KJE-3900

Master Thesis in Organic Chemistry

Reductions of barbituric acid based compounds

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Contents

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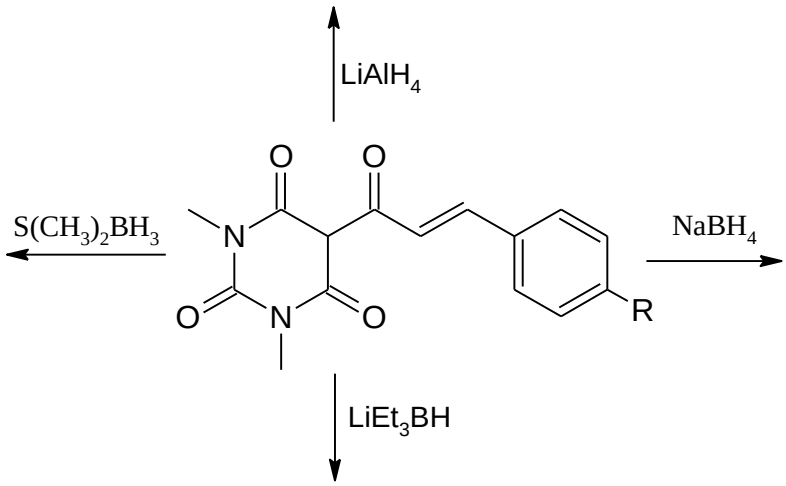
I want to thank my office- and laboratory- friends, especially Ivar Kristian Thomassen who I spent the most time with.

Symbols and abbreviations

Ac	acetyl
δ	chemical shift (ppm)
J	coupling constant
°C	degree Celsius
d	doublet
dd	double doublet
$CDCl_3$	deuterated chloroform
DMSO-d_6	deuterated dimethyl sulphoxide
EtOH	ethanol
g	gram
Hz	hertz
IR	infrared spectroscopy
MS	mass spectroscopy
MHz	mega hertz
MeOH	methanol
mg	milligram
mL	millilitre
mmol	milli mole
min	minutes
m	multiplet
NMR	nuclear magnetic resonance
ppm	part per million
s	singlet
THF	tetrahydrofuran
t	triplet
cm^{-1}	wave number, reciprocal centimetre

Summary

Chalconoids with different para- substituents on the phenyl ring were attempted reduced with different reducing agents. The starting materials were synthesized according to earlier discovered procedures by members of the group.



No successful reductions were performed with temperatures ranging from 0 °C to 80 °C depending on the reducing agent used. A successful reduction of 5-acetyl-1,3-dimethylbarbituric acid was made in order to investigate if the acetyl group could actually be reduced.

1 Background

1.1 History of barbituric acid

Barbituric acid, or malonylurea, was discovered in 1863 by the German chemist Adolph von Baeyer [1]. The synthesis was accomplished by condensing urea (an animal waste product) with diethyl malonate (an ester derived from the acid of apples) [2]. Barbituric acid is pharmacologically inactive, but its derivatives, the barbiturates, have been widely used in the past because of their biological properties. One example is the use as hypnotics; they can provide any degree of hypnosis from mild sedation to total anaesthesia [3]. Approximately 2500 derivatives have been synthesised, but only about 50 of these have found clinical acceptance [4].

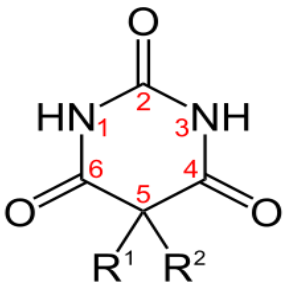


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Figure 1: General structure of the barbiturates (barbituric acid, R^1=R^2=H).

Certain structural criteria have to be met in order that a barbituric acid derivative has significant pharmacological activity. Those barbiturates without any substituent, or only one, at the C-5 position are essentially lacking in pharmacological activity. The active derivatives can be divided into three chemical classes, the 5,5-disubstituted barbiturates, the 1,5,5-trisubstituted barbiturates, and the 5,5.disubstituted thiobarbiturates (the oxygen at C-2 is replaced by sulphur in the thiobarbiturates). Each of these classes can further be sub-divided depending on the type of substituent groups in the molecule (alkyl, aryl, alkenyl, etc.). The nature of such groups can grossly affect pharmacological properties. In general, the total number of carbon atoms contained in substituent groups influences the lipid solubility of the compound [5].

The first useful derivatives, Veronal (5,5-diethylbarbituric acid, also called barbital), was synthesized by Emil Fischer and Joseph von Mering in 1902, and the results were published in 1903 [3].

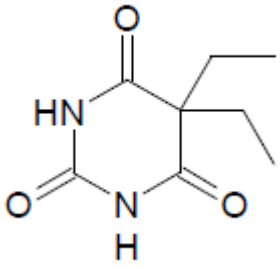

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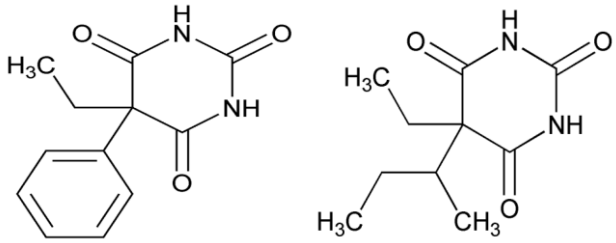
Figure 2: Structure of barbital (Veronal)

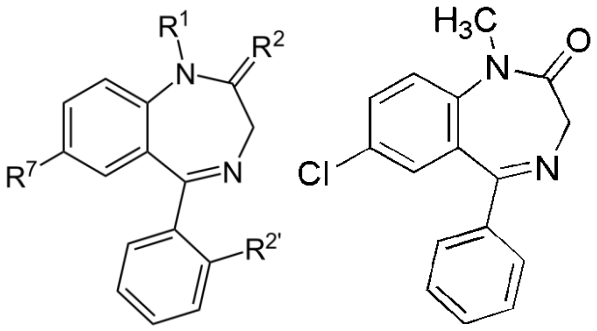
Nowadays, the use of barbiturates is limited to quite specific therapeutic applications. Phenobarbital [6] and butabarbital [7] are still used as sedatives in cases of gastrointestinal and asthmatic functional disorders, as well as to antagonize the adverse central stimulant effects of some drugs. Other uses include cases of withdrawal syndromes of hypnosedative agents, treatment of certain types of epilepsy, emergency treatment of some types of convulsions and management of acute traumatic brain injury.



3 **4**

Figure 3: Structure of phenobarbital (**3**) and butabarbital (**4**)

Because of the addiction potential of these drugs and the high risk of overdose, most barbiturates have been replaced by the less dangerous benzodiazepines. Diazepam, better known as valium, is a derivative of benzodiazepines, and nowadays it is widely commercialized worldwide [8].



5 **6**

Figure 4: General structure of benzodiazepines (**5**) and diazepam (**6**).

1.2 Chalcones

The generic term “Chalcone” is given to compounds consisting of the 1,3-diphenylprop-2-en-1-one framework [9]. In this framework two aromatic rings (A and B) are linked by a three carbon α,β- unsaturated carbonyl system (**Figure 5**). Due to the enone system, such molecules present relatively low redox potentials and will more likely undergo electron transfer reactions.

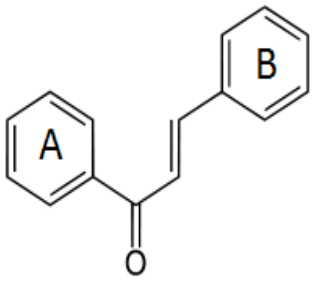


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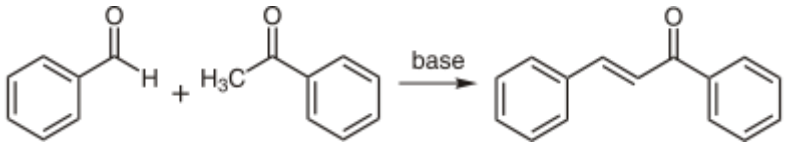
Figure 5: Chalcone core (1,3-diphenylprop-2-en-1-one)

Chalcones are usually synthesized by the base-catalysed Claisen- Schmidt condensation (aldol condensation) of an aldehyde and an appropriate ketone in a polar solvent like methanol [10].



8 **9** **7**

Scheme 1: Synthesis of chalcone

A large number of chalcones present cytotoxic and anticancer activity toward a number of cancer cell lines (human tumor cells). Hydroxy-substituted compounds for instance display a diverse array of pharmacological activities such as anticancer and anti-HIV [11, 12].

From earlier research in the group a large number of chalconoids (chalcones in which one of the phenyl rings is substituted by another ring), with different substituents, was reported. These compounds where synthesized from barbituric acid. Kinase testing revealed that only a few of them where exhibiting biological activity. As the biological testing takes place in an aqueous environment, it is necessary to use substances that are water soluble. The biggest

problem with earlier synthesized compounds has been their low solubility in water. By synthesizing compounds with higher water solubility this could show if they have inhibiting effects on kinases.

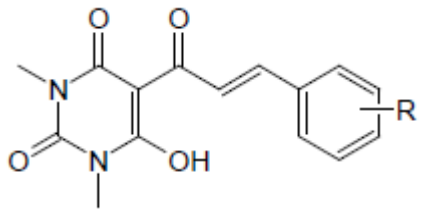


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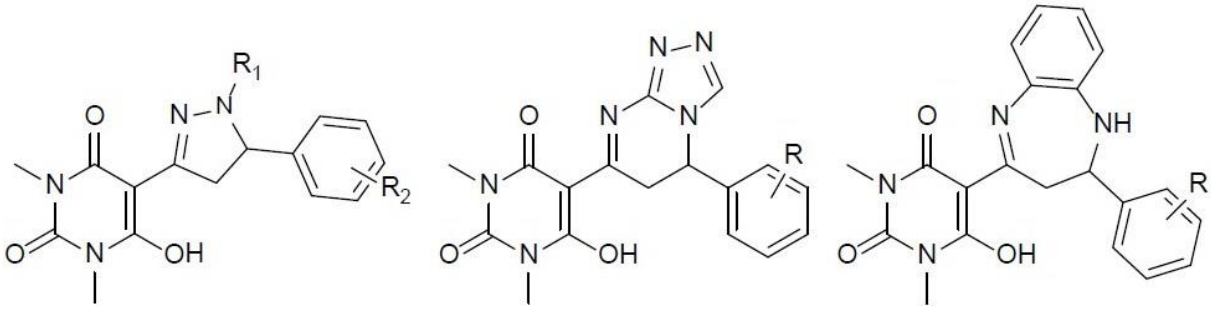
Figure 6: Structure of chalcone with barbituric acid moiety

Earlier synthesized 5-, 6- and 7- member ring heterocyclic compounds that are reported by members of the group are showed in Figure 7 [14].



12 **13** **14**

Figure 7: Chemical structures of 5-, 6- and 7- member ring heterocyclic compounds.

These compounds have been tested for kinase activities. They are active to some extent, but have low water solubility [13- 15].

1.3 Flavonoids

Flavonoids are a class of plant secondary metabolites, and commonly found in fruit, plants, and vegetables among other things. The flavonoid backbone consists of three different rings (A, B and C) as shown in **Figure 8** [16].

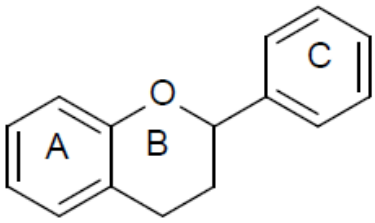


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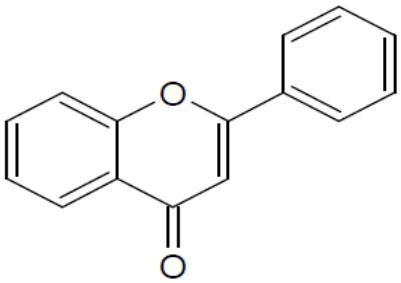
Figure 8: Basic structure of flavonoid.

According to the IUPAC nomenclature they can be classified into three main classes; namely flavones (**16**), isoflavonoids (**17**) and neoflavonoids (**18**). These classes can further be subdivided according to the substitution patterns of the rings [17].



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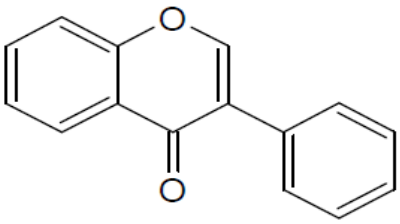

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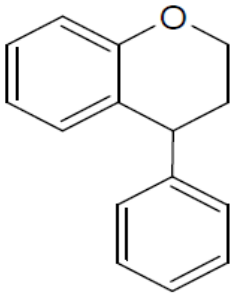

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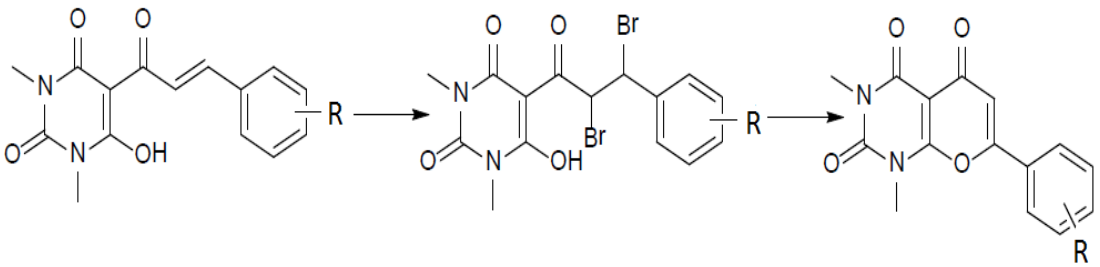
Figure 9: Molecular backbone of flavone (**16**), isoflavonoid (**17**) and neoflavonoid (**18**)

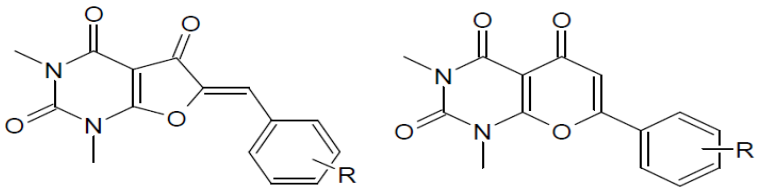
Flavonoids can be synthesized by cyclisation of chalcones (**Scheme 2**). This was attempted by a member of the group. Reactivity of the double bond of chalcones was investigated by bromination on the double bond with different substituents on the aromatic ring. In addition, the conditions for cyclisation for chalcones were examined by changing the substituents on the aromatic ring of chalcones.



11 **19** **20**

Scheme 2: Synthetic route for target flavonoids.

The results revealed a difficulty to control five- or sex- member ring formation, a mixture of the two isomers were obtained (**20** and **21**) [15], but in most cases no product were accomplished.



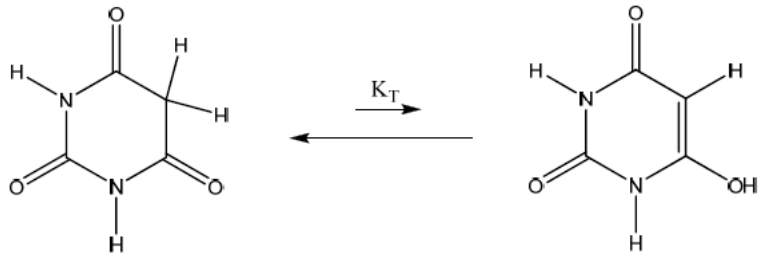
21 **20**

Figure 10: Results after cyclisation of chalcone.

Acid and base catalyzed ring closing was also performed, but no ring closing was obtained.

1.4 Barbituric acid properties: tautomerism, solvation and substitution effect of the barbituric acid ring

Nitrogen and oxygen containing heterocyclic compounds have been interesting in biology due to their pharmaceutical action, mainly because of their ability to make hydrogen bonds. Barbituric acid derivates are one of the most used pyrimidines in medicine [18]. One interesting aspect with pyrimidine derivates is the possibility of tautomerism. In solid state most pyrimidine derivatives occur in the keto, rather than the enol form [19]. Barbituric acid is interesting in the sense that it can exhibit two kinds of tautomerism- transfer of either the imine hydrogen or methylene hydrogen to keto oxygen. The triketo form of barbituric acid is found to be the most stable form in crystals and in solution [20- 21]. It exists in the same form in non-polar solvents [22]. In water- free acid, the keto form predominates over the enol form [23, 24]. Only the keto form is observable in DMSO [25, 26]; here the proton NMR spectrum shows the presence of methylenic protons and the absence of lines corresponding to the protons bonded to unsaturated carbon atoms. Also, on addition of D_2O to barbituric acid solutions in DMSO, the methylenic signal disappears due to exchange with deuterium. This ability to exchange is a well- known property of β- dicarbonyl compounds.



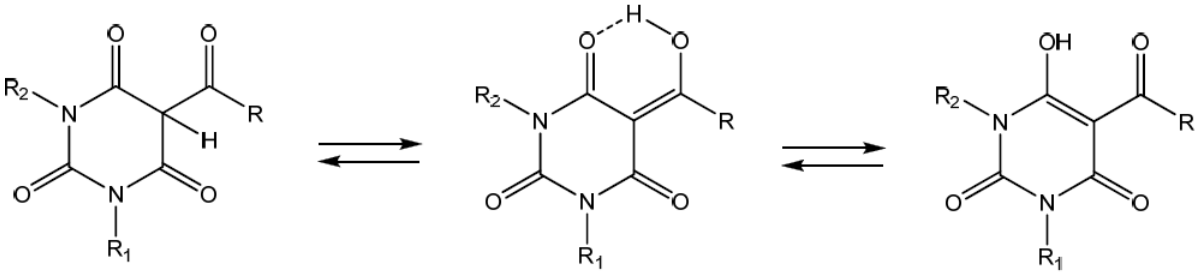
22 **22`**

Scheme 3: Relation between the keto form and the enol form of barbituric acid in water-free acid (the value of K_T comes from UV measurements).

Introduction of substituents at the 5- position (see **Figure 1**) results in an increase in the importance of the hydroxyl form because the substituent comes in the plane of the ring and, therefore, the greater delocalization of charge stabilizes the 4- hydroxy system; the results have been explained by inductive effects. Quantum calculation by the AM1 (Austin Model 1) revealed the effect of monosubstitution at the C- 5 position. It was found that the keto- enol energy separation decreases from the value of 11.4 kcal/mol in the unsubstituted compound. The differences varies in the order –H > $-CH_3$ ≈ $-C_2H_5$ > -OH > -F > -Cl > -I > -Br > $-NH_2$ > -SH > $-NO_2$. For the latter two substituents, the difference is negative, because of the greater stability of the 4- hydroxy form compared to the triketo form [24].

The dipole moment for the keto form of barbituric acid are very small (0.68 D), and therefore very little stabilization occurs in the aqueous solution. On the other hand, the dipole moment for the enol form is much higher (3.91 D), and interaction with the solvent produces higher stabilisation. This means that the differences in energies between the two forms decrease on salvation. The dipole moments for the derivatives are similar (≈ 4), except the enol form of dialuric acid (OH- sustituent), which has a lower dipole moment (2.4 D) than the rest of the enol systems [27, 28].

In the solid state, when the hydrogens are replaced by an ethyl group at both nitrogens, giving 1.3- diethylbarbituric acid, the compound exists in the triketo form. For the N,N-disubstituted- 5- acyl derivatives of barbituric acid, the acyl group is involved in a keto- enol equilibrium. A proton transfer can occur through an intramolecular hydrogen bond. This will induce the mono hydroxy form (**Scheme 4**) [29].



23 **23`** **23``**

Scheme 4: Keto- enol equilibrium for N,N- disubstituted- 5- acyl derivatives of barbituric acid

1.5 Reducing agents: $S(CH_3)_2BH_3$, $NaBH_4$, $LiAlH_4$ and $LiEt_3BH$

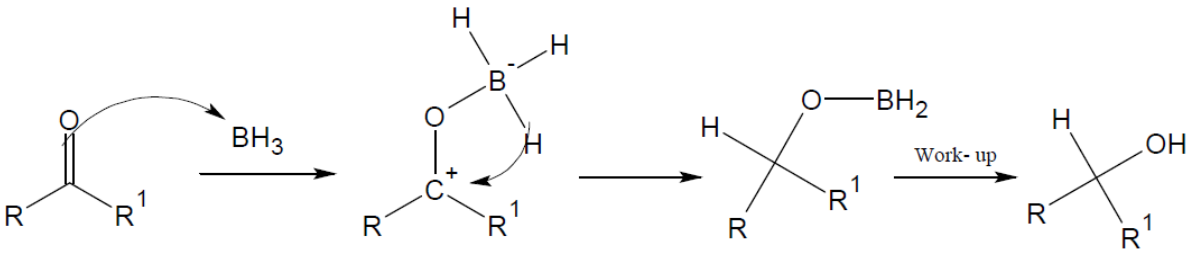
Table 1: Reactivities for various reducing agents [30- 34]

Red. agent	Imine	Aldehyde	Ketone	Ester	Amide	Carboxylic acid
BH_3	Not reduced	Alcohol (slowly)	Alcohol (slowly)	Alcohol (slowly)	Amine	Alcohol
$NaBH_4$	Not reduced	Alcohol	Alcohol	Alcohol* (slowly)	Not reduced	Not reduced
$LiAlH_4$	Amine	Alcohol	Alcohol	Alcohol	Amine	Alcohol (slowly)
$LiEt_3BH$	Not reduced	Alcohol	Alcohol	Alcohol	Alcohol (from 3° amide)	Not reduced

*α- alkoksy esters are reduced to the corresponding alcohol

Borane, BH_3, is a gas with the structure B_2H_6, but it can be "tamed" as a liquid by complexing it with diethyl ether, THF, or dimethyl sulphide (DMS).The borane dimethyl sulphide complex($S(CH_3)_2BH_3$, DMSB) gives improved stability compared to the borane- THF complex. Borane complexes are commonly used for the reduction of carboxylic acid, lactones, amides, halides and other functional groups. It is especially good for the reduction of carboxylic acids to alcohols. In addition, it reduces aldehydes, ketones, and alkenes [35- 37].

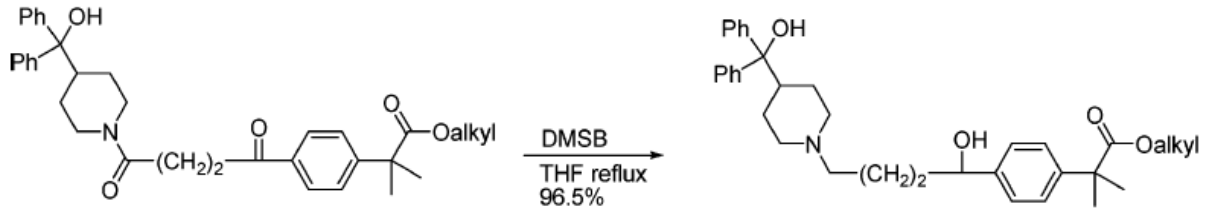
Borane reduces electron- rich carbonyl groups fastest. This is due to their desire to accept an electron pair into its empty p orbital. Because of this the carbonyl group in acyl chlorides will not be reduced. Normal ketones will be reduced slowly [38] (see **scheme 5**).



24 **25** **26** **27**

Scheme 5: Borane reduction of ketone

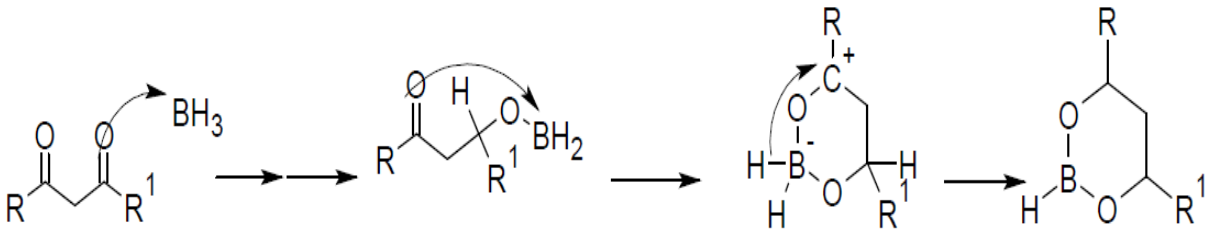
One example of an amide reduction with DMSB is shown in **scheme 6** [39].



28 **29**

Scheme 6: DMSB reduction, produces terfenadine in high yield

Reduction of a 1,3- diketone is shown in **scheme 7**.



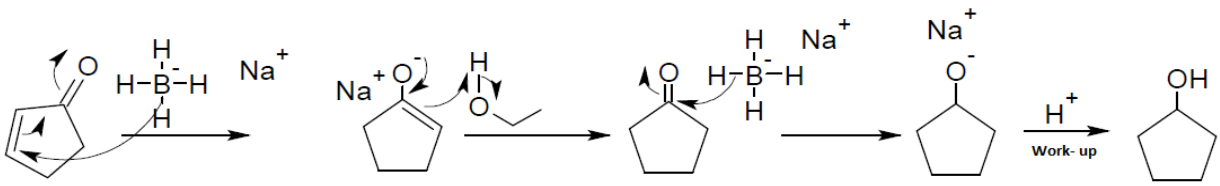
30 **31** **32** **33**

Scheme 7: Reduction of a 1,3- diketone (without work- up).

Sodium Borohydride ($NaBH_4$) reduces aldehydes and ketones to the corresponding alcohols at or near 25 °C. Esters, epoxides, lactones, carboxylic acids, nitro groups and nitriles are normally not reduced under these conditions. Sodium Borohydride is commercially available as a solid, in powder or pellets, or as a solution in various solvents.

$NaBH_4$ reductions are usually performed in ethanol or methanol, often with an excess of reagent. Work- up procedures can include water or ammonium chloride (NH_4Cl).

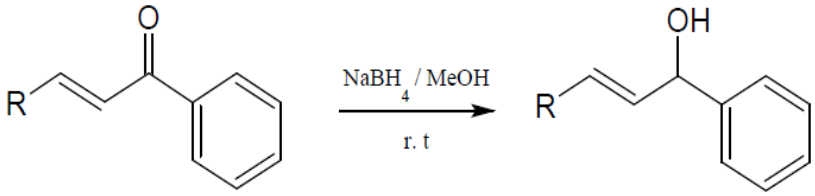
$NaBH_4$ could reduce α- β unsaturated ketones to the corresponding alcohol by a conjugate addition, followed by direct addition to the double bond (**Scheme 8**) [40, 41].



34 **35** **36** **37** **38**

Scheme 8: $NaBH_4$ reduction of α- β- conjugated system (here 2- cyclopenten- 1- one) in ethanol.

Reduction of a chalcone with $NaBH_4$ in methanol will give the corresponding allyl alcohol (see **scheme 9**). Reduction with $LiAlH_4$ will produce a mixture of allyl alcohol, saturated alcohol and saturated ketone together with other unidentified products [42].

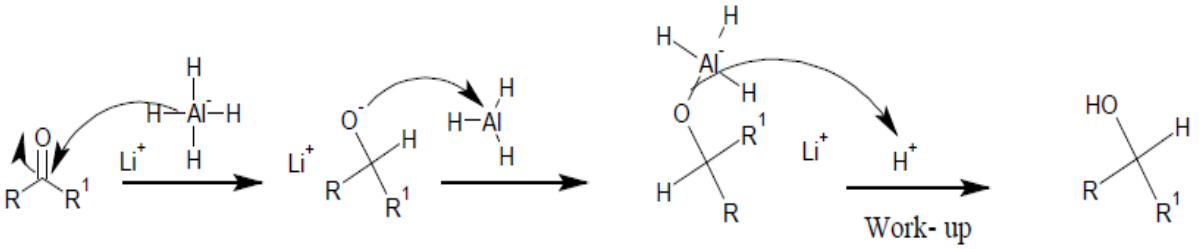


39 **40**

Scheme 9: Reduction of chalcone by $NaBH_4$ (R = groups like p(Cl)-C_6H_4 and m(OBn)-C_6H_4, >90 % yield)

Lithium aluminium hydride ($LiAlH_4$, LAH) is a powerful hydride- transfer reagent that readily reduces carboxylic acids, esters, lactones, anhydrides, amides and nitriles to the corresponding alcohols or imines. In addition, aldehydes, ketones, epoxides, alkyl halides, and other functional groups are reduced by LAH. LAH is commercially available as a dry, grey solid or as a solution in organic solvents like ethyl ether and THF [43].

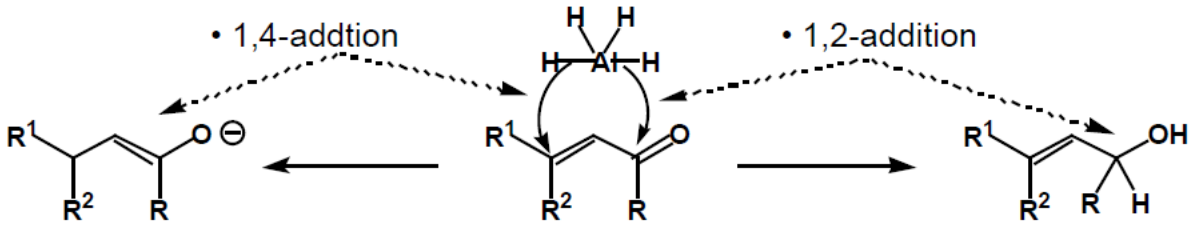
The Fieser work- up is one of several work- up procedures for LAH reductions. In this work-up, following reduction with n grams of LAH, n mL of water is added droppwise, then n mL of 15 % NaOH solution, and in the end 3n mL of water. This provides a granular inorganic precipitate that is easy to rinse and filter [44].



24 **41** **42** **27**

Scheme 10: LAH reduction of ketone

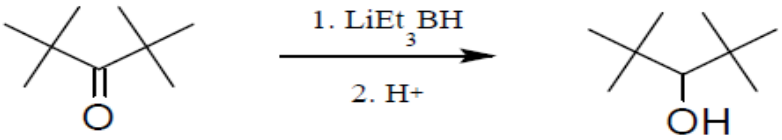
Reduction of enones is very dependent on the exact structure of the enone. Direct addition (1,2 addition) will be the preferred one, unless the carbonyl group is sterically hindered. (**Scheme 11**) [45].



44 **43** **45**

Scheme 11: LAH reduction of enone

Lithium triethylborohydride ($LiEt_3BH$, Super hydride) is a powerful reducing agent. In many cases it is even more powerful than LAH. This is due to the electron donating ethyl groups (inductive effect). Super hydride could reduce even sterically hindered compounds like the one shown in **scheme 12** [46, 47].



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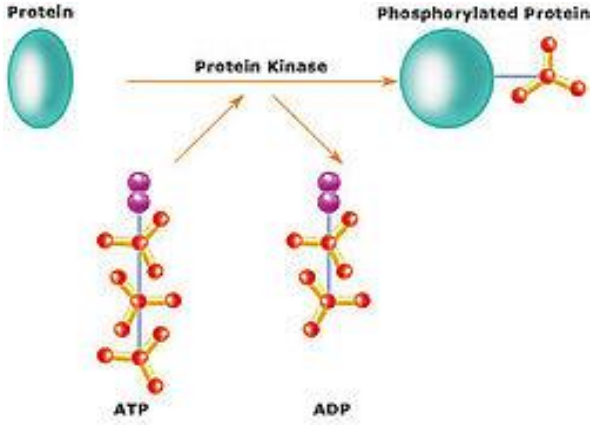
Scheme 12: Reduction of sterically hindered ketone (2, 2, 4, 4- tetramethyl- 3- pentanone) by Super hydride.

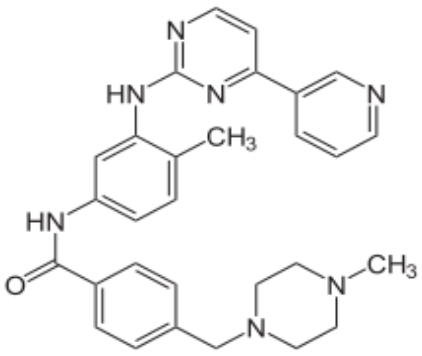
1.6 Kinases and kinase inhibitors

A kinase is an enzyme that adds a phosphate group to a compound. Normally this happens by the transfer of this group from a nucleoside triphosphate such as adenosine triphosphate (ATP) to an acceptor molecule. This could be a sugar (as in hexokinase and glucokinase), a protein (as in glycogen phosphorylase kinase), another nucleotide (as in nucleoside diphosphate kinase), or a metabolic intermediate such as oxaloacetate (as in PEP carboxylase). The reaction catalyzed by a kinase is a phosphorylation. Kinases are mainly used to transmit signals and control complex processes in cells. One of the largest groups of kinases is protein kinases, which act on and modify the activity of specific proteins [48, 49].



Scheme 13: Protein phosphorylation

Phosphorylation is a necessary step in some types of cancer and inflammatory diseases. These diseases could be treated by inhibiting the protein kinases, and therefore the phosphorylation. Therefore, protein kinase inhibitors are used as drugs. Imatinib (Glivec ®) was the first produced kinase inhibitor, and is used for treatment of Chronic Myelogenous Leukemia (CML) [50- 52].



48

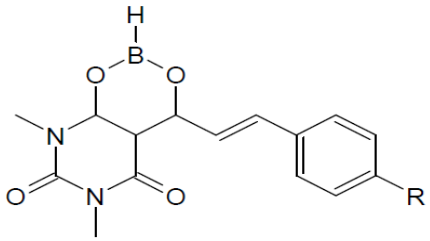
Figure 11: Structure of Imatinib

2. Aim of project

The aim of this project was to reduce barbituric acid based compounds. A successful reduction would hopefully give a more water soluble compound, and therefore a more biological active molecule. The reductions can be divided in two parts; A. Reduction with borane (BH_3) which is electrophilic, B. Reduction with other hydrides which is nucleophilic.

Part A

A successful borane reduction will give compound **49**. In addition to increasing water solubility this compound could be used for further studies- like hydroboration of an alkene followed by transformation into functionalized amino borates.

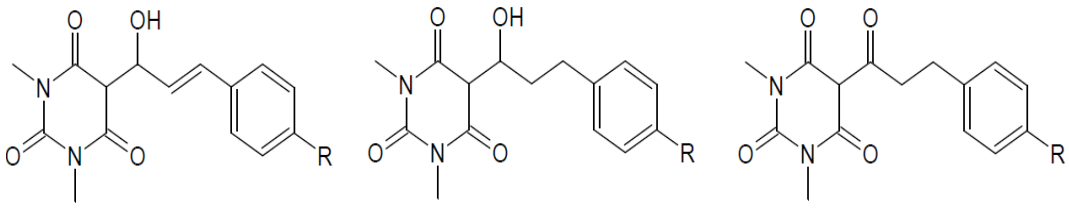


49

Figure 12: Target molecule after BH_3 reduction

Part B

Reduction with hydrides like $NaBH_4$, $LiAlH_4$ and $LiEt_3BH$ can give different products- like e.g. **50**, **51** and **52**



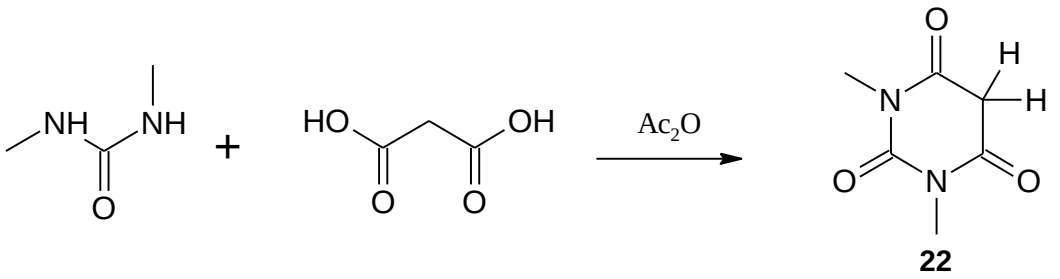
50 **51** **52**

Figure 13: Possible products after reduction

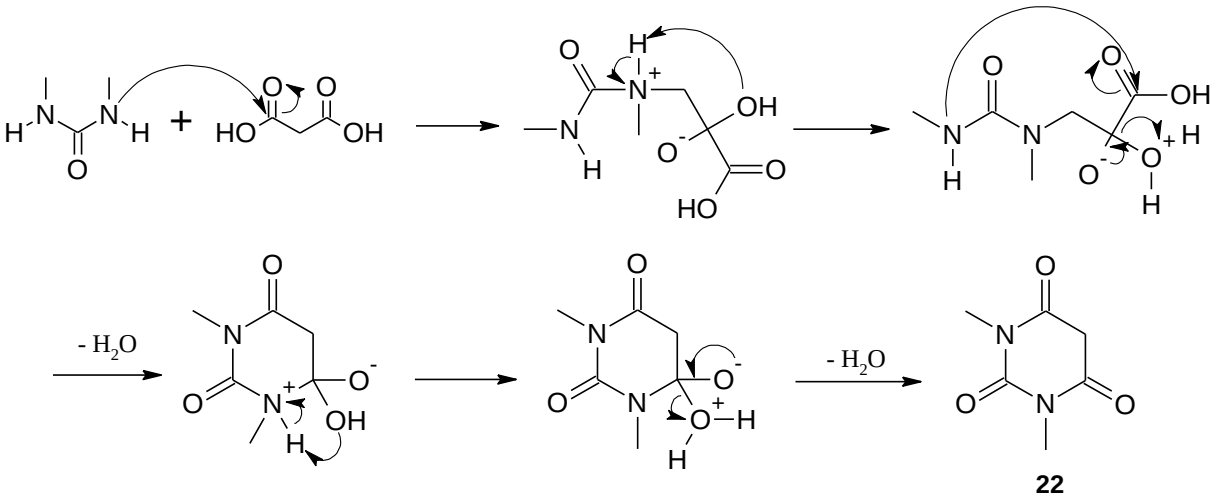
3. Results and discussion

3.1 Preparation of starting materials

Starting compounds 5-cinnamoyl-1,3-dimethylpyrimidine-2,4,6-trione (**55**), (E)-5-(3-(4-methoxyphenyl)acrylolyl)-1,3-dimethylpyrimidine-2,4,6-trione (**56**) and (E)-1,3-dimethyl-5-(3-(4-nitrophenyl)acrylolyl)pyrimidine-2,4,6-trione (**57**) were prepared in a three- step procedure. 1,3-dimethylbarbituric acid (**22**) was first prepared from N,N-dimethylurea and malonic acid in acetic acid (**Scheme 14** and **Scheme 15**). This method was published by Adolf von Baeyer [1], and performed with some minor modifications, like the use of N,N-dimethylurea instead of urea. Purification of **22** was not necessary as spectroscopic data confirmed that the substance was sufficiently pure for subsequent use.



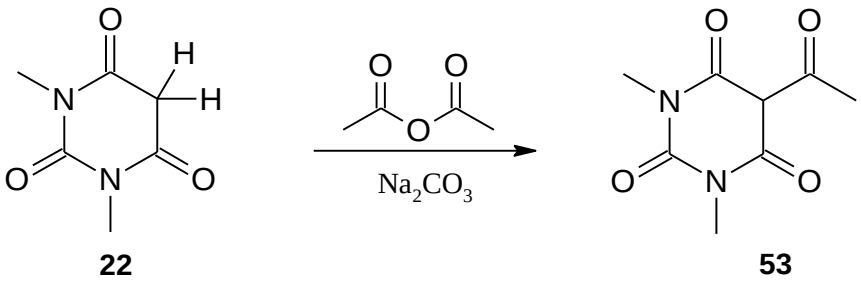
Scheme 14: Synthesis of 1,3-dimethylbarbituric acid (**22**)



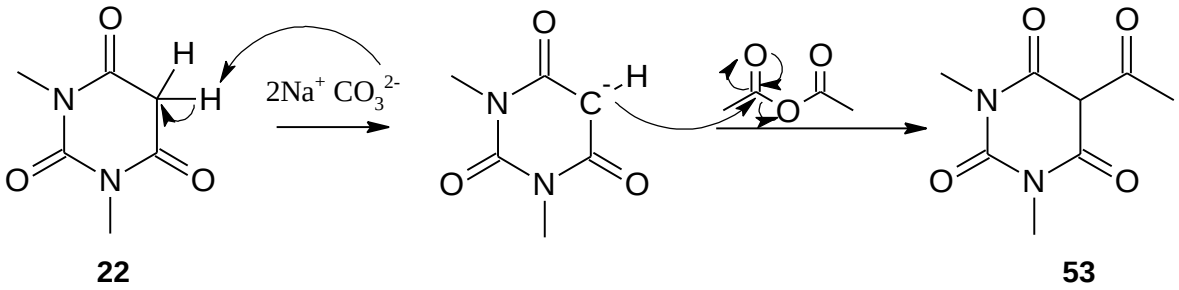
Scheme 15: Possible mechanism for compound **22**

The experiments were repeated because of lack of starting substance. After three experimental runs yields of 61 %, 73 % and 85 % were accomplished. The highest yield was obtained with more rapid heating. No exothermic reaction was observed with slowly heating of mixture.

The next step was the acetylation of **22** with acetic anhydride, and 5-acetyl-1,3-dimethylbarbituric acid (**53**) was obtained (**Scheme 16** and **Scheme 17**). As in the previous step purification of **53** was not necessary.



Scheme 16: Synthesis of 5-acetyl-1,3-dimethylbarbituric acid (**53**)



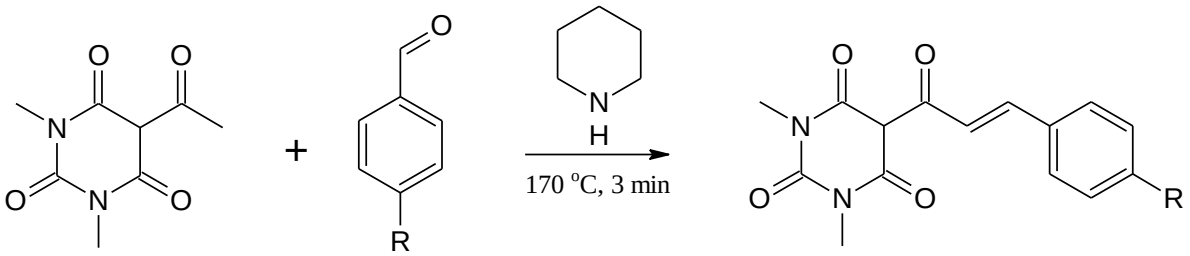
Scheme 17: Mechanism for the synthesis of compound **53**

Yields after repeated experiments were 63 %, 73 % and 79 %. The increase in yield may be caused due to cleaner starting material in the previous step, as higher yields of substance **22** gave higher yields of compound **53**. More impurities along with the starting substance may have caused unwanted side reactions. This was confirmed by NMR- and GC/MS- analysis which showed minor impurities especially in the first experimental run (which gave 63 % yield). More experience which comes from repeated attempts can also have an influence on the result.

The last step was the reaction of 5-acetyl-1,3-dimethylbarbituric acid (**53**) with the appropriate ortho- substituted benzaldehyde and the use of piperidine as base (**scheme 18**).

Piperidine deprotonates compound **53**, forms **58**, and an aldol condensation reaction results (**Scheme 19**). The reaction was run under solvent- free condition. Earlier investigation by a member of the group [14] showed that piperidine was a more efficient base than pyridine and triethyl amine. The mixture was heated to 170°C or 130 °C. Experience revealed that the addition of piperidine at 170°C was a critical stage. The mixture had to be stirred vigorously when base was added; otherwise the solution was hardened because of the high temperature.

The product yield depended on the R- group of the reagent, whether it was hydrogen (**55**), the electron donating methoxy group (**56**) or the electron accepting nitro group (**57**). (See **table 2**).



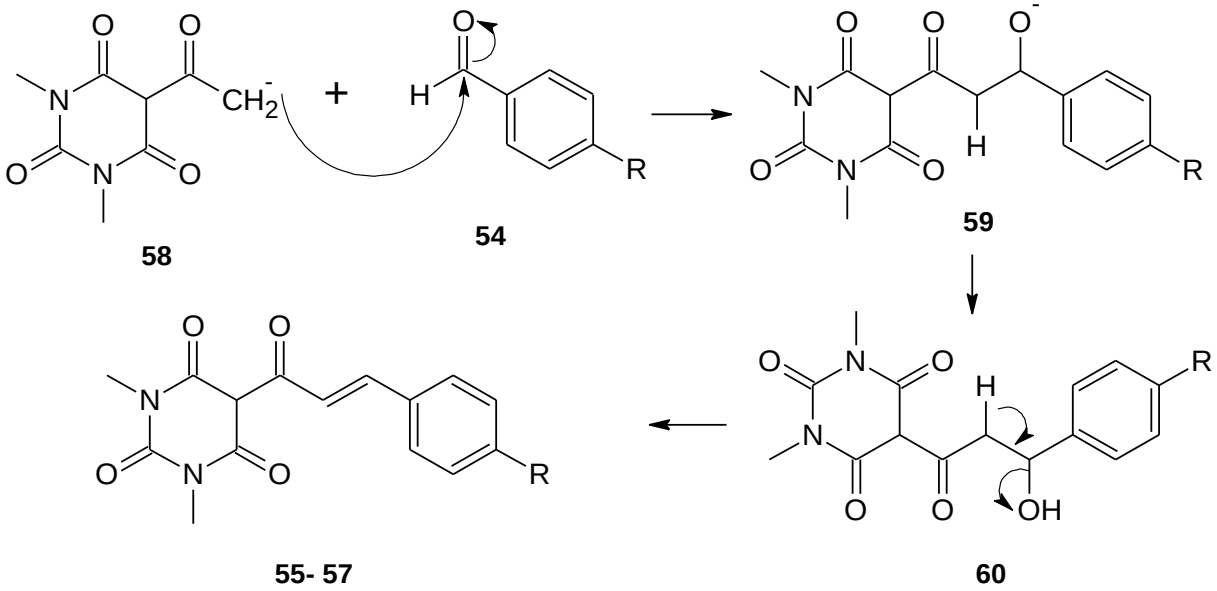
53 **54**

55: R= H

56: R= OMe

57: R= NO_2

Scheme 18: Synthesis of para- substituted chalconoids (**55– 57**).



58 **54** **59**

55- 57 **60**

Scheme 19: Synthesis of Compounds **55- 57** from aldol condensation reaction

The yield depended on the R- group of the reagent, whether it was hydrogen (**55**), the methoxy- donor group (**56**) or the nitro- acceptor group (**57**). Compound **56** has the highest yield and substance **57** the lowest yield. This relation in yield is confirmed with earlier studies by the group [14]. As shown in **table 2** the yield of compound **56** and **57** is not very different whether the temperature was 130 °C or 170 °C. For compound **55** the difference in yields is bigger. Whether this relation is repeated when more experiments are run, or it just is random is not known since no optimization of yields for different temperatures was conducted.

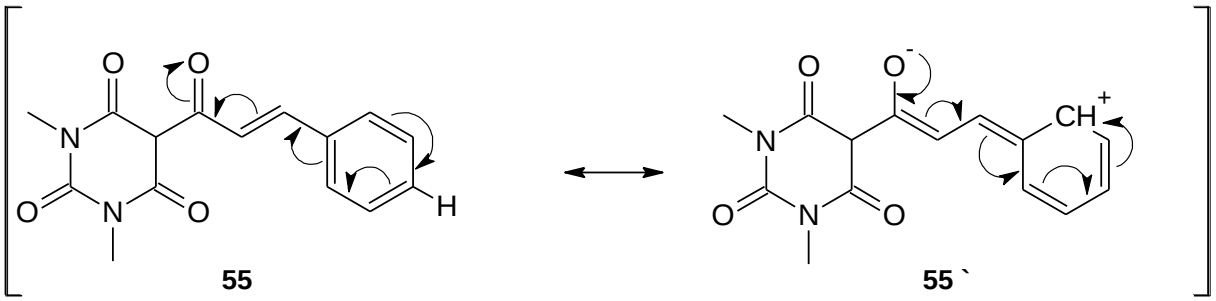
Table 2: Experimental temperature and yields for compounds **55**- **57**

	Exp. 1-3		Exp. 4-6		Exp.7	
Compound	Temp. (°C)	Yield (%)	Temp. (°C)	Yield (%)	Temp. (°C)	Yield (%)
55	130	60	170	71	170	78
56	130	83	170	86		
57	130	35	170	32		

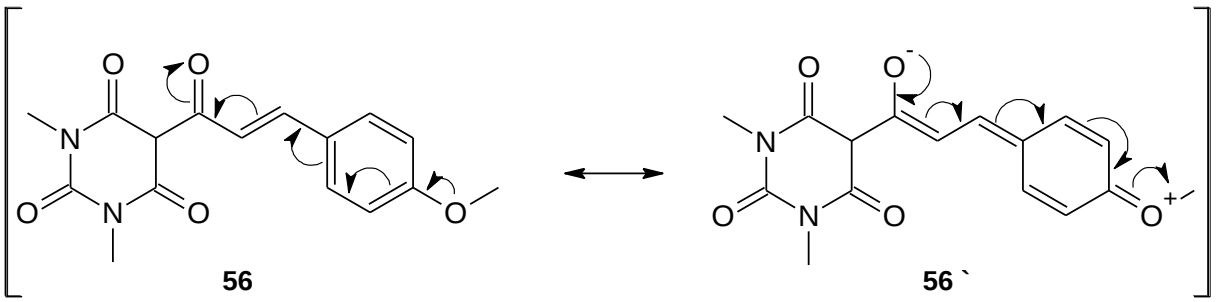
3.2 Reduction of chalconoids

Three different para- substituted chalconoids (**55- 57**) were reduced by four reducing agents, namely borane dimethyl sulphide complex (DMSB), sodium borohydride ($NaBH_4$), lithium aluminium hydride ($LiAlH_4$) and superhydride ($LiEt_3BH$). The experiments were not run as a normal screening experiment, where the different experiments would just be run with variables at low and high values. Instead the experiments are also performed with different variable values between low- and high.

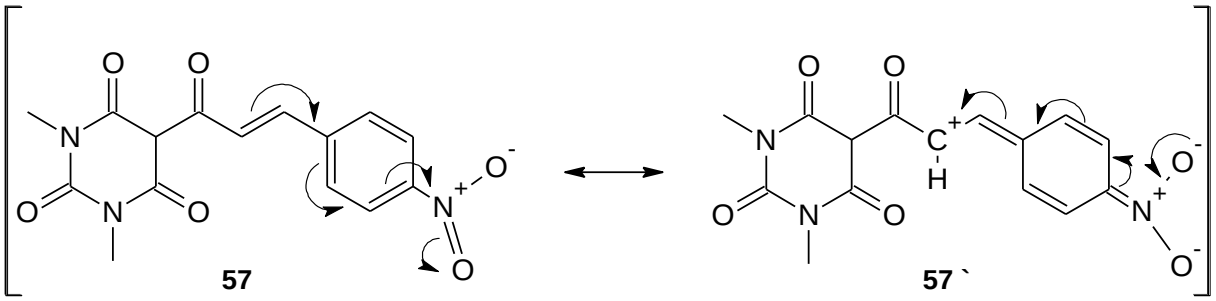
Theoretically different results could be expected from reduction of compounds **55- 57** due to their resonance structures (**Scheme 20- 22**). Compound **56**, with its electron donating methoxy group, should be more difficult to reduce (lower yield) because of better stabilization of the arenium cations, and therefore more electrons to stabilize the δ+ charge at the carbonyl carbon. This will make it harder for hydride ions to attack. Compound **57** should be easier to reduce due to destabilization of the arenium cations, and therefore destabilization of the δ+ charge at the carbonyl carbon. The ease to reduce compound **55** should be somewhere in between **56** and **57**.



Scheme 20: Possible resonance structure of compound **55**



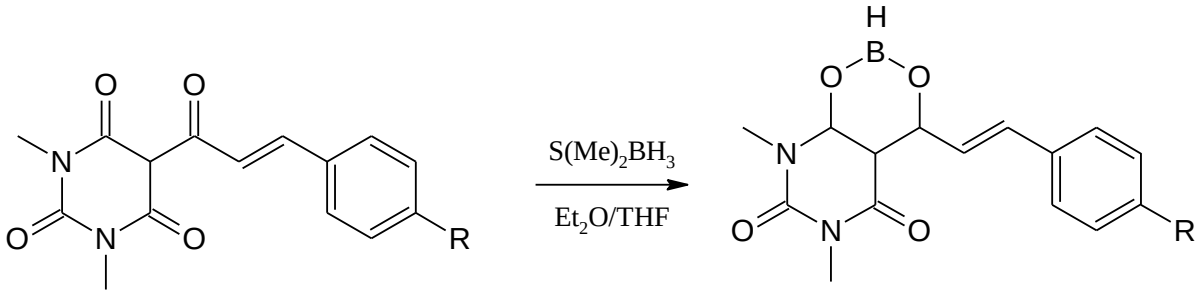
Scheme 21: Possible resonance structure of compound **56**



Scheme 22: Possible resonance structure of compound **57**

3.2.1 Reduction by borane dimethyl sulphide complex

A successful reduction by DMSB should give compounds **61- 63**. A possible mechanism follows the one shown in **scheme 7** (**section 1.5**).



55: R= H

56: R= OMe

57: R= NO_2

61: R= H

62: R= OMe

63: R= NO_2

Scheme 23: Borane reduction of para- substituted chalconoids

Experimental variables for this reduction were reaction time, reaction temperature, type of solvent and the substrate/reducing agent mol ratio (**table 3**). Compounds **55- 57** were attempted to reduce under the same experimental conditions. The choice of solvent between Et_2O and THF didn't matter for the results when used in temperatures of 0 °C and 20 °C. When experiments were run at temperatures from 40 °C and above, THF was used because of its higher boiling point.

Table 3: Experimental variables for the borane reduction

Experimental variable	Lowest value	Highest value
1. Reaction time	30 min	48 h
2. Reaction temperature	0 °C	70 °C
3. Solvent	Et_2O, THF or both	
4. Ratio substrate/reducing agent	1 mol substrate/ 3 mol red. agent	2 mol substrate/ mol red. agent

Several experiments were run on ice bath; reaction times were varied between 30 min and 3 hours. The ratio of substrate to reducing agent were increased in favour of reducing agent as nothing seemed to happen with more substrate or equal values. Changing solvent from Et_2O to THF didn't work either. All attempts to reduce these compounds at 0 °C failed, as NMR – and MS- analysis confirmed that just the starting material were present. This indicated that the temperature may have been too low for a successful reduction.

Multiple experiments were then run at room temperature with reaction times of 30 min, 1 hour, 2 hours, 3 hours, 6 hours, 24 hours and 48 hours. The number of equivalents of DMSB

was varied along with the different reaction times, and the solvent was varied between Et_2O, THF and both. As before no product was obtained, just starting material.

As the temperature was raised towards 70 °C impurities were obtained (see **table 4**). These impurities were not analysed. TLC failed since no good separation could be obtained on the silica plates. Variation in reaction time and the ratio of substrate and reducing agent, didn't give any clear difference in results.

Table 4: Obtained results after reduction of compounds **55- 57** with DMSB

Compound	Reaction temp.: 0 °C	Reaction temp.: 20 °C (Room temp.)	Reaction temp.: 40-70 °C
55	Starting material	Starting material	Impurities
56	Starting material	Starting material	Impurities
57	Starting material	Starting material	Impurities

Figure 14 shows one example of a ^1H NMR spectra (in $CDCl_3$) for the result after reaction of compound **55** with DMSB. This experiment was run in 60 °C for 1 hour. The figure shows unknown impurities, along with a peak at 3,47 ppm witch probably is a methanol or ether peak. No peaks are present downfield from the region of 7-7,5ppm in the spectra. No double bond from the enone in compound **55** is present. This protons were originally located at around 8 and 8,6 ppm. The aromatic protons in compound **55**, if present, have coincided with the chloroform peak. The methyl- protons in the 1,3-dimethylbarbituric acid ring were located in the 3,37- 3,40ppm area, but are now probably shifted up field (her at 3,27ppm).

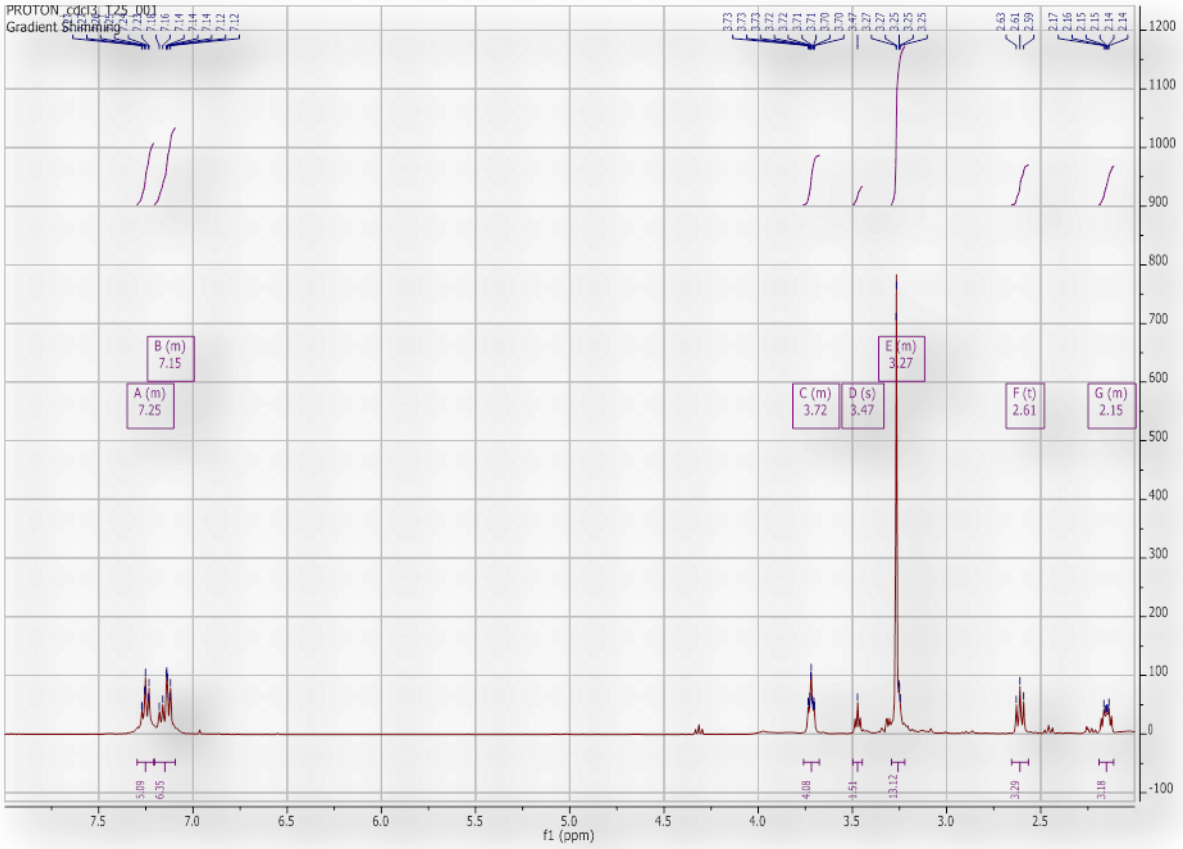


Figure 14: ^{1}H NMR spectra for reaction of compound **55** with DMSB

The ^{1}H NMR spectra for the results after reaction of compound **56** with DMSB (60 °C, 1 hour) is even harder to interpret (**Figure 15**). The chloroform top is her at 7,26ppm as a singlet.

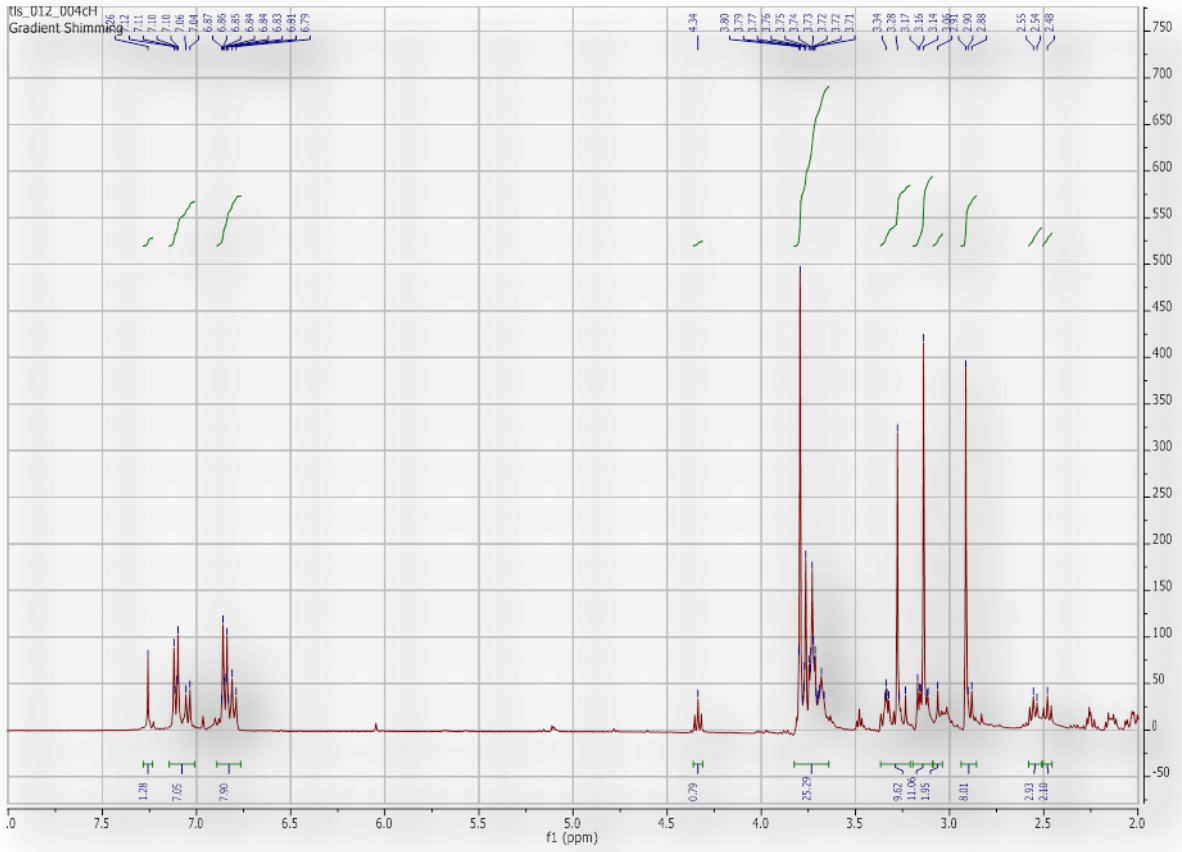


Figure 15: ^{1}H NMR spectra for reaction of compound **56** with DMSB

In the case for attempted reduction of compound **57** with DMSB (**Figure 16**) at 60 °C (1 hour) two multiplets are located at 7,29ppm and 8,11ppm. This is further apart than the peaks in the earlier showed spectres.

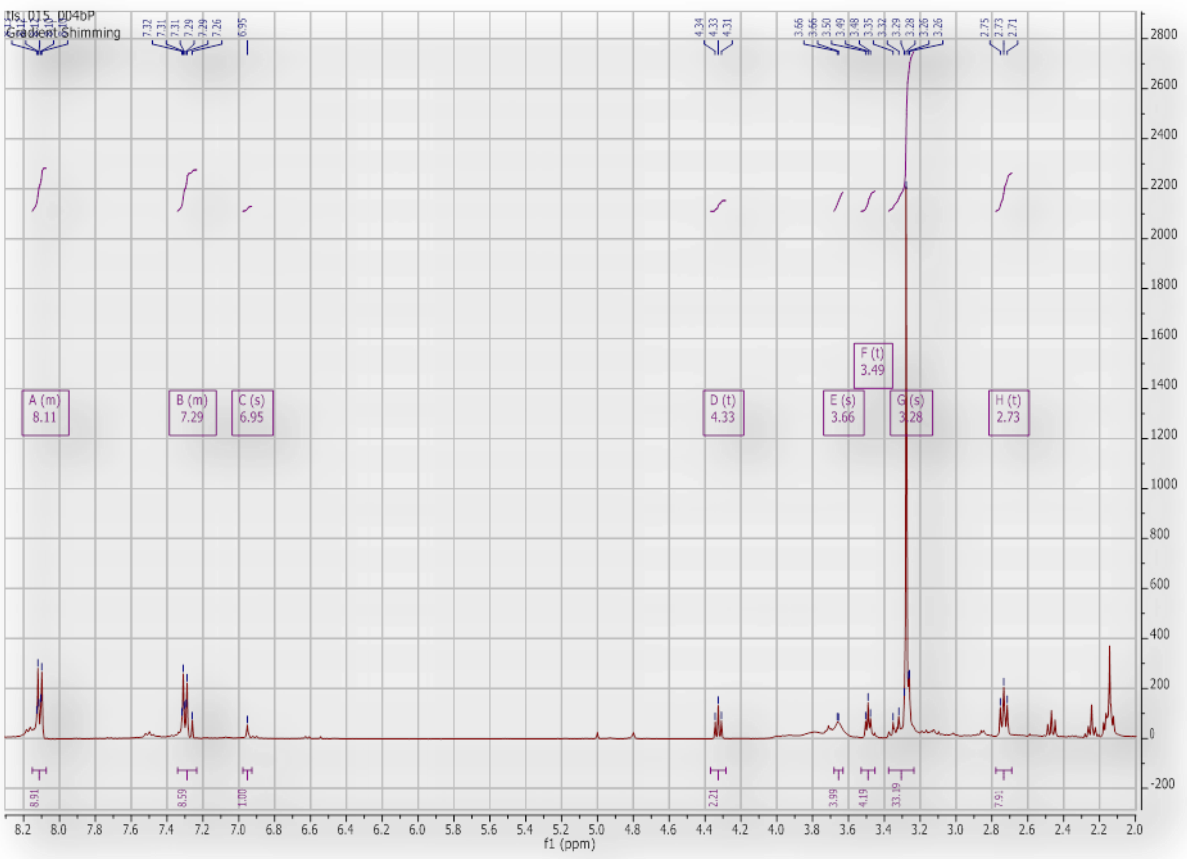
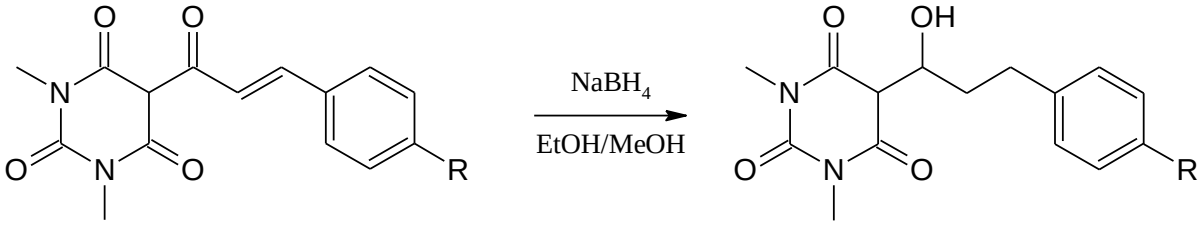


Figure 16: ^{1}H NMR spectra for reaction of compound **57** with DMSB

It is difficult to draw any conclusions of the difference in reactivity for compounds **55-57** from these experiments.

3.2.2 Reduction by $NaBH_4$

Compounds **64- 66** are possible products after reduction with $NaBH_4$. A possible mechanism could be like the one shown in **scheme 8** (**section 1.5**). Other possible outcomes after reduction could be a reduction of just the carbonyl group in the α- β conjugated system (and obtain compound **50**), or reduction of the double bound in the same system (and obtain compound **52**). This study could help to answer this.



55: R= H

56: R= OMe

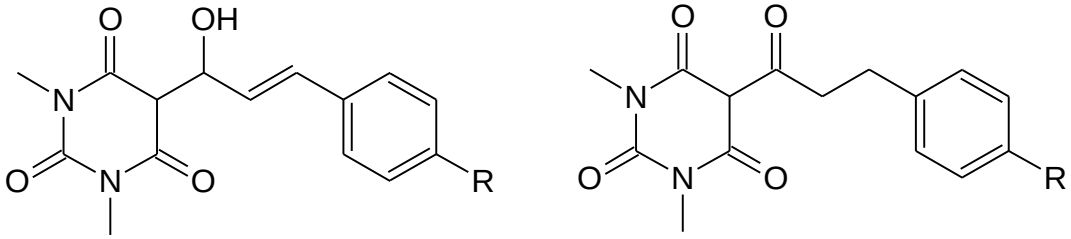
57: R= NO_2

64: R= H

65: R= OMe

66: R= NO_2

Scheme 24: $NaBH_4$ reduction of para- substituted chalconoids



50 **52**

Figure 17: Other possible products after reduction of structures **55- 57**

Experimental variables for the use of $NaBH_4$ are shown in **table 5**.

Table 5: Experimental variables for $NaBH_4$ reduction

Experimental variable	Lowest value	Highest value
1. Reaction time	30 min	24h
2. Reaction temperature	0 °C	80 °C (for EtOH)
3. Solvent	MeOH/EtOH	
4. Ratio substrate/reducing agent	1 mol substrate/ 5 mol red. agent	2 mol substrate/ mol red. agent
5. Work up	H_2O, NH_4Cl	

Like the reduction with use of DMSB, reduction with $NaBH_4$ at 0 °C didn't work. Reaction at higher temperature for compound **55** and **56** gave no results either. Neither reaction times of 30 minutes, 1 hour, 2 hours, 3 hours, 6 hours or 24 hours gave any expected results. Even experiments run in dry methanol, excess of $NaBH_4$, and temperatures up to 80 °C didn't give expected products. For compound **57** unknown impurities were obtained with a reaction temperature at room temperature or above (**table 6**).

Table 6: Obtained results after reduction of compounds **55- 57** with $NaBH_4$

Compound	Reaction temp.: 0 °C	Reaction temp.: 20 °C (Room temp.)	Reaction temp.: 60-80 °C
55	Starting material	Starting material	Starting material
56	Starting material	Starting material	Starting material
57	Starting material	Impurities	Impurities

One experiment with compound **57** was run at room temperature for 24 hours and the results are presented in **Figure 18**. As earlier two muliplets are in located in the aromatic region (her 8,21ppm and 7,51ppm). The chloroform peak is her shown as a doublet at 7,24ppm. One interesting and unknown singlet is found at 4,84 ppm.

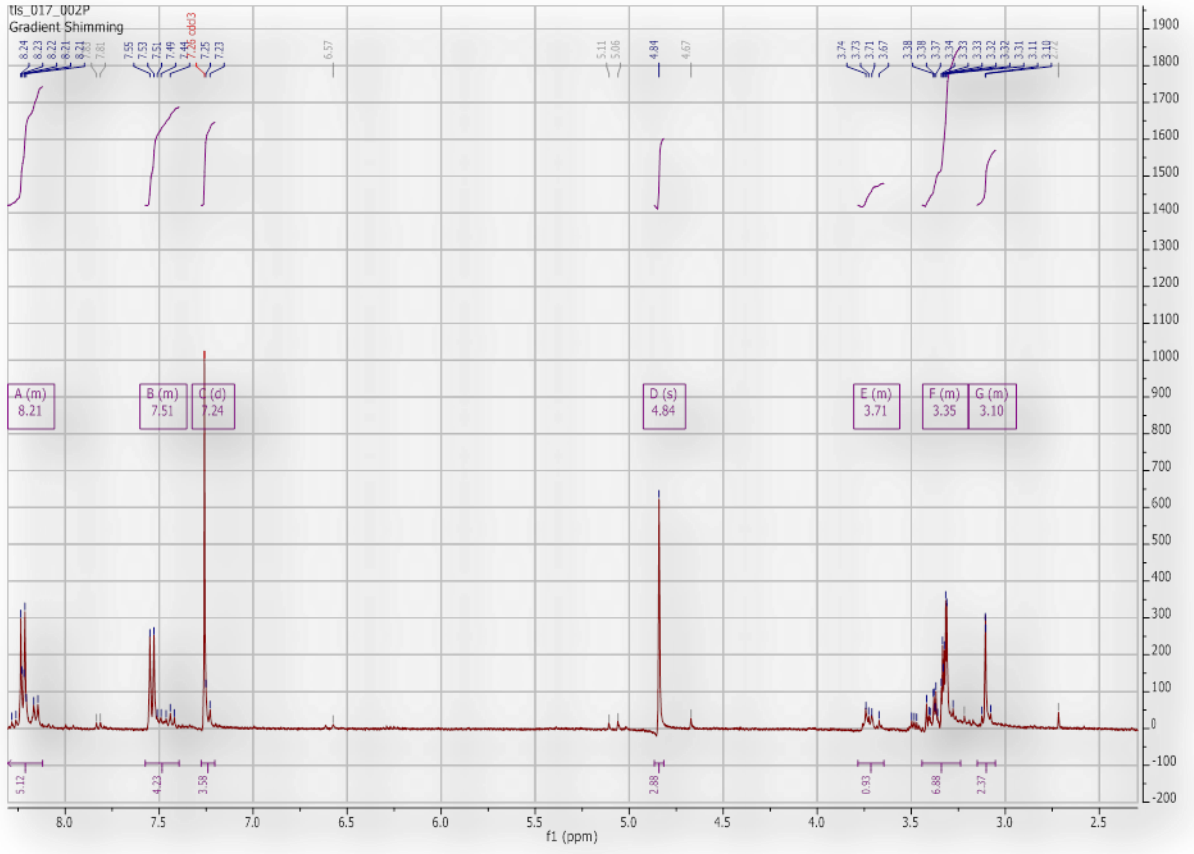


Figure 18: ^1H NMR spectra for reaction of compound **57** with $NaBH_4$ at room temperature

One similar ^{1}H NMR spectra are achieved after reaction of this compound with $NaBH_4$ at 60 °C for 1 hour (**Figure 19**).

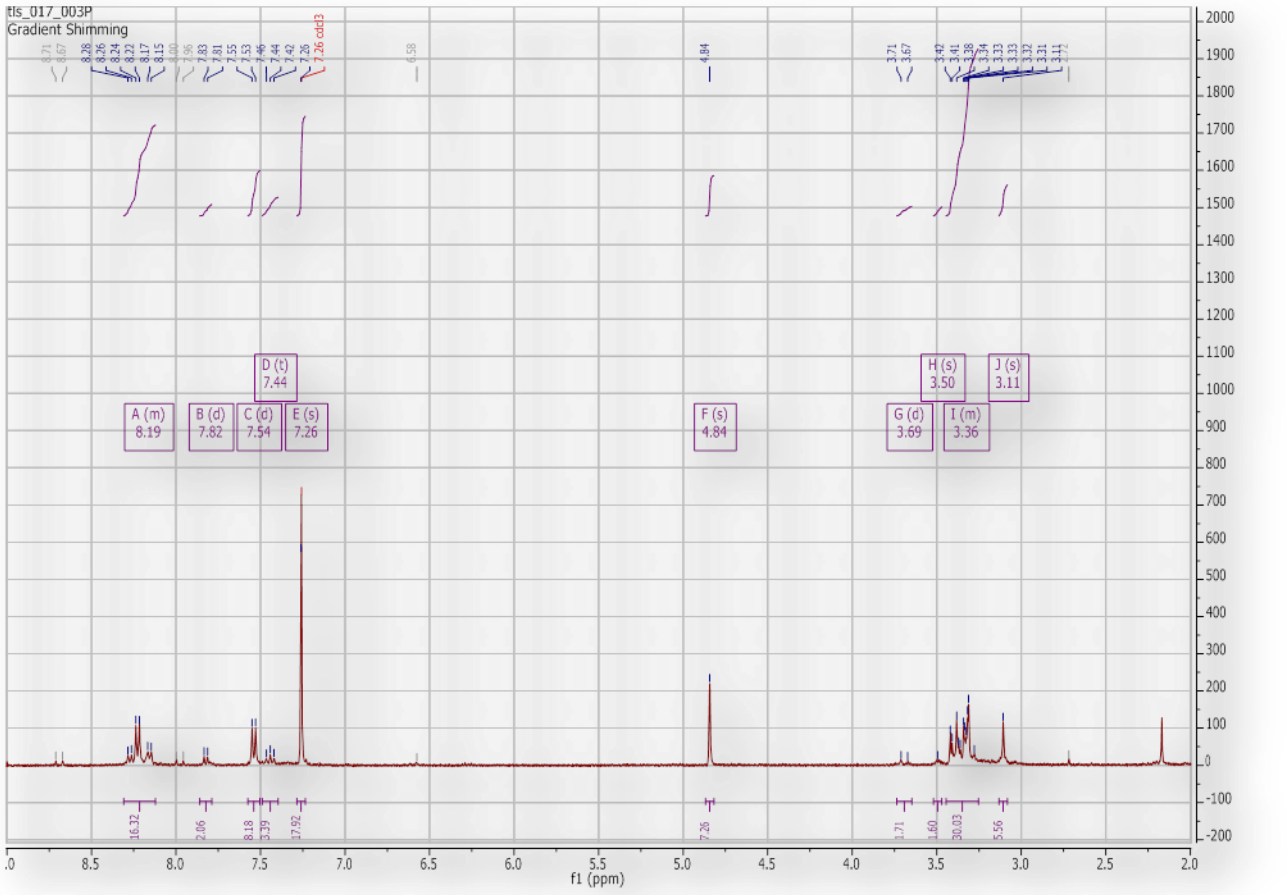
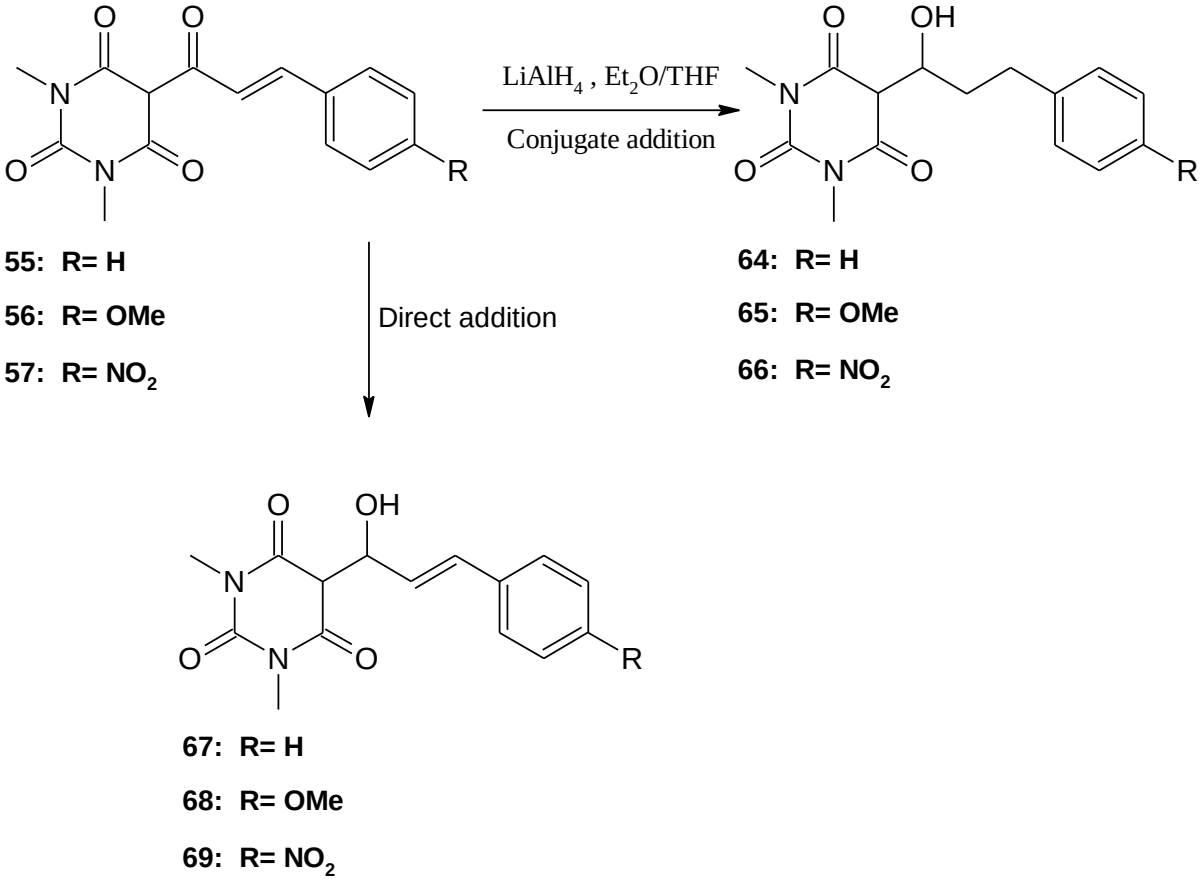


Figure 19: ^{1}H NMR spectra for reaction of compound **57** with $NaBH_4$ at 60 °C

The fact that something seems to happen when reacting compound **57**, with its electron withdrawing nitro group, with a reducing agent (her $NaBH_4$) are in accordance with what is anticipated. The result however is not as expected. The impurities were not analysed.

3.2.3 Reduction by $LiAlH_4$

Since $NaBH_4$ didn't give any successful reductions, $LiAlH_4$ (LAH), which is a stronger reducing agent, was used. Compounds **64- 69** are possible products with a successful reduction with use of $LiAlH_4$.



Scheme 25: Direct- and conjugate- addition by $LiAlH_4$ of para- substituted chalconoids

Experimental variables for use of LAH are shown in **table 7**.

Table 7: Experimental variables for LAH reduction

Experimental variable	Lowest value	Highest value
1. Reaction time	10 min	24 h
2. Reaction temperature	0 °C	60 °C
3. Solvent	Et_2O/THF (or both)	
4. Ratio substrate/reducing agent	1 mol substrate/ 5 mol red. agent	2 mol substrate/ mol red. agent
5. Addition rate of substrate	0 (all added at once)	15 min
6. Work up	Fieser method, Glaublers salt ($Na_2SO_4 \cdot 10H_2O$), acid quench	

Just as for DMSB and $NaBH_4$, reactions at 0 °C were unsuccessful (see **table 8**). At room temperature pure substrate resulted when compound **55** and **56** were mixed with LAH. Reaction times for different experiments were 10 minutes, 30 minutes, 2 hours, 3 hours, 5 hours and 24 hours. An increase in reaction time was useless. As LAH is very stable in THF this was the first choice of solvent. Et_2O was used in later experiments because LAH is more soluble in Et_2O. But the choice of solvent didn't matter for the result.

Table 8: Obtained results after reduction of compounds **55- 57** with LAH

Compound	Reaction temp.: 0 °C	Reaction temp.: 20 °C (Room temp.)	Reaction temp.: 60°C
55	Starting material	Starting material	Impurities/ reaction mixture
56	Starting material	Starting material	Impurities/ reaction mixture
57	Starting material	Impurities	Impurities/ reaction mixture

For substance **57** experimentation at 20 °C with LAH gave several unidentified products (**Figure 20**).

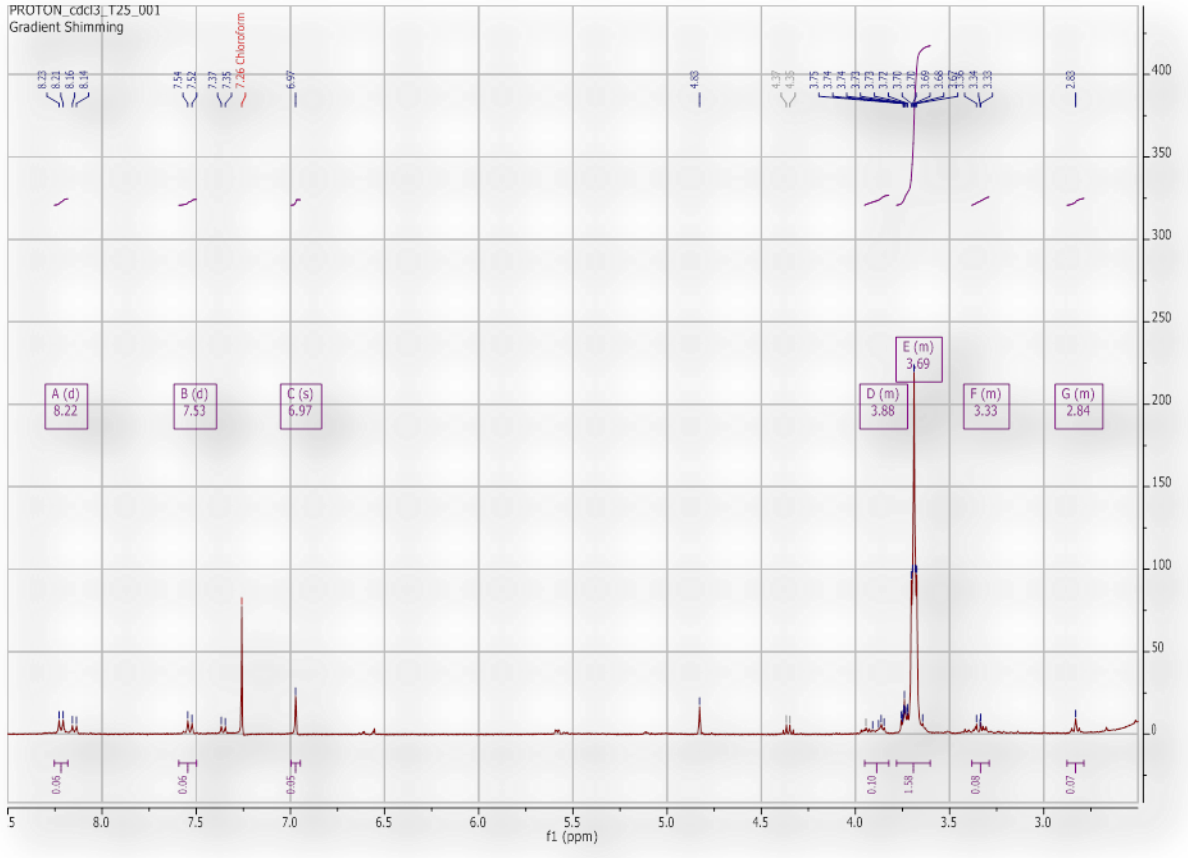


Figure 20: ^1H NMR spectra for reaction of compound **57** with LAH at 20 °C

At 60 °C the NMR spectra became messy and it was difficult to see if any starting material were present, just different products witch not could be structure determined Figure **21** and **22** shows the result for compound **55**.

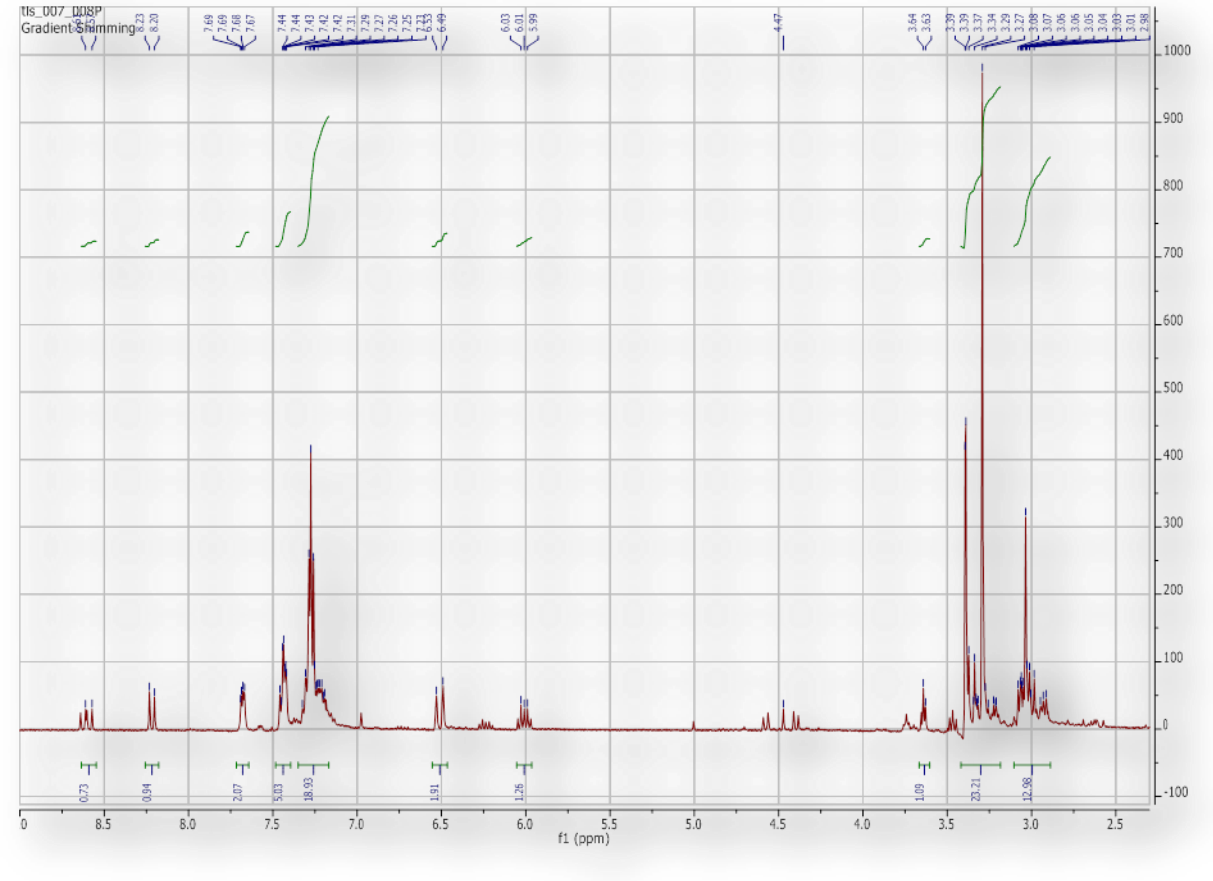


Figure 21: ^{1}H NMR spectra for reaction of compound **55** with LAH at 60 °C (**part A**)

Two small peaks were registered at 16,4ppm and 17,6ppm (**Figure 22**). Normally the peak for the enolic proton in the pyrimidine ring of compound **55** is around 17,0ppm.

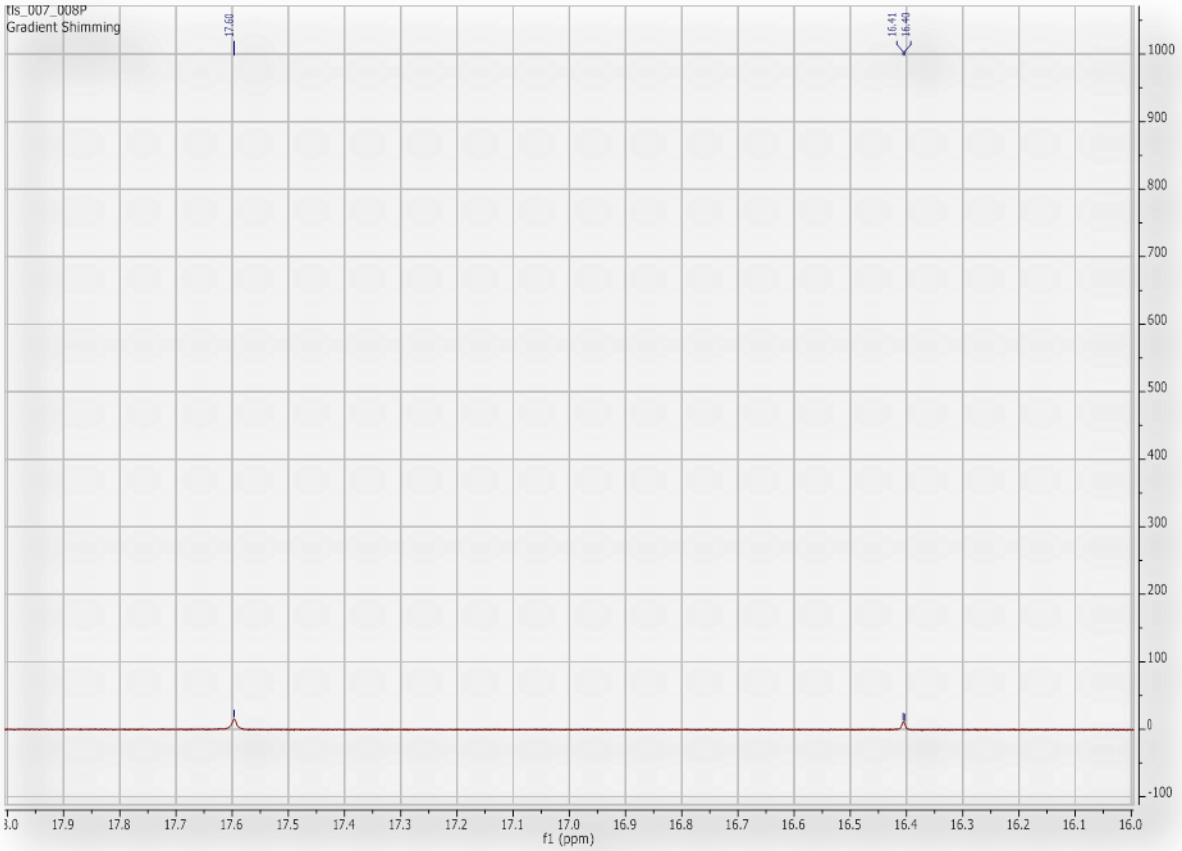


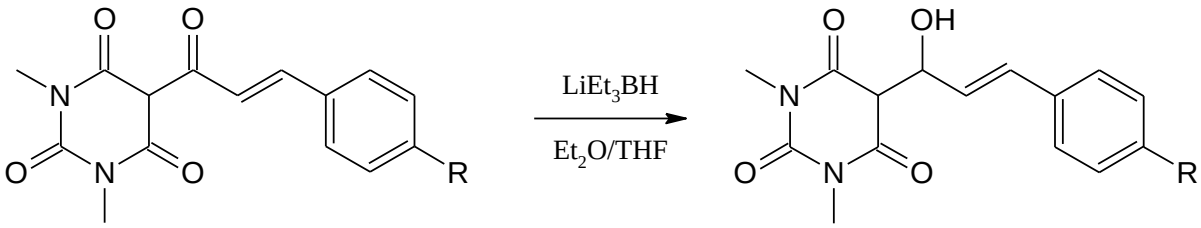
Figure 22: ^{1}H NMR spectra for reaction of compound **55** with LAH at 60 °C (**part B**)

Addition rate of the substrate, to an excess of the reducing agent, was also varied in some experiments (see **method 2** in experimental section) in hope that the addition of a small amount at a time would help to get the desired product, without unwanted side reactions. Whether the addition rate was 5 minutes, 15 minutes or all substrate was added at once made no difference for any of the compounds.

When LAH was used as solid the experiments were run for 2 hours or longer since the tablet dissolved slowly in Et_2O and THF. Spectroscopic data gave the same results for the use of LAH in solution.

3.2.4 Reduction by superhydride

Superhydride is a more reactive hydride donor due to inductive effect. If one reason behind the unsuccessful reductions are steric hindrance at the α- β unsaturated ketone, then superhydride would be a better choice than LAH for this reduction. Possible obtained compounds could be substances **67-69**.



55: R= H

56: R= OMe

57: R= NO_2

67: R= H

68: R= OMe

69: R= NO_2

Scheme 26: Possible product after superhydride reduction of para- substituted chalconoids

Experimental variables for use of superhydride are shown in **table 9**:

Table 9: Experimental variables for reduction with superhydride

Experimental variable	Lowest value	Highest value
1. Reaction time	10 min	24 h
2. Reaction temperature	0 °C	60 °C
3. Solvent	Et_2O/THF (or both)	
4. Ratio substrate/reducing agent	1 mol substrate/ 4 mol red. agent	2 mol substrate/ mol red. agent
5. Work up	H_2O, NH_4Cl	

Attempts to reduce compounds **55- 57** with superhydride involved variation of temperature, type of solvent and number of equivalents of substrate compared to superhydride in the same manner as for LAH experiments. Different reaction times were 10 minutes, 30 minutes, 2 hours, 4 hours and 24 hours for different experimental runs.

The results were much alike for experiments with superhydride as for LAH, and it was therefore difficult to distinguish their difference in reducing effects on compounds **55- 57** (**table 10**).

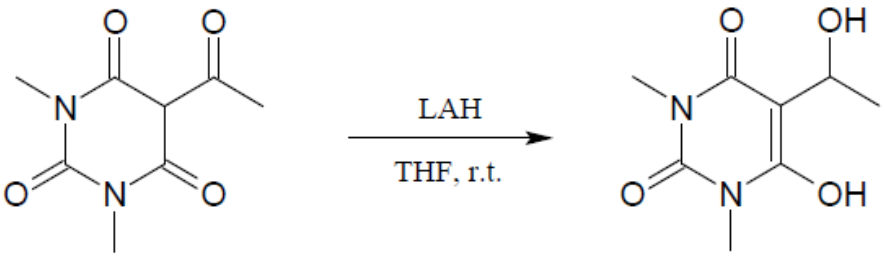
Table 10: Obtained results after reduction of compounds **55- 57** with superhydride

Compound	Reaction temp.: 0 °C	Reaction temp.: 20 °C (Room temp.)	Reaction temp.: 60°C
55	Starting material	Starting material	Impurities/ reaction mixture
56	Starting material	Starting material	Impurities/ reaction mixture
57	Starting material	Impurities	Impurities/ reaction mixture

3.2.5 Reduction of 5- acetyl-1,3-dimethylbarbituric acid

Compound **53** was tried to reduce to investigate if the main reason behind the unsuccessful reductions of reagents **55- 57** are the conjugated system.

This reduction proved to be successful with use of LAH and substance **70** was produced. This particular experiment was run for 30 min at 20 °C with a substrate- reducing agent ratio of 1:2. The yield was not registered after purification.



53 **70**

Scheme 27: Achieved product after reduction by LAH at room temperature

TLC analysing revealed that 50:50 of Et_2O and hexane was the best solvent system for compound **70**. From this flash column chromatography was used for purification. ^{1}H NMR for the accomplished product is shown in **Figure 23** and **24**.

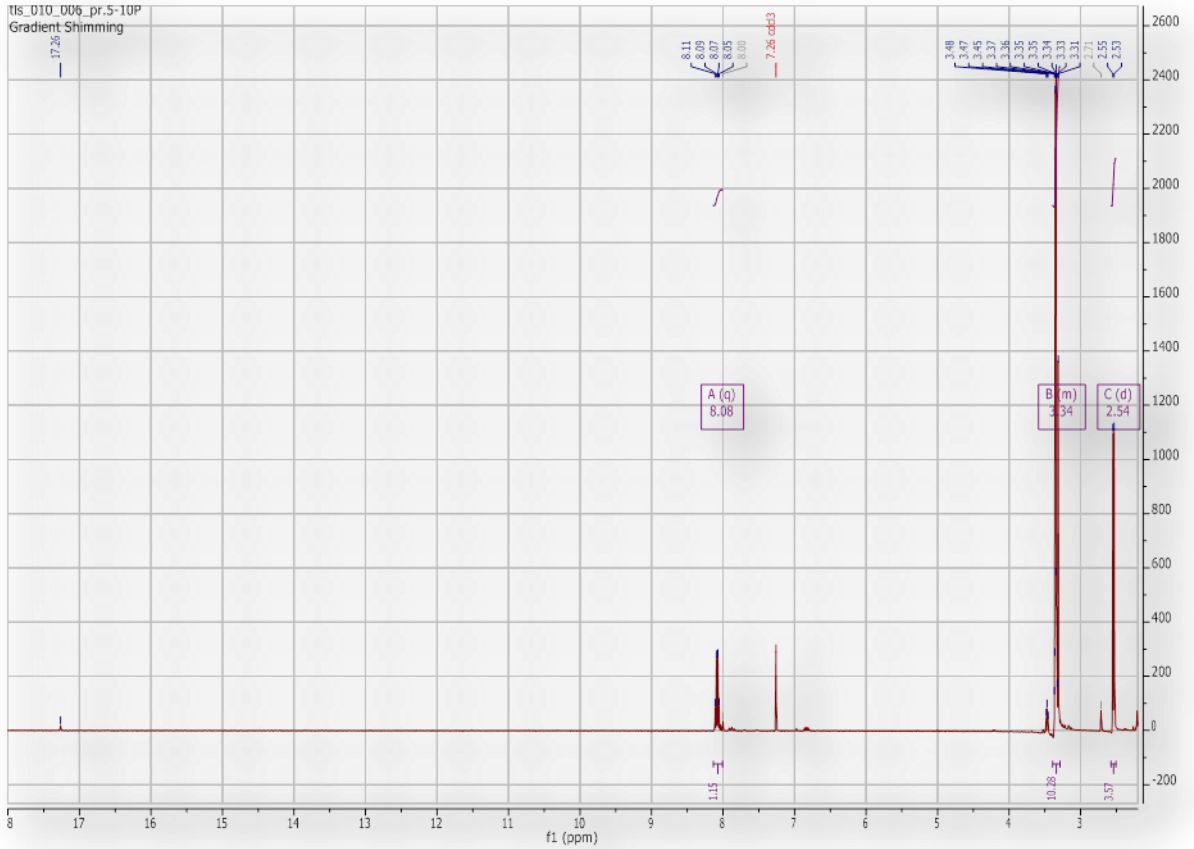


Figure 23: ^{1}H NMR spectra for compound **70**

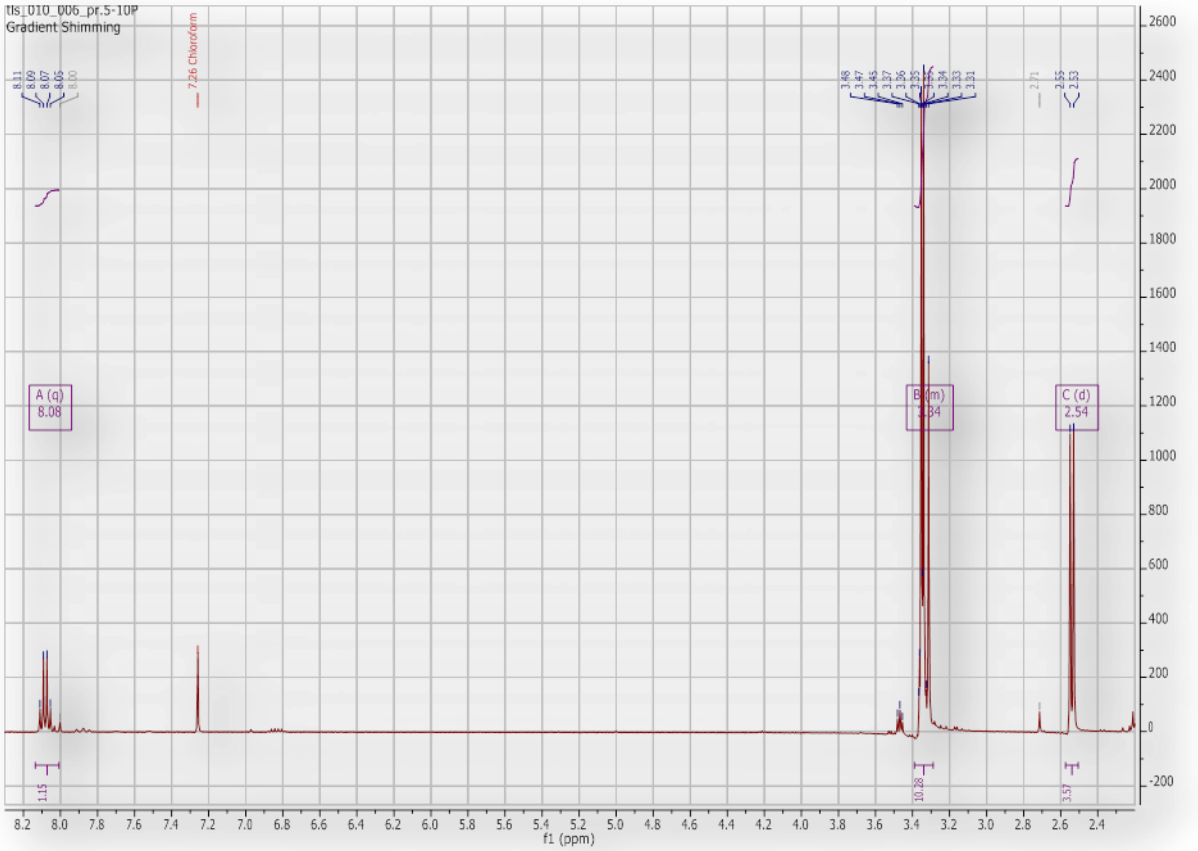


Figure24: ^{1}H NMR spectra for compound **70**

The proton sitting on the α- carbon with the OH- group is found as a quartet at 8,08ppm. The three protons in the β- position (on the acetyl group) are seen as a doublet at 2,54ppm. The six methyl protons are located at 3,34ppm. Some impurities has most likely coincided with this peak and made it a multiplet. The enolic proton is located at 17,26ppm.

4. Conclusions

No successful reductions, neither for compound **57** with its electron withdrawing group or compounds **55** and **56**, were achieved in these experiments. Conjugation between the aromatic ring and α-β unsaturated carbonyl could be the main reason behind this. This was confirmed by an effective reduction of 5-acetyl-1,3-dimethylbarbituric acid.

Reactions run at 0 °C proved to be useless for substances **55-57** since only starting material were present. Experiments performed at room temperature seemed to differ depending on the electronic structure of the chalconoid. Compound **57**, with its electron accepting nitro group gave the most promising results. However these results were not the wanted product, but some unknown substances.

When temperatures approached 60- 80 °C more impurities could be seen in the spectroscopic data. This especially was the case when stronger reducing agents like LAH and superhydride were used.

Maybe even higher temperatures, above 100 °C, are needed for successful reductions. This could be something for future outlook.

5. Experimental section

5.1 General

Solvents and reagents were purchased from Sigma- Aldrich, Fluka, Aesar, Kenetyl, SAFC and Merck. Reagents were used without further purification. Solvents like diethyl ether and methanol were obtained from Solvent Dispensing System (SDS) supplied by Glass Contour. THF was freshly distilled from sodium benzophenone.

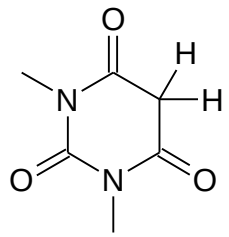
A Varian Mercury400 plus (399.65/100.54 MHZ) spectrometer were used to identify new compounds. ^{1}H NMR and ^{13}C NMR spectra were recorded on this instrument. Samples from the experiments were dissolved in $CDCl_3$ and DMSO-d_6. Chemical shifts (δ) are reported in parts per million (ppm). TMS (δ= 0,000 ppm) is used as internal standard. Coupling constant (J) are measured in Hertz (Hz). Signals multiplicities are registered as singlet (s), doublet (d), triplet (t), quartet (q) multiplet (m) or as a combination of these.

IR spectra were recorded on a Varian 7000e FT-IR spectrometer, and the wavenumber are reported in reciprocal centimetres (cm^{-1}).

GC/MS were recorded on a Thermo Scientific ITQ 1100 GC/MS instrument equipped with a XXX column.

5.2 Synthesis of starting material

Synthesis of 1,3-dimethylbarbituric acid (22)



22

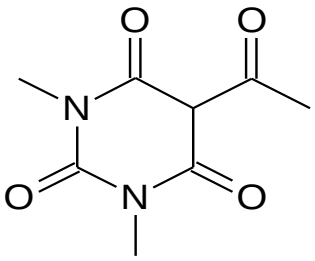
Dimethylurea (1, 0 eq.) and malonic acid (1,1 eq) were mixed in an flask, and acetic anhydride (1,8 eq.) was added with a syringe. The mixture was slowly heated to 90 °C in an oil bath, and stirred with a magnetic stirrer. When the exothermic reaction started the oil bath was removed from the hot plate, and the temperature rose to 125 °C. After cooling the solution was heated to 125 °C one more time, and then cooled to room temp. Isopropanol was added to the solution causing a white precipitate to appear. The white precipitate was filtered and allowed to dry at room temperature -in a desiccator.

From dimethylurea (4,45 g; 50,5 mmol) and malonic acid (5,60 g; 53,8 mmol): 6,70 g (85 %); white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.67 (s, 2H), 3.30 (s, 6H) ppm.

All other spectra were in accordance with earlier reported material.

Synthesis of 5-acetyl-1,3-dimethylbarbituric acid (53)



53

1,3-dimethylbarbituric acid (**22**), 1 eq, was suspended in a small amount of water and a concentrated water solution of sodium bicarbonate ($NaHCO_3$, 1 eq.) was added. After gas evolution ceased, the insoluble part was filtered off and acetic anhydride (2 eq.) was added to the stirred solution. A white precipitate formed after about 5 minutes. The mixture was stirred overnight, and then the white precipitate was filtered, washed with a little H_2O and

dissolved in 10 % ammonium hydroxide (NH_4OH). Hydrochloric acid (HCl) was added until pH was well below 1; the temperature of the solution rose and a white precipitate formed. The precipitate was filtered and allowed to dry at room temperature.

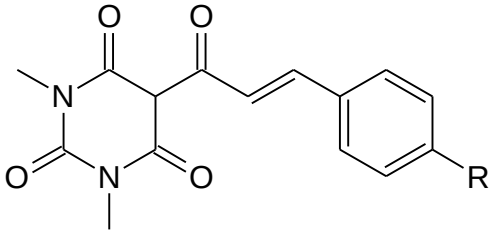
From compound **22** (5.25 g; 33.6 mmol)and $NaHCO_3$ (2.82 g; 33.6 mmol): 5.27 g (79 %) white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.27 (s, 1H), 3.37 (d, 3H), 3.33 (d, 3H), 2.72 (s, 3H) ppm.

All other spectra were in accordance with previously reported material.

Synthesis of chalconoids

General procedure



55: R= H

56: R= OMe

57: R= NO_2

5-acetyl-1,3-dimethtlbarbituric acid (**53),** 1 eq., was mixed with required benzaldehydes (2 eq.). The mixture was heated to the specified temperature (170 °C or 130 °C) in an oil bath for two minutes, and 0,1 mL of piperidine was added. The solution was heated for an additional three minutes, and then allowed to cool. Ethanol was added to the mixture and the solution was heated to the boiling point. The solution was allowed to cool at room temperature, and then the precipitate was filtered out and washed with ethanol. The resulting solid compounds **55- 57** were allowed to dry at room temperature.

5-cinnamoyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (55):

From **53** (1.01 g; 5,10 mmol) and benzaldehyde (1,00 mL; 9,85 mmol): 1,15 g (78 %); paled yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.03 (d, J= 1.4 Hz, 1H), 8.59 (dd, J= 15.9, 1.4 Hz, 1H), 8.01 (d, J = 15.9 Hz, 1H), 7.69 (m, 2H), 7.43 (d, J = 5.1, 2.0 Hz, 3H), 3.40 (s, 3H), 3.38 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 183.96, 169.98, 161.44, 150.49, 146.78, 134.84, 131.41, 129.29, 129.12, 120.56, 97.47, 28.28, 28.06 ppm.

IR (v_{max}): 3109, 3057, 2952, 1716, 1656, 1612, 1525, 1483, 1425, 1217, 989, 920, 796, 750, 697 cm^{-1}.

MS spectra were in accordance with earlier reported work

(E)-5(3-(4-methoxyphenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1h,3H,5H)-trione (56):

From **53** (0,93 g; 4,69 mmol) and p-anisaldehyde (1,15 mL; 4,47 mmol): 1,28g (86 %), bright yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 16.96 (d, J = 1.4 Hz, 1H), 8.47 (d, J = 15.7, 1.4 Hz, 1H), 8.01 (d, J = 15.8 Hz, 1H), 7.67 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 184.11, 170.02, 162.65, 161.68, 147.05, 131.41, 127.76, 117.99, 114.71, 93.97, 77.16, 55.64, 28.30, 28.09 ppm.

IR (v_{max}): 3108, 2955, 2845, 1711, 1654, 1622, 1598, 1506, 1481, 1418, 1257, 1168, 1017, 976, 824, 758 cm^{-1}

MS spectra were in accordance with earlier reported work

(E)-1,3-dimethyl-5-(3-(4-nitrophenyl)acryloyl)pyrimidine-2,4,6(1H,3H,5H)-trione (57):

From **53** (0,34 g; 1,72 mmol) and 4-nitrobenzaldehyde (0,52 g; 3,44 mmol): 0,20 g (35 %); yellow solid

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 17.11 (d, J = 1.4 Hz, 1H), 8.69 (dd, J = 15.9, 1.4 HZ, 1H), 8.28 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 15.9 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 3.42 (s, 3H), 3.39 (s, 3H) ppm.

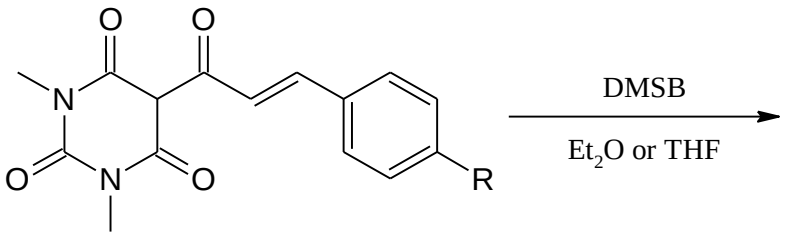
IR (v_{max}): 3101, 3079, 2962, 1716, 1654, 1622, 1599, 1483, 1336, 1210, 1018, 989, 848, 793, 750, 699 cm^{-1}.

^{13}C NMR and MS spectra were in accordance with earlier reported material.

5.3 Reductions of chalconoids

All glassware (flask, condenser etc.) were properly cleaned and dried between each experiment. Equipments like a magnetic stirrer and a condenser were used, and experiments were run under argon atmosphere. Dry solvents were used (besides reactions with us of $NaBH_4$ in ethanol).

Reductions by Dimethyl Sulphide Borane (DMSB)



55: R= H

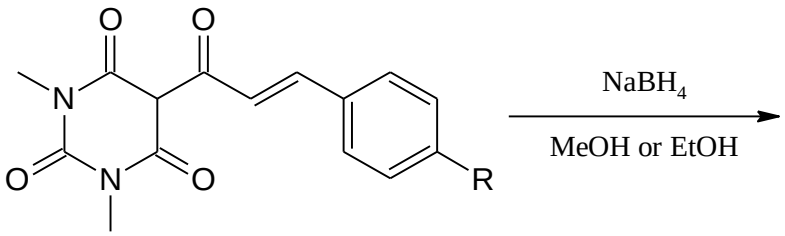
56: R= OMe

57: R= NO_2

Compounds **55- 57** were dissolved in a minimum of Et_2O or THF (or both) in a two-necked flask. DMSB as a 5M ether solution were added with a syringe. The mixture was kept in argon atmosphere and equipped with a water cooler. The solution were stirred with a magnetic stirrer in a time period, and then quenched with Methanol. The temperature varied between 0 °C (ice bath), 20 °C (room temperature) and 40- 70 °C (oil bath). THF was used when temperature exceeded 40 °C.

The solution was dried with $MgSO_4$ or Na_2SO_4, following filtration and then evaporation to get the crude product.

Reductions by sodium borohydride ($NaBH_4$)



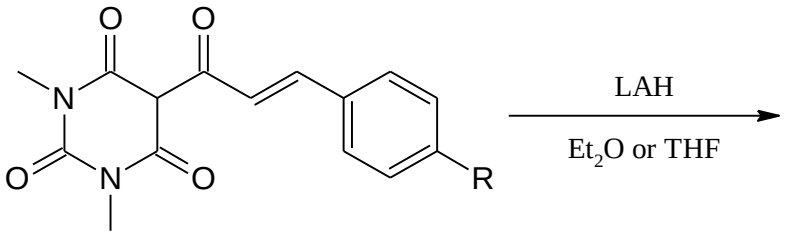
55: R= H

56: R= OMe

57: R= NO_2

A tablet or part of a tablet of $NaBH_4$ was dissolved in methanol or ethanol in a three necked flask. The flask was equipped with a condenser and an addition funnel. A solution of compounds **55- 57** was added from the funnel to the stirred mixture. The temperature was varied from 0 – 80 °C. Ethanol was preferred when temperature exceeded 65 °C. Work up procedures used were NH_4Cl (aq) or H_2O. After work up the two layers were separated and extracted (3/4 times) with Et_2O. The combined organic layers were dried with $MgSO_4$ or Na_2SO_4. The solvent was evaporated and the crude product was obtained.

Reductions by lithium aluminium hydride (LAH):



55: R= H

56: R= OMe

57: R= NO_2

Reactions were performed using one of the methods described below.

Method 1:

Compounds **55- 57** were dissolved in Et_2O or THF (or both) in a two- necked flask as described for DMSB. LAH as a 2M THF solution was added with a syringe. Work up procedures included Fieser method or the use of Glaublers salt ($Na_2SO_4 \cdot 10H_2O$) at 0 °C.

Quenching with Fieser method involves cooling of the reaction in ice bath to 0 °C, then adding X mL of water for a reaction ran with X grams of LAH. X mL of 15 % aqueous sodium hydroxide was added to the solution, followed by addition of 3X mL of water.

The mixture was allowed to warm to room temperature and stirred for about 30 minutes. Anhydrous magnesium sulphate ($MgSO_4$) was used as drying agent. The mixture was filtered over celite.

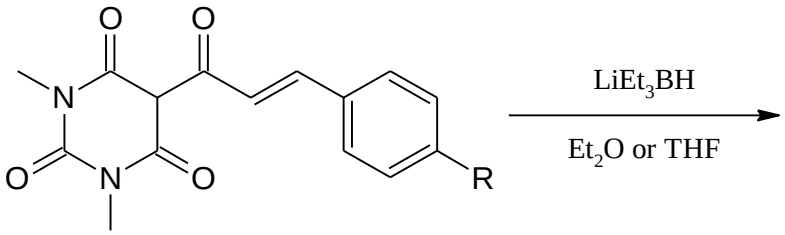
Glauber's salt was made from recrystallizing sodium sulphate (Na_2SO_4) with water. The reaction was cooled to 0 °C and then the salt was added until hydrogen evolution no longer was evident. The mixture was spontaneously warmed to room temperature and filtered over celite.

The crude product was obtained after evaporation.

Method 2:

A tablet or a crushed part of a tablet of LAH was dissolved in THF in a three- necked flask, and followed the same equipment setup as for $NaBH_4$. A solution of compounds **55- 57** was added with a tap- funnel with different addition rates. The flask was heated to a gentle reflux. The reaction was later quenched with saturated aqueous sodium sulphate followed by the addition of 10 % sulphuric acid. The two layers were separated and re- extracted with Et_2O (3/4 times). The solution was dried with Na_2SO_4, filtrated, and then evaporated.

Reduction by superhydride ($LiEt_3BH$)



55: R= H

56: R= OMe

57: R= NO_2

A 1M solution of superhydride in THF was added to a solution of compounds **55- 57**, and followed **method 1** for LAH (but H_2O or NH_4Cl (aq) were used as quenching agents).

6. References

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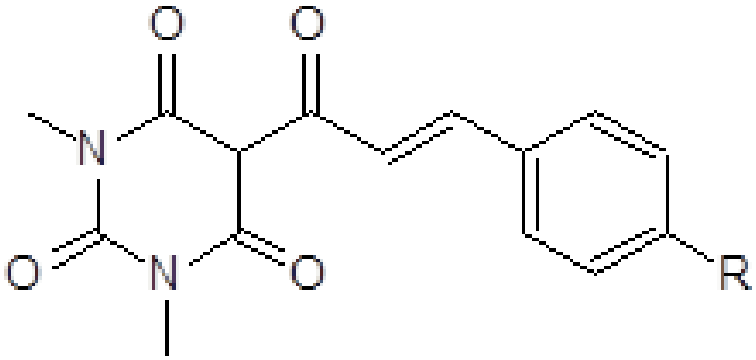
7. Appendices

Spectroscopic data for chalconoids 55-57

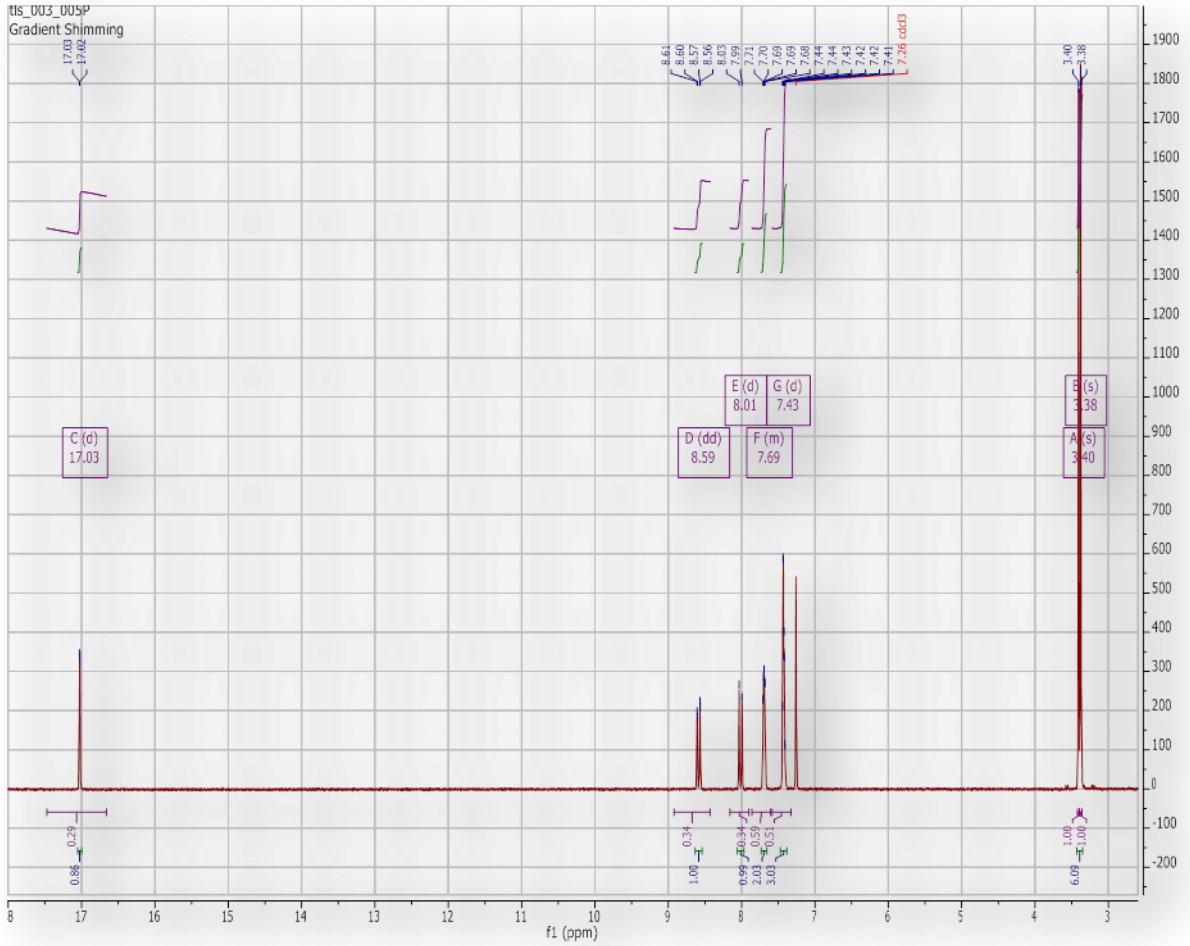


55: R= H

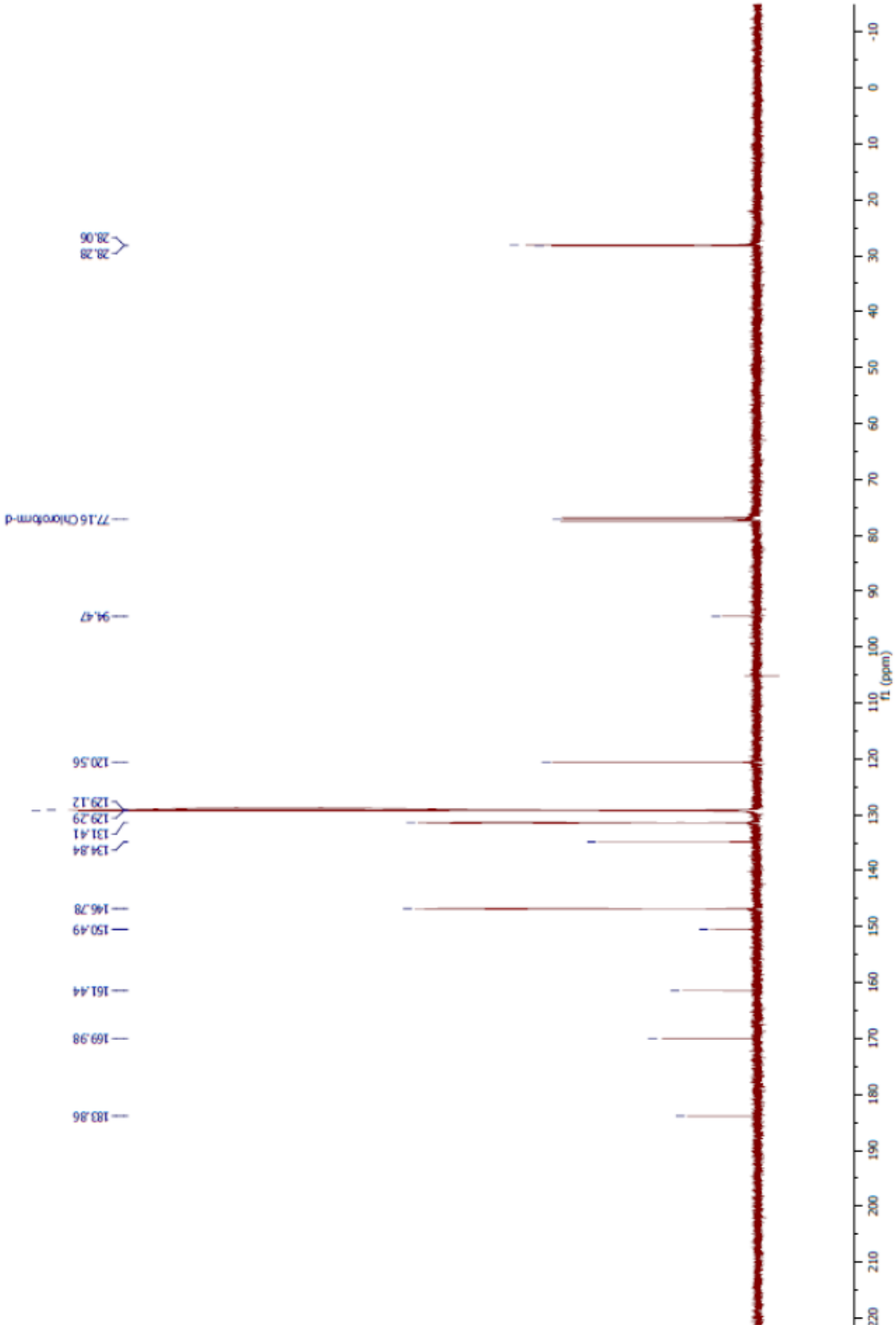
56: R= OMe

57: R= NO_2

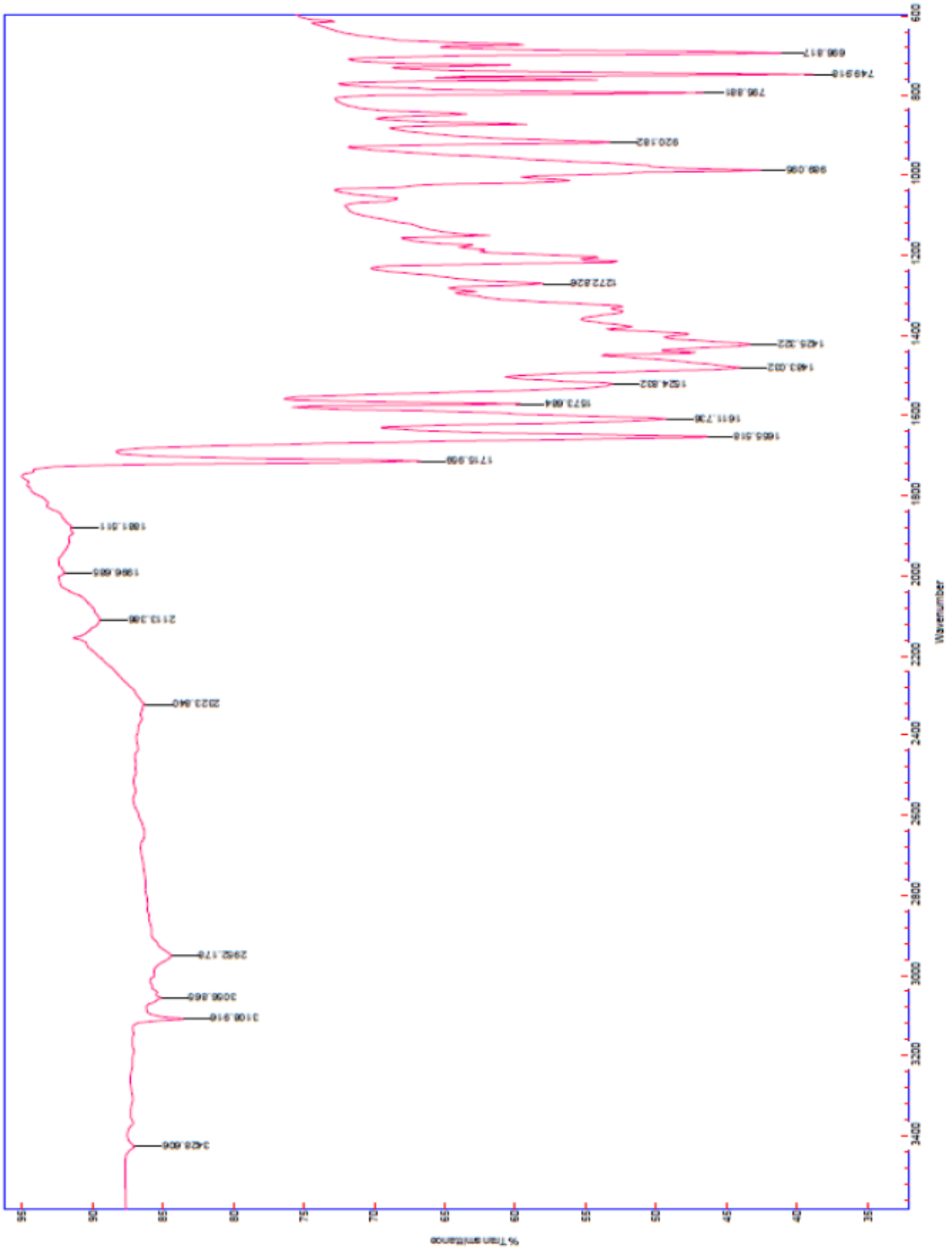
^{1}H NMR spectrum of 55



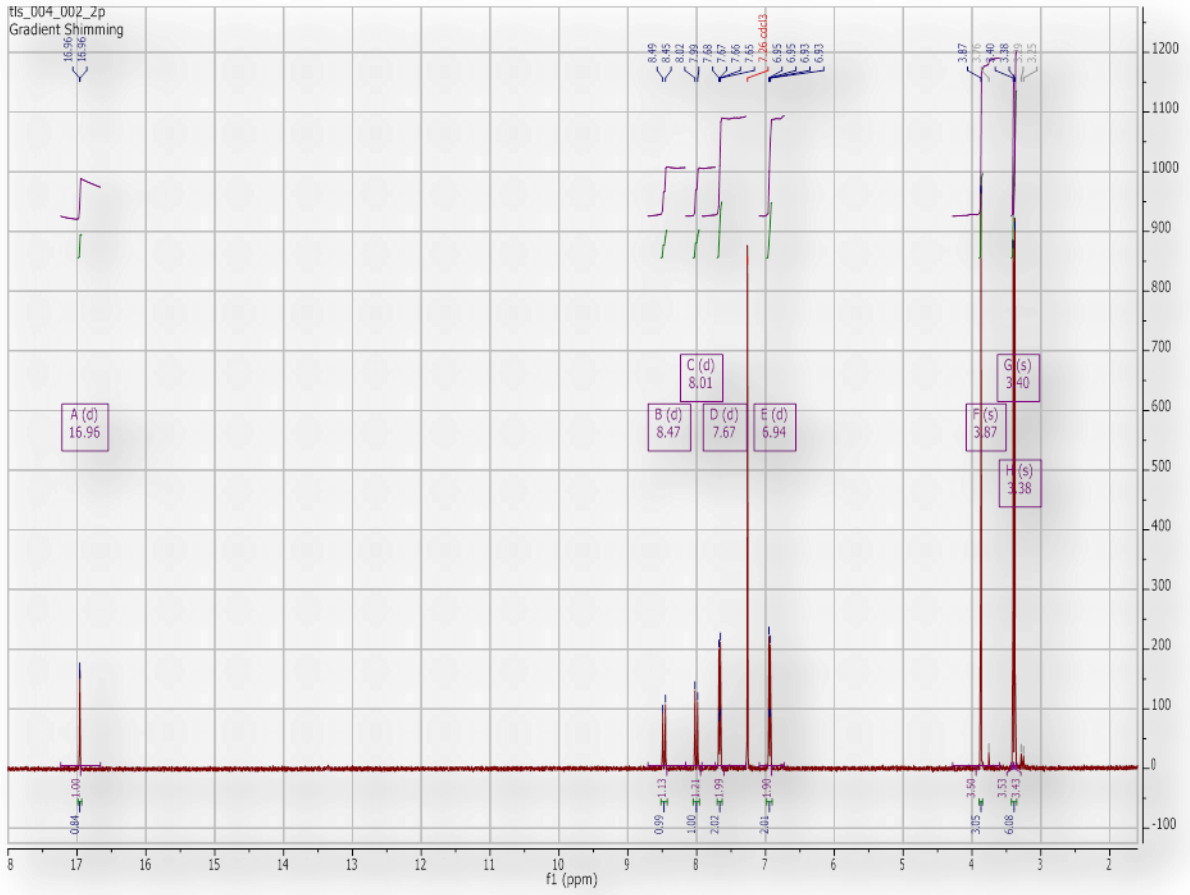
^{13}C NMR spectrum of 55



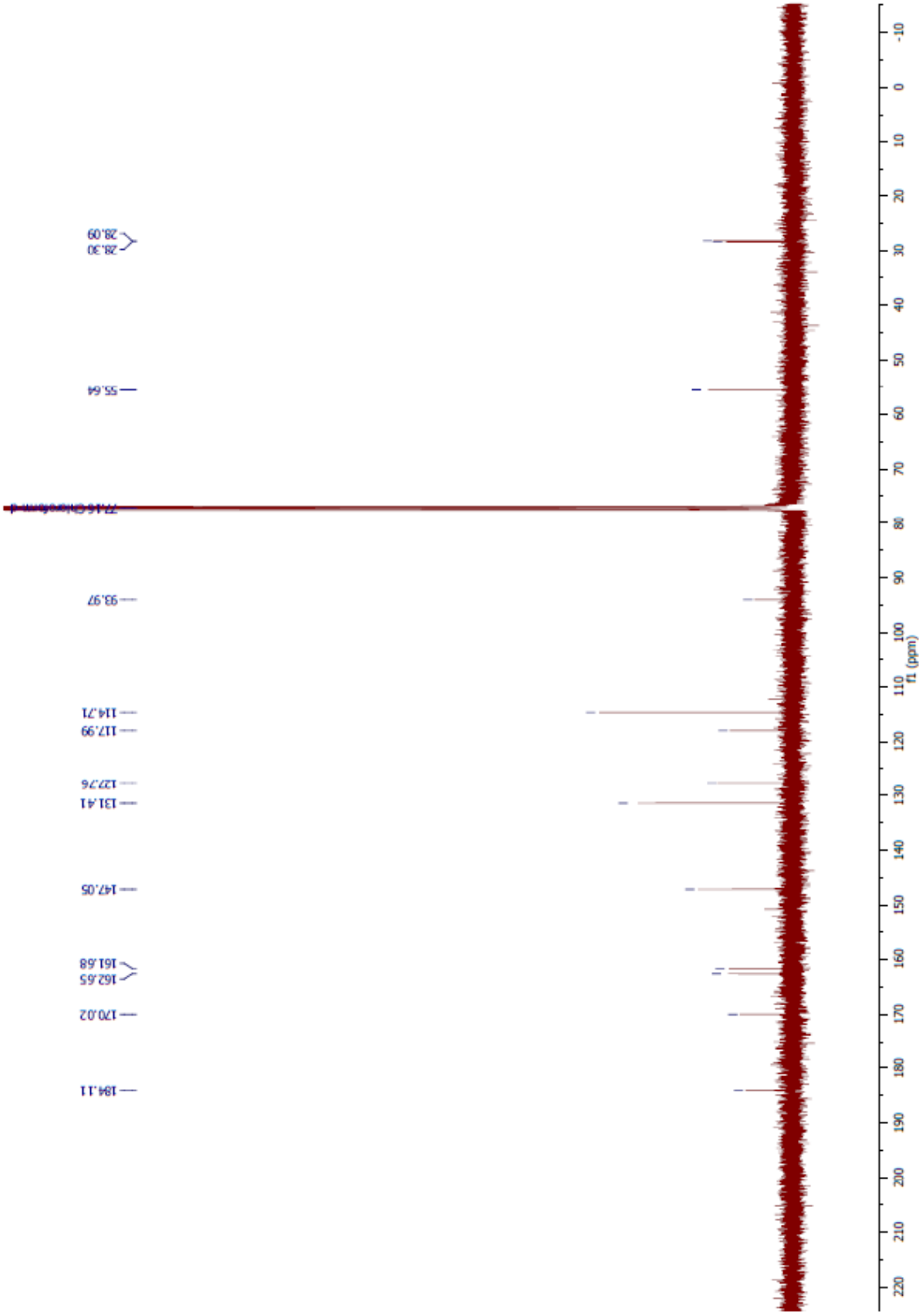
IR spectrum of 55



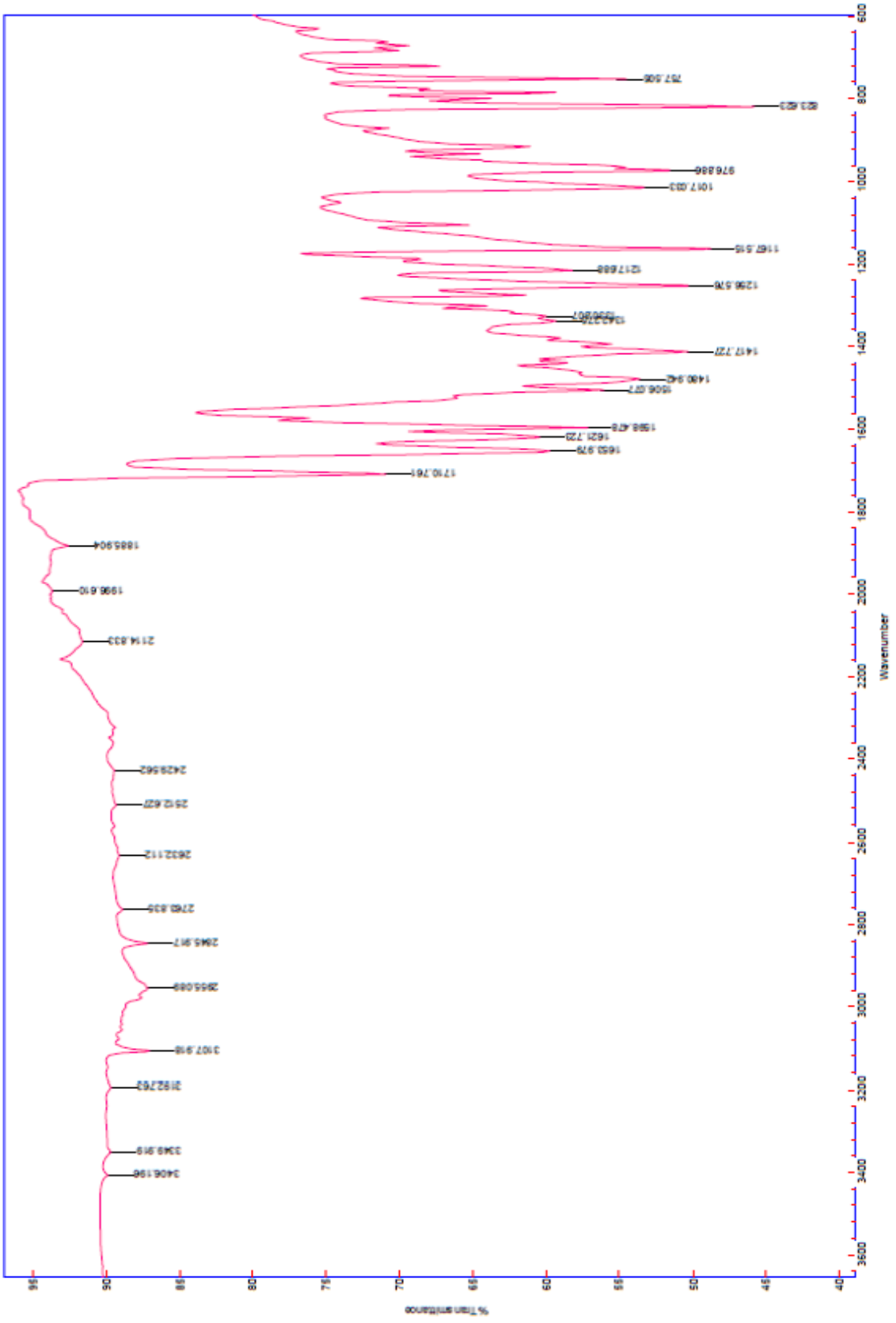
^{1}H NMR spectrum of 56



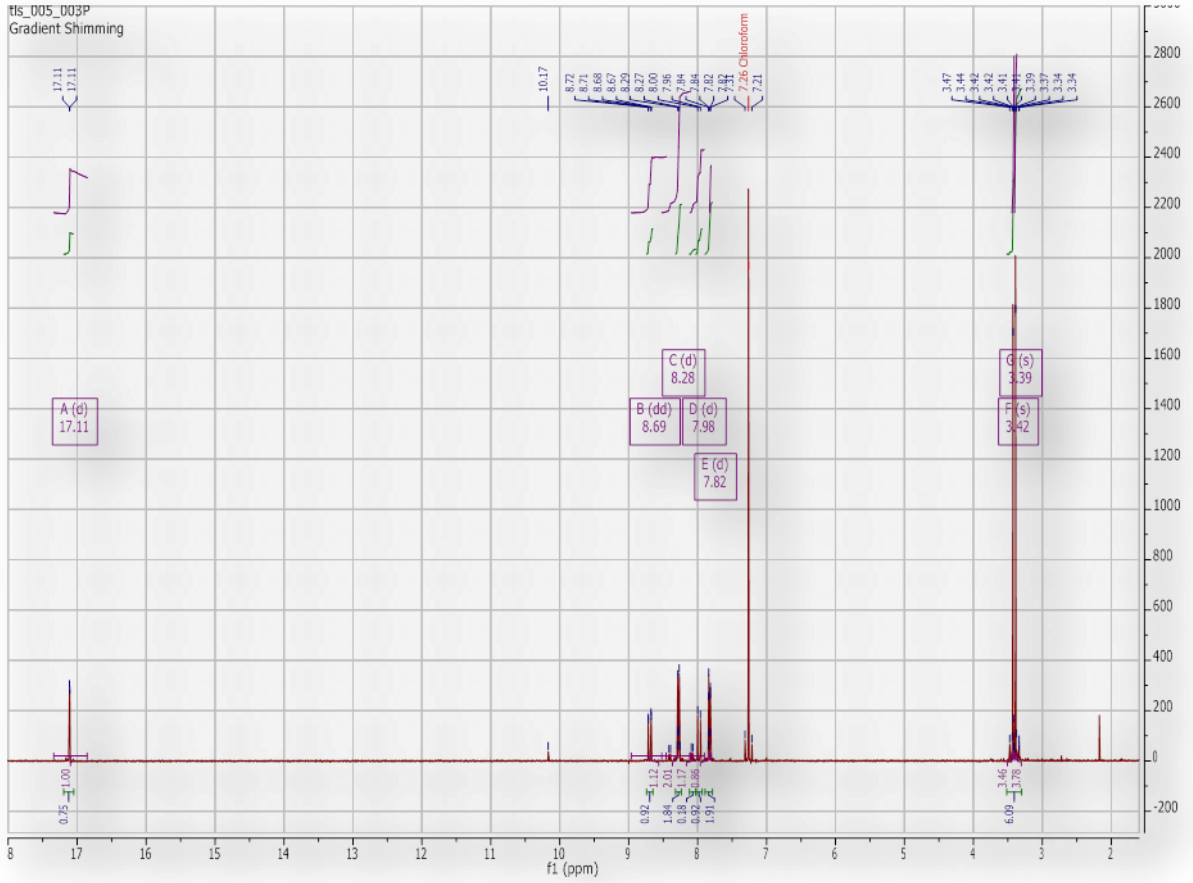
^{13}C NMR spectrum of 56



IR spectrum of 56



^{1}H NMR spectrum of 57



IR spectrum of 57