,3-dithiane derivatives of benzaldehyde (**98** and **99**) were obtained in

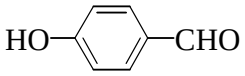
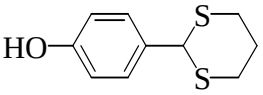
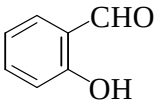
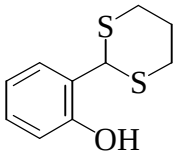
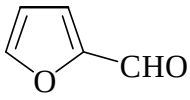
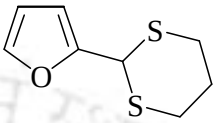
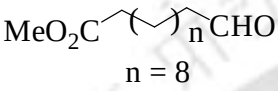
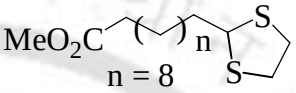
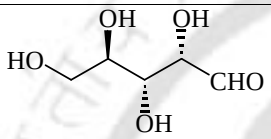
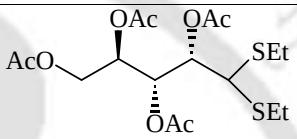
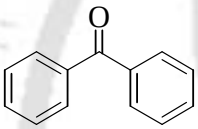
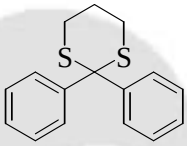
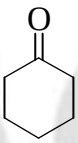
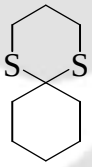
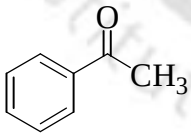
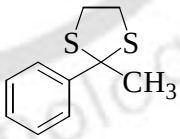
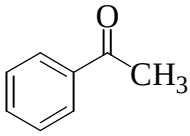
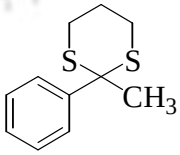
very good yields, on reaction with 1,2-ethanedithiol (C) or 1,3-propanedithiol (D) with benzaldehyde respectively, by following identical reaction conditions (run 2 and 3). The conversion of benzaldehyde to the corresponding 1,3-dithiolane derivative **98** was completed within 10 min., which is much faster as compared to the earlier reported procedure.[40] In addition, 1,3-dithiolane derivative of benzaldehye (**98**) was obtained by distillation instead of troublesome chromatographic separation, whereas 1,3-dithiane of benzaldehyde (**99**) was obtained directly by recrystallisation. The structures of compound **98** and **99** were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. By following above typical reaction procedure, both acyclic and cyclic dithioacetals of 4-methoxybenzaldehyde (**101**, **66** and **34**) were prepared in very good yields on treatment of 4-methoxybenzaldehyde with the respective thiols or dithiols (run 4-6). All the products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR and elemental analyses as well as melting point checking and all are in full agreement with the expected products **101**, **66** and **34**. Likewise, 2,4-dimethoxybenzaldehyde, 4-nitrobenzaldehyde and 2-naphthaldehyde (run 7-9) were converted to the corresponding dithioacetals (**103, 132** and **112**) under identical reaction conditions. The results are summarized in the Table 2 and products are fully characterized by recording IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and melting point. The data of the individual compound is mentioned in experimental section. Then, we had paid our attention to find out whether the same procedure is compatible with other substrates having different protecting groups. We have observed that our synthetic protocol can be implemented in presence of a large number of other protecting groups such as TBS, allyl, benzyl, acetyl and benzoyl (run 10-15). The results were summarized in Table 2 and the products were also characterized by usual spectroscopic technique and elemental analyses and checking of melting point. Likewise, other aldehydes such as alkenyl and aliphatic aldehyde (run 16 and 17) were converted to the desired dithioacetals (**25** and **119**) under identical conditions. It is important to highlights that hydroxyl aldehydes (run 18 and 19) can be easily protected to the desired dithioacetals (**114** and **29**) without acetylating the hydroxyl group under reaction conditions. More interestingly, highly acid sensitive substrates such as 2-furaldehyde and ester aldehyde (run 20 and 21) were also converted to the corresponding

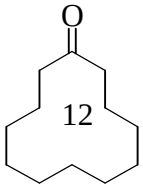
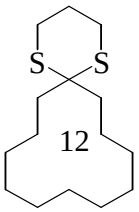
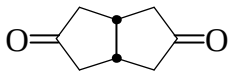
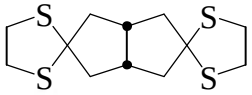
dithioacetals (**134** and **120**) in fairly good yields. The product **134** was confirmed by usual spectroscopic technique as shown in figures **13-15**. By using our protocol, D-arabinose can be transformed to the corresponding diethyl dithioacetal derivative **135**. The product diethyl dithioacetal of D-arabinose **135** was confirmed by spectroscopic technique by converting it into the acetyl derivative. Next, our aim was to prepare dithioketals from the corresponding ketones by following the similar reaction conditions, which was unsuccessful by our earlier method. We have also noticed that dithioketals **87**, **136-140** can be prepared from the corresponding carbonyl compounds in good yields in reasonable time (run 23-29) as shown in the Table 2. The IR, ^{1}H NMR and ^{13}C NMR spectra are given in figures **16-18** for the confirmation of structure **87**. The results are summarized in the Table 2 and the products are characterized by taking IR, ^{1}H NMR, ^{13}C NMR spectra, checking of melting point as well as elemental analysis and their values are incorporated in the experimental section. It is important to highlights that a highly hindered ketone benzophenone was smoothly converted to the corresponding 1,3-dithiane derivative of benzophenone **136** in 35 min, which is much faster than previously reported many methods. This observation shows the efficiency of the method under solvent-free conditions.

Table 2 Protection of various carbonyl compounds to the corresponding dithioacetals using acetyl chloride

Run	Substrate	Thiol or Dithiol	Time min	Product[a]	Product No.	Yield /%
1		A	25		**131**	98
2		C	10		**98**	99
3		D	10		**99**	97

4		B	5		**101**	97
5		C	2		**66**	95
6		D	2		**34**	95
7		D	4		**103**	98
8		B	15		**132**	90
9		D	10		**112**	93
10		D	5		**105**	88
11		D	5		**133**	86
12		D	2		**106**	83
13		D	5		**107**	95
14		D	12		**109**	89
15		D	15		**110**	87
16		D	10		**25**	84
17		C	17		**119**	89

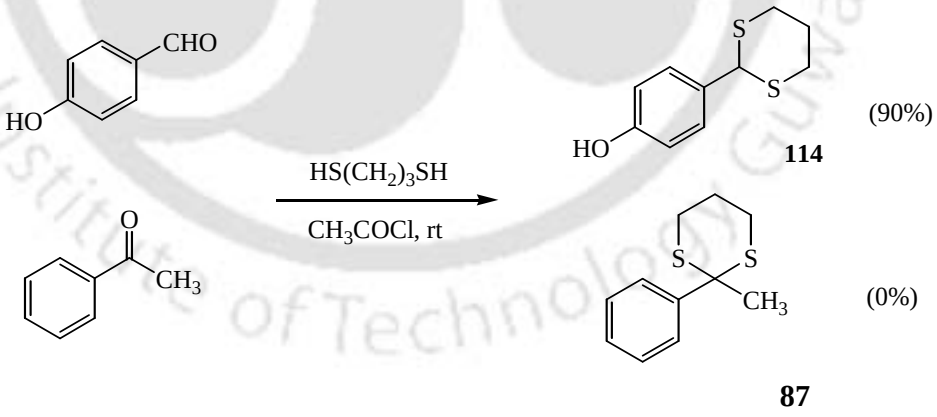
18		D	11		**114**	94
19		D	3		**29**	95
20		D	7		**134**	68
21		C	10		**120**	65
22		B	30		**135**	65
23		D	35		**136**	85
24		C	20		**137**	95
25		D	20		**138**	80
26		C	12		**121**	96
27		D	15		**87**	95

28		D	25		**139**	93
29		C	15		**140**	85

Thiol used: A = PhSH, B = EtSH, C = $HSCH_2CH_2SH$ and D = $HSCH_2CH_2CH_2SH$

The formation of the protected compound can be rationalized as follows. We believe that hydrochloric acid is the actual catalyst, which is generated from acetyl chloride on reaction with thiol during the reaction time.

We realized that the methodology could be further applied for chemoselective protection of aldehyde in presence of a ketone due to their reactivity difference. For this verification, when an equimolar mixture of 4-hydroxybenzaldehyde and acetophenone was treated with 1,3-propanedithiol in presence of 0.1 equiv. amount of acetyl chloride, then only 1,3-dithiane derivative of 4-hydroxybenzaldehyde (**114**) was obtained in 90% yield along with 95% recovery of the acetophenone as shown in scheme 38.



Scheme 38

In summary, we have devised a very simple and convenient synthetic protocol for the preparation of various dithioacetals or dithioketals from their corresponding carbonyl

compounds in the presence of wide range of other protecting groups chemoselectively using a catalytic amount of acetyl chloride under solvent-free conditions and without cubersome aqueous work-up. In addition, this methodology provides dithioacetal or dithioketal much faster than earlier reported procedure. Moreover, it can be applied for chemoselective protection of aldehyde group in the presence of ketone. It is noteworthy to mention that no acetylation takes place during the experimental conditions. Due to its operational simplicity, generality and efficacy, this method is expected to have much wider applicability for conversion of various carbonyl compounds to the corresponding dithioacetals. We have also noted that other acid chlorides can also be used for similar transformations. The main drawback of this procedure is that acetyl chloride is corrosive and difficult to use for a large-scale reaction.

CHAPTER I

PART II

(SECTION B)

NEW SYNTHETIC PROTOCOL FOR THIOACETALIZATION OF CARBONYL COMPOUNDS BY USING CATALYTIC AMOUNT ACETYL CHLORIDE

EXPERIMENTALS

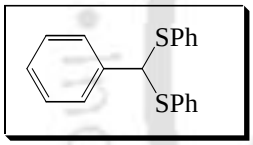
Experimental

General procedure for thioacetalization of carbonyl compounds:

To a mixture of an aldehyde (10 mmol) and dithiol (10 mmol) or thiol (22 mmol) was added a catalytic amount of acetyl chloride (72 μL, 1 mmol) at room temperature. The reaction mixture was kept for stirring at the same temperature and monitored by TLC. After completion of the reaction, the product was obtained by direct recrystallisation or by distillation under reduced pressure. In case of a ketone, acetyl chloride (144 μL, 2 mmol) was used as catalyst otherwise the same procedure was followed as above.

The characterization data of the following compounds **25**, **34**, **66**, **98**, **99**, **101**, **103**, **105**, **106**, **107**, **109**, **110**, **112**, **114**, **119** and **120** are given in the previous chapter in the experimental section.

Benzaldehyde diphenyl dithioacetal (131):



Nature: White solid

Yield: 98%

R_f: 0.76 (Hexane/EtOAc = 9.9: 0.1)

Melting Point: 56 °C [lit.[35] 51-52 °C]

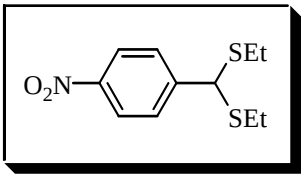
IR (KBr): cm^{-1} 3063, 3027, 1588, 1491, 1440, 1173, 1081, 1025, 748, 702

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (s, 1H, ArCH-), 7.21-7.36 (m, 15H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 60.35, 126.19, 127.73 (2C), 127.81 (2C), 127.99, 128.41 (2C), 128.78 (3C), 132.46 (3C), 133.71, 134.45 (2C), 139.57

Elemental Analysis	**Calculated**	**Found**
$C_{19}H_{16}S_2$	C 73.98	C 73.90
308.47	H 5.23	H 5.31
	S 20.79	S 20.82

4-Nitrobenzaldehyde diethyldithioacetal (132):



Nature: Yellow gummy liquid

Yield: 90%

R_f: 0.92 (Hexane/EtOAc = 9.8: 0.2)

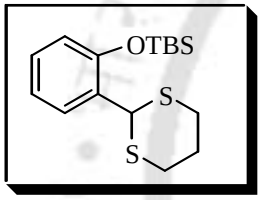
IR (Neat): cm^{-1} 3073, 2969, 1599, 1521, 1347, 1265, 1108

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, 6H, *J* = 7.32 Hz, 2× -SCH_2CH_3), 2.49-2.67 (m, 4H, 2× -SCH_2CH_3), 4.98 (s, 1H, ArH), 7.64 (d, 2H, *J* = 8.56 Hz, ArH), 8.20 (d, 2H, *J* = 8.56 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): 14.08 (2C), 26.21 (2C), 51.57, 123.72 (2C), 128.51 (2C), 147.10, 148.10

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{15}O_2NS_2$	C 51.33	C 51.25
257.38	H 5.87	H 5.96
	S 24.92	S 24.78

2-[2å-*tert*-Butyldimethylsilyloxy phenyl]-1,3-dithiane (133):



Nature: White solid

Yield: 86%

R_f: 0.82 (Hexane/EtOAc = 9.5: 0.5)

Melting Point: 88 °C

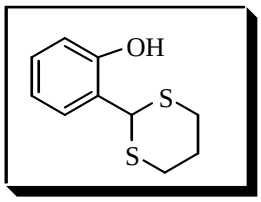
IR (KBr): cm^{-1} 3073, 2960, 2893, 2863, 1587, 1429, 1270, 1183, 1091, 916, 835, 788

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.01 (s, 6H, 2x -$Si(CH_3)_2$), 0.81 (s, 9H, -$SiC(CH_3)_3$), 1.64-1.71(m,1H, -SCH_2CHCH_2S-), 1.86-1.91 (m,1H, -SCH_2CHCH_2S-), 2.60-2.66 (m, 2H, -SCH_2-), 2.73-2.80 (m, 2H, -SCH_2-), 5.34 (s, 1H, ArCH-), 6.53 (d, 1H, *J* = 8.28 Hz, ArH), 6.70 (t, 1H, *J* = 7.56 Hz, ArH), 6.85-6.90 (m, 1H, ArH), 7.28 (dd, 1H, *J* = 1.68 Hz, *J* = 7.56 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): -4.34 (2C), 18.25, 25.27, 25.77 (3C), 32.48 (2C), 44.74, 118.79, 121.65, 128.99, 129.10, 129.74, 151.73

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{26}OSiS_2$	C 58.84	C 58.67
326.60	H 8.02	H 7.96
	S 19.64	S 19.56

2-[2-Hydroxyphenyl]-1,3-dithiane (29):



Nature: White solid

Yield: 95%

R_f: 0.39 (Hexane/EtOAc = 9:1)

Melting Point: 132 °C

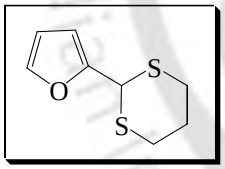
IR (KBr): cm^{-1} 3411, 2960, 2899, 2848, 1593, 1516, 1455, 1358, 1271, 1091, 856

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85-1.95 (m, 1H, -SCH_2C*H*CH_2S-), 2.11-2.18 (m, 1H, -SCH_2C*H*CH_2S-), 2.86-2.91(m, 2H, -SCH_2-), 3.00-3.08 (m, 2H, -SCH_2-), 5.42 (s, 1H, ArCH-), 6.48 (s, 1H, -OH), 6.86 (t, 2H, *J* = 9.0 Hz, ArH), 7.19 (t, 1H, *J* = 7.8 Hz, ArH), 7.30 (d, 1H, *J* = 7.8 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.81, 31.62 (2C), 47.04, 117.16, 120.78, 123.72, 129.13, 130.05, 154.21

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}OS_2$	C 56.56	C 56.62
212.34	H 5.70	H 5.52
	S 30.20	S 30.17

2 –Furfuryl-1,3-dithiane (134):



Nature: Pale yellow liquid

Yield: 68%

R_f: 0.63 (Hexane/EtOAc = 9:1)

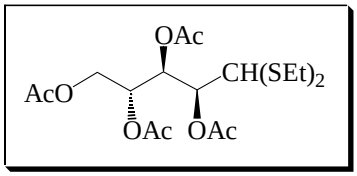
IR (Neat): cm^{-1} 2904, 1496, 1424, 1276, 1163, 1015, 943, 743

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92-2.01 (m, 1H, -SCH_2C*Ha*H*b*CH_2S-), 2.08-2.16 (m, 1H, - SCH_2CHa*Hb*CH_2S-), 2.88-2.93 (m, 4H, 2x -SCH_2-), 5.20 (s, 1H, -SCHS-), 6.32 (dd, 1H, *J* = 2.0 Hz, *J* = 3.2 Hz, H-4), 6.37 (d, 1H, *J* = 3.1 Hz, H-3), 7.34 (d, 1H, *J* = 1.9 Hz, H-5)

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.22, 30.24 (2C), 41.99, 107.83, 110.56, 142.27, 151.66

Elemental Analysis	**Calculated**	**Found**
$C_8H_{10}OS_2$	C 51.58	C 51.39
186.30	H 5.41	H 5.33
	S 34.42	S 34.23

2,3,4,5-Tetra-*O*-acetyl diethyl dithioacetal-D-arabinose (135):



Nature: White solid

Yield: 65%

R_f: 0.49 (Hexane/EtOAc = 7.5: 2.5)

Melting point: 74 °C

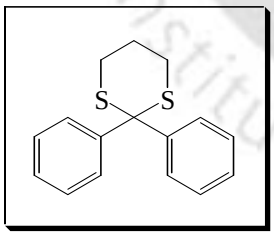
IR (KBr): cm^{-1} 2980, 2945, 2893, 1767, 1454, 1377, 1265, 1208, 1034, 942, 850

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22-1.28 (t, 6H, *J* = 7.4 Hz, -SCH_2CH_3), 2.05 (s, 3H, -OCH_3), 2.08 (s, 3H, -OCH_3), 2.11 (s, 3H, -OCH_3), 2.12 (s, 3H, -OCH_3), 2.57-2.71 (m, 4H, -SCH_2-), 3.89 (d, 1H, *J* = 8.2 Hz, H-1), 4.07 (dd, 1H, *J* = 5.84 Hz, *J* = 12.44 Hz), 4.29(dd, 1H, *J* = 2.92 Hz, *J* = 12.4 Hz), 5.08-5.16 (m, 1H, H-4), 5.29 (dd, 2H, *J* = 3.88 Hz, *J* = 11.48 Hz), 5.75 (dd, 1H, *J* = 5.6 Hz, *J* = 8.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.94, 14.27, 20.69 (3C), 20.89 (2C), 24.76, 51.64, 62.08, 60.71, 69.35, 69.46, 70.68, 169.50, 169.87, 169.99, 170.66

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{28}O_8S_2$	C 48.06	C 48.21
424.53	H 6.65	H 6.67
	S 15.12	S 15.03

2,2-Diphenyl-1,3-dithiane (136):



Nature: White solid

Yield: 85%

R_f: 0.87 (Hexane/EtOAc = 9.9: 0.1)

Melting Point: 107-109°C

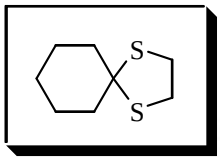
IR (KBr): cm^{-1} 3063, 2955, 2899, 2832, 1598, 1496, 1445, 1286, 1158, 1009, 861, 753, 699

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97-2.03 (m, 2H, -$SCH_2CH_2CH_2$S-), 2.78-2.79 (m, 4H, 2x-SCH_2-), 7.24-7.36 (m, 6H, ArH), 7.69 (m, 4H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.47, 29.37 (2C), 62.76, 127.55 (2C), 128.40 (3C), 129.31 (3C), 142.55 (2C)

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{16}S_2$	C 70.54	C 70.67
272.44	H 5.92	H 5.75
	S 23.54	S 23.42

1, 4-Dithiaspiro[4, 5]decane (137):



Nature: Viscous liquid

Yield: 95%

R_f: 0.96 (Hexane/EtOAc = 9.9: 0.1)

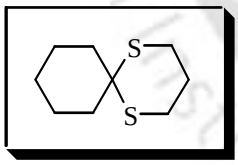
IR (Neat): cm^{-1} 2930, 2853, 1440, 1271, 1132, 1030

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40-1.44 (m, 2H, -CH_2-), 1.60-1.66 (m, 4H, -CH_2-), 1.98-2.01 (m, 4H, -CH_2-), 3.28 (s, 4H, -SCH_2-)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.93, 26.12 (2C), 38.30 (2C), 42.83 (2C), 68.79

Elemental Analysis	**Calculated**	**Found**
$C_8H_{14}S_2$	C 55.12	C 55.08
174.33	H 8.09	H 8.17
	S 36.79	S 36.69

1,4-Dithiaspiro[5.5]decane (138):



Nature: Colourless liquid

Yield: 80%

R_f: 0.75 (Hexane/EtOAc = 9.9:0.1)

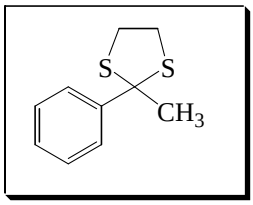
IR (Neat): cm^{-1} 2930, 2853, 1440, 1265, 1127, 1015, 907, 861, 764

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43-1.49 (m, 2H, -CH_2-), 1.60-1.67 (m, 4H, -CH_2-), 1.96-2.02 (m, 6H, -SCH_2*CH_2*CH_2S- and 2 x -CH_2-), 2.79-2.83 (m, 4H, 2 x -SCH_2-)

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.97 (2C), 25.79 (2C), 25.87, 26.12, 37.86 (2C), 50.32

Elemental Analysis	**Calculated**	**Found**
$C_9H_{16}S_2$	C 57.39	C 57.14
188.36	H 8.56	H 8.50
	S 34.05	S 34.23

2-Methyl-2-phenyl-1,3-dithiolane (121):



Nature: Viscous liquid

Yield: 96%

R_f: 0.91 (Hexane/EtOAc = 9.9: 0.1)

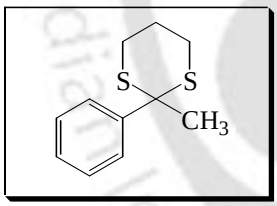
IR (Neat): cm^{-1} 2971, 2935, 1598, 1491, 1445, 1276, 1071, 1030, 774, 702

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.14 (s, 3H, -CH_3), 3.31-3.47 (m, 4H, 2x -SCH_2-), 7.18-7.23 (m, 1H, ArH), 7.28-7.32 (m, 2H, ArH), 7.72-7.75 (m, 2H, ArH)

^{13}C NMR (400 MHz, $CDCl_3$): δ 28.60, 33.78, 33.81, 40.21 (2C), 68.51, 126.68, 126.98, 127.90, 128.19, 145.82

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}S_2$	C 61.17	C 61.23
196.34	H 6.16	H 6.13
	S 32.66	S 32.24

2-Methyl-2-phenyl-1,3-dithiane (87):



Nature: Colorless oil

Yield: 95%

R_f: 0.90 (Hexane/EtOAc = 9.9: 0.1)

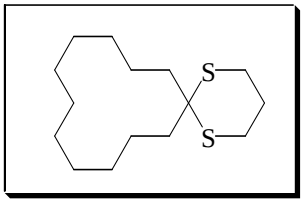
IR (Neat): cm^{-1} 3063, 2909, 2832, 1603, 1496, 1440, 1388, 1286, 1189, 1071, 764, 702

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79 (s, 3H, -CH_3), 1.89-1.99 (m, 2H, -$SCH_2C\mathit{H}_2CH_2$S-), 2.71-2.78 (m, 4H, 2 x -SCH_2-), 7.23-7.27 (m, 1H, ArH), 7.34-7.39 (m, 2H, ArH), 7.92-7.95 (m, 2H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.57, 27.98 (2C), 32.67, 53.88, 126.95, 127.67 (2C), 128.45 (2C), 143.69

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{14}S_2$	C 62.81	C 62.56
210.36	H 6.71	H 6.65
	S 30.49	S 30.12

1,4-Dithiaspiro[4,11]hexadecane (139):



Nature: White solid

Yield: 93%

R_f: 0.75 (Hexane/EtOAc = 9.9: 0.1)

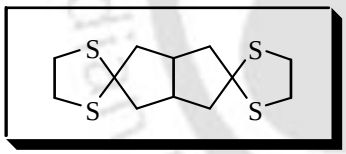
Melting Point: 92 °C

IR (KBr): cm^{-1} 2950, 2852, 1475, 1439, 1342, 1275, 1239, 917

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (m, 18H, $-CH_2-$), 1.90-2.00 (m, 6H, $-SCH_2-$), 2.80 (t, 4H, *J* = 5.68 Hz, $-CH_2-$)

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{28}S_2$	C 66.11	C 66.03
272.52	H 10.35	H 10.34
	S 23.53	S 23.38

1,3-Dithiolanes of *cis*-bicyclo[3.3.0]octane-3,7-dione (140):



Nature: White solid

Yield: 85%

R_f: 0.62 (Hexane)

Melting Point: 175-177°C

IR (KBr): cm^{-1} 2957, 2920, 2843, 1426, 1275, 1210, 974

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (dd, 4H, *J* = 7.1 Hz, *J* = 13.2 Hz, $-CH_2-$), 2.37-2.40 (dd, 4H, *J* = 7.1 Hz, *J* = 13.2 Hz, $-CH_2-$), 2.79-2.87 (m, 2H, $-CH_2-$), 3.26-3.34 (m, 8H, $-SCH_2-$)

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{18}S_4$	C 49.61	C 49.43
290.54	H 6.24	H 6.18
	S 44.15	S 44.10

CHAPTER I

PART II

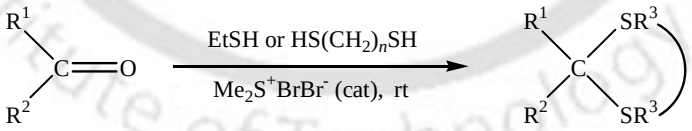
(SECTION C)

NEW SYNTHETIC METHODOLOGY FOR THIOACETALIZATION OF CARBONYL COMPOUNDS BY INVOLVING BROMODIMETHYLSULFONIUM BROMIDE

RESULTS AND DISCUSSION

Results and Discussion

Though we have developed two new synthetic methodologies for thioacetalization of carbonyl compounds, still there is a scope to develop new synthetic methodology by using a new and mild catalyst. Gradually changing the current working practices to greener alternatives as well as environmental demands,[70] there is a need for a solvent-free and catalytically efficient alternative for thioacetalization of carbonyl compounds, which might also work under milder and economically cheaper reaction conditions. We envisioned that bromodimethylsulfonium bromide, which can generate HBr in the reaction medium on reaction with alcohol,[73] might be a useful pre-catalyst for the protection of carbonyl compounds as dithioacetals. Previously, bromodimethylsulfonium bromide has been utilized for the conversion of alcohols to the corresponding alkyl bromides,[73] enones to the α-bromoenones,[74] oxidation of thiols to the disulfides[75] and deprotection of dithioacetals to the corresponding carbonyl compounds.[76] However, the versatility of this reagent has not been well studied earlier. Very recently, we have demonstrated the utility of this reagent for tetrahydropyranylation / depyranylation of alcohols and phenols.[77] The above successful result encouraged us to study further whether bromodimethylsulfonium bromide can be applied for thioacetalization of carbonyl compounds or not. In this chapter, we would like to discuss a simple and practical synthetic protocol for thioacetalization by involving bromodimethylsulfonium bromide as a new catalyst under solvent-free conditions, depicted in scheme 39.



R^1 = aryl /alkyl; R^2 = H / alkyl / aryl; R^3 = Et, -$(CH_2)_n$-, *n* = 2,3

Scheme 39

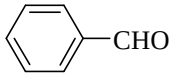
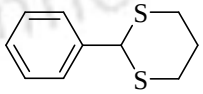
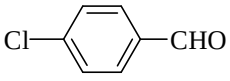
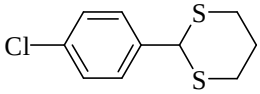
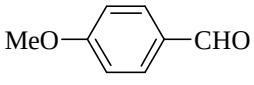
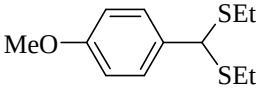
The required catalyst bromodimethylsulfonium bromide was prepared by following the literature procedure.[76] The aldehyde, which is a precursor of compound **14**, was prepared

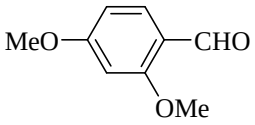
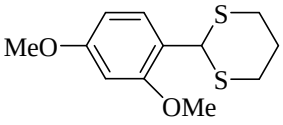
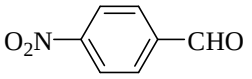
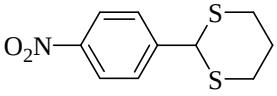
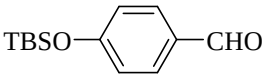
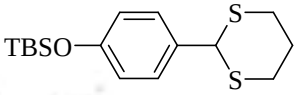
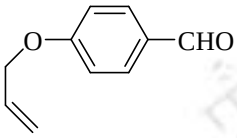
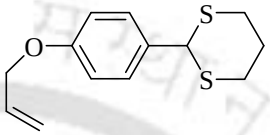
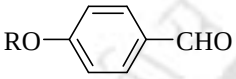
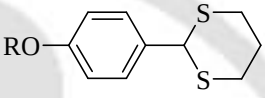
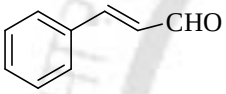
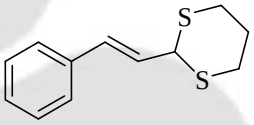
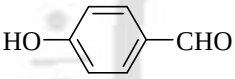
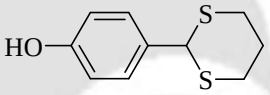
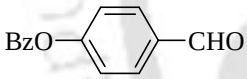
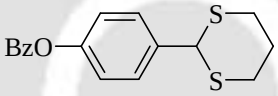
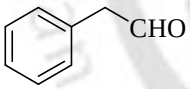
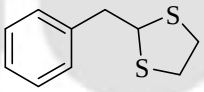
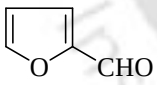
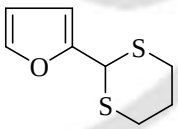
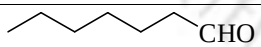
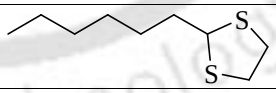
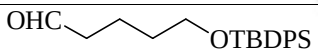
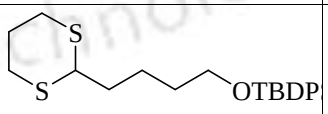
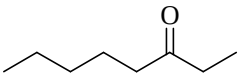
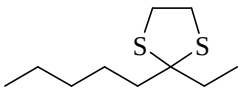
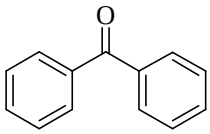
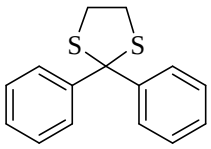
from 1,5-pentanediol by selective mono protection of the alcohol using *tert*-butyldephenylsilyl chloride by following the literature procedure.[78] The remaining aldehydes were procured from the market and used them directly.

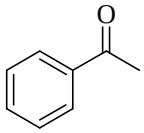
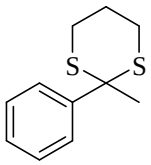
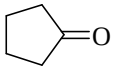
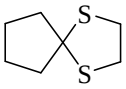
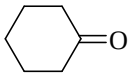
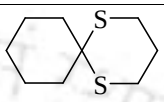
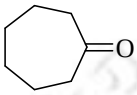
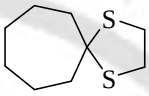
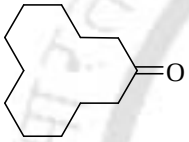
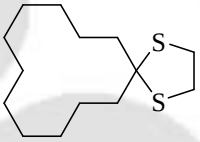
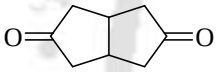
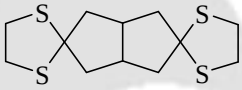
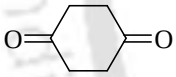
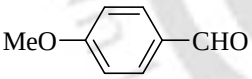
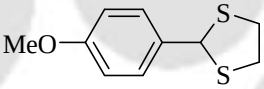
Then, we have attempted optimization the reaction conditions for protection of a wide variety of carbonyl compounds into the corresponding dithioacetals. When a mixture of benzaldehyde (1 mmol) and 1,3-propanedithiol (1.1 mmol) was treated with a catalytic amount of bromodimethylsulfonium bromide (0.05 mmol) without any solvent at room temperature, it was smoothly transformed to the corresponding 2-phenyl-1,3-dithiane (**99**) in very good yield. The product **99** was characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. Moreover, the data was matched with the compounds, which was prepared by earlier methods. This result encourages us to investigate further the usefulness of the catalyst. Similarly, 4-chlorobenzaldehyde was converted to the corresponding 1,3-dithiane derivative of 4-chlorobenzaldehyde (**141)** under identical reaction conditions. Likewise, various aromatic aldehydes were converted easily to the corresponding acyclic or cyclic dithioacetals **25**, **101**, **103**, **105**, **106**, **110, 114, 142** and **143** chemoselectively, on treatment with thiol or dithiol in the presence of the same catalyst in solvent-free mode without affecting the other protecting groups such as benzoyl, allyl, cyclohexenyl and TBS ether. The IR, ^{1}H NMR and ^{13}C NMR spectra of the compound **143** are shown in the figures **19-21** for confirmation of the structure. The results are summarized in the Table 3. Next, we had converted phenyl acetaldehyde, 2-furaldehyde, heptanal and 5-*tert*-butyldiphenylsilyloxy pentan-1-al to the corresponding dithioacetal derivatives **144**, **134, 117** and **14** respectively, under identical reaction conditions using either 1,2-dithiol or 1,3-dithiol. Moreover, various dithioacetals derivatives **145, 146, 87, 147, 138, 148-150** were obtained in very good yields from the corresponding acyclic ketones or cyclic ketones or diketones by employing the same catalyst under solvent free conditions**.** The structures of compounds **145** and **150** are confirmed by recording IR, ^{1}H NMR and ^{13}C NMR spectra, which are shown in the figures **22-26**. Remarkably, by using our protocol both aliphatic, aromatic aldehydes, and various ketones were transformed easily to the corresponding dithioacetals without non-aqueous work up. All the results are summarized in the Table 3 and all the products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analyses. It is

important to mention that no brominations occur at the double bond or at the α position of the ketone or even in the highly electron rich aromatic ring. It is pertinent to mention that a highly acid sensitive substrate, 2-furaldehyde, can be easily protected to the corresponding dithioacetal derivative **134** under identical condition at a much faster rate as well as much higher yield than it was by a recently reported procedure.[40] These results clearly demonstrate the efficiency and generalization of the procedure. It is worthwhile to mention that thioacetalization can be carried out at higher scale of the carbonyl compounds. For example, when a mixture of 4-methoxybenzaldehyde (1.36 g, 10 mmol) and 1,2-ethanedithiol (0.84 mL, 10 mmol) was treated with the catalyst bromodimethylsulfonium bromide (0.111 g, 0.5 mmol), it was smoothly converted within 3 min to the corresponding 1,3-dithiolane derivative of 4-methoxybenzaldehyde **66**. The product was obtained 1.98 g by recrystallisation without column chromatography in 93% yield, which was characterized by melting point, IR and NMR spectra. The capability of bromodimethylsulfonium bromide for thioacetalization in large scale was also investigated to establish the potentiality of the procedure. For this study, when a mixture of 4-methoxybenzaldehyde (13.6 g, 100 mmol), 1,2-ethanedithiol (8.4 mL, 100 mmol) was treated with bromodimethylsulfonium bromide (1.1 g, 5 mmol) at room temperature, it was smoothly converted to the corresponding dithioacetal derivative **66** within 2-3 min. The pure protected compound **66** was obtained in 95 % yield after recrystallisation.

Table 3. Protection of various carbonyl compounds to the corresponding dithioacetals using bromodimethylsulfonium bromide as catalyst

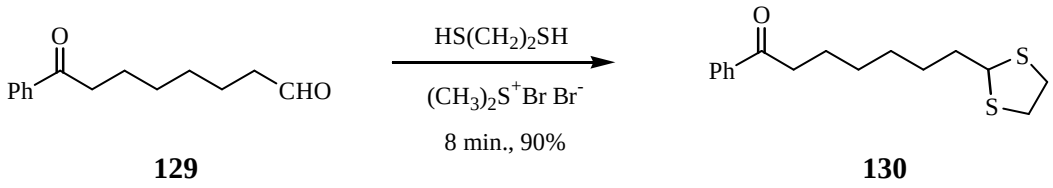
Substrate	Thiol or dithiol used[a]	Time min/ [h]	Product[b]	Product No.	Yi-eld[c] %
	A	15		**99**[d]	90
	A	35		**141**[d]	82
	B	25		**101**[d]	86

	A	10		**103**[d]	96
	A	35		**142**[d]	70
	A	10		**105**[d]	89
	A	25		**106**[d]	95
 R = cyclohexenyl	A	25	 R = cyclohexenyl	**143**[d]	91
	A	12		**25**[d]	94
	A	10		**114**[d]	95
	A	30		**110**[d]	94
	C	15		**144**[d]	84
	A	5		**134**[d]	98
	C	7		**117**[d]	65
	A	10		**14**[d]	73
	C	8		**145**[e]	87
	C	[12]		**146**[e]	83

	A	30		**87**[e]	88
	C	4		**147**[e]	90
	A	7		**138**[e]	93
	C	6		**148**[e]	83
	C	12		**149**[e]	90
	C	50		**140**[f]	92
	C	60		**150**[f]	89
	C	3		**66**[g]	95

[a]Thiol or dithiol used: A = $HSCH_2CH_2CH_2SH$, B = EtSH, C = $HSCH_2CH_2SH$. [b] Products were characterized by IR, ^1H NMR, ^{13}C NMR elemental analysis. [c]Isolated yield. [d]Reaction was carried out with 0.05 equivalent amount of catalyst. [e]Reaction was carried out with 0.15 equivalent amount of catalyst. [f]Reaction was carried out with 0.30 equivalent amount of catalyst. [g]Reaction was carried out with 100 mmol scale.

Furthermore, the aldehyde group of a keto-aldehyde (**129**) was protected to the corresponding dithioacetals **130** chemoselectively using 0.05 equivalent amount of the same catalyst in 90% yield under solvent-free condition, as shown in scheme 40.



129 **130**

Scheme 40

The formation of dithioacetals from the carbonyl compounds can be explained as follows. The catalyst bromodimethylsulfonium bromide on reaction with thiol or dithiol gives HBr in the reaction medium, which is the actual catalyst for the thioacetalization. We have also noted that pH of the reaction mixture is ~ 2-3 while carrying out the reaction.

In conclusion, we have demonstrated that both acyclic and cyclic dithioacetals can be prepared in very high yields from the corresponding carbonyl compounds using the bromodimethylsulfonium bromide as catalyst under solvent-free reaction conditions. This methodology can also be applied for a large scale reaction without involving solvent and chromatographic separation. In addition, this methodology can be applied for chemoselective protection of aldehyde group for thioacetalization in the presence of ketonic group. It is noteworthy to mention that no bromination takes place during the experimental conditions and the reaction can be performed in presence of other protecting groups without affecting them.

CHAPTER I

PART II

(SECTION C)

NEW SYNTHETIC METHODOLOGY FOR THIOACETALIZATION OF CARBONYL COMPOUNDS BY INVOLVING BROMODIMETHYLSULFONIUM BROMIDE

EXPERIMENTALS

Experimental

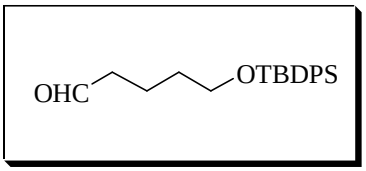
Preparation of bromodimethylsulfonium bromide:

Dimethyl sulfide (18.3 ml, 25 mmol) was taken in 50 ml of dry dichloromethane in a 150 ml standard joint conical flask. Then, 13 ml of bromine was added slowly into it by dissolving it in 50 ml of dry dichloromethane at ice-bath temperature over a period of 30 min. During the addition, light orange crystals of bromodimethylsulfonium bromide begin to separate out. After the addition of bromine was completed, the crystals of bromodimethylsulfonium bromide were collected by filtration. The solid material was then washed with dry hexane and dried under vacuum. The crystalline product was obtained 45 g in 81% yield, m.p. 80 ^{o}C.

Preparation of 5-*tert*-Butyldiphenylsilyloxy pentan-1-al.

To solution of 0.520 g of 1,5-pentanediol (5 mmol) in CH_2Cl_2 (3 ml) was added 0.9 ml of *i*-Pr_2NEt and kept it for stirring. Then, 0.415 ml (1.6 mmol) of *tert*-butyldiphenyl-silyl chloride (TBDPSCl) was added dropwise to the above reaction mixture under N_2 atmosphere at room temperature. The solution was stirred for 2 h at room temperature. After completion of the reaction, the solvent was removed in rotavapor to get a crude residue, which was finally purified through a silica gel column. The product was obtained 1.54 g in 90% as a colourless liquid.

The compound 5-*tert*-Butyldiphenylsilyloxy pent-1-ol (0.69 g, 2 mmol) in CH_2Cl_2 was added pyridinium chlorochromate (0.52 g, 2.4 mmol) in portion at ice-bath temperature and left for stirring. After completion of the reaction, 30 ml of diethyl ether was added into it and the organic layer was passed through a short silica gel column. The colourless organic layer was concentrated in rotavapour to get crude desired aldehyde in 90% in almost pure state.



Nature: Colourless liquid

R_f = 0.60; SiO_2-TLC (Hexane /EtOAc = 99:1)

IR (Neat): cm^{-1} 3068, 2940, 2863, 2725, 1726, 1588, 1470, 1424, 1393, 1112, 1004, 825, 702

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 9H, -SiC$(CH_3)_3$), 1.58-1.63 (m, 2H, -CH_2-), 1.76-1.78 (m, 2H, -CH_2-), 2.42 (t, 2H, *J* = 5.5 Hz, -*CH_2*CHO), 3.70 (t, 2H, *J* = 6.0 Hz, -OCH_2-), 7.37-7.45 (m, 5H, ArH), 7.67-7.70 (m, 5H, ArH), 9.76 (t, 1H, *J* = 2.24 Hz, CHO)

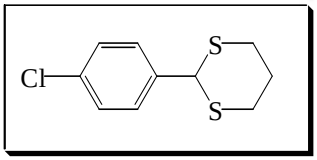
Elemental Analysis	**Calculated**	**Found**
$C_{21}H_{28}O_2Si$	C 74.07	C 74.24
340.54	H 8.29	H 8.16

General procedure for thioacetalization:

To a mixture of an aldehyde (1 mmol) and thiol (2.2 mmol) or dithiol (1.1 mmol) was added a catalytic amount of bromodimethylsulfonium bromide (0.011 g, 0.05 mmol) and kept for stirring at room temperature. After completion of the reaction, it was neutralized by addition of two drops of saturated solution of $NaHCO_3$. Then the reaction mixture was passed through a silica gel column without aqueous work up to get the desired dithioacetal. In case of a ketone, 0.033 g of bromodimethylsulfonium bromide (0.15 mmol) was used as pre-catalyst otherwise the same procedure was followed for getting dithioketals.

The characterization data of the following compounds **25**, **66**, **87**, **99**, **101**, **103**, **105**, **106**, **110**, **114**, **117**, **129**, **130** are given chapter **IA** in the experimental section whereas compounds **134**, **138** and **140** are mentioned chapter **IB** in the experimental section.

2-[4å-Chlorophenyl]-1,3-dithiane (141):



Nature: White solid

Yield: 82%

R_f: 0.49 (Hexane/EtOAc = 9.9: 0.1)

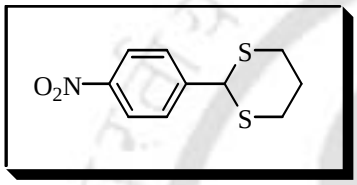
Melting Point: 91 °C

IR (KBr): cm^{-1} 3048, 2904, 2822, 1598, 1486, 1424, 1281, 1178, 1091, 1009, 830, 769, 671

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85-1.97 (m, 1H, -SCH_2C*Ha*HbCH_2S-), 2.13-2.18(m, 1H, -SCH_2CHa*Hb*CH_2S-), 2.87-2.92 (m, 2H, -SCH_2-), 3.00-3.08 (m, 2H, -SCH_2-), 5.13 (s, 1H, ArCH-), 7.30 (d, 2H, *J* = 7.5 Hz, ArH), 7.41 (d, 2H, *J* = 7.5 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{11}ClS_2$	C 52.05	C 52.21
230.78	H 4.80	H 4.73
	S 27.79	S 27.62

2-[4å-Nitrophenyl]-1,3-dithiane (142):



Nature: Light yellow solid

Yield: 70%

R_f: 0.80 (Hexane/EtOAc = 9:1)

Melting Point: 148°C [Lit.[27] 141-142 °C]

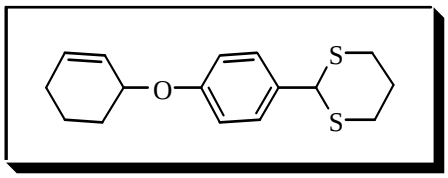
IR (KBr): cm^{-1} 3073, 2960, 2909, 2848, 1609, 1521, 1424, 1352, 1276, 1117, 861, 728

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91- 2.02 (m, 1H, -SCH_2C*Ha*HbCH_2S-), 2.16-2.28 (m, 1H, -SCH_2CHa*Hb*CH_2S-), 2.92- 2.98 (m, 2H, -SCH_2-), 3.05- 3.15 (m, 2H, -SCH_2-), 5.24 (s, 1H, ArCH-), 7.65 (d, 2H, *J* = 8.8 Hz, ArH), 8.20 (d, 2H, *J* = 8.8 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 31.8, 50.4, 124.0, 129.0, 146.3,147.8

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{11}NO_2S_2$	C 49.77	C 49.87
241.33	H 4.59	H 4.53
	N 5.80	N 5.62
	S 26.57	S 26.71

2-[4å-Cyclohexenyloxyphenyl]-1,3-dithiane (143):



Nature: White solid

Yield: 91%

R_f: 0.45 (Hexane/EtOAc = 9.9: 0.1)

Melting Point: 103-104 °C

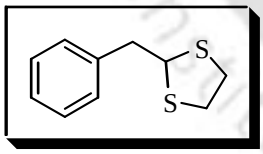
IR (Neat): cm^{-1} 2940, 2899, 1609, 1506, 1245, 1173, 1030, 948, 764

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57-1.65 (m, 2H, -CH_2-), 1.76-1.89 (m, 2H, -CH_2-), 1.91-2.03 (m, 1H, -SCH_2C*Ha*H*b*CH_2S-), 2.05- 2.18 (m, 3H, -SCH_2CHa*Hb*CH_2S- and -CH_2-), 2.84-2.92 (m, 2H, -SCH_2-), 3.01-3.15 (m, 2H, -SCH_2-), 3.54-3.55 (m, 1H,-CH=CH*CH*O-), 5.10 (s, 1H, ArCH-), 5.81 (dd, 1H, *J* = 2.0 Hz, *J* = 10.0 Hz, -CH=*CH*CHO-), 6.03-6.08 (m, 1H, -CH_2*CH*=CHCHO-), 6.87 (d, 2H, *J* = 8.8 Hz, ArH), 7.37 (d, 2H, *J* = 8.8 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.37, 24.93, 25.04, 29.80, 32.24 (2C), 38.08, 50.94, 116.38, 126.87, 128.95, 129.36, 131.00, 131.18 (2C), 154.14

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{20}OS_2$	C 65.71	C 65.52
292.47	H 6.89	H 6.81
	S 21.93	S 21.79

2-Benzyl-1, 3-dithiolane (144):



Nature: Colourless liquid

Yield: 84%

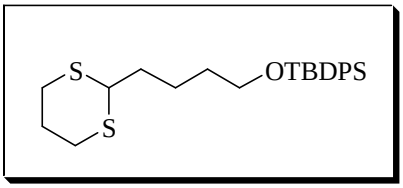
R_f: 0.36 (Hexane/EtOAc = 9:1)

IR (Neat): cm^{-1} 3037, 2925, 2843, 1598, 1501, 1424, 1286, 1132, 1030, 846, 738

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (d, 2H, *J* = 7.1 Hz, $PhCH_2$-), 3.08- 3.21 (m, 4H, 2 x -SCH_2-), 4.66 (t, 1H, *J* =7.1 Hz, $PhCH_2$*CH*-), 7.16-7.26 (m, 5H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}S_2$	C 61.17	C 61.31
196.34	H 6.16	H 6.10
	S 32.66	S 32.43

2-[4å-*tert*-Butyldiphenylsilyloxy butane]-1,3-dithiane (14):



Nature: Colourless liquid

Yield: 73%

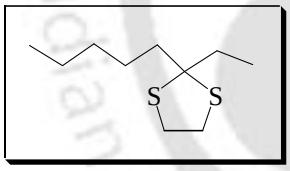
R_f: 0.70 (Hexane/EtOAc = 9.5:0.5)

IR (Neat): cm^{-1} 3068, 2935, 2863, 1588, 1434, 1260, 1107, 835, 748, 707, 620, 508

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 9H, -SiC(CH_3)$_3$), 1.57-1.59 (m, 2H, -CH_2-), 1.75-1.79(m, 2H, -CH_2-), 1.83-1.93 (m, 2H, -SCH_2CH_2), 2.61-2.83 (m, 6H, -SCH_2 &-CH_2-), 3.65 (t, 1H, *J* = 5.8 Hz, -OCH_2-), 3.70 (t, 1H, *J* = 7.1 Hz, -CH), 7.32-7.42 (m, 5H, ArH), 7.64-7.67 (m, 5H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{24}H_{34}OS_2Si$	C 66.92	C 66.78
430.75	H 7.96	H 7.84
	S 14.89	S 15.02

2-Ethyl-2-pentyl-1, 3-dithiolane (145):



Nature: Colourless liquid

Yield: 87%

R_f: 0.83 (Hexane)

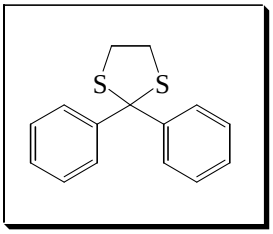
IR (Neat): cm^{-1} 2960, 2930, 2868, 1460, 1383, 1281, 1132, 984, 897, 851, 810, 733, 692

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 3H, *J* = 7.0 Hz, -CH_3), 0.99 (t, 3H, *J* = 7.30 Hz, -CH_3), 1.21-1.31 (m, 4H, -CH_2-), 1.38-1.46 (m, 2H, -CH_2-), 1.84-1.93 (m, 4H, -CH_2-), 3.21 (bs, 4H, -SCH_2-)

^{13}C NMR (100 MHz, $CDCl_3$): δ11.16, 14.01, 22.53, 26.58, 31.95, 36.12, 39.37 (2C), 42.88, 72.41

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{20}S_2$	C 58.76	C 58.54
204.40	H 9.86	H 9.79
	S 31.38	S 31.09

2,2-Diphenyl-1, 3-dithiolane (146):



Nature: White solid

Yield: 83%

R_f: 0.46 (Hexane)

Melting Point: 100-103°C [Lit.[27] 104-105 °C]

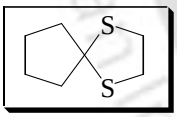
IR (KBr): cm^{-1} 2930, 2848, 1598, 1486, 1450, 1419, 1276, 1086, 748, 702

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (s, 4H, 2 x -SCH_2-), 7.16-7.26 (m, 6H, ArH), 7.56 (d, 4H, *J* = 7.1 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 40.13 (2C), 127.19 (2C), 127.93 (5C), 128.16 (5C), 144.57

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{14}S_2$	C 69.72	C 69.55
258.41	H 5.46	H 5.41
	S 24.82	S 24.61

1,4-Dithiaspiro[4.4]nonane (147):



Nature: Colourless liquid

Yield: 90%

R_f: 0.92 (Hexane)

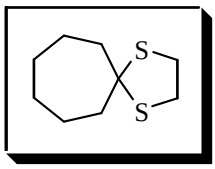
IR (Neat): cm^{-1} 2960, 2924, 2878, 1449, 1275, 1168, 1101, 978, 851, 692

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74-1.77 (m, 4H, -CH_2-), 2.07-2.14 (m, 4H, -CH_2-), 3.30 (s, 4H, 2 x -SCH_2-)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.48 (2C), 39.37 (2C), 43.92 (2C), 70.86

Elemental Analysis	**Calculated**	**Found**
$C_7H_{12}S_2$	C 52.45	C 52.12
160.30	H 7.55	H 7.50
	S 40.00	S 39.85

1,4-Dithiaspiro[4.6]undecane (148):



Nature: White solid

Yield: 83%

R_f: 0.92 (Hexane)

Melting Point: 56°C

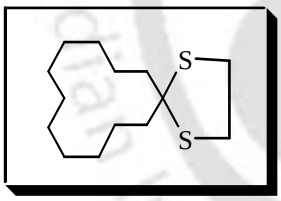
IR (KBr): cm^{-1} 2919, 2842, 1460, 1424, 1275, 1244, 1234, 1152, 1101, 963, 846, 692

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (m, 8H, $-CH_2-$), 2.17-2.19 (m, 4H, $-CH_2-$), 3.26 (s, 4H, $-SCH_2-$)

^{13}CNMR (100 MHz, $CDCl_3$): δ 25.62 (2C), 28.55 (2C), 38.84 (2C), 46.11 (2C), 71.88

Elemental Analysis	**Calculated**	**Found**
$C_9H_{16}S_2$	C 57.39	C 57.18
188.36	H 8.56	H 8.48
	S 34.05	S 33.87

1,4-Dithiaspiro[4.11]hexadecane (149):



Nature: White solid

Yield: 90%

R_f: 0.81 (Hexane)

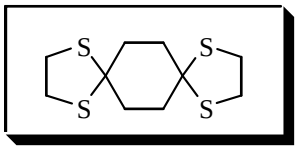
Melting Point: 88°C

IR (KBr): cm^{-1} 2955, 2858, 1470, 1440, 1045, 799, 738, 687

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18-1.51 (m, 18H, $-CH_2-$), 1.95 (dd, 4H, *J* = 7.6 Hz, *J* = 8.3 Hz, $-CH_2-$), 3.22 (s, 4H, $-SCH_2-$)

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{26}S_2$	C 65.05	C 65.30
258.49	H 10.14	H 10.06
	S 24.81	S 24.63

1,4,9,12-Tetrathiadispiro[4.2.4.2]tetradecane (150):



Nature: White solid

Yield: 89%

R_f: 0.56 (Hexane/EtOAc = 9.9: 0.1)

Melting Point : 187-191°C [Lit.192-194°C]

IR (KBr): cm^{-1} 2966, 2945, 2914, 2832, 1424, 1281, 1224, 1096, 1091, 866, 820, 692, 579

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (s, 8H, -CH_2-), 3.23 (s, 8H, -SCH_2-)

^{13}C NMR (100 MHz, $CDCl_3$): δ 38.48 (2C), 42.18 (6C), 66.96 (2C)

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{16}S_4$	C 45.41	C 45.20
264.50	H 6.10	H 6.03
	S 48.49	S 48.31

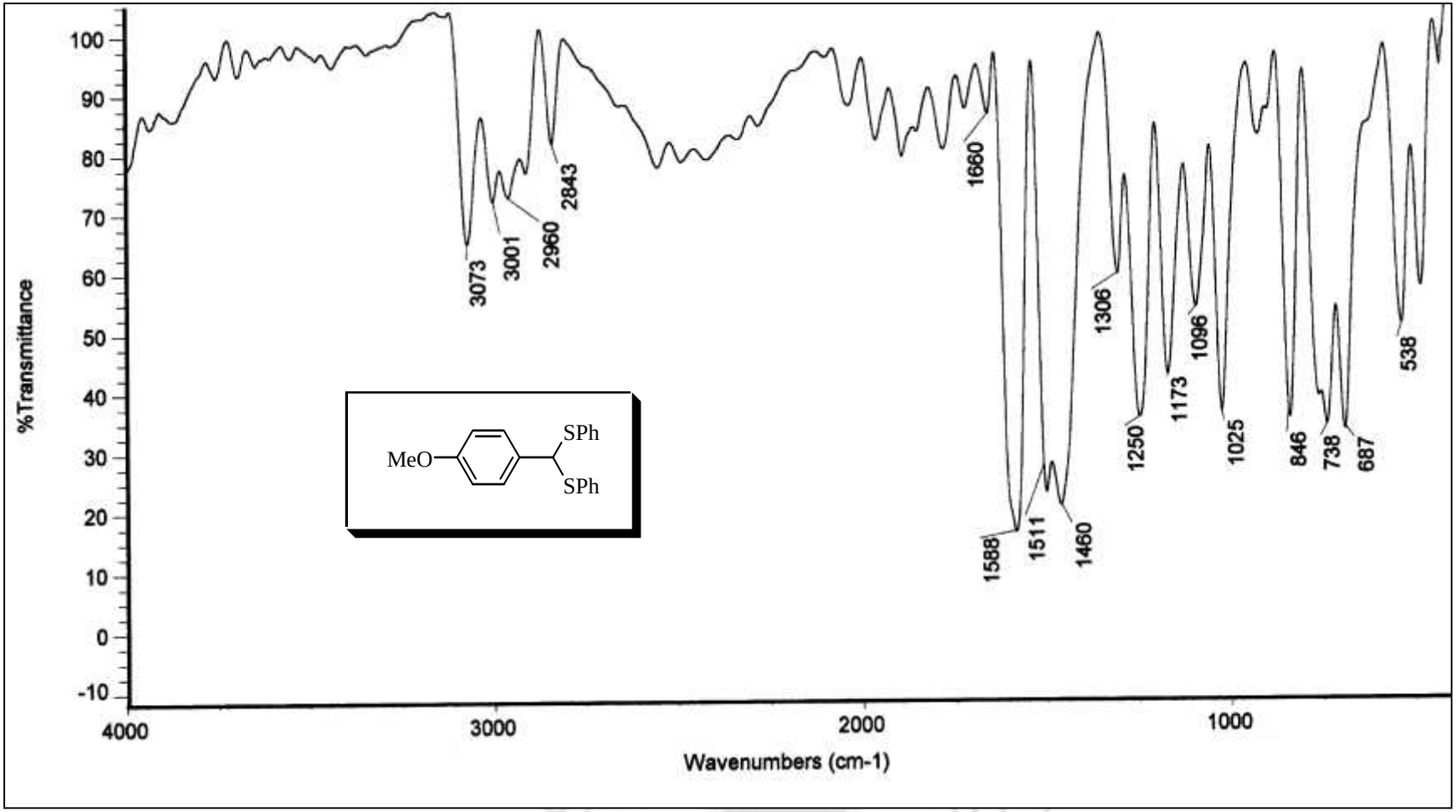


Figure 1: IR Spectrum of Diphenyldithioacetal of 4-Methoxybenzaldehyde (KBr) (102)

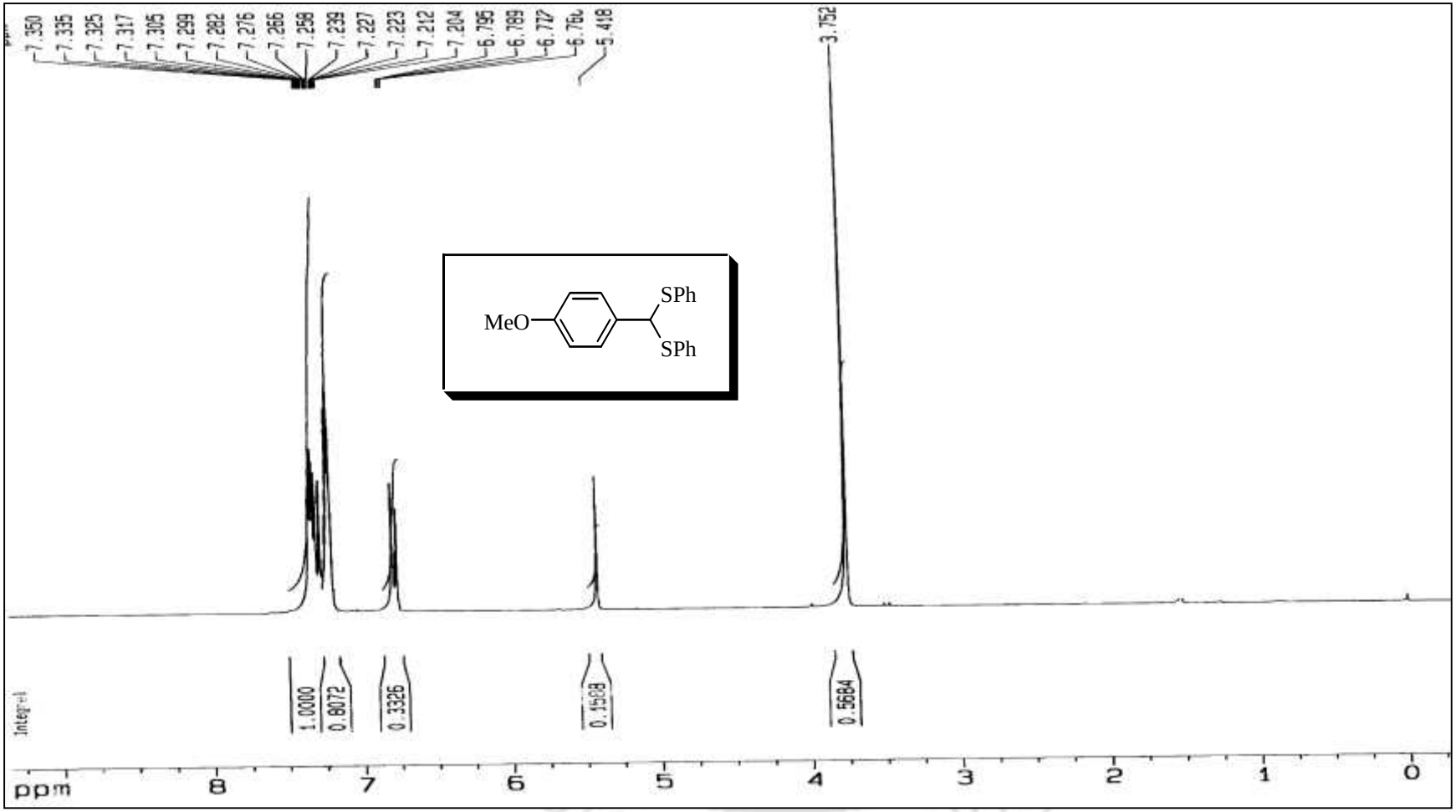


Figure 2: ^{1}H NMR Spectrum of Diphenyldithioacetal of 4-Methoxybenzaldehyde (300 MHz, $CDCl_3$) (102)

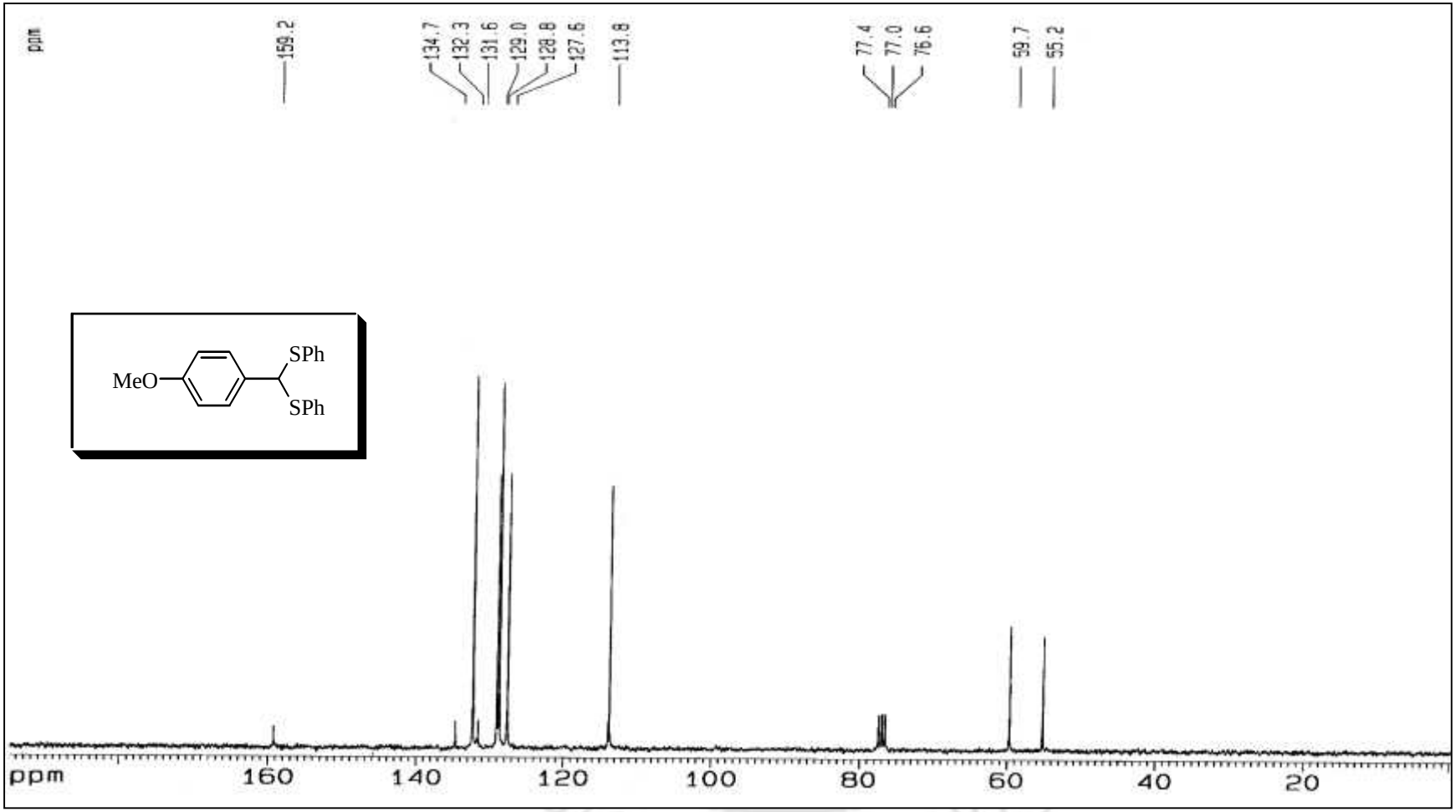


Figure 3: ^{13}C NMR Spectrum of Diphenyldithioacetal of 4-Methoxybenzaldehyde (75 MHz, $CDCl_3$) (102)

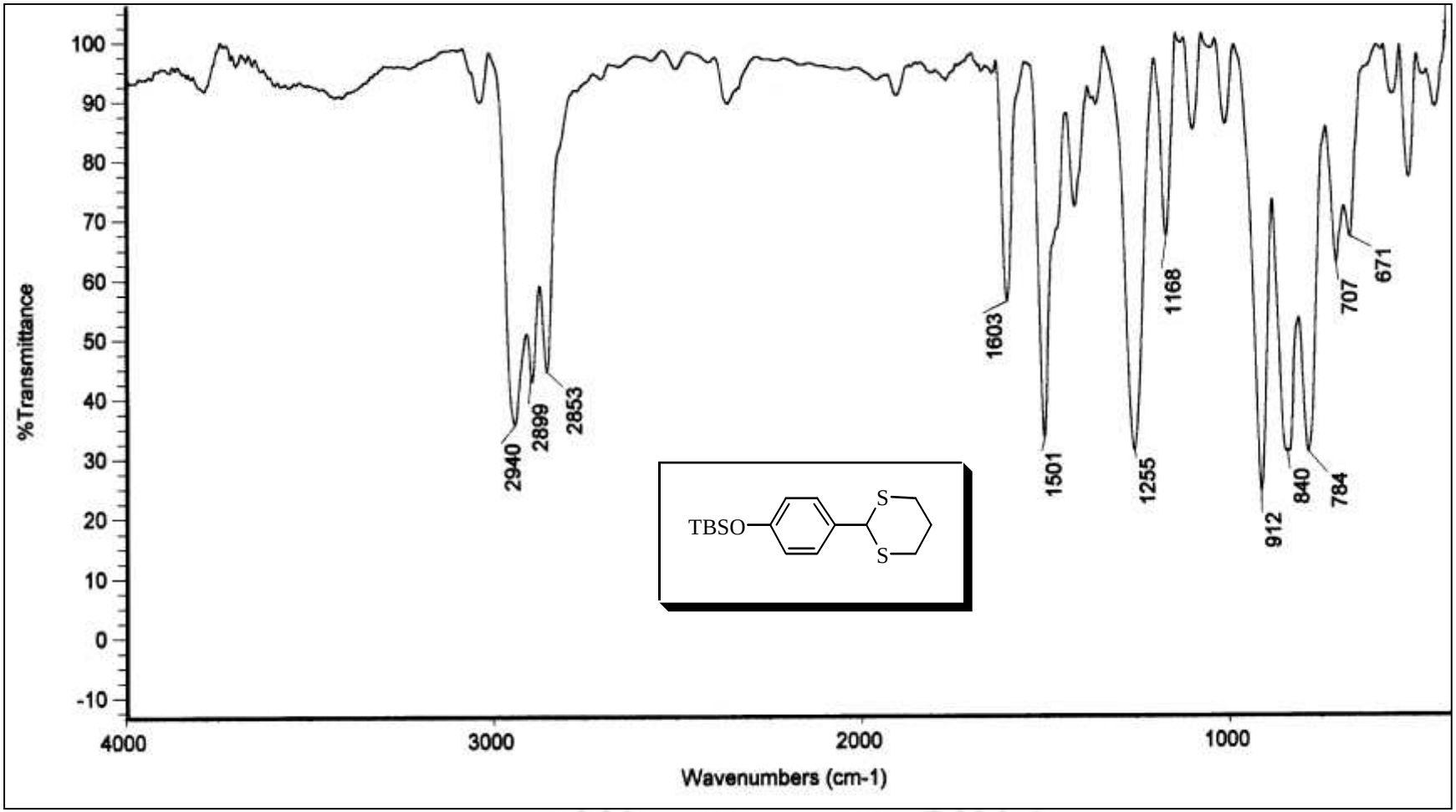


Figure 4: IR Spectrum of 2-[4-*tert*-Butyldimethylsilyloxyphenyl]-1,3-dithiane (KBr) (105)

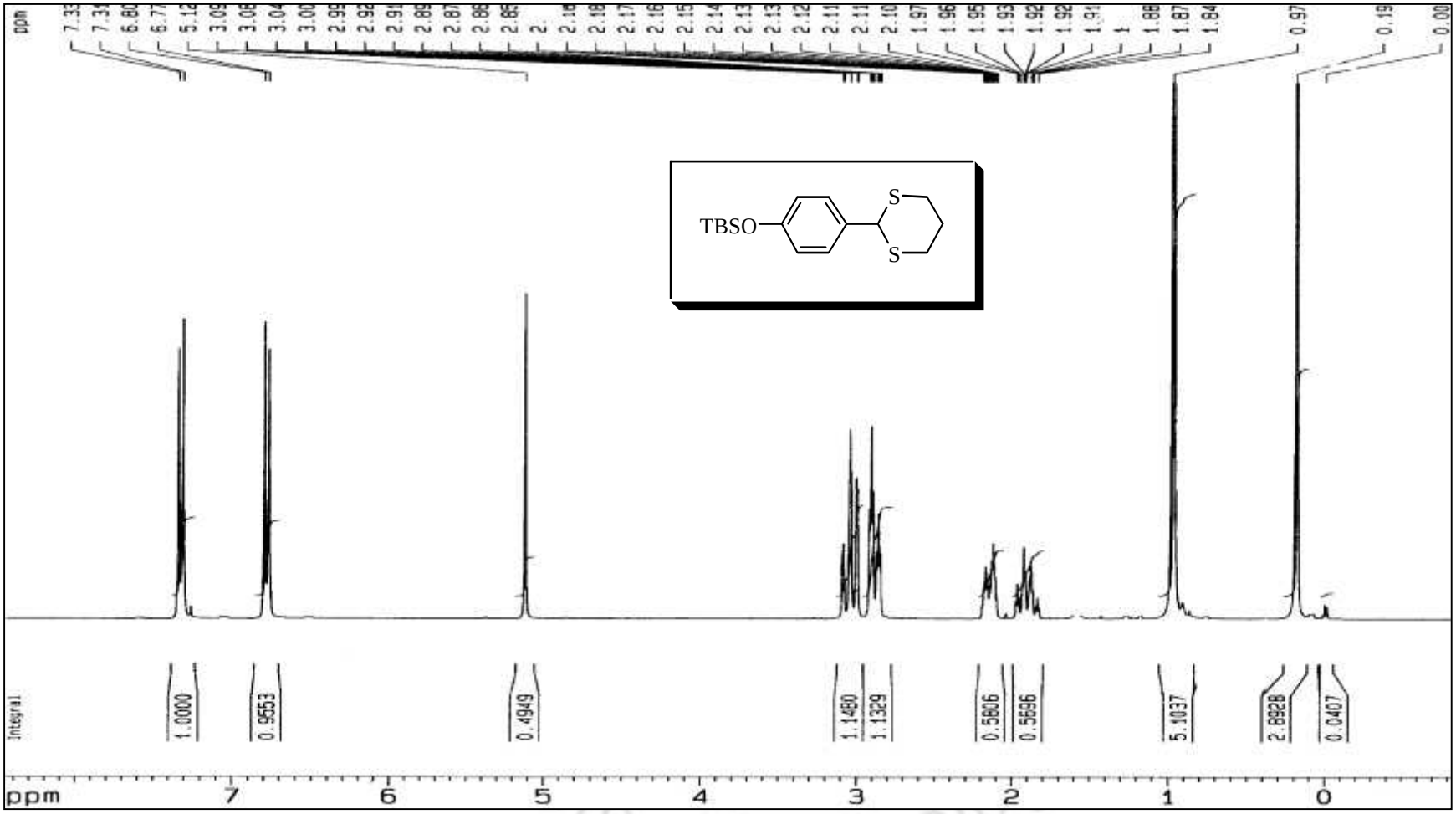


Figure 5: ^{1}H NMR Spectrum of 2-[4ỉ-*tert*-Butyldimethylsilyloxyphenyl]-1,3-dithiane (400 MHz, $CDCl_3$) (105)

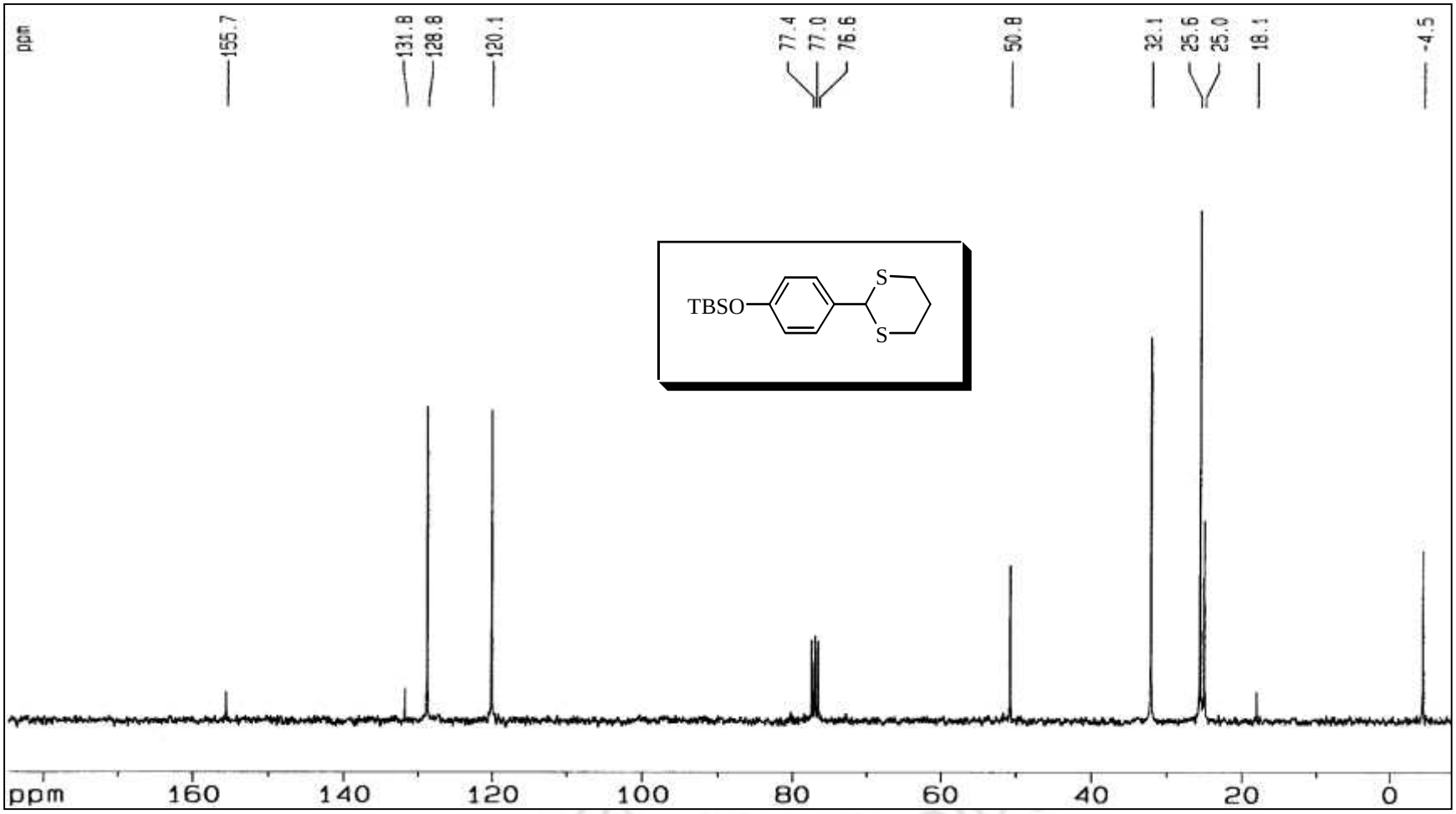


Figure 6: ^{13}C NMR Spectrum of 2-[4ꞌ-*tert*-Butyldimethylsilyloxyphenyl]-1,3-dithiane (100 MHz, $CDCl_3$) (105)

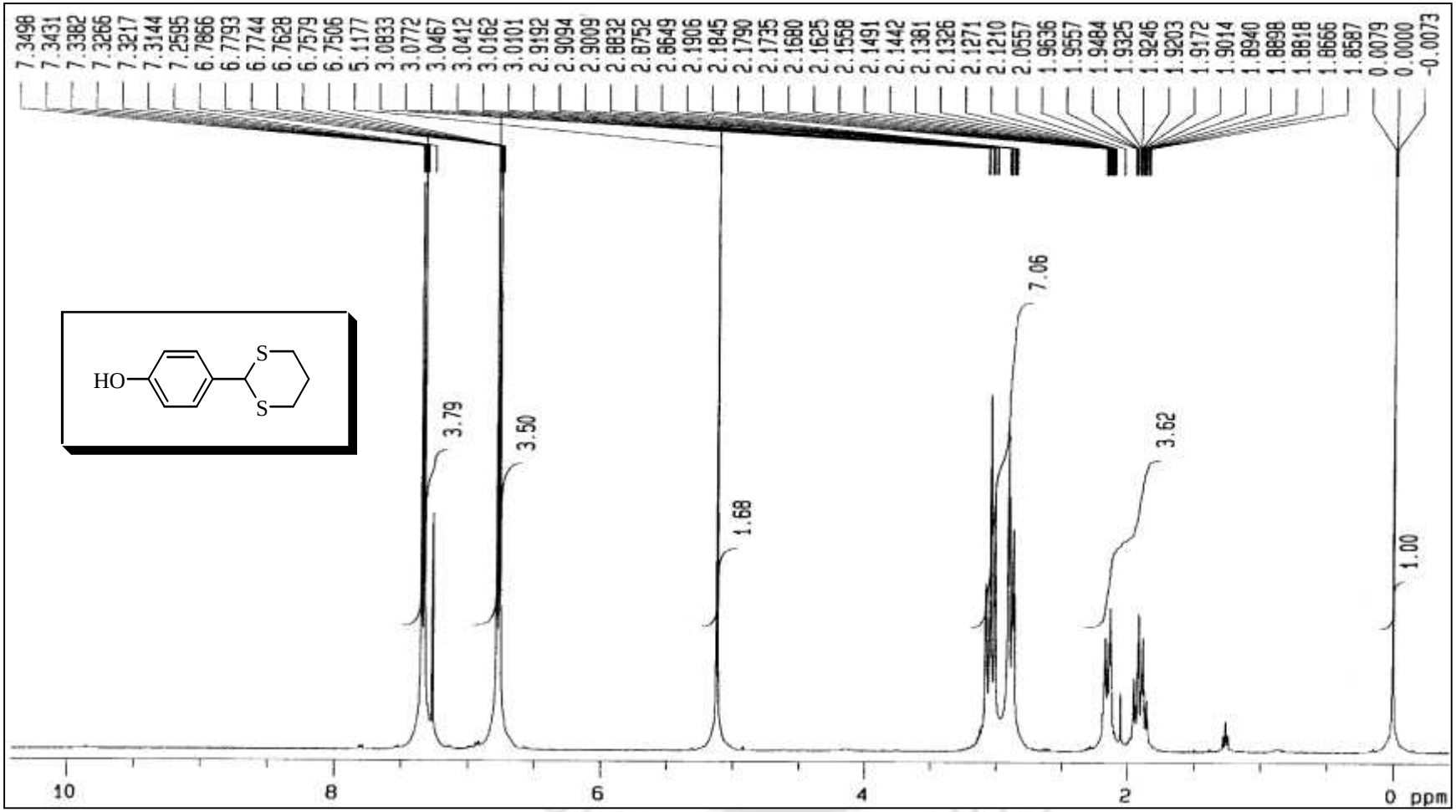


Figure 7: ^{1}H NMR Spectrum of 2-[4à-Hydroxyphenyl]-1,3-dithiane (400 MHz, $CDCl_3$) (114)

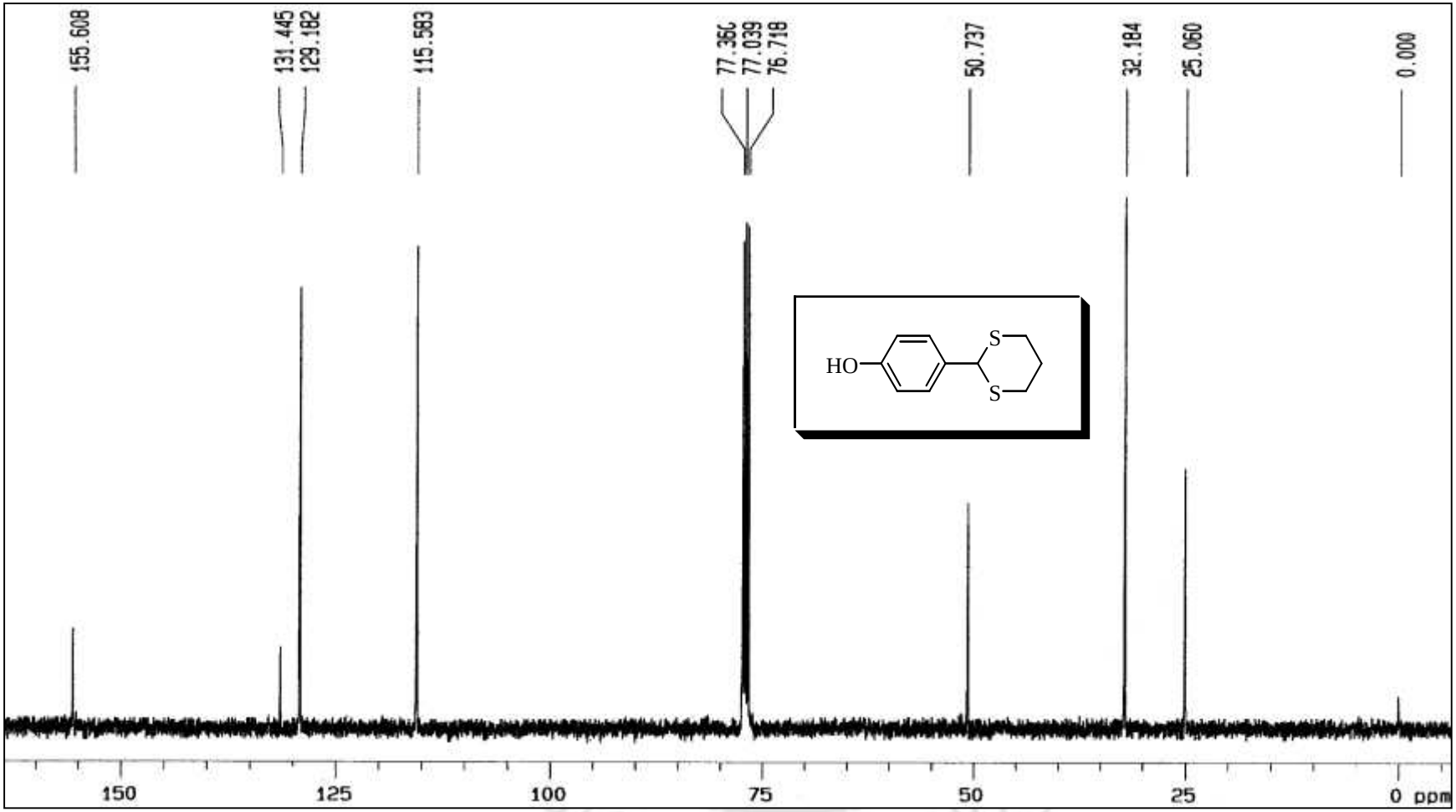


Figure 8: ^{13}C NMR Spectrum of 2-[4ⴰ-Hydroxyphenyl]-1,3-dithiane (100 MHz, $CDCl_3$) (114)

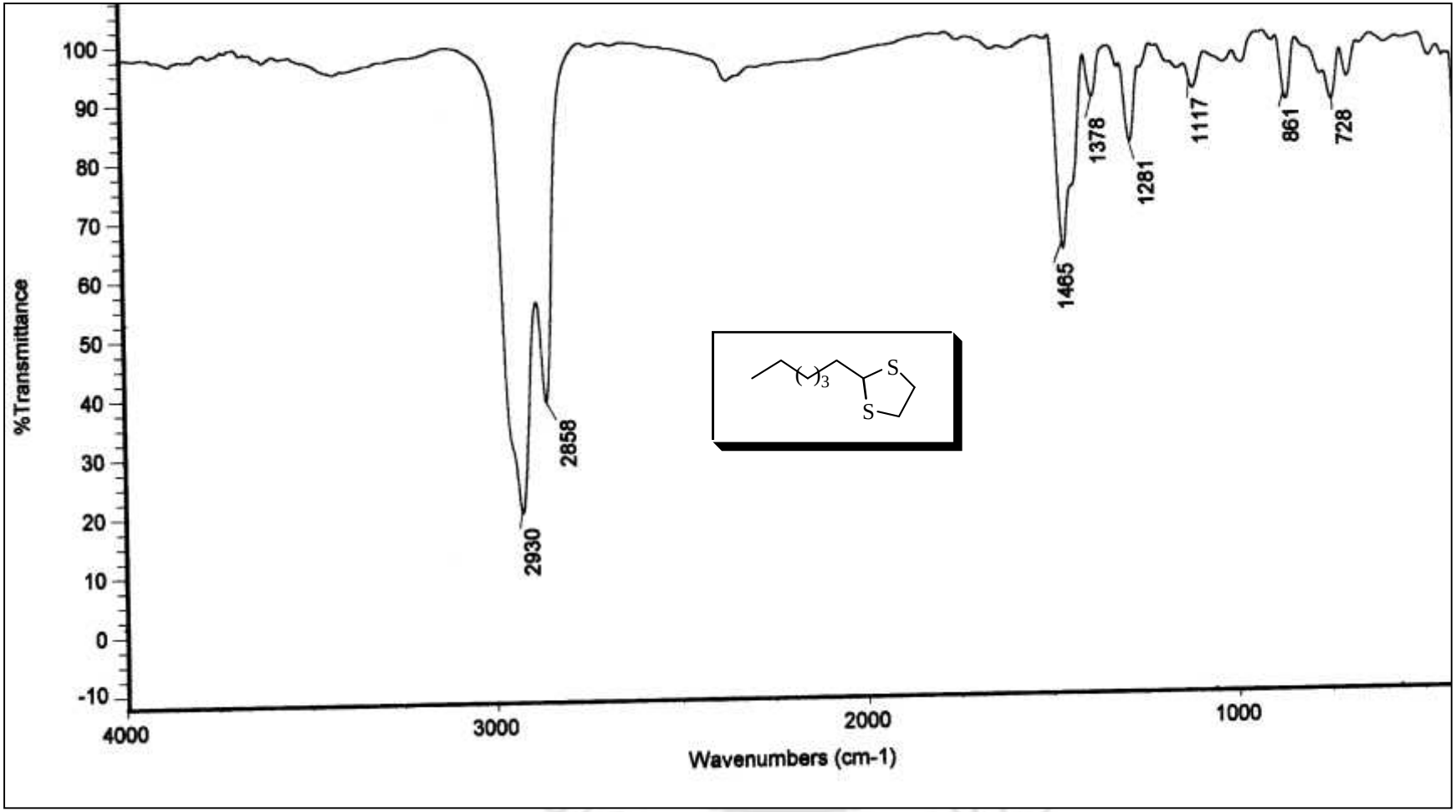


Figure 9: IR Spectrum of 2-Hexyl-1,3-dithiolane (Neat) (117)

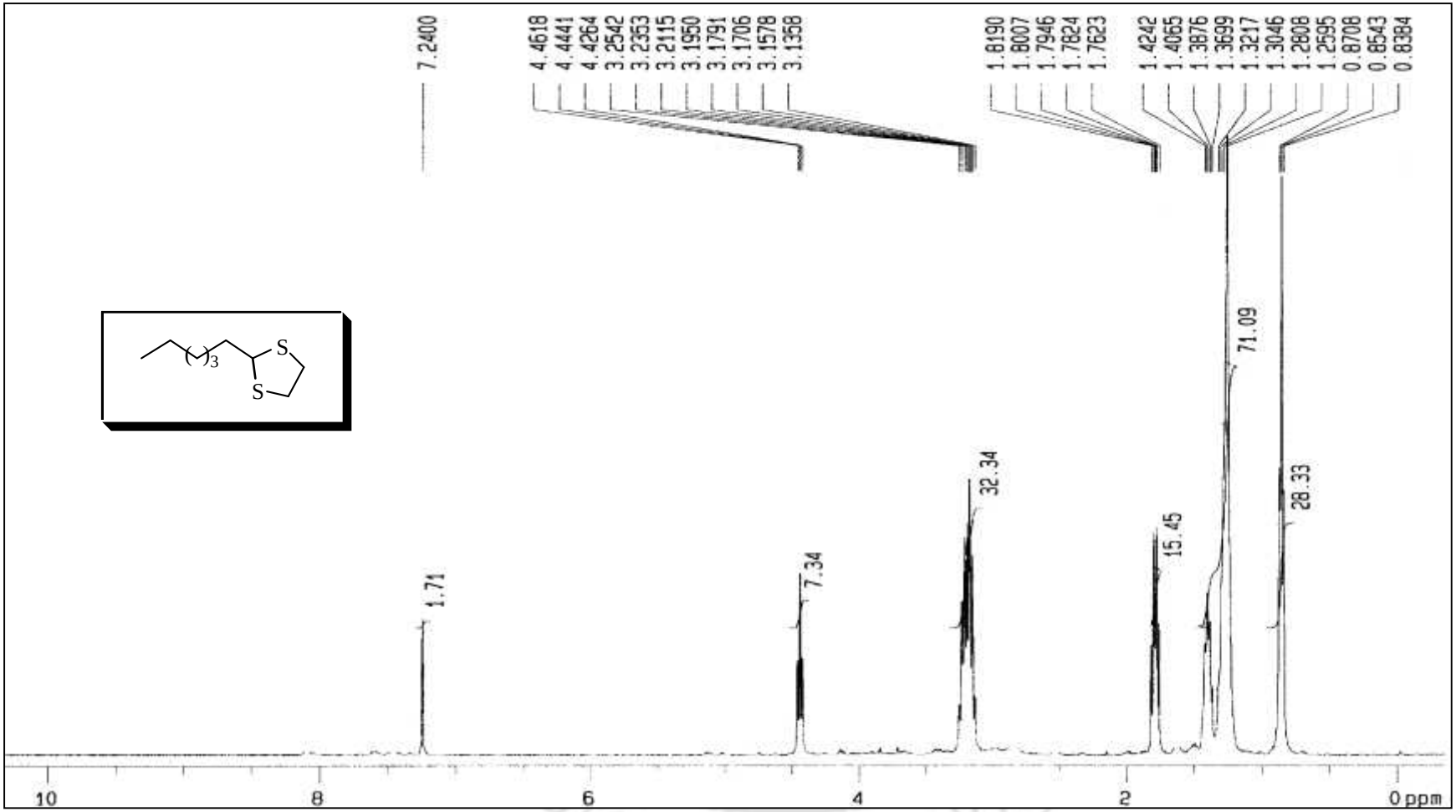


Figure 10: ^{1}H NMR Spectrum of 2-Hexyl-1,3-dithiolane (400 MHz, $CDCl_3$) (117)

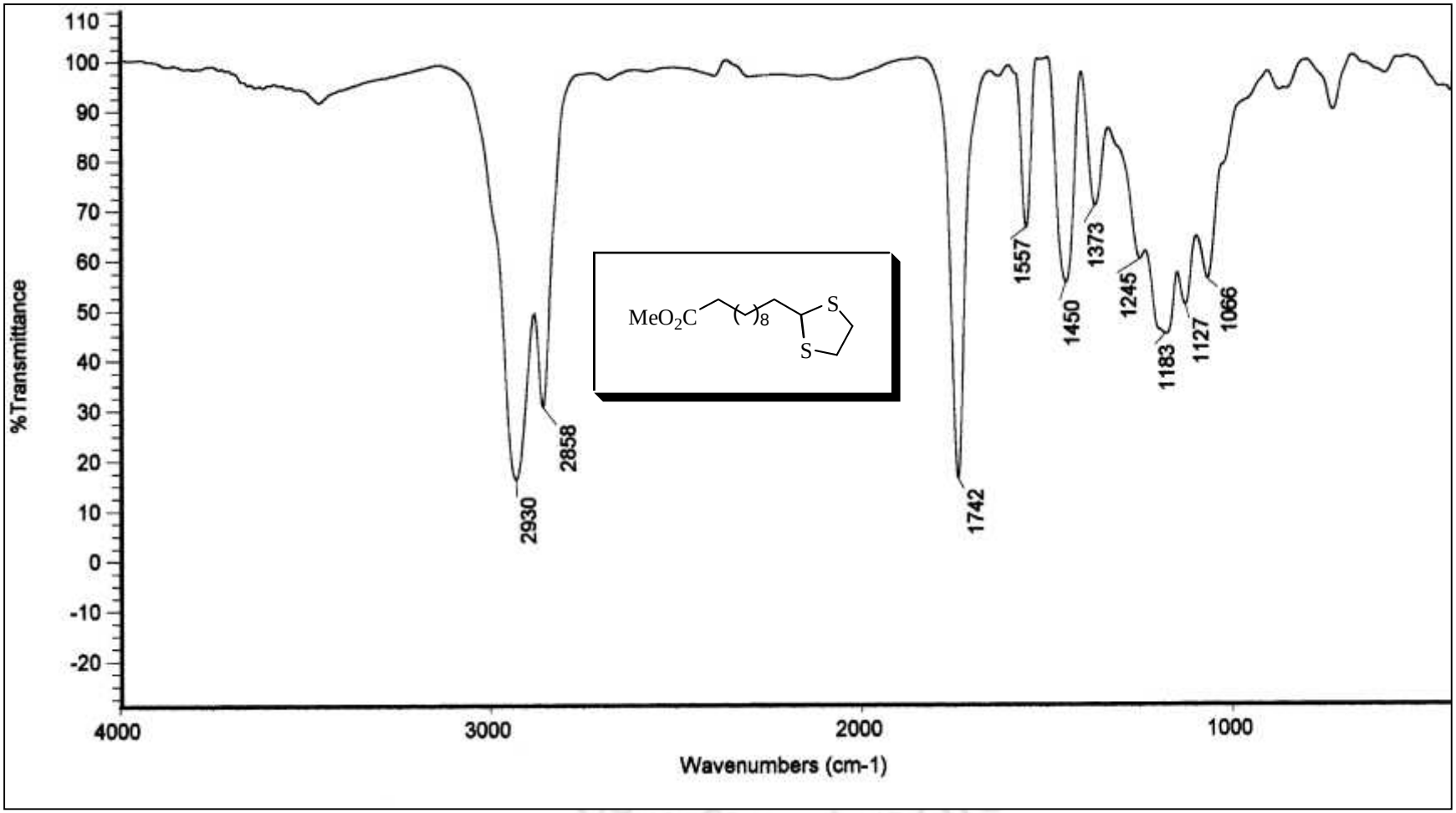


Figure11: IR Spectrum of 2-[10̀-Carboxymethyldecane]-1,3-dithiolane (Neat) (120)

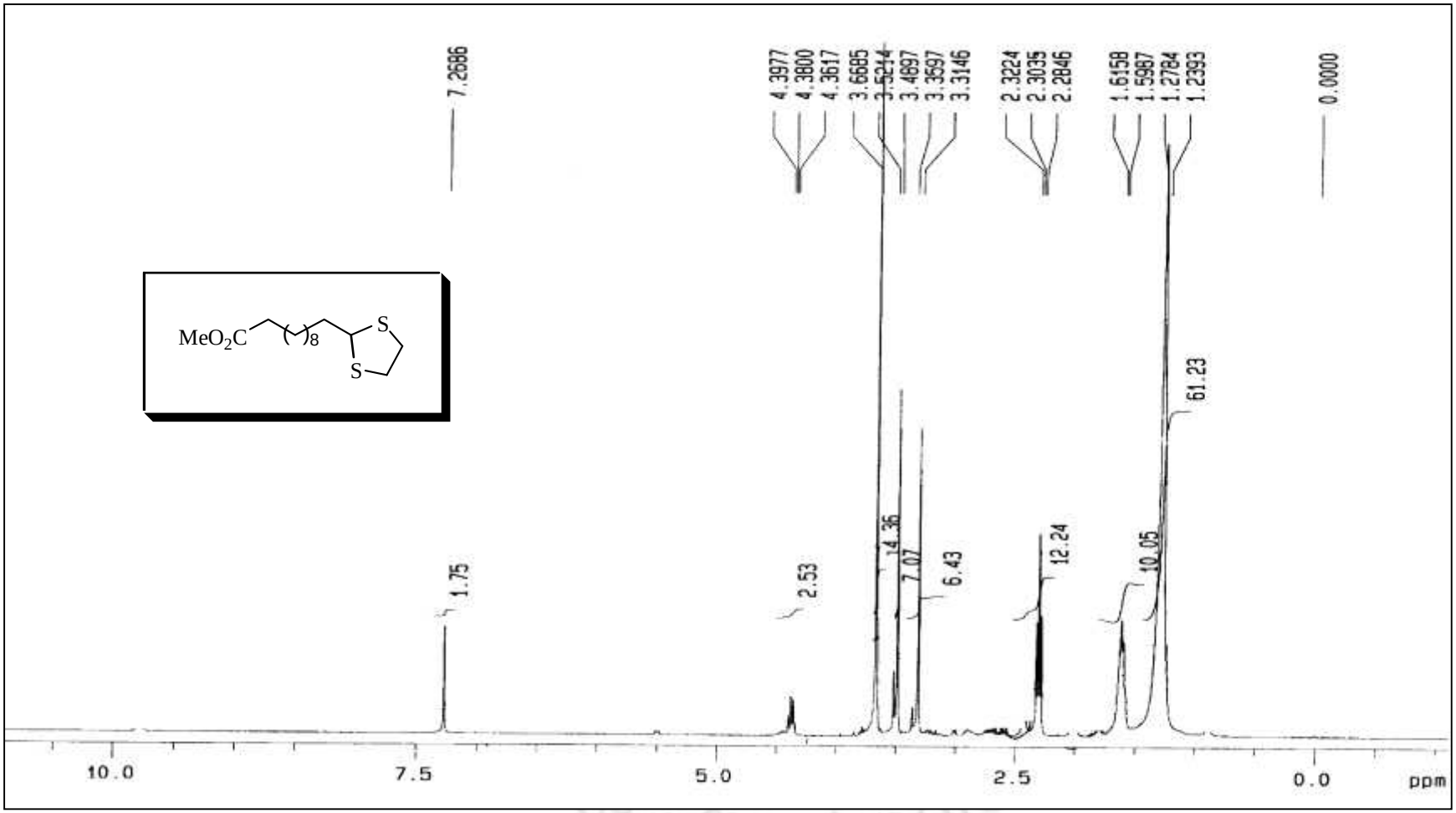


Figure12: ^{1}H NMR Spectrum of 2-[10̀-Carboxymethyldecane]-1,3-dithiolane (400 MHz, $CDCl_3$) (120)

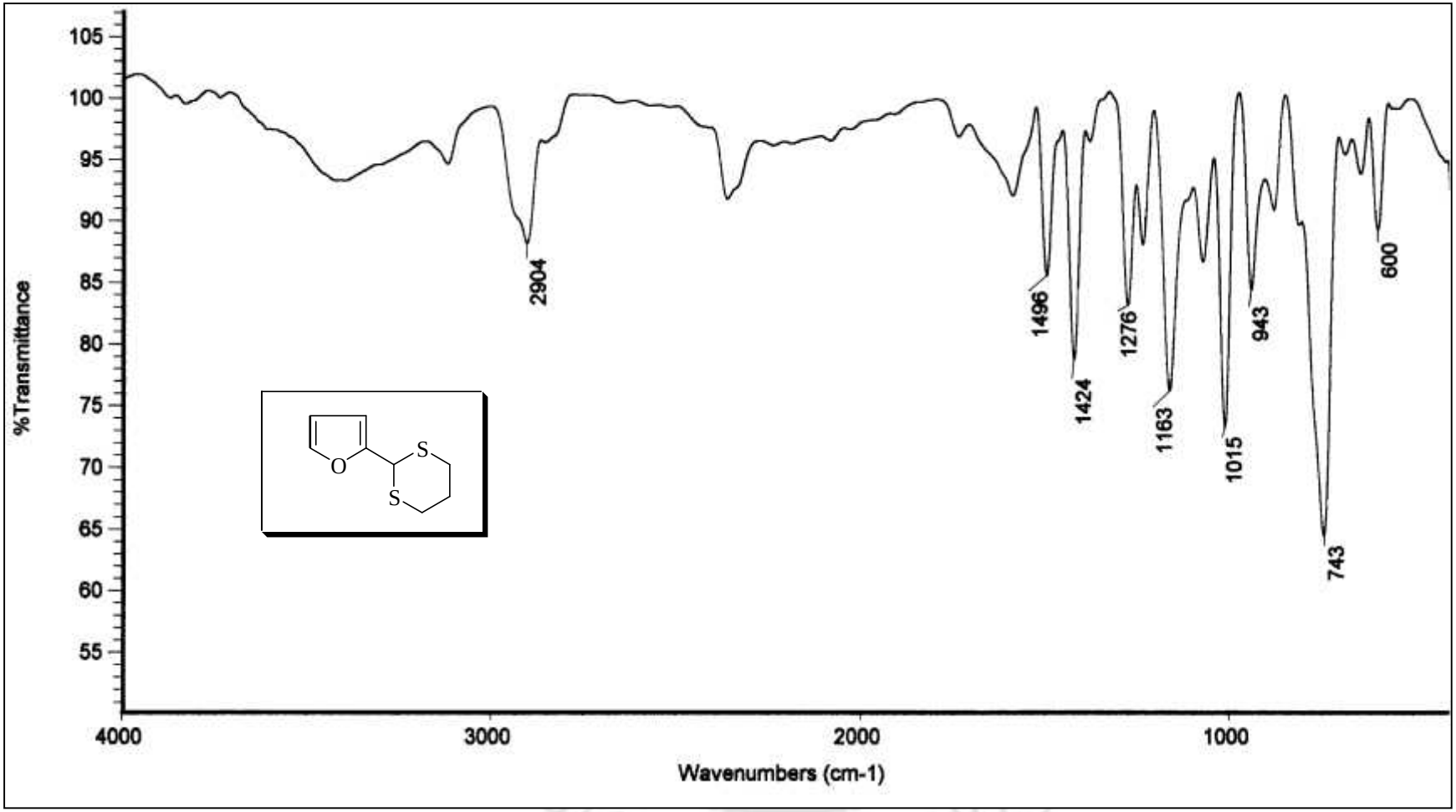


Figure 13: IR Spectrum of 2-Furfuryl-1,3-dithiane (Neat) (134)

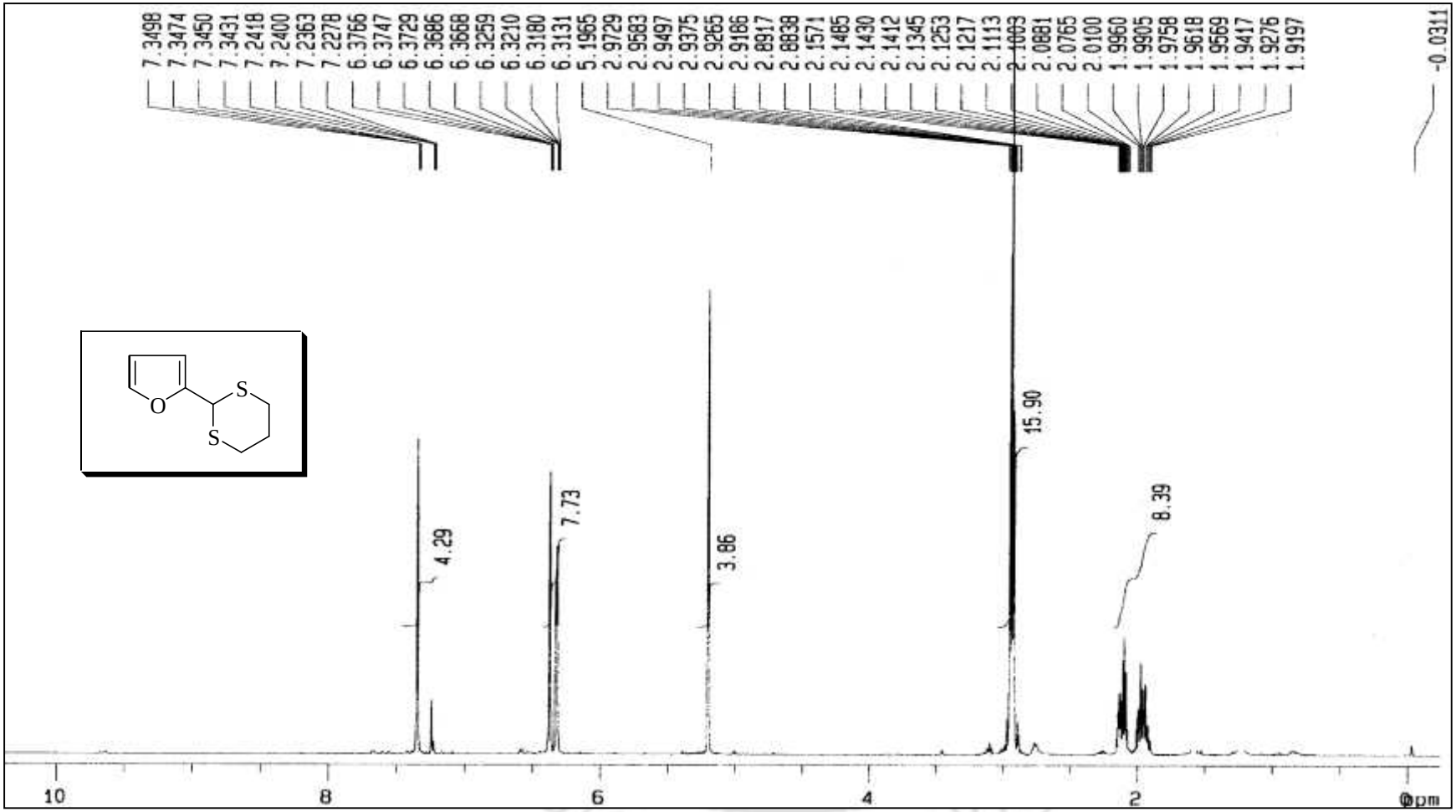


Figure 14: ^{1}H NMR Spectrum of 2-Furfuryl-1,3-dithiane (400 MHz, $CDCl_3$) (134)

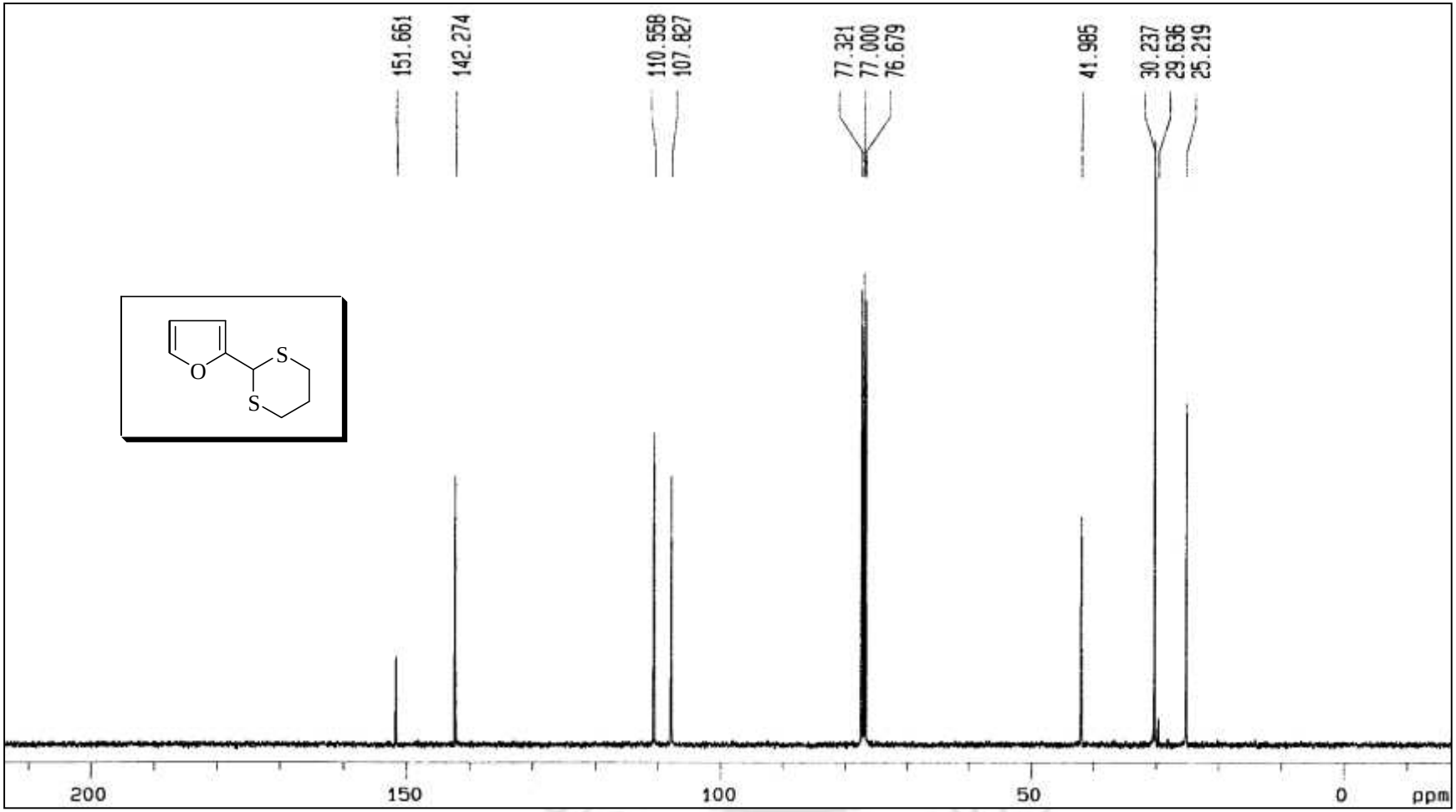


Figure 15: ^{13}C NMR Spectrum of 2-Furfuryl-1,3-dithiane (100 MHz, $CDCl_3$) (134)

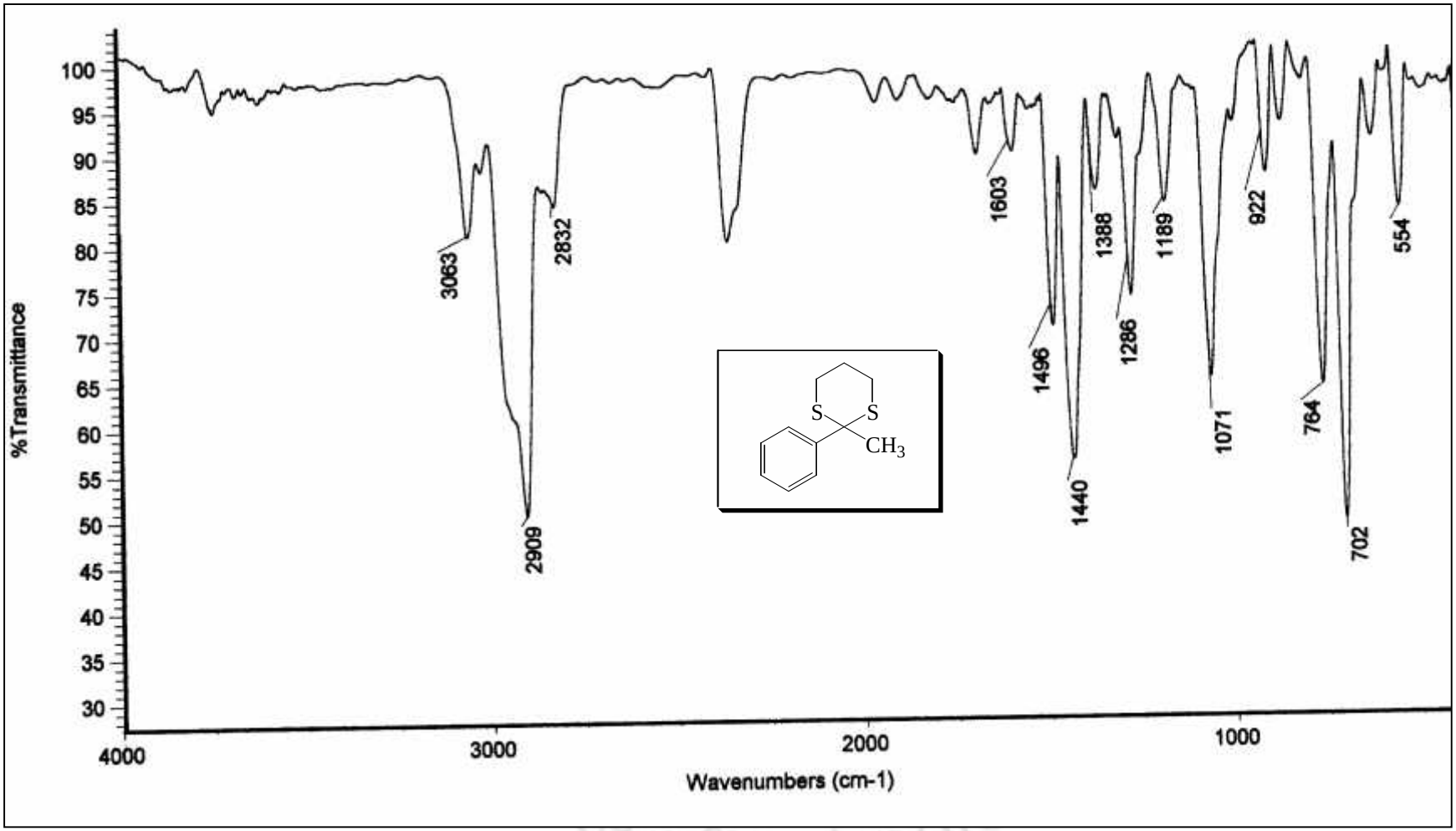


Figure 16: IR Spectrum of 2-Methyl-2-phenyl-1,3-dithiane (Neat) (87)

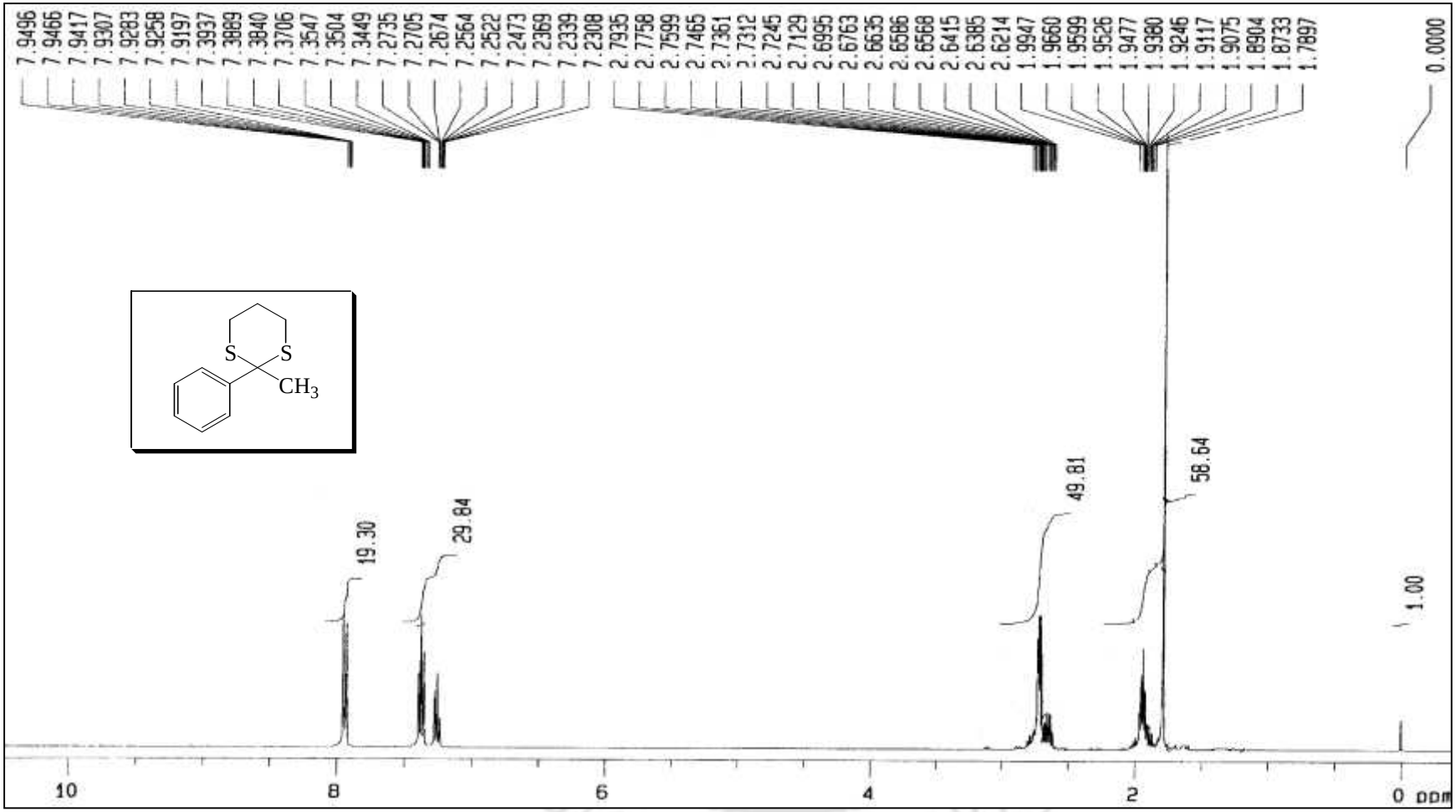


Figure 17: ^{1}H NMR Spectrum of 2-Methyl-2-phenyl-1,3-dithiane (400 MHz, $CDCl_3$) (87)

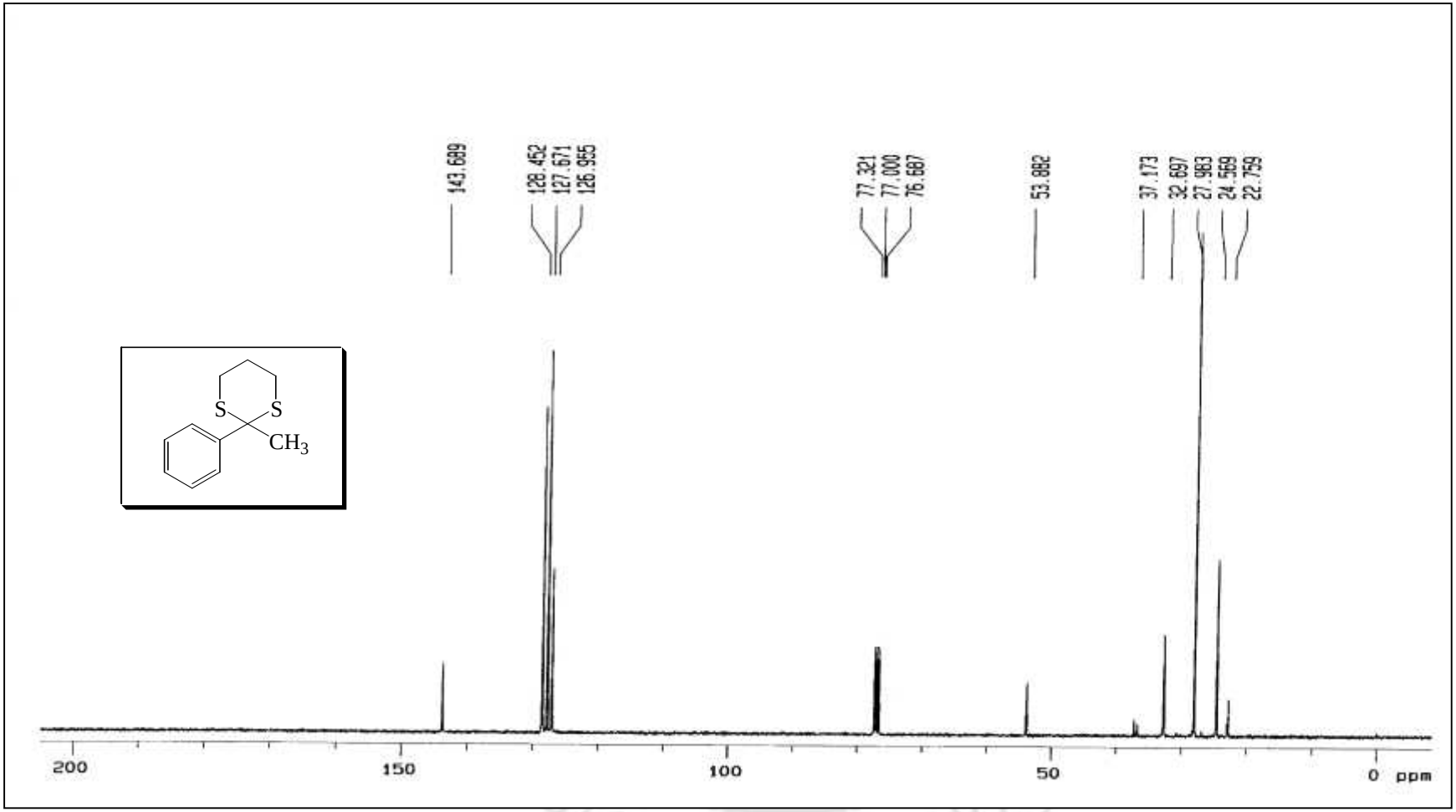


Figure 18: ^{13}C NMR Spectrum of 2-Methyl-2-phenyl-1,3-dithiane (100 MHz, $CDCl_3$) (87)

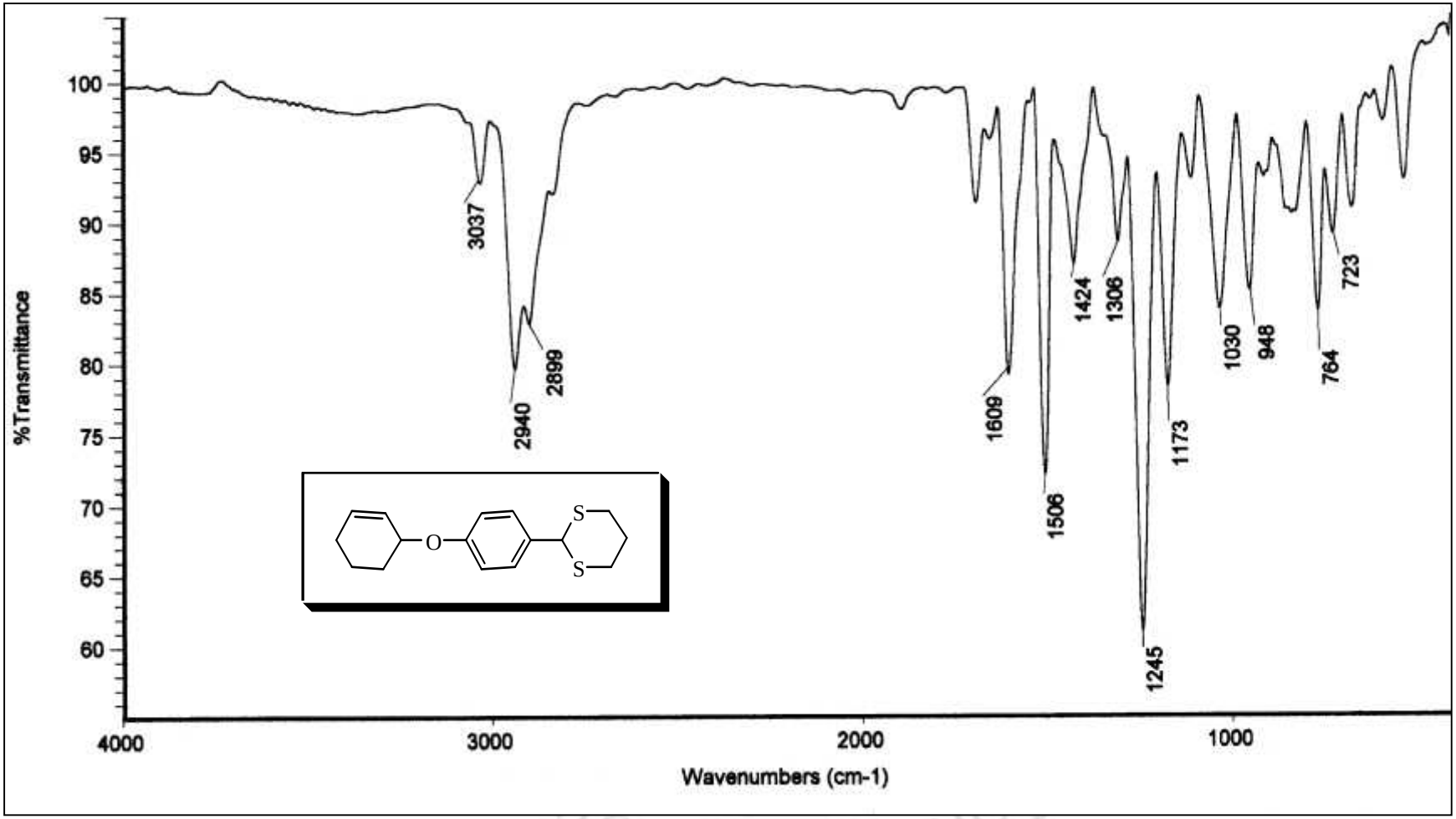


Figure 19: IR Spectrum of 2-[4̀-Cyclohexenylphenyl]-1,3-dithiane (KBr) (143)

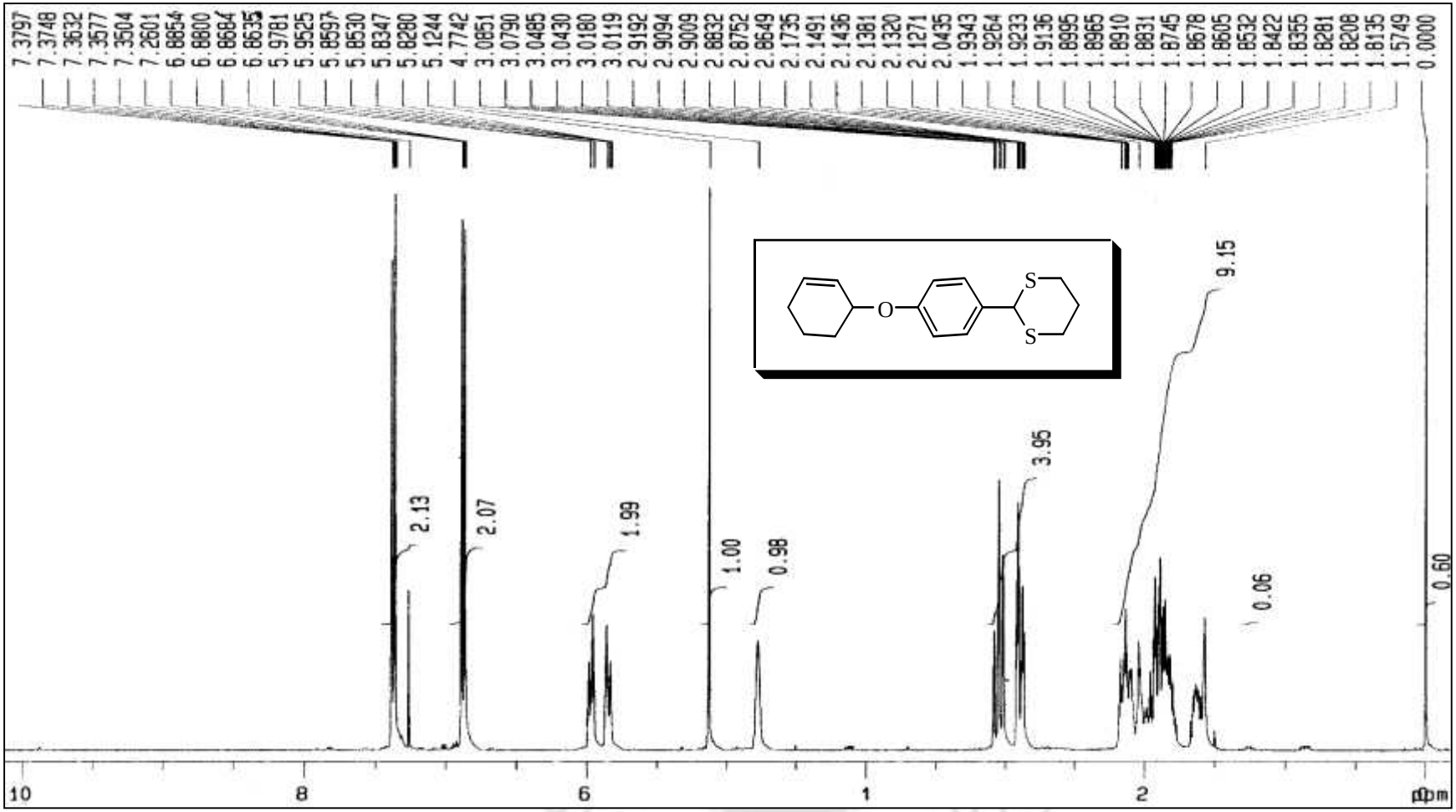


Figure 20: ^{1}H NMR Spectrum of 2-[4ā-Cyclohexenyloxyphenyl]-1,3-dithiane (400 MHz, $CDCl_3$) (143)

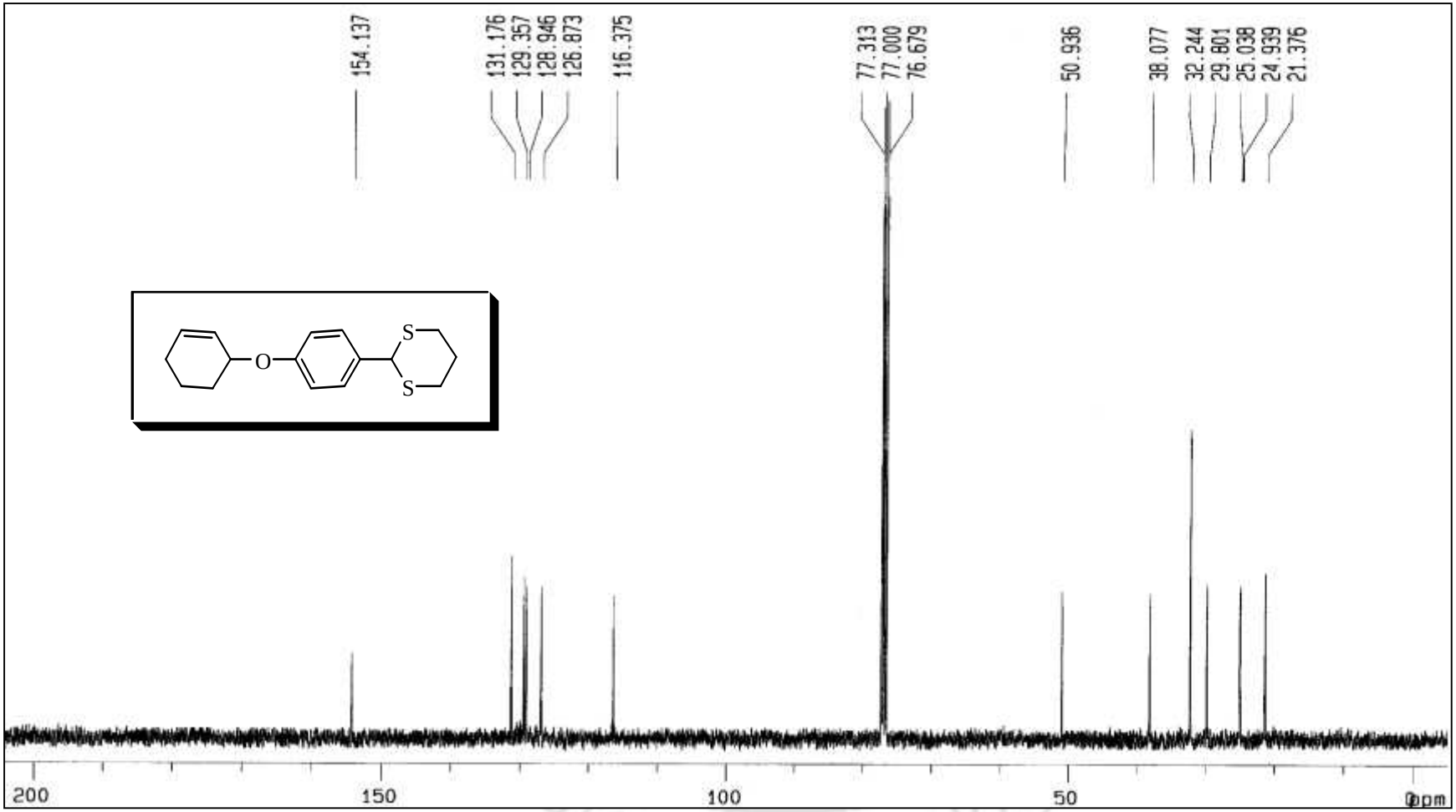


Figure 21: ^{13}C NMR Spectrum of 2-[4ᵌ-Cyclohexenylphenyl]-1,3-dithiane (100 MHz, $CDCl_3$) (143)

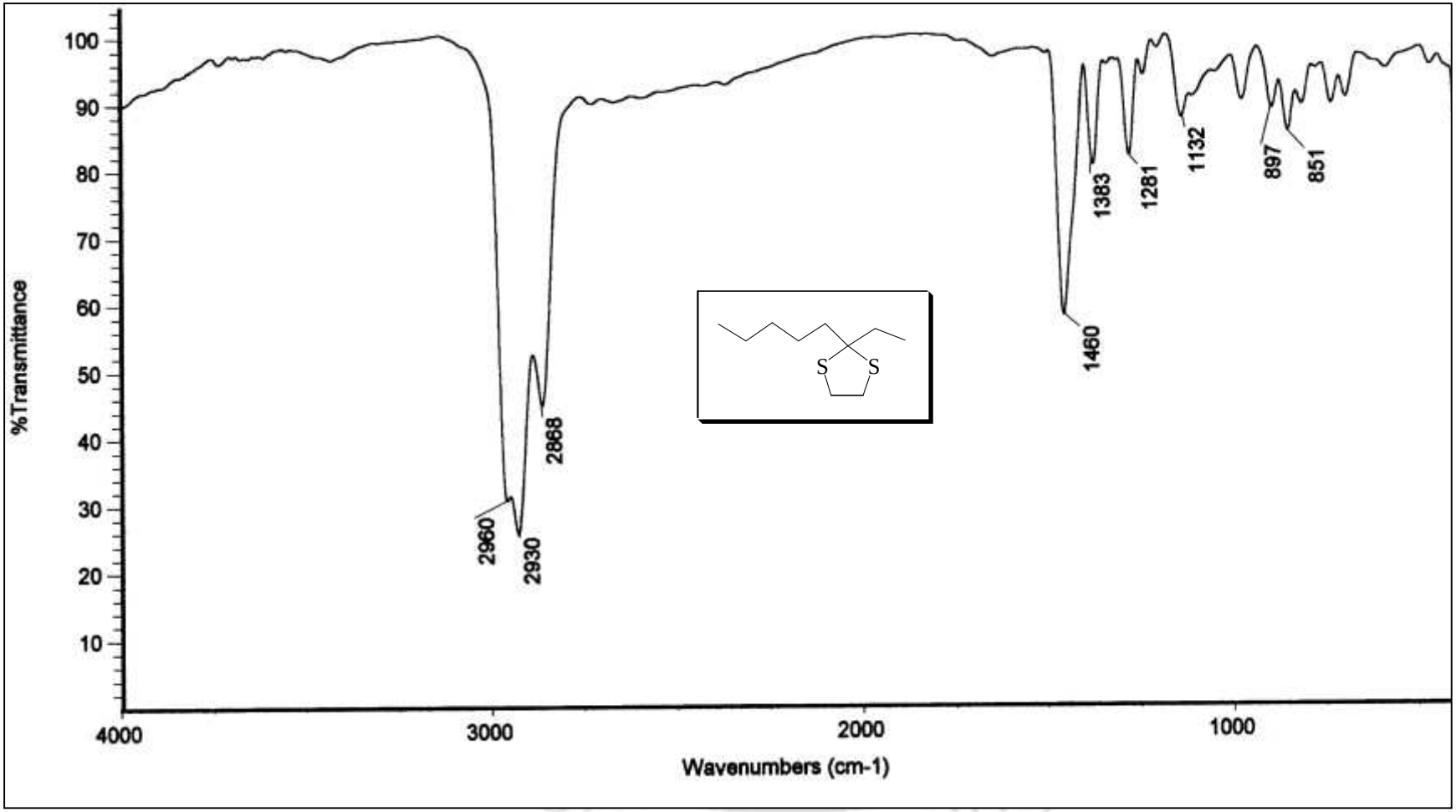


Figure 22: IR Spectrum of 2-Ethyl-2-pentyl-1,3-dithiolane (Neat) (145)

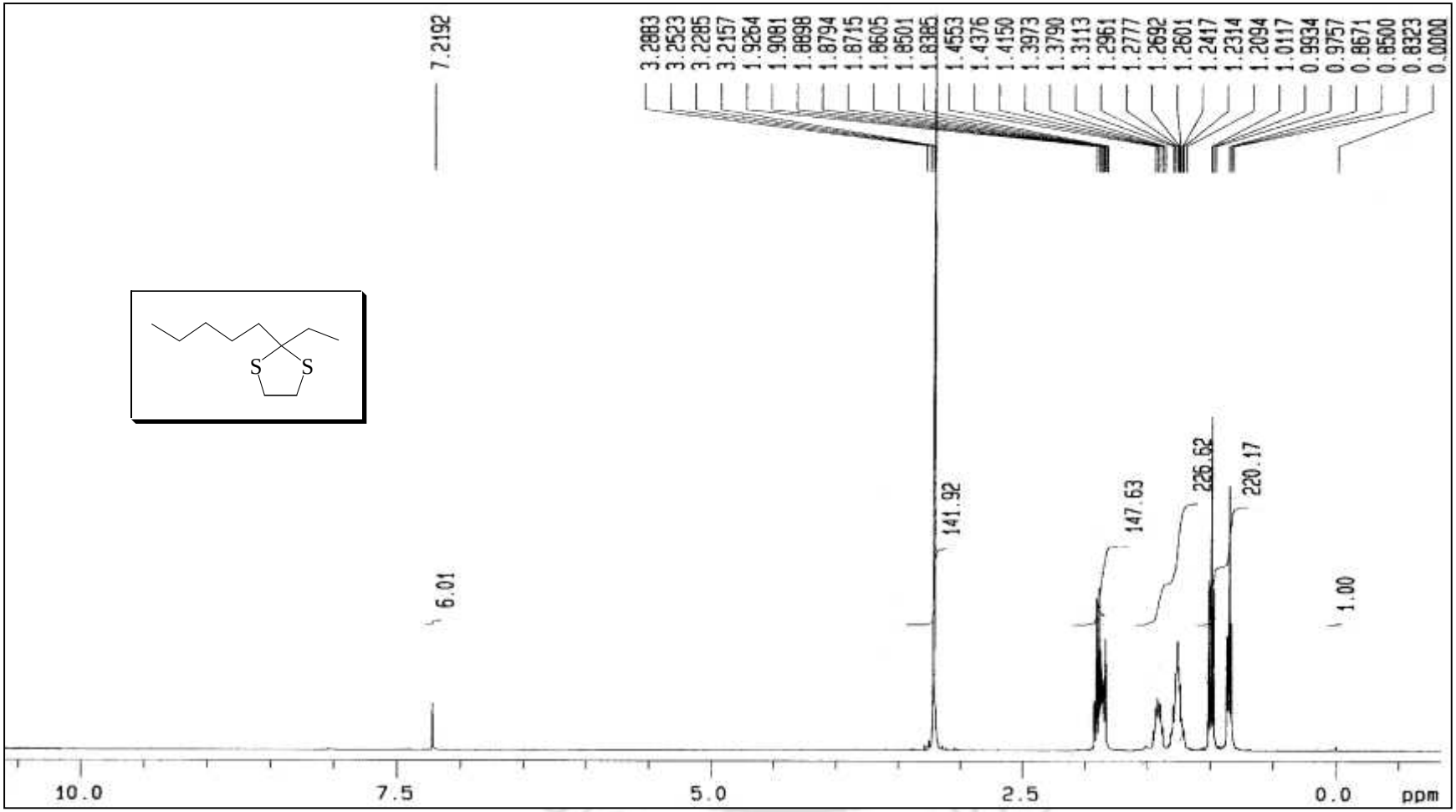


Figure 23: ^{1}H NMR Spectrum of 2-Ethyl-2-pentyl-1,3-dithiolane (400 MHz, $CDCl_3$) (145)

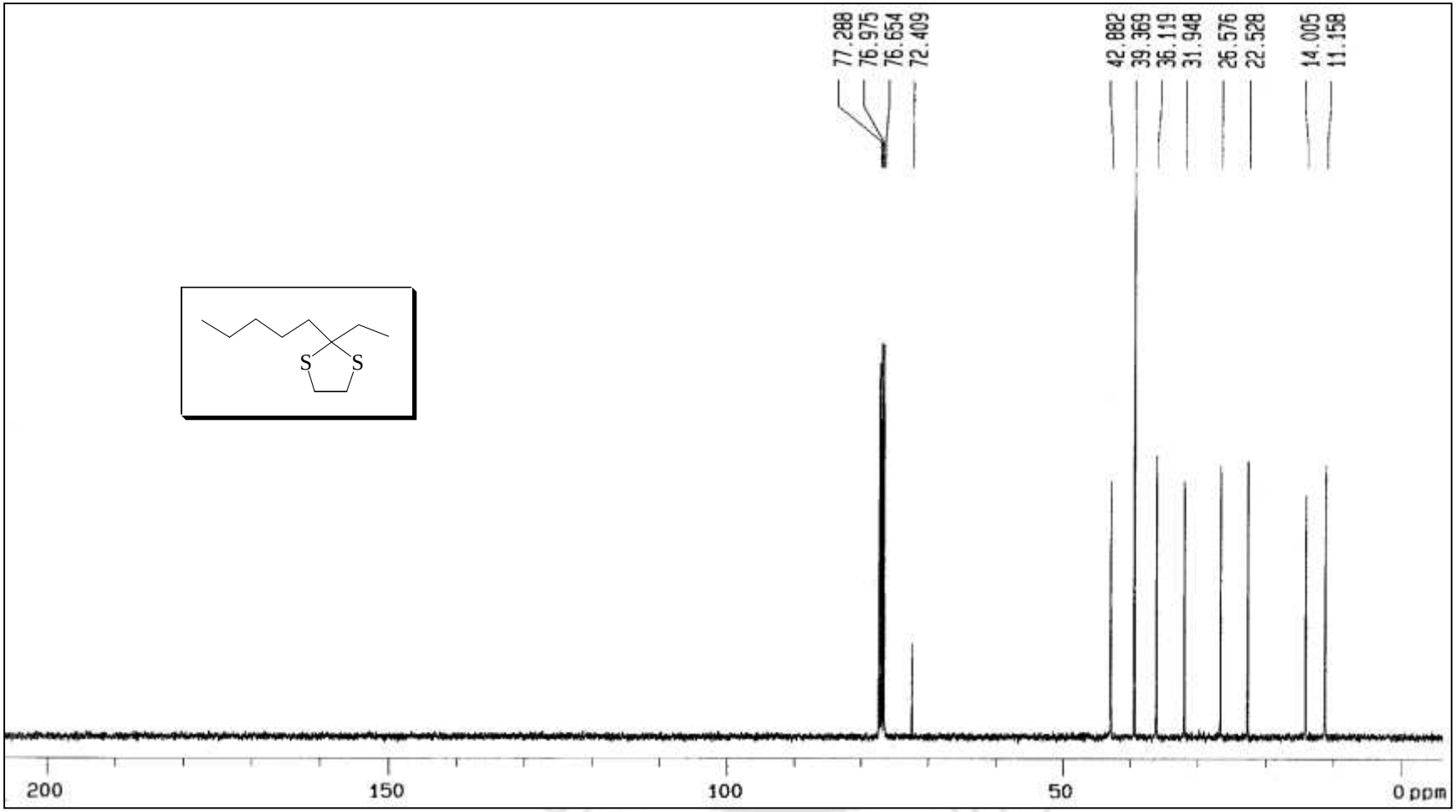


Figure 24: ^{13}C NMR Spectrum of 2-Ethyl-2-pentyl-1,3-dithiolane (100 MHz, $CDCl_3$) (145)

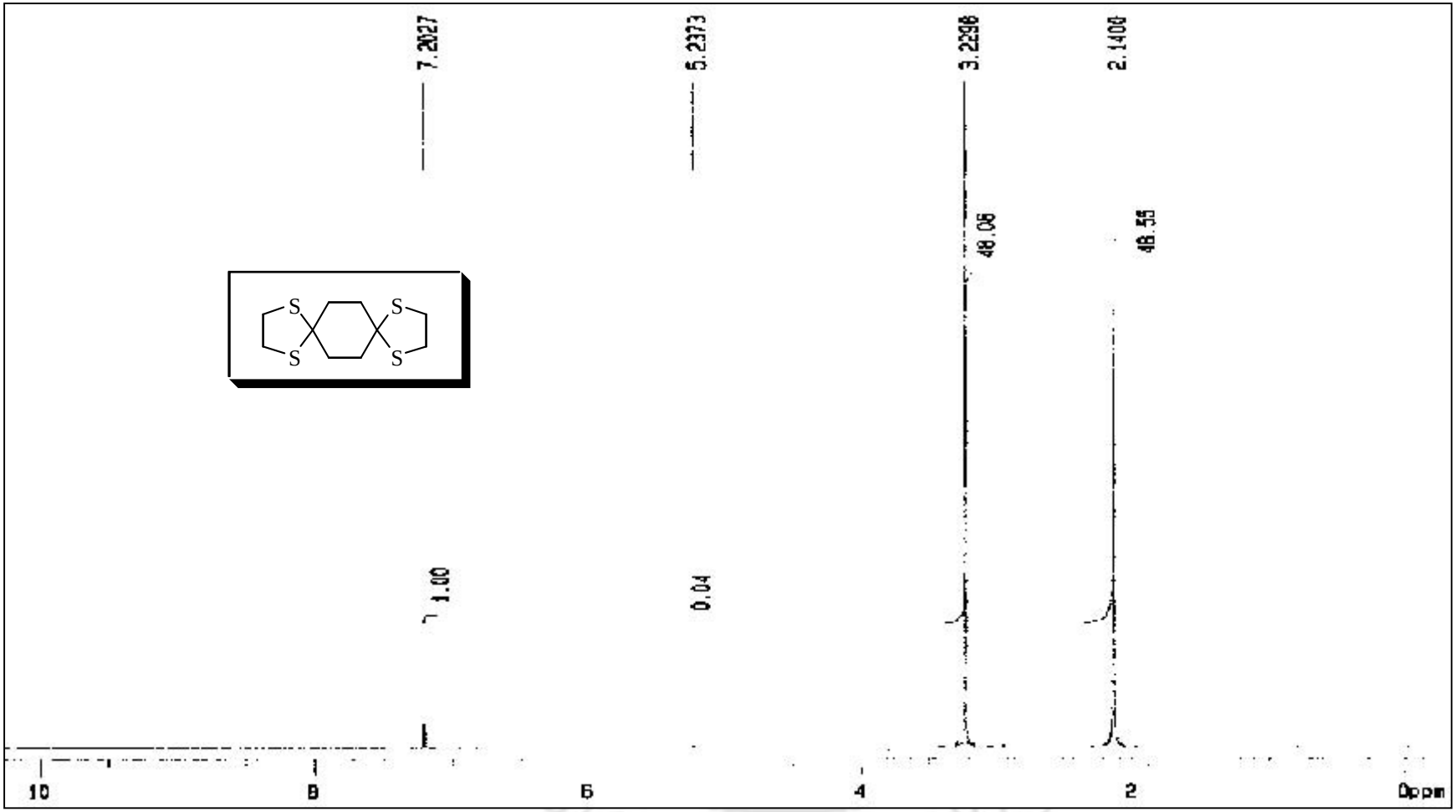


Figure 25: ^{1}H NMR Spectrum of 1,4-Cyclohexanedione diethylenethioacetal (400 MHz, $CDCl_3$) (150)

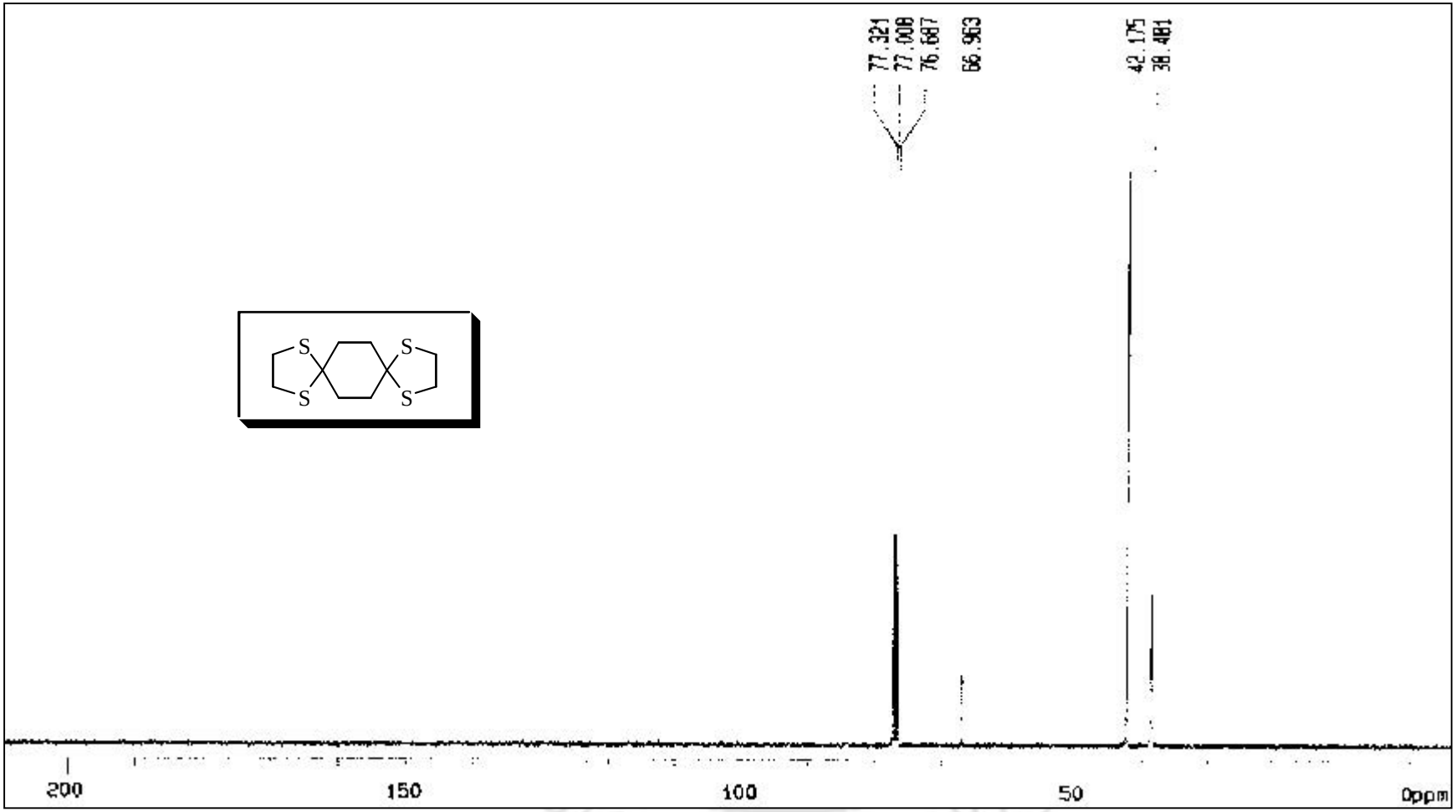


Figure 26: ^{13}C NMR Spectrum of 1,4-Cyclohexanedione diethylenethioacetal (100 MHz, $CDCl_3$) (150)

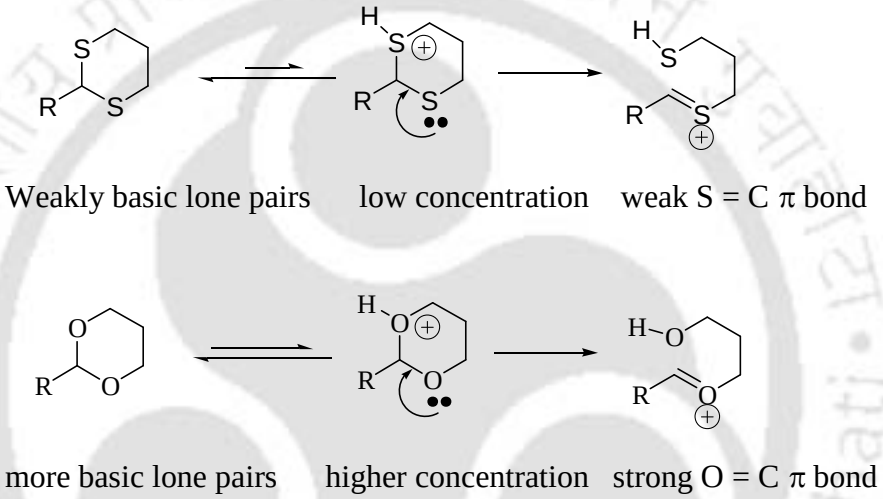
CHAPTER II

PART I

LITERATURE SURVEY ON THE SYNTHETIC METHODOLOGY FOR CLEAVAGE OF DITHIOACETALS TO THE CARBONYL COMPOUNDS

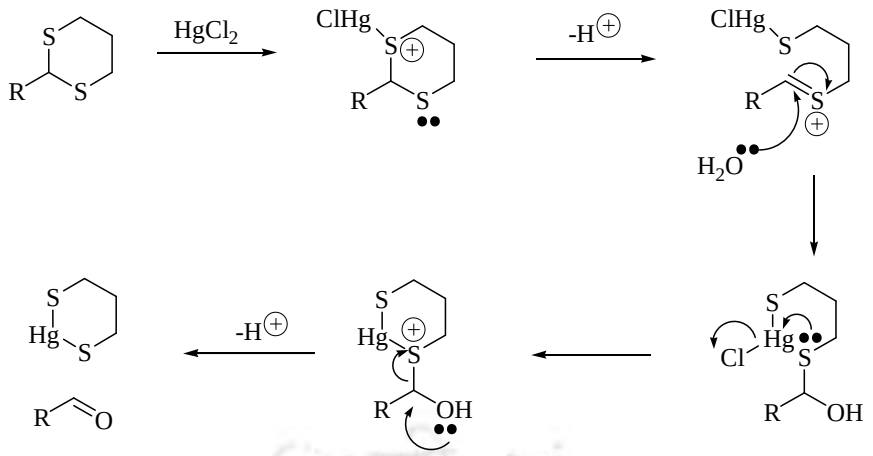
Introduction

We have already addressed the application and usefulness of dithioacetals in organic synthesis in the previous chapter I. When a dithioacetal group is introduced in the molecule as a protecting group then it must be hydrolyzed at some stage to regenerate the carbonyl group which was originally masked. Unfortunately, deprotection of dithioacetal to the corresponding carbonyl compound encounters some difficulty especially for complex and sensitive substrates. Conventionally, the deprotection of dithioacetal to the corresponding carbonyl compounds are difficult under acidic as compared to the *O,O*-acetal and *O,O*- ketal as shown in scheme 41. The reasons are shown in the scheme 41.



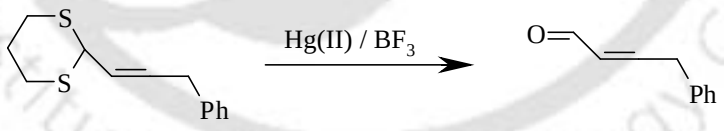
Scheme 41

Conceptually, the demasking of dithioacetals can be overcome by the following three different ways. The first way, the hydrolysis can be achieved in the presence of heavy metal ions,[79] which acts as a good electrophile. The cleavage of the dithioacetals to the corresponding carbonyl compounds are conventionally performed by using a heavy metal salts such as mercuric(II) chloride because mercury(II) and sulfides form strong coordination complexes, and mercury catalyses the reaction by acting as a sulfur-selective Lewis acid as shown in scheme 42.



Scheme 42

It has been observed that the reaction mixtures become acidic while the hydrolysis is carried out by using mercury(II) chloride. Therefore, different additives have been used into the reaction mixture such as calcium carbonate, barium carbonate, cadmium carbonate, or mercuric oxide to neutralize the acid, which is formed in the reaction medium during hydrolysis. Unfortunately, the method based on mercury(II) salts have some serious drawbacks such as heavy metals are highly toxic, requirement of excess salts and difficult to isolate the product from reaction mixture which ultimately costs low yield. For sensitive substrates, Vedejs and Fuchs[80] have shown that the demasking of dithioacetals can be achieved successfully by combination of mercury(II) oxide and boron trifluoride as depicted in scheme 43.

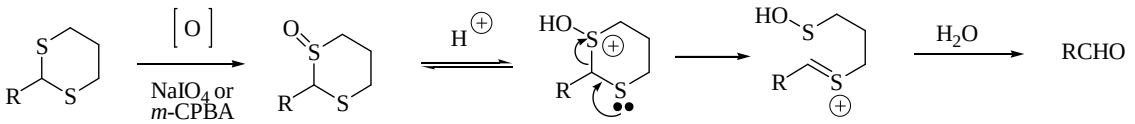


25 **151**

Scheme 43

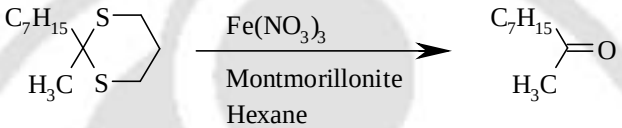
The cleavage of dithioacetals are also known in the literature by employing other metal salts or metals such as $CuCl_2$/CuO,[81] $TiCl_4$,[82] Ag and Cd.[83]

Secondly, the deprotection of dithioacetals or ketals can also be done by oxidation of sulfur to a higher oxidation state followed by hydrolysis as shown in scheme 44.



Scheme 44

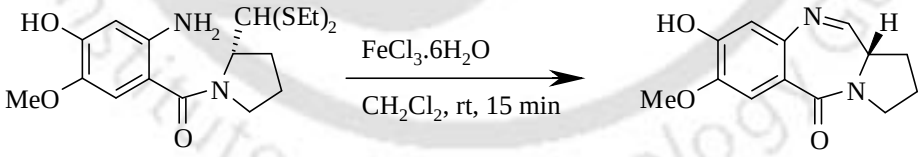
By utilizing oxidation conception, Hirano and Clark *et al* have reported[84] the oxidative cleavage of cyclic thioacetals to the carbonyl compounds by using solid $Fe(NO_3)_3$ and Montmorillonite K10 in hexane. The method is applicable for aliphatic, alicyclic, aromatic and unsaturated dithioacetals as represented in scheme 45.



152 **153**

Scheme 45

Recently, Kamal *et al* have reported[85] the dethioacetalization reaction by employing $FeCl_3{\cdot}6H_2O$ under mild conditions. They have also demonstrated that their protocol can be applied for the synthesis of DNA-interactive pyrrolo[2.1-c][1,4]benzodiazpine (PBD), which is known as antitumour antibiotics, as shown in scheme 46.

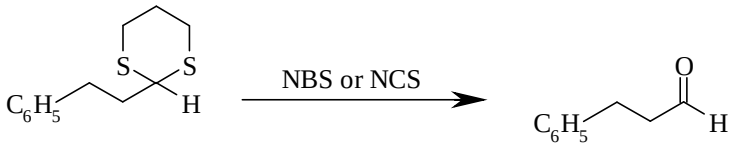


154 **155**

Scheme 46

Similarly, Corey and Erickson have described[86] the oxidative cleavage of dithioacetals by employing *N*-bromo- or *N*-chlorosuccinimide to the corresponding carbonyl compounds as depicted in scheme 47. The use of *N*-bromo- or *N*-chlorosuccinimide with silver ion has some advantages for the cleavages of unsaturated dithianes because of olefins are

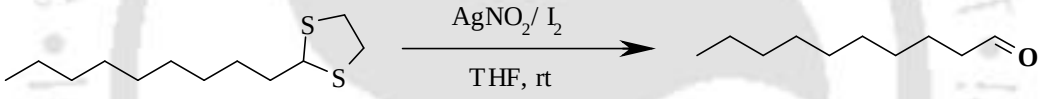
unaffected during reaction conditions. Sometimes 2,6-lutidine and 2,4,6-collidine are also employed to buffer the reagents in applications to acid sensitive substrates. However, this method has drawback such as it requires an excess amount expensive silver.



156 **157**

Scheme 47

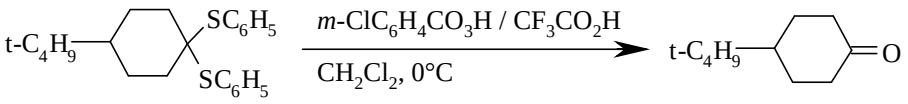
In the similar manner, Node *et al* have reported[87] the deprotection of dithioacetals into the corresponding carbonyl compounds by employing silver nitrite and iodine in THF at room temperature as shown in scheme 48. They have proposed that iodonium ion is responsible for hydrolysis, which is generated from iodine assisted by silver salts. The main drawback that it also eventually requires highly expensive silver salts.



118 **158**

Scheme 48

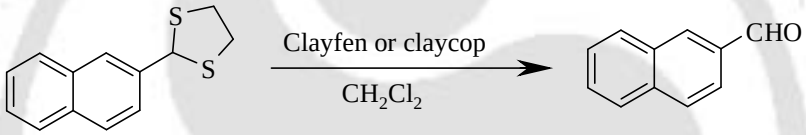
Likewise, a convenient and mild method for the regeneration of carbonyl compounds from their diphenyl- and diethyl dithioacetal derivatives was reported[88] by Cossy using a mixture of 2 equivalent amount of trifluoroacetic acid and 1.5 equivalent amount of 3-chloroperbenzoic acid at ice-bath temperature in dichloromethane as depicted in scheme 49. This protocol has some disadvantages such as 1,3-dithiane derivative of cyclododecanone did not undergo cleavage to the parent ketone under the reaction conditions. In addition, other protecting groups such TBS and trityl may not survive during experimental conditions because of trifluoroacetic acid.



159 **160**

Scheme 49

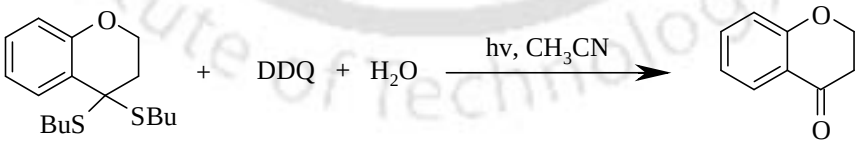
Cornelis and Laszlo group have also shown[89] the use of clay-supported metal nitrates such as clay-supported ferric nitrate (clayfen) or clay supported cupric nitrate (claycop) for the cleavage of dithioacetals to the corresponding carbonyl compounds as represented in scheme 50. A wide variety of dithioacetals are cleaved under the reaction conditions. It has been proposed that clayfen or claycop released NO^+, which is the active source for cleavage of dithioacetals. However, it is difficult to separate out the by-product makes the method inconvenient for general purpose.



161 **162**

Scheme 50

Sankararaman and Mathew have reported[90] the photochemical and thermal deprotection of thioacetals and ketals in acetonitrile solvent using DDQ as oxidant as represented in scheme 51.



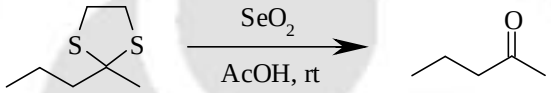
163 **164**

Scheme 51

Later on, Tanemura and his group have also investigated[91] the deprotection of dithioacetals by using DDQ in CH_3CN-H_2O. The main draw back is unwanted side product thioester is formed particularly in the cleavage of 1,3-dithiane derivative bearing

electron-donating group on the benzene ring. In addition, the reactions of 1,3-dithiolanes with DDQ are very slow and also provided poor yield. Moreover, in case of aliphatic 1,3-dithiane derivatives, many unidentified products are obtained with the parent aldehyde. Furthermore, the hydrolysis was unsuccessful for aliphatic and aromatic 1,3-dithiolanes derivatives by this method.

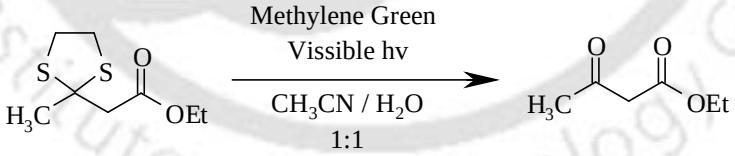
Haroutounian have reported[92] that selenium dioxide can be used as oxidizing reagent for cleavage of 1,3-dithiolanes to the corresponding carbonyl compounds in acetic acid as solvent at room temperature. Various dithioacetal derivatives containing benzylic and acetate groups are smoothly hydrolyzed without affecting them under the reaction conditions as shown in scheme 52. However, use of excess acid may cause cleavage of sensitive protective groups. In addition, selenium dioxide is highly toxic.



165 **166**

Scheme 52

By photochemically, Epling and Wang have reported[93] the cleavage of dithioacetal particularly 1,3-dithiolane or 1,3-dithiane derivatives to the aldehydes or ketones using methylene green as sensitizer in the presence of visible light as shown in scheme 53. By applying this method

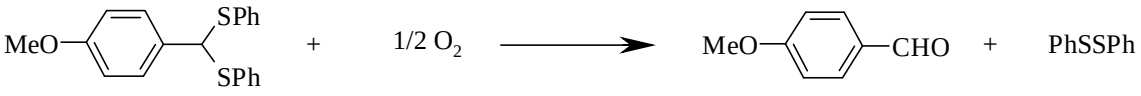


167 **168**

Scheme 53

By involving oxidizing strategy, Komatsu and Suzuki have reported[94] the deprotection of dithioacetals with air in the presence of a catalytic amount of bismuth(II) nitrate pentahydrate at room temperature to the original carbonyl compounds. They have proposed that molecular oxygen is responsible for the deprotection of dithioacetals

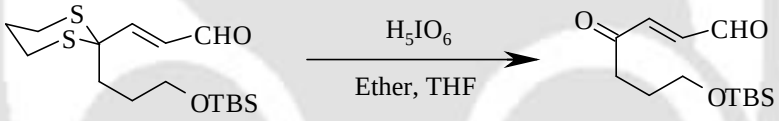
because the same reaction is failure while it was carried out under argon atmosphere without using air. This idea was supported by the formation of disulfide as another major products as represented in scheme 54.



102 **65**

Scheme 54

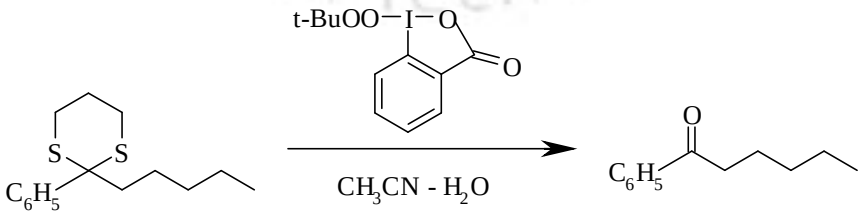
A noble method for deblocking of dithioacetals to the corresponding carbonyl compounds using periodic acid under non-aqueous medium has been demonstrated by Rokach and his group.[95] This method is applicable for cleavage of dithioacetals containing sensitive functional groups such as isopropylidene, TBS, TBDPS ethers, benzoyl, amide, dienyl ester, isomerizable double bonds as depicted in scheme 55. The main drawback is requirement of 2 equivalent of periodic acid for 1 equivalent of the substrate.



169 **170**

Scheme 55

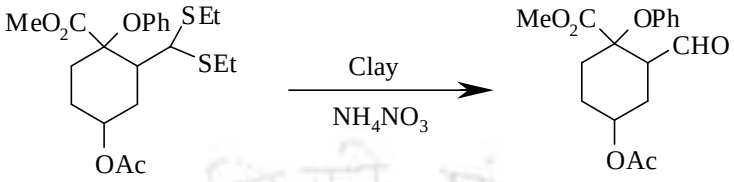
Ochiai *et al* have shown[96] that dithioacetals can be hydrolyzed to the parent carbonyl compounds using 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1H)-one in acetonitrile-water, as shown in scheme 56.



171 **172**

Scheme 56

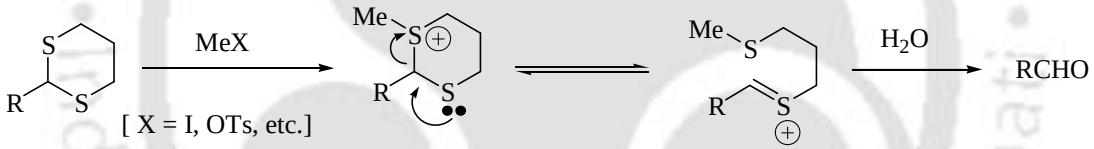
Meshram *et al* have shown[97] the cleavage of dithioacetals to the corresponding carbonyl compounds under mild conditions using ammonium nitrate supported in clay. Esters and ethers groups are stable under the reaction conditions, as represented in scheme 57. Unfortunately, the method was failure to deprotect thioketals selectively in the presence of an acetonide group.



173 **174**

Scheme 57

The third way, the cleaveage of dithioacetals or dithioketals to the corresponding carbonyl compounds can over come by alkylation with a good electrophilic reagent such as methyl iodide followed by hydrolysis as shown in scheme 58.

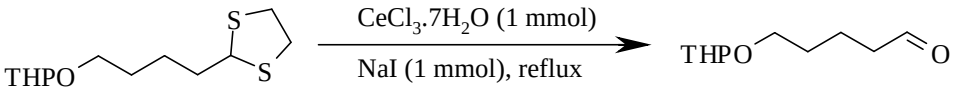


Scheme 58

By using one of the ideas, several other methods have been developed over the years for hydrolysis of dithioacetals or dithioketals to the corresponding carbonyl compounds, which has been compiled in 1999.[98]

By the way, some more methods have been devised by using various non-metallic reagents having electrophilic property. Very recently, Jadav and his group reported[99] the selective hydrolysis of dithioacetals into the corresponding carbonyl compounds by employing a combination of cerium(III) chloride and NaI in acetonitrile under refluxing conditions as depicted in scheme 59. This method is highly chemoselective for cleavage of dithioacetals without affecting benzylic double bonds as well as highly acid sensitive functional groups such as prenyl, THP and MOM groups. However, the disadvantages of

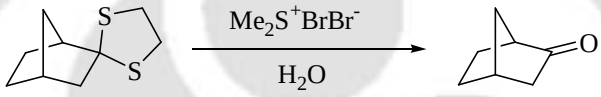
this procedure are harsh reaction conditions and involvement of highly expensive cerium salts.



175 **176**

Scheme 59

By using non-metallic electrophilic reagent such as bromodimethylsulfonium bromide, Olah and his group reported[100] the cleavage of the dithioacetals to the corresponding carbonyl compounds as shown in scheme 60.

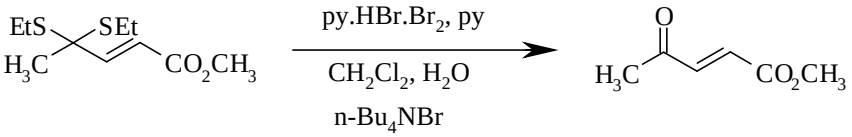


177 **178**

Scheme 60

The advantage of the method is that no brominations occur at the aromatic ring or at the α position to the keto group. On the other hand, the disadvantages of the reagent are: the reagent itself is hygroscopic in nature and also needs an excess amount of reagent. Again, Olah and his group reported[101] the cleavage of dithioacetals to the corresponding carbonyl compounds by involving *in situ* generation of bromodimethylsulfonium bromide from *t*-butyl bromide and dimethyl sulfoxide. The main drawbacks of this procedure are: the reaction has to be performed under inert atmosphere and heating conditions.

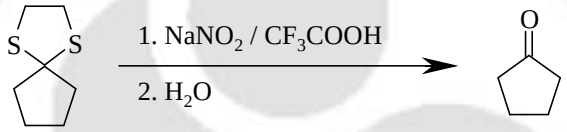
Similarly, O'Doherty and Bates have reported[102] the hydrolysis of thioacetals and thioketals to the corresponding carbonyl compounds by employing pyridinium hydrobromide perbromide and n-tetrabutylammonium bromide as a phase-transfer catalyst in dichloromethane and water system as shown in scheme 61. The significance of the method is neither double bond nor aromatic rings are brominated during reaction conditions.



179 **180**

Scheme 61

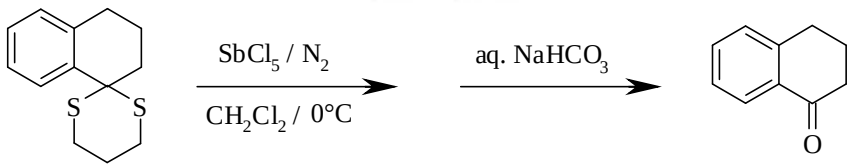
The disadvantage of this method is the requirement of hazardous reagents such as molecular bromine and HBr for the preparation of pyridinium hydrobromide perbromide. By generating electrophilic species NO^+, Olah and his group have reported[103] the cleavage of dithioacetals to the corresponding carbonyl compounds by employing either nitrosonium hydrogen sulfate or sodium nitrite/ sodium nitrate in combination with excess trifluoroacetic acid or nitronium tetrafluoroborate as represented in scheme 62.



147 **181**

Scheme 62

Kamata *et al* have reported[104] the transformation of 1,3-dithianes into the corresponding carbonyl compounds by treating with antimony pentachloride ($SbCl_5$) in CH_2Cl_2 under nitrogen atmosphere at 0 °C. Under the reaction conditions, dithianes are deprotected into the corresponding ketones, aldehydes, and ketoester in good to excellent yields as depicted in scheme 63. The reaction is initiated through a single electron transfer (SET) process to generate dithioacetal dications, which undergoes ultimately carbon-sulfur bond cleavage to afford the ring opening dications. Then, the intermediate is hydrolyzed by water to the corresponding carbonyl compounds.



182 **183**

Scheme 63

From the literature survey, it reveals to us that there is a scope to find out better synthetic protocols for dethioacetalization reactions.

Therefore, our main goal is to succeed whether non-metallic electrophilic species bromonium (Br^+) ion can be applied for cleavage of dithioacetals and dithioketals. With this main theme our plans are:

i) To find out better synthetic methodologies for deprotection of various dithioacetals to the corresponding carbonyl compounds by employing an environmentally benign reagent such organic ammonium tribromide (OATB), which was not exploited earlier.

ii) To investigate whether various metal peroxo oxidation of bromide ion to the bromonium can be extended further other valuable organic transformation such as hydrolysis of dithioacetals and dithioketals other than bromination reactions.

iii) To observe the compatibility of other protecting groups while finding out a better methodology.

iv) To execute a better methodology whether the hydrolysis of dithioacetals work under environmentally benign and catalytic manner, which was not studied so far in our knowledge.

PART II

(SECTION A)

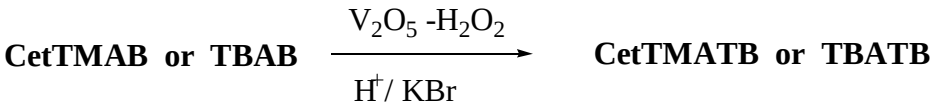
NEW SYNTHETIC METHOD FOR CLEAVAGE OF DITHIOACETALS BY EMPLOYING ORGANIC AMMONIUM TRIBROMIDE

RESULTS AND DISCUSSION

Results and Discussion

Dithioacetal and dithioketals are considered as attractive protecting groups for carbonyl functionalities in the total synthesis of complex natural products.[6] Lithium anions of cyclic dithioacetals particularly anions of 1,3-dithianes have been exploited as acyl carbanion equivalent in many synthetic sequences.[3] Out of the various dithioacetals, diethyldithioacetal is extensively used as a protecting group in carbohydrate chemistry to prepare acyclic derivatives of monosacaccharides.[105] Although a large number of methods have been developed for their regeneration of the carbonyl compounds from the corresponding dithioacetals as discussed in the previous chapter, still there is a need to find out better alternatives. The existing deprotection procedures are i) by using heavy metals[79,80] such as mercury or other heavy metals,[81-83] which are inherently toxic and expensive; ii) by employing Fe(III) salts;[84,85] iii) by utilizing some halonium ion sources.[86,87,100-102] Unfortunately, the methods particularly based on halonium ion sources have certain drawbacks such as use of a molar excess reagents NBS or NCS, also requires expensive silver salts in case of olefinic compounds and to obtain better yield; relatively drastic reaction conditions, long reaction time and inert atmosphere; the method involving pyridiniumhydrobromide perbromide requires pyridine, HBr and molecular bromine, which are toxic and hazardous. Therefore, it seems that there is still a greater scope for development of newer methods, which proceed under mild, economically cheaper and environmentally favorable conditions. Immediately, we perceived that organic ammonium tribromides, which is also a good source of bromonium ion, might be useful reagents for various organic transformations and can be exploited further for deprotection of dithioacetals or dithioketals to the parent carbonyl compounds. The organic ammonium tribromide, namely TBATB is well known in the literature for oxidative bromination.[106] It seems to us that organic ammonium tribromides have both electrophilic and oxidizing property.

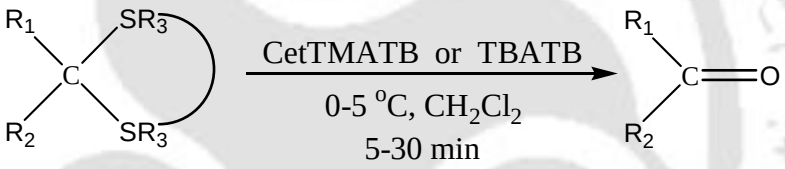
Recently, we have reported[107] the synthesis of various organic ammonium tribromides (OATB) as depicted in scheme 64, which can be applied for various bromination reactions.[108]



Scheme 64

We have also demonstrated that brominated products can be used for the synthesis of flavones and aurones derivatives.[109] These results stimulate us to study whether organic ammonium tribromide can be used for dethioacetalization reaction or not because it is not studied earlier.

In this chapter, we would like to discuss that organic ammonium tribromides (OATB) particularly tetrabutylammonium tribromide (TBATB) and cetyltrimethylammonium tribromide (CetMATB) are useful reagents for oxidative cleavage of dithioacetals as shown in scheme 65.



R_1 = alkyl or aryl or sugar residue,

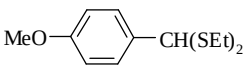
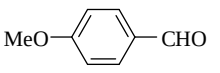
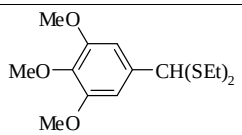
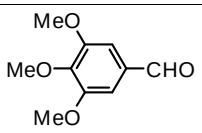
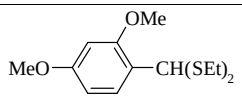
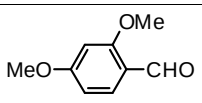
R_2 = H or alkyl, R_3 = Et, $-(CH_2)_3-$

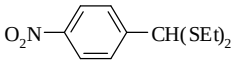
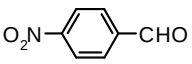
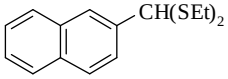
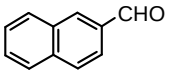
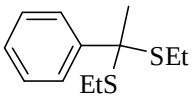
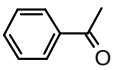
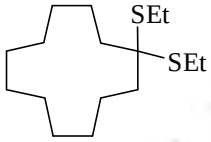
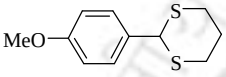
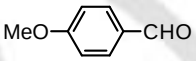
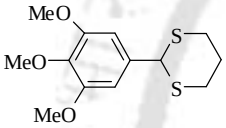
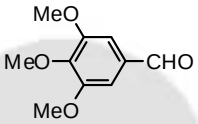
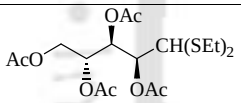
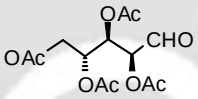
Scheme 65

The starting dithioacetals **34**, **38**, **101**, **111**, **132**, **135**, **184**, **185**, **186**, **187** and **188** were prepared for our investigation by the reaction of the respective carbonyl compounds with ethanethiol or 1,3-propanedithiol in the presence of boron trifluoride etherate[22] or conc. hydrochloric acid,[21] by following literature procedures. The characterization data of these compounds are given in the experimental section. But, some compounds data such as compound **34**, **101**, **111**, **132** and **135** are already mentioned in the previous chapter. ^{1}H NMR and ^{13}C NMR spectra of compounds **132**, **188** and **135** are shown in figures **27-32** respectively, for confirmation of their structures. We have also found later on that all the dithioacetals and dithioketals can be much easily prepared by our methods.[110-112]

After preparation of starting materials, we are very keen to find out an appropriate reaction conditions for deprotection of dithioacetals. After several trials, we have found out a suitable reaction condition. When a diethyl dithioacetal of 4-methoxybenzaldehyde (**101**) was treated with cetyltrimethylammonium tribromide (CetTMATB, Method A) in dichloromethane at 0–5 ^{o}C, it smoothly converted to the 4-methoxybenzaldehye (**65**) within 5 min. The product **65** was characterized by recording IR spectrum, ^{1}H NMR and elemental analysis, which are given in the experimental section. It was exactly matched with the spectra of 4-methoxybenzaldehye. This result further inspired us whether other organic ammonium tribromide such as TBATB can be used for similar transformation or not. Then, the compound **101** was also treated with tetrabutylammonium tribromide (TBATB, Method B) under identical reaction conditions. The reaction was completed 30 min. The product **65** was identical with the product obtained by CetTMATB method. Similarly, diethyl dithioacetal of 3,4,5-trimethoxybenzaldehyde was converted to the corresponding 3,4,5-trimethoxy-benzaldehyde without any difficulty on treatment with either CetMATB or TBATB, respectively. Likewise, various acyclic diethyl dithioacetals **185**, **132**, **111**, **186**, **187**, **188**, **34**, **38** and **135** were hydrolyzed to the corresponding carbonyl compounds **190**, **191**, **162**, **85**, **192**, **193**, **65**, **189**, **and 194** respectively, on treatment with either CetTMATB or TBATB. The ^{1}H NMR spectra of **191**, **193** and **194** are shown in the figures **33-35** for confirmation of the structures. The results are summarized in Table 4. The products are compared with the authentic compound by co-IR, mix melting point as well as characterized by ^{1}H NMR, and elemental analyses. Interestingly, we have not observed any aromatic ring bromination or any other bromination by this procedure.

Table 4. Cleavage of various dithioacetals by organic ammonium tribromides

Substrate	Substrate No.	Method	Time in min	Product	Product No.	Yield (%)
	**101**	A B	5 30		**65**	93 94
	**184**	A B	15 5		**189**	95 96
	**185**	A B	5 5		**190**	85 80

	**132**	A B	30 30		**191**	90 88
	**111**	A B	5 15		**162**	95 94
	**186**	A B	5 2		**85**	78 95
$CH_3(CH_2)_{10}CH(SEt)_2$	**187**	A B	30 30	$CH_3(CH_2)_{10}CHO$	**192**	85 82
	**188**	A B	15 15		**193**	75 70
	**34**	A B	30 25		**65**	88 91
	**38**	A B	30 30		**189**	82 86
	**135**	A B	30 30		**194**	68 65

In conclusion, we have devised a simple and useful method for the regeneration of parent carbonyl compounds from the corresponding dithioacetals by employing cetyltrimethyl-ammonium tribromide (CetTMATB) or tetrabutylammonium tribromide (TBATB) under very mild reaction conditions. Due to its operational simplicity, generality and efficacy, this method is expected to have wider applicability for the cleavage of dithioacetals. A similar cleavage also might be possible by using other organic ammonium tribromides as well as other dithioacetals, which is under investigation.

PART II

(SECTION A)

NEW SYNTHETIC METHOD FOR CLEAVAGE OF DITHIOACETALS BY EMPLOYING ORGANIC AMMONIUM TRIBROMIDES

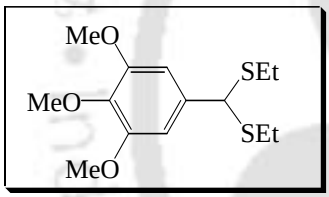
EXPERIMENTALS

Experimental

Genaral procedure for thioacetalisation of carbonyl compounds by boron trifluoride etherate method:

A mixture of aldehyde or ketone (5 mmol) and ethanethiol (12.5 mmol) or 1,3-propanedithiol (5.5 mmol) was taken in 10 ml dichloromethane. To the above reaction mixture, 0.13 ml of boron trifluoride etherate ($BF_3{\cdot}OEt_2$) was added slowly. The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, it was neutralized with saturated sodium bicarbonate solution. Then, it was extracted with 50 ml of dichloromethane and the organic layer was washed with water and dried over anhydrous sodium sulfate. After concentration of organic extract provided a crude residue, which was finally passed through a silica gel column to get the desired diethyl dithioacetals derivatives.

3,4,5-Trimethoxybenzaldehyde diethyldithioacetal (184):



Nature: Viscous liquid

Yield: 90%

R_f: 0.72 (Hexane/EtOAc = 9:1)

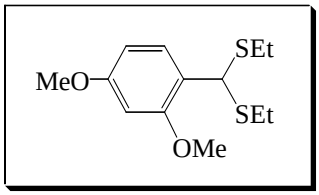
IR (Neat): cm^{-1} 2964, 2930, 2832, 1589, 1504, 1457, 1418, 1375, 1328, 1240, 1182, 1127,1007

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, 6H, *J* = 7.08 Hz, 2 x -CH_2CH_3), 2.54-2.66 (m, 4H, 2 x -SCH_2CH_3), 3.84 (s, 3H, -OCH_3), 3.88 (s, 6H, 2 x -OCH_3), 4.87 (s, 1H, -ArCH-), 6.70 (s, 2H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12 (2C), 26.29 (2C), 52.71, 55.91 (2C), 60.60, 104.37 (2C), 135.92, 137.16, 152.93 (2C)

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{22}O_3S_2$	C 55.59	C 55.67
302.46	H 7.33	H 7.21
	S 21.20	S 21.15

2à,4à-Dimethoxybenzaldehyde diethyldithioacetal (185) :



Nature: Viscous liquid

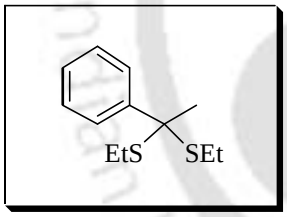
Yield: 80%

R_f: 0.70 (Hexane/EtOAc = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.2 (t, 6H, *J* = 7.32 Hz, 2x- SCH_2CH_3), 2.47-2.61 (m, 4H, 2x -SCH_2-), 3.78 (s, 3H, -OCH_3) 3.81(s, 3H, -OCH_3), 5.42 (s, 1H, ArH), 6.42 (d, 1H, *J* = 2.2 Hz, ArH), 6.48 (dd, 1H, *J* = 8.52 Hz, *J* = 8.2 Hz, ArH), 7.48 (d, 1H, *J* = 8.56Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{16}O_2S_2$	C 55.35	C 55.24
260.42	H 7.74	H 7.83
	S 24.63	S 24.56

Acetophenone diethyldithioacetal (186):



Nature: Viscous liquid

Yield: 76%

R_f: 0.96 (Hexane/AcOEt = 9.9: 0.1)

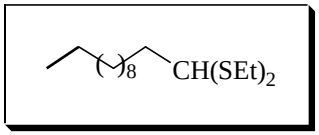
IR (Neat): cm^{-1} 2968, 2927, 2868, 1595, 1489, 1445, 1373, 1263, 1202, 1063, 975

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, 6H, *J* = 7.6 Hz, 2x -CH_2CH_3), 2.036 (s, 3H, -CH_3), 2.52 (q, 4H, *J* = 7.6 Hz -SCH_2-), 7.23-7.37 (m, 3H, ArH), 7.71 (d, 2H, *J* = 7.04 Hz, ArH)

^{13}C-NMR (400 MHz, $CDCl_3$): δ 24.56, 27.98 (2C), 32.67, 53.88, 126.95, 127.67 (2C).

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{18}S_2$	C 63.66	C 63.78
226.39	H 8.01	H 8.13
	S 28.33	S 28.21

Diethyldithioacetal of dodacanal (187):



Nature: Syrupy liquid

Yield: 65%

R_f: 0.89 (Hexane)

IR (Neat): cm^{-1} 2930, 2863, 1460, 1378,1265

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.6 Hz, $-CH_3$), 1.24-1.27 (m, 24H, $-CH_2-$ and 2x $-SCH_2CH_3$), 1.76-1.81 (m, 2H, $-CH_2-$), 2.54-2.73 (m, 4H, 2x $-SCH_2CH_3$), 3.78 (t, 1H, *J* = 7.08 Hz, -SCHS-)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.08, 14.47, 22.66, 24.00, 24.06 (2C), 27.46, 29.14, 29.32, 29.44, 29.58 (3C), 31.87, 36.04, 51.40

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{34}S_2$	C 66.13	C 66.29
290.58	H 11.79	H 11.58
	S 22.07	S 21.99

Cyclododecanone diethyldithioacetal (188):

Nature: White solid

Yield: 85%

R_f: 0.93 (Hexane/AcOEt = 9.8: 0.2)

Melting point: 43.6 °C

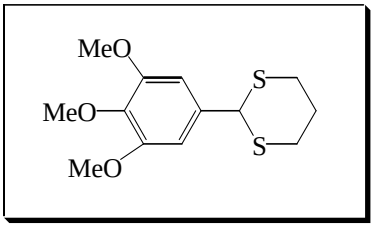
IR (KBr): cm^{-1} 2939, 2863, 1454, 1372, 1265, 1239, 1050, 978, 763

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, 6H, *J* = 7.6 Hz, 2x $-CH_2CH_3$), 1.33-1.36 (m, 14H, $-CH_2-$), 1.46-1.48 (m, 4H, $-CH_2-$) 1.66-1.70 (m, 4H, $-CH_2-$), 2.56- 2.63 (q, 4H, *J* = 7.56 Hz $-SCH_2CH_3$)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.74 (2C), 20.22 (2C), 22.26 (2C), 22.46 (2C), 22.57 (2C), 25.90, 26.20 (2C), 33.40 (2C), 64.84

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{32}S_2$	C 66.60	C 66.37
288.56	H 11.17	H 11.20
	S 22.22	S 22.15

2-[3,4â 5â-Trimethoxyphenyl]-1,3-dithiane (38):



Nature: White solid

Yield: 90%

R_f: 0.35 (Hexane/AcOEt = 9:1)

Melting Point: 94 °C

IR (Neat): cm^{-1} 1585, 1503,1128

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89-1.97 (m, 1H, - SCH_2CHCH_2S-), 2.13-2.18 (m, 1H, -SCH_2CHCH_2S-), 2.87-3.09 (m, 4H, -SCH_2-), 3.83 (s, 3H, -OCH_3), 3.86 (s, 6H, -2x -OCH_3), 5.12 (s, 1H, ArCH-), 6.71 (s, 2H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}O_3S_2$	C 64.15	C 64.27
243.42	H 7.45	H 7.27
	S 26.35	S 26.13

Preparation of diethyl dithioacetal 2,3,4,5-Tetra-O-acetyl-D-arabinose (135)

A mixture of D-arabinose (10.78 g, 71.8 mmol) and ethanethiol 50 ml was treated with 37% HCl (excess) and kept for vigorous stirring 30 minutes on a magnetic stirrer. The excess ethanethiol was removed in rotavapor and the residue was dried over vacuum pump. Then, the crude product was kept for acetylation with acetic anhydride in pyridine. After stirring it overnight, pyridine was removed by co-evaporation with toluene. The pure acetylated product was obtained by purification on a silica gel column. The characterization data is given in the chapter **I** of part **II** in sec **B** on page 60.

Preparation of Cetyltrimethylammonium Tribromide (CetTMATB)

An amount of 0.06 g (0.33 mmol) vanadium pentoxide (V_2O_5) was added to 5 ml (44.15 mmol) 30% hydrogen peroxide (H_2O_2) taken in a pre-cooled 100 ml beaker. The reaction mixture was stirred at 0-5 °C in an ice bath till the solution became a clear reddish-brown. It was diluted with 110 ml of water and poured into a 500 ml beaker. To it was added a solution of 4.89 g (41.07 mmol) of potassium bromide

(KBr) and 5g (13.74 mmol) of cetyltrimethylammonium bromide (CTMAB) dissolved in 150 ml of water and stirred at ice bath temperature. Then, 25 ml of 1M sulfuric acid (H_2SO_4) was added in small portions to the above solution. The reaction mixture was stirred another 2 h at the same temperature until all yellow crystals are precipitated out. The product was isolated by suction filtration using Whatman 1 filter paper. The compound was then dried in a vacuum using anhydrous cacium chloride ($CaCl_2$) as desiccant. The product was obtained as bright yellow microcrystals. The yield of the product was 5.52 g (96 %). M.p. 87-88 °C

Preparation of Tetrabutylammonium Tribromide (TBATB)

0.05 g (0.27 mmol) of vanadium pentoxide (V_2O_5) was added to 5 ml (44.12 mmol) of 30% Hydrogen peroxide (H_2O_2) taken in a pre-cooled 250 ml beaker. The reaction mixture was stirred at the same ice-bath temperature till the solution became a clear reddish-brown. To it was added a solution of 3.7 g (31.09 mmol) of potassium bromide (KBr) and 5 g (15.53 mmol) of tetrabutylammonium bromide (TBAB) dissolved in 35 ml of water. To this, 50 ml of 1M sulfuric acid was added in small portions. Magnetic stirring was continued for a further period of 2 h at ice bath temperature. The product was isolated by filtration using Whatman 1 filter paper. The compound was then dried in vacuum. The yield of the product was 7.4 g (99.5%). M.p. 75 °C (Lit. m. p. 76°C).

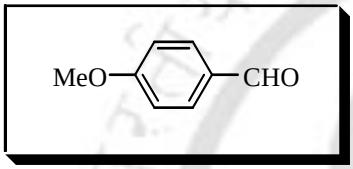
A typical procedure for cleavage of dithioacetals: Method A

To a well stirred solution of diethyldithioacetal (0.3 mmol) in CH_2Cl_2 (7 ml) at 0-5°C was added 0.157 g (0.3 mmol) of cetyltrimethylammonium tribromide (CetTMATB) and stirring was continued at the same temperature. The reaction was completed within 5-30 min. as monitored by TLC. The reaction mixture was quenched by adding a 5% solution of sodium metabisulfite (1 × 10 ml), and finally extracted with CH_2Cl_2 (2 × 15 ml). The organic layers were washed with water (2 × 20 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crude product, which was finally purified by column chromatography on silica gel (hexane/EtOAc = 9:1).

Method B

To a stirred solution of diethyldithioacetal (0.83 mmol) in CH_2Cl_2 (7 ml) at 0-5°C was added 0.4 g (0.83 mmol) of tetrabutylammonium tribromide (TBATB). The reaction was completed within 5-30 min, which was monitored by TLC. Usual work-up and purification procedures were followed to get the desired carbonyl compounds.

4-Methoxybenzaldehyde (65):



Nature: Light yellow liquid

Yield: Method A, 93%; **Method B,** 94%

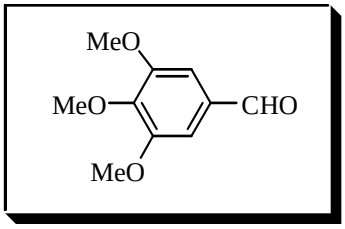
IR (**Neat**)**:** cm^{-1} 2938, 2839, 1684, 1599, 1260, 1161, 834

^{1}H NMR (**400 MHz, $CDCl_3$**)**:** δ 3.89 (s, 3H, -OCH_3), 7.0 (d, 2H, *J* = 8.52 Hz, ArH), 7.84 (d, 2H, *J* = 8.32 Hz, ArH), 9.88 (s, 1H, -CHO)

^{13}C NMR (**100 MHz, $CDCl_3$**): δ 55.54, 114.0(2C), 129.84, 132.17 (2C), 164.55, 190.85

Elemental Analysis	**Calculated**	**Found**
$C_8H_8O_2$	C 70.58	C 70.42
136.15	H 5.92	H 5.85

3,4,5-Trimethoxybenzaldehyde (189):



Nature: White solid

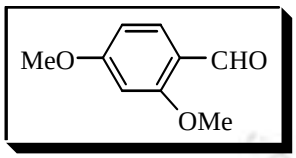
Yield: Method A: 95%; **Method B:** 96%

Melting point: 73 °C [Lit. 73-75 °C]

^{1}H NMR (**400 MHz, $CDCl_3$**)**:** δ 3.94 (s, 9H, 3x-OCH_3), 7.14 (s, 2H, ArH), 9.87(s, 1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}O_4$	C 61.22	C 61.34
196.202	H 6.16	H 6.13

2, 4-Dimethoxybenzaldehyde (190):



Nature: White solid

Yield: Method A, 85%; **Method B,** 80%

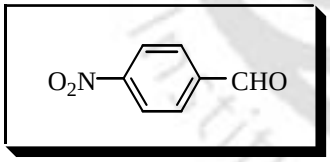
Melting Point: 41-43°C [lit. Mp. 42-45°C]

IR (**Neat):** cm^{-1} 1684, 1592, 1331, 1234,1131

^{1}H NMR (**300 MHz, $CDCl_3$):** δ 3.88 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 6.45 (d, 1H, *J* = 1.91 Hz, ArH), 6.55 (dd, 1H, *J* = 1.62 Hz, *J* = 8.62 Hz, ArH), 7.81 (d, 1H, *J* = 8.67 Hz, ArH), 10.29 (s, 1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_9H_{10}O_3$	C 65.05	C 65.23
166.18	H 6.06	H 6.17

4-Nitrobenzaldehyde (191):



Nature: Light yellow solid

Yield: Method A, 90%**; Method B,** 88%

Melting point: 102-105°C [Lit. 105-108°C]

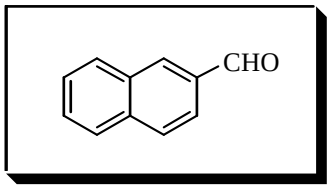
IR (**Neat):** cm^{-1} 1710, 1609, 1541, 1352, 1203

^{1}H NMR (**400 MHz, $CDCl_3$**): δ 8.08 (d, 2H, *J* = 8.67 Hz, ArH), 8.40 (d, 2H, *J* = 8.61 Hz, ArH), 10.17(s, 1H, -CHO)

^{13}C-NMR (400 MHz, $CDCl_3$): δ 124.29 (2C), 130.47(2C), 140.00(2C), 190.28

Elemental Analysis	**Calculated**	**Found**
$C_7H_5O_3N$	C 55.64	C 55.49
151.12	H 3.33	H 3.23
	N 9.27	N 9.13

2- Napthaldehyde (162):



Nature: White solid

Yield: Method A, 95%**; Method B,** 94%

R_f: 0.40 (Hexane/AcOEt = 9.5: 0.5)

Melting Point: 59-62°C

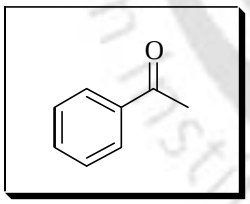
IR (KBr): cm^{-1} 2828, 1692, 1342,1164

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.66 (m, 2H, ArH), 7.89-8.01 (m, 4H, ArH), 8.34 (s, 1H, ArH), 10.15 (s, 1H, -CHO)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 122.69, 127.05, 128.04, 129.07 (2C), 129.49, 132.57, 134.03, 134.58, 136.40, 192.29

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_8O$	C 84.59	C 84.41
156.18	H 5.16	H 5.11

Acetophenone (85):



Nature: Liquid

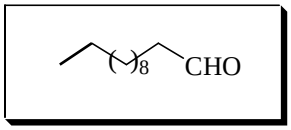
Yield: Method A, 78%; **Method B,** 95%

IR (Neat): cm^{-1} 1690, 1598, 1460, 1362,1270.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.61 (s, 3H, $-CH_3$), 7.45-7.60 (m, 3H, ArH), 7.96 (d, 2H, *J* = 7.47 Hz, ArH).

Elemental Analysis	**Calculated**	**Found**
C_8H_8O	C 79.97	C 79.78
120.15	H 6.71	H 6.85

Dodecyl Aldehyde (192):



Nature: Colourless liquid

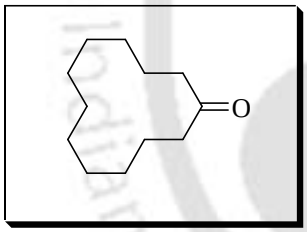
Yield: Method A, 78%; **Method B,** 95%

IR (Neat): cm^{-1} 2930, 2863, 1737, 1460

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 6.9 Hz -CH_3), 1.05-1.55 (bs, 18H, -CH_2-), 2.20-2.70 (m, 2H, -CH_2-), 9.80 (t, 1H, *J* = 6.6 Hz, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{24}O$	C 78.20	C 78.01
184.32	H 13.12	H 13.04

Cyclododecanone (193):



Nature: White solid

Yield: Method A, 75%; **Method B,** 70%

Melting Point: 59-61°C [Lit. Mp. 59-61°C]

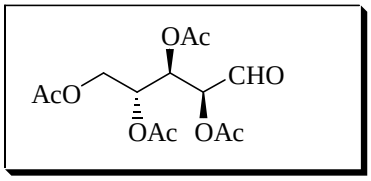
IR (KBr): cm^{-1} 1716, 1475, 1444, 1209, 732

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25-1.31 (m, 14H, -CH_2-), 1.71 (quin, 4H, *J* = 6.1 Hz, 2× -CH_2-), 2.47 (t, 4H, *J* = 6.3 Hz, 2× -CH_2-)

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.25, 22.50 (2C), 24.15 (2C), 24.53 (2C), 24.68 (2C), 40.32 (2C), 212.95

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{22}O$	C 79.06	C 79.32
182.31	H 12.16	H 12.23

2,3,4,5-Tetra-O-acetyl-D-arabinose (194):



Nature: White solid

Yield: Method A, 68%; **Method B,** 65%

R_f: 0.30 (Hexane/AcOEt = 6.5: 3.5)

IR (KBr): 2950, 2879, 1762, 1731, 1373, 1276, 1235, 1214, 1132, 1066, 1035, 927, 856

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 9H, -$COCH_3$), 2.20 (s, 3H, -$COCH_3$), 4.19 (dd, 1H, *J* = 4.6 Hz, *J* = 12.6 Hz, H-5′), 4.33 (dd, 1H, *J* = 2.6 Hz, *J* = 12.6 Hz, H-5), 5.27 (m, 1H, H-4), 5.39 (d, 1H, *J* = 2.2 Hz, H-2), 5.69 (dd, 1H, *J* = 2.1 Hz, *J* = 8.8 Hz, H-3), 9.48 (s, 1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}O_9$	C 49.06	C 48.88
318.28	H 5.70	H 5.63

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
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PART II

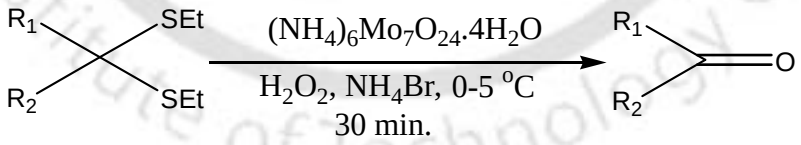
(SECTION B)

NEW SYNTHETIC PROTOCOL FOR HYDROLYSIS OF DITHIOACETALS BY USING OXIDATION OF AMMONIUM BROMIDE PROMOTED BY AMMONIUM HEPTAMOLY-DATE AND HYDROGEN PEROXIDE

RESULTS AND DISCUSSION

Results and Discussion

Though we have demonstrated that various organic tribromides can be used for cleavage of dithioacetals derivatives to the corresponding carbonyl compounds. However, this method has several drawbacks such as i) they have to prepare prior to use although they are quite stable for a long time, ii) they are relatively expensive and iii) require large amount of reagent in weight for deprotection of per mmol of the dithioacetals or dithioketals because of high molecular weight of the organic ammonium tribromides. We have found in literature[113] that ammonium molybdate, catalytic amount perchloric acid and hydrogen peroxide can oxidize bromide ion to the bromonium ion. Then, we thought that reactive bromonium ion might be useful species, which can be captured in the reaction medium for deprotection of dithioacetals. In view of practical and environmental[70] demands, we found significant advantage in using a nontoxic and inexpensive metal salt such as ammonium heptamolybdate instead of heavy metals such as mercury(II) salts. Recently we have also shown[114] that bromination reactions can also be achieved by generating *in situ* the active brominating agent tribromide (Br_3^-) on reaction with V_2O_5, H_2O_2 and tetrabutylammonium bromide (TBAB). This observation tempted us that *in situ* generated tribromide might reacts with dithioacetals for deprotection. In this chapter, we would like to discuss the oxidative cleavage of a various diethyldithioacetals into the parent carbonyl compounds using ammonium bromide in presence of ammonium heptamolybdate, catalytic amount perchloric acid and excess amount of hydrogen peroxide as shown in scheme 66.



R_1 = aryl / alkyl/ sugar residue, R_2 = H

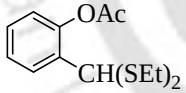
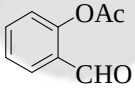
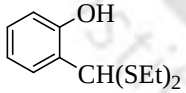
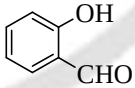
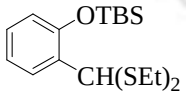
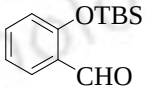
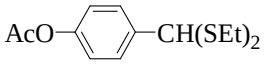
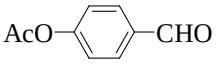
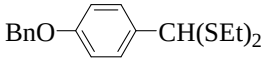
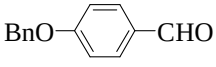
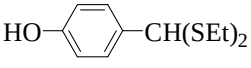
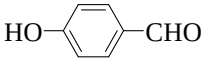
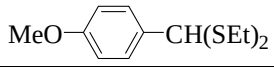
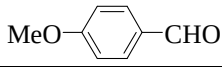
R_1 = aryl, R_2 = alkyl

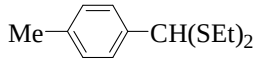
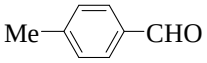
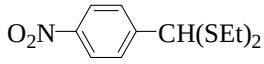
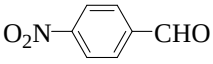
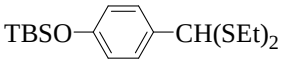
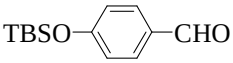
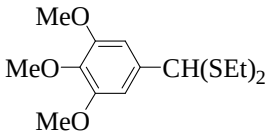
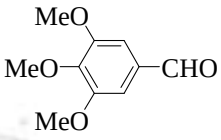
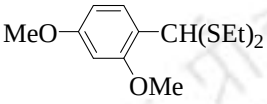
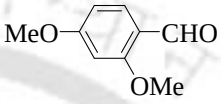
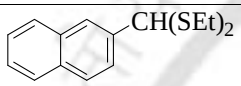
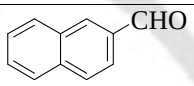
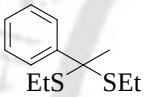
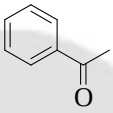
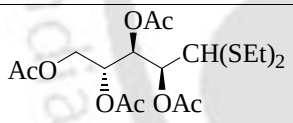
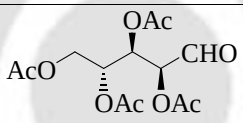
Scheme 66

The starting diethyldithioacetals **195**, **196**, **197**, **198**, **199**, **200**, **101**, **201**, **132**, **202**, **184**, **185**, **111**, **186**, **187** and **135** were prepared by the reaction of carbonyl compounds with

ethanethiol in presence of catalytic amount boron trifluoride etherate[22] or conc. hydrochloric acid,[21] using literature procedures as shown in Table 5. The characterization data of the compounds **195**, **196**, **198**, **199**, **200**, **201** and **202** are given in the experimental section. Next, we were interested to study whether dethioacetalization can be achieved as per our speculation or not. Various conditions were tried, a 1:6:0.2:10:0.05 substrate to ammonium bromide to ammonium heptamolybdate tetrahydrate to hydrogen peroxide to perchloric acid stiochiometry was found to be optimal (ostensibly to speed conversions to products with high yields) and that CH_2Cl_2/H_2O solvent gave good yields. The reaction is completed within a short period. The results are summarized in Table 5. The products are compared with the authentic compound as well as characterized by spectroscopic techniques. Interestingly, we have not observed any aromatic ring bromination or any other bromination by this procedure. The characterization data of the hydrolyzed product are given in the experimental section except those are mentioned in the previous chapter.

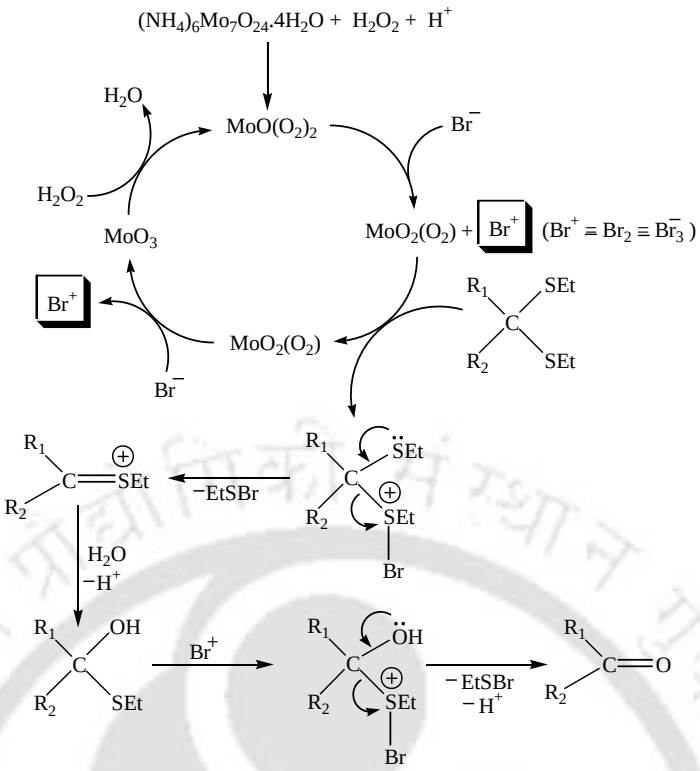
Table 5: Cleavage of various diethyldithioacetals by ammonium bromide in presence of ammonium heptamolybdate, H_2O_2, and perchloric acid

Substrate	Substrate No.	Time in Min	Product[a]	Product No.	% yield[b]
	**195**	65		**203**	84
	**196**	60		**82**	82
	**197**	55		**204**	85
	**198**	65		**205**	75
	**199**	60		**206**	88
	**200**	55		**207**	80
	**101**	40		**65**	85

	**201**	35		**208**	83
	**132**	65		**191**	77
	**202**	50		**209**	75
	**184**	35		**189**	80
	**185**	50		**190**	82
	**111**	40		**162**	84
	**186**	35		**85**	70
$CH_3(CH_2)_{10}CH(SEt)_2$	**187**	40	$CH_3(CH_2)_{10}CHO$	**192**	60
	**135**	70		**194**	60

[a] Products have been characterized by comparing IR, NMR of the authentic samples.[b] Isolated yield.

The formation of the product can be explicable that ammonium heptamolybdate reacts with H_2O_2 in presence of catalytic amount perchloric acid to give diperoxomolybdate (VI), which oxidize the bromide (Br^-) to Br^+(which might also exist as Br_2 or Br_3^-). Then the reactive species Br^+ reacts with diethyldithioacetal to form bromosulfonium complex, which is hydrolyzed by water to hemithioacetal and finally to the parent carbonyl compounds as represented in scheme 67.



Scheme 67

In conclusion, we have devised a simple and useful method for the regeneration of parent carbonyl compounds from the corresponding diethyldithioacetals by employing ammonium bromide in presence of ammonium heptamolybdate, catalytic amount perchloric acid and H_2O_2 under a very mild and environmentally safer reaction conditions. Due to its operational simplicity, generality and efficacy, this method is expected to have wider applicability for the cleavage of diethyldithioacetals. A similar cleaveage also might be possible by using other organic ammonium bromides such as tetrabutylammonium bromide or cetyltrimethylammonium bromide as well as other dithioacetals, which is under investigation.

PART II

(SECTION B)

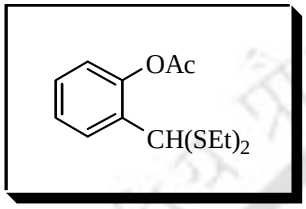
NEW SYNTHETIC PROTOCOL FOR HYDROLYSIS OF DITHIOACETALS BY USING OXIDATION OF AMMONIUM BROMIDE PROMOTED BY AMMONIUM HEPTAMOLYBDATE AND HYDROGEN PEROXIDE

EXPERIMENTALS

Experimental

The dithioacetals **195**, **196**, **198**, **199**, **200**, **201**, and **202** were prepared by following boron trifluoride etherate procedure as described in previous section A. Some of the substrates and their corresponding carbonyl compounds data are mentioned in the earlier section A in the experimental section.

2-Acetoxybenzaldehyde diethyldithioacetal (195):



Nature: Viscous liquid

Yield: 87%

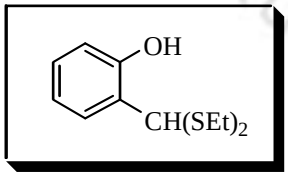
R_f: 0.78 (Hexane/AcOEt = 9.8: 0.2)

IR (Neat): cm^{-1} 2971, 2935, 1778, 1491, 1460, 1388, 1199, 1102, 927

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 6H, *J* = 7.2 Hz, 2× -SCH_2CH_3), 2.40 (s, 1H, -$OCOCH_3$), 2.55-2.63 (m, 4H, 2× -SCH_2CH_3), 5.16 (s, 1H, ArCH-), 7.11 (d, 1H, *J* = 8.0 Hz, ArH), 7.31-7.34 (m, 2H, ArH), 7.74 (d, 1H, *J* = 7.74 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}O_2S_2$	C 57.74	C 57.58
270.42	H 6.71	H 6.84
	S 23.72	S 23.53

2-Hydroxybenzaldehyde diethyldithioacetal (196):



Nature: Viscous liquid

Yield: 85%

R_f: 0.48 (Hexane/AcOEt = 9.9:0.1)

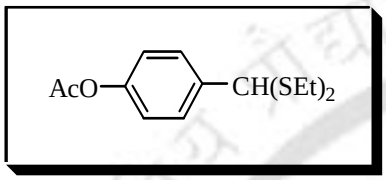
IR (Neat): cm^{-1} 3404, 2970, 2928, 2881, 1598, 1499, 1456, 1367, 1272, 1230, 1164, 1089, 758

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, 6H, *J* = 7.6 Hz, -SCH_2CH_3), 2.52-2.61 (m, 4H, 2× -SCH_2CH_3), 5.14 (s, 1H, ArCH-), 6.88 (t, 2H, *J* = 7.6 Hz, ArH), 6.99 (s, 1H, -OH), 7.2 (m, 2H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.18 (2C), 26.44 (2C), 49.13, 117.63, 120.31, 123.41, 129.40, 129.64, 154.88

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{16}OS_2$	C 57.85	C 57.72
228.38	H 8.21	H 8.29
	S 28.08	S 28.30

4-Acetoxybenzaldehyde diethyldithioacetal (198):



Nature: Viscous liquid

Yield: 87%

R_f: 0.75 (Hexane/AcOEt = 9.5: 0.5)

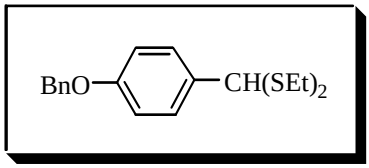
IR (Neat): cm^{-1} 2971, 2925, 1767, 1609, 1506, 1455, 1378, 1224, 1173, 1020, 912, 866, 764

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, 6H, *J* = 5.6 Hz, -CH_2CH_3), 2.29 (s, 3H, $OCOCH_3$), 2.52-2.59 (m, 4H, -S*CH_2*CH_3), 4.92 (s, 1H, ArCH-), 7.05 (d, 2H, *J* = 8.0 Hz, ArH), 7.45 (d, 2H, *J* = 8.8 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.25 (2C), 21.15, 26.21 (2C), 51.75, 121.54 (2C), 128.76 (2C), 137.99, 150.01, 169.32

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}O_2S_2$	C 57.74	C 57.49
270.42	H 6.71	H 6.81
	S 23.72	S 23.64

4-Benzyloxybenzaldehyde diethyldithioacetal (199):



Nature: Viscous liquid

Yield: 78%

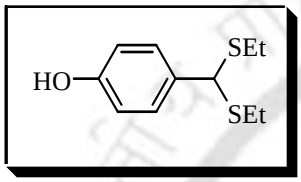
R_f: 0.84 (Hexane/AcOEt = 9.9: 0.1)

IR (Neat): cm^{-1} 2973, 2934, 1601, 1513, 1455, 1394, 1252, 1179, 1013, 848, 752

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, 6H, *J* = 7.32 Hz, 2x -SCH_2CH_3), 2.39-2.56 (m, 4H, 2x -SCH_2CH_3), 4.83 (s, 1H, ArCH-), 4.97 (s, 2H, -OCH_2Ph), 6.90 (d, 2H, *J* = 8.56 Hz, ArH), 7.23-7.36 (m, 7H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{18}H_{22}OS_2$	C 67.88	C 67.74
318.50	H 6.96	H 6.84
	S 20.14	S 20.28

4-Hydroxy diethyldithioacetal (200):



Nature: Viscous liquid

Yield: 78%

R_f: 0.64 (Hexane/AcOEt = 9:1)

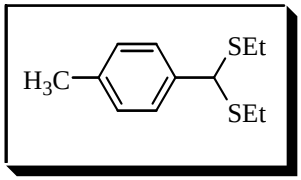
IR (Neat): cm^{-1} 3369, 2967, 2869,1605,1509, 1446,1374, 1262,1168, 1102, 1051

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, 6H, *J* = 7.56 Hz, 2x -SCH_2CH_3), 2.38-2.63 (m, 4H, 2x -SCH_2CH_3), 4.90 (s, 1H, ArCH-), 6.16 (bs, 1H, -OH), 6.77 (d, 2H, *J* = 8.52 Hz, ArH), 7.29 (d, 2H, *J* = 8.52 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15, 14.20, 26.21 (2C), 51.64, 115.33 (2C), 128.93 (2C), 132.32, 155.10

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{16}OS_2$	C 57.85	C 57.75
228.38	H 7.06	H 7.20
	S 28.08	S 28.37

4-Methylbenzaldehyde diethyldithioacetal (201):



Nature: Viscous liquid

Yield: 78%

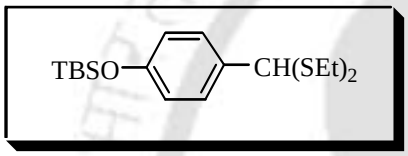
IR (Neat): cm^{-1} 2966, 2923,1509, 1449, 1264

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 1.22 (t, 6H, *J* = 7.32 Hz, 2x–SCH_2CH_3). 2.33 (s, 3H, -CH_3), 2.47-2.64 (m, 4H, 2x -SCH_2-), 4.90 (s, 1H, ArCH-), 7.13 (d, 2H, *J* = 8.08 Hz, ArH), 7.33 (d, 2H, *J* = 8.04 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.23 (2C), 21.08, 26.15 (2C), 52.04,127.49 (2C), 129.12(2C),137.33,137.46

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{18}S_2$	C 63.66	C 63.47
226.408	H 8.01	H 8.09
	S 28.33	S 28.23

4-*tert*-Butyldimethylsilyloxy benzaldehyde diethyldithioacetal (202):



Nature: Liquid

Yield: 95%

R_f: 0.95 (Hexane/AcOEt = 9.8: 0.2)

IR (Neat): cm^{-1} 2960, 2935, 2863, 1603, 1506, 1465, 1265, 1163, 922, 846, 789, 702

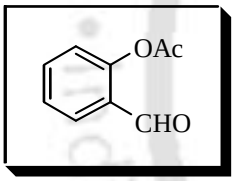
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 6H, -$Si(CH_3)_2$), 0.98 (s, 9H, -$SiC(CH_3)_3$), 1.21 (t, 6H, *J* = 7.6 Hz, -SCH_2CH_3), 2.51-2.58 (m, 4H, -SCH_2CH_3), 4.90(s, 1H, ArH), 6.78(d, 2H, *J* = 7.6 Hz, ArH), 7.3 (d, 2H, *J* = 7.2 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{30}OSiS_2$	C 59.59	C 59.70
342.64	H 8.82	H 8.69
	S 18.72	S 18.64

A typical procedure for deprotection:

To a stirred solution of ammonium heptamolybdate tetrahydrate (0.248 g, 0.2 mmol) in water (1 ml) were added 30% hydrogen peroxide solution (1.2 ml, 10 mmol) and 70% perchloric acid (0.014 ml, 0.1 mmol) at 0-5°C. After stirring for 10 min, ammonium bromide (0.294 g, 3 mmol) was added in portion; immediately the colour changes to deep yellow from light yellow. Then, the substrate (1 mmol) in dichloromethane (2 ml) was slowly added dropwise into it. The reaction was monitored by checking TLC and its reaction time was mentioned in the Table 5. The reaction mixture was finally extracted with CH_2Cl_2 (15 × 2) and the organic layers were dried over anhydrous Na_2SO_4. The organic extract was concentrated in *vacuo* to give the crude product, which was finally purified by column chromatography on silica gel to afford the desired product.

2-Acetoxybenzaldehyde (203):



Nature: Liquid

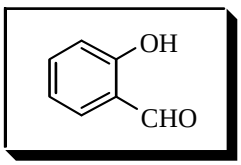
Yield: 84%

IR (Neat): cm^{-1} 1783, 1706, 1614, 1465, 1373, 1194, 1025, 917, 758

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.120 (s, 3H, -$COCH_3$), 7.18-7.41 (m, 2H, ArH), 7.62-7.66 (m, 1H, ArH), 7.88 (dd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz ArH), 10.11 (s, 1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_9H_8O_3$	C 65.85	C 65.74
164.16	H 4.91	H 4.87

2-Hydroxybenzaldehyde (Salicylaldehyde) (82):

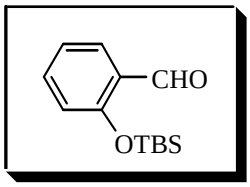


Nature: Colourless liquid

Yield: 82%

IR (Neat): cm^{-1} 3232, 3058, 2853, 1665, 1460, 1286, 1199, 764

2-*tert*-Butyldimethylsilyloxy benzaldehyde (204):



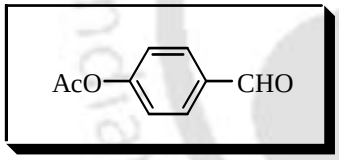
Nature: Liquid

Yield: 85%

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08(s, 6H, -Si(CH_3)$_2$), 0.83 (s, 9H, -SiC(CH_3)$_3$), 6.69(d,1H, *J* = 8.28 Hz, ArH), 6.83(t, 1H, *J* = 7.41 Hz, ArH), 7.29(t,1H, *J* = Hz, ArH), 7.61 (d,1H,*J* = Hz, ArH), 10.27 (s,1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{20}SiO_2$	C 66.05	C 66.27
236.39	H 8.53	H 8.45

4-Acetoxybenzaldehyde (205):



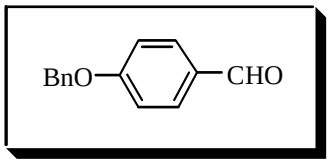
Nature: Viscous liquid

Yield: 75%

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, -OCOCH_3), 7.26 (d, 2H, *J* = 8.0 Hz, ArH), 7.78 (d, 2H, *J* = 8.8 Hz, ArH), 9.87 (s, 1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_9H_8O_3$	C 65.85	C 65.74
164.16	H 4.91	H 4.87

4-Benzyloxybenzaldehyde (206):



Nature: White solid

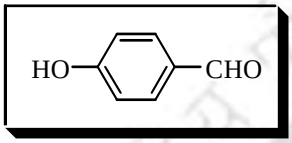
Yield: 88%

Melting Point: 73 °C [Lit. 72-74 °C]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15 (s, 2H, -OCH_2Ph), 7.08 (d, 2H, *J* = 8.70 Hz, ArH), 7.33-7.45 (m, 5H, ArH), 7.84 (d, 2H, *J* = 8.61 Hz, ArH), 9.89 (s, 1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{12}O_2$	C 79.23	C 79.12
212.24	H 5.70	H 5.83

4-Hydroxy benzaldehyde (207):



Nature: Solid

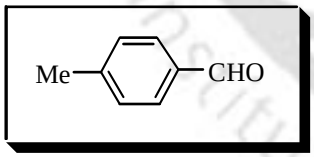
Yield: 80%

Melting Point: 117°C [Lit. 117-119°C]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (bs, 1H, -OH), 7.33 (d, 2H, *J* = 8.32 Hz, ArH), 7.88 (d, 2H, *J* = 8.04 Hz, ArH), 9.96 (s, 1H, CHO)

Elemental Analysis	**Calculated**	**Found**
$C_7H_6O_2$	C 68.85	C 68.65
122.12	H 4.95	H 5.05

4-Methyl benzaldehyde (208):



Nature: Colourless liquid

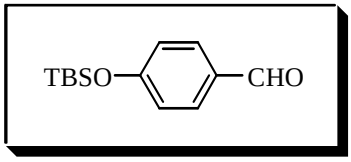
Yield: 83%

IR (Neat): cm^{-1} 1701, 1609, 1286, 1219,1168

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, -CH_3), 7.33 (d, 2H, *J* = 8.32 Hz, ArH), 7.88 (d, 2H, *J* = 8.04 Hz, ArH), 9.96 (s, 1H, CHO)

Elemental Analysis	**Calculated**	**Found**
C_8H_8O	C 79.97	C 80.05
120.51	H 6.71	H 6.58

4-*tert*-Butyldimethylsilyloxy benzaldehyde (209):



Nature: Colourless liquid

Yield: 95%

R_f: 0.50 (Hexane/AcOEt = 9.8: 0.2)

IR (Neat): cm^{-1} 1705, 1603, 1511, 1275, 1157, 912, 845

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.25 (s, 6H, -Si(CH_3)$_2$), 0.99 (s, 9H, -SiC(CH_3)$_3$), 6.94 (d, 2H, *J* = 8.52 Hz, ArH), 7.89 (d, 2H, *J* = 8.6 Hz, ArH), 9.88 (s,1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{20}O_2Si$	C 66.05	C 66.22
236.39	H 8.53	H 8.45

PART II

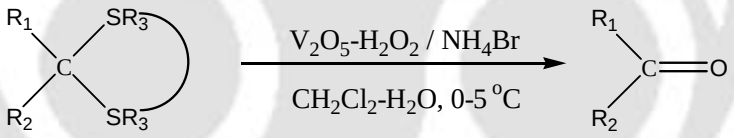
(SECTION C)

NEW SYNTHETIC PROTOCOL FOR DETHIOACETALIZATION BY INVOLVING VANADIUM PENTOXIDE-HYDROGEN PEROXIDE CATALYSED OXIDATION OF AMMONIUM BROMIDE

RESULTS AND DISCUSSION

Results and Discussion

We have devised two synthetic methodologies using organic ammonium tribromides[115] and molybdenum peroxo complexes oxidation of bromide ion to the bromonium ion[116] for demasking of dithioacetals. The drawbacks using organic ammonium tribromides are pointed out in the results and discussions earlier chapter. Though some of the demerits of organic ammonium tribromide method was over come by the molybdenum methodology, still there is some drawbacks, which gives us further opportunity to find out better methodology. The disadvantage of molybdenum methodology is that it works promoted manner and takes relatively longer reaction times. Taking cues from the knowledge of the activity of vanadium bromoperoxidase (VBrPO),[117] which catalyses bromination of marine natural products as well as our earlier results,[114] we wanted to investigate whether vanadium peroxo complexes oxidation of bromide ion to the bromonium ion can be used for deprotection or not. In this chapter, we would like to discuss an environmentally acceptable deprotection protocol of dithioacetals and ketals involving V_2O_5 as a promoter, hydrogen peroxide and ammonium bromide as the source of active oxygen and bromide, respectively as shown in scheme 68. The promoter (V_2O_5), oxidant (H_2O_2) and ammonium bromide are environmentally acceptable chemicals



R_1 = aryl, alkyl, sugar residue

R_2 = H, alkyl, aryl; R_3 = Et, $-(CH_2)_3-$

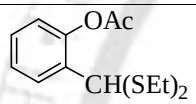
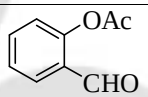
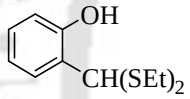
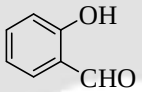
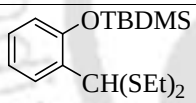
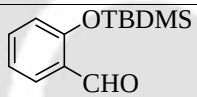
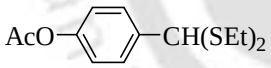
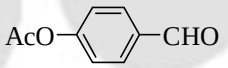
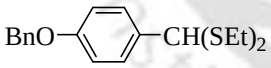
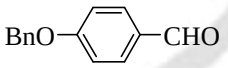
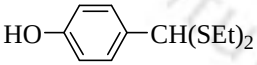
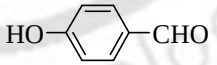
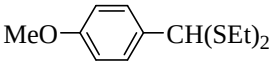
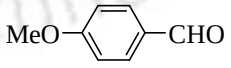
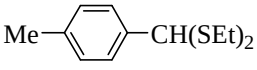
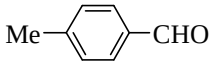
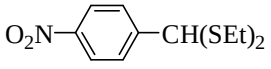
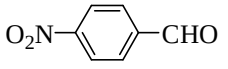
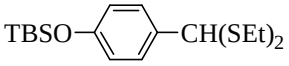
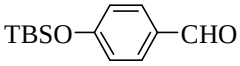
Scheme 68

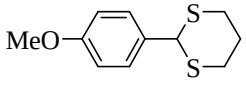
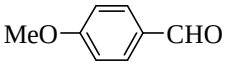
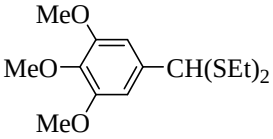
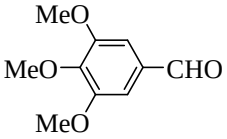
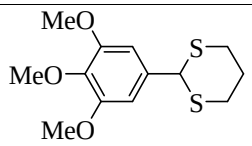
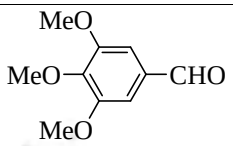
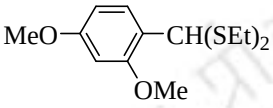
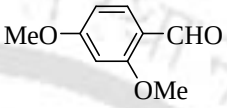
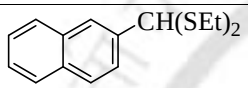
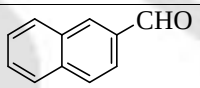
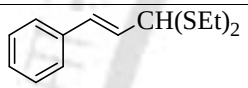
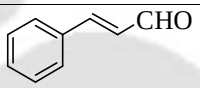
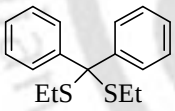
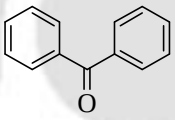
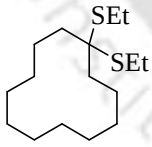
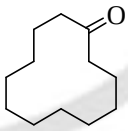
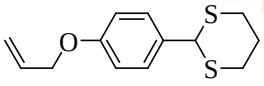
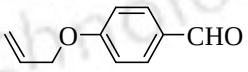
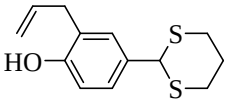
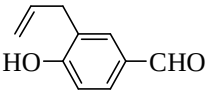
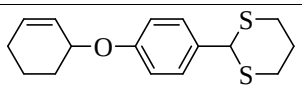
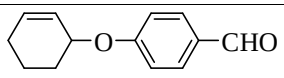
For our requirement, we prepared various acyclic dithioacetals and cyclic dithioacetals by using boron trifluoride etherate by following literature procedure. Some of the analysis data of the starting dithioacetals are given in the experimental section. Most of the compounds data are already mentioned in the previous chapters. ^{1}H NMR spectrum of compound **210** is shown in figure **36** for confirmation of the structure.

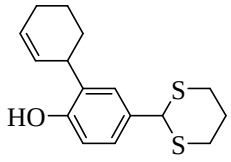
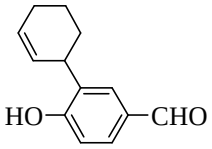
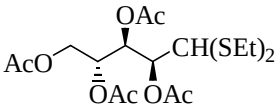
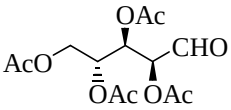
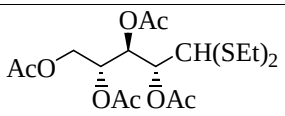
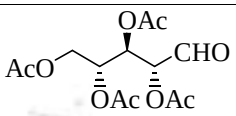
Subsequently, we have attempted for optimization of the reaction conditions for deprotection of dithioacetals and ketals to obtain the desired carbonyl compounds. We have found that a 1:1:0.1:10 substrate to ammonium bromide to vanadium pentoxide to

hydrogen peroxide in dichloromethane-water solvent (5:1, 6 mL per mmol of substrate) give best results. Following the above typical reaction procedure, the compound 2-acetoxybenzaldehyde diethyldithioacetal (**195**) reacts smoothly to give deprotected compound 2-acetoxybenzaldehyde (**203**) in a very good yield. Similarly, various acyclic dithioacetals, cyclic dithioacetals and ketals were smoothly converted to the carbonyl compounds in good yields under identical reaction conditions. The results are summarized in Table 6 and the deprotected products are compared with the corresponding authentic samples by co-IR, ^{1}H NMR and elemental analyses. The ^{1}H NMR spectra of compound **151** and **218** are given in figure **37** and figure **38**, respectively.

Table 6. Cleavage of various thioacetals and ketals by employing V_2O_5 catalyzed oxidation of ammonium bromide by H_2O_2

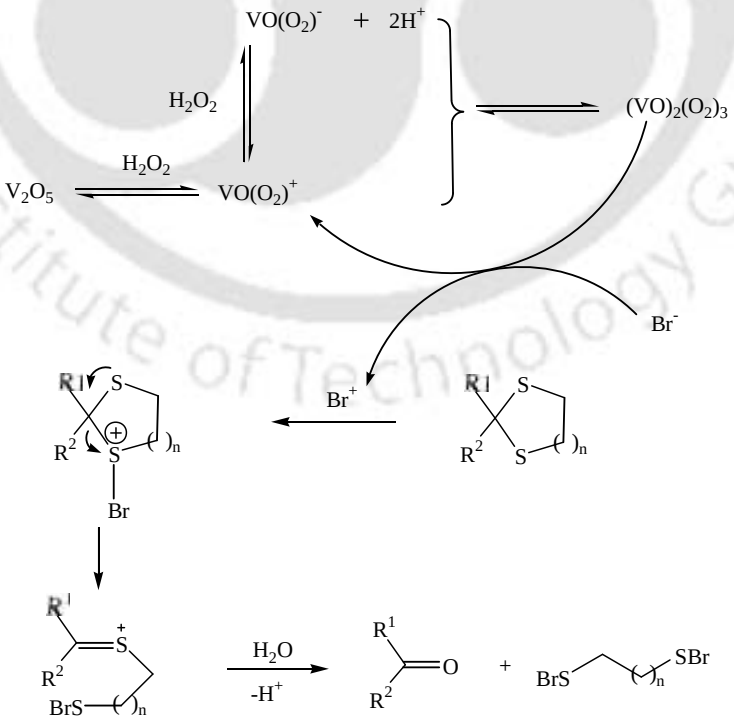
Substrate (**1**)	Substrate No.	Time in min	Product (**2**)[a]	Product No.	Yield (%)[b]
	**195**	50		**203**	84
	**196**	40		**82**	60
	**197**	40		**204**	96
	**198**	45		**205**	75
	**199**	40		**206**	93
	**200**	75		**207**	65
	**101**	37		**65**	91
	**201**	37		**208**	95
	**132**	75		**191**	95
	**202**	45		**209**	95

	**34**	45		**65**	90
	**184**	97		**189**	94
	**38**	50		**189**	80
	**185**	45		**190**	85
	**111**	37		**162**	95
	**210**	36		**151**	90
$CH_3(CH_2)_{10}CH(SEt)_2$	**187**	55	$CH_3(CH_2)_{10}CHO$	**192**	82
	**211**	38		**215**	95
	**188**	95		**193**	60
	**106**	40		**216**	83
	**212**	40		**217**	63
	**143**	1.5		**218**	75

	**213**	2.0		**219**	78
	**135**	245		**194**	70
	**214**	215		**220**	66

[a] Products have been characterized by co-IR with the authentic compounds, ^{1}H NMR and elemental analyses of the samples. [b]Isolated yields.

This method has been further extended for the preparation of open chain sugar compounds **194** and **220** from compound **135** and **214**, respectively. The probable mechanism for the cleavage of thioacetals can be explained as follows. Vanadium pentoxide reacts with H_2O_2 to generate reactive peroxovandate (V) intermediates, which oxidize bromide (Br^-) to the Br^+. The reactive bromonium ion can undergo further oxidation to Br_2 or Br_3^-, which might exist in solution. Then the reactive species Br^+ reacts with dithioacetals to form dibromosulfonium complex, which is finally hydrolyzed by water to the parent carbonyl compound as shown in scheme 69.



Scheme 69

In conclusion, we have demonstrated a simple and efficient method for the regeneration of parent carbonyl compounds from their corresponding dithioacetals or ketals selectively by ammonium bromide promoted by V_2O_5-H_2O_2 under very mild conditions. It is significant to note that neither olefinic double bond nor aromatic substrates are brominated under the experimental reaction conditions. Due to its operational simplicity, generality and efficacy, this method is expected to have wider applicability for the cleavage of thioacetals chemoselectively. A similar deprotection reaction also might be possible by using other alkali metal bromide, which is under investigation.

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PART II

(SECTION C)

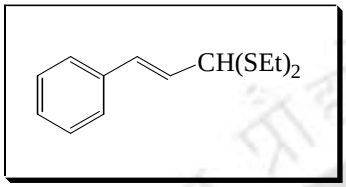
NEW SYNTHETIC PROTOCOL FOR DETHIOACETALIZATION BY INVOLVING VANADIUM PENTOXIDE-HYDROGEN PEROXIDE CATALYSED OXIDATION OF AMMONIUM BROMIDE

EXPERIMENTALS

Experimental

Some of the dithioacetals such **210**, **211**, **212** and **214** were prepared by following boron trifluoride etherate procedure as described in previous section A. Some of the substrates and their corresponding carbonyl compounds data are mentioned in the earlier Section A and Section B in the experimental part.

Cinnamaldehyde diethyldithioacetal (210):



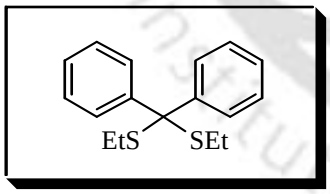
Nature: Light yellow Liquid
Yield: 85%
R_f: 0.72 (Hexane/AcOEt = 9.9: 0.1)

IR (Neat): cm^{-1} 3032, 2976, 2930, 2873,1609, 1501, 1455, 1265, 963, 758, 697

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 6H, *J* = 7.4 Hz, 2x -SCH_2CH_3), 2.59-2.75 (m, 4H, 2x -SCH_2CH_3), 4.52 (d, 1H, *J* = 8.74 Hz, -SCHS-), 6.12-6.20 (m, 1H, -CH=C*H*-CH-), 6.53 (d, 1H, *J* =15.63 Hz, Ar-C*H*=CH-), 7.21-7.40 (m, 5H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}S_2$	C 65.49	C 65.76
238.42	H 7.61	H 7.49
	S 26.90	S 26.68

Benzophenone diethyldithioacetal (211):



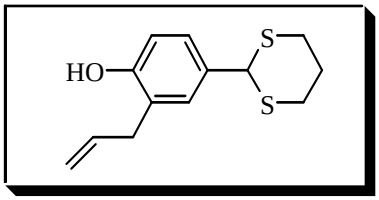
Nature: Viscous liquid
Yield: 82%
R_f: 0.75 (Hexane)

IR (Neat): cm^{-1} 3058, 2981, 2935, 2868, 1603, 1501, 1450, 1271, 1040, 984, 743, 702

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (t, 6H, *J* = 7.2 Hz, 2 × -CH_2CH_3), 2.33 (m, 4H, -CH_2CH_3), 7.25 (m, 6H, ArH), 7.51 (m, 4H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{20}S_2$	C 70.78	C 70.54
288.48	H 6.99	H 7.07
	S 22.23	S 22.31

2-[4̊-Hydroxy-3-allyl-phenyl]-1,3-dithiane (212):



Nature: Colourless liquid

Yield: 83%

R_f: 0.60 (Hexane /AcOEt = 9:1)

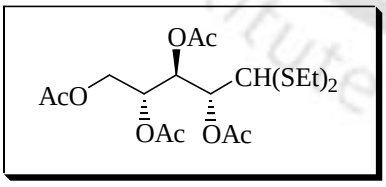
IR (Neat): cm^{-1} 3421, 2904, 1608, 1505, 1429, 1270, 1178, 1116, 911

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (m, 1H, -SCH_2*CH*CH_2S-), 2.15 (m, 1H, -SCH_2*CH*CH_2S-), 2.88 (m, 2H, -SCH_2-), 3.05 (m, 2H, -SCH_2-), 3.36 (d, 2H, *J* = 6.12 Hz, -*CH_2*CH=CH_2-), 5.10 (s, 1H, ArCH-), 5.15 (m, 2H, - CH_2CH=*CH_2*-), 5.43 (s, 1H, -OH), 5.99 (m, 1H, -*CH*=CH_2), 6.73 (d, 1H, *J* = 7.32 Hz, ArH), 7.20 (d, 2H, *J* = 7.08 Hz, ArH)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.03, 32.10 (2C), 34.97, 50.83, 115.95, 116.71, 125.78, 127.19, 129.73, 131.36, 136.07, 154.20

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{16}OS_2$	C 61.86	C 61.69
252.40	H 6.39	H 6.47
	S 25.41	S 25.24

Diethyl dithioacetal of 2,3,4,5-tetra-*O*-acetyl-D-Ribose (214):



Nature: Viscous liquid

Yield: 60%

R_f: 0.50 (Hexane /AcOEt = 9:1)

IR (Neat): cm^{-1} 2971, 2935, 1757, 1450, 1378, 1224, 1055, 965, 871, 610

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, 6H, *J* = 7.6 Hz, 2× -SCH_2*CH_3*), 2.05 (s, 3H, -OAc), 2.08 (s, 6H, 2× - OAc), 2.16 (s, 3H, - OAc), 2.59-2.76 (m, 4H, 2× -S*CH_2*CH_3), 3.96 (d, 1H, *J* = 6.0 Hz, -SCHS-), 4.13 (q, 1H, H-2), 4.43 (dd, 1H, *J* = 3.2 Hz, *J* = 12.0 Hz, H-4), 5.34-5.41 (m, 2H, H-5 & H-5′), 5.65 (dd, 1H, *J* = 3.6 Hz, *J* = 6.0 Hz, H-3)

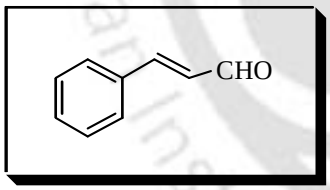
^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15, 20.80 (2C), 24.97, 25.04, 62.14, 69.72, 71.11, 72.02, 169.27 (2C), 169.63 (2C), 169.83 (2C), 170.61 (2C)

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{28}O_8S_2$	C 48.09	C 48.20
424.54	H 6.64	H 6.48
	S 15.10	S 15.17

A typical deprotection procedure:

Into a stirred solution of vanadium pentoxide (0.018 g, 0.1 mmol) in water (1 ml) was added 30% hydrogen peroxide solution (0.6 ml, 5 mmol) at 0-5°C and stirring was continued. The color of the solution was changed to the clear dark brown- red after 25 min, and ammonium bromide (0.1 g, 1.0 mmol) was added into it. After 10 min of stirring at the same temperature, the substrate dithioacetal (1.0 mmol) was added slowly by dissolving in dichloromethane (5 ml). Stirring was continued further and after 50% conversion as monitored by TLC another 0.6 ml (5 mmol) H_2O_2 was added. The reaction time was mentioned in the Table 6.

Cinnamaldehyde (151):



Nature: Pale yellow Liquid

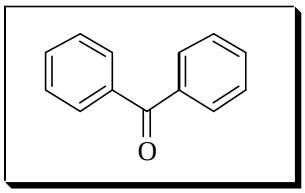
Yield: 90%

IR (Neat): cm^{-1} 1680, 1629, 1460, 1127, 978

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (dd, 1H, *J* = 7.7 Hz, *J* = 16 Hz ArCH=*CH*CHO), 7.37-7.42 (m, 3H, ArH), 7.50 (d, 1H, *J* = 16 Hz, Ar*CH*=CHCHO), 7.54-7.57 (m, 2H, ArH), 9.72 (d, 1H, *J* = 4.9 Hz, -CHO)

Elemental Analysis	**Calculated**	**Found**
C_9H_8O	C 81.79	C 81.59
132.16	H 6.10	H 6.21

Benzophenone (215):



Nature: White solid

Yield: 95%

Melting Point: 47°C [Lit. 48-49°C]

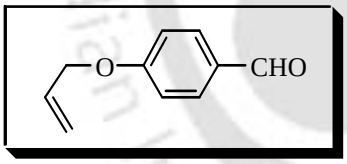
IR (KBr): cm^{-1} 1669, 1598, 1449, 1280, 947

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (t, 4H, *J* = 7.8 Hz, ArH), 7.60 (t, 2H, *J* = 7.6 Hz ArH), 7.80-7.82 (m, 4H, ArH)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 128.25 (4C), 130.04 (4C), 132.41 (2C), 137.52 (2C), 196.79

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{10}O$	C 85.69	C 85.53
182.22	H 5.53	H 5.44

4-Allyloxybenzaldehyde (216):



Nature: Colourless liquid

Yield: 83%

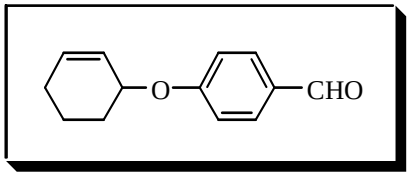
IR (Neat): cm^{-1} 1695, 1603, 1506, 1265, 1168, 1004

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (d, 2H, *J* = 5.1 Hz, -OCH_2CH=CHaH_b), 5.33 (dd, 1H, *J* = 1.2 Hz, *J* = 10.5 Hz, -OCH_2CH= C*Ha*H_b), 5.44 (dd, 1H, *J* = 1.2 Hz, *J* = 17.3 Hz, -OCH_2CH= CHa*H_b*), 6.01-6.10 (m, 1H, -OCH_2*CH*= CHaH_b), 7.01 (d, 2H, *J* = 8.8 Hz, ArH), 7.84 (d, 2H, *J* = 8.8 Hz, ArH), 9.87 (s, 1H, -CHO)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 68.95, 114.94 (2C), 118.34, 129.94, 131.94 (2C), 132.21, 163.55,190.81

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{10}O_2$	C 74.06	C 74.27
162.19	H 6.21	H 6.14

4-Cyclohexenyloxybenzaldehyde (218):



Nature: Colourless liquid

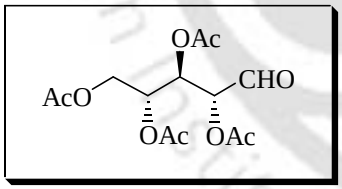
Yield: 80%

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64-2.18 (m, 6H, -CH_2-), 4.91 (s, 1H, -CH_2*CH*O-), 5.85 (dd, 1H, *J* = 1.96 Hz, *J* = 10.0 Hz, -CH=*CH*CHO-), 6.00-6.05 (m, 1H, -CH_2*CH*=CH-), 7.01 (d, 2H, *J* = 8.8 Hz, ArH), 7.81 (d, 2H, *J* = 7.56 Hz, ArH), 9.87 (s, 1H, -CHO)

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.77, 24.96, 28.11, 71.10, 115.59 (2C), 125.16, 129.60, 131.99 (2C), 133.05, 163.10,190.71

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{14}O_2$	C 77.20	C 77.32
202.25	H 6.98	H 6.77

2,3,4,5-Tetra-*O*-acetyl-D- Ribose (220):



Nature: White solid

Yield: 70%

IR (KBr): 2950, 2879, 1762, 1731, 1373, 1276, 1235, 1214, 1132, 1066, 1035, 927, 856

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97 (s, 3H, -$COCH_3$), 2.06 (s, 3H, -$COCH_3$), 2.09 (s, 3H, -$COCH_3$), 2.19 (s, 3H, -$COCH_3$), 4.17 (dd, 1H, *J* = 4.3 Hz, *J* = 12.6 Hz, H-5′), 4.37 (dd, 1H, *J* = 2.6 Hz, *J* = 12.6 Hz, H-5), 5.31 (m, 1H, H-4), 5.45 (d, 1H, *J* = 2.5 Hz, H-2), 5.61 (dd, 1H, *J* = 2.5 Hz, *J* = 8.8 Hz, H-3), 9.50 (s, 1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}O_9$	C 49.06	C 48.82
318.28	H 5.70	H 5.74

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
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PART II

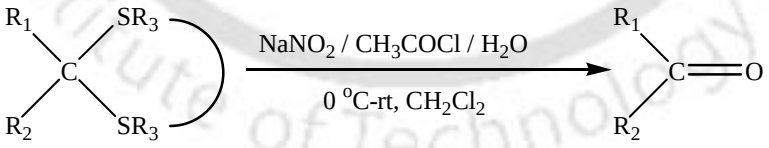
(SECTION D)

NEW SYNTHETIC PROCEDURE FOR REGENERATION OF CARBONYL COMPOUNDS FROM THEIR CORRESPONDING DITHIOACETALS USING A COMBINATION OF SODIUM NITRITE AND ACETYL CHLORIDE

RESULTS AND DISCUSSION

Results and Discussion

In the **Chapter II** of the **Part II** in the **Section A**, **Section B** and **Section C**, we have shown that bromonium ion can be applied for dethioacetalization reaction. We have also developed first time catalytic synthetic protocol for deprotection of dithioacetals by involving bromonium ion by employing peroxovaanadium oxidation of bromide ion to the bromonum ion. Although this procedure is quite effective as compared to the other methods, still we were interested whether some other method can be devised by using a combination of other reagents. The usual standard procedure for cleavage of dithioacetals is by involving mainly a suitable electrophile, which is captured by soft nucleophile sulfur atom followed by hydrolysis with water. Then, we realize whether the electrophilic species such as NO^+ can be employed for regeneration of carbonyl compounds from the corresponding protected compounds or not as we are working mainly to develop a new synthetic methodology. After going through the literature, we have noticed that sodium nitrite in combination with trifluoroacetic acid,[103] isoamyl nitrite[118] and a mixture of nitrogen oxides[119] have been used for deprotection of dithioacetals to the carbonyl compounds. However, these procedures have some drawback such as incompatibility with other protecting group like TBS ethers due to large excess of trifluoroacetic acid, drastic reaction conditions and longer reaction times,[118] and provide low yield for enolizable ketone.[119] In this chapter, we would like to discuss that sodium nitrite in combination with acetyl chloride is a useful reagent system for cleavage of dithioacetals under a mild reaction conditions as depicted in scheme 70.



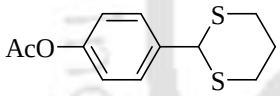
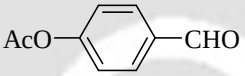
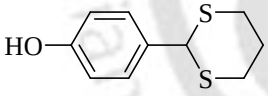
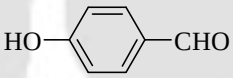
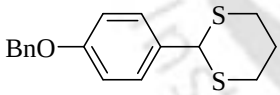
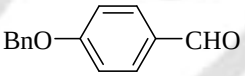
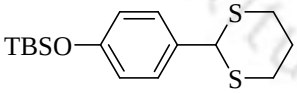
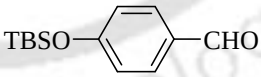
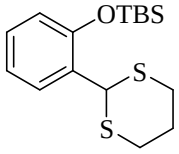
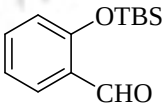
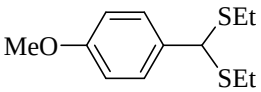
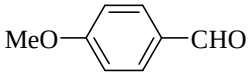
R_1 = alkyl / aryl / sugar residue; R_2 = H / alkyl / aryl;

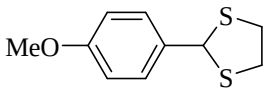
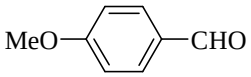
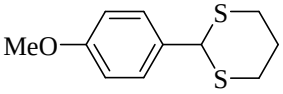
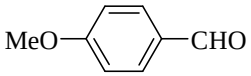
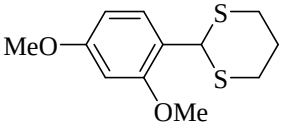
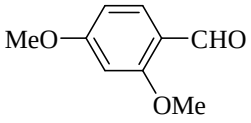
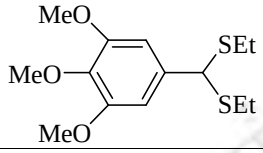
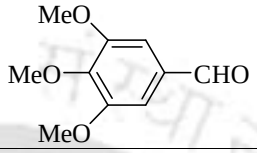
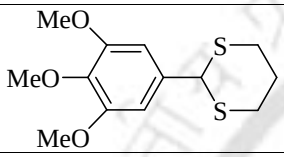
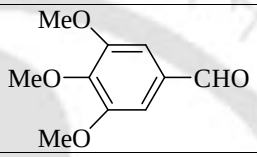
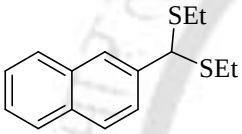
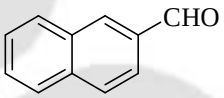
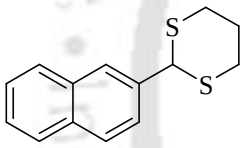
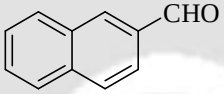
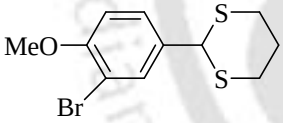
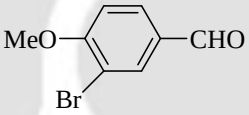
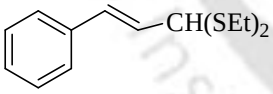
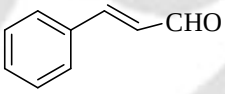
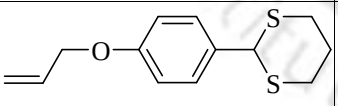
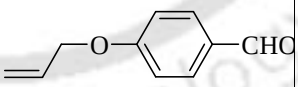
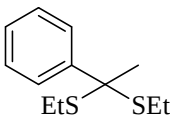
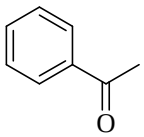
R_3 = Et, - $(CH_2)_2$-, -$(CH_2)_3$-

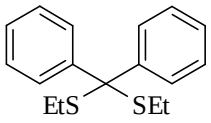
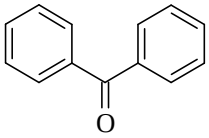
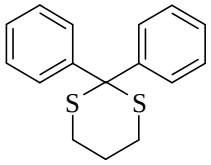
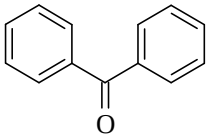
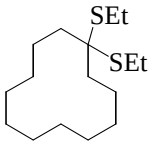
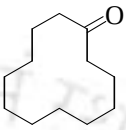
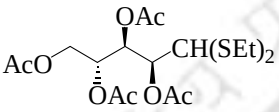
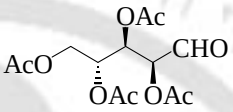
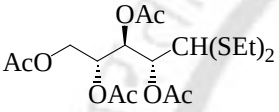
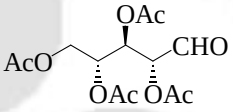
Scheme 70

As per our requirement, we prepared various acyclic and cyclic dithioacetals by employing our method or followed by other method. When the compound **109** was treated with 2 equivalent amount of $NaNO_2$-CH_3COCl (1:1) mixture at 0-5 ^oC, it was smoothly converted to the product **205** in good yield. The product was identified by comparison of IR and ^1H NMR with the authentic sample spectra. Similarly, the compound **111** was transformed to the compound **207** in good yields by following identical procedure without acetylation of the hydroxyl group. Likewise, various acyclic and cyclic dithioacetals **107-188 (**Table 7**)** were cleaved chemoselectively to the parent carbonyl compounds (**205-193)** under identical conditions without affecting other protecting groups. Moreover, by using our protocols diethyldithioacetals of carbohydrate compounds such as **135** and **214** can be transformed easily into the corresponding open chain aldehydic sugars **194** and **220,** respectively.

Table 7. Cleavage of Various Dithioacetals Using $NaNO_2$-CH_3COCl / H_2O in CH_2Cl_2

Substrate	Substrate No.	Time in min	Product[a]	Product No.	Yield[b] (%)
	**109**	225		**205**	85
	**114**	15		**207**	90[c]
	**107**	45		**206**	97
	**105**	70		**209**	85
	**133**	45		**204**	94
	**101**	90		**65**	98

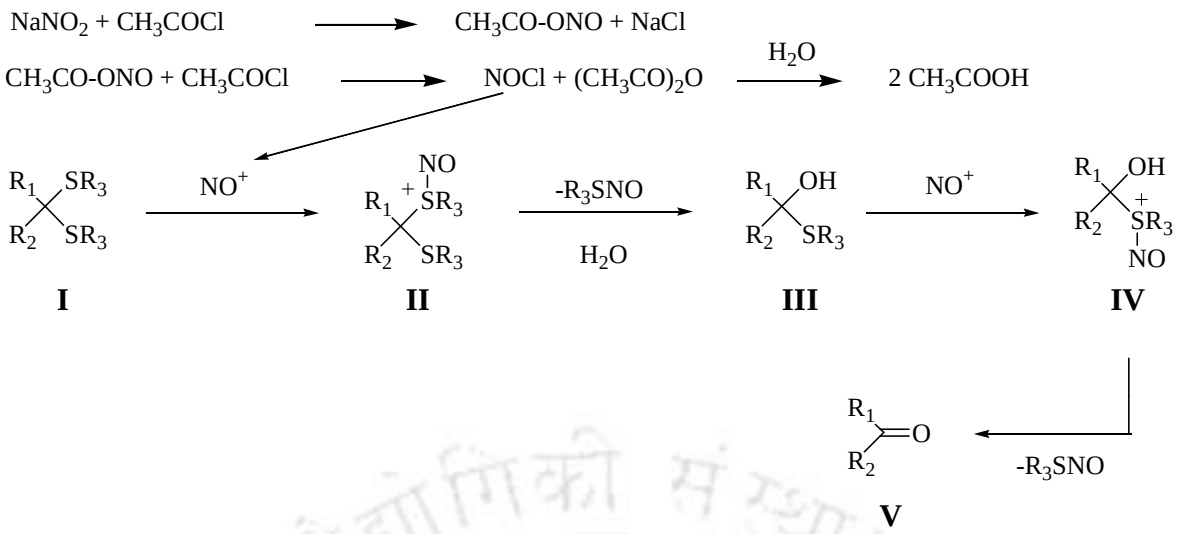
	**66**	30		**65**	95
	**34**	45		**65**	90
	**103**	45		**190**	97
	**184**	45		**189**	96
	**38**	90		**189**	96
	**111**	60		**162**	95
	**112**	45		**162**	96
	**221**	45		**222**	80
	**210**	30		**151**	95
	**106**	40		**216**	97
$CH_3(CH_2)_{10}CH(SEt)_2$	**187**	70	$CH_3(CH_2)_{10}CHO$	**192**	82
	**186**	70		**85**	90

	**211**	45		**215**	87
	**136**	45		**215**	90
	**188**	45		**193**	78
	**135**	45		**194**	75
	**214**	60		**220**	72

[a] Products have been characterized by co-IR with the authentic compounds, ^{1}H NMR and elemental analyses of the samples. [b]Isolated yields.
[c]After addition of the substrate, water was added after 2 min. instead of 5 min.

The starting dithoacteals **133** and its hydrolyzed **204** products were characterized by recording IR, ^{1}H NMR as shown in the figures **39-41**.

The formation of the parent carbonyl compounds from their corresponding dithiacetals can be rationalized as follows. Sodium nitrite reacts with acetyl chloride to form acetyl nitrite, which ultimately generates a highly reactive species NO^+ ion. Then the reactive species NO^+ reacts with sulfur atom to form a complex[118], which is finally hydrolyzed by water to provide the carbonyl compound, as represented by scheme 71.



Scheme 71

In conclusion, we have demonstrated mild and easy to handle procedure for deprotection of dithioacetals to the parent carbonyl compounds by using a mixture of sodium nitrite and acetyl chloride, which is a useful addition to the existing procedures. In addition, this methodology is compatible with the presence of a large number of other protecting groups such as acetyl, benzyl, benzoyl, TBS ether, allyl and also provide good yield for enolizable ketones.

PART II

(SECTION D)

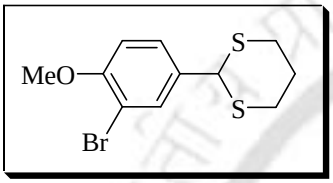
NEW SYNTHETIC PROCEDURE FOR REGENERATION OF CARBONYL COMPOUNDS FROM THEIR CORRESPONDING DITHIOACETALS USING A COMBINATION OF SODIUM NITRITE AND ACETYL CHLORIDE

EXPERIMENTALS

Experimental

The characterization data of all dithioacetals and their corresponding carbonyl compounds are mentioned in the previous **Chapter I** and **Chapter II** in the experimental section except the dithioacetal derivative **221** and its corresponding aldehyde **222**.

2-[3å-Bromo-4å-methoxyphenyl]-1,3-dithiane (221):



Nature: White solid

Yield: 87%

R_f: 0.75 (Hexane/AcOEt = 9.5: 0.5)

IR (KBr): cm^{-1} 2945, 2889, 2832, 1598, 1485, 1408, 1270, 1050, 1009, 901, 768

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (m, 1H, -SCH_2*CH*CH_2S-), 2.16 (m, 1H, -SCH_2*CH*CH_2S-), 2.9(m, 2H, -SCH_2-), 3.03 (m, H, -SCH_2-), 3.88 (s, 3H, -OCH_3), 5.08 (s, 1H, ArCH-), 6.85 (d, 1H, *J* = 8.56 Hz, ArH), 7.38 (dd, 1H, *J* = 1.96 Hz, *J* = 8.04 Hz, ArH), 7.67 (d, 1H, *J* = 2.2 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.95, 32.05 (2C), 49.94, 56.29, 111.65, 111.83, 127.93, 132.71, 155.84, 158.98

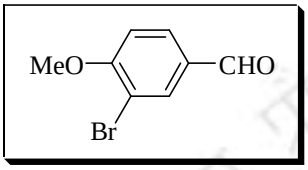
Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{13}BrOS_2$	C 43.28	C 43.36
305.25	H 4.29	H 4.34
	S 21.01	S 21.09

A typical procedure for deprotection of Dithioacetals

The reaction mixture of $NaNO_2$ (0.138 g, 2 mmol) and AcCl (142 μL, 2 mmol) in CH_2Cl_2 (3 ml) was stirred for 10 min at 0-5 °C. Then, the substrate (1 mmol) in CH_2Cl_2 (2 ml) was added into the above reaction mixture at the same temperature. After stirring for 5 min, water (1 ml) was added into it and the reaction mixture was brought to room temperature. The reaction was completed in short time as shown in the Table 7. Finally,

the reaction mixture was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (2× 15 ml). The organic layer was washed with water (2 × 20 ml) and dried over Na_2SO_4. Evaporation of the solvent gave a crude residue, which was purified by column chromatography on silica gel to obtain the desired compounds.

3-Bromo-4-methoxybenzaldehyde (222):



Nature: White solid

Yield: 80%

Melting point: 52 °C [Lit. 51-54 °C]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (s, 3H, -OCH_3), 7.01 (d, 1H, *J* = 8.4 Hz, ArH), 7.82 (dd, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz, ArH), 8.08 (d, 1H, *J* = 2.0 Hz, ArH), 9.80 (s, 1H, -CHO)

Elemental Analysis	**Calculated**	**Found**
$C_8H_7BrO_2$	C 48.27	C 48.35
199.05	H 3.54	H 3.59

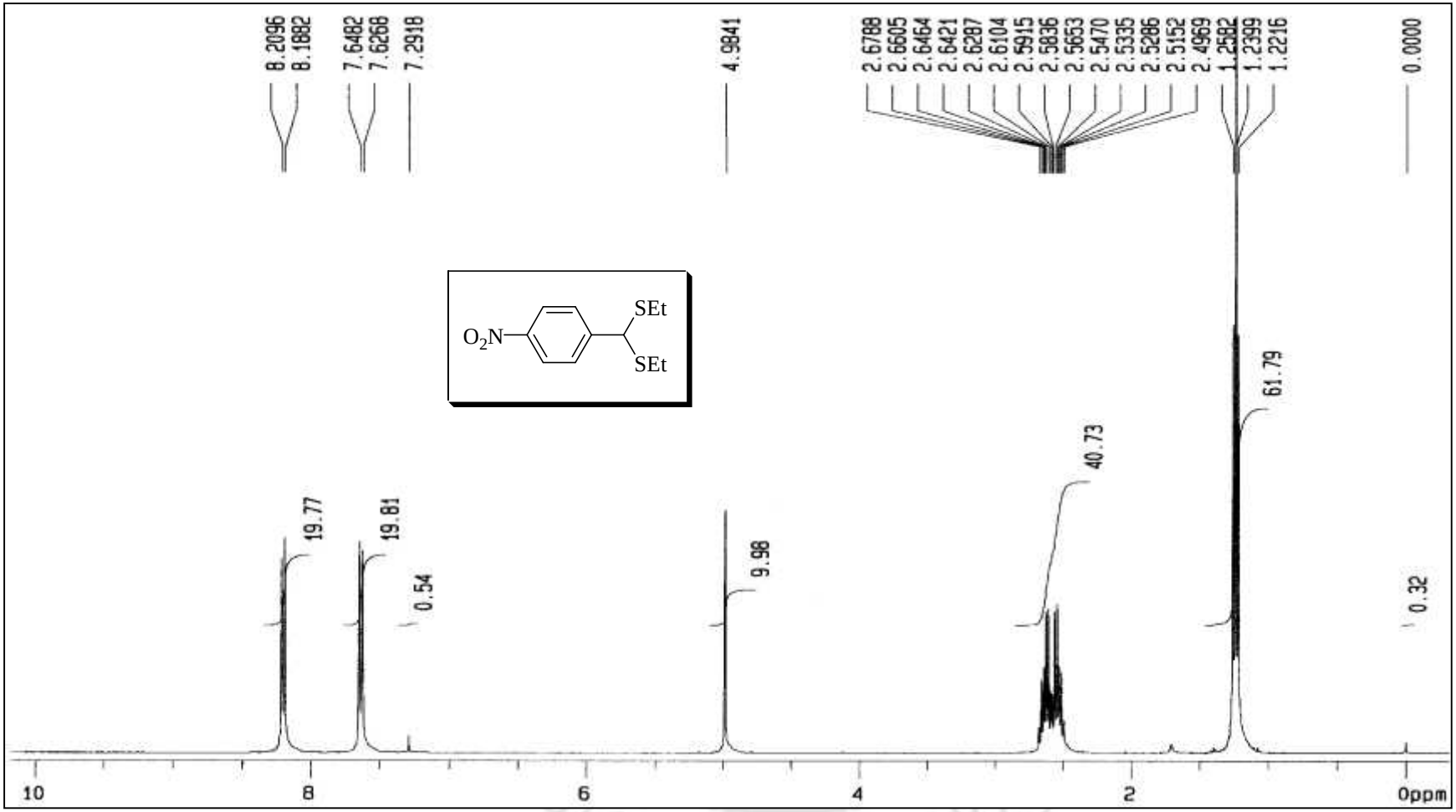


Figure 27: ^{1}H NMR Spectrum of diethyldithioacetal of 4-Nitrobenzaldehyde (400 MHz, $CDCl_3$) (132)

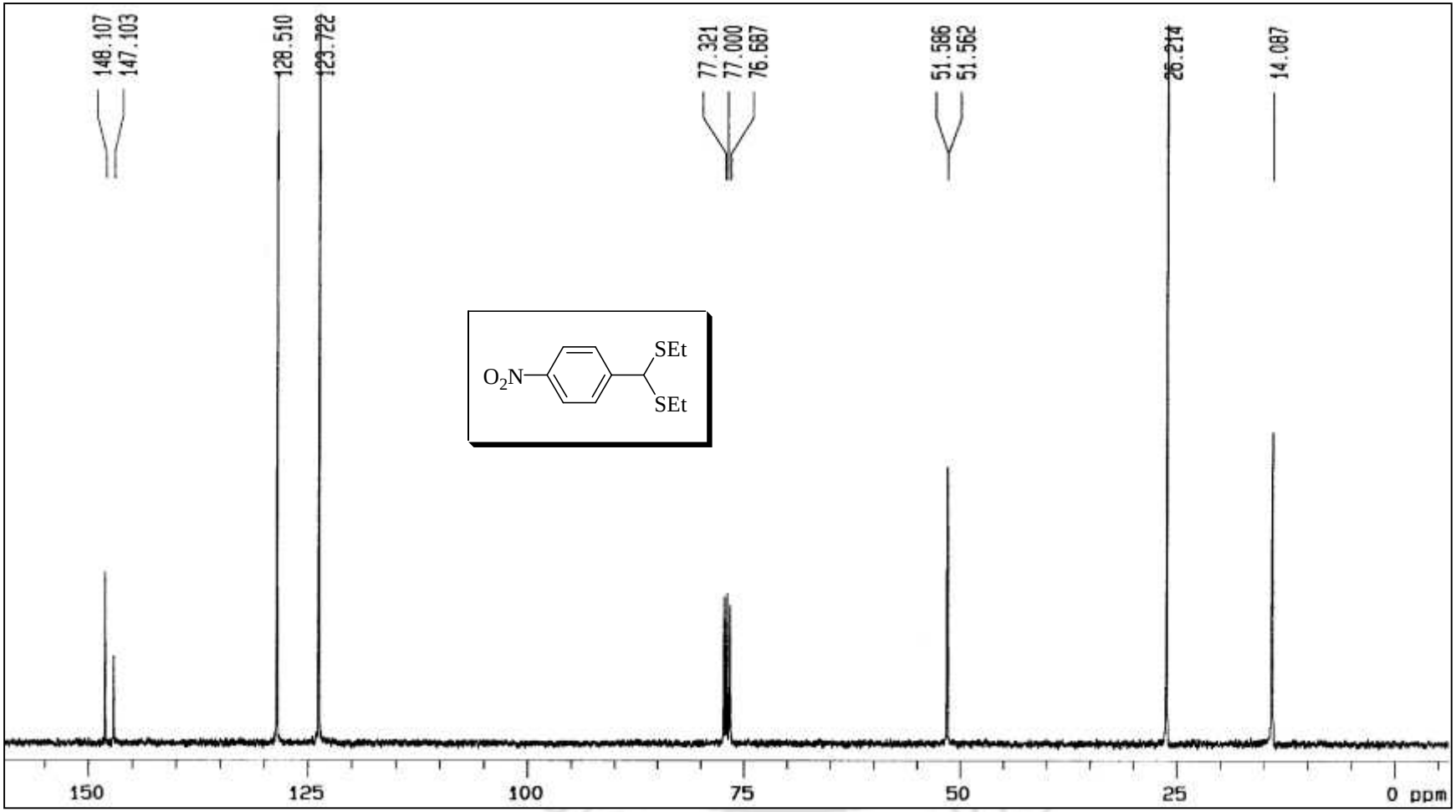


Figure 28: ^{13}C NMR Spectrum of diethyldithioacetal of 4-Nitrobenzaldehyde (100 MHz, $CDCl_3$) (132)

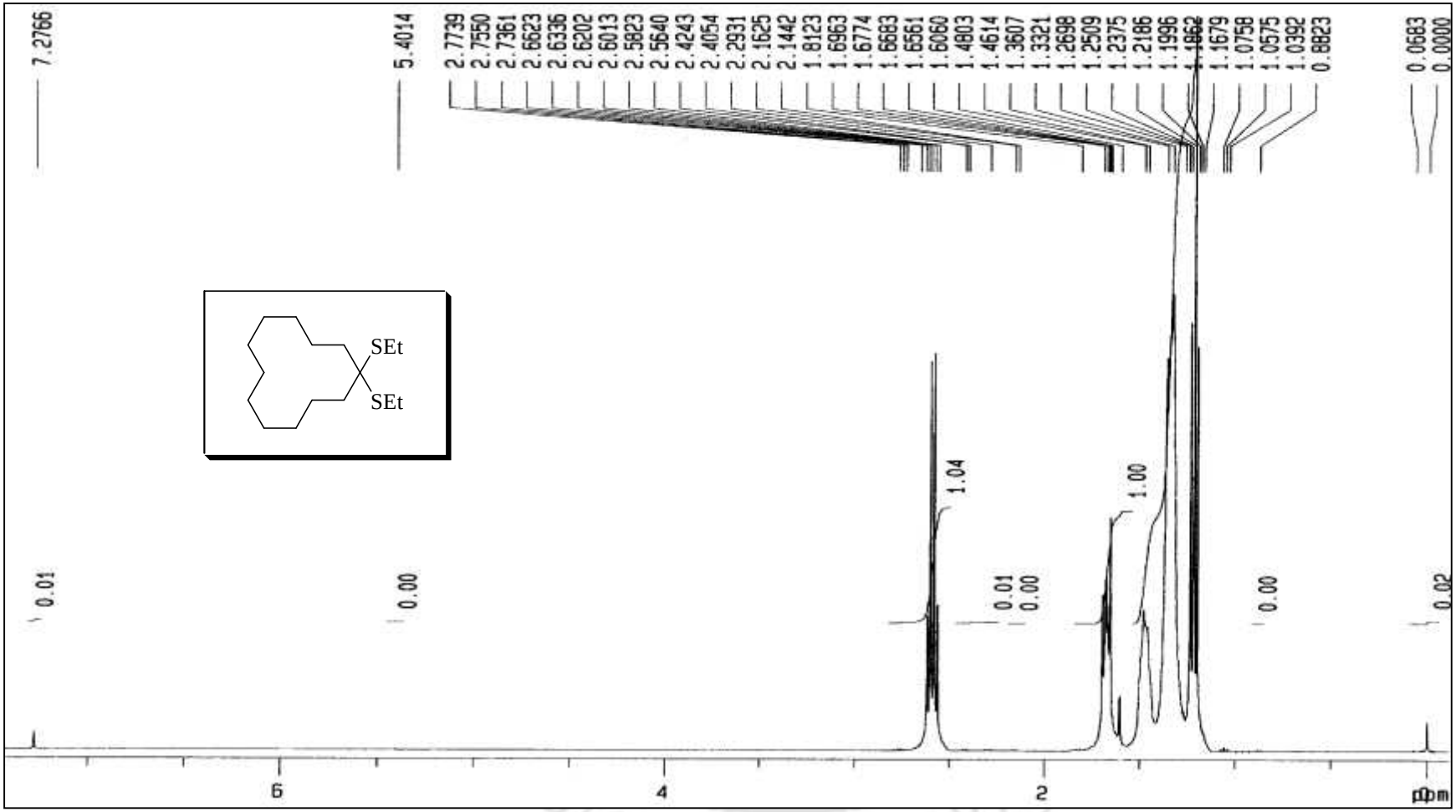


Figure 29: ^{1}H NMR Spectrum of diethyldithioacetal of Cyclododecanone (400 MHz, $CDCl_3$) (188)

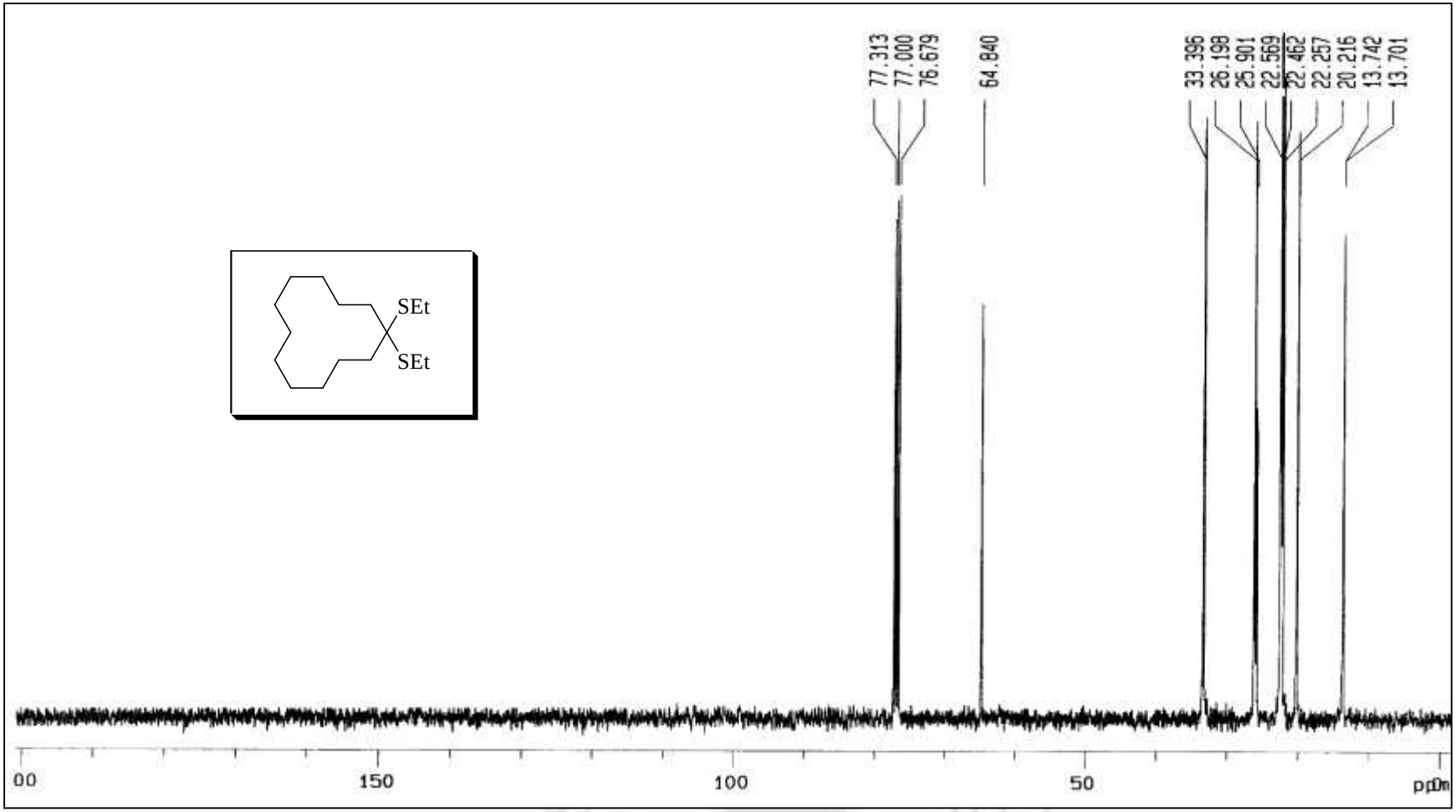


Figure 30: ^{13}C NMR Spectrum of diethyldithioacetal of Cyclododecanone (100MHz, $CDCl_3$) (188)

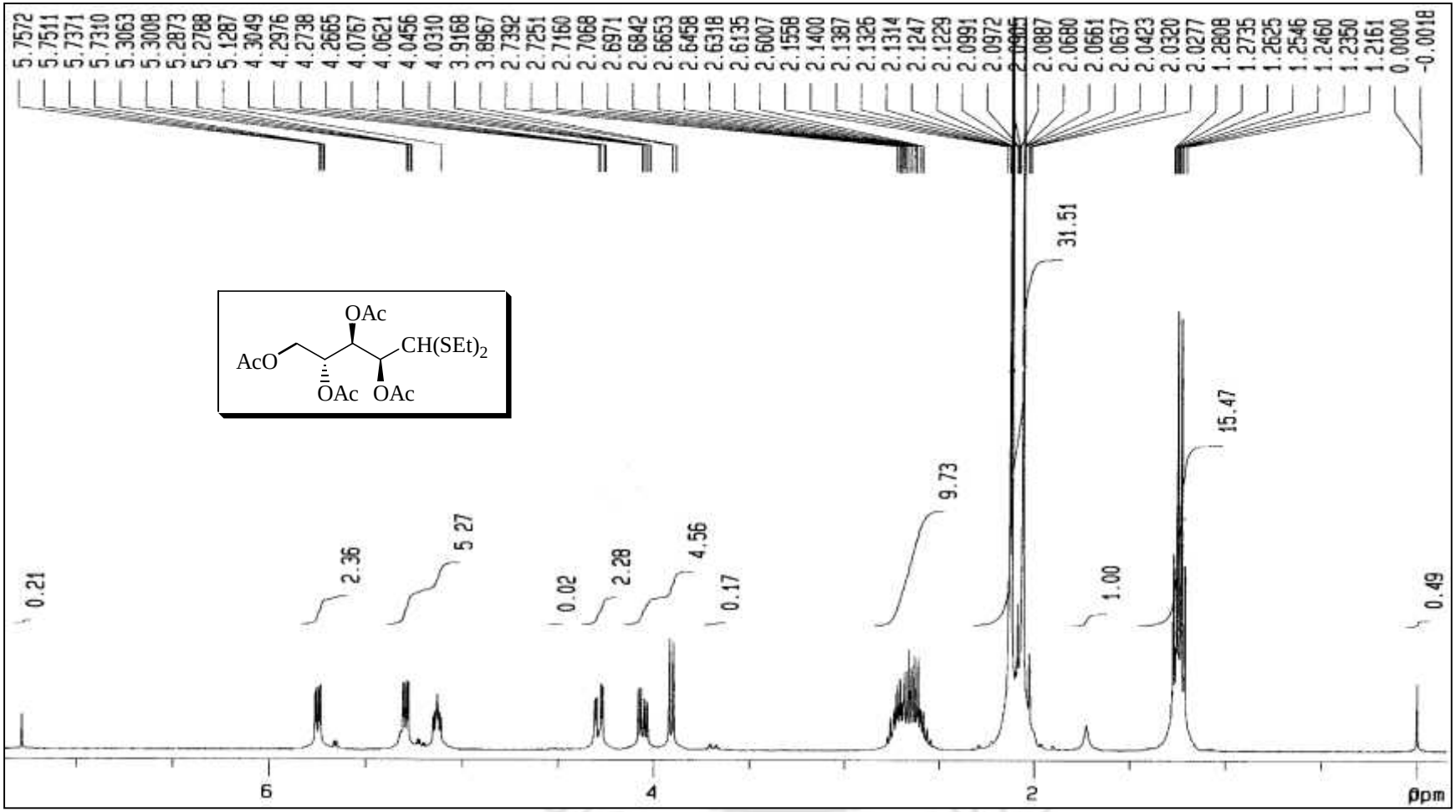


Figure 31: ^{1}H NMR Spectrum of Diethyldithioacetal of tetraacetate Arabinose (400 MHz, $CDCl_3$) (135)

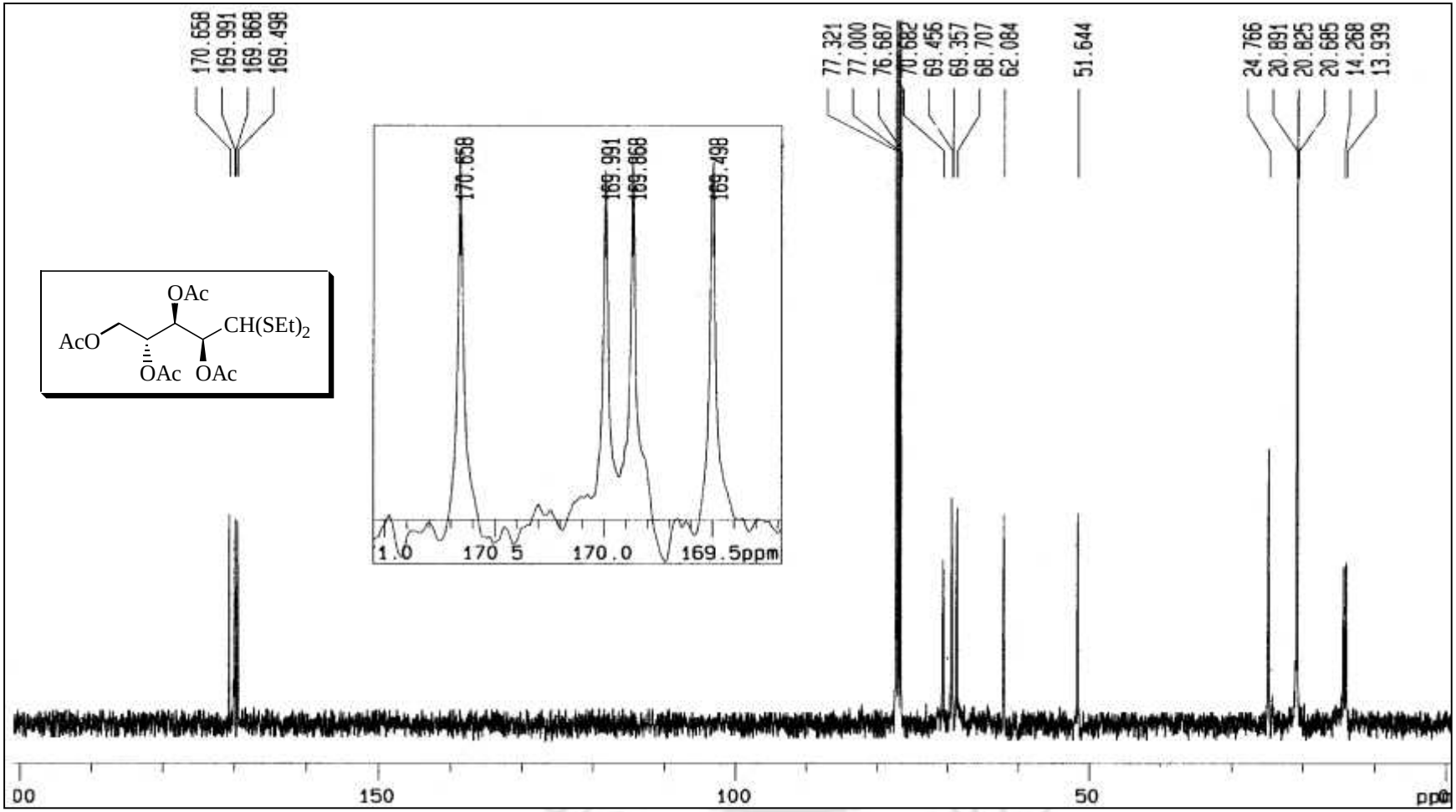


Figure 32: ^{13}C NMR Spectrum of Diethyldithioacetal of tetraacetate Arabinose (100 MHz, $CDCl_3$) (135)

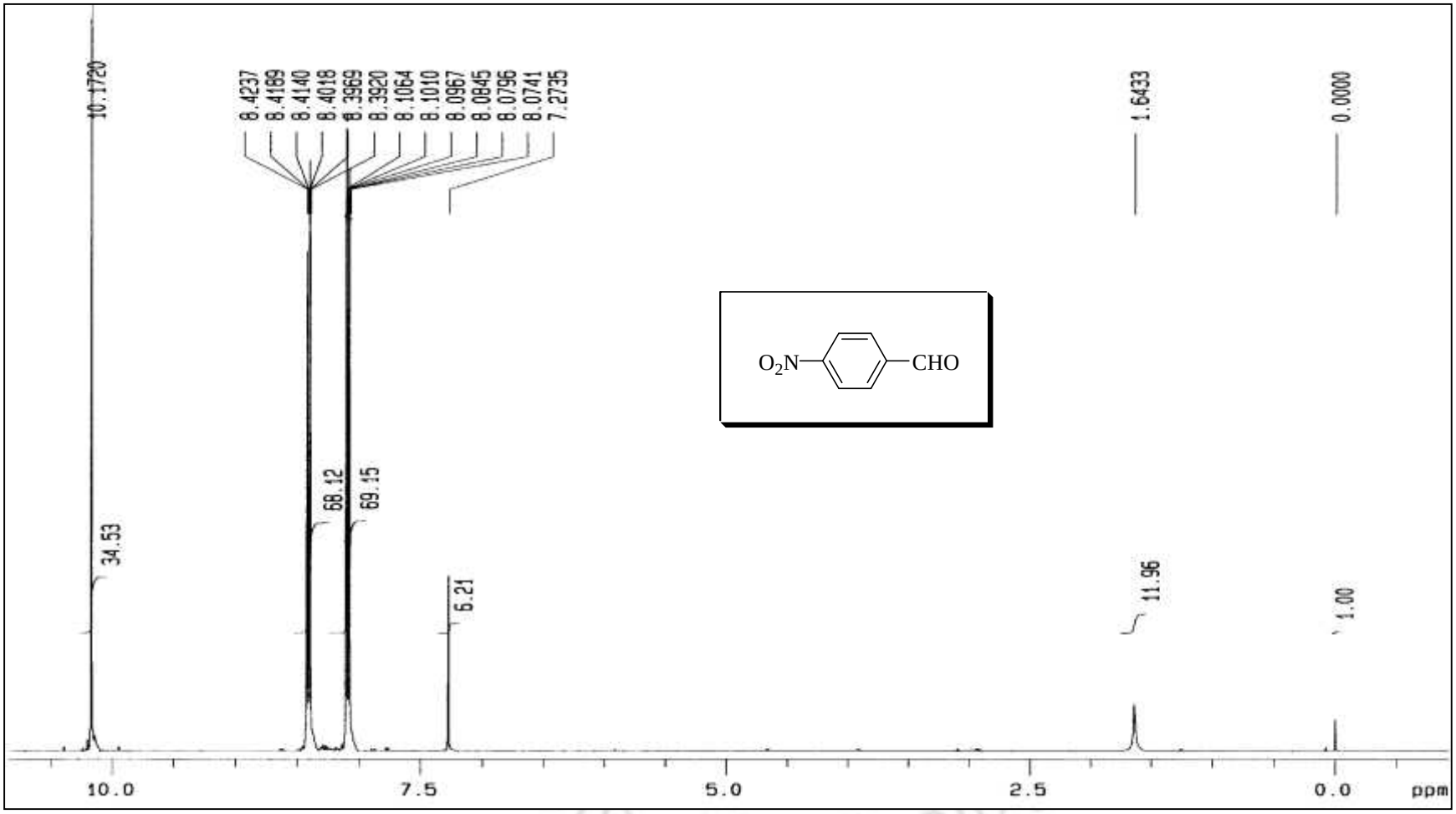


Figure 33: ^{1}H NMR Spectrum of 4-Nitrobenzaldehyde (400MHz, $CDCl_3$) (191)

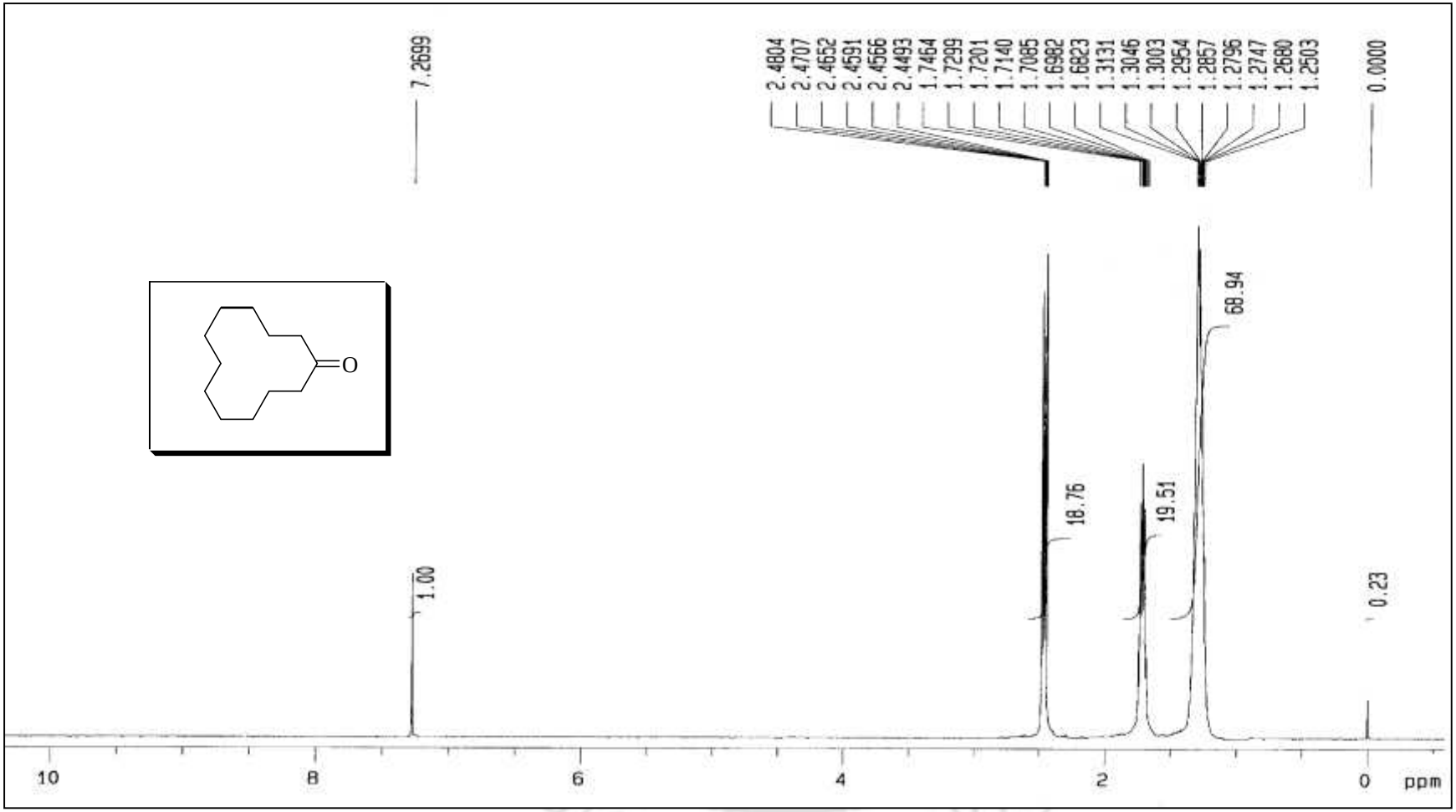


Figure 34: ^{1}H NMR Spectrum of Cyclododecanone (400MHz, $CDCl_3$) (193)

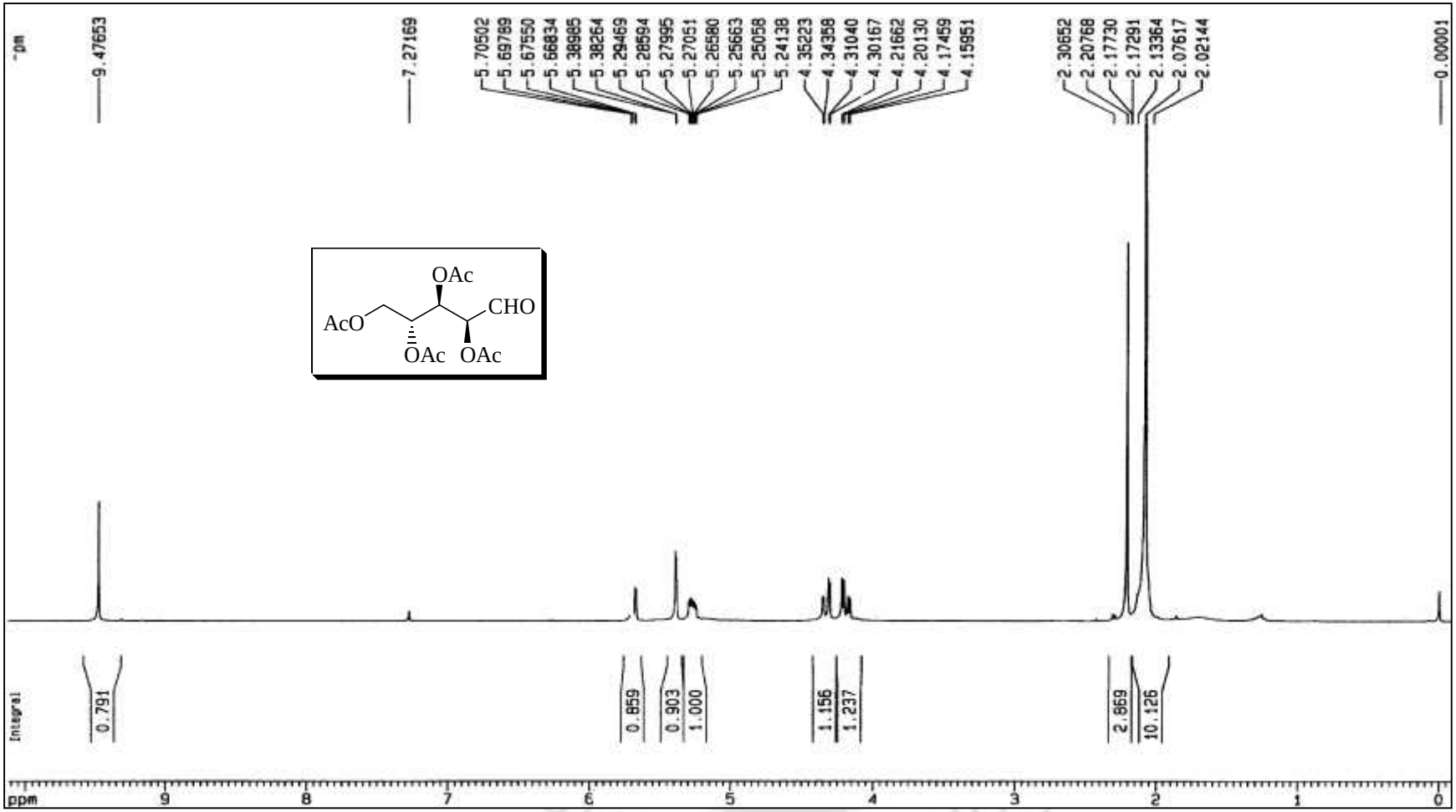


Figure 35: ^{1}H NMR Spectrum of Tetraacetate Arabinose (300 MHz, $CDCl_3$) (194)

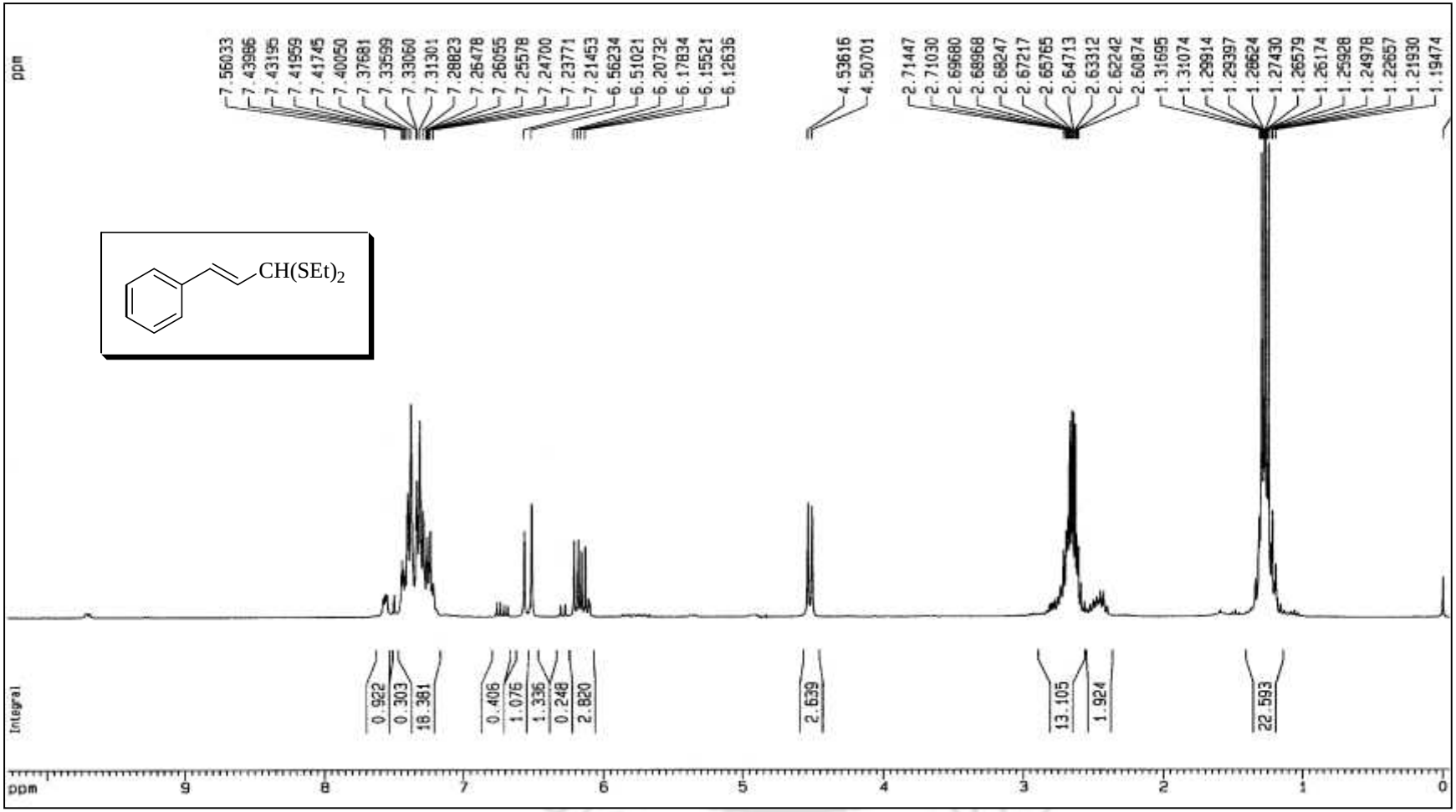


Figure 36: ^{1}H NMR Spectrum of Diethyldithioacetal of Cinnamaldehyde (300MHz, $CDCl_3$) (210)

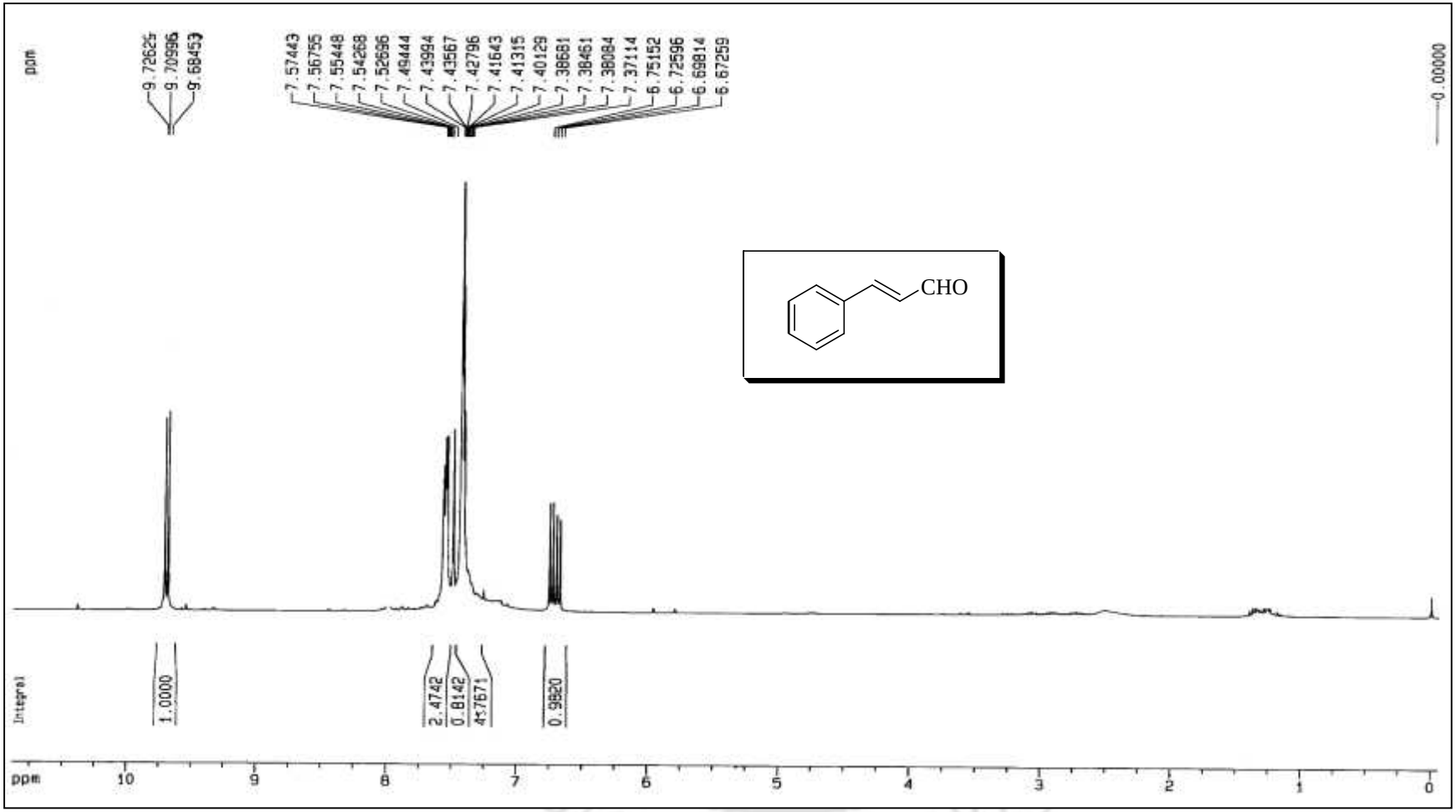


Figure 37: ^{1}H NMR Spectrum of Cinnamaldehyde (300MHz, $CDCl_3$) (151)

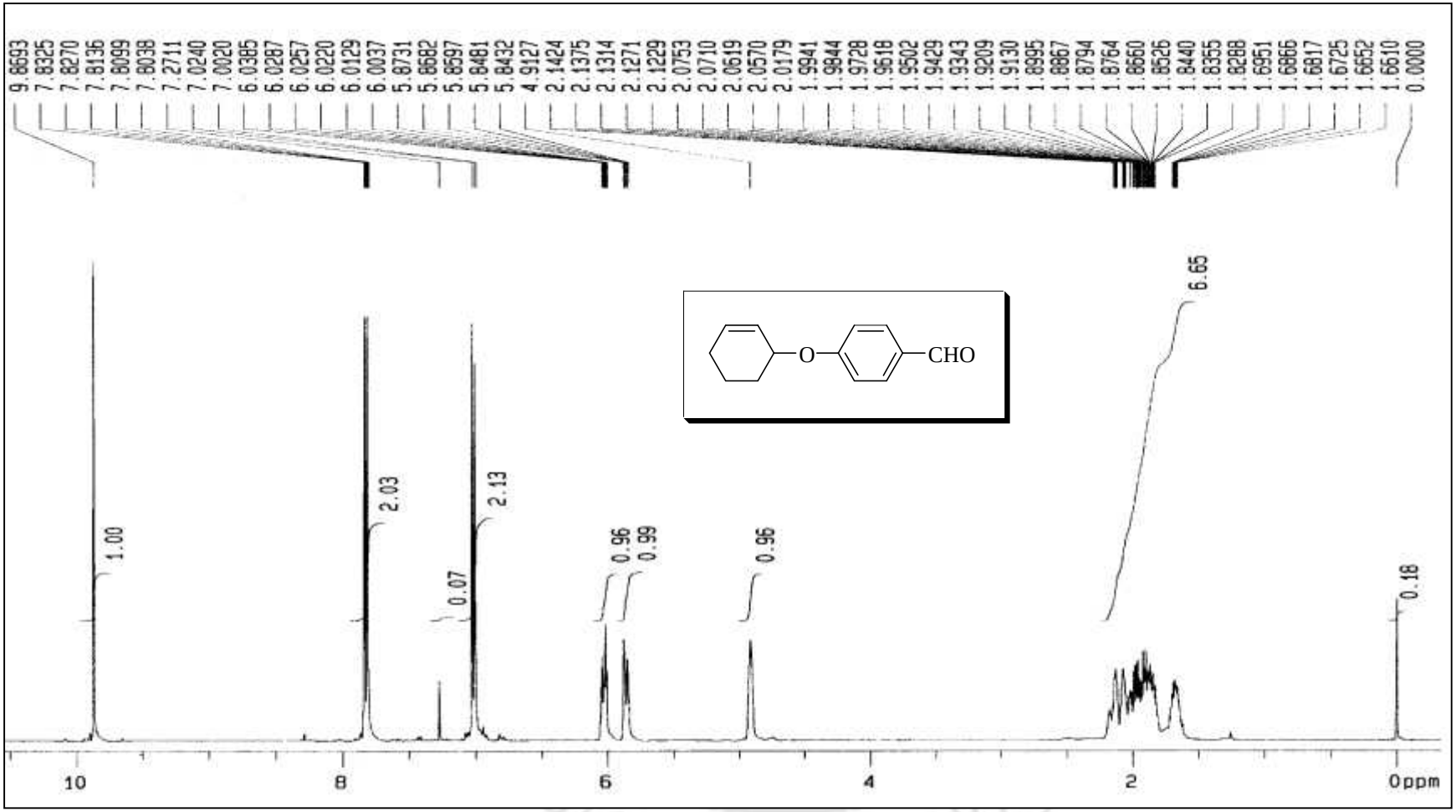


Figure 38: ^{1}H NMR Spectrum of 4-Cyclohexenyloxybenzaldehyde (400MHz, $CDCl_3$) (218)

Figure 39: ^{1}H NMR Spectrum of 2[2à-*tert*-Butyldimethylsilyloxyphenyl]-1,3-dithiane (400MHz, $CDCl_3$) (133)

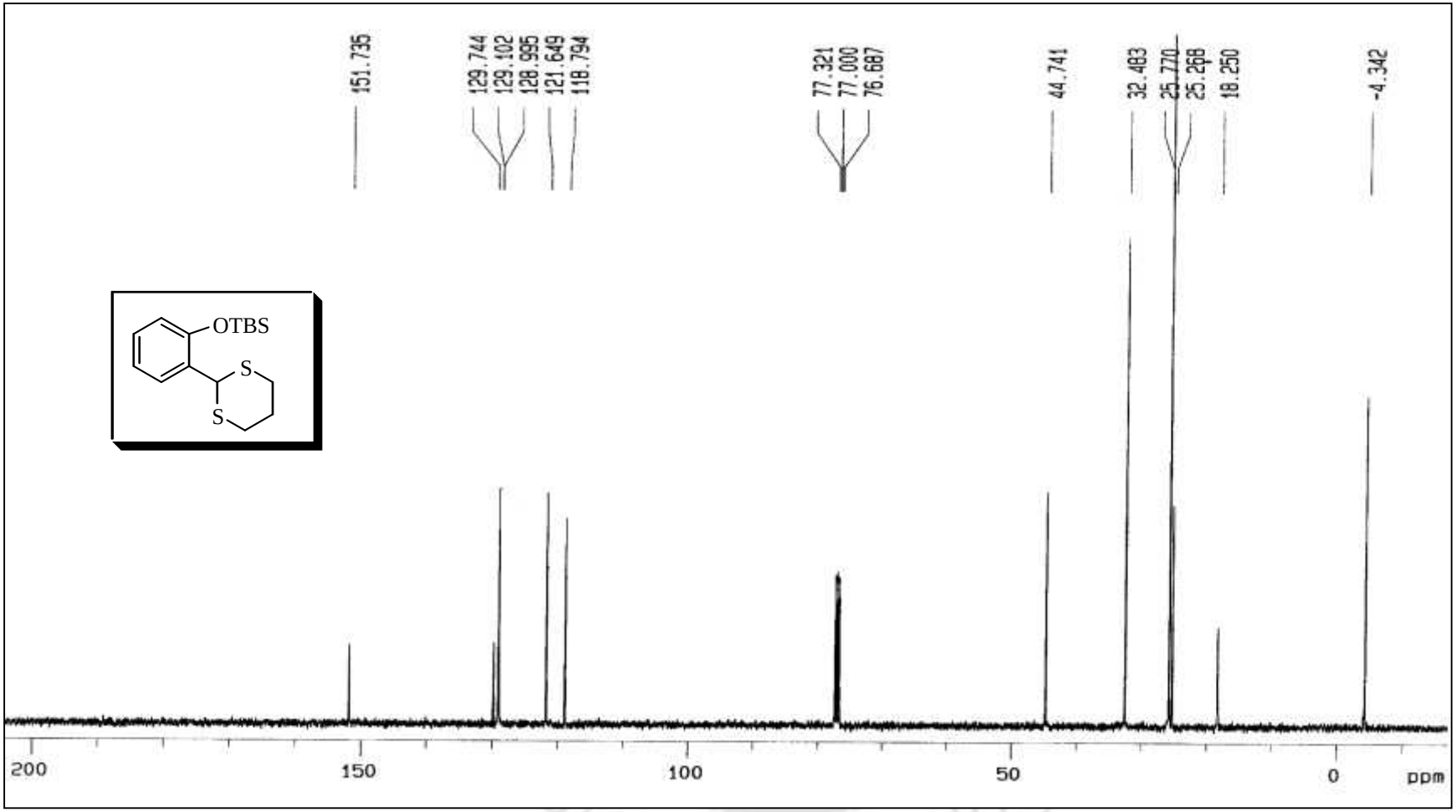


Figure 40: ^{13}C NMR Spectrum of 2[2à-*tert*-Butyldimethylsilyloxyphenyl]-1,3-dithiane (100MHz, $CDCl_3$) (133)

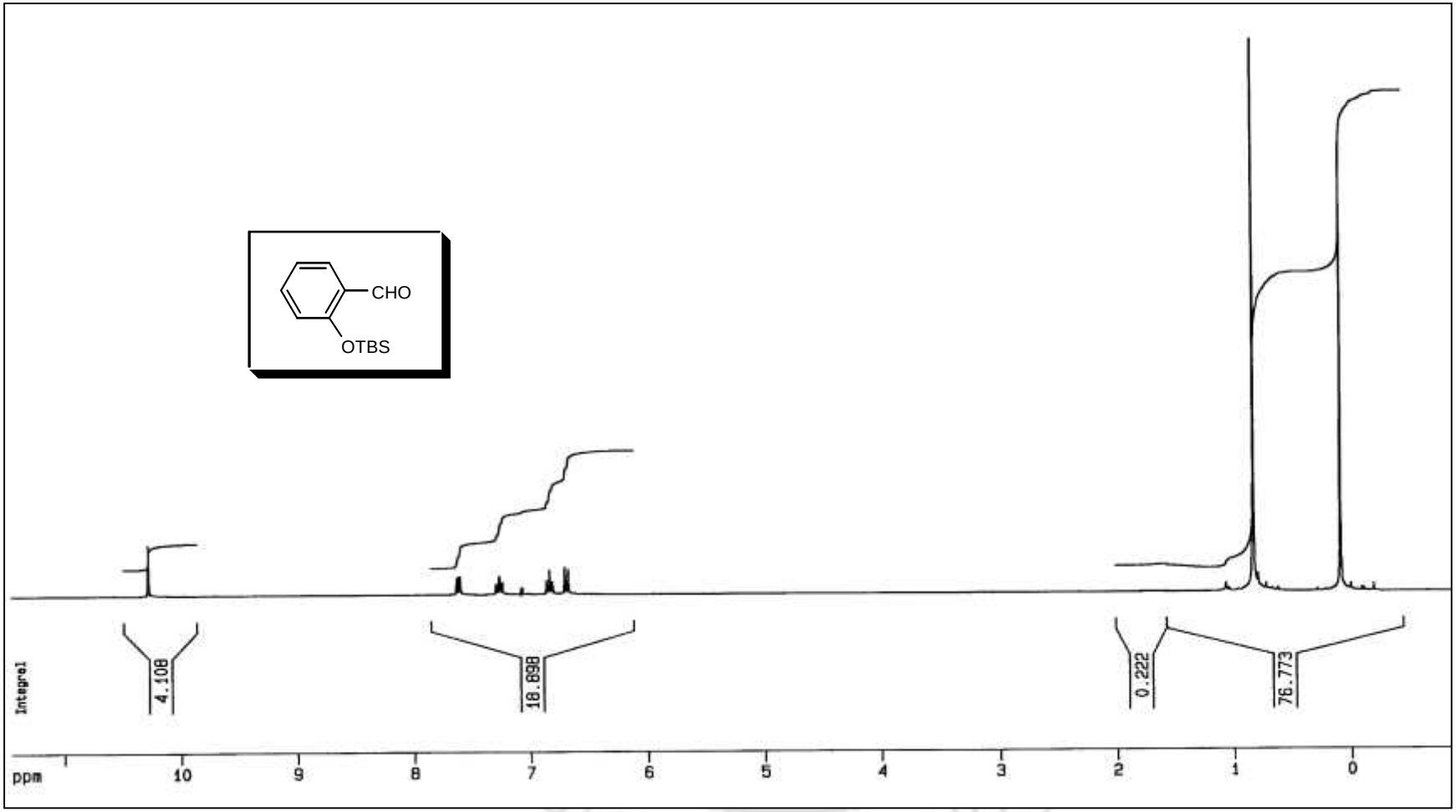


Figure 41: ^{1}H NMR Spectrum of 2à-*tert*-Butyldimethylsilyloxybenzaldehyde (300MHz, $CDCl_3$) (204)

CHAPTER II

PART I & II

(SECTION E)

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CHAPTER III

PART I

BRIEF LITERATURE SURVEY ON THE CLEAVAGE OT *TERT*-BUTYLDIMETHYL-SILYL (TBS) ETHERS TO THE HYDROXYL COMPOUNDS

Introduction

The hydroxyl group is present in a number of biologically active compounds such as nucleosides, carbohydrates, steroids, macrolides, polyethers, peptides, and amino acids. The protection-deprotection strategy for a free hydroxyl group has become a common feature to manipulate other functional groups particularly in polyfunctional natural and non-natural product synthesis. In multifunctional molecules, the selective protection of one functional group in the presence of others becomes essential that has been emphasized by the development of a number of new methods. Several protecting groups have been cited in the literature for the protection of hydroxyl groups. Among them, silyl ether is one, which is most frequently used for protection of hydroxyl groups in organic synthesis.

The silylation of alcohols as *O*-silyl ether was first introduced in the late 1950′s to increase the volatility and stability of polar compounds during gas chromatography and mass spectrometry. Due to their easy and recently developed selectivity of attachment, a host of di- and tri-alkyl silyl groups have been commonly used for protection of free hydroxyl groups over the last three decades. The reason for the wide popularity of the silicon protecting groups is that they are easily formed and cleaved under the mild reaction condition and their relative stability can be finely tuned by simply varying the substituents on the silicon.[1] As a general rule, the bulkier the substituents, the greater the stability of the *O*-silyl ethers towards the acids and base. Relative stability of trialkyl silyl ethers towards acid catalyzed hydrolysis are as fellows:

TMS ≈ DMPS ≈ MDPS< TES ~ DMIPS ≈ Pr_3Si ≈ Bu_3Si < TPS < MDIPS < TBS < TDS< TIPS < TBDPS < DTBMS.

Similarly, if the same protecting group is used to protect two or more hydroxyl groups, the silyl ether derived from less sterically encumbered alcohol is usually the first to be deprotected. In general, an increase in substituent size on either the silicon or the alcohol carbon decreases the rate of desilylation.[1a]

The electronic factors also play an important role in determining the stability, which can be exploited to differentiate stability under acidic and basic conditions. Generally, electron withdrawing substituents on silicon accelerate the base catalysed hydrolysis of silyl ethers while electron donating groups accelerate acid catalyzed hydrolysis.[1c] Among various silyl ethers, TBS ether has become one of the most popular silyl ether

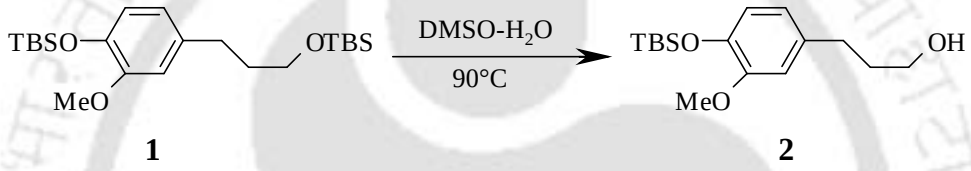
protecting groups used extensively in chemical synthesis. The TBS ether group was first introduced by Stork[2] in 1968. It is easily introduced with a variety of reagents, has the virtue of being quite stable to a variety of organic reactions, and is readily removed under conditions that do not attack other functional groups. It has excellent stability toward base, but is relatively sensitive to acid. The ease of introduction and removal of the TBS ether at the later stage are influenced by steric factors that often allow for its selective introduction in multi-functionalized sterically differentiated molecules. This chapter contains a brief review on the method for the cleavage of TBS ether.

A large number of methods[3] for deprotection of TBS ethers are known in the literature. Nelson and Crouch[4] have thoroughly reviewed the selective deprotection of silyl ethers in the presence of other like or unlike silyl ethers. Our present review has been focused on some of the very recent methods for the cleavage of TBS ethers based on their importance, merits and demerits.

One of the most effective ways for the cleavage of TBS, TBDPS and TDS silyl ethers is usually achieved by the exploitation of fluoride ion because of its high affinity towards silicon. The strength of the Si-F bond has been claimed as the main driving force of the reaction between TBS ethers and fluoride anion.[5] For successful deprotection of various TBS ether, tetrabutylammonium fluoride has been extensively used till date.[5] But the main disadvantage is the high cost of the reagent itself. In addition, many other routes for the deprotection of the trialkylsilyl ethers have been developed by involving one form of fluoride or another such as boron trifluoride etherate,[6a] hydrofluoric acid,[6b] fluorosilicic acid,[6c] ammonium fluoride,[6d] silicon fluoride,[6e] and lithium tetrafluoro-borate.[6f] The use of tetrabutylammonium fluoride has some serious limitations due to the strong basicity of the 'naked' fluoride ion in THF[7] which directly affects cleavage of TBS ethers to the β-ketol system[5a] and of phenolic compounds[8] and may promote β-elimination reactions,[9] transacylations,[10] and other base catalysed side reactions.[11] In addition, the phase transfer properties of the tetrabutylammonium cation often causes difficulties in work-up and purification of the products. Although the development of acidic reagents like boron trifluoride etherate,[6a] hydrofluoric acid[6b] and fluorosilicic acids[6c] overcomes some of these difficulties, restrictions towards acid sensitive functionalities remain. Use of relatively mild lithium tetrafluoroborate[6f] seems to be promising in this endeavor, but these reactions usually take longer times. Again, as a reagent lithium tetrafluoroborate is not very practical being moisture-sensitive, irritant and relatively costly.[12]

Wilson and Keay have reported[13] the basic reagent for selective deprotection of phenolic TBS ether by using K_2CO_3 in aqueous ethanol.

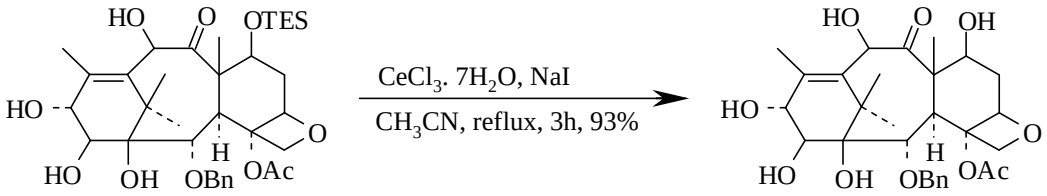
Maiti and Roy have reported a procedure[14] for selective cleavage of primary, allylic and homoallylic, primary benzylic and aryl *tert*-butyldimethylsiltyl ethers under neutral conditions using a combination of H_2O and DMSO at 90 °C. A large number of other protecting groups such as methylenedioxy ethers, benzyl ethers, methyl esters, aldehyde functionality and a highly acid sensitive group such as THP ethers are unaffected under the reaction conditions. Primary TBS ethers are selectively cleaved in presence of aryl TBS ethers as shown in the scheme 1. However, secondary TBS ethers are intact under the reaction conditions.



1 **2**

Scheme 1

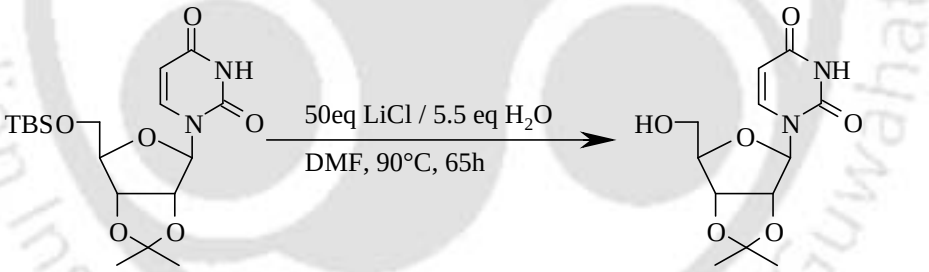
Bartoli *et al* have shown[15] the use of reagents $CeCl_3 \cdot 7H_2O$ in combination with NaI for the deprotection of various trialkylsilyl ethers such as triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS), triisopropyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) ethers in acetonitrile. Use of cerium(III) chloride heptahydrate in acetonitrile has some advantages as nitro, esters, *tert*-butyloxycarbonyl (BOC), acetate, benzyl and THP ether groups survive under the reaction conditions. Further, TBS ethers bearing stereogenic centers can be cleaved by providing the parent alcohols with complete retention of the original configuration and even E-Z isomerisation was not observed under the reaction conditions. Compelx molecules, e.g., baccatin II derivative can also be deprotected without migration of acetate and the oxetane ring is left intact as shown in scheme 2. But, the cost of the reagent is the main drawback of this protocol.



3 **4**

Scheme 2

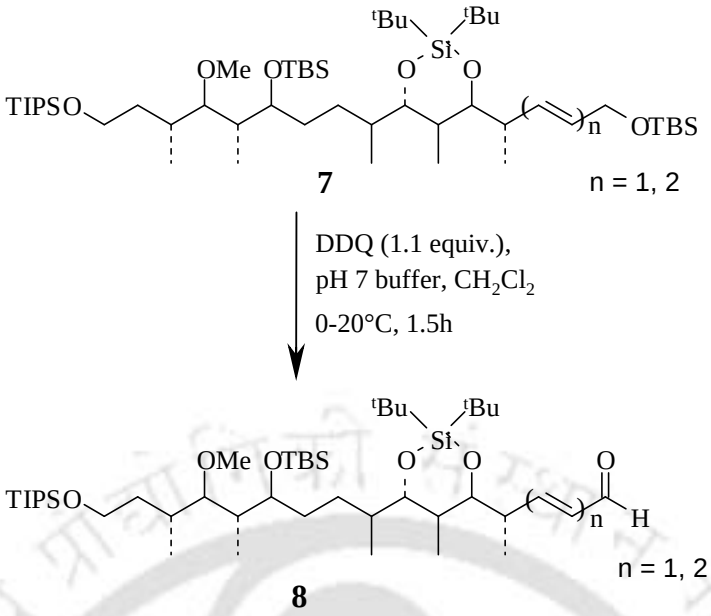
Farras *et al* have demonstrated[16] the selective cleavage of *tert*-butyldimethylsilyl ethers in the presence of *tert*-butyldiphenylsilyl by employing a combination of H_2O and a concentrated solution of LiCl in DMF at 90°C. This method seems to be appropriate for the cleavage of TBS ethers in the presence of other sensitive functional groups such as isopropylidine as shown in scheme 3 under strictly neutral reaction medium. However, this method has certain drawbacks as it requires excess amount of reagent (50 mmol) and longer reaction time as well as harsh reaction conditions. Moreover, this method was unsuccessful for cleavage of aryl silyl ethers.



5 **6**

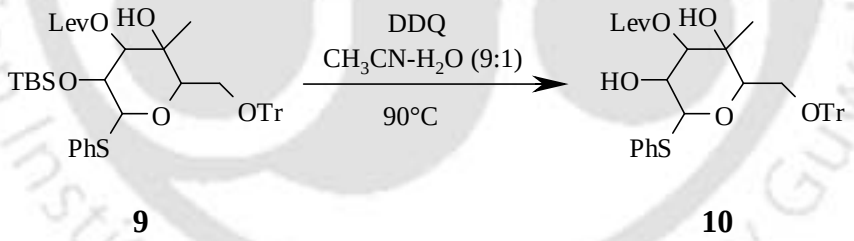
Scheme 3

Paterson group have achieved[17] the selective oxidation/deprotection of allylic and benzylic silyl ethers to aldehyde by using DDQ under neutral conditions (pH 7 buffer). During the synthesis of aplyronine A, a 24-membered cytotoxic macrolide isolated from the sea hare *aplysia kurodal*, they have observed that DDQ is an efficient reagent for cleavage of allylic silylethers to the allylic aldehyde. The most important significance of this protocol is that sterically hindered silyl ethers such as TIPS, secondary TBS ethers and PMB did not cleave under the reaction conditions as shown in the scheme 4.



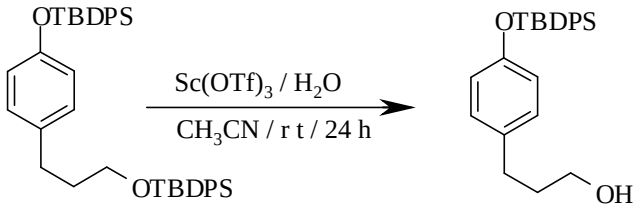
Scheme 4

However, Kakarla group[18] have shown the selective cleavage of TBS ether to the corresponding alcohol by employing DDQ in wet acetonitrile without over oxidation as well as detriment of other sensitive functional groups, as represented in scheme 5.



Scheme 5

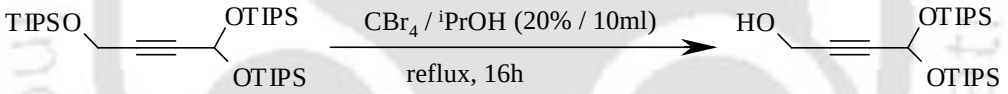
Oriyama and his group reported a convenient synthetic protocol for cleavage of primary and secondary alkyl trialkylsilyl ethers in the presence of aryl silyl ethers using catalytic amount of $Sc(OTf)_3$.[19] They have also demonstrated that a primary TBS or TBDPS ethers cleaved selectively in presence of phenolic TBS or TBDPS ether under the reaction condition as represented in scheme 6.



11 **12**

Scheme 6

Lee and co-workers reported[20] the selective cleavage of primary and secondary TBS, TBDPS and TIPS ethers to their corresponding alcohols by employing carbon tetrabromide (CBr_4) in methanol under refluxing conditions. In isopropanol, the desilylating rate is very slow which allows selective deprotection of primary triisopropyl silyl ether in presence of secondary one, as shown in scheme 7. However, this method is not applicable for substrates containing acid sensitive functionalities such as acetal/ketal, tetrahydropyranyl ether, silyl ester because they are also hydrolyzed during the reaction conditions.

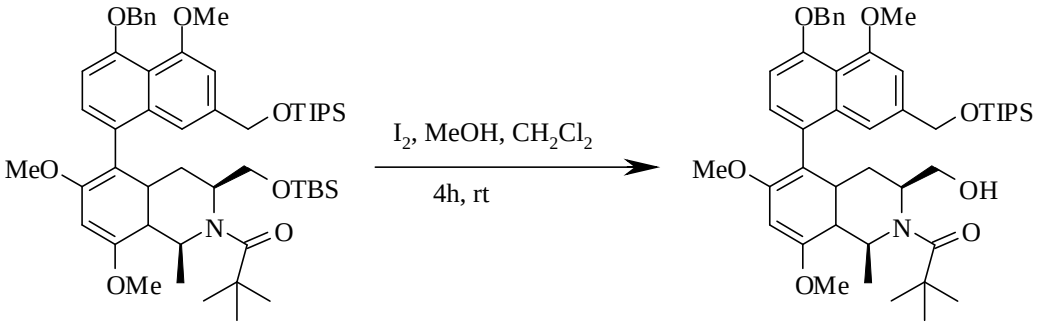


13 **14**

Scheme 7

Later on, Lee *et al* modified this method[21] and it was further applied in carbohydrate molecules for regioselective TBS ethers cleavage under photochemical reaction conditions.

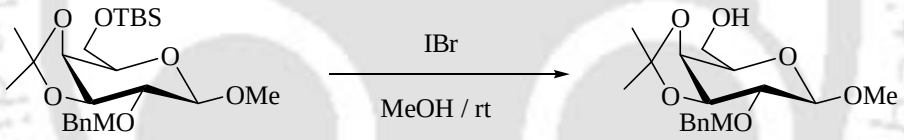
Lipshutz and Keith have shown[22] the application of 1% iodine in methanol for selective cleavage of trialkyl silyl ethers in presence of aryl silyl ethers. This method is also applicable for TBDPS and TIPS ethers cleavage but it takes relatively much longer reaction times for completion. The rate discriminate is sufficient for selective cleavage of primary TBS ether in presence of primary TIPS ether as represted in scheme 8.



15 **16**

Scheme 8

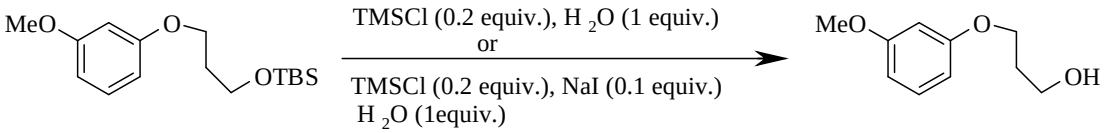
Kartha and Field have demonstrated[23] the facile deprotection of TBS ethers of simple alcohols, carbohydrates and nucleosides on treatment with iodine monobromide in methanol at room temperature. Under the reaction condtions a large number of sensitive functional groups such as acetals, PMB ethers, TBDPS ethers, esters and amides are stable as shown in scheme 9. But the method fails to deprotect the substrate containing a thio group at the anomeric position of carbohydrate compounds.



17 **18**

Scheme 9

Grieco and Markworth have reported[24] that a combination of TMSCl and water or TMSCl and NaI in water for selective cleavage of alkyl TBS in presence of aryl silyl ethers as shown in scheme 10. They have proposed that *in situ* generated HCl or HI is responsible for hydrolysis of TBS ether. But it was unsuccessful for cleavage of aryl silyl ethers by this method. The main drawback of this protocol is it requires longer reaction times and expensive TMSCl.

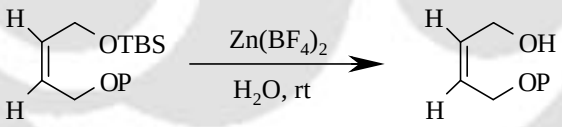


19 **20**

Scheme 10

Ramasamy and Averett had shown[25] the selective removal of TBS ethers in presence of TBDPS ethers by employing new reagent *O*-(Benzotrizol-1-yl)-N,N,N,N,-tetra-methyluronium tetrafluoroborate(TBTU), a source of hydrofluoric acid and boric acid in reaction medium which may be cause for silyl ethers cleavage. However, during the experimental conditions other sensitive functional groups such, as THP, DMT ethers and isopropylidine group did not survived. Moreover, TBTU is expensive and use of excess reagent makes it inconvenient for general purpose.

Ranu and his group reported[26] the deprotection of TBS ethers by using zinc tetrafluro-borate in water at room temperature. A large number of functional groups such as carbonyl, esters, urethanes, double or triple bonds are not affected under the reaction conditions. A substrate containing a highly acid sensitive group such as THP ether is stable during the reaction, as shown in scheme 11. However, side reactions may occur due to nucleophilicity of the fluoride ion.



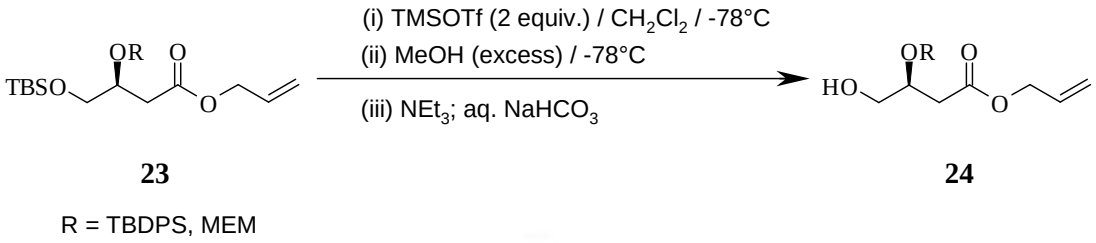
21 **22**

P = THP, Ac, Bz and TBDPS

Scheme 11

Hunter and co-workers have modified[27] the chemoselective silyl ethers deprotection by employing TMSOTf followed by breakdown of the *bis*-silyloxinium ion produced as intermediate in methanol as shown in scheme 12. This method is applicable for both primary and secondary silyl ethers as well as chemoselective with respect to TBDPS, TIPS, ester, ketal, MEM, acetate, benzoate and N-Boc functionalities. The

disadvantage of this protocol is the reagent itself is highly expensive and difficult to handle.

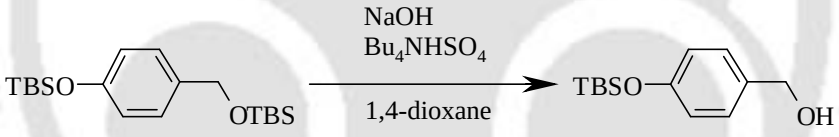


23 **24**

R = TBDPS, MEM

Scheme 12

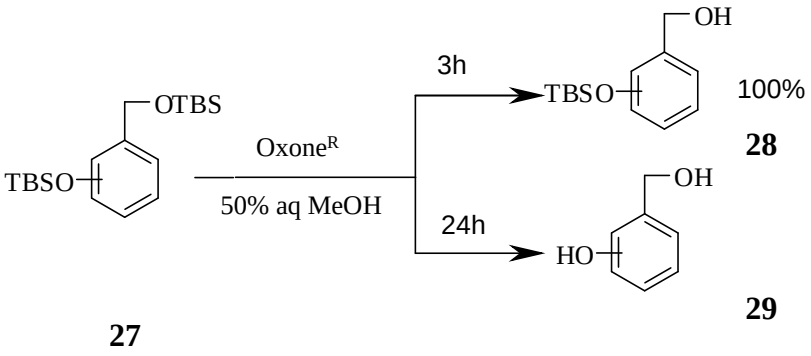
Crouch and his group[28] demonstrated the selective deprotection of aryl TBS ethers in presence of alkyl TBS ethers to provide phenols in good to excellent yields by using 10 equivalents amount of NaOH and catalytic Bu_4NHSO_4 in biphasic solvent system. Alkyl silyl ethers and other base sensitive functional groups such as ester, acetate do not affect during the experimental conditions, which allows ultimately chemoselective deprotection of aryl silyl ether as shown in scheme 13.



25 **26**

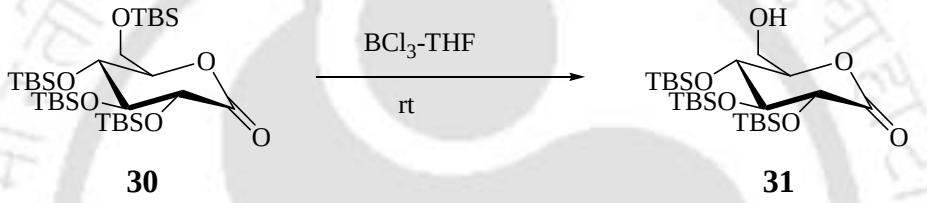
Scheme 13

Yadav and his co-workers described[29] the selective cleavage of primary and aryl TBS ethers by employing potassium peroxymonosulfate, which is known as oxone, in 50% aqueous methanol under mild conditions. Primary TBS ethers can be selectively deprotected to the corresponding alcohol in presence of aryl TBS ethers whereas secondary and *tert*-silyl ethers are stable under the reaction conditions as represented in scheme 14. THP, *N*-Boc and *N*-CBz groups are unaffected under the reaction conditions although the pH of the reaction mixture ~2.8.



Scheme 14

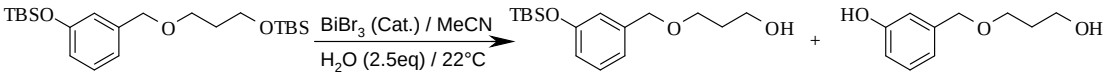
Yang *et al* have shown[30] that BCl_3 in THF is a useful reagent for regioselective cleavage of primary TBS ethers in presence of secondary TBS ethers in carbohydrate chemistry as depicted in scheme 15.



Scheme 15

Later on, Yadav's group again reported[31] that $InCl_3$ for selective cleavage of alkyl TBS ethers in presence of aryl TBS ethers in aqueous CH_3CN under refluxing condition. All the sensitive functional groups such as Boc, CBz, Obz, OAc, O-allyl, OTBDPS, esters and olefinic groups are stable under the reaction conditions. Harsh reaction condition and cost of the reagent are two important drawbacks of this protocol.

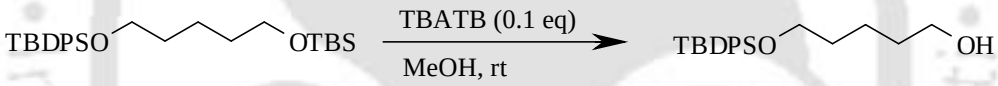
Bajwa and his co-workers have shown[32] the selective cleavage of alkyl TBS ethers in presence of aryl silyl ethers using catalytic amount of $BiBr_3$ in wet acetonitrile at room temperature. The reaction conditions are sufficiently mild for selective deprotection of TBS ethers allowing esters, ethers, sulfonamides and benzyl carbamates inert as represented in scheme 16. They have also pointed out that the hydrolysis can be achieved by bismuth bromide in water. The main drawback is that bismuth bromide is relatively expensive.



32 **33** **34**

Scheme 16

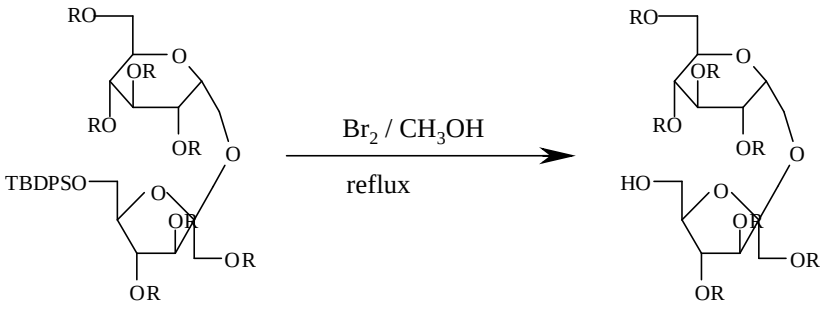
Gopinath and Patel have demonstrated[33] that organic ammonium tribromide, namely tetrabutylammonium tribromide (TBATB) is a useful reagent for selective cleavage of TBS ethers in methanol at room temperature. Several other protecting groups such as OBn, OBz, OAc, THP ether and even isopropylidine groups are stable under the reaction condition. They have also mentioned that the substrates containing double or triple bonded TBS ether are cleaved selectively without affecting either double or triple bond during reaction conditions. The TBS ethers can also be selectively hydrolyzed in presence of TBDPS ethers as shown in scheme 17. The disadvantage of this protocol is the reagent has to be prepared prior to use. In addition, it is comparatively expensive reagent.



35 **36**

Scheme 17

Barros *et al* reported[34] molecular bromine in methanol as a good combination for the deprotection of a *tert*-butyldiphenylsilyl (TBDPS) ether in the presence of other groups such as methyl ester, methyl ether, benzyl, tosylate, and benzoate or tri-*O*-methyl gallate under refluxing conditions as shown in scheme 18. The scope of the reagent has been further extended for deprotection of silyl amines and silyl esters, and it has also shown good selectivity in the removal of a TBS ether in presence of a TBDPS one. The disadvantage of this protocol is that molecular bromine is hazardous and difficult to handle.



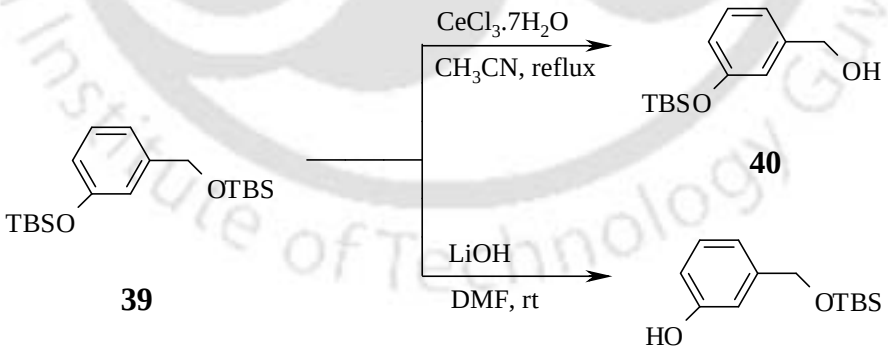
37 **38**

R = Bn, Bz, Gal(OMe)$_3$

Scheme 18

Recently, Yoon and his group reported the cleavage of TBS ether of aliphatic alcohols in THF-MeOH or methanol chemoselectively to the corresponding alcohol using a sub-stoichiometric amount of decaborane[35] at room temperature under nitrogen. But, this method was unsuccessful for the cleavage of aryl TBS ether, TBDPS, and TIPS ether. One of the important drawbacks is that the reagent is air sensitive.

Ankala and Fenteany have developed[36] two different reaction conditions for selective cleavage of TBS ethers by using two different reagents. Alkyl TBS ethers are cleaved in presence of aryl TBS ethers by employing $CeCl_3.7H_2O$ in acetonitrile whereas deprotection of aryl TBS ethers are possible in presence of alkyl TBS ethers by using LiOH/DMF under mild condition as depicted in scheme 19.

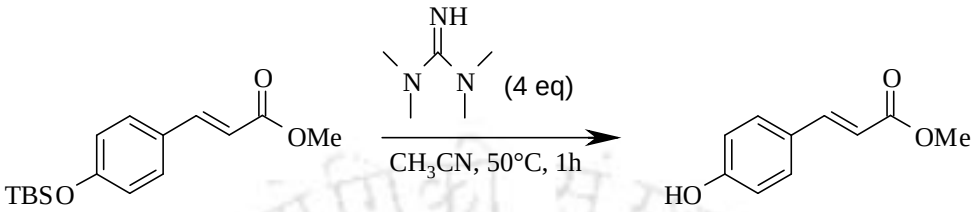


39 **40** **41**

Scheme 19

Very recently, Oyama and Kondo have shown[37] that 1,1,3,3-tetramethylguanidine (TMG), a nitrogen base, is a convenient and useful reagent for chemoselective deprotection of TBS ethers groups on acidic hydroxyl groups such as phenol and carboxylic acid without affecting aliphatic TBS group as depicted in scheme 20. They

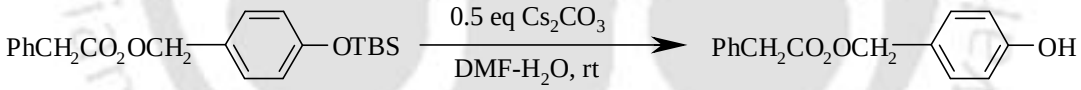
have shown that phenolic silyl ethers bearing an electron-withdrawing group are deprotected more easily than those bearing an electron-donating group. Phenolic TBS or TBDPS ethers are completely desilylated without affecting aliphatic TBS or TBDPS ethers under the reaction conditions.



42 **43**

Scheme 20

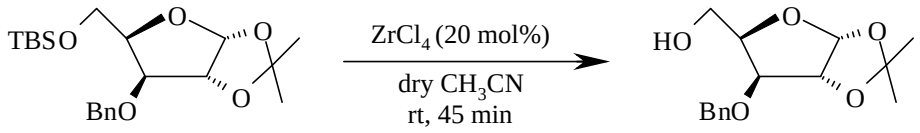
Jiang and Wang have described[38] the selective cleavage of aryl silyl ether to phenol by using cesium carbonate in DMF-H_2O at room temperature. The aryl sily ethers are cleanly cleaved to give the corresponding phenols in presence of TBS ether of alcohols. Various other groups such as esters, THP, sulfonate groups and phenyloxycarbonyl protected alcohols are unaffected during reaction conditions as represented in scheme 21.



44 **45**

Scheme 21

Sharma and his group reported[39] a synthetic protocol for selective deprotection of TBS ethers by using 20 mol% $ZrCl_4$ in short time in acetonitrile as depicted in scheme 22. The study also demonstrated that both acid and base sensitive groups as well as allylic and benzylic groups are unaffected under the reaction conditions. This method is also applicable in sugar and terpene chemistry.



46 **47**

Scheme 22

From the literature survey, it is quite clear that many reagents have been utilized to demonstrate regio- and chemoselective deprotection of various TBS ethers over the years. We have also highlighted their advantages and disadvantages in the above discussion. However, we feel that a very simple method can still be devised by employing a less expensive reagent. Hence, our research problem aims to investigate whether the cleavage of TBS ether is possible by involving a new reagent, which is not reported earlier.

PART II

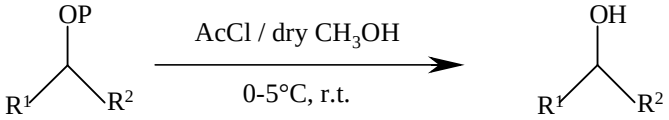
(SECTION A)

NEW SYNTHETIC PROTOCOL FOR CLEAVAGE OT TERT-BUTYLDIMETHYLSILYL (TBS) ETHERS TO THE HYDROXYL COMPOUNDS

RESULTS AND DISCUSSION

Results and Discussion

Protection-deprotection strategy is a very common tactics in polyfunctional natural and non-natural product syntheses. As far as hydroxyl group protection is concerned, silyl ethers play a pivotal role in carbohydrate and nucleoside chemistry due to their easy installation and inherent stability under basic and mild acidic conditions, with *tert*-butyldimethylsilyl (TBS) ether and *tert*-butyldiphenylsilyl (TBDPS) ether being two of the most important examples. Though a wide variety of reagents have been developed for their removal, still there is a need to develop better alternatives, which might work under mild conditions. For this purpose, a variety of fluoro, bromo, and chloro compounds have been devised over the years for the deprotection of TBS ether, which has already been discussed in in part Iof chapter III. Unfortunately, some of the methods have drawbacks such as harsh reaction conditions, failure to deprotect aryl *tert*-butyldimethylsilyl ethers, require long reaction times, involvement of expensive reagents, incompatibility with other protecting groups such as a thio group at anomeric position of the carbohydrate compounds, over oxidation, unwanted product such as acetate instead of alcohols, and requirement of a large excess of reagents. Consequently, what is needed is a methodology, which might work under mild conditions by involving economically cheaper reagents. During the development of new synthetic methodologies for protection of carbonyl compounds such as dithioacetals, we have observed that acetyl chloride in methanol[40] can be used as a source for generating dry hydrochloric acid *in situ*, which can be utilized ultimately for protection of various carbonyl compounds as dithioacetals and dithioketals, which has already been in chapter I part II in section B. These results prompted us to find out whether acetyl chloride in combination with methanol can also be used for deprotection of *tert*-butyldimethylsilyl (TBS) ethers, which was not investigated earlier by others. This chapter contains successful results for deprotection of varios *tert*-butyldimethylsilyl (TBS) and *tert*-butyldiphenylsilyl (TBDPS) ethers by employing catalytic amounts of acetyl chloride in methanol as represented in scheme 23.



R^1 = aryl / alkyl / sugar residue / nucleoside

R^2 = H / alkyl: P = TBS / TBDPS

Scheme 23

For our investigation, we had prepared various TBS ethers from the corresponding requisite alcohols. Various TBS ethers such as compound **25**, **35** and **48-71** were prepared by following standard literature procedure and their detailed characterization data are given in the experimental section. The IR and ^{1}H NMR spectra of compounds **64**, **35**, **75**, **77** and **79** are shown in figures **1-11** respectively. The compound **56** was prepared from the ester aldehyde **97**, by reduction with sodium borohydride followed silylation with TBSCl.using standard procedure which was already mentioned in scheme **33** in chapter I part II section A. The IR and ^{1}H NMR spectra of compounds **56** and **35** are shown in the figures **1-4**, respectively. The compound **67** was prepared from ethyl-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (which was prepared by the reported procedure from D-glucose in a number of steps[41] by silylation with TBSCl. The spectra of the silylated product **67** are shown in figures **5-7** for confirmation of its structure. The other silylated starting material **68** was prepared by silylation with TBDMSCl from the corresponding hydroxyl compound, which was also prepared by the reported procedure.[42] The compound **69** was obtained from D-galactose using standard procedure[43] and followed by silylation reaction with TBDMSCl. The structure of the compound **69** was confirmed by spectroscopic techniques as shown in figures **8-9**. The compound **70** was prepared directly from thymidine. However, the compound 71 was obtained by selective mono protection of thymidine followed by acetylation with acetic anhydride and pyridine. The IR and ^{1}H NMR are shown in the figures **10-11**.

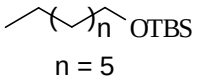
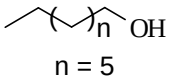
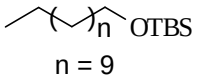
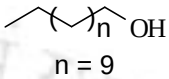
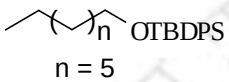
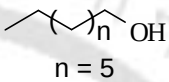
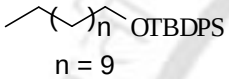
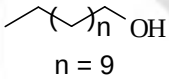
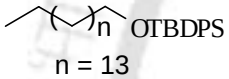
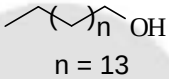
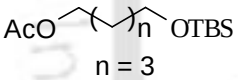
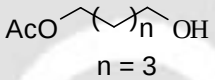
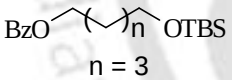
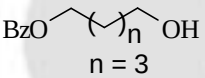
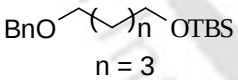
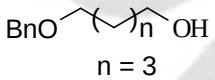
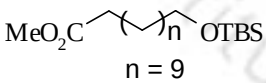
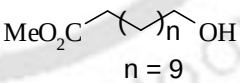
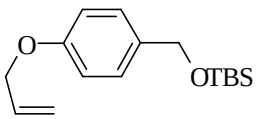
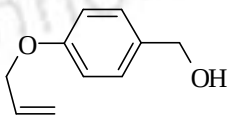
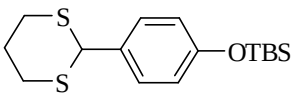
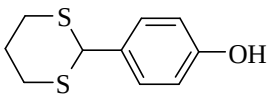
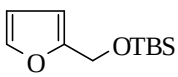
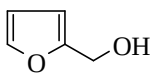
First, we attempted the reaction of *tert*-butyldimethyl silyl ether of 1-octanol (**48**) with 0.15 equivalent amounts of acetyl chloride in dry methanol at 0-5°C. After 5 min. the TLC shows a clear disappearance of starting material and usual work-up of the reaction mixture provided the corresponding desired alcohol **72** in 98% yield. Similarly, *tert*-butyldimethyl silyl ether of 1-dodecanol (**49**) was deprotected smoothly to the corresponding alcohols (97%) under same experimental conditions. The deprotected compounds **72** and **73** were characterized by IR, ^{1}H NMR. The disappearance of the signals in the region δ 0.05 (s, 6H, $Si(CH_3)_2$) and δ 0.89 (s, 9H, $SiC(CH_3)_3$) in ^{1}H NMR spectra clearly indicate the deprotection of *tert*-butyldimethyl silyl ether to their corresponding alcohols. In addition, the deprotected compounds also showed strong band at ~3396 cm^{-1} in the IR spectra, which clearly indicate the presence of –OH group in the products. It is interesting to mention that no acetylation occurs during the reaction conditions. Next, we were interested to study whether this methodology can be applied

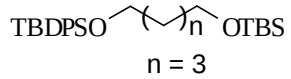
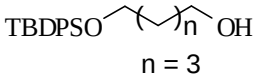
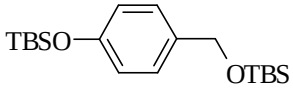
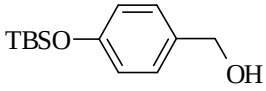
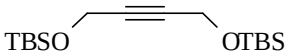
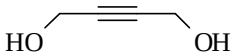
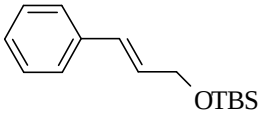
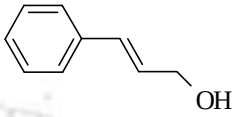
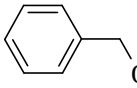
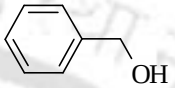
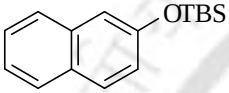
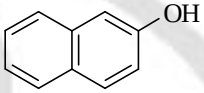
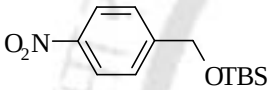
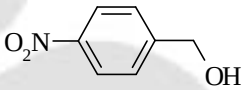
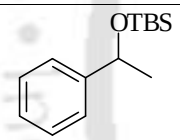
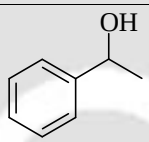
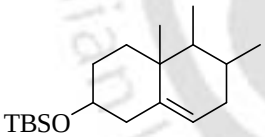
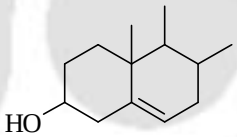
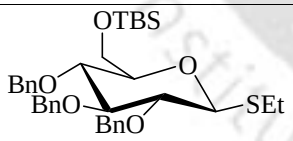
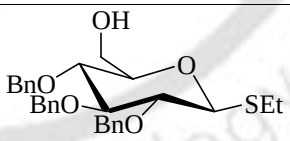
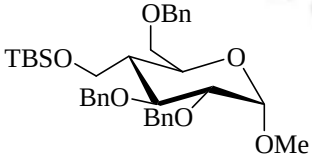
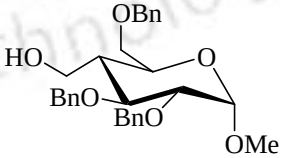
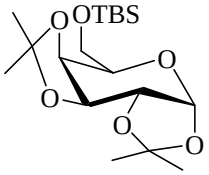
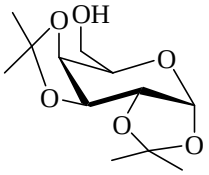
for deprotection of stable silyl ethers such as *tert*-butyldiphenyl silyl (TBDPS) ethers. We observed that various *tert*-butyldiphenyl silyl ethers of octanol (**50**), dodecanol (**51**) and hexadecanol (**52**) are easily deprotected to the corresponding alcohols **72-74** in very good yield on treatment with 0.15 equivalent amount of acetyl chloride in dry methanol at room temperature. We have noticed that it requires relatively longer reaction times for deprotection of TBDPS ethers compare to TBS ethers as shown in Table 1. Our method takes relatively less time and also provide better yield for the cleavage of TBDPS ethers as compared to the recently published LiCl in DMF method.[16]

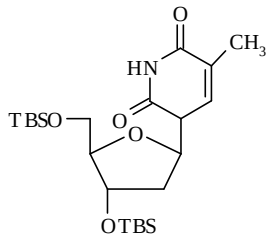
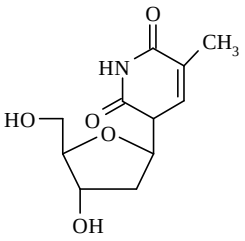
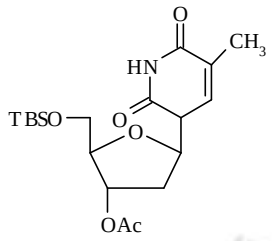
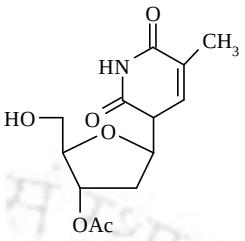
We have examined the intramolecular chemoselective transformation of various TBS ethers **53-58** containing other protecting groups such as acetate, benzoate, benzyl, ester, allyl and thioketal. The formation of the hydroxyl compounds such as **75-80** clearly demonstrate chemosective desilylation of various silyl ethers to the corresponding alcohols, as shown in Table 1, without disturbing other protecting groups. Remarkably, the acid sensitive TBS ether (**56**) undergoes cleavage unaffecting the ester group under the reaction conditions. This procedure also works with the TBS ether containing a thioketal group e.g. **58**, which might be difficult to deprotect by other reported methods.[24] The hydrolyzed product 78 was characterized by IR and ^{1}H NMR as shown in figures **12** and **13**. It is important to highlight that a highly acid sensitive substrate TBS ether of furfuryl alcohol (**59**) can also be smoothly deprotected to the corresponding furfuryl alcohol (**81**) under identical conditions. Interestingly, our protocol can be further extended for chemoselective deprotection of TBS ethers due to reactivity difference. For examples, compound **35** and **25** can be deprotected selectively into the product **36** and **26**, respectively in the presence of TBDPS ether and aryl TBS ether. The structure of **36** was confirmed by recording IR and ^{1}H NMR as shown in figures **14** and **15**. By following the above procedure, TBS ethers **60** and **61** are also deprotected into the corresponding products **82** and **83** in good yield without any chlorination either at double bond or triple bond.

We extended our methodology for cleavage of various benzylic silyl ethers **62** and **64** into the alcohols **84** and **86** in high yields using same reaction conditions.

Table 1. Deprotection of various TBS ethers to the parent hydroxyl compounds using catalytic amounts of CH_3COCl in dry CH_3OH

Substrate	Substrate No.	Time min/ [h]	Product	Product Number	Yield %
 n = 5	**48**	5	 n = 5	**72**	98
 n = 9	**49**	7	 n = 9	**73**	97
 n = 5	**50**	[2.0]	 n = 5	**72**	97
 n = 9	**51**	[4.0]	 n = 9	**73**	95
 n = 13	**52**	[2.3]	 n = 13	**74**	96
 n = 3	**53**	2	 n = 3	**75**	80
 n = 3	**54**	2	 n = 3	**76**	82
 n = 3	**55**	5	 n = 3	**77**	87
 n = 9	**56**	3	 n = 9	**78**	98
	**57**	8		**79**	96
	**58**	[5]		**80**	95
	**59**	35		**81**	85

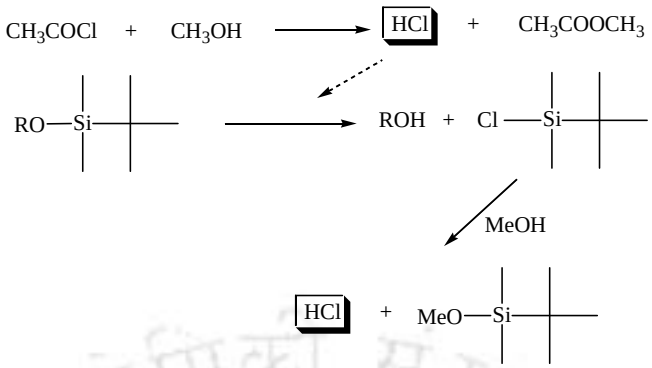
	**35**	4		**36**	86
	**25**	45		**26**	80
	**60**	7		**82**	87
	**61**	10		**83**	94
	**62**	[5]		**84**	93
	**63**	15		**85**	89
	**64**	5		**86**	85
	**65**	35		**87**	82
	**66**	[4.0]		**88**	90
	**67**	8		**89**	88
	**68**	40		**90**	90
	**69**	40		**91**	87

	**70**	[2.5]		**92**	90
	**71**	[1]		**93**	95

Next, we were also interested to find out whether our method could be applied for the cleavage of phenolic TBS ether or not. We have also noticed that the TBS ethers (**63)** deprotected cleanly to the corresponding phenol **85** in very high yield under similar conditions. The compound **85** is characterized by recording IR and melting point, which exactly matches with the authentic 2-naphthol. Then, our methodology can be further extended for deprotection of various secondary TBS ethers under the identical reactions e.g. **65** and **66**. It is important to mention that the deprotection of TBS ether **66** takes less reaction time to the corresponding alcohol (**88**) than earlier reported method.[33] Lastly, we had turned our attention to the deprotection of various TBS ethers of carbohydrates and nucleosides. The TBS ethers **67**, **68**, and **69** were converted into the respective parent hydroxyl compounds **89**, **90**, and **91** in good yields under similar reaction conditions. Importantly, a thio group at the anomeric position in compound **67** was unaffected under the experimental conditions, whereas it is usually affected by the earlier reported procedure.[23] It is also noteworthy to mention that OMe ether group at anomeric position as in case of **68** as well as highly acid sensitive isopropylidene group for example **69**, did also survive under the reaction conditions The hydrolyzed products **89** and **91** were characterized by recording IR, ^{1}H NMR and ^{13}C NMR as shown in figures**16-20**. Likewise, various nucleosidic silyl ethers **70-71** were smoothly converted to the parent nucleosides **92** and **93** in good yields.

The deprotected compound **93** was confirmed by recording IR and ^{1}H NMR as shown in figures **21** and **22**. The formation of the product can be rationalized as follows. We believe that acetyl chloride reacts with methanol to generate dry hydrochloric acid, which

reacts with silyl ethers to provide the parents hydroxyl compounds as represented in scheme 24.



Scheme 24

In conclusion, we have described a new, efficient, and regio- as well as chemoselective protocol for deprotection of TBS and TBDPS ethers using catalytic amount of acetyl chloride in dry methanol under very mild conditions. The salient features of the present method include: i) the ease of operations ii) high efficiency iii) mild conditions iv) chemoselectivity, which may be used extensively in organic synthesis. In addition, the selective deprotection of alkyl *tert*-butyldimethylsilyl ether can be possible in the presence of aryl-*tert*-butyldimethyl ethers. Moreover, a wide variety of other protecting groups such as acetyl, benzyl, benzoyl, thioketals, esters and isopropylidine as well as highly acid sensitive furfuryl TBS ether also survive under the experimental conditions. A similar transformation might be possible by using other acetyl chlorides, benzoyl chloride which is under investigation.

PART II

(SECTION A)

NEW SYNTHETIC PROTOCOL FOR CLEAVAGE OT TERT-BUTYLDIMETHYL-SILYL (TBS) ETHERS TO THE HYDROXYL COMPOUNDS

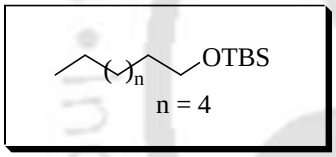
EXPERIMENTALS

Experimental

General procedure for the preparation of *tert*-Butyldimethylsilyl ethers of alcohols and phenols:

To a mixture of alcohol or phenol (1 mmol) and TBDMSCl (1.2 mmol) in dry CH_2Cl_2 or DMF (3 ml) was added imidazole (3 mmol) at room temperature. The reaction mixture was kept stirring until the reaction completed as shown in TLC at the same temperture. The reaction mixture was neutralized diluted with 2N HCl and extracted with dichloromethane. The aqueous part was extracted once more with CH_2Cl_2. The combined organic part was dried over anhydrous Na_2SO_4 and it concentrated in rotavapor. Finally, the residue was passed through a silica gel column to obtain the desired silyl ether.

***tert*-Butyldimethylsilyl ether of octanol (48):**

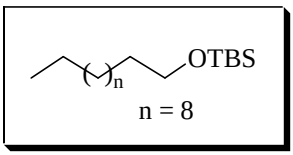


Nature: Colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (s, 6H, -Si(C*H*$_3$)$_2$), 0.90 (t, 3H, *J* = 7.08 Hz, -CH_2*CH*$_3$), 1.05 (s, 9H, -SiC(C*H*$_3$)$_3$), 1.29 (bs, 8H, -CH_2-), 1.38 (m, 2H, -*CH*$_2$$CH_3$), 1.48 (m, 2H, -O*CH*$_2$$CH_2$-), 3.78 (t, 2H, *J* = 6.60 Hz, -O*CH*$_2$$CH_2$-),

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{32}OSi$	C 68.78	C 68.57
244.49	H 13.19	H 13.27

***tert*-Butyldimethylsilyl ether of dodecanol (49):**



Nature: Colourless liquid

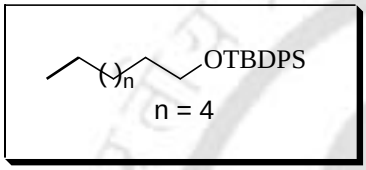
IR (Neat): cm^{-1} 2966, 2930, 2858, 1465, 1255, 1102, 835, 779

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H, -Si(C*H*$_3$)$_2$), 0.88 (t, 3H, *J* = 7.2 Hz, -CH$_2$*CH*$_3$), 0.89 (s, 9H, -SiC(C*H*$_3$)$_3$), 1.26 (bs, 18H, -CH$_2$-), 1.46-1.53 (m, 2H, -*CH*$_2$CH$_2$OTBS), 3.60 (t, 2H, *J* = 6.9 Hz, -CH$_2$OTBS)

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.27 (2C), 18.37, 22.69, 25.81, 25.98 (4C), 29.35, 29.45, 29.65 (4C), 31.92, 32.90, 63.35

Elemental Analysis	**Calculated**	**Found**
$C_{18}H_{40}OSi$	C 71.92	C 71.74
300.60	H 13.41	H 13.23

***tert*-Butyldiphenylsilyl ether of octanol (50):**



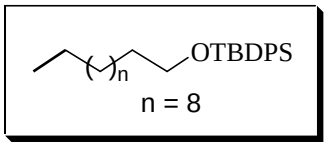
Nature: Colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 7.08 Hz, -CH$_2$*CH*$_3$), 1.05 (s, 9H, -SiC(C*H*$_3$)$_3$), 1.25 (bs, 10H, -CH$_2$-), 1.52-1.59 (m, 2H, -OCH$_2$*CH*$_2$-), 3.64 (t, 2H, *J* = 6.60 Hz, -O*CH*$_2$CH$_2$-), 7.34-7.43 (m, 6H, ArH), 7.63-7.72 (m, 4H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12, 19.21, 22.67, 25.76, 26.86 (2C), 29.34, 31.83, 32.57, 64.01, 127.54 (5C), 129.45 (2C), 134.18, 135.57 (5C)

Elemental Analysis	**Calculated**	**Found**
$C_{24}H_{36}OSi$	C 78.20	C 78.34
368.63	H 9.84	H 9.59

***tert*-Butyldiphenylsilyl ether of dodecanol (51):**



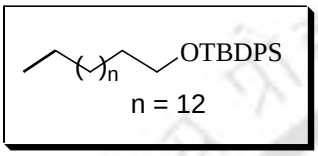
Nature: Colourless liquid

IR (Neat): cm^{-1} 3058, 2925, 2858, 1593, 1465, 1429, 1388, 1107, 820, 702, 615

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, -CH_2CH_3), 1.05 (s, 9H, -$SiC(CH_3)_3$), 1.30 (bs, 18H, -CH_2-), 1.55 (m, 2H, -CH_2CH_2O-), 3.65 (t, 2H, -CH_2CH_2O-), 7.35 (m, 6H, ArH), 7.65 (m, 4H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{28}H_{44}OSi$	C 79.18	C 79.34
424.74	H 10.44	H 10.57

***tert*-Butyldiphenylsilyl ether of hexadecanol (52):**

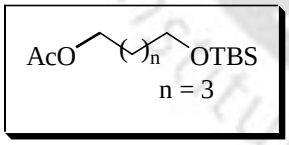


Nature: Colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 7.08 Hz, -CH_2CH_3), 1.05 (s, 9H, $SiC(CH_3)_3$), 1.23 (bs, 26H, -CH_2-), 1.51-1.56 (m, 2H, -CH_2CH_2O-), 3.62 (t, 2H, *J* = 6.84 Hz, -CH_2CH_2O-), 7.34-7.39 (m, 6H, ArH), 7.68-7.70 (m, 4H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{32}H_{52}OSi$	C 79.93	C 79.75
480.85	H 10.90	H 10.98

5-*O*-Acetyl-1-*tert*-butyldimethylsilyloxypentane (53):



Nature: Colourless liquid

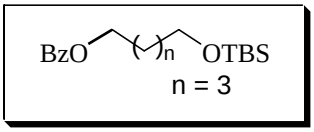
IR (Neat): cm^{-1} 2960, 2935, 2868, 1747, 1475, 1373, 1250, 1112, 1045, 840, 779

^{1}H NMR (400 MHz, $CDCl_3$): δ (s, 6H, -$Si(CH_3)_2$), 0.85 (s, 9H, -$SiC(CH_3)_3$), 1.36 (m, 2H, -CH_2-), 1.50 (m, 2H, -CH_2-), 1.63 (m, 2H, -CH_2-), 1.99 (s, 3H, -$COCH_3$), 3.57 (t, 2H, *J* = 6.3 Hz, -CH_2OTBS), 4.01 (t, 2H, *J* = 6.6 Hz, -CH_2OAc)

^{13}C NMR (100 MHz, $CDCl_3$): δ -5.35, 18.29, 20.97, 22.21, 25.90, 28.34, 32.33, 62.86, 64.50, 171.20

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{28}O_3Si$	C 59.95	C 59.72
260.45	H 10.83	H 10.75

5-O-Benzoyl-1-*tert*-butyldimethylsilyloxy pentane (54):



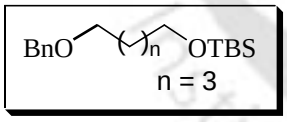
Nature: Colourless liquid

IR (Neat): cm^{-1} 2940, 2858, 1721, 1583, 1429, 1337, 1301, 1112, 943

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 6H, -Si$(CH_3)_2$), 0.83 (s, 9H, -SiC$(CH_3)_3$), 1.47 (m, 2H, -CH_2-), 1.54 (m, 2H, -CH_2-), 1.74 (m, 2H, -CH_2-), 3.57 (t, 2H, *J* = 6.3 Hz, -CH_2OTBS), 4.26 (t, 2H, *J* = 6.6 Hz, PhCOO*C*H_2-), 7.39 (t, 1H, *J* = 7.8 Hz, ArH), 7.44 (t, 1H, *J* = 7.8 Hz, ArH), 7.54 (m, 1H, ArH), 8.00 (dd, 1H, *J* = 1.2 Hz, *J* = 7.3 Hz, ArH), 8.09 (dd, 1H, *J* = 1.2 Hz, *J* = 7.1 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{18}H_{30}O_3Si$	C 67.03	C 66.91
322.52	H 9.38	H 9.25

5-*O*-Benzyl-1-*tert*-butyldimethylsilyloxy pentane (55):



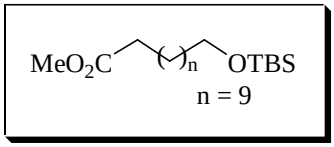
Nature: Colourless liquid

IR (Neat): cm^{-1} 2960, 2935, 2858, 1506, 1470, 1460, 1368, 1255, 1102, 1009, 840

^{1}H NMR (300 MHz, $CDCl_3$): δ -0.01 (s, 6H, -Si$(CH_3)_2$), 0.83 (s, 9H, -SiC$(CH_3)_3$), 1.50 (m, 6H, -CH_2-), 3.43 (t, 2H, *J* = 6.5 Hz, -CH_2OTBS), 3.57 (t, 2H, *J* = 6.4Hz, PhCH_2O*C*H_2-), 4.46 (s, 2H, -OC*H*$_2$Ph), 7.31 (m, 5H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{32}O_2Si$	C 68.86	C 68.92
296.52	H 10.88	H 10.75

12-Carboxymethylate-1-*tert*-butyldimethylsilyloxy dodecane (56):



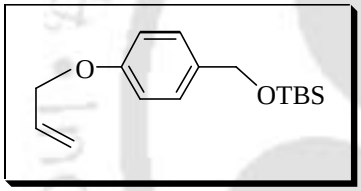
Nature: Colourless liquid

IR (Neat): cm^{-1} 2945, 2858, 1752, 1470, 1255, 1178, 1107, 846

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00 (s, 6H, -Si(CH_3)$_2$), 0.85 (s, 9H, -SiC(CH_3)$_3$), 1.22 (m, 18H, -CH_2-), 2.25 (t, 2H, *J* = 7.3 Hz, -COCH_2-), 3.55 (t, 2H, *J* = 6.3 Hz, -CH_2OTBS), 3.62 (s, 3H, -OCH_3)

Elemental Analysis	**Calculated**	**Found**
$C_{19}H_{40}O_3Si$	C 66.22	C 65.98
344.61	H 11.70	H 11.75

***tert*-Butyldimethylsilyl ether of 4-Allyloxybenzyl alcohol (57):**



Nature: Colourless liquid

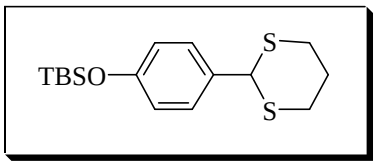
IR (Neat): cm^{-1} 2955, 2929, 2863, 1615, 1516, 1470, 1250, 1096, 1034, 855

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 6H, Si(CH_3)$_2$), 0.93 (s, 9H, SiC(CH_3)$_3$), 4.52 (d, 2H, *J* = 1.2 Hz, O*C*H_2CH=CH_2), 4.66 (s, 2H, -CH_2OTBS), 5.27 (dd, 1H, *J* = 1.0 Hz, *J* = 10.5 Hz, -OCH_2CH=*C*H_2), 5.40 (dd, 1H, *J* = 1.4 Hz, *J* = 15.8 Hz, -OCH_2CH=*C*H_2), 6.06 (m, 1H, -OCH_2*C*H=CH_2), 6.88 (d, 2H, *J* = 8.6 Hz, ArH), 7.22 (d, 2H, *J* = 8.3 Hz, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.20, 18.42, 25.97, 64.69, 68.85, 114.48, 117.55, 127.48, 133.41, 133.76,157.65

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{26}O_2Si$	C 69.01	C 68.82
278.47	H 9.41	H 9.47

2-[4-*tert*-butyldimethylsilyloxyphenyl]-1,3-dithiane (58):



Nature: White crystal solid

Yield: 87%

R_f: 0.62 (Hexane/AcOEt = 9.9: 0.1)

Melting Point: 82.6°C

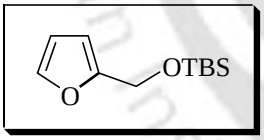
IR (KBr): cm^{-1} 2955, 2929, 2893, 1608, 1511, 1470, 1419, 1270, 1173, 912

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.19 (s, 6H, 2 × $SiCH_3$), 0.97 (s, 9H, $Si(CH_3)_3$), 1.83-1.98 (m, 1H, -SCH_2*CH* CH_2S-), 2.10-2.19 (m, 1H, -SCH_2*CH* CH_2S-), 2.85- 2.92 (m, 2H, -SCH_2-), 2.99-3.10 (m, 2H, -SCH_2-), 5.12 (s, 1H, ArCH-), 6.78 (d, 2H, *J* = 8.4 Hz, ArH), 7.30 (d, 2H, *J* = 8.4 Hz, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ -4.5 (2C), 18.1 25.0, 25.6 (2C), 32.1(2C), 50.8, 120.1 (2C), 128.8 (2C), 131.8, 155.7

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{26}OS_2Si$	C 58.84	C 58.60
310.60	H 8.02	H 7.95
	S 19.63	S 19.70

***tert*-Butyldimethylsilyl ether of furfuryl alcohol (59):**



Nature: Colourless liquid

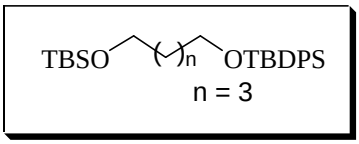
IR (Neat): cm^{-1} 2960, 2935, 2863, 1603, 1506, 1470, 1255, 1158, 1076, 1015, 840

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 6H, -$Si(CH_3)_2$), 0.88 (s, 9H, -$SiC(CH_3)_3$), 4.62 (s, 2H, -CH_2OTBS), 6.14 (d, 1H, *J* = 3.2 Hz, 3-H), 6.23 (dd, 1H, *J* = 1.7 Hz, *J* = 3.2 Hz, 4-H), 7.28 (dd, 1H, *J* = 0.9 Hz, *J* = 1.7 Hz, 5-H)

^{13}C NMR (100 MHz, $CDCl_3$): δ -5.28, 18.42, 25.87, 58.14, 107.20, 110.15,142.03

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{20}O_2Si$	C 62.22	C 61.97
212.36	H 9.49	H 9.42

1-*tert*-Butyldiphenylsilyl-5-*tert*-butyldimethylsilyl ether of 1,5-pentane diol (35):



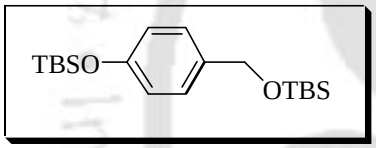
Nature: Colourless liquid

IR (Neat): cm^{-1} 2945, 2858, 1599, 1475, 1399, 1260, 1107, 846

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H, -Si$(CH_3)_2$), 0.89 (s, 9H, -SiC$(CH_3)_3$), 1.04 (s, 9H, -SiC$(CH_3)_3$), 1.49 (m, 6H, -CH_2-), 3.60 (t, 2H, *J* = 6.3 Hz -OC*H*$_2$$CH_2$-), 3.66 (t, 2H, *J* = 6.6 Hz, -OC*H*$_2$$CH_2$-), 7.39(m, 5H, ArH), 7.68 (m, 5H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{27}H_{44}O_2Si_2$	C 70.99	C 7.15
456.81	H 9.71	H 9.83

Bis (*tert*-butyldimethylsilyl) ether of 4-hydroxybenzyl alcohol (25):



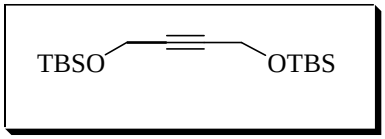
Nature: Colourless liquid

IR (Neat): cm^{-1} 2960, 2945, 2899, 2868, 1614, 1516, 1475, 1255, 1091, 922, 851, 779

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 6H, -Si$(CH_3)_2$), 0.18 (s, 6H, -Si$(CH_3)_2$), 0.93 (s, 9H, -SiC$(CH_3)_3$), 0.98 (s, 9H, -SiC$(CH_3)_3$), 4.66 (s, 2H, -CH_2OTBS), 6.79 (d, 2H, *J* = 8.4 Hz, ArH), 7.17 (d, 2H, *J* = 8.4 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{19}H_{36}O_2Si_2$	C 64.71	C 64.79
352.66	H 10.29	H 10.42

Bis(*tert*-butyldimethylsilyl) ether of 1,4-Butynediol (60):



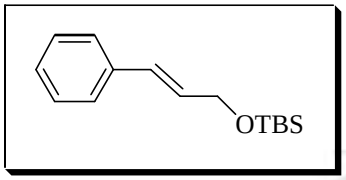
Nature: Light yellow liquid

IR (Neat): cm^{-1} 2955, 2934, 2863, 1465, 1357, 1255, 1137, 1070, 840

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.12 (s, 12H, 2x -Si$(CH_3)_2$), 0.91 (s, 18H, 2x -SiC$(CH_3)_3$), 4.34 (s, 4H, -OCH_2-)

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{34}O_2Si_2$	C 61.08	C 61.43
314.61	H 10.89	H 10.97

***tert*-butyldimethylsilyl ether of cinnamyl alcohol (61):**



Nature: light yellow liquid

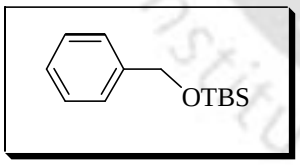
IR (Neat): cm^{-1} 3032, 2960, 2930, 2858, 1649, 1598, 1470, 1255, 1127, 1071, 968

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.01 (s, 6H, -Si$(CH_3)_2$), 0.84 (s, 9H, -SiC$(CH_3)_3$), 4.41 (d, 2H, *J* = 6.8 Hz -OCH_2-), 6.17 (m, 1H, PhCH=*CH*-), 6.49 (d, 1H, *J* = 15.8 Hz Ph*CH*=CH-), (s, 2H, -CH_2OTBS), 7.22 (m, 5H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ -5.30, 18.43, 25.96, 63.88, 126.35, 127.28, 128.30, 128.43, 128.47, 131.23,137.08

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{24}OSi$	C 72.52	C 72.43
248.44	H 9.74	H 9.70

1-*tert*-Butyldimethylsilyl ether of benzyl alcohol (62):



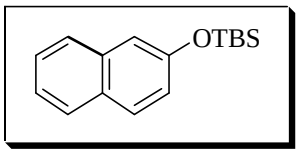
Nature: Colourless liquid

IR (Neat): cm^{-1} 2962, 2936, 2860, 1483, 1377, 1256, 1210, 1099, 1073, 845, 780, 729

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 6H, -Si$(CH_3)_2$), 0.88 (s, 9H, -SiC$(CH_3)_3$), 4.43 (d, 1H, -CH_2Ph), 4.82 (d, 1H, -CH_2Ph), 7.25 (m, 5H. ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{24}OSi$	C 72.52	C 72.43
248.44	H 9.74	H 9.70

***tert*-Butyldimethylsilyl ether of 2-naphthol (63):**



Nature: Colourless gummy liquid

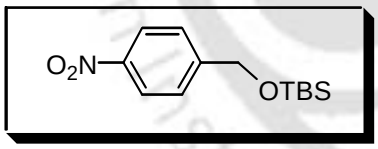
IR (Neat): cm^{-1} 3058, 2966, 2940, 2863, 1634, 1603, 1506, 1470, 1363, 1260, 1230, 1173, 1132, 1015, 933, 851

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.25 (s, 6H, $Si(CH_3)_2$), 1.02 (s, 9H, $SiC(CH_3)_3$), 7.07(dd, 1H, *J* = 3.2 Hz, *J* = 8.7 Hz, 3-ArH), 7.19 (d, 1H, *J* = 2.4 Hz,1-ArH) , 7.30(t, 1H, *J* = 7.0 Hz, 6-ArH), , 7.38 (t, 1H, *J* = 7.0 Hz, 7-ArH), 7.68 (d, 1H, *J* = 8.7 Hz, ArH, 4-ArH), 7.72 (d, 1H, *J* = 9.0 Hz, 5-ArH), 7.76 (d, 1H, *J* = 8.1 Hz, 8-ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.30, 18.30, 25.70, 114.90, 122.10, 123.70, 126.10, 126.70, 127.60, 129.30, 134.60,153.50

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{22}OSi$	C 74.36	C 74.10
258.43	H 8.58	H 8.50

***tert*-Butyldimethylsilyl ether of 4-nitrobenzyl alcohol (64):**



Nature: Light yellow liquid

Yield: 94%

Reaction time: 10 min.

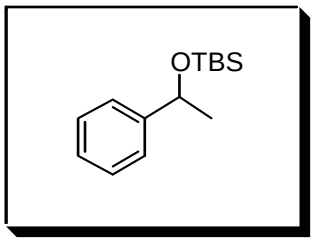
IR (Neat): cm^{-1} 2955, 2935, 2863, 1614, 1521, 1475, 1352, 1265, 1102, 1020, 856

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 6H, $Si(CH_3)_2$), 0.96 (s, 9H, $SiC(CH_3)_3$), 4.83 (s, 2H, CH_2OTBS), 7.49 (d, 2H, *J* = 8.7 Hz, ArH), 8.20 (d, 2H, *J* = 9.0 Hz, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.40, 18.30, 25.80, 64.00, 123.50, 126.30, 146.00, 149.00

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{21}O_3NSi$	C 58.39	C 58.15
267.40	H 7.92	H 7.84
	N 5.24	N 5.39

***tert*-Butyldimethylsilyl ether of 1-phenyl ethanol (65):**



Nature: Colourless liquid

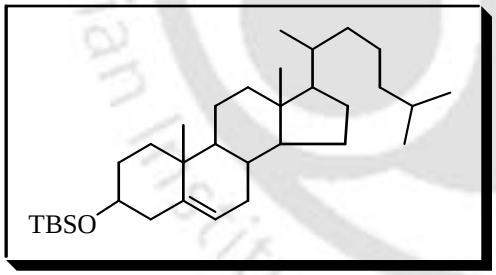
IR (Neat): cm^{-1} 3037, 2960, 2935, 2863, 1470, 1368, 1260, 1102, 1035, 963, 846, 784

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 3H, -Si(CH_3)$_2$), 0.09 (s, 3H, -Si(CH_3)$_2$), 0.93 (s, 9H, -SiC(CH_3)$_3$), 1.45 (d, 3H, *J* = 6.0 Hz, -CH*CH*$_3$), 4.91 (q, 1H, *J* = 6.3 Hz, -O*CH*CH_3), 7.24-7.30 (m, 5H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.80, 18.42, 25.90, 27.20, 70.80, 125.20, 126.60, 128.00

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{24}OSi$	C 71.12	C 70.93
236.43	H 10.23	H 10.18

3-*tert*-Butyldimethylsilyl ether of cholesterol (66):



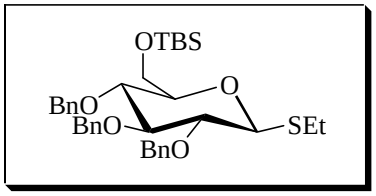
Nature: White solid

IR (Neat): cm^{-1} 2930, 2858, 1665, 1460, 1378, 1255,1112

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H, -SiCH_3), 0.12 (s, 3H, -SiCH_3), 0.82 (s, 6H, 2x -CH_3), 0.83 (s, 9H, -SiC(CH_3)$_3$), 0.85 (d, 3H, *J* = 6.3 Hz, -CH*CH*$_3$), 0.94 (s, 6H, 2x-CH_3), 1.00-1.50 (m, 22H, -CH- and -CH_2-), 1.75 (m, 2H, -CH_2-), 1.94 (m, 2H, -CH_2-), 2.12 (m, 1H, -CH-), 2.20 (m, 1H, -CH-), 3.42 (q,1H, *J* = 6.Hz, -OCH-), 5.25 (m, 1H, = CH-)

Elemental Analysis	**Calculated**	**Found**
$C_{33}H_{60}OSi$	C 79.13	C 78.94
500.92	H 12.07	H 12.32

Ethyl 6-*O*-*tert*-butyldimethylsilyl-2,3,4-tri-*O*-benzyl-1-thio- -D-glucopyranoside (67):



Nature: Gummy liquid

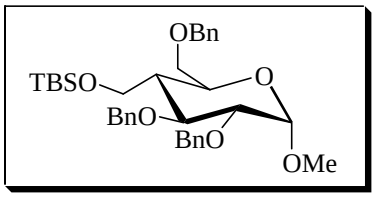
IR (Neat): cm^{-1} 3032, 2945, 2868, 1603, 1465, 1363, 1260, 1163, 1091, 846, 753

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 3H, -Si(CH_3)$_2$), 0.02 (s, 3H, -Si(CH_3)$_2$), 0.85 (s, 9H, -SiC(CH_3)$_3$), 1.25 (t, 3H, *J* = 7.3 Hz, -SCH_2*CH_3*), 2.63-2.71 (m, 2H, -S*CH_2*CH_3), 3.21-3.24 (m, 1H, H-5), 3.46 (t, 1H, *J* = 9.0 Hz, H-3), 3.56 (t, 1H, *J* = 9.3 Hz, H-2), 3.61 (t, 1H, *J* = 9.0 Hz, H-4), 3.75 (dd, 1H, *J* = 3.8 Hz, *J* = 11.2 Hz, H-6), 3.80 (dd, 1H, *J* = 2.0 Hz, *J* = 11.7 Hz, H-6′), 4.38 (d, 1H, *J* = 9.8 Hz, H-1), 4.62 (d, 1H, *J* = 10.2 Hz, -O*CH*Ph), 4.68 (d, 1H, *J* = 10.2 Hz, O*CH*Ph), 4.79 (dd, 2H, *J* = 4.6 Hz, *J* = 10.7 Hz, OCH_2Ph), 4.85 (dd, 2H, *J* = 4.0 Hz, *J* = 10.3 Hz, OCH_2Ph), 7.19-7.33 (m, 15 H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ -5.37, -5.04, 15.19, 18.30, 24.34, 25.89 (3C), 62.30, 75.06, 75.46, 75.87, 77.68, 80.03, 81.83, 84.40, 86.62, 127.69, 127.81, 127.93, 128.00, 128.29, 128.38, 128.46, 138.09, 138.32, 138.52

Elemental Analysis	**Calculated**	**Found**
$C_{35}H_{48}O_5SSi$	C 69.04	C 69.25
608.91	H 7.95	H 7.82
	S 5.27	S 5.23

4-Methyl-*O*-*tert*-butyldimethylsilyl-2,3,6-tri-*O*-benzyl-1- -D-methylglucopyranoside (68):



Nature: Gummy liquid

Yield: 90%

Reaction time: 2.5 h

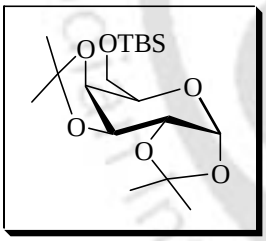
IR (Neat): cm^{-1} 2929, 2858, 1603, 1459, 1362, 1260, 1106, 1060, 845, 742, 701

^{1}H NMR (300 MHz, $CDCl_3$): δ -0.12 (s, 3H, -$SiCH_3$), -0.05 (s, 3H, -$SiCH_3$), 0.83 (s, 9H, -$SiC(CH_3)_3$), 1.86 (t, 1H, *J* = 10.8 Hz, H-4), 3.38 (s, 3H, -OCH_3), 3.39-3.44 (m, 1H, H-1), 3.53-3.66 (m, 3H, -CH_2- & H-2), 3.88 (dd, 1H, *J* = 1.8 Hz, *J* = 10.5 Hz, H′-6), 3.95 (d, 1H, *J* = 10.8 Hz, H-5), 4.06 (t, 1H, *J* = 9.9 Hz, H-3), 4.43 (d, 1H, *J* = 12.3 Hz, -OCH_2-), 4.61 (m, 3H, -OCH_2- & H-6), 4.65 (d, 1H, *J* = 12.6 Hz, -OCH_2-), 4.77 (d, 1H, *J* = 12.6 Hz, -OCH_2-), 5.01(d, 1H, *J* = 12.0 Hz, -OCH_2-), 7.26-7.37 (m, 15H, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.80, -5.50, 18.10, 25.80, 44.80, 55.00, 58.30, 68.30, 69.30, 73.00, 73.40, 75.30, 75.70, 81.70, 98.50, 127.60, 127.70, 127.80, 127.90, 128.20, 128.40, 138.20, 138.40, 139.10

Elemental Analysis	**Calculated**	**Found**
$C_{35}H_{48}O_6Si$	C 70.91	C 70.68
592.84	H 8.16	H 8.24

6-*O*-*tert*-Butyldimethylsilyl-1,2, 3,4-di-isopropylidene galactose (69):



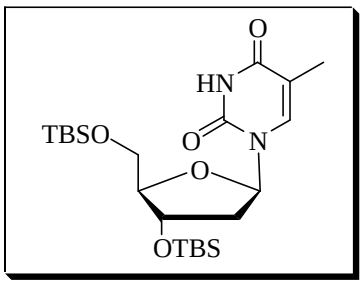
Nature: Yellowish gummy liquid

IR (Neat): cm^{-1} 2940, 2863, 1475, 1388, 1255, 1219, 1112, 1076, 1009, 846

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H, -$Si(CH_3)_2$), 0.90 (s, 9H, -$SiC(CH_3)_3$), 1.33 (s, 6H, =$C(CH_3)_2$), 1.44 (s, 3H, =CCH_3), 1.54 (s, 3H, =CCH_3), 3.70-3.86 (m, 3H, H-2, H-3, H-5), 4.30 (dd, 2H, *J* = 2.3 Hz, *J* = 7.2 Hz, H-4, H-6), 4.60 (dd, 1H, *J* = 1.6 Hz, *J* = 7.9 Hz, H-6′), 5.52 (d, 1H, *J* = 4.9 Hz, H-1)

Elemental Analysis	**Calculated**	**Found**
$C_{18}H_{34}O_6Si$	C 57.72	C 57.87
374.55	H 9.15	H 9.31

Bis (*tert*-butyldimethylsilyl) ether of thymidine (70):



Nature: White solid

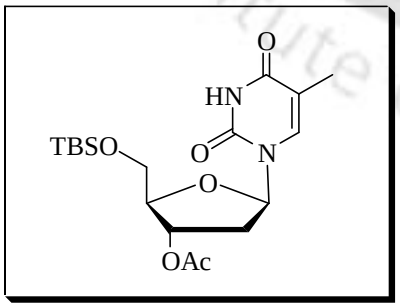
Melting Point: 115 °C

IR (Neat): cm^{-1} 3180, 3057, 2950, 2929, 2858, 1700, 1465, 1362, 1270, 1101, 1065, 1029, 835, 778

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H, -$SiCH_3$), 0.07 (s, 6H, -$SiCH_3$), 0.88 (s, 9H, -$SiC(CH_3)_3$), 0.91 (s, 9H, -$SiC(CH_3)_3$), 1.91(s, 3H, -CH_3), 1.94-2.03 (m, 1H, H-2), 2.21-2.28 (m, 1H, H′-2), 3.75 (dd, 1H, *J* = 2.3 Hz, *J* = 13.7 Hz H-4), 3.84-3.92 (m, 2H, -OCH_2-), 4.37-4.41 (m, 1H, H-3), 6.30-6.35 (m, 1H, H-1), 7.46 (s, 1H, =CH-), 9.01 (s, 1H, NH)

Elemental Analysis	**Calculated**	**Found**
$C_{22}H_{42}O_5N_2Si_2$	C 56.13	C 56.34
470.75	H 8.99	H 8.89
	N 5.95	N 6.12

3′-Acetyl-5′-*tert*-Butyldimethylsilyl ether of thymidine (71):



Nature: White solid

IR (Neat): cm^{-1} 3247, 3083, 2940, 2863, 1736, 1700, 1465, 1372, 1255, 1203, 1121, 1014, 835, 783

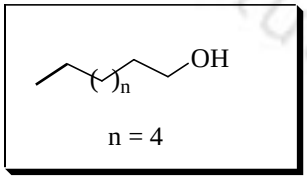
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 6H, -Si(CH_3)$_2$), 0.93 (s, 9H, -SiC(CH_3)$_3$), 1.93 (S, 3H, -CH_3), 2.11 (s, 3H, -$COCH_3$), 2.12 (m, 2H, H-2, H-2′), 2.41 (dd, 1H, *J* = 5.2 Hz, *J* = 13.7 Hz), 3.92 (d, 2H, *J* = 1.8 Hz, -CH_2OTBS), 4.10 (d, 1H, *J* = 1.1 Hz,), 5.25 (d, 1H, *J* = 5.9 Hz), 6.38 (dd, 1H, *J* = 5.2 Hz, *J* = 9.2 Hz), 7.55 (d, 1H, *J* = 1.1 Hz, ArH), 9.12 (s, 1H, NH)

Elemental Analysis	**Calculated**	**Found**
$C_{18}H_{30}O_6N_2Si$	C 54.25	C 54.16
398.53	H 7.59	H 7.49
	N 7.03	N 7.11

General procedure for deprotection of silylethers:

To a stirred solution of TBS ether (1 mmol) in dry MeOH (3 ml) was added acetyl chloride (11 μL, 0.15 mmol) at ice-bath temperature. The reaction mixture was stirred at ice-bath temperature to room temperature. After completion of the reaction, CH_2Cl_2 was added (20 ml) into it. Then, the reaction mixture was neutralized with 10% $NaHCO_3$ solution (1 ml) and the organic layer was washed with water (10 ml). Finally, the organic layer was dried (Na_2SO_4) and concentrated in rotavapour to give a crude residue, which was purified on silica gel column chromatography. The final desired products were obtained in good to excellent yields.

Octanol (72):



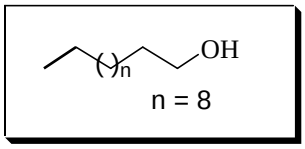
Nature: Colorless liquid

Yield: 98%

Reaction time: 5 min

IR (Neat): cm^{-1} 3365, 2930, 2863, 1465, 1378, 1061

Dodecanol (73):



Nature: Colorless liquid

Yield: 97%

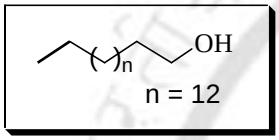
Reaction time: 7 min

IR (Neat): cm^{-1} 3396, 2925, 2848, 1460, 1050, 758, 728

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.9 Hz, -CH_2*CH_3*), 1.26 (bs, 18H, -CH_2-), 1.57 (m, 2H, -*CH_2*CH_2OH), 1.67 (s, 1H, -OH), 3.64 (t, 2H, *J* = 6.6 Hz, -*CH_2*OH)

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{26}O$	C 77.35	C 77.12
186.34	H 14.07	H 13.89

Hexadecanol (74):



Nature: White solid

Yield: 96%

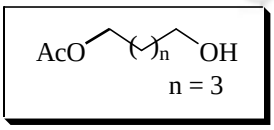
Reaction time: 2.3 h

IR (Neat): cm^{-1} 3324, 2924, 2858, 1470, 1065, 727

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 6.56 Hz, -CH_2*CH_3*), 1.23 (bs, 27H, -CH_2-, & -OH), 1.50-1.55 (m, 2H, -*CH_2*CH_2OH), 3.62 (t, 2H, *J* = 6.6 Hz, -CH_2*CH_2*OH)

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{34}O$	C 79.27	C 79.34
236.387	H 14.13	H 14.20

5-*O*-Acetyl-1-pentanol (75):



Nature: Colourless liquid

Yield: 80%

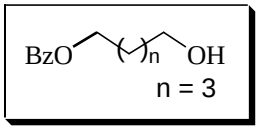
Reaction time: 2 min

IR (Neat): cm^{-1} 3447, 2935, 2868, 1742, 1465, 1404, 1368, 1235, 1045, 897, 851

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35-1.74 (m, 7H, -CH_2- & -OH), 2.05 (s, 3H, -$COCH_3$), 3.67 (t, 2H, *J* = 6.4 Hz, -C*H_2*OH), 4.08 (t, 2H, *J* = 6.6 Hz, -CH_2OAc)

Elemental Analysis	**Calculated**	**Found**
$C_7H_{14}O_3$	C 57.52	C 57.68
146.18	H 9.65	H 9.47

5-*O*-Benzoyl-1-pentanol (76):



Nature: Colourless liquid

Yield: 82%

Reaction time: 2 min.

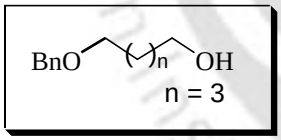
IR (Neat): cm^{-1} 3421, 3068, 2940, 2868, 1726, 1614, 1460, 1393, 1281, 1189, 1122, 717

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (m, 3H, -CH_2- & -OH), 1.59 (m, 2H, -CH_2-), 1.75 (m, 2H, -CH_2-), 3.62 (t, 2H, *J* = 6.4 Hz, -C*H*$_2$OH), 4.27 (t, 2H, *J* = 6.6 Hz, PhCOOC*H*$_2$-), 7.37 (t, 2H, *J* = 7.8 Hz, ArH), 7.49 (t, 1H, *J* = 7.6Hz, ArH), 7.96 (d, 2H, *J* = 7.1 Hz ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.36, 28.55, 32.32, 62.73, 64.87, 128.33, 129.53, 130.39, 132.85, 166.68

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{16}O_3$	C 69.21	C 68.98
208.25	H 7.74	H 7.86

5-*O*-Benzyl-1-pentanol (77):



Nature: Colourless liquid

Yield: 87%

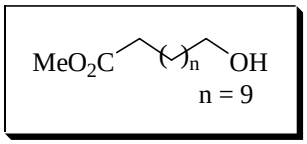
Reaction time: 5 min

IR (Neat): cm^{-1} 3416, 2935, 2863, 1609, 1501, 1455, 1368, 1265, 1209, 1096, 1055, 1030, 805

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31-1.70 (m, 7H, -CH_2- & -OH), 3.47 (t, 2H, *J* = 6.4 Hz, -C*H*$_2$OH), 3.63 (t, 2H, *J* = 6.4Hz, PhCH_2OC*H*$_2$-), 4.48 (s, 2H, -OCH_2Ph), 7.32 (m, 5H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{18}O_2$	C 74.19	C 74.39
194.27	H 9.34	H 9.27

12-Carboxymethylate-1-dodecanol (78):



Nature: Colourless liquid

Yield: 98%

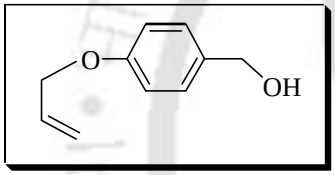
Reaction time: 3 min

IR (Neat): cm^{-1} 3442, 2925, 2858, 1737, 1460, 1358, 1255, 1209, 1055, 1112, 876

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (m, 18H, -CH_2-), 1.61 (bs, 1H, -OH), 2.30 (t, 2H, *J* = 6.8 Hz, -C*H*$_2$OH), 3.64 (t, 2H, *J* = 5.9 Hz, -$COCH_2$-), 3.67 (s, 3H, -OCH_3)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{26}O_3$	C 67.79	C 67.56
230.35	H 11.38	H 11.23

4-Allyloxybenzylalcohol (79):



Nature: Colourless liquid

Yield: 96%

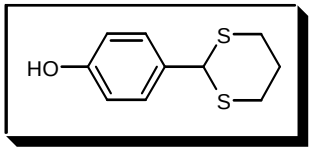
Reaction time: 8 min.

IR (Neat): cm^{-1} 3350, 2930, 2879, 1619, 1511, 1460, 1424, 1373, 1301, 1240, 1189, 1122, 1009, 1034, 938, 825

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 1H, -OH), 4.53-4.55 (m, 2H, -O*CH*$_2$CH=CH_2), 4.56 (s, 2H, -C*H*$_2$OH), 5.27 (dd, 1H, *J* = 1.0 Hz, *J* = 10.5 Hz, OCH_2CH=*CH*$_2$), 5.40 (dd, 1H, *J* = 1.4 Hz, *J* = 15.8 Hz, OCH_2CH=*CH*$_2$), 6.04 (m, 1H, OCH_2*CH*=CH_2), 6.89 (d, 2H, *J* = 8.5 Hz, ArH), 7.30 (d, 2H, *J* = 8.6 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}O_2$	C 73.15	C 72.90
164.20	H 7.37	H 7.17

2-[4̊-Hydroxyphenyl]-1,3-dithiane (80):



Nature: White solid

Yield: 95%

Reaction Time: 5 h

R_f: 0.38 (Hexane/EtOAc = 9:1)

Melting point: 156-158°C

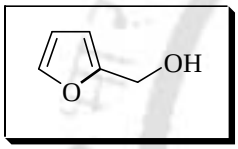
IR (KBr): cm^{-1} 3370, 2940, 2894, 2807, 1609, 1516, 1450, 1363, 1250, 1173, 1112, 851, 774

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85-1.96 (m, 1H, -$SCH_2CHaHbCH_2S$-), 2.12-2.19 (m, 1H, -$SCH_2CHaHbCH_2S$-), 2.86-2.92 (m, 2H, -SCH_2-), 3.01-3.08 (m, 2H, -SCH_2-), 5.12 (S, 1H, ArCH-), 6.77 (d, 2H, *J* = 8.2 Hz, ArH), 7.31 (d, 2H, *J* = 8.3 Hz, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.06, 32.18 (2C), 50.74, 115.58 (2C), 129.18 (2C), 131.45, 155.61.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}OS_2$	C 56.56	C 56.34
212.34	H 5.69	H 5.63
	S 30.20	S 32.01

Furfuryl alcohol (81):



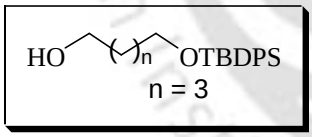
Nature: Colourless liquid

Yield: 85%

Reaction time: 35 min

IR (Neat): cm^{-1} 3375, 2940, 2879, 1634, 1501, 1429, 1158, 1009, 922, 815, 748

5-*tert*-Butyldiphenylsilyl ether of pentane 1,5-diol (36):



Nature: Colourless liquid

Yield: 86%

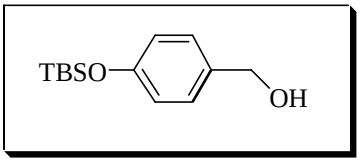
Reaction time: 4 min

IR (Neat): cm^{-1} 3396, 3068, 2940, 2863, 1598, 1470, 1429, 1399, 1112, 820, 712

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H, -$SiC(CH_3)_3$), 1.56 (m, 7H, -CH_2- & -OH), 3.62 (t, 2H, *J* = 6.4 Hz -OCH_2CH_2-), 3.67 (t, 2H, *J* = 6.2 Hz -OCH_2CH_2-), 7.40 (m, 5H, ArH), 7.68 (m, 5H, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{21}H_{30}O_2Si$	C 73.63	C 73.63
342.55	H 8.83	H 8.83

4-*tert*-Butyldimethylsilyl ether of 4-hydroxybenzyl alcohol (26):



Nature: Colourless liquid

Yield: 80%

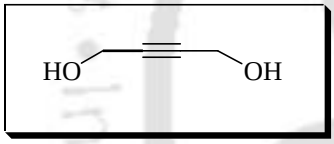
Reaction time: 45 min

IR (Neat): cm^{-1} 3365, 2970, 2945, 2863, 1618, 1521, 1485, 1260, 1019, 916, 840, 783

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.19 (s, 6H, -Si(CH_3)$_2$), 0.98 (s, 9H, -SiC(CH_3)$_3$), 1.62 (s, 1H, -OH, D_2O exchangeable), 4.60 (s, 2H, -C*H*$_2$OH), 6.82 (d, 2H, *J* = 8.4 Hz, ArH), 7.23 (d, 2H, *J* = 8.4 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{22}O_2Si$	C 65.50	C 65.47
238.40	H 9.30	H 9.43

2-Butyne-1,4-diol (82):



Nature: Light yellow liquid

Yield: 87%

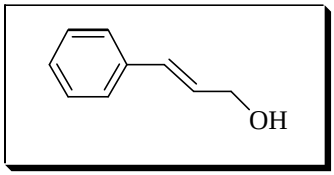
Reaction time: 7 min

IR (Neat): cm^{-1} 3370, 2925, 2868, 1639, 1434, 1358, 1230, 1132, 1015

^{1}H NMR (400 MHZ, Acetone-*d6*): δ 4.23 (brs, 4H, 2× -*CH*$_2$OH), 4.39 (brs, 2H, 2× -OH)

Elemental Analysis	**Calculated**	**Found**
$C_4H_6O_2$	C 55.81	C 55.73
86.09	H 7.02	H 7.17

Cinnamyl alcohol (83):



Nature: Light yellow liquid

Yield: 94%

Reaction time: 10 min

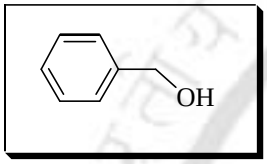
IR (Neat): cm^{-1} 3356, 3026, 2923, 2849, 1654, 1599, 1496, 1452,1093, 1014, 970

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 1H, -OH, D_2O exchangeable), 4.25 (d, 2H, *J* = 7.1 Hz -OCH_2-), 6.30 (m, 1H, PhCH=*CH*-), 6.54 (d, 1H, *J* = 15.9 Hz, Ph*CH*=CH-), 7.24 (m, 5H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 63.69, 126.44, 127.67, 128.46, 128.57, 131.12,136.63

Elemental Analysis	**Calculated**	**Found**
$C_9H_{10}O$	C 80.56	C 80.23
134.18	H 7.51	H 7.66

Benzyl alcohol (84):



Nature: Colourless liquid

Yield: 93%

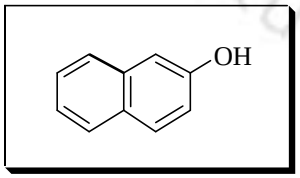
Reaction time: 5 h

IR (Neat): cm^{-1} 3369, 3027, 2868, 1505, 1460, 1209, 1019, 737, 702

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.78 (s, 1H, -OH), 4.69 (s, 2H, -CH_2Ph), 7.27-7.37 (m, 5H, ArH)

Elemental Analysis	**Calculated**	**Found**
C_7H_8O	C 77.75	C 77.48
108.14	H 7.46	H 7.73

2-Naphthol (85):



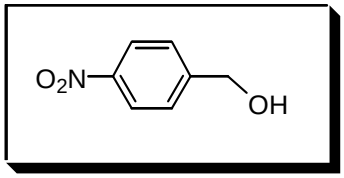
Nature: Black solid

Yield: 89%

Reaction time: 15 min.

Melting Point: 121-122 °C [Lit. 122-123 °C]

4-Nitrobenzyl alcohol (86):



Nature: Colourless liquid

Yield: 85%

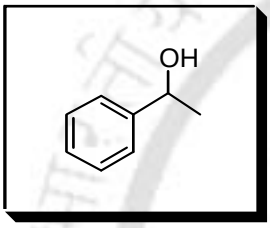
Reaction time: 5 min

IR (Neat): cm^{-1} 2955, 2935, 2863, 1614, 1521, 1475, 1352, 1265, 1102, 1020, 856

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09 (s, 1H, -OH), 4.84 (s, 2H, -*CH*$_2$OH), 7.54 (d, 2H, *J* = 9.0 Hz, ArH), 8.22 (d, 2H, *J* = 9.0 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_7H_7O_3N$	C 54.90	C 54.73
153.14	H 4.61	H 4.86
	N 9.15	N 9.32

1-phenylethanol (87):



Nature: Colorless liquid

Yield: 82%

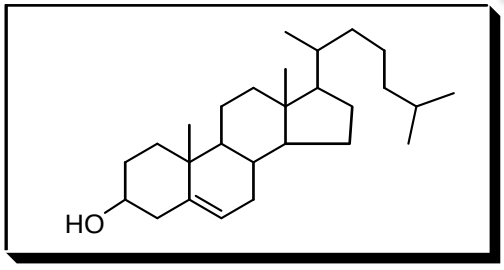
Reaction time: 35 min

IR (Neat): cm^{-1} 3396, 3042, 2981, 2940, 1609, 1501, 1460, 1373, 1301, 1204, 1081, 1025, 907, 769

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (d, 3H, *J* = 6.0 Hz, -CH_3), 1.97 (s, 1H, -OH), 4.89 (q, 1H, -*CH*OH), 7.24-7.35 (m, 5H, ArH), 8.22 (d, 2H, *J* = 9.0 Hz, ArH)

Elemental Analysis	**Calculated**	**Found**
$C_8H_{10}O$	C 78.65	C 78.86
122.17	H 8.25	H 8.43

Cholesterol (88):



Nature: White solid

Yield: 90%

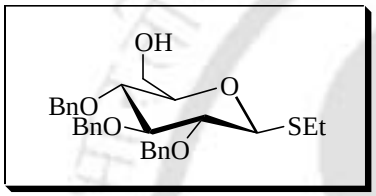
Reaction time: 4 h

IR (Neat): cm^{-1} 3342, 2930, 2863, 1619, 1465, 1378, 1137, 1061, 1030, 963, 810;

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68 (s, 3H, -CH_3), 0.86 (d, 3H, *J* = 1.68 Hz, -CH_3), 0.87 (d, 3H, *J* = 1.72 Hz, -CH_3), 0.91 (d, 3H, *J* = 6.6 Hz, -CH_3), 1.01 (s, 3H, -CH_3), 1.07-1.22 (m, 4H, -CH-), 1.23-1.51 (m, 2H, -CH-), 1.56 (bs, 16H, -CH_2-), 1.78-1.87 (m, 2H, -CH_2-), 1.95-2.03 (m, 2H, -CH_2-), 2.20-2.31 (m, 2H, =CH*CH_2*-), 3.49-3.55 (m, 1H, -*CH*OH), 5.35-5.36 (t, 1H, *J* = 2.68 Hz, =CH-).

Elemental Analysis	**Calculated**	**Found**
$C_{27}H_{46}O$	C 83.87	C 84.02
386.66	H 12.00	H 12.17

Ethyl 2,3,4-tri-*O*-benzyl-1-thio- -D-glucopyranoside(89):



Nature: White solid

Yield: 88%

Reaction time: 8 min

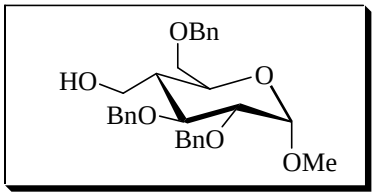
IR (Neat): cm^{-1} 3355, 3032, 2909, 2863, 1608, 1459, 1362, 1219, 1080, 1034, 1004, 845, 747, 701

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, 3H, *J* = 7.3 Hz, -SCH_2CH_3), 1.95 (bs, 1H, OH, D_2O exchangeable), 2.71-2.80 (m, 2H, -S*CH_2*CH_3), 3.35-3.39 (m, 1H, H-5), 3.41 (t, 1H, *J* = 9.3 Hz, H-3), 3.58 (t, 1H, *J* = 9.3 Hz, H-2), 3.70 (t, 1H, *J* = 8.8 Hz, H-4), 3.87 (d, 1H, *J* = 11.5 Hz, -O*CH*Ph), 4.50 (d, 1H, *J* = 9.8 Hz, H-1), 4.65 (d, 1H, *J* = 11 Hz, -O*CH*Ph), 4.74 (d, 1H, *J* = 11 Hz, -O*CH*Ph), 4.86 (d, 2H, *J* = 12.4 Hz, -O*CH_2*Ph), 4.89 (d, 1H, *J* = 10.0 Hz, -O*CH*Ph), 4.92 (dd, 2H, *J* = 6.8 Hz, *J* = 11 Hz, H-6, H-6′), 7.25-7.38 (m, 15 H, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.16, 25.20, 62.15, 75.17, 75.57, 75.74, 75.76, 77.69, 79.27, 81.77, 85.27, 86.47, 127.71, 127.77, 127.89, 127.96, 128.07, 128.29, 128.41, 128.46, 128.52, 137.90 (2C), 138.41

Elemental Analysis	**Calculated**	**Found**
$C_{29}H_{34}O_5S$	C 70.42	C 70.64
494.65	H 6.93	H 7.08
	S 6.48	S 6.10

Methyl 2,3,6-tri-*O*-benzyl-1- -D-glucopyranoside (90):



Nature: Gummy liquid

Yield: 90%

Reaction time: 40 min

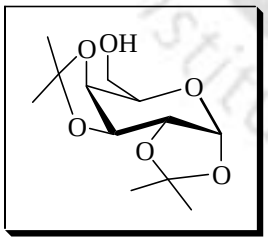
IR (Neat): cm^{-1} 3457, 3032, 2930, 2894, 1609, 1455, 1358, 1096, 1050, 743, 702

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68 (bs, 1H, -OH), 1.86 (m, 1H, H-4), 3.37 (s, 3H, -OCH_3), 3.55 (d, 1H, *J* = 3.4 Hz), 3.58 (t, 2H, *J* = 2.4 Hz, -OCH_2-), 3.61 (m, 2H), 3.68 (dd, 1H, *J* = 3.4 Hz, *J* = 11.4 Hz, H-6), 3.83 (m, 1H, H-5), 3.58 (t, 1H, *J* = 10.24 Hz, H-3), 4.47 (d, 1H, *J* = 11.96 Hz, OCH_2), 4.61 (d, 1H, *J* = 11.96 Hz, OCH_2), 4.66 (m, 1H, -OCH_2-), 4.69 (d, 1H, *J* = 3.2 Hz, H-1), 4.77 (d, 1H, *J* = 11.96 Hz, –OCH_2), 4.99 (d, 1H, *J* = 11.2 Hz. –OCH_2), 7.32 (m, 15, ArH)

^{13}C NMR (100 MHz, $CDCl_3$): δ 46.07, 55.19, 59.50, 68.20, 70.48, 72.88, 73.53, 75.19, 75.44, 81.49, 98.45, 127.76, 127.87, 128.09, 128.35, 128.39, 128.43, 128.51, 137.66, 138.18, 138.42

Elemental Analysis	**Calculated**	**Found**
$C_{29}H_{34}O_6$	C 72.78	C 72.57
478.58	H 7.16	H 7.25

1,2,3,4-Di-*O*-isopropylidene-D-galactose (91):



Nature: Yellowish gummy liquid

Yield: 87%

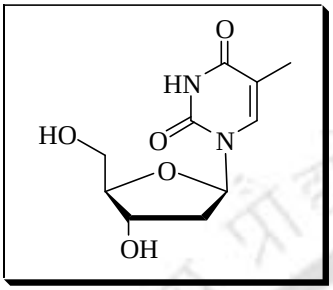
Reaction time: 40 min.

IR (Neat): cm^{-1} 3493, 2991, 2935, 1460, 1383, 1255, 1219, 1173, 1076, 1009, 892

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 6H, =$C(CH_3)_2$), 1.46 (s, 3H, =CCH_3), 1.54 (s, 3H, =CCH_3), 2.28 (bs, 1H, OH, D_2O exchangeable), 3.75 (t, 1H, *J* = 7.3 Hz, H-4), 3.82-3.90 (m, 2H, H-2 and H-5), 4.27 (d, 1H, *J* = 7.9 Hz, H-3), 4.34 (dd, 1H, *J* = 2.3 Hz, *J* = 4.9 Hz, H-6), 4.62 (dd, 1H, *J* = 2.3 Hz, J = 7.9 Hz, H-6′), 5.57 (d, 1H, *J* = 5.0 Hz, H-1)

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{20}O_6$	C 55.37	C 55.46
260.28	H 7.74	H 7.68

Thymidine (92):



Nature: White solid

Yield: 90%

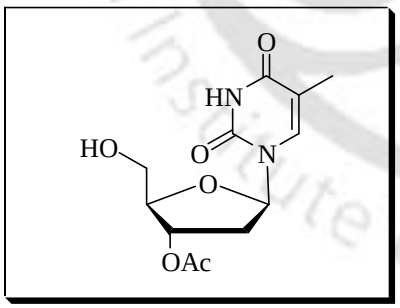
Reaction time: 2.5 h

Melting point:188 °C [Lit.187-189 °C]

IR (Neat): cm^{-1} 3324, 3165, 3032, 2843, 1711, 1481, 1445, 1286, 1117, 1071, 1020, 968, 897

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{14}O_5N_2$	C 49.59	C 49.67
242.23	H 5.83	H 5.98
	N 11.57	N 11.36

3à-Acetoxy thymidine (93):



Nature: White solid

Yield: 95%

Reaction time: 1 h

IR (Neat): cm^{-1} 3472, 3201, 3068, 2929, 1710, 1669, 1475, 1249, 1111, 1075, 1024, 881, 788, 578

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (s, 3H, $=CCH_3$), 2.11 (s, 3H, $-COCH_3$), 2.40 (bs, 3H, $-CH_2-$ & -OH), 3.92 (s, 2H, $-OCH_2-$), 4.10 (bs, 1H, H-3), 5.36 (bs, 1H, H-4), 6.27 (bs, 1H, H-1), 7.55 (s, 1H, = CH-), 9.50 (s, 1H, -NH-)

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{16}O_6N_2$	C 50.70	C 50.34

284.27	H 5.67	H 5.76
	N 9.85	N 9.69

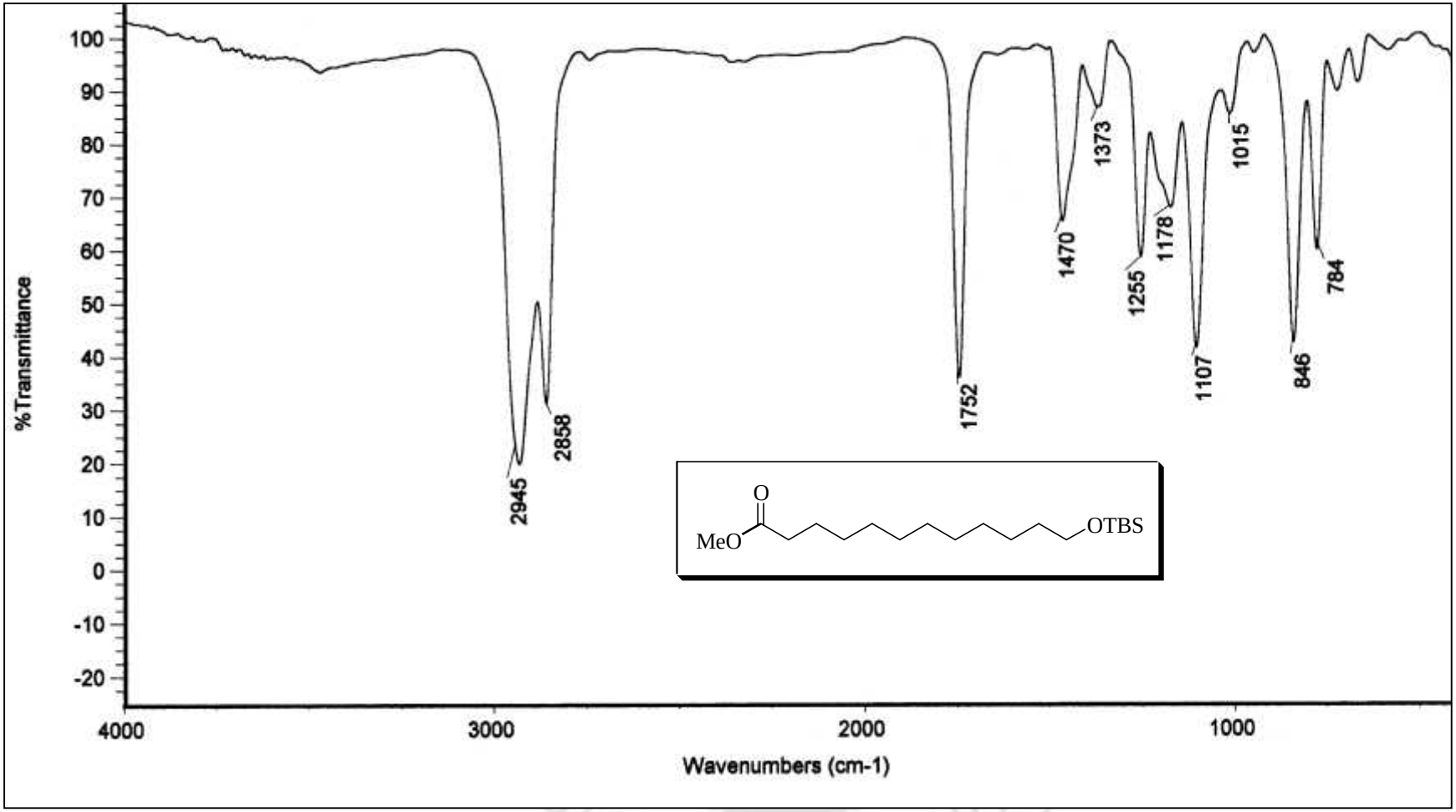


Figure 1: IR Spectrum of 1-*tert*-butyldimethylsilyloxy methyl-12-carboxylate dodacane (Neat) (56)

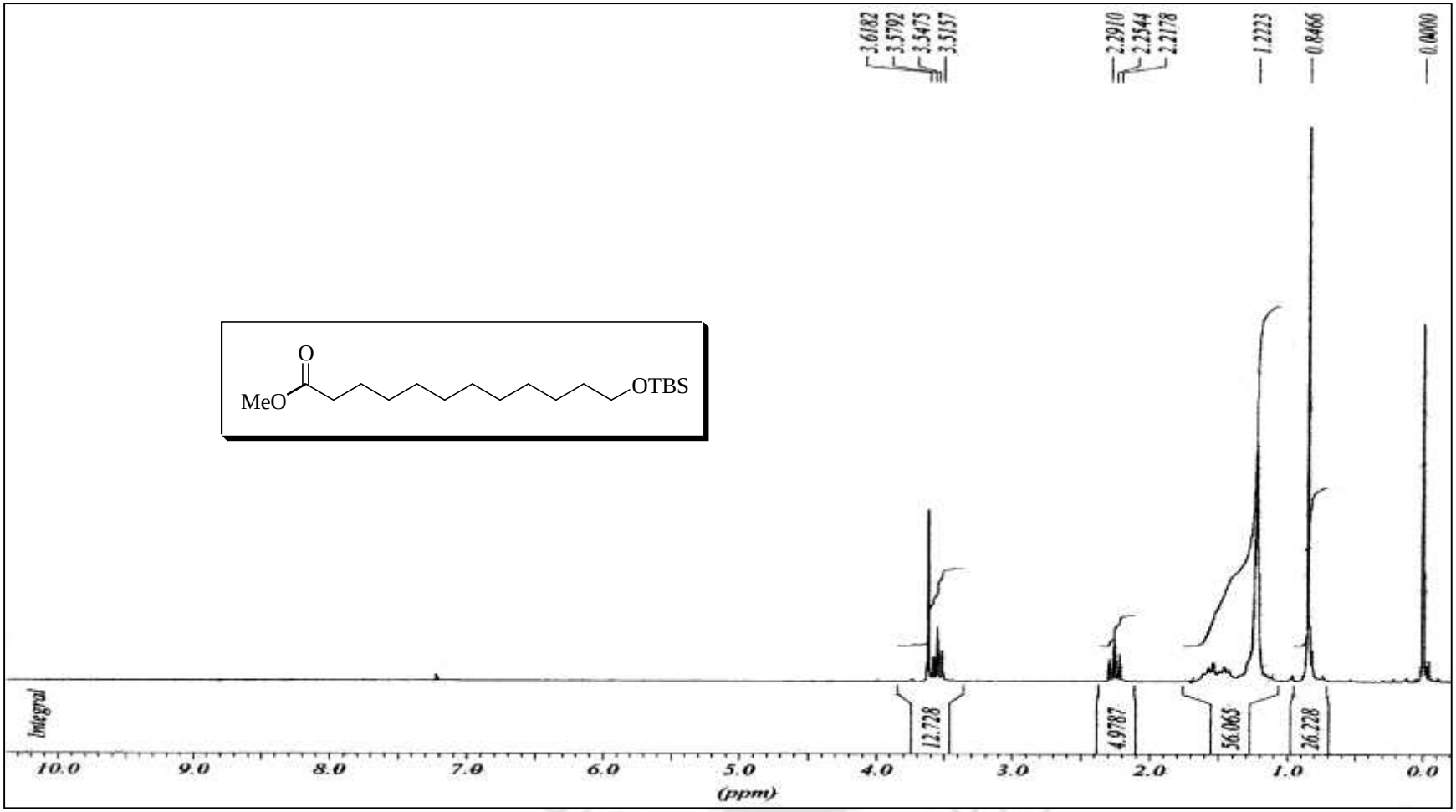


Figure 2: ^{1}H NMR Spectrum of 1-*tert*-butyldimethylsilyloxy methyl-12-carboxylate dodacane (200 MHz, $CDCl_3$) (56)

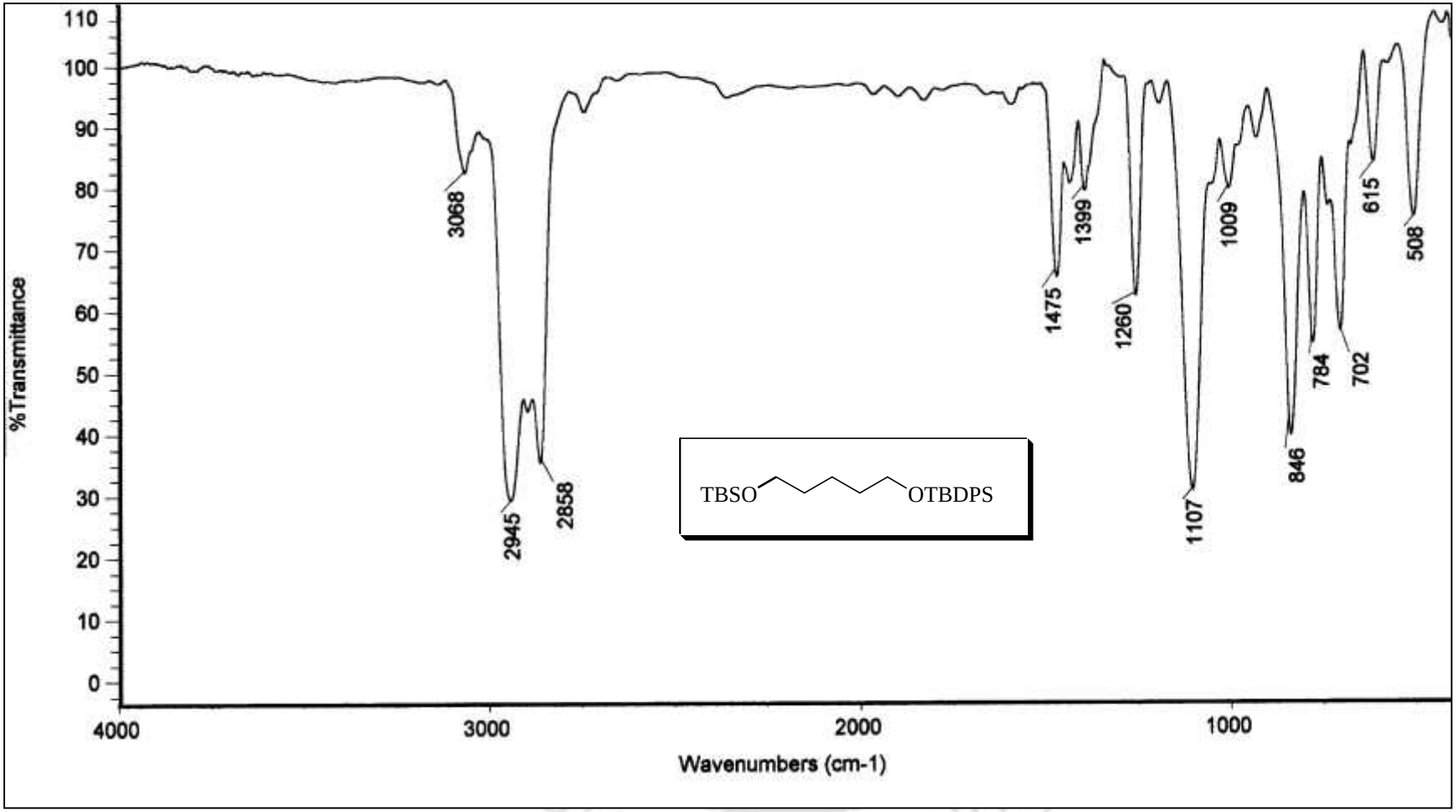


Figure 3: IR Spectrum of 5-*tert* butyldiphenylsilyloxy-1-*tert*-butyldimethylsilyloxypentane (Neat) (35)

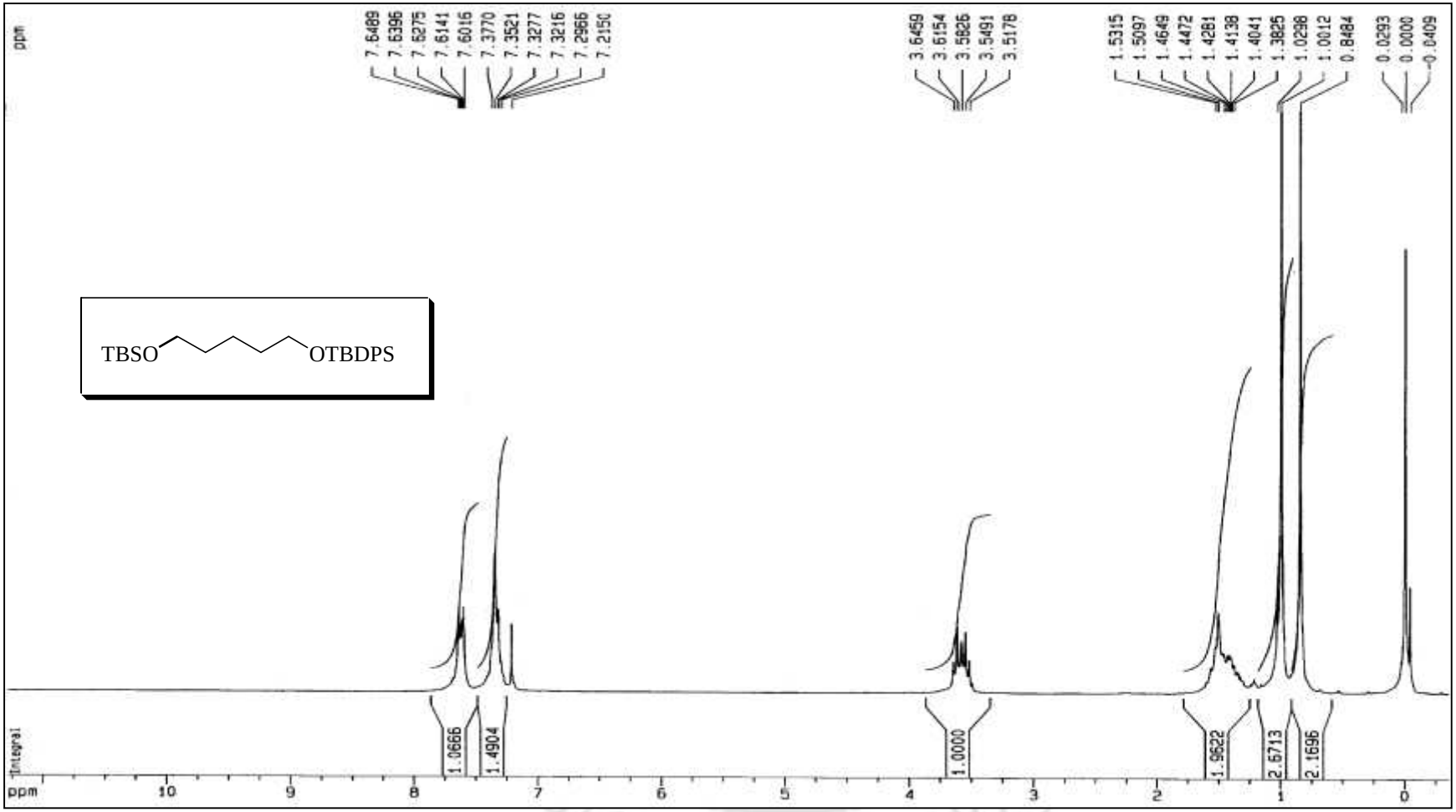


Figure 4: ^{1}H NMR Spectrum of 5-*tert* butyldiphenylsilyloxy-1-*tert*-butyldimethylsilyloxypentane (200 MHz, $CDCl_3$) (35)

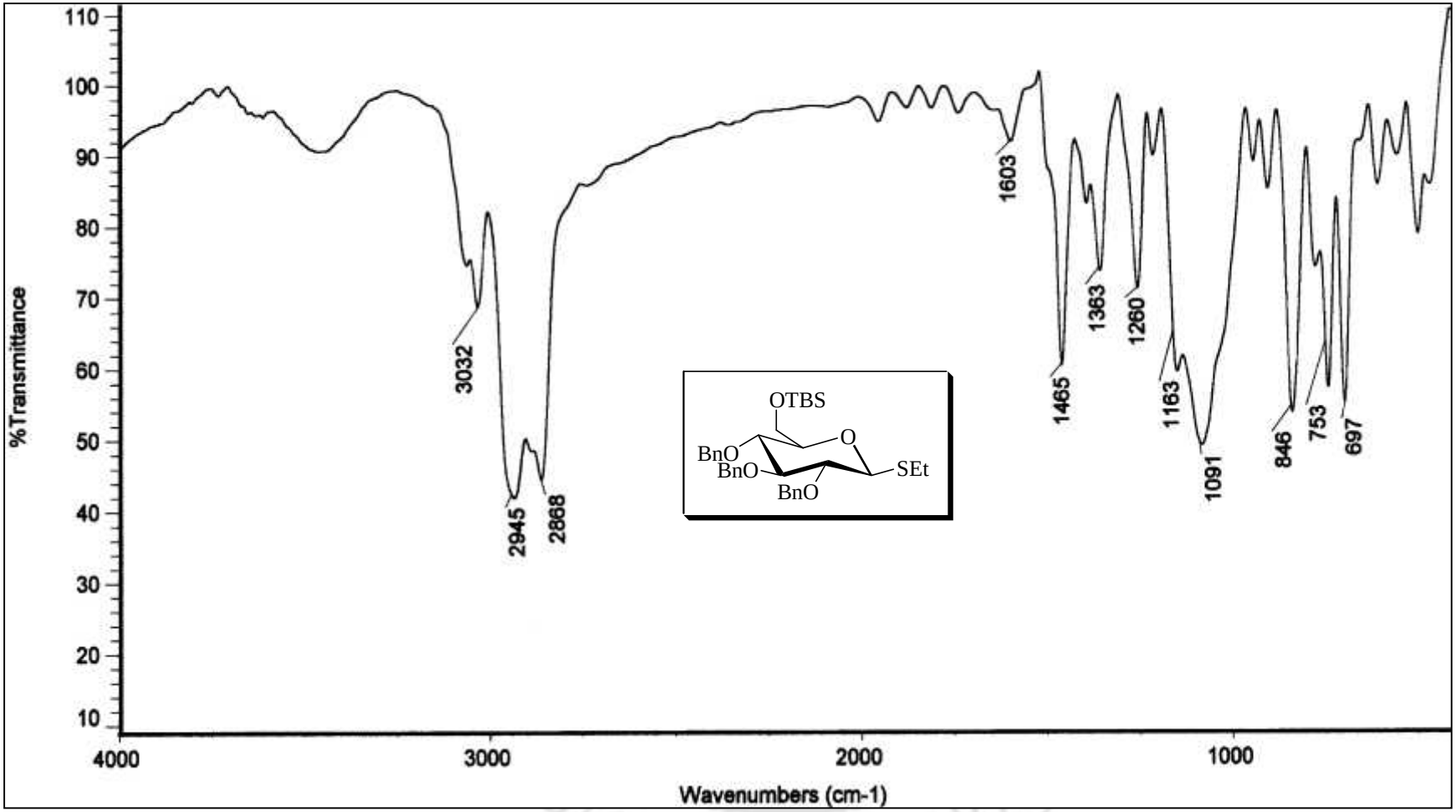


Figure 5: IR Spectum of Ethyl 6-*O*-*tert*-butyldimethylsilyl-2,3,4-tri-*O*-benzyl-1-thio- -D-glucopyranoside (Neat) (67)

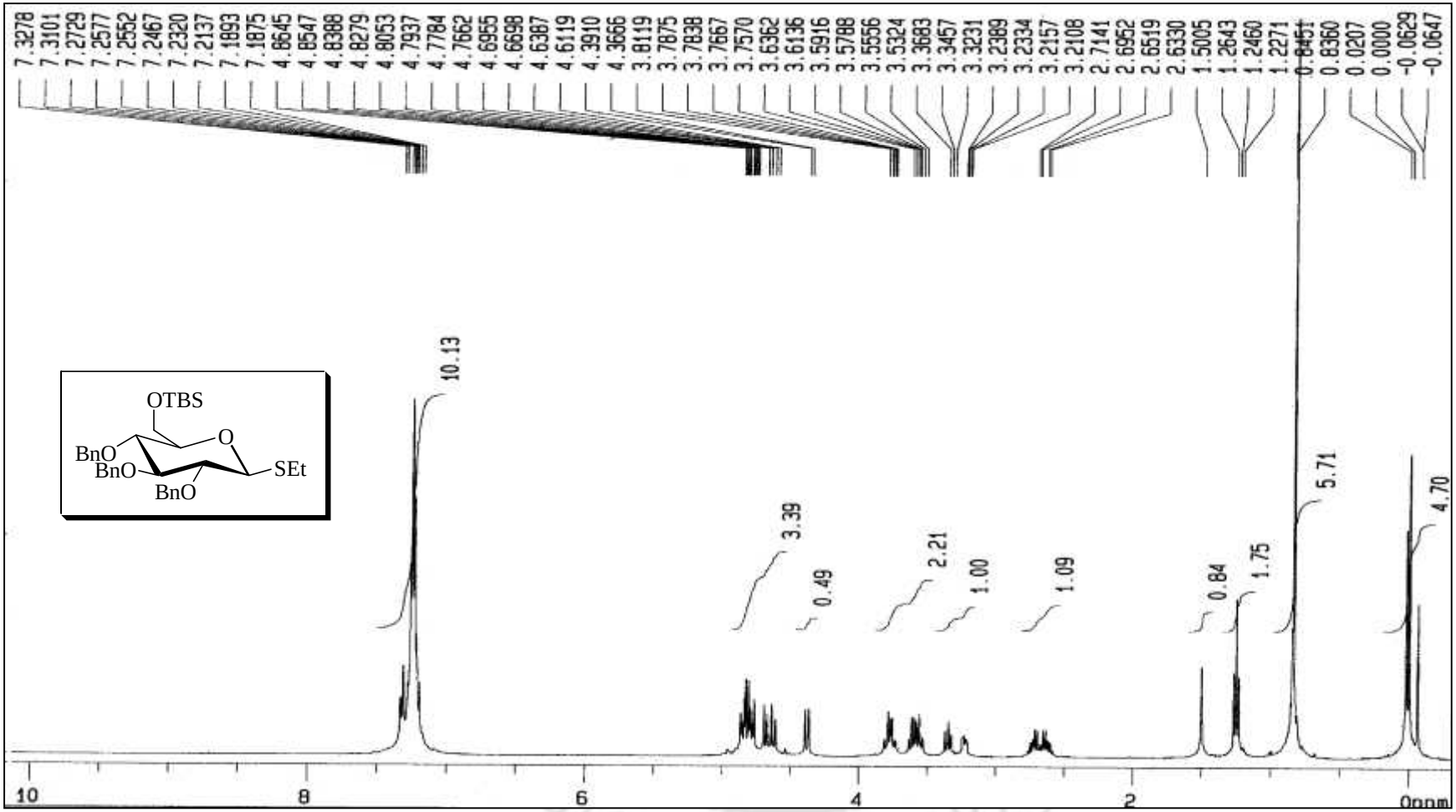


Figure 6: ^{1}H NMR Spectum of Ethyl 6-*O*-*tert*-butyldimethylsilyl-2,3,4-tri-*O*-benzyl-1-thio- -D-glucopyranoside (400 MHz, $CDCl_3$) (67)

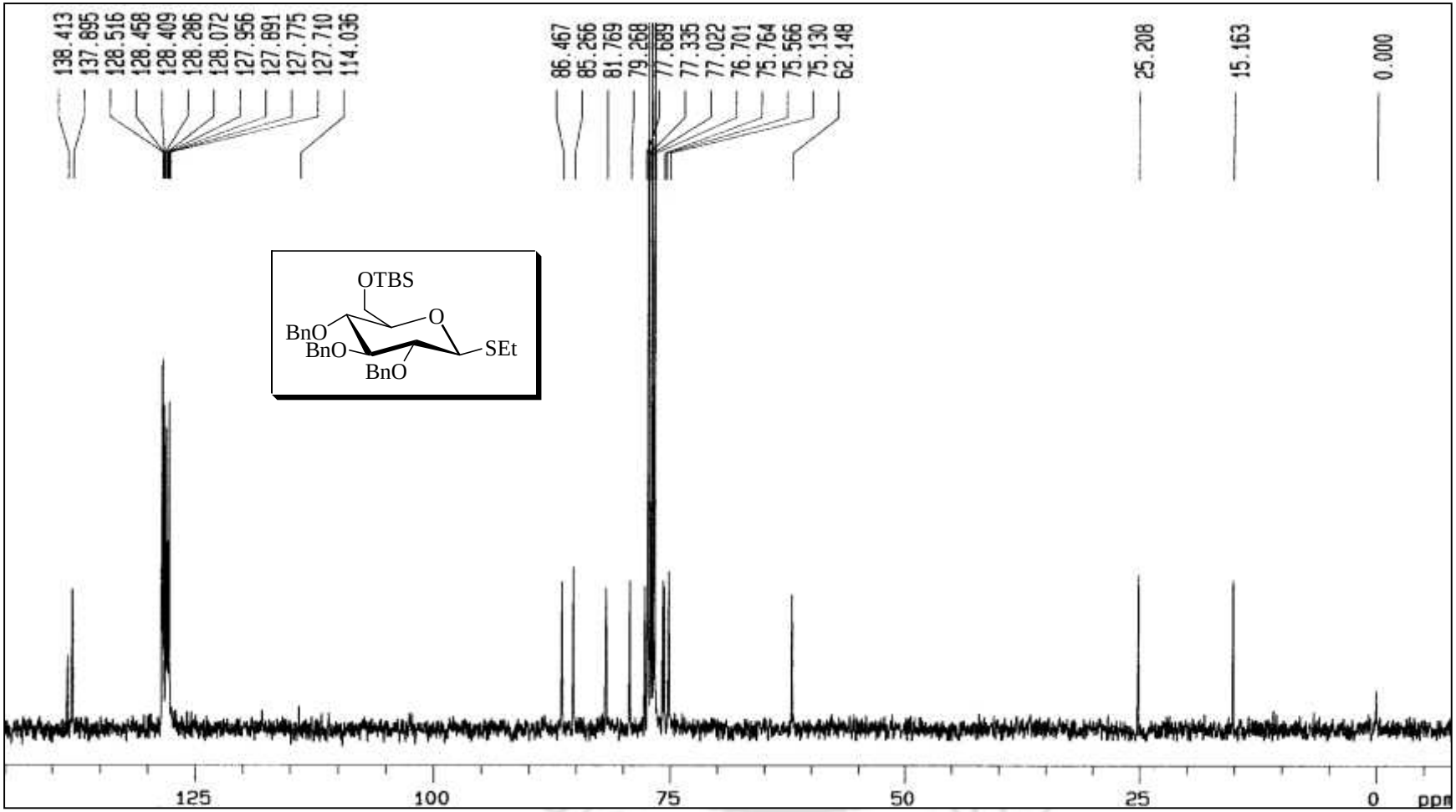


Figure 7: ^{13}C NMR Spectum of Ethyl 6-*O*-*tert*-butyldimethylsilyl-2,3,4-tri-*O*-benzyl-1-thio- -D-glucopyranoside (100 MHz, $CDCl_3$) (67)

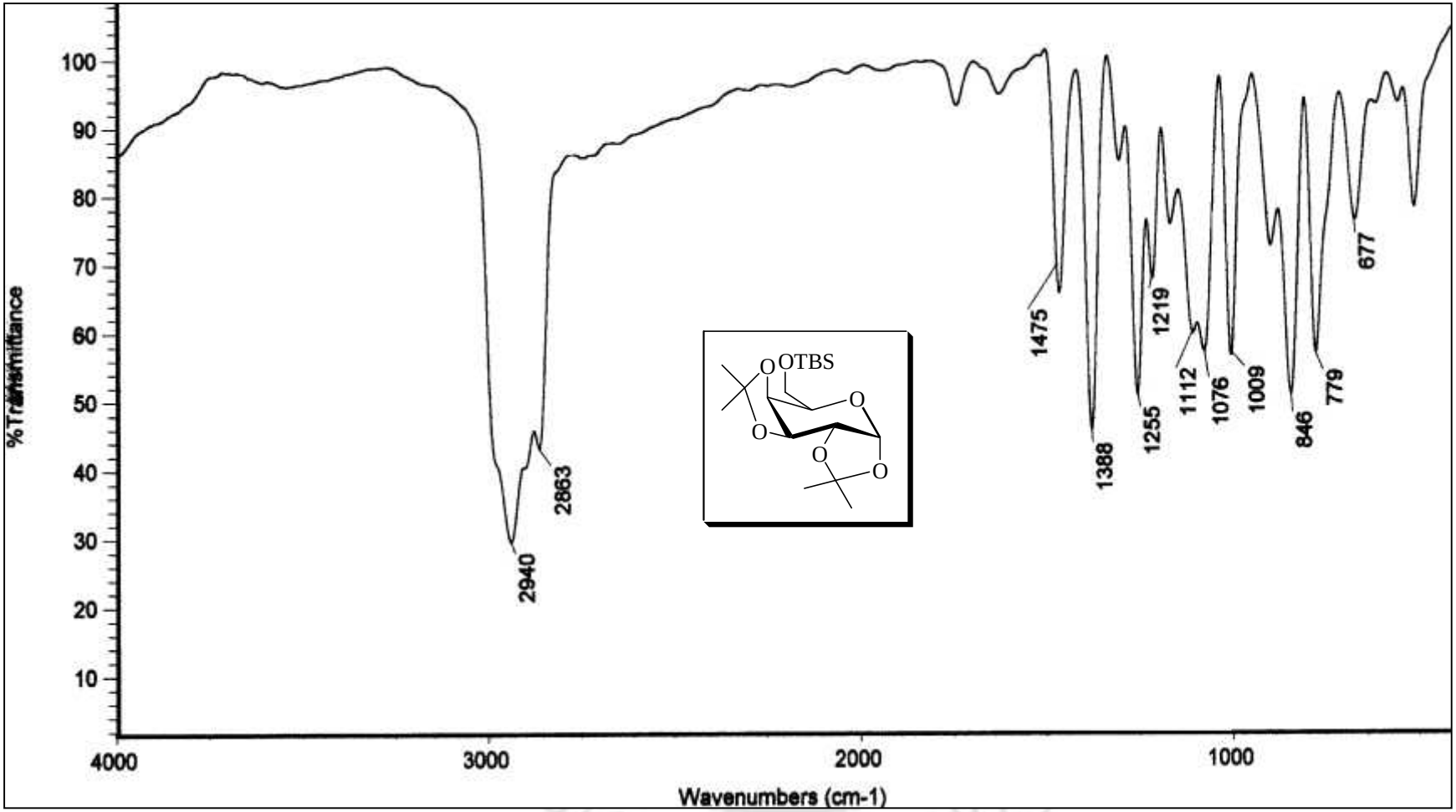


Figure 8: IR Spectrum of 6-O-*tert*-butyldimethylsilyl- 1,2, 3,4-di-*O*-isopropylidene galactose (Neat) (69)

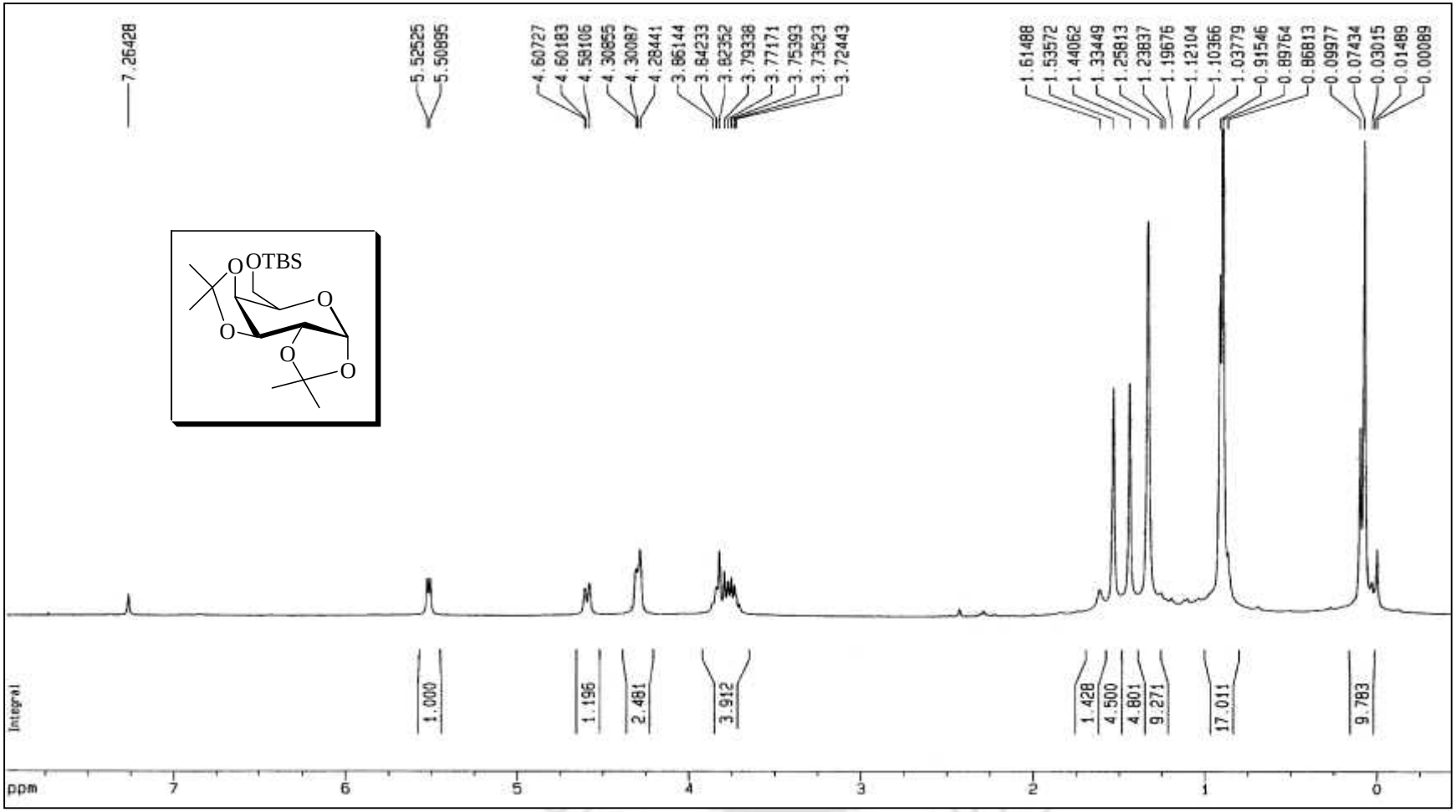


Figure 9: ^{1}H NMR Spectrum of 6-O-*tert*-butyldimethylsilyl- 1,2, 3,4-di-*O*-isopropylidene galactose (300 MHz, $CDCl_3$) (69)

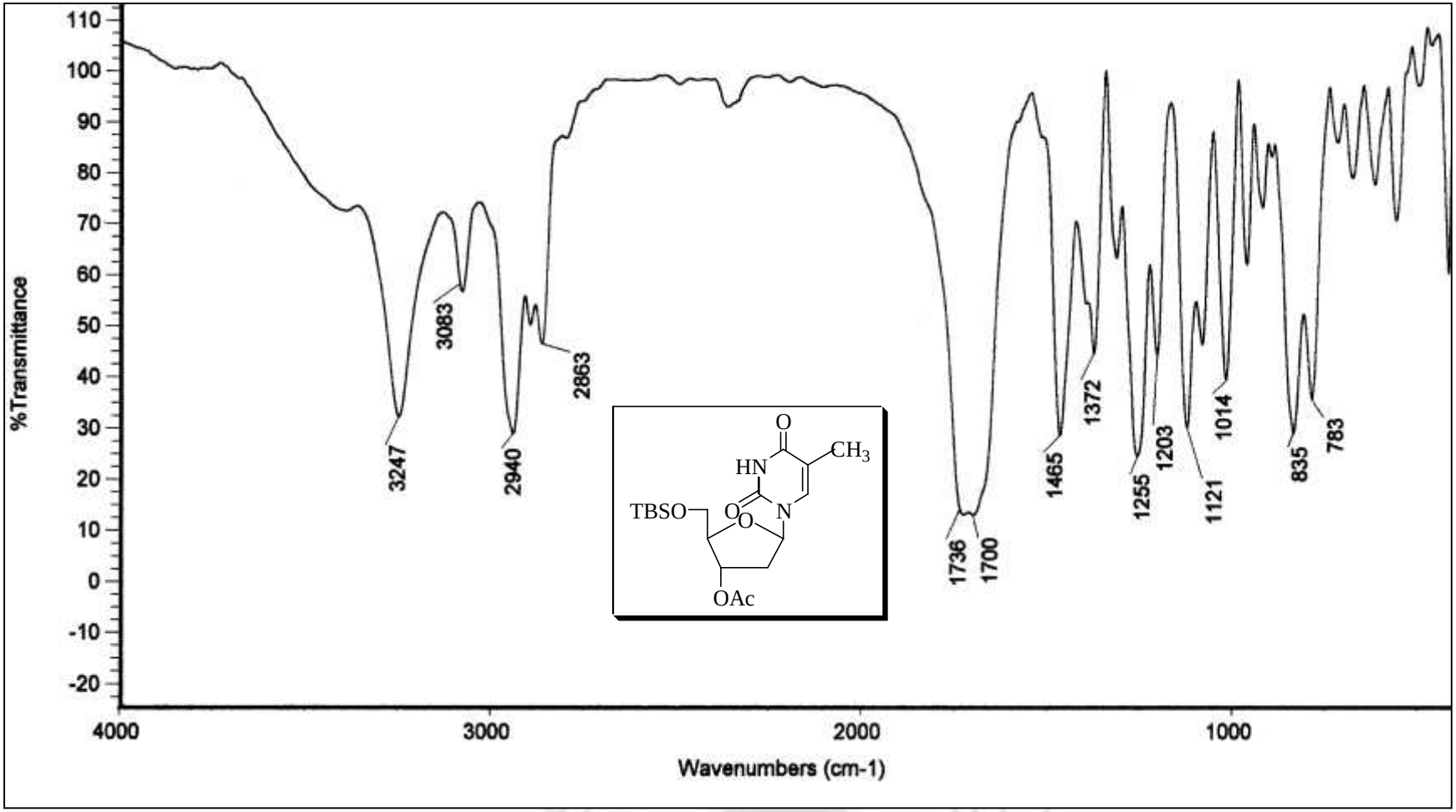


Figure 10: IR Spectrum of 3à-Acetyl-5à-*tert*-Butyldimethylsilyloxy thymidine (KBr) (71)

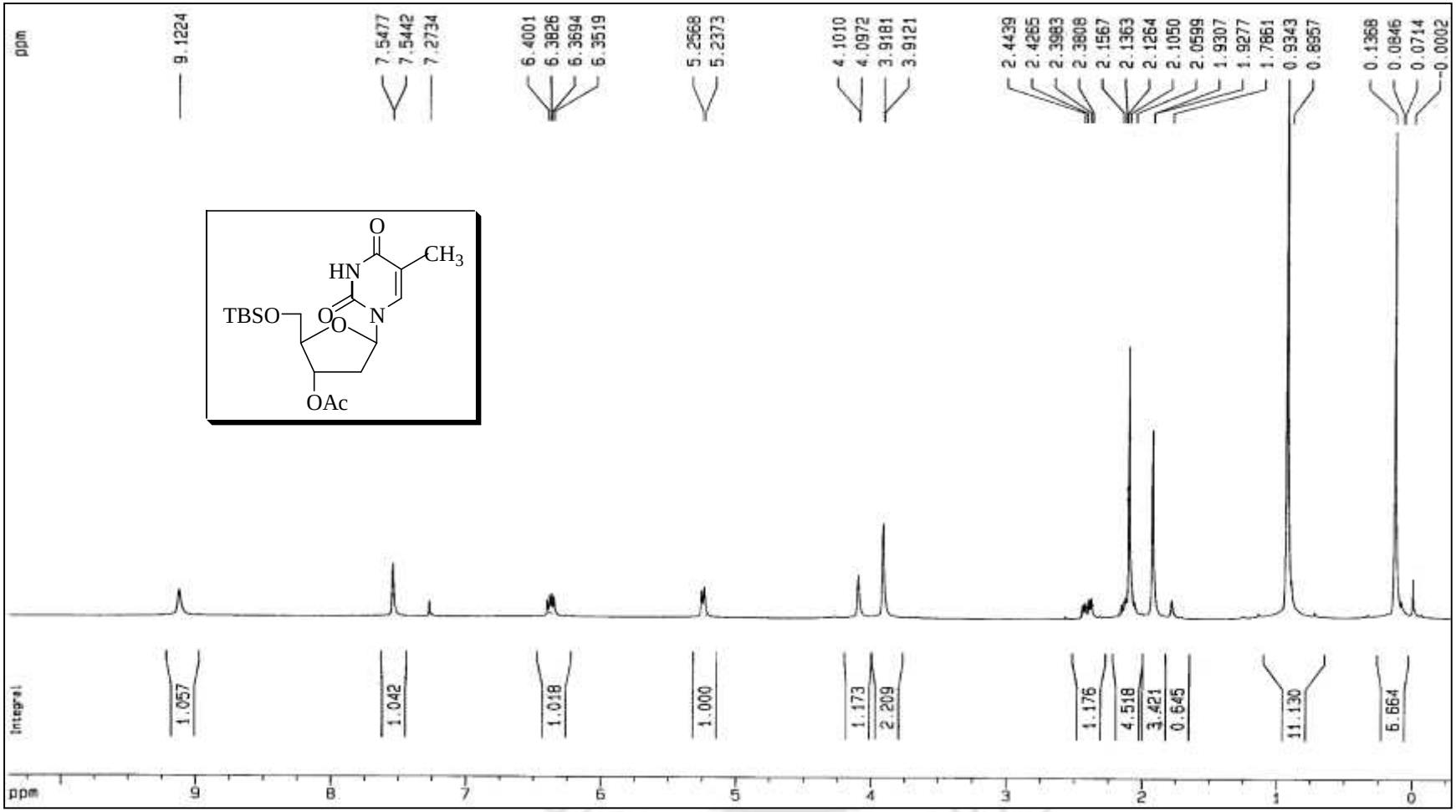


Figure 11: ^{1}H NMR Spectrum of 3à-Acetyl-5à-*tert*-Butyldimethylsilyloxy thymidine (300 MHz, $CDCl_3$) (71)

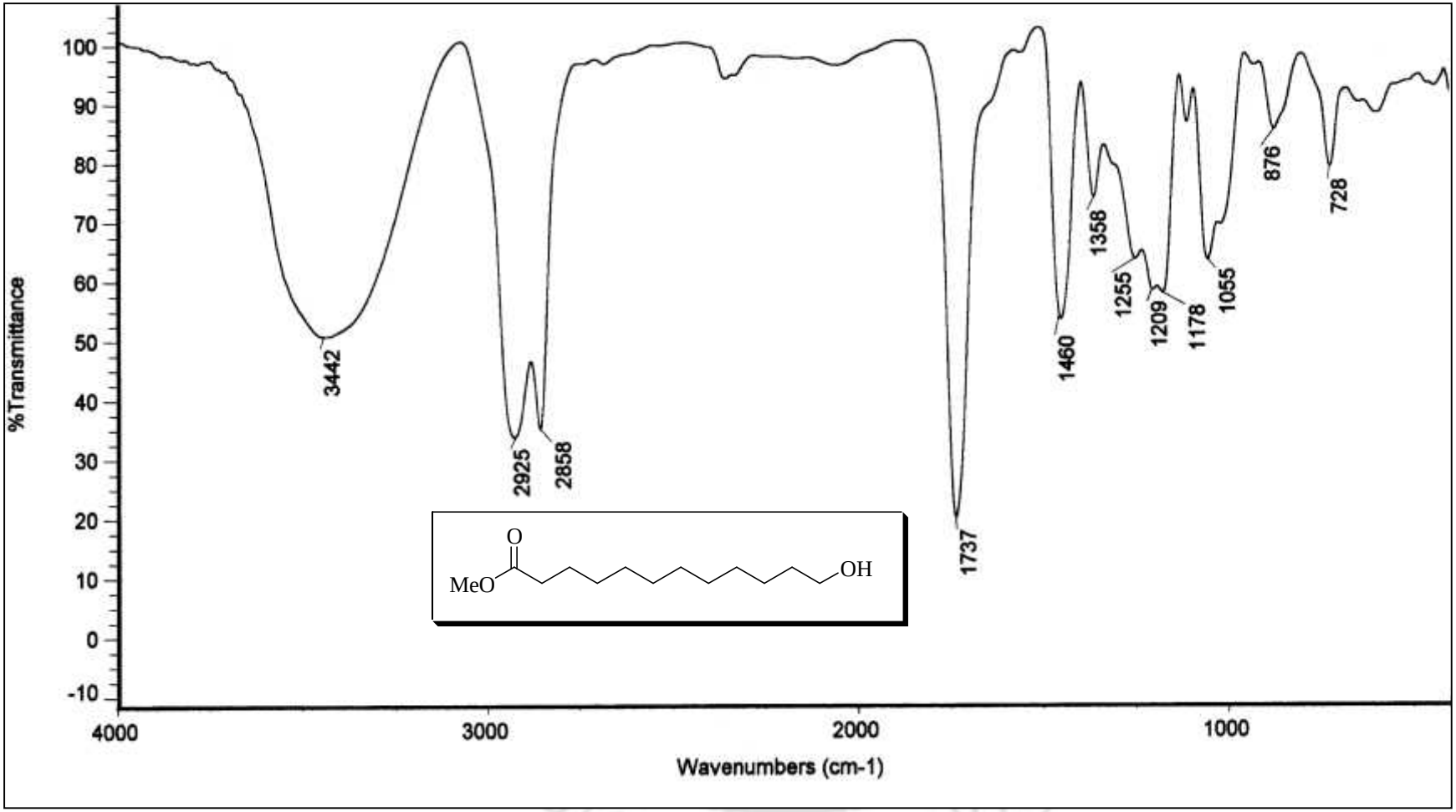


Figure 12: IR Spectrum of Methyl-12-carboxylate dodacanol (Neat) (78)

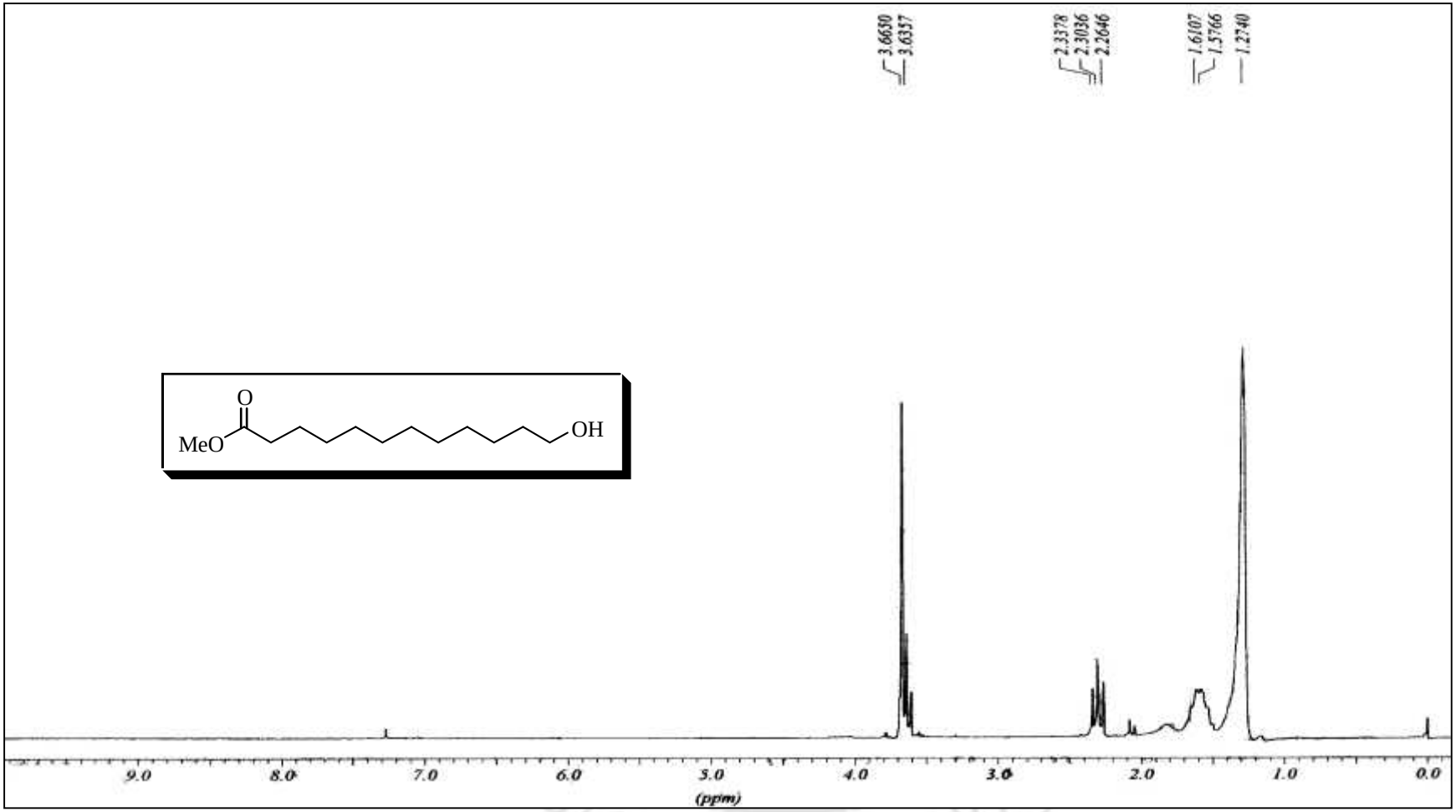


Figure 13: ^{1}H NMR Spectrum of Methyl-12-carboxylate dodacanol (200 MHz, $CDCl_3$) (78)

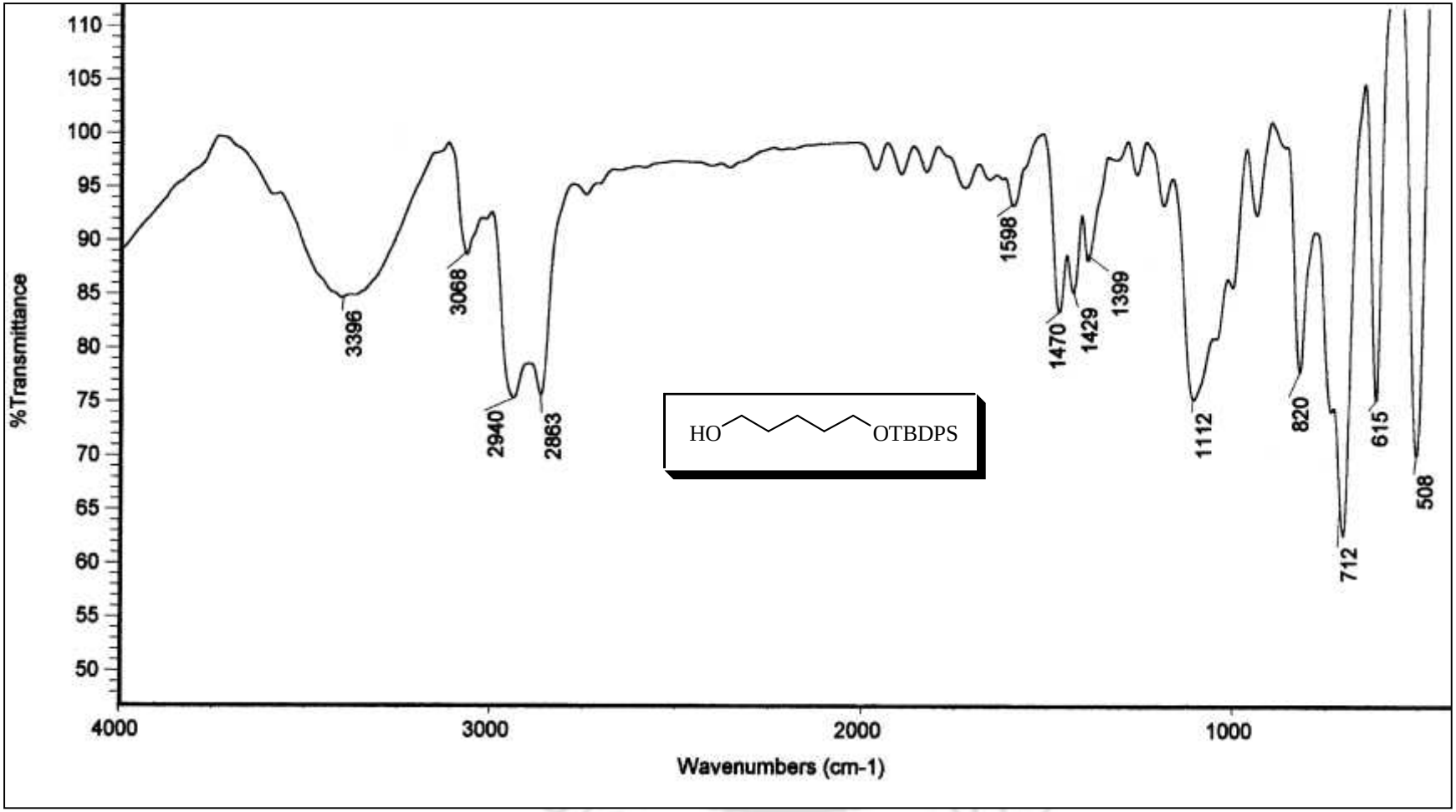


Figure 14: IR Spectrum of 5-*tert* butyldiphenylsilyloxy-pentanol (Neat) (36)

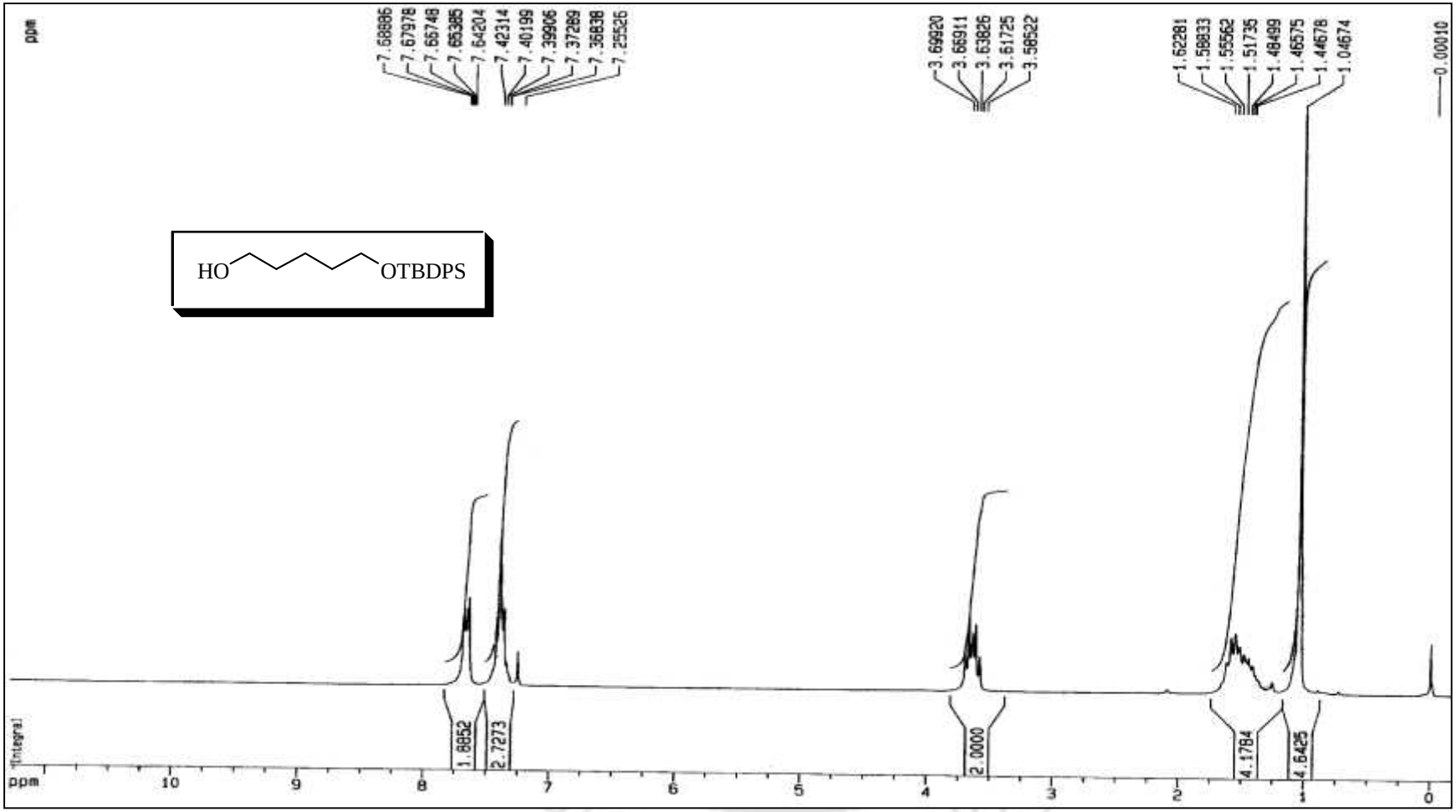


Figure 15: ^{1}H NMR Spectrum of 5-*tert* butyldiphenylsilyloxy-pentanol (300 MHz, $CDCl_3$) (36)

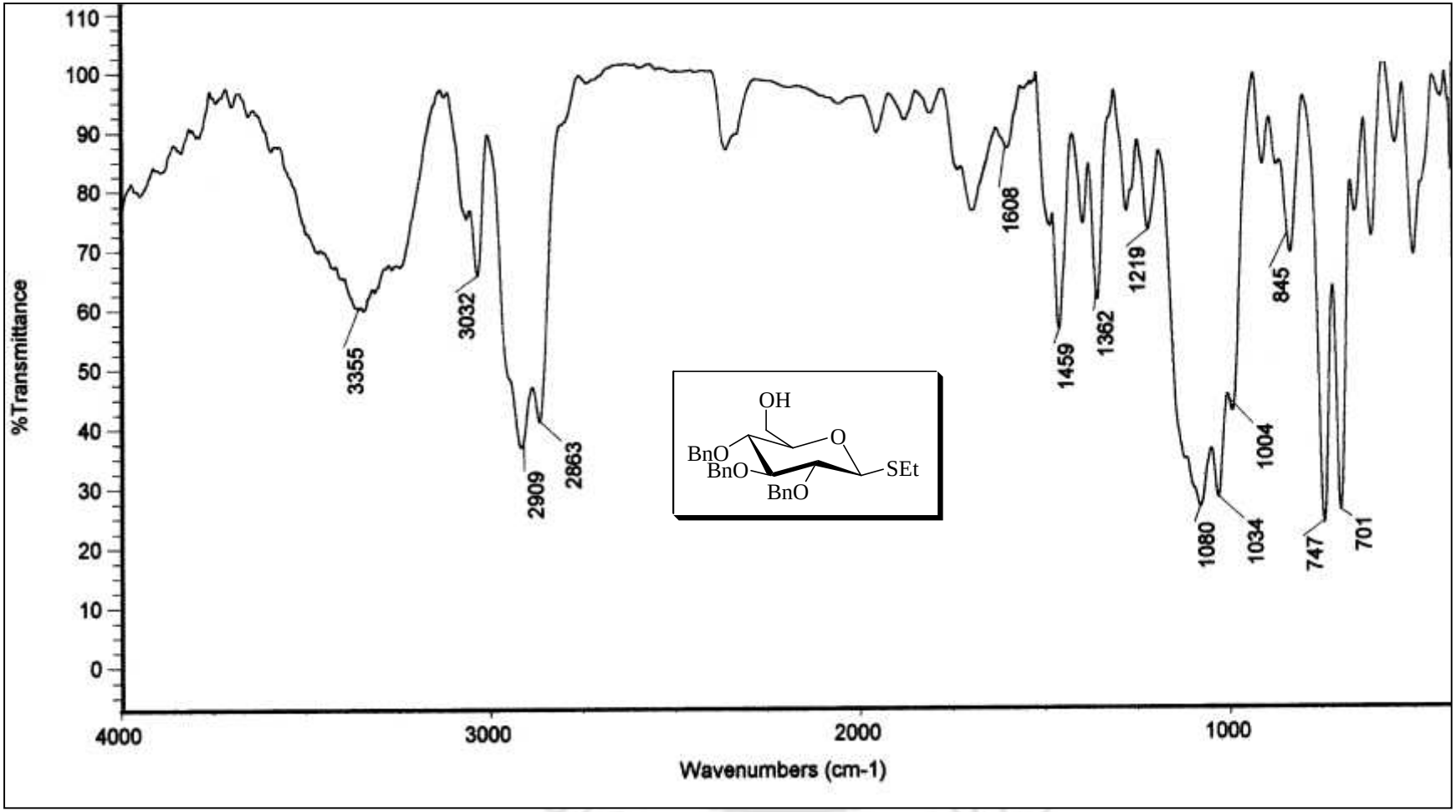


Figure 16: IR Spectrum of 2,3,4-tri-*O*-benzyl-1-thio- -D- ethyl glucopyranoside (KBr) (89)

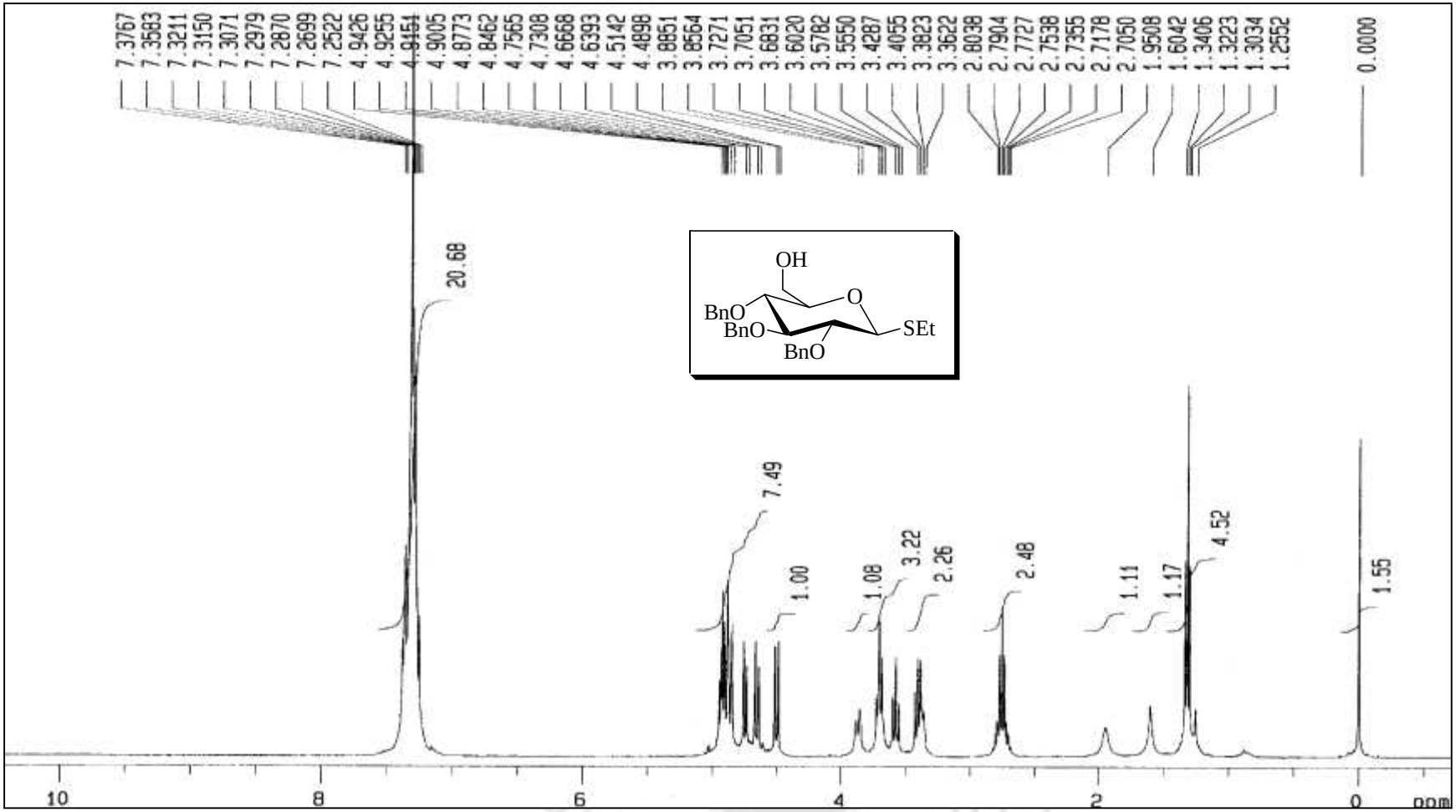


Figure 17: ^{1}H NMR Spectrum of 2,3,4-tri-*O*-benzyl-1-thio- -D- ethyl glucopyranoside (400 MHz, $CDCl_3$) (89)

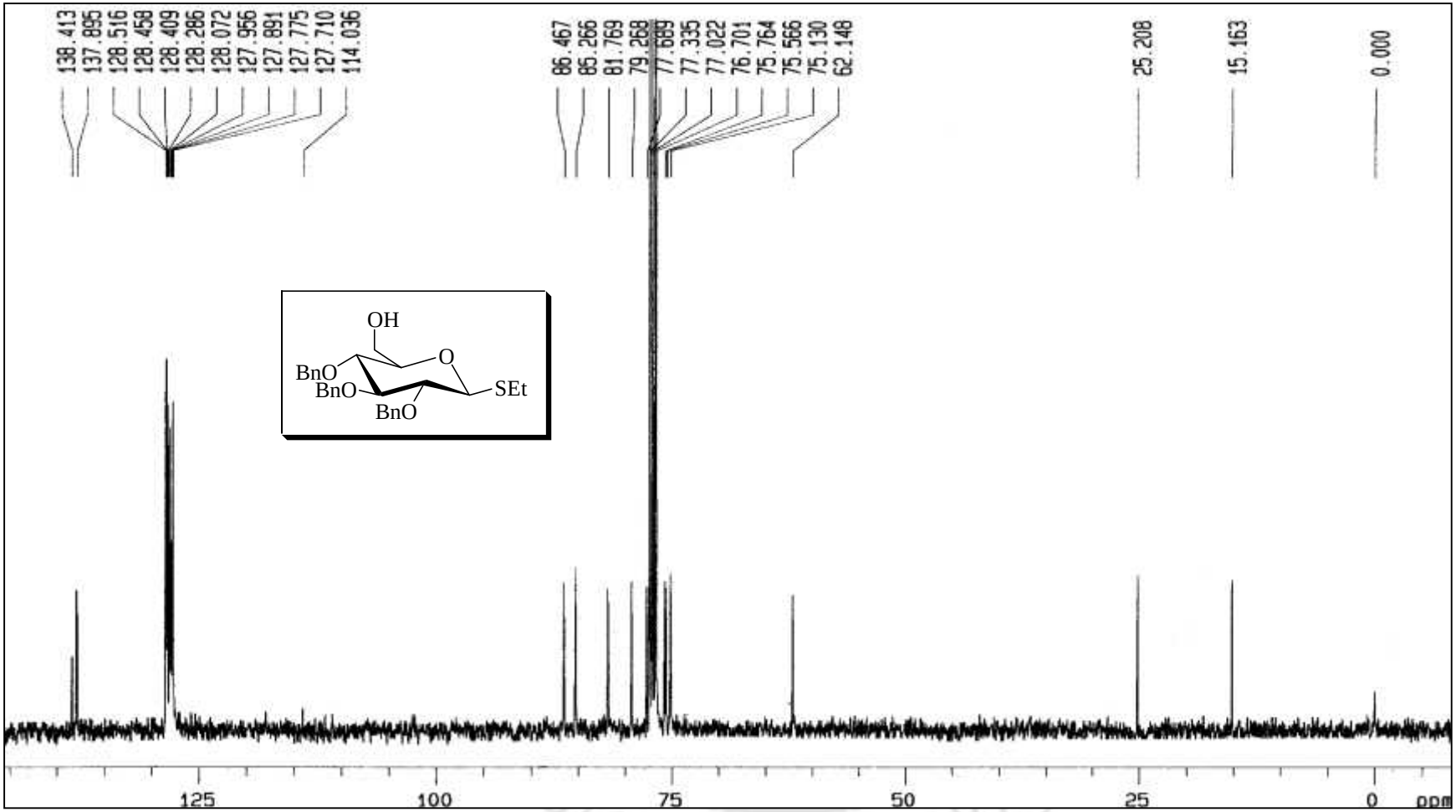


Figure 18: ^{13}C NMR Spectrum of 2,3,4-tri-*O*-benzyl-1-thio- -D- ethyl glucopyranoside(100 MHz, $CDCl_3$) (89)

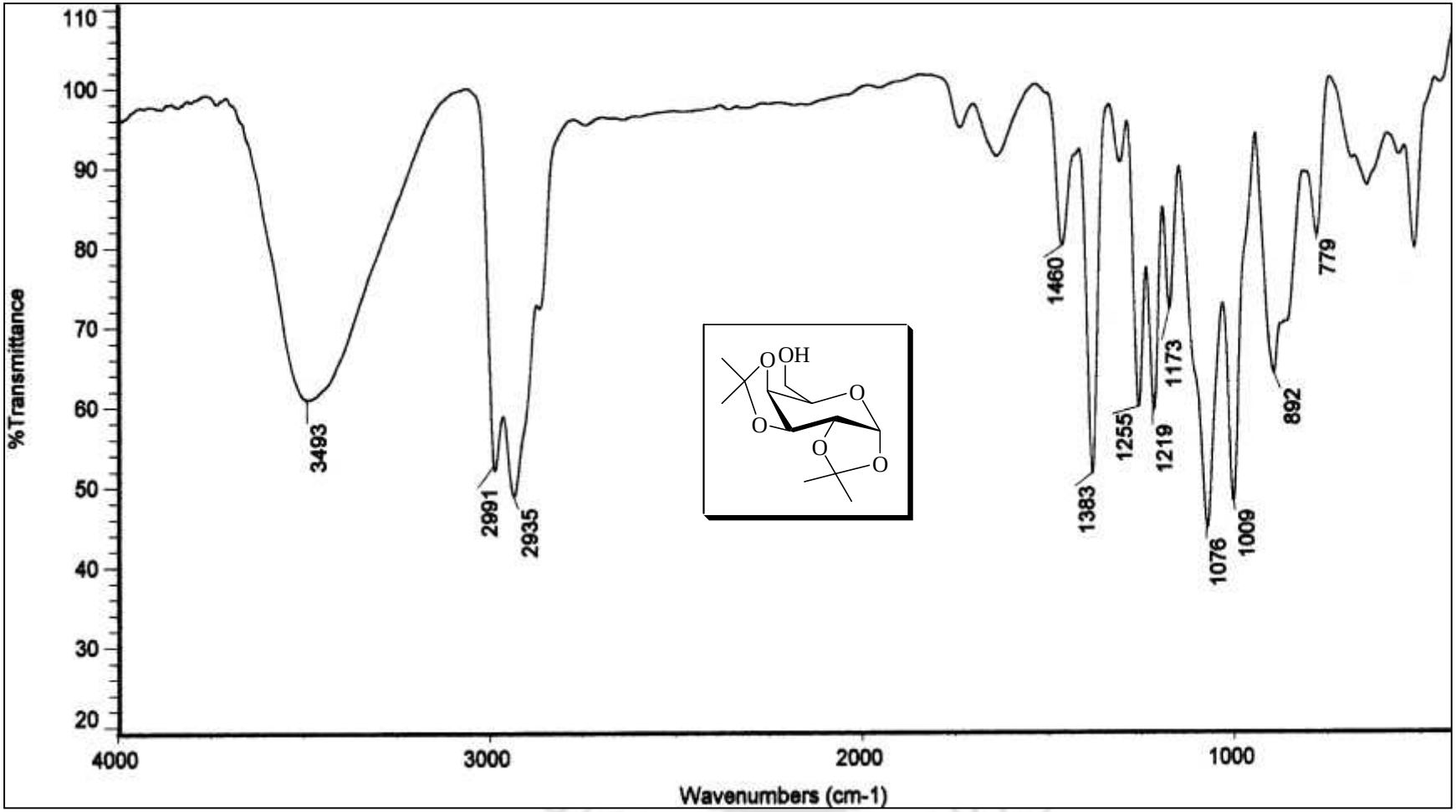


Figure 19: IR Spectrum of 1,2, 3,4-di-*O*-isopropylidene galactose (Neat) (91)

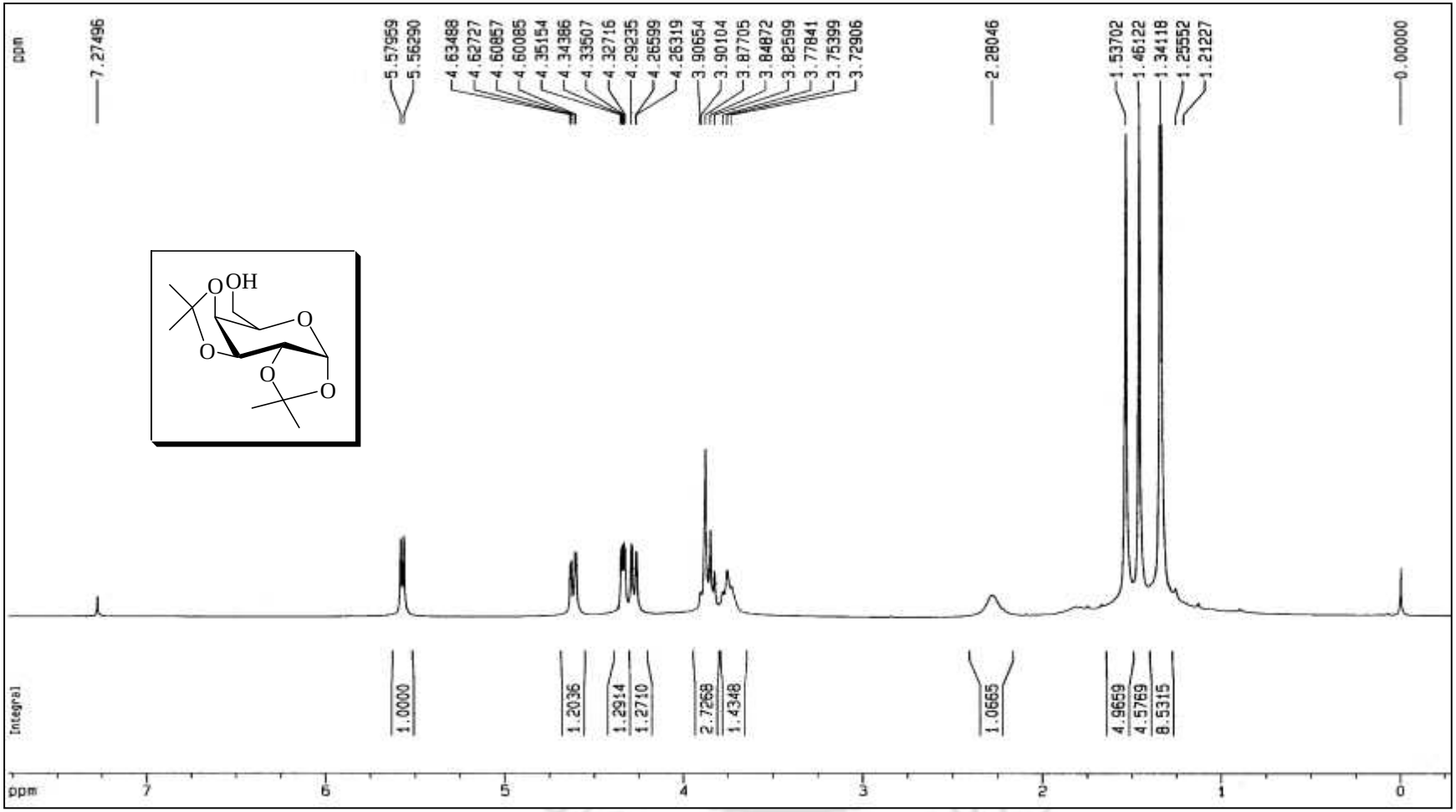


Figure 20: ^{1}H NMR Spectrum of 1,2, 3,4-di-*O*-isopropylidene galactose (300 MHz, $CDCl_3$) (91)

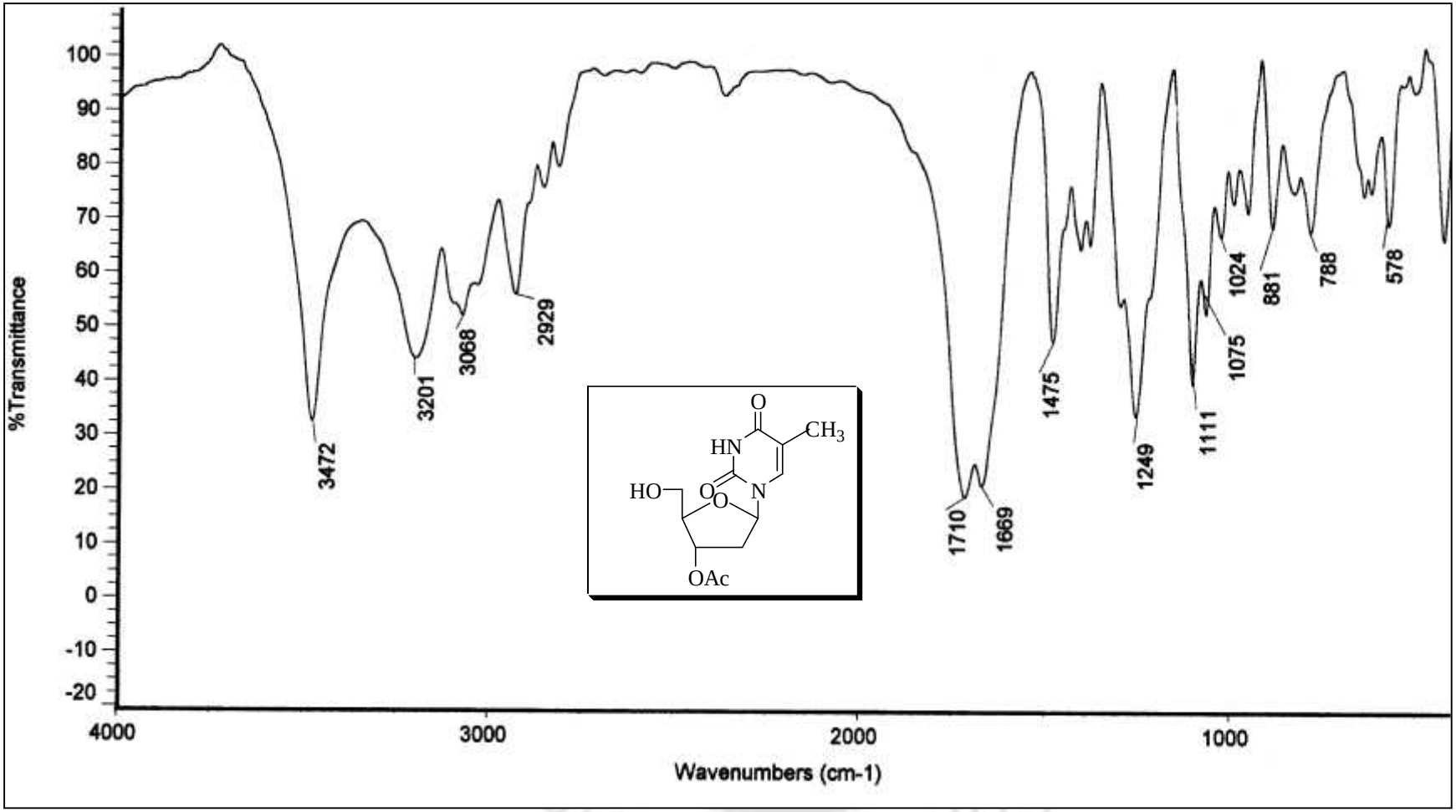


Figure 21: IR Spectrum of 3à-acetoxy thymidine (KBr) (93)

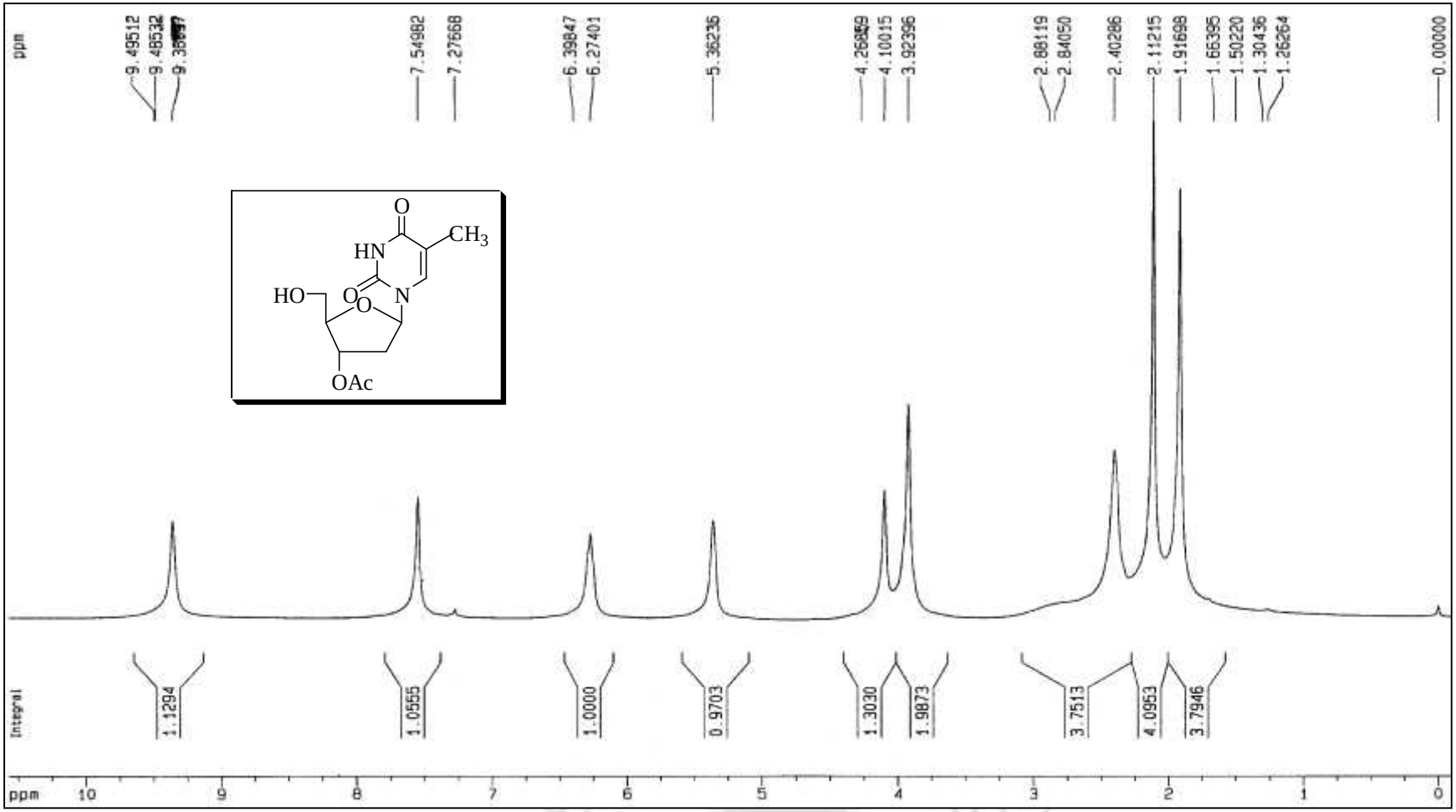


Figure 22: ^{1}H NMR Spectrum of 3à-acetoxy thymidine (300 MHz, $CDCl_3$) (93)

PART I & II
(SECTION B)

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Appendix

Conclusion and future scope

We have developed three new synthetic methodologies for thioacetalization of carbonyl compounds by using anhydrous nickel(II) chloride, acetyl chloride and bromodimethylsulfonium bromide as catalyst or pre-catalyst, which are discussed in the Chapter I of the Part II in Section A, Section B and Section C respectively. The salient features of these methodologies are: mild reaction conditions, good yields, no side reactions such as chlorination or bromination either at the double bond or triple bond or even in the aromatic rings and, which are some of the major advantages. The method developed by using bromodimethylsulfonium bromide is highly effective in terms of reaction time and yields. Moreover, work-up procedure is hassle free as compared to the earlier reported procedures. These successful results again open up to look for new catalyst or reagents for thioacetalization reactions. Some of the cyclic thioacetals particularly 1,3-dithiane derivatives of aldehydes can be used for natural product synthesis, which is under investigation. Similarly, we have accomplished four synthetic methodologies by using reactive species bromonium ion (Br^+) and nitrosonium ion (NO^+). We have also shown first time in the literature that organic ammonium tribromides are quite useful for deprotection of dithioacetals and dithioketals. The problem associated with this procedure is the requirement an equivalent amount of valuable and relatively expensive organic ammonium tribromides. Therefore, we would like to find out another suitable reaction conditions or solvent system so that less amount of reagent is required for dethioacetalization. In the second procedure for dethioacetalization reaction, we have demonstrated that diperoxomolybdenium complex mediated oxidation of bromide ion to the bromonium ion, which can be further utilized for dethioacetalization reactions. This method usually works in the promoted manner. Therefore, we would also like to investigate whether similar transformation can be achieved by using other molybdenum salts as well as by involving other bromide ion source, which might provide better result for dethioacetalization. Lastly, we have also shown that a wide variety of dithioacetals or dithioketals can be successfully hydrolyzed into the corresponding parent carbonyl compounds in very good yields at 0-5 ^oC by involving vanadium pentoxide-hydrogen peroxide catalyzed oxidation of ammonium bromide in dichloromethane-water solvent system. This methodology is also found to be superior as compared to the previous one because it works in the catalytic manner. In addition, this procedure is very mild, environmentally benign, efficient and highly chemoselective. No side reactions are observed such as bromination either at the double

bond or aromatic ring or even oxidation at the sulfur center. We have also demonstrated that *in situ* generated electrophile Br^+ can be employed for deprotection of dithioacetals or dithioketals, which is mechanistically more interesting.

The future scope left for us includes; i) chemoselective hydrolysis of different kinds of dithioacetals, which is present in the same molecule such as cyclic five membered dithioacetal versus six membered dithioacetal ii) it might be possible to hydrolyze dithioacetals by employing other alkali metal bromides such as sodium bromide, potassium bromide etc, which has to be investigated. In addition, there is a scope to accomplish the hydrolysis of various dithioacetals by using isolated molybdenum and vanadium peroxo complexes. By using 1-thioglycosides as donor molecule, it might be possible to synthesize O-glycosides in aqueous medium by involving suitable acceptor molecule.

We have also accomplished that NO^+ ion can be used for dethioacetalization reaction. By using this reactive intermediate, we would like to investigate other some application in organic synthesis.

We have successfully demonstrated that catalytic amount acetyl chloride in methanol is a good combination for desilylation reaction of *tert*-butyldimethylsilyl (TBS) ether. We would like to study further whether other acid chloride such as oxalyl chloride might provide better result.

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1. Nickel(II) chloride as an efficient and useful catalyst for chemoselective thioacetalization of aldehydes

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