Practical synthetic methods for three unstable, unsaturated bromomethyl ketones, and on the use of near-orthogonal experiments for synthetic exploration.

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à Valentine et Elisabeth

Abstract

The present thesis is a summary of results presented in five published papers. The first three papers describe the development of scalable synthetic procedures for three unstable, unsaturated, bromomethyl ketones. The final two papers describe a new principle of screening designs when the objective is to identify the important experimental variables. These designs are based on near-orthogonal experiments.

The three ketones synthesised are 1-bromobut-3-en-2-one, (**1**), 1,3-dibromobut-3-en-2-one (**2**), and 1-bromobut-3-yn-2-one (**3**). The syntheses were carried out over several steps starting from 2-ethyl-2-methyl-1,3-dioxolane (the ethylene acetal of 2-butanone). The starting acetal was converted to 2-(1-bromoethyl)-2-(bromomethyl)-1,3-dioxolane in almost quantitative (98%) yield. The dibromoacetal was dehydrobrominated with potassium *tert*-butoxide to yield 2-(bromomethyl)-2-vinyl-1,3-dioxolane. This compound is the key-intermediate for the synthesis of all three ketone. Acetal deprotection of 2-(bromomethyl)-2-vinyl-1,3-dioxolane by formolysis, microwave-assisted hydrolysis, or treatment with ferric chloride on silica afforded **1** in 75–90% yields. Addition of bromine to the vinyl group of 2-(bromomethyl)-2-vinyl-1,3-dioxolane gave the tribrominated acetal, 2-(bromomethyl)-2-(1,2-dibromoethyl)-1,3-dioxolane. Mono-dehydrobromination with DBU gave 2-(bromomethyl)-2-(1-bromovinyl)-1,3-dioxolane, and bis-dehydrobromination with potassium *tert*-butoxide to gave 2-(bromomethyl)-2-ethynyl-1,3-dioxolane. These acetals were the deprotected with ferric chloride on silica to yield **2** (75–80%) and **3** (75–80%).

The experimental condition for the dibromination of 2-ethyl-2-methyl-1,3-dioxolane were adjusted according to an experimental design based on near-orthogonal experiments. The principles behind such designs are described in the two final papers of this thesis.

A new strategy is presented for the design of explorative experiments in synthetic chemistry when the objective is to identify the important experimental variables. The methodology is based on Taylor expansion (response surface) models and the principles are: A grid of possible settings of the experimental variables is laid out in the experimental domain. These experiments define a candidate design matrix, $\mathbf{D}_C$.

From $\mathbf{D}_C$, a candidate model matrix, $\mathbf{X}_C$ is defined by appending columns for each variable in the Taylor model $\mathbf{X}_C$ is then factored by Singular Value Decomposition (SVD), and $\mathbf{X}_C = \mathbf{U}\ \mathbf{S}\ \mathbf{V}^T$. The rows in $\mathbf{X}_C$ that are most parallel to the singular column vectors in $\mathbf{V}$ are selected, and the corresponding experiments in $\mathbf{D}_C$ are identified. This gives the experimental design. The selected experiments are nearly orthogonal and they span the dimensions of the model space. The experiments can be run in sequence and thus, they allow for a systematic search, one experiment at a time.

The design principles are illustrated by an example on the dibromination of an acetal. Four variables were studied, and from twelve experiments, all main effects, and all two-factor interaction effects were estimated. From the response surface model, conditions for quantitative yield were predicted and a mole scale synthesis carried out under these conditions afforded 98% yield of the isolated pure, >97%, product.

An extension of these principles to cope with the general problem of screening can be described as follows. The variation displayed by the first selected experiment is removed from the model matrix by projections. This removes one dimension of the model space. The reduced model matrix is the factored by SVD and the second experiment is selected, the procedure is then repeated until all dimensions of the model space have been spanned by the selected near-orthogonal experiments.

The experiments can be run in sequence and thus allow for a systematic search, one experiment at a time. It is shown that subset selections from such designs in combination with PLS modelling can be used to identify the important variables. The principles are illustrated with two examples: (a) a dibromination of an acetal with four experimental variables, and (b) a synthesis of an enamine by condensing a ketone and morpholine in the presence of molecular sieves in which seven experimental variables are involved. In the acetal bromination, it was found that five experiments out of twelve were sufficient for identifying the most important variables. In the enamine example, eight experiments out of thirty were sufficient.

Keywords in context

Acetal bromination, dehydrobromination, acetal deprotection, unsaturated bromomethyl ketones, experimental design, screening experiments, singular value decomposition, PLS modelling, enamine synthesis.

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Tromsø, April 2015

Papers included in the thesis:

I

Synthesis of 1-Bromo-3-butyn-2-one and 1,3-Dibromo-3-buten-2-one.

Mekonnen, A.; Westerlund, A.; Havelkova, M.; **Descomps, A**.; Carlson, R.,

Synthetic Communications **2009,** *39* (14), 2472-2480.

II

Improved Synthesis of 1-Bromo-3-buten-2-one.

Carlson, R.; **Descomps, A**.; Mekonnen, A.; Westerlund, A.; Havelkova, M.,

Synthetic Communications **2011,** *41* (19), 2939-2945.

III

Deprotection of Acetals from Unsaturated, Unstable Bromoketones.

Descomps, A.; Carlson, R.,

Synthetic Communications **2014,** *44* (6), 757-761.

IV

Orthogonal Experiments in the Development of Organic Synthetic Processes.

Carlson, R.; Simonsen, G.; **Descomps, A**.; Carlson, J. E.,

Organic Process Research & Development **2009,** *13* (4), 798-803 .

V

Identification of Important Experimental Variables in Organic Synthetic Procedures by Near-Orthogonal Experiments.

Carlson, R.; Simonsen, G.; **Descomps, A**.; Carlson, J. E.,

Organic Process Research & Development **2012,** *16* (8), 1371-1377.

List of abbreviations and symbols

α	Alpha
β	Beta
$CDCl_3$	Chloroform-d
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAD	Dimethyl acetylenedicarboxylate
DEAD	Dimethyl acetylenedicarboxylate
Et_2O	Diethyl ether
$FeCl_3$	Iron III Chloride
GC	Gas Chromatography
IR	Infrared
KBr	Potassium bromide
Li_2CO_3	Lithium carbonate
MS	Mass spectroscopy
$(n\text{-Bu})_4NBr/NaOH$	Tetrabutyl ammonium bromide/Sodium hydroxide
$(n\text{-hexyl})_4NBr/NaOH$	Tetrahexyl ammonium bromide/Sodium hydroxide
$(n\text{-Bu})_4NHSO_4/NaOH$	Tetrabutyl ammonium hydrogen sulphate/Sodium hydroxide
$(n\text{-Bu})_4NBr/KOH$	Tetrabutyl ammonium bromide/Potassium hydroxide
NMR	Nuclear Magnetic Resonance
SiO_2	Silicon dioxide
$^{t}BuOK$	Potassium *tert*-butoxide
THF	Tetrahydrofuran

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I. Introduction

1. Overview

This thesis may be considered as the final step of a very long chemistry journey initiated by Professor Rolf Carlson, the supervisor of the project, more than 20 years ago. Like many projects this one started by a fortuitous discovery. It was a gas chromatography analysis of a complex reaction mixture suggesting the presence of a rather exotic molecule (compound **1**, fig. 1.1), which became the trigger. The molecule's synthesis, which was a spinoff of the original project, gradually became a venture of its own. Over the years several students, graduate students and researchers have brought their contributions. Through those attempts one new molecule[1], exhibiting the same distinctiveness[2], i.e. an α-bromomethyl ketone with an α unsaturated bond (compound **2**, fig. 1.1), awoke the curiosity and from one molecule the focus was now on two molecules. Later again, this time during this project, it was clear that yet another new and interesting molecule could be synthesized from the precursors (compound **3**, fig. 1.1).
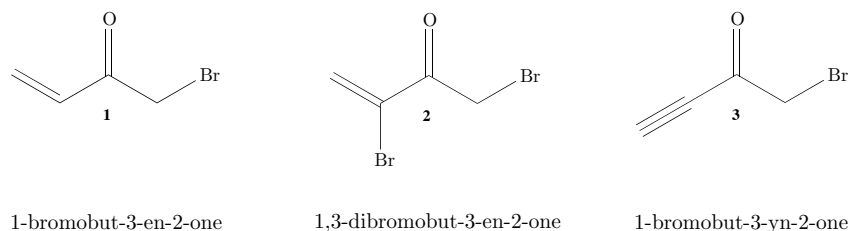

| 1-bromobut-3-en-2-one | 1,3-dibromobut-3-en-2-one | 1-bromobut-3-yn-2-one |

Figure 1.1 The three target of this project

Since those molecules were synthetically related an obvious task became to develop a convergent synthesis. This would make those three molecules more "attractive" if one

would like to explore their chemical properties in the future. It would also greatly simplify the "logistic" if the starting material were not different. It will be shown that this goal was partly reached in the first paper published and totally toward the end of the project when an easy acetal deprotection was identified to be one of the key steps. Once all those parameters were under control it was possible to do some explorative chemistry in order to find some useful chemistry pathway and to validate them as suitable building blocks "synthons"[3] (i.e. a fundamental part of a molecule to be synthesized which can be seen as the basis of a synthetic path). The purity of the starting material has to be high in order to avoid side reactions, and if not absolutely pure, all the others chemicals must be known and characterized in order to avoid or understand side reactions.

Several problems have arisen due to the properties of the 3 targets molecules. First, they had never been made and the lack of procedures forced all the people involved to look for new solutions. Secondly, it was clear from the beginning that those molecules would be (due to containing several functional groups and low molecular mass) rather unstable. Purification or separation by column chromatography being impossible for large amounts of product[4], distillation remains the only mean of obtaining pure compounds. Leaving no other choice than to have a very straightforward last step. Thirdly, it has been anticipated (with reason), that the compounds could exhibit lachrymose effects[5] and hence making the work-up of a scaled-up procedure (with laboratory equipment) more difficult to handle.

Organic chemistry reactions for a given transformation are often plentiful. For that the role of a chemist, helped by his knowledge and experience, is either to choose the suitable one or even sometimes to develop new ones according to the direction of his study. While many reactions works well on a milligram scale, involving several fancy compounds, complex mechanisms, tedious work-up and pro rata high cost, to scale-

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up leads the chemists to revise the synthetic route. The milligram scale is obviously the first step, allowing characterizing and confirming the existence and identity of a molecule. By employing more robust (cheaper, well documented, reaction mechanism which have not just been "suggested" without any consideration for orbital theory or kinetic or even basic thermodynamics), less complex reactions (less equilibrium phases mostly/ more balanced reaction equations) and procedures (due to the fact that physical rate like time, heat processes are affected by scale) it is possible to transfer the knowledge acquired from previous steps to a larger scale.

Finally, to have enough reagents in order to do some explorative chemistry is necessary if not compulsory.

The amount of work done before by those involved in the project to synthesize **1** gave a solid understanding of what the difficulties are and which directions to choose. Several problems still needed to be solved to fulfil the criteria mentioned earlier. The tentatively called "zebrasil" [6]filtration setup to get rid off the potassium bromide in the second step was cumbersome and could not be scaled-up to more than 0.5 mol and was time consuming. The acetal deprotection, as it will be presented later, had turned out to be very difficult. The previous attempts (published and unpublished) were also far from satisfactory. The 1-bromo-3-buten-2-one was never completely pure and due to the mixture with other by-products it was very prone to polymerization. The reaction time for such a deprotection was also very long (24h), low yielding, not up scalable and resulting in a very dark mixture. The earlier procedures preconized purification trough columns. The target molecules being very sensitive, this purification process led to an even lower yield.

2. Use as potential building block

All four carbon of **1** (taken as reference for both **1** and **2**) are functionalised and there are three strongly electrophilic sites. Several types of reaction can occur competitively: 1,2-addition, 1,4-addition and sequential addition. Nucleophilic substitution of the bromine can also be performed. Single functional group conversion (oxidation, reduction...) can also be performed. It can play the role of dienophile in Diels-Alder reaction or various concerted mechanism reactions. (Fig. 2.1)
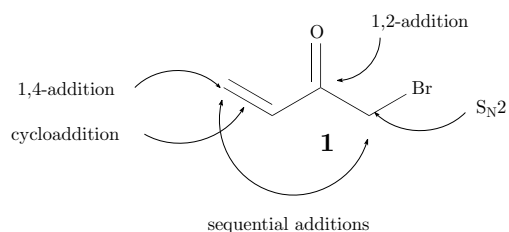
Fig. 2.1 Possible reaction sites of 1

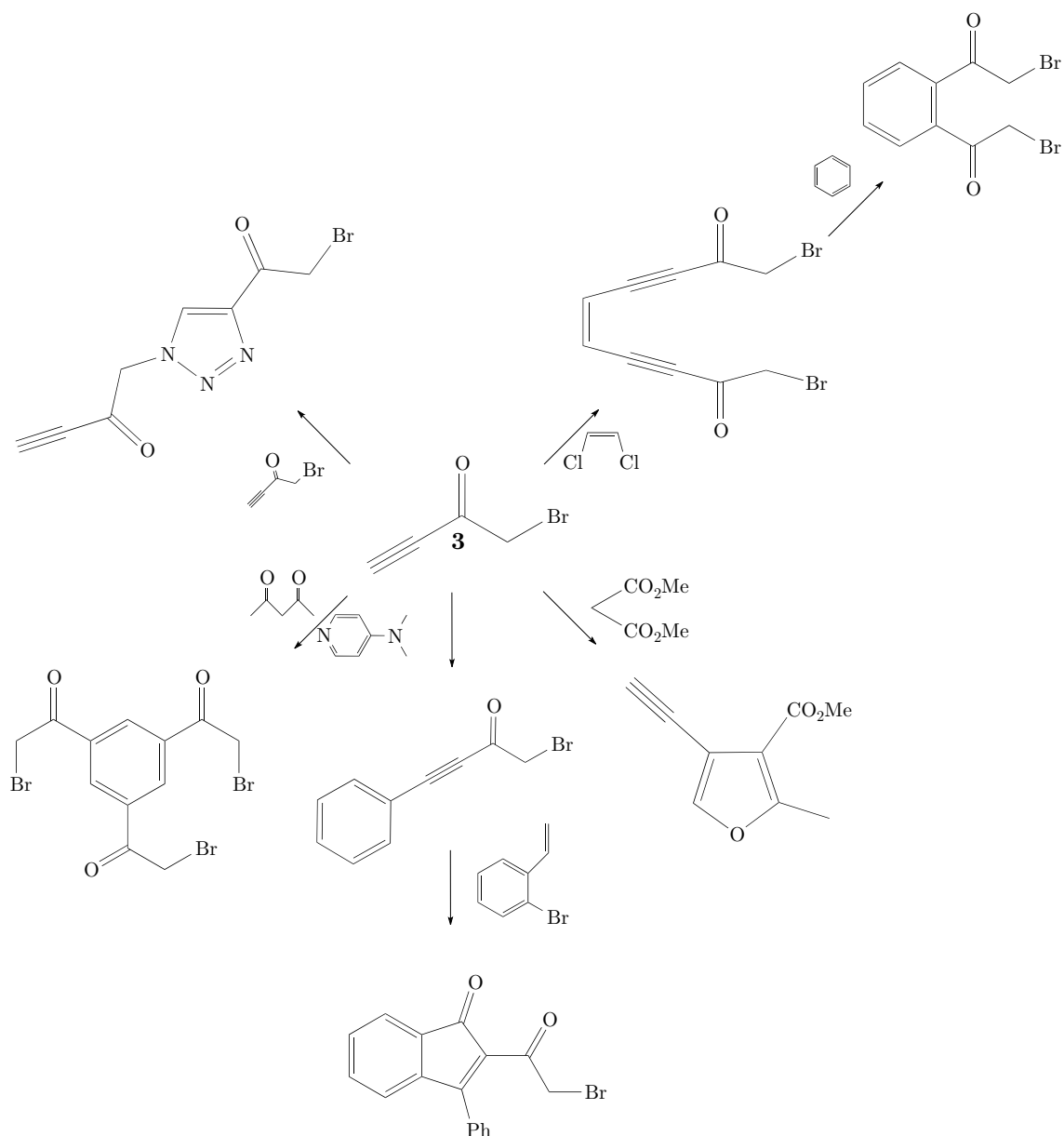For **3** different cycloadditions involving alkynes can be performed as well as coupling reactions. (Fig 2.2)
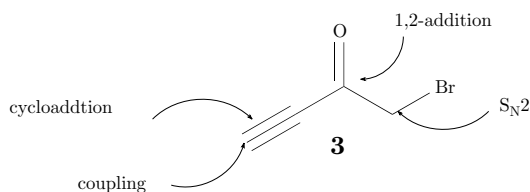
Fig. 2.2 Possible reaction sites of 3
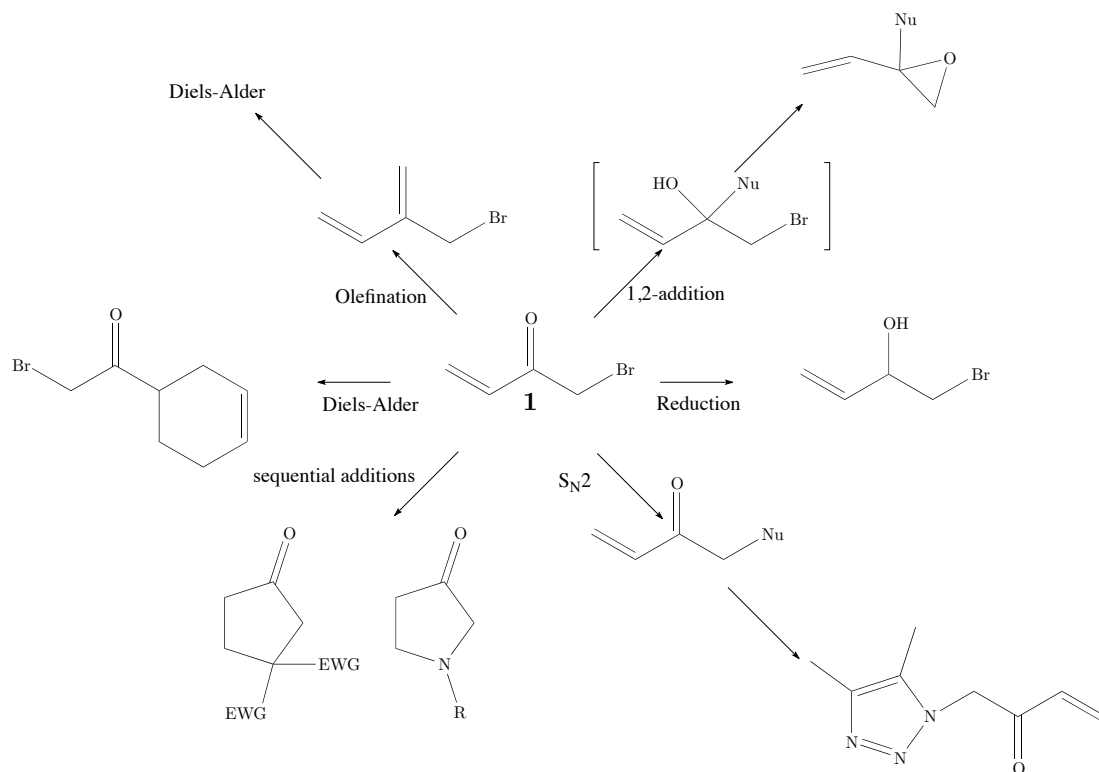
Scheme 2.1 Possible one or two steps reaction with 1

Scheme 2.1 shows how to access in few steps, mainly one, to interesting molecules by simple functional group conversion with **1**.

*Scheme 2.2 Attempted reactions with **3** by Dr. Alemayehu Mekonnen.*

(unpublished work and not fully characterized products)

Scheme 2.2 shows different reactions, mainly leading to heteroaromatic molecules from **3.** It is a tribute to Dr. Alemayehu Mekonnen.

3. About unsaturated bromomethylketones

3.1 Survey of methods for α bromination of ketones

Halomethylketones are known to be challenging to synthesize through direct halogenation of their ketone equivalents. Under acidic conditions the substitutions mostly occurs at the most substituted carbon and rarely at the methyl group while under basic conditions, the methyl group is prone to be polyhalogenated (Haloform reaction). Different indirect routes, often consisting of several steps, have been developed as well as exotic reactions involving rare reagents.

Arndt-Eistert synthesis via diazoketone:

The very first general method [7] to produce bromomethylketones. An activated carboxylic acid (Scheme 3.1), e.g. with a double bond, reacts with diazomethane in a one-carbon homologation to yield an α-diazoketone. Subsequent attack with hydrobromic acid leads to the bromination of the lesser-substituted α-carbon.
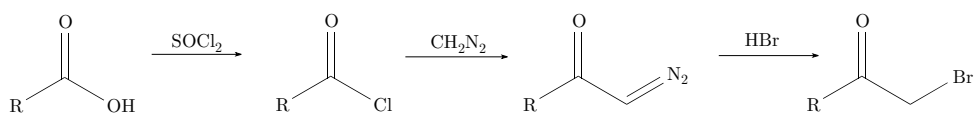

Scheme 3.1 Arndt-Eistert synthesis via diazoketone

However it is not suitable for larger scale synthesis since diazomethane is explosive, carcinogenic and acutely toxic.

Direct α bromination of dissymmetric methylketone:

Whereas logically not readily accessible by direct bromination, some dissymmetric methylketone can be monobrominated at the less substituted carbon in presence of

methanol as solvent (Scheme 3.2).[8] The presence of bromomethyl ketal as by product requires hydrolysis during the workup. Here the reaction can be scaled-up but was not suitable for the vinylmethyl ketone of this thesis.
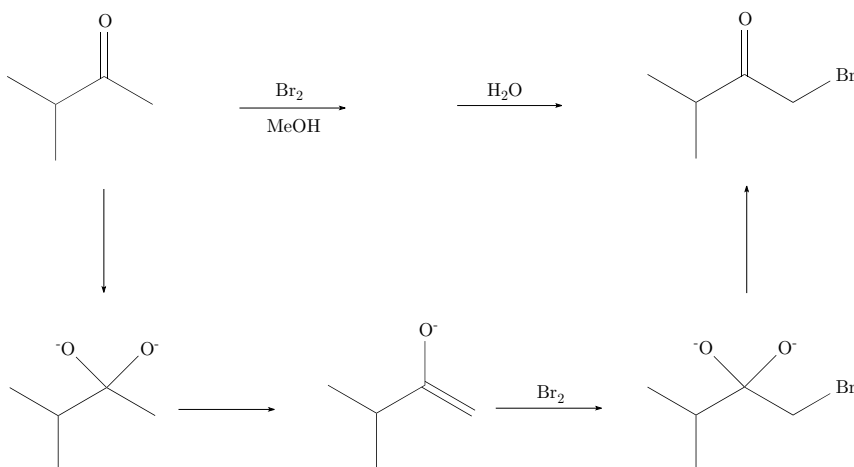
Scheme 3.2 direct α bromination of dissymmetric

Halogenation of enamines:

By a deprotection of immonium salts[9] which was first racemized by the action of Trifluoroacetic acid. (Scheme 3.3)
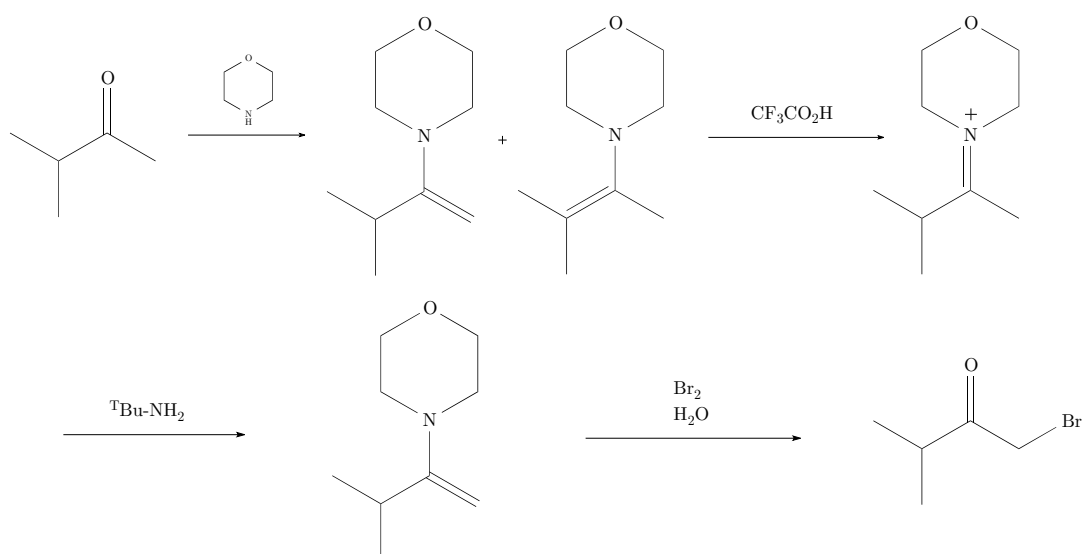
Scheme 3.3 halogenation of enamines

N-bromosuccinimide (NBS):

Direct radical α bromination of unsaturated ketones with NBS has the benefit that neither excess hydrogen bromide nor excess free bromine is present during the reaction, with the benefit that side reactions can largely be eliminated. However the reaction rate is quite slow and sometimes no bromination happens at all. [2c]

Addition of bromine to α,β-unsaturated ketones occurs mostly at the allylic position (scheme 3.4) and not at the carbon α to the carbonyl group.[10] The consequence is that only bromomethyl alkenyl ketones lacking allylic hydrogens can be synthesized with NBS.
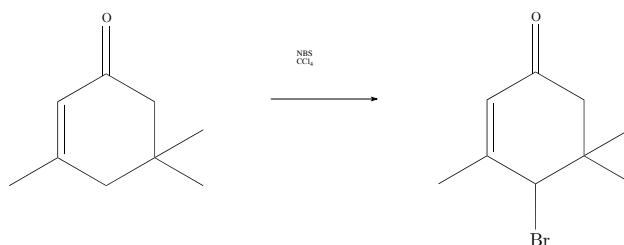
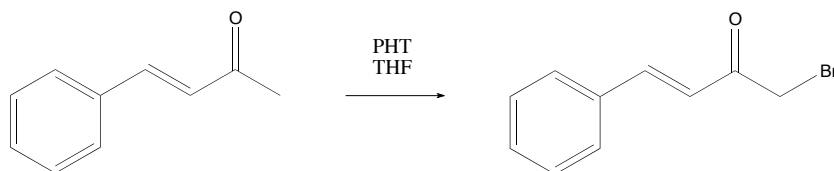*Scheme 3.4 Bromination with NBS.*

Cupric bromide:

Bromination with cupric bromide [11] (Scheme 3.5) has been reported using high dilution technique. Low yields are often the major problem. Moreover scaling-up such procedure would imply oversized laboratory equipment.
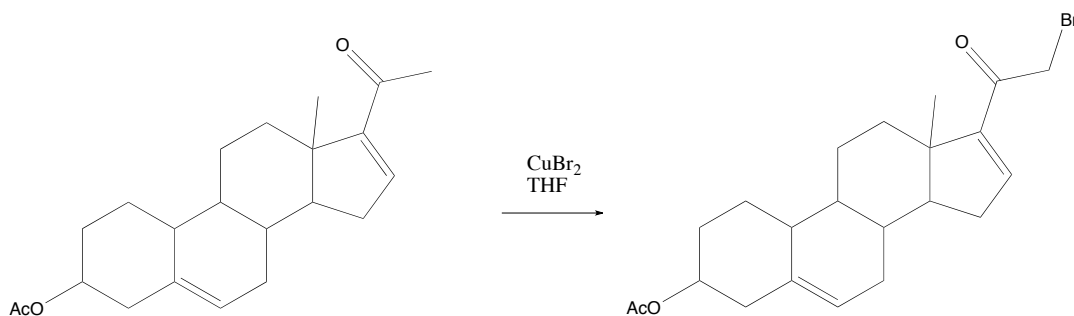
Scheme 3,5 Bromination with cupric bromide.

Trisbromides:

At least six different bromination methods have been reported for synthesis of bromomethyl vinyl ketone.[2a, 12] The first employs (pyrrolidone)$_3$•HBr$_3$ also called PHT. (Scheme 3.6) This reagent has not been verified on any substrate with allylic hydrogens. Whether or not it can work on other α,β-unsaturated ketones have to be tested. The same is true for 2-carboxyethyltriphenyl-phosphonium tribromide (Scheme 3.18). Moreover 2-carboxyethyltriphenyl-phosphonium tribromide does not react with isolated double bonds.[12b]


Scheme 3.6 Bromination with PHT or carboxyethyltriphenyl-phosphonium tribromide.

Phenyltrimethylammonium tribromide (PTAT) has been used for bromination of α,β-unsaturated ketones. However, this method does give poor results with conjugated ketones.[13] Competitive kinetic experiments where mixtures of ketones and olefins were treated with PHT or PTAT have shown that the enol is at least 10^6 times more reactive than the olefin.[12a] Those experiments were carried out using a low effective bromine concentration.

Poly-bromo-carbonyl compounds:

The use of 2,4,4,6-tetrabromocyclohexa-2,5-dienone as brominating agent[14] has been successful for both open chain α,β-unsaturated ketones and steroid ketones (Scheme 3.8). It is a common source of electrophilic bromine but it has been reported that numerous side-products and over-halogenated materials are typically formed in lieu of the desired material. [15]
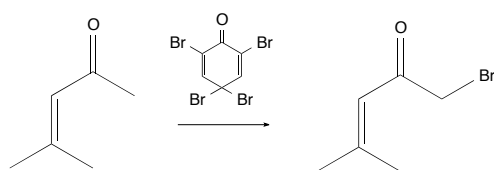

Scheme 3.7 Open chain bromination with 2,4,4,6-tetrabromo-cyclohexa-2,5-dienone.

Bromination with 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane has been performed on five different conjugated ketones, methyl styryl ketone, mesityloxide (Scheme 3.7), 4,4-dimethyl-cyclohex-2-en-1-one, 2-benzal-cyclohexanone (Scheme 3.9) and 2-isopropylidiene-5-methyl-cyclohexanone.[16] Reported yield were satisfactory (40-90%) but some dibrominated products were sometimes also produced.
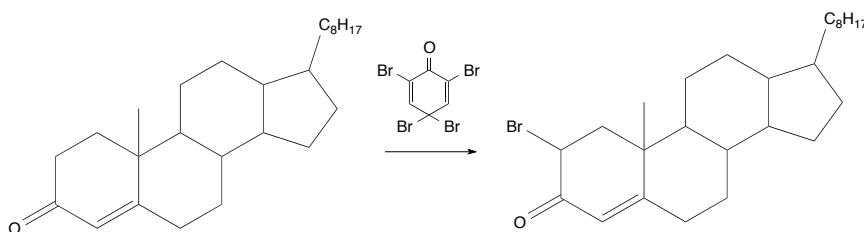

Scheme 3.8 Steroid bromination with 2,4,4,6-tetrabromo-cyclohexa-2,5-dienone.
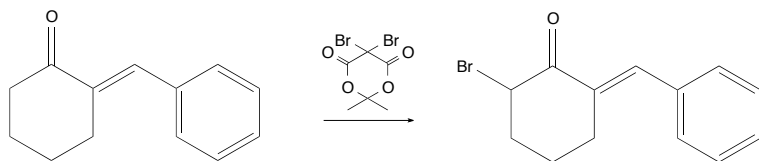
*Scheme 3.9 Bromination with 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane.*

5,5-Dibromobarbituric acid or 5-bromobarbituric[17], two brominating agents easily synthesized from barbituric acid, were also reported to work well on saturated and α,β-unsaturated carbonyl compound like 4-methylpent-3-en-2-one (Scheme 3.10) .
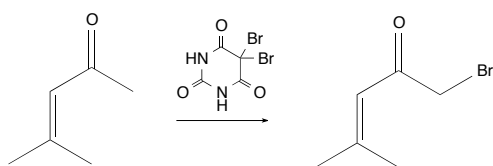
Scheme 3.10 Bromination with 5,5-dibromobarbituric acid.

Electrochemical bromination:

An α'-bromination of α,β-unsaturated ketones by an electrochemical procedure has been described (Scheme 3.11), the yields were nevertheless not reported.[18]
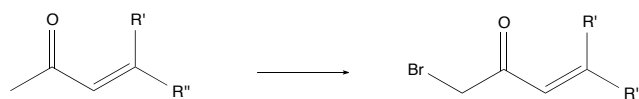

R'= H, R''= C_6H_{13}
R'= H, R''= Pr
R'= H, R''= Ph
R'= R''= Me

Scheme 3.11 Electrochemical bromination

Silyl enol ether:

An indirect bromination method has been reported.[19] The bromination of silyl enol ethers in tetrachloromethane, where an α,β-unsaturated ketone is transformed into a kinetically unstable silyl enol ether, which is subsequently trapped by a halonium source. (Scheme 3.12) As it will be mentioned in the next paragraph, attempts to synthesize 1-bromo-3-buten-2-one by selective bromination of 2-trimethylsiloxy-1,3-butadiene failed. 1,3,4-tribromo-2-butanone was formed as product.
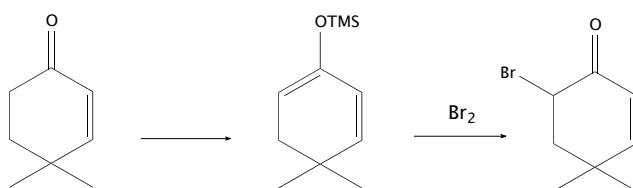
*Scheme 3.12 Bromination of silyl enol ethers.*

Halomethylation type:

The transformation of an α,β-unsaturated aldehyde to the corresponding halohydrin via the addition of a carbenoid followed by an oxidation step (Scheme 3.13) has been reported as an efficient two-pot procedure to access α,β-unsaturated α'-bromoketone.[20]
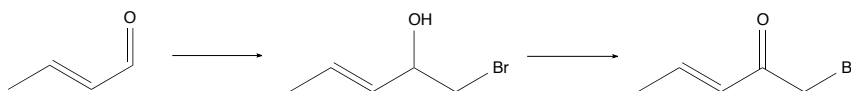
Scheme 3.13 Two steps halomethylation of an aldehyde.

13

Via Weinreb Amide:

A direct synthesis of variously functionalized α,β-unsaturated α′-haloketones has been reported [21]by a chemoselective addition of halomethyllithium carbenoids to Weinreb amides (Scheme 3.14) at −78 °C. It seemed a good way but obviously not practical for large-scale synthesis with laboratory equipment.
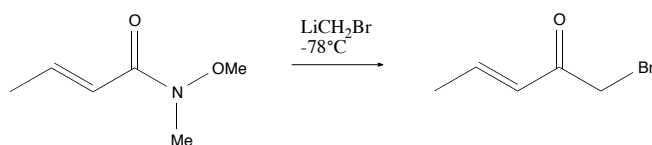
*Scheme 3.14 Chemoselective reaction of Halomethyllithium with Weinreb amide.*

None of those methods were convenient due to bad properties for scaling up. It was therefore decided to optimize the method previously developed in the group.

3.2 History of the project

Many project descriptions often use general textbooks or publications to give an overview. This would be useless for the present one. Indeed no description is available since the syntheses have never been reported by anyone. So, for the description, it was therefore more pertinent to gather information from previous group members. Most of the results, being partial or total failures, were never published. A summary of details selected from lab books, discussions and presentations is presented here.

When the project started in January 2009, a lot of work had been done earlier in order to find a procedure for the synthesis of **1**. Even though it seemed an easy task judging from the apparent simplicity of the target molecules many challenging difficulties had arisen during those many years. For this reason the synthesis's description of **1** can really bring some insight.

The straightforward strategy (scheme 3.21) would be to do a direct bromination followed by an elimination.[22]
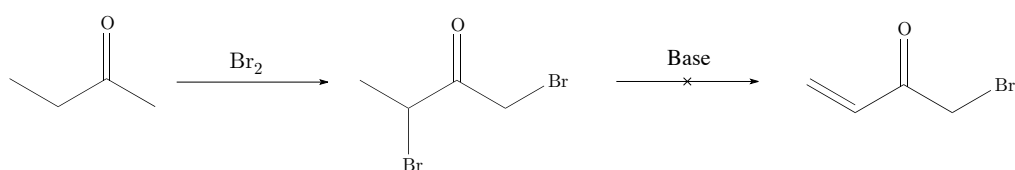
Scheme 3.21 Impossible direct bromination followed by elimination

The alpha bromination of ketones has always been a delicate task.[23] It is worth mentioning that publications on this topic are still regularly published.[24] Under acidic conditions (Scheme 3.22), bromo-subsitution of methylene protons and methine protons occurs faster than at methyl groups[2c]. The reversibility of bromination in the presence of hydrogen bromide frequently leads to mixtures of

isomeric bromoketones in the reaction of unsymmetrical ketones with bromide. [25] Also since under basic condition the reaction mechanism goes via the formation of an enolate, successive halogenations are faster due to the inductive effect of the halogen that makes the other hydrogens more acidic. This cascade of step leading to polyhalogenated compounds is called Haloform reaction. (Scheme 3.23).[26]
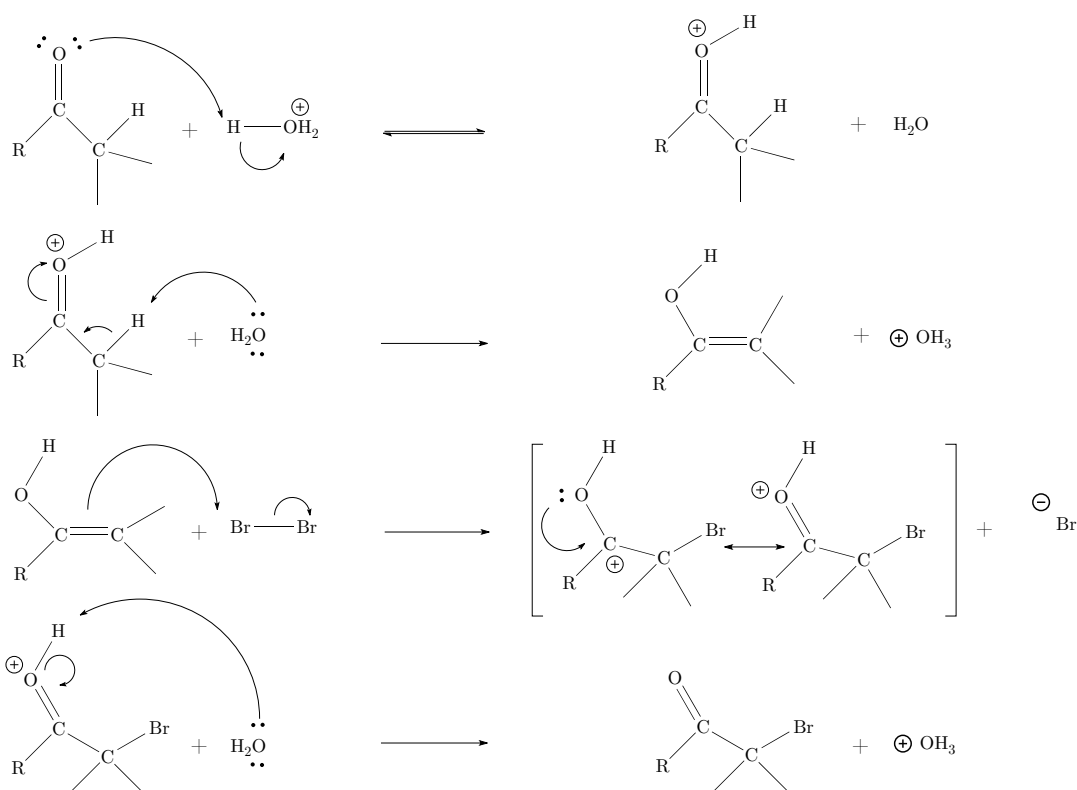

Scheme 3.22 Bromination of ketone under acidic condition

It appears clearly that those mechanisms lead often, if not all the time, to polybrominations. In the case of the methyl ethyl ketone however, the polybromination with 2 equivalents of bromine results in the desired dibrominated product and proceeds smoothly[23].
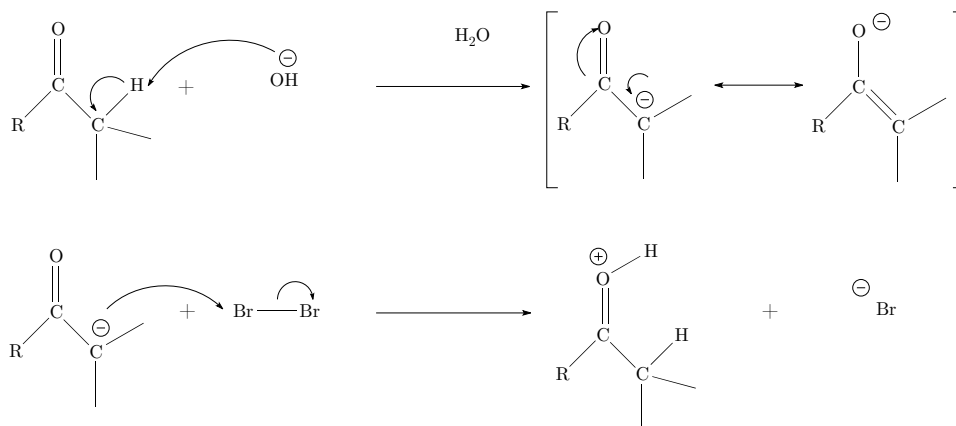
Scheme 3.23 Haloform reaction

In addition the Favorskii 1,2-rearrengement may take place (scheme 3.24).[27] The reaction of α-halo ketones (Cl, Br, I) with nucleophilic base or an amine as a base leads to an ester or an amide respectively.
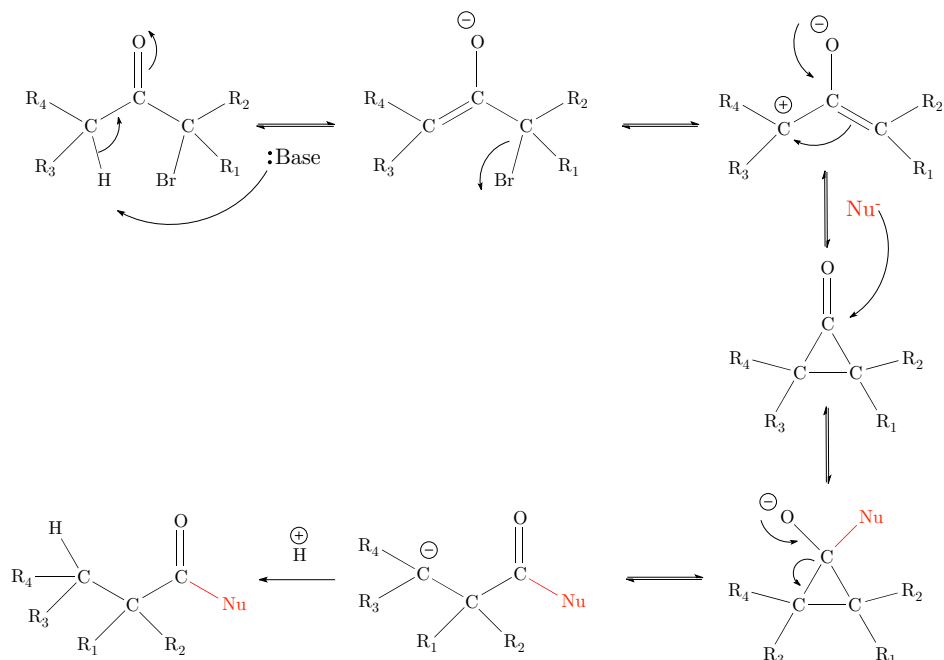
Scheme 3.24 Favorskii 1,2-rearrengement

Considering those mechanisms, another synthetic route had to be developed. For the first approach [1] the route was to prepare the 2-trimethylsilyloxy-1,3-butadiene from methyl vinyl ketone.[28] It was then treated with 2 equivalents of elemental bromine, followed by triethylamine. (Scheme 3.25) The enol would have been hydrolysed. Unfortunately it was the 1,3-dibromobut-3-en-2-one that was obtained (scheme 3.26). The discovery of this never reported molecule led to another project and finally joined the project of this thesis (chap II).
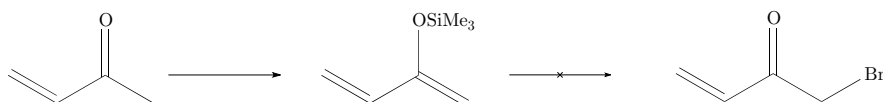
*Scheme 3.25 First approach to synthesize of **1** through silyloxy intermediate*
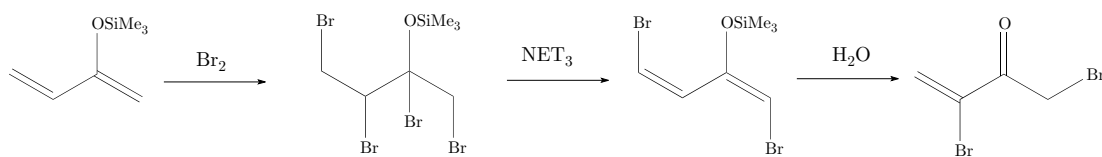
*Scheme 3.26 First synthesis of 1,3-dibromobut-3-en-2-one*

The second approach was via the acetalisation of ketones with subsequent dibromination, followed by elimination and deprotection of the ketone (scheme 3.27). The idea behind was of course to avoid the Favorskii rearrangement. Also, it was found that the acetalisation of saturated α-bromketones was, in contrast with the great number of publications dealing with acetalisation of non-halogenated ketones, an almost non-existent topic in the literature.[29] One obvious reason could be the rearrangement of α-haloketones under acidic condition.[30] Carlson et al. published a convenient general procedure[31] but the route of the general procedure for the total synthesis of the brominated methyl vinyl ketone remained unchanged; the ketone would first be protected before subsequent bromination. Since acetals are acid labile and bromination yields highly acid conditions, the chosen acetal groups should be the most stable. The reactions attempted were classical, well known and well documented.[32] But there were, once again, a lot of surprises to be discovered.
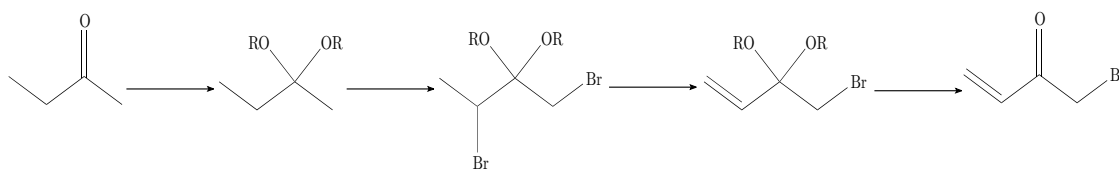
Scheme 3.27 Second approach to synthesize the bromo methyl vinyl ketone.

No problem did appear during the acetalisation of the ketone. Several methods were tested (ketal, dioxolane) with good to very good results. (Scheme 3.28)
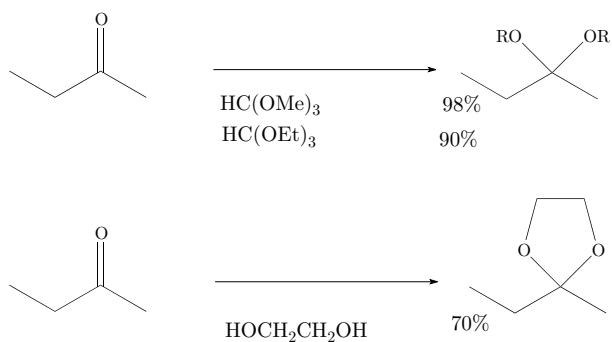
Scheme 3.28 Acetalisation of the ketone precursor.

Since the best yield was obtained using the ketal protective group, the attempts for the bromination were done on it.

Regrettably noncyclic α,α'-dibromoacetals are prone to decomposition during bromination.[33] It is believed to be due to the to the in-situ release of methanol in an equilibrium. (Scheme 3.29)
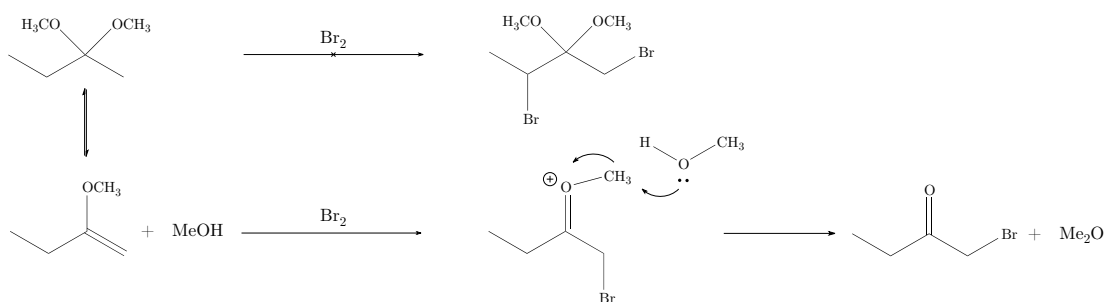
Scheme 3.29 Bromination of noncyclic α,α'-dibromoacetals

To achieve good overall yield a better procedure had to be developed for the two steps acetal protection, bromination of the methyl ethyl ketone, since only 56% overall yield of the dibrominated acetal was obtained.

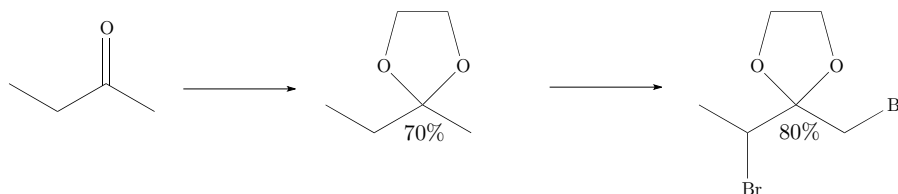
Scheme 3.30 Two-step acetal protection, bromination.

Later, methyl ethyl dioxolane (**4** cf. chap. II for notation) became available for purchasing at reasonable price. It remained then to find a good procedure for the elimination step. The yield was, at the beginning not satisfactory at all. (Scheme 3.30)

As shown in table 3.1, a large number of combinations of solvent and base were explored for the dehydrobromination (scheme 3.31), in accordance with what is usually used for this type of reaction. Most of those combinations led to unsatisfactory result.

Table 3.1 Tested bases and solvents[34]

Bases	Solvents
NaOH + PTC	CH_2Cl_2 / H_2O
KOH + 18-crown-6	Et_2O
NaOMe	Dioxane
NaOEt	$MeOCH_2CH_2OMe$
TEA	THF
i-PrNEt$_2$	Hexane
NaH	Toluene
NaNH$_2$	Xylene
LDA	
DBU	
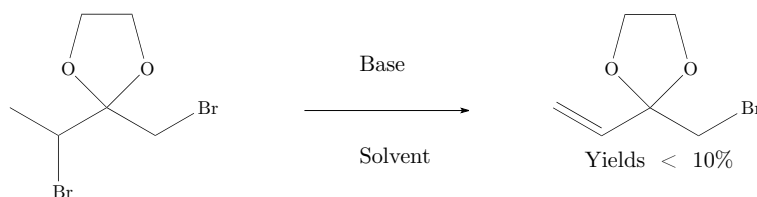
Scheme 3.31 Dehydrobromination

At last, ^{t}BuOK in THF was found to perform very well. Good yield and 100 % conversion could be obtained, but finely divided KBr formed made filtration totally impossible. Large volumes of water were needed to dissolve the bromide and extraction was not practical. Centrifugation worked only for small-scale experiments. A so called Zebrasil filtration[6] could overcome some of the problems. By alternately adding the sticky paste, resulting from solvent evaporation of the reaction mixture, and silica in a column, the filtration could be performed.

For the last step (Scheme 3.32) a conversion of 100% is necessary since the bromoketone cannot be separated from the acetal. This last step became "the Achilles heel" of the synthetic route.
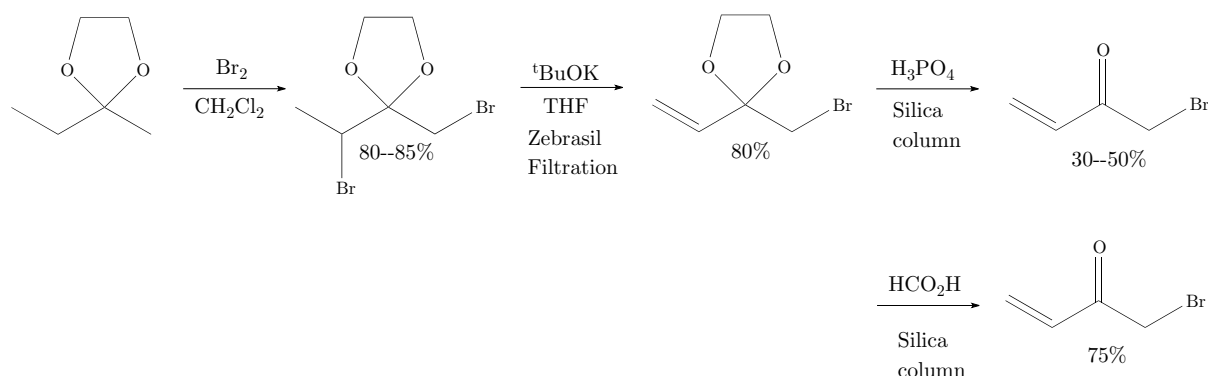
Scheme 3.32 Acetal deprotection

Whereas acetal deprotection is a very well documented reaction[35], almost no publications mention success when the acetal has a halogen in the α position (scheme 3.11).[36] Whether it is due to a lack of interest or the difficulty of such a reaction, which is probably due to the strong electron withdrawing effect of the halogen group on the acetal, decreasing the basicity character of the oxygen. [36a]

Many reaction types and reagents were tested (Table 3.2). The fact that **1** is prone to polymerization in acidic media and very unstable molecule, did bring another layer of struggle. Nevertheless, H_3PO_4 and formic acid were found to give a 100% conversion. The reaction times were very long for such transformation. The yields were low and chromatographic purifications were needed.

Finally a first procedure could be published. (Scheme 3.33).[6]

Scheme 3.33 First procedure published

Table 3.2 Different methods attempted for the acetal deprotection[34]

Reagents	Temp. (^{o}C)	Time (h)	Conversion(%)
Hydrolysis			
Wet silica	room temp.	24	0
Water, p-TsOH	room temp.	24	0
Water, NafionH	room temp.	24	0
HBr (48%)	room temp.	24	10
H_3BO_3, water	room temp.	24	5
HBr (48%), H_3BO_3	50	24	100
H_3PO_4 (85%), Et_2O	50	24	77
H_3PO_4 (42%), Et_2O	50	24	100
Transacetalisation			
Cyclohexanone, NafionH	room temp.	120	67
p-Methoxybenzaldehyde, NafionH	room temp.	72	25
Benzaldehyde, NafionH	room temp.	96	52
p-Nitrobenzaldehyde, NafionH	room temp.	96	97
Acetone, NafionH	60	24	97
$FeCl_3$/Silica 8 ww%, acetone	room temp.	24	1-2
$FeCl_3$, acetone	room temp.	24	25
Acidolysis			
Trifluoroacetic acid anhydride	0	1	black tar
Acetic acid anhydride	0	1	black tar
Formic acid	room temp.	24	100

4. Aims

The objectives of this thesis were:

- Validate, improve and scale-up the synthesis of **1 by** using cheap, commercially available starting materials.

-Develop methods that do not rely on chromatography.

- To isolate **1** in pure form.

- Develop an elegant and efficient way to synthesis **2** and **3** by a convergent route based on the synthesis of **1.**

- Synthesise **2** and **3** in pure form without any chromatographic separations.

- Investigate the target compounds as building blocks for synthesis.

- Use optimisation to improve important steps in the synthesis.

- Develop new optimisations methods for rapid identification of important experimental variables either by Orthogonal Experiments or by Near-Orthogonal Experiments

II. Results and discussion

"Simplicity is a great value but it requires hard work to achieve it and education to understand it. And to make matters worth: complexity sells better!"

Edsger W. Dijkstra

In the introduction the different strategies that led to the synthesis of **1** were presented. The main objectives of the work presented were to find a better procedure in terms of yield, convenience and time, based or not, on the previous route. As said previously, this synthesis led to one other target molecule, i.e. the 1,3-dibromo-3-buten-2-one (**2**), and later to another one, the 1-bromo-3-butyn-2-one (**3**). It was decided to have the procedure for the synthesis of **1** unchanged. Besides some undeniable flaws, it was clear the first published procedure concerning this molecule had succeeded to overcome many problems encountered previously. It would have been risky and inconsistent with the gathered knowledge to start from scratch. Since the first paper in 2001, no other papers have been suggesting another way to synthesize **1**. As a matter of fact, for some reason, in spite of the possible synthetic uses, no publications have found a use for **1**. The rather poor yield (especially for the last step), the two chromatographic separations, and the long reaction time of the last reaction could have certainly refrained many chemists. Strongly believing in its potential as a highly versatile building block we wanted to propose either a convergent multi target synthesis based on the original one, a refined procedure or both.

1.Synthesis of the compounds

1.1 Overview

The routes (roman numbers) of all the target molecules (**1**,**2** and **3**) will be used as the skeleton of this chapter and is given in scheme 1.1. Each route is explained in detail step by step (capital letters). The improvements, modifications and novelties are the summaries of the three first papers (papers I, II and III).
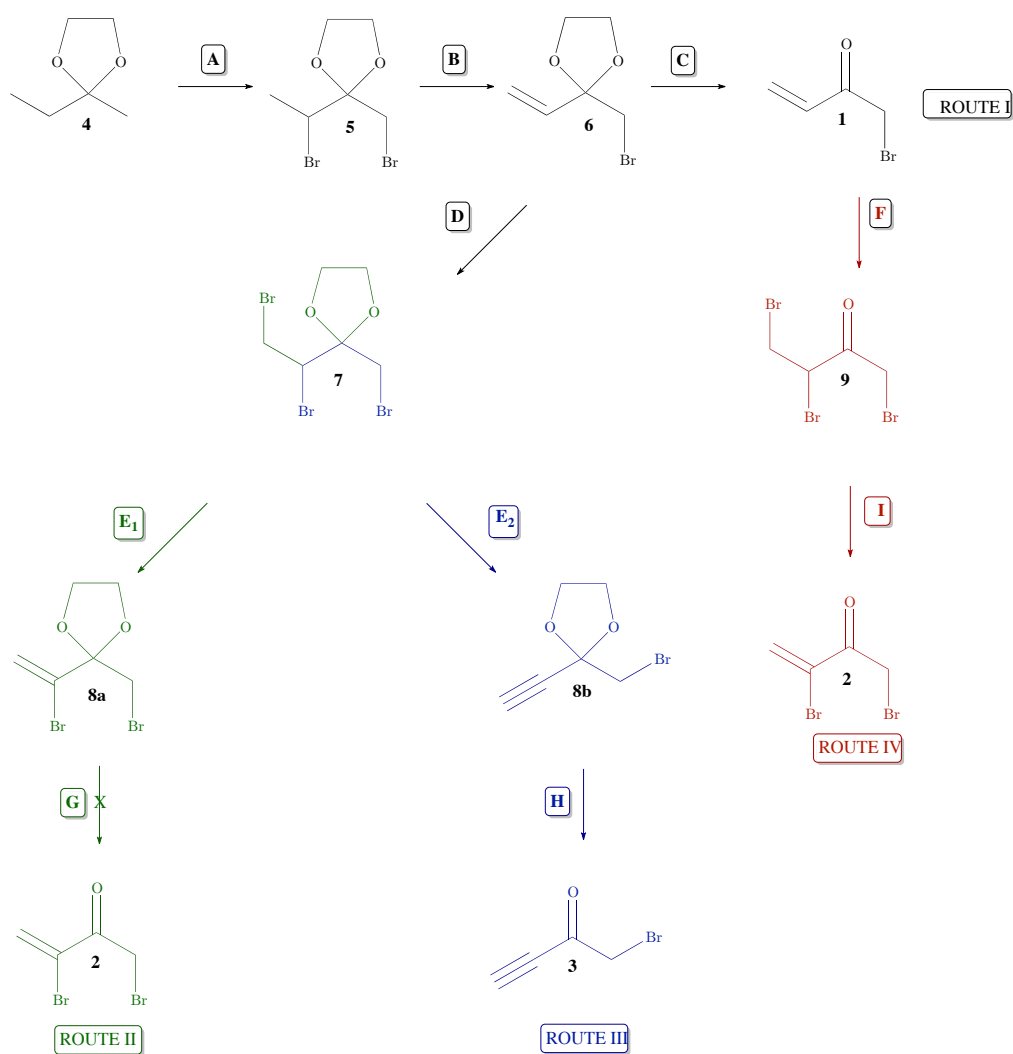
Scheme 1.1 Overview of the different routes

1.2 Synthesis of **1** via Route I

This route takes advantage of the improvements made as published in paper I, II and III. This route consists of a total of 3 steps since no satisfactory solutions were found to combine step **B** and **C** in a one-pot strategy.

The dibromination **A** in CH_2Cl_2, for which the mechanism is shown in schema 1.2, has been optimized using the method described in paper IV (chap. 3).
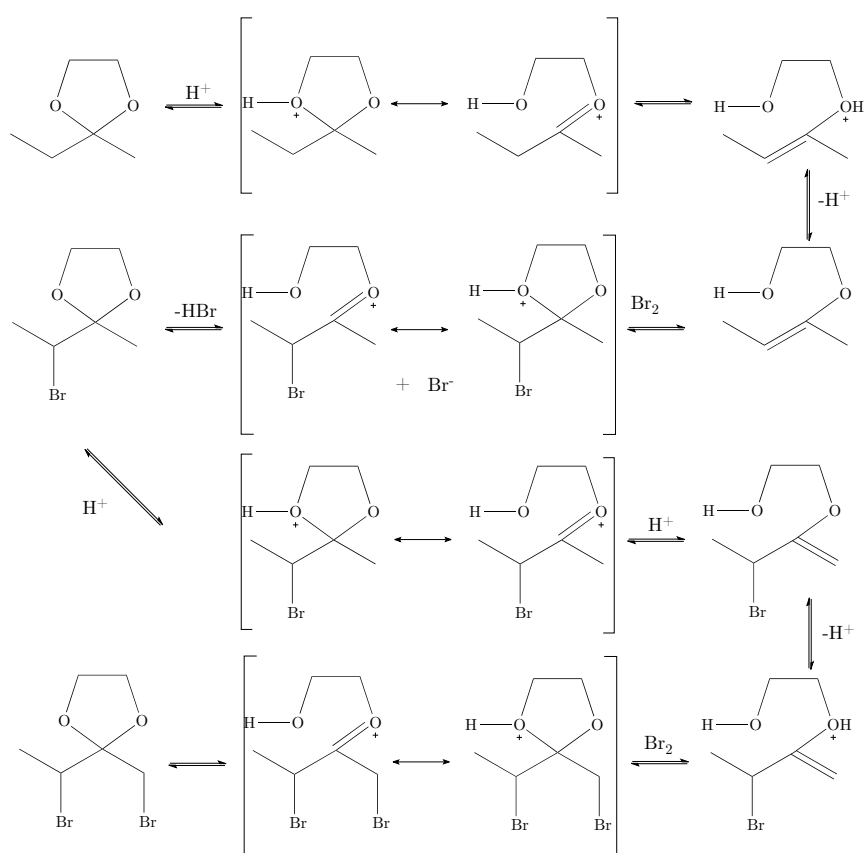
Scheme 1.2 dibromination of 4

The 98 % yield obtained is almost quantitative. It has also been scaled up to 1 mole. The important linear variable found was the temperature and the important interaction variable was between the stirring rate and the rate of bromine addition. It was scaled-up with success with no yield reduction up to 1 mole batch, i.e. 116 gr

of **4**. No further purification of the product was needed. Step **B**, a monodehydrobromination in THF with ^{t}BuOK at room temperature is a smooth reaction but had the inconvenience to produce KBr. It makes the work-up, especially when scaled-up, very difficult due to impossible filtration of the solution. KBr plugs any processes of filtration. In paper I several methods were presented to overcome this. In all of them evaporation of the solvent at first is needed. A classical steam distillation of the reaction cake can be done, but this method is time consuming, especially with large batches, but provides good yield. Otherwise the dissolution of the cake in water followed by extraction with Et_2O provided a very good and new alternative. Thanks to this method another long procedure could be avoided. Whereas large amount of water is needed, this method became the most used even with large batches. With this method, **6** is obtained in very good yield (80-85%) and in pure form. Step **C**, the acetal cleavage of **6** was the most challenging step of this route. Indeed, an acetal with an electron withdrawing substituent like bromine in the α position reacts slowly[36b]. To overcome this problem the second paper describes a procedure that takes advantages of microwave heating.

Heating a reaction in organic chemistry has always been one of the most important parameters to control. Difficult to control, undergoing a gradient from the heating source to the heart of the recipient used, several solutions have emerged. The first step forward had been the Bunsen burner in 1854 followed by its amelioration like the Meker burner. With the democratization of electricity at the beginning of the XX century other devices appeared. The electric hot plate brought a much safer way to heat but had the disadvantage to slowly change the temperature. The oil bath or the sand bath suffer also considerably of this "latency". Later, softer heating methods like the heating mantle were developed. The latter can be adapted to the shape of the reaction vessel. Even more recently Teflon mantle with integrated thermocouple plugged to a calculator succeed in giving a greater control over the temperature variation.

Nevertheless, all those methods have in common to also heat the glassware and to be less compatible (at laboratory scale) with reactions under pressure. While inorganic chemistry has been benefiting of the microwave technology since the end of the 70s, the implementation in organic chemistry is from the middle of the 80s[37]. In contrast to other technologies such as combinatorial chemistry or computational chemistry the application has been slow to be part of the routine of the chemist. Now the gap reduced and many chemical reactions are promoted by this technology. [38] In contrast, in microwave heating, the microwave energy is introduced into the chemical container remotely and direct access by the microwave radiation to the reaction vessel is achieved. The microwave radiation goes through the walls of the vessel and heats only the reactants and solvent, not the reaction vessel itself. Since most of the time the apparatus is coupled to a calculator, the temperature rise will be constant, which means less by-products and/or decomposition products. In pressurized systems, it is possible to rapidly raise the temperature far above the conventional boiling point of the solvent used.

Microwaves are electromagnetic waves and there are electric and magnetic components. Charged particles start to migrate or rotate as the electric field is applied.[39] It leads to additional polarization.[39] Because the concerted forces applied are quickly changing direction, heating happens. A Rapid heating is typically observed and if dielectric solvents are used, superheating can occur to those solvents.[40] Superheating result in that the boiling points of solvents can be raised by up to 26°C above their conventional values. [41]

The principal contributing effect seems due to a thermal effect. The thermal effect may be due to a faster initial heating or to the occurrence of narrow region with higher temperature.

So under microwave activation hydrolysis in a two-phase system performs much better than with conventional heating conditions. One of the phases is formic acid

and water; the other is pentane and Et$_2$O. This two phases system was allowed to be heated up to 100°C.

This carefully chosen two-phase system protect **1** from the aggressive acid layer and helps to displace the equilibrium to achieve complete conversion since esterification of the by-product glycol with formic acid may occurs giving bis-formate esters of diethylene glycol. This remains in the aqueous phase upon extraction. Since there is water and formic acid, it is not clear if a hydrolysis or a formolysis occurs. The formate ion is a better nucleophile than water but it may be that the consumption of the hydronium ion H$_3$O$^+$ participating to the reaction shift the equilibrium toward the formation of water, making it more available.
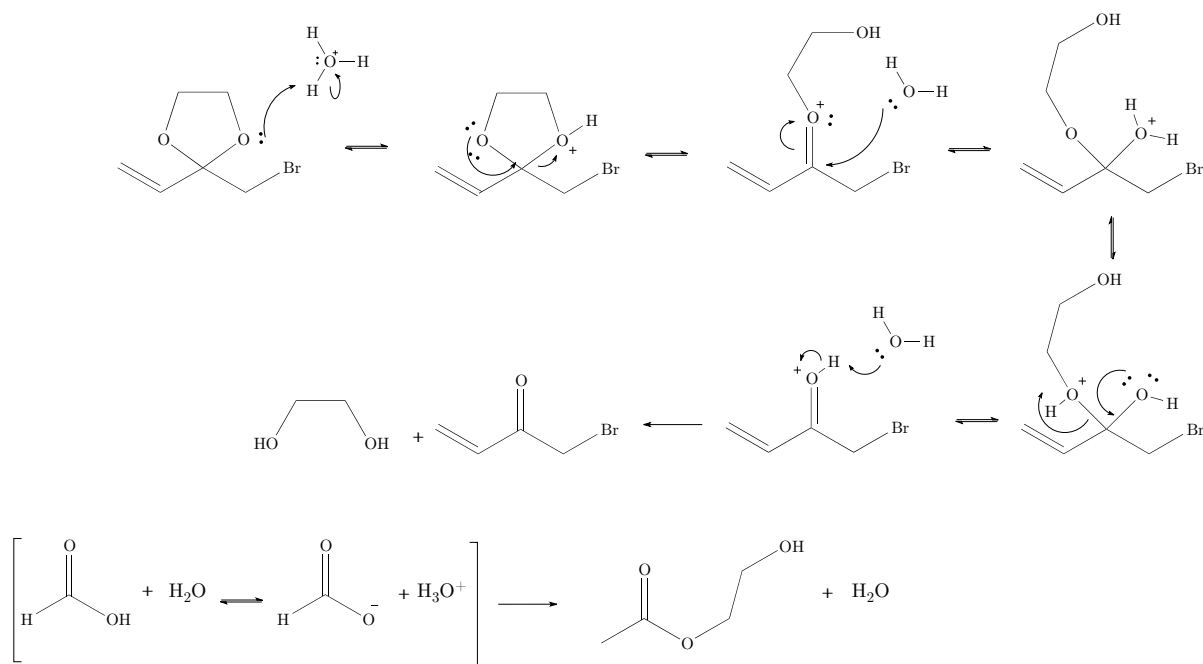
Scheme 1.3 Mechanism of acetal deprotection

The product obtained in good yield (75%) is pure enough to be used later without any chromatographic purification, is less prone to polymerization and is rapidly available from the very stable acetal precursor.

Paper III describes a simplified procedure of the use of ferric chloride on silica for the acetal deprotection. In previous papers[42] it was mentioned that the dry

heterogeneous reagent had to be prepared through several steps including dissolution of iron (III) chloride in acetone, evaporation of it and vacuum drying at room temperature for several hours. After trying the reagent and the method to prepare product with great success on **1**, the possibility to keep the reagent readily available was attempted. The chemical activity dropped drastically, making the reagent useless within two or three days. Even under inert dry atmosphere the reagent seemed to lose its activity. Also whereas "Sen and co-workers" have reported[42a, 43] that the reaction is faster when non-absorbed $FeCl_3 \cdot 6H_2O$ in CH_2Cl_2 is used, this methodology failed completely for the acetal removal from compound **6**. With the idea to develop a procedure avoiding the long preparation on absorbed silica, the heterogeneous reagent was simply prepared by mixing $FeCl_3$ with silica without solvent. After a quick stirring, the acetal also mixed in silica, was directly added. The yield obtained (80-90%)with this method was, at least, as good as the previous method. The ethereal solution obtained after the filtration of the powder was simply washed with water as sole work-up.

1.3 Synthesis of **2** and **3** via Route II and III.

These routes consist of steps **A** and **B** in common with route I as explained previously. Still with the goal to find a convergent synthesis of **1**, **2** and **3** from the same starting material in mind and having less side reactions. In publication I both good and bad results are presented. The attempts to perform step **D** (the dibromination of the double bound of **6**) and E_2 in a one-pot strategy to synthesize **8b** failed. The different addition of bases and phase transfer agents such as (*n*-Bu)$_4$NBr/NaOH, (*n*-hexyl)$_4$NBr/NaOH or (*n*-Bu)$_4$NHSO$_4$/NaOH after the bromination step D in heptane failed. Both **8a** and **8b** were formed under those conditions. When (*n*-Bu)$_4$NBr/KOH was used, **8b** was the only product but the

yields were generally not good. With solvents like CH_2Cl_2 or $CHCl_3$ carbenes could be generated upon strong basic condition during step **D**. They would react in situ with **8b** while it is formed. Also, because of high reactivity of carbenes due to high energy and its lack of selectivity, no addition of scavengers could avoid this. It is also well known that THF has never been a suitable solvent for bromination.[44] Bromine reacts in an oxidative process (violently if the two species are not solvated) with THF to produce γ-butyrolactone. [44] The one-pot strategy was therefore abandoned.

However the selective mono or bis-dehydrobromination steps E_1 and E_2 were a success. By choosing between two different, strong non-nucleophilic bases it was possible to obtain 100% conversion of **7** into either **8a** or **8b**. With one equivalent DBU in THF at room temperature, **7** could be monodehydrobrominated in good yield. With a bit more than two equivalents of ^{t}BuOK in THF at room temperature, **7** could be bis-dehydrobrominated in good yield. Luckily enough ^{t}BuOK's pKa was too low to deprotonate the acidic proton of the acetylene.

This strategy remained unchanged from this point.

For step **G** and **H** the attempts to cleave the acetal with Lewis or Brønsted acid were not successful. Aqueous boric acid did not work at all. Transacetalisation [45] did not work either. The first paper of this thesis describes a modification of the first method published. [6] It uses the same formolysis reaction but it was found that a two-phase solvent system with pentane would protect the product from the aggressive acidic layer. The reaction temperature could also be raised, thus decreasing the reaction time from 24h to 6h. This method gives a good yield (74%) for deprotecting **8b** but the product obtained contains impurities and polymerizes very rapidly. Unfortunately this reaction works only with **8b** to produce **3**. All attempts to deprotect **8a** lacked success. Subsequently, when the microwave-assisted deprotection was developed (paper II), experiments on **8a** and **8b** were made. With the same procedure no reactions occurred with **8a**. This method, which revealed itself to be

very efficient for the deprotection of **6** and **8b** (74% yield), was not adequate to deprotect the dibrominated acetal.

Since **8a** has two bromines in the α position on either side of the carbon with the ketal group, one can explains this failure due to strong electron withdrawing effect of the bromines.

Attempts to use formic acid alone or with pentane at different concentrations/temperatures resulted in a hypothetic very fast decomposition of 2 in situ. Neither the product nor the starting material could be retrieved.

Those routes became fully available when the $FeCl_3$-SiO_2 procedure was proven successful also for the acetal deprotection on **E₁** with a yield of 70-75%[1]. A part from a longer reaction time and a slight lowering of yield, a universal method was finally accessible for the acetal deprotection.

1.4 Synthesis of **2** via Route IV

This route was attempted before the other method had been developed since the acetal deprotection of **8a** was reluctant to all methods applied. Through step **F, 1** was smoothly brominated into **9** in CH_2Cl_2 at 0°C. **9** was obtained in very good yield (94%) and good purity. On the other hand step **I** turned out to be more challenging. **9** treated with weak amine bases gave no conversion and when treated with strong bases like DBU, alkoxides or hydroxide it gave a mixture of several products due to decomposition and Favorskii rearrangement. But when treated with Li_2CO_3/12-crown-4 in THF **9** could be isolated in poor yield (31%) after 24h. The very low solubility of Li_2CO_3 in THF made the use of crown ester necessary. This route became obsolete when $FeCl_3$-SiO_2 was found to work for **8a.**

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[1] The yield reported in paper III for the deprotection of **E₁** is not correct.

1.5 Final overview

The following general route can be summarized this way (schema 1.4). It is much more efficient in terms of yield and purity than the previous one. The route is now completely convergent. No chromatographic separations are needed as well as any distillations. All the reaction times are very short. All the reactions could be scaled-up up to a satisfactory size to be practical for a chemist exploring their synthetic uses. Planning experiments with **1**,**2** and **3** would become much easier and the product is available immediately after the deprotection. **1** and **3** are also much less prone to polymerization. They can be kept for several days in the freezer free from solvent and in the absence of magnesium oxide. Due to its chemical nature **3** remains much more unstable. For the synthesis of **1** the microwave-activated formolysis remained the most adequate solution. It is still a faster route and the possible amount synthesized is enough for several explorative experiments.
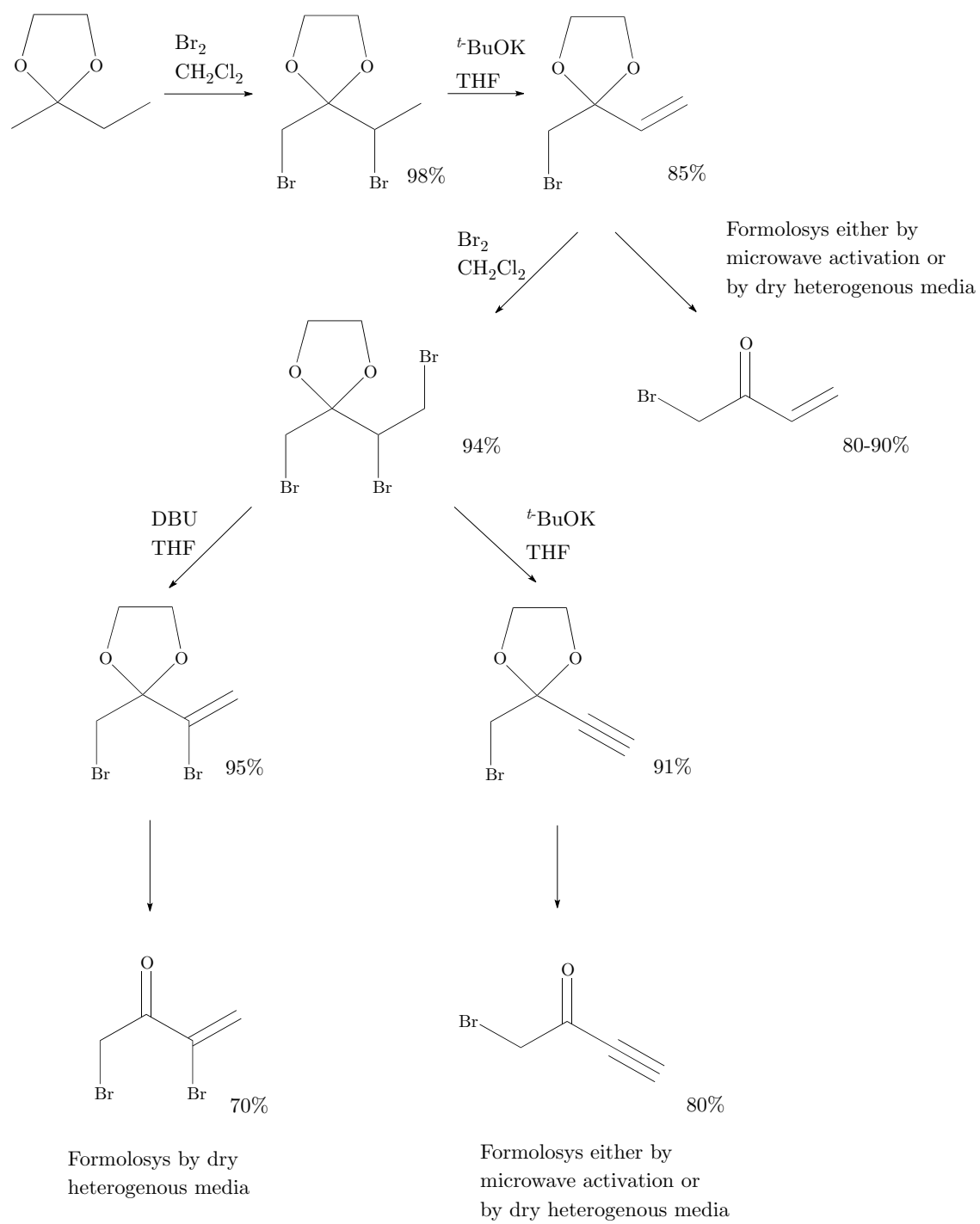
Scheme 1.4 General final route with yield.

2. Unsaturated Bromomethyl as starting material

Since 1,4 addition reaction on **1** had already being explored by A. Westerlund et al. [46], it was decided to focus efforts on different paths. Four different types of transformations were chosen. Each of them could lead to interesting molecules in a one step strategy. 1) The classical Wittig reaction was used as a model for 1,2 addition. 2) Nucleophilic substitution of bromine by sodium azide for subsequent click chemistry. 3) Concerted Diels-Alder cycloaddition on the double or triple bond and 4) their reactivity toward enamine as an example of enolate chemistry. [2]

2.1 Wittig as a model for 1,2 addition

Enynes and ynones (α,β-acetylenic ketones) have become very interesting in the past two decades. [47,48] Their conjugated systems are prone to undergo various metal catalysed reactions, metathesis, ring closure and their synthesis are sometimes complex. A simple one step functional group conversion from the carbonyl of **3** to a methylene would form an enyne with bromine in the α position. This specie has never been described in literature. The same conversion on **1** would lead to a bromomethyl substituted 1,3-diene rarely described. [49]

It is described that the Wittig reaction, or related olefination, [50] (scheme 2.1) are known to proceed very poorly with α,β-unsaturated ketones. [51] In most cases the

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[2] The author would like to mention a detail concerning the period of the explorative chemistry. The department of chemistry of Tromsø had at that time no HPLC, elemental analysis, UHLPC, GC-MS and only one very old GC with very few different columns to choose from. Several departments shared the NMR when this one was not shut down for some time. Arrangements between other departments could not provide free or frequent access to the missing equipment. Many reactions investigated resulted in complex mixture almost impossible to separate. Very little information could be gathered in order to decide if a reaction showed promising results. At last the group working on this project was uniquely one PhD student after the first year. Obviously no knowledge or advice could be gathered with other chemists on the subject.

attack of the Wittig or related reagent occurs as a 1,4-conjugate addition during the first step of the reaction. This is partly due to the decrease in electrophilicity of the carbonyl function when conjugated. Since a 1,2-addition is necessary in order to produce the olefination of the ketone, the results do not produce dienes. Often, in the best-case scenario, a mixture was obtained.


$$R^1R^2C\text{-}X \qquad \overset{R^3}{\underset{R^4}{C}}{=}O \longrightarrow$$

$$^1R^2RC\text{---}CR^3R^4 \qquad \text{and/or} \qquad ^1R^2RC\text{---}CR^3R^4$$

X= PR_3	Wittig
X= $P(O)R_2$	Horner-Wittig
X= $P(O)(OR)_2$	Wadsworth-Emmons
X= sulfur containing	Julia
X= silicon containing	Peterson

$$^1R^2RC{=}CR^3R^4 \quad + XO^-$$
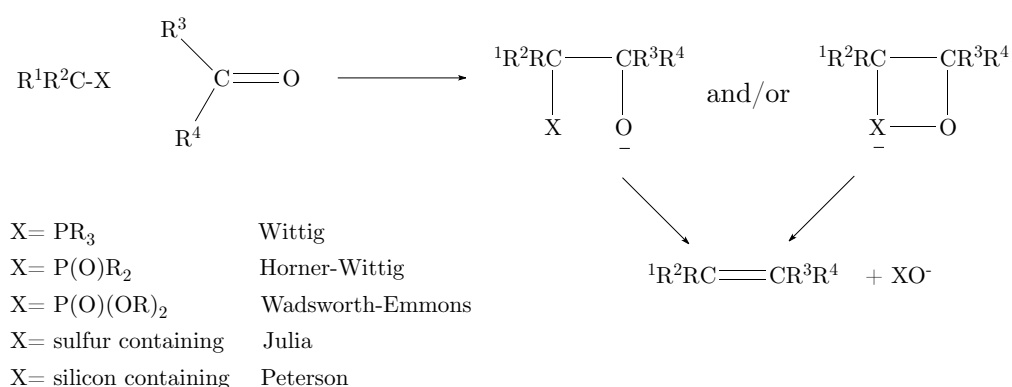
Scheme 2.1 The main different reaction for olefination of ketones.

Some of the few papers in the literature[52], which succeed to selectively have only the 1,2-addition, were, for most of them, using α,β-unsaturated aldehydes .[53]

Nevertheless many attempts have been made to produce diene from **1** based on the most pertinent publications that provided different modifications. Most of them deal with the use of NaH to form the Wittig or related adduct. All the experiments were unsuccessful. Compound **1** being much more reactive than the unsaturated ketone used in the publications it has not even been possible to obtain the 1,4 Michael addition type product. At very low temperature no reaction occurred. Raising it slowly led to nothing or to too many products according to GC.

2.2 Click chemistry following nucleophilic substitution.

One of the very useful reactions for mol. **1**, **2** and **3** could be the click chemistry.[54] The displacement of the bromide for an azide which then reacts with a alkyne to give 1,4-disubstituted 1,2,3-triazoles with substituents not previously incorporated on it (fig. 1.1). Leading the way to new reactions like Michael addition, Robinson annulation[55], coupling reaction, Diels-Alder and Wittig derivatives.
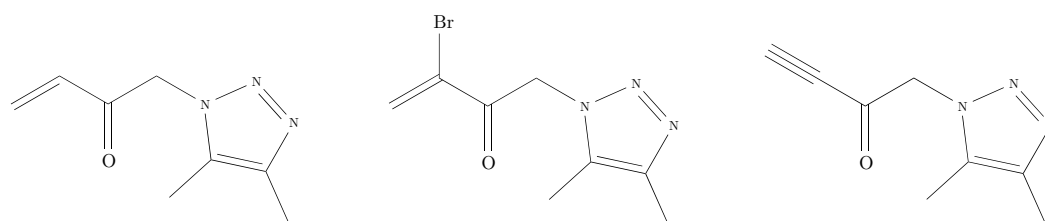
*Fig. 2.1 Possible products from click chemistry on **1,2** and **3**.*

At the time of the trials the only molecule available was **1**. Many attempts were made, (mainly in a one-pot strategy in order to consume faster the intermediate moieties)[56] but the outcomes of those different methods were never conclusive. High dilution, great variations of temperature, different solvent, order of addition or phase transfer catalyst[57] in order to have lower amount of nucleophile available to avoid selectively problem between the 2 nucleophilic sites in competition. The lack of GC-MS in the laboratory didn't simplify the interpretation of the results. Simple GC or TLC detected many products in each experiment. The close retention times suggested that separation would be in vain. Being in a way blind, the effort to optimize the rate of one of the product could lead to nowhere. It seems that nucleophilic substitution of the bromine competes with other reaction after this one occurred since the strategy to perform the substitution on the protected ketone does not work at all. Indeed, the ketal group can be considerate as bulky as a neopentyl

group and so prevent reactions that need a certain special geometry to take place. This steric hindrance on such small molecules sometimes can be either beneficial or in this case very cumbersome. In this case it prohibited all possibilities to perform what was wanted. Nucleophilic substitution on the bromine was not pursued further.

2.3 Diels-Alder reaction.

Diels-Alder reaction on **1**, **2** and **3** with the simplest possible diene, i.e. butadiene, in order to easily access new molecules never referenced (cf. Scifinder in April 2015) (Fig. 2.2) have been performed with success in our lab. Whether or not those products can be synthesized in a simpler way (which certainly exists) was not of interest or relevant. The main idea was to have a general picture of the reactivity of the starting materials as a dienophile and to see if a major product could be isolated without any focus on the regio- or enantioselectivity. After many failed attempts a procedure with Lewis Acid in CH_2Cl_2 was developed. The smoothness and the outcome vary according to the starting material but a general method was possible to setup. The problem arose from the ease of polymerization and sensitivity to temperature of the products upon heating.
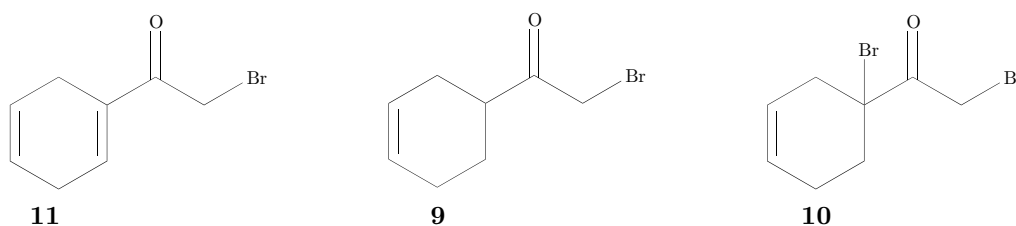
Fig. 2.2 Outcome of Diels-Alder chemistry on ***1, 2*** *and* ***3***.

The procedure had to perform well under mild condition that can be unfavourable for a Diels-Alder reaction with a diene without any electron donating groups since

generally, Diels-Alder reactions only proceed at a good rate when either diene or dienophile is activated by an electron donating or withdrawing substituent respectively.

As expected, no reaction occurs when the sole reagents were added together. The next reactions were done in presence of water or just water.[58] The outcomes were a mixture of several compounds. The use of a chaotropic salt[59] to reduce a bit the hydrophobic interaction caused by water (it was assumed the water was forcing too much the reaction) was also unsuccessful. Only Lewis Acid (LA) catalyzed reaction remained. Under normal conditions their Frontier molecular orbital (FMO's) was too far apart to be transformed into a Diels-Alder adduct. With LA in organic solvents accelerations are of the order of 10^4 to 10^6. The beneficial effects of LA are for reagents containing Lewis-basic sites close to the reaction center, like the ketone group in the target molecules (TM) of this thesis. Coordination takes place at a lone pair on one of the reactants and, hence, has a $\eta1$ σ-character.[60] The solvents for these processes are apolar such as dichloromethane, cyclic alkenes or benzene. Protic solvents and water must be avoided because of their strong interactions with the catalyst and the reacting system. But it has frequently been reported [61] that Lewis-acid catalyzed 4+2 cycloaddition reactions can sometimes benefit from the presence of water as a co-solvent [62] as long as the most active Lewis acids such as $TiCl_4$ and $AlCl_3$ are not used. Those modifications were discarded since water turned out to have negative impact on the TM.

Efforts were then focused only on Lewis-acid catalyzed reactions. The enormous amount of publications dealing with this subject and the large number of LA would make the trials very precarious without a good methodology of selection strategy.

Carlson et al. referenced [63] a set of 20 descriptors compiled from different source for 116 different LA in a principal components analysis (cf. chap III). The idea behind is that the systematic variation of those descriptors can be described by only two of

those, t_1 and t_2, in a loading plot. Thus, a suitable 2 dimensional spread of all properties is done. This projection can be used to select suitable candidates. In this case, acids found on the periphery of the loading plot will give a maximum of dissimilarities. A subset of nine LA were then selected and tested. $AlCl_3$, $CoCl_2$, $MnCl_2$, PCl_3, $SiCl_4$, $SnCl_4$, $TiCl_3$, $TiCl_4$ and $ZnCl_2$.

Among those $SnCl_4$ revealed to be rather efficient and most importantly could perform with **1**, **2** and **3**. Others, like $AlCl_3$, performed mainly just with **1.**

A rapid optimization with three variables (amount of diene, temperature, amount of catalyst) using an internal standard calibration with GC area of the product as response was done.

The reaction performs best at room temperature with three equivalents of butadiene and 0.2% mol. equivalent of catalyst.

The reactivity and the lack of of by-products follow this order. **1** gives the best result, followed by **3** and finally **2.** It is worth mentioning that even though the 3 SM are unstable molecules, **2** is by far the most unstable and the hardest to isolate in pure form. This can maybe explain the results.

The spectra presented in the appendix are given after only a simple work-up without any kind of purifications. It shows the feasibility of those reactions and shows that almost a major product can be synthesized.

2.4 2+2 cycloaddition of **3** with enamines as enolate chemistry.

Once the synthesis of **3** had met the requirements for having it in good yield and satisfactory purity, it was possible to start exploring its synthetic use in reaction. It was decided to focus the research on the possibilities that could produce the conjugated ynone. Being an electron poor acetylene group, it should undergo reaction like 2+2 cycloaddition with electron rich functionalized groups. Given the large quantity of chemical groups meeting this requirement (enamines, enamino esters,

substituted β-aminoenones...). Those reactions are important strategies for natural products synthesis, well documented and their variations are numerous. (Scheme 2.2)[65]. However no publications mention the use of ynone with a halogen in the α position of the carbonyl group.

In order to determine the synthetic scope of this compound its reaction with enamines was investigated. Introduced by Gilbert Stork[64] they can be considerate as virtual enolates. Their structure may be regarded as a resonance hybrid. Electrophilic reagents can attack at either the nitrogen atom to give ammonium salt or the carbon atom in β position of the nitrogen to give an iminium salt. Enamines are also easily hydrolysed by acid to give ketones or enols. Commonly used for reactions are the enamines made from cyclic ketones with pyrrolidine, piperidene or morpholine as substituents. (Fig. 2.3) According to the electrophile used, it yields often interesting bridged ring or polycyclic products. However no publications mention the use of ynone with a halogen in α position of the carbonyl group.
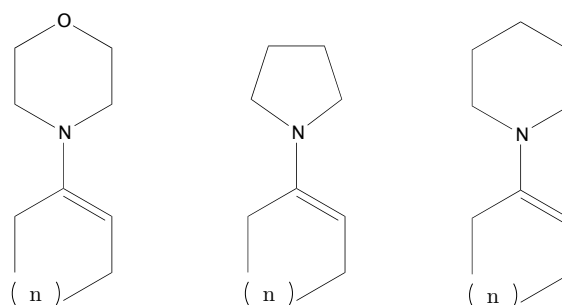
Fig. 2.3 Commonly used enamines for synthetic applications

For example by reacting halogenated unsaturated methylvinylketone with enamines generated from cyclic ketones, Danishefsky and al.[66] obtained a [4.3.1]-bridged ring system product through an α, α' annulation.

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They explained it as a cascade reaction of a Michael addition, a proton transfer and a nucleophilic attack with expulsion of the halogen. The hydrolysis of the iminium salt gives the [4.3.1]-bridged ring system product. (Scheme 2.3)
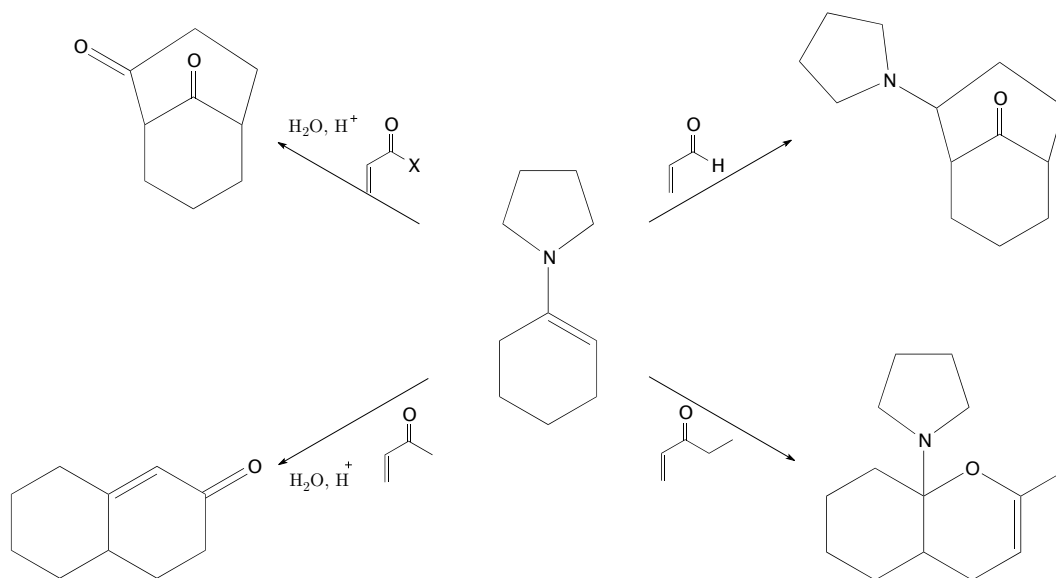
Scheme 2.2 Different outcomes from enamines and unsaturated ketone as electrophile.[65, 67]
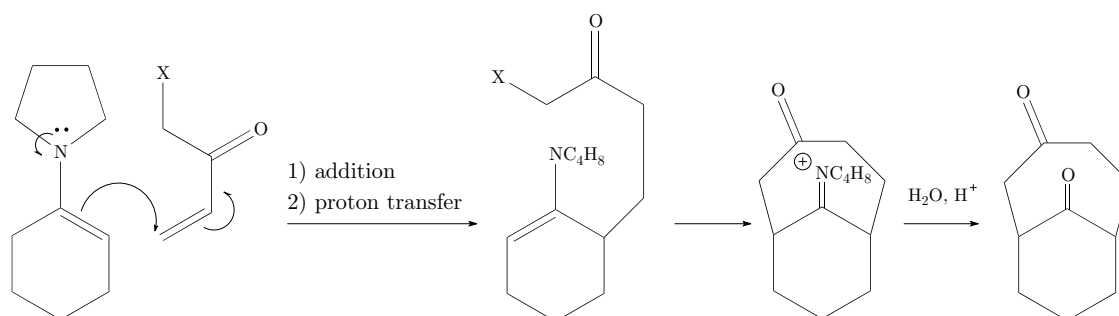
Scheme 2.3 α, α' annulation[66]

Having no interest in repeating this reaction with **1** with the sole goal to get better yield (they only tried both with chorine and iodine as X), it was found more pertinent to try it with **3** in order to get a conjugated double bond in the newly formed ring. This would provide an extra functionalization for further transformations (Scheme 2.4).
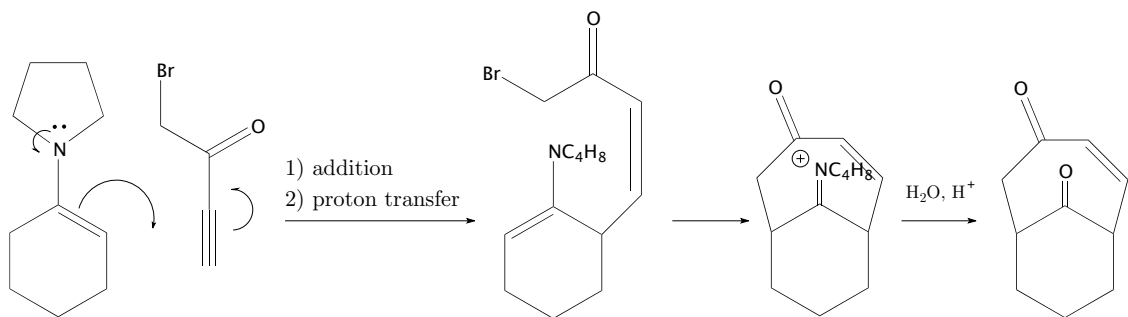
*Scheme 2.4 Possible **α, α'** annulation with **3***

Since a competitive 2+2 cycloaddition yielding a cyclobutene that can undergo a rearrangement, often with ring enlargement may occurs[68], (scheme 2.5) the possibility to find conditions to choose between those two paths was investigated.
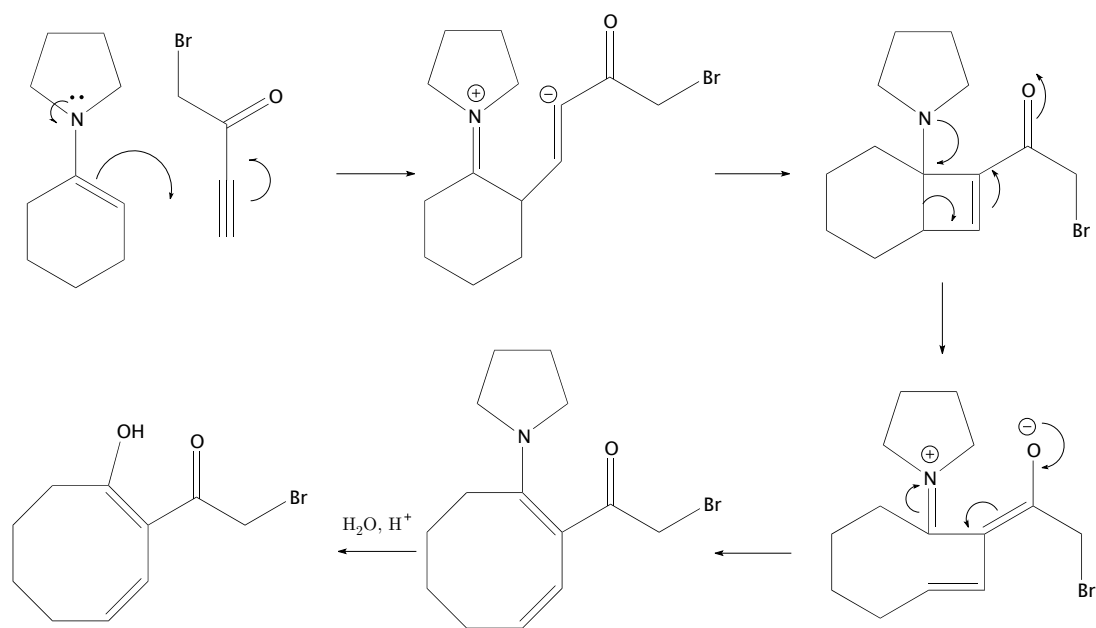
Scheme 2.5 Possible 2+2 cycloaddition followed by ring enlargement with 3^{68}

Literature describes[69] methanol or other protic polar solvents as good media for initial nucleophilic addition[70] followed by proton transfer from the enamine to the acetylene triple bond. Also, due to the degree of ρ-π overlap between the nitrogen lone pair of electrons and the double bond, the nucleophilicity of the enamine double bond changes depending on the substituent on the nitrogen group. For example the more effective ρ-electron donating pyrrolidine group enhances the nucleophilicity of the enamine double bond by increasing the electron density and so promoting the formation of the cyclobutene moiety, with pyrrolidinyl enamine as exception since it leads to pyrrolizine derivatives. But it also seems that the reaction of less electron-rich alkenes (Morpholine vs. pyrrolidine) with less electron-deficient acetylenes (ynone vs. propiolate) for which the interaction of the LUMO of the acetylene and the HOMO of the alkene can dominates.

Enamines from cyclic ketones react with ethyl propiolate, dimethyl acetylenedicarboxylate (DMAD) or dimethyl acetylenedicarboxylate (DEAD) in-situ

to give an intermediate cyclobutene adduct which in some cases may be isolated. On heating those cyclobutenes, undergo, if not too unstable, bond rearrangement with expansion of the cyclic ketone ring by two carbon atoms. Sometimes treatment with cold dilute acid results in a second reaction pathway to form Michael-type adduct of the ester and cyclic ketone.

However, the rich literature dealing with this subject describes the outcome as very dependant of the solvent, temperature, the size of the ring and the substituents on the nitrogen and hence gives a lot of different by-products that are difficult to identify. Each combination may give a large variation in products making the choice even more delicate.

Nevertheless, no paper describes those reactions with acetylene having a halogen in the α position of the activating group (those types of reactions are mainly done with propiolate or dimethyl acetylenedicarboxylate).

During the course of the experiments several solvents, temperatures and enamines substituents were investigated. As described, the results were often inconsistent and it became difficult to draw any kind of conclusion.

Moreover all the intermediates were unfortunately unstable and with some few exceptions decomposed upon work-up giving no chance to know whether or not it was mainly a Michael addition or a 2+2 cycloaddition as the initial step.

Since the α, α' annulation or the Michael-type moiety requires the hydrolysis of the intermediate (iminium salt or the cyclobutene) 1N HCl solution was injected in-situ to see if the hydrolysed product would be more stable.

Using Et_2O as solvent, 4-(cyclohex-1-en-1-yl)morpholine as enamine at room temperature it was possible, upon in-situ hydrolysis, to get a somehow stable pure compound. But the NMR spectra were not consistent with a product supposedly

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formed from neither the hydrolysis of the cycloaddition[71] nor by nucleophilic addition. The ^{1}H NMR spectra as well as the ^{13}C NMR spectra revealed nevertheless that the bromine had disappeared somehow since typical chemical shit for CO-CH$_2$-Br was not observable. Also, direct analysis of the reaction mixture with MS/MS orbit trap before addition of HCl revealed the presence of a moiety having the mass corresponding to C$_{14}$H$_{21}$O$_2$Br (314,07 **g.mol^{-1}**).

The infrared spectrum showed two strong absorption bands typical for ketone and for C=C-O.

Since Et$_2$O was the solvent it seemed more reasonable to assume that the first step was a cycloaddition.[72]

After resolution of the structure by 1D and 2D NMR spectra a mechanism has been proposed. It may be the hydrolysis of the cyclobutene intermediate that could lead to the final product. The first step would be the hydrolysis of the cyclobutene double bound. Then an equilibrium between the ketone and the enol in acid media would lead to the protonation of the morpholine moiety, making it a leaving group resulting in a reverse Michael addition. The ring opening of the cyclobutene after rearrangement leads to form a bromo hydroxymethylene methyl ketone. A ring closure via nucleophilic substitution under acidic condition generate, as sole product at average yield, a rather exotic 3-(2H)-furanon-yl linked to a cyclohexene (**12**) (Scheme 2.6).
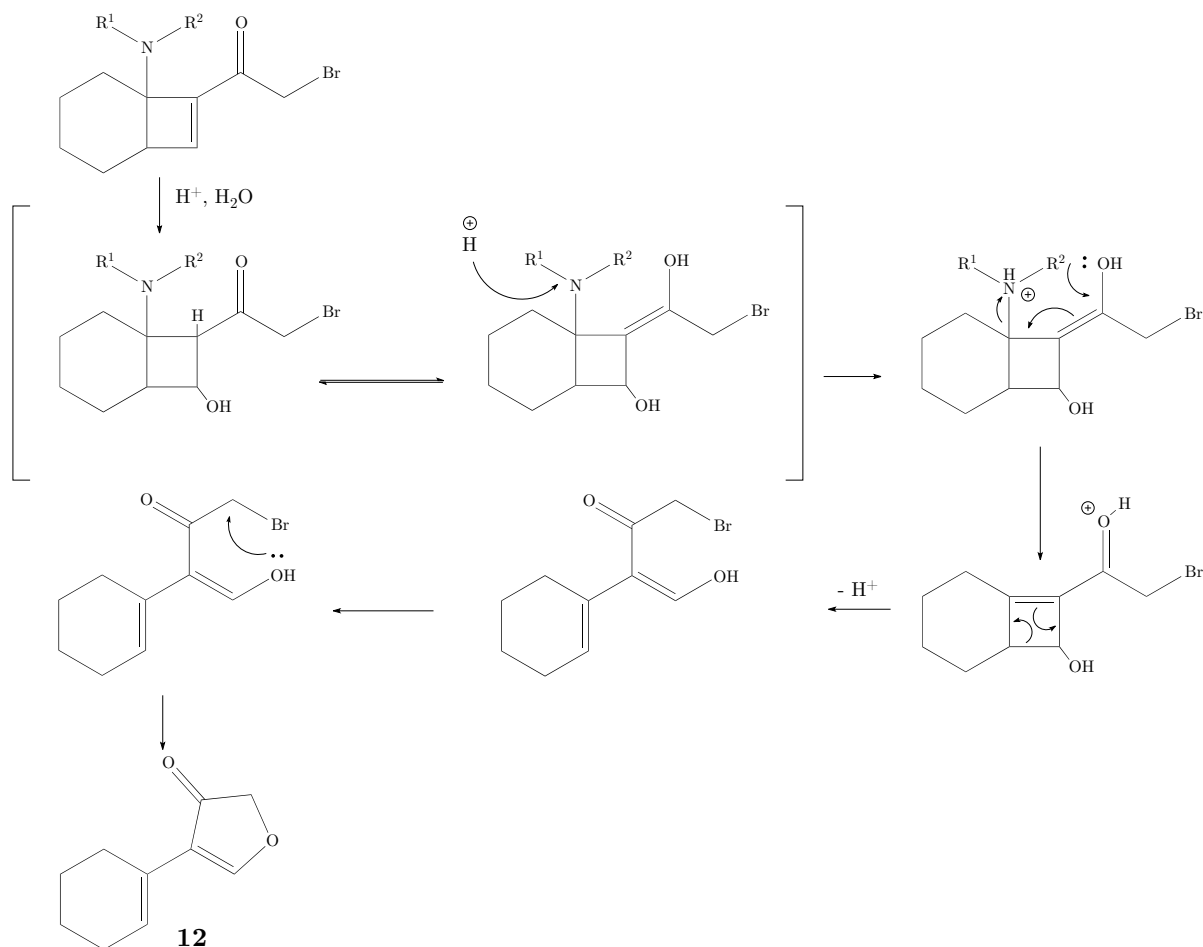
*Scheme 2.6 Proposed mechanism yielding to **12***

Branncock et al.[68] mentioned another mechanism specific to the enamine made from cyclohexanone that could lead to same product upon hydrolysis. (Scheme 2.7) It supposedly goes through the addition of a secondary amine, which would have to be present in only trace amounts, to the intermediate bicyclooctane, followed by elimination of the bridgehead amine group with subsequent rearrangement into an enaminones chain and regeneration of the secondary amine (in that publication it was only the pyrrolidine group explored as amine substituent). This proposed mechanism to explain an exception to the typical $+2$ ring enlargement seems unlikely. It is questionable if the pyrrolidine moiety can rearrange by proton transfer to become a leaving group.
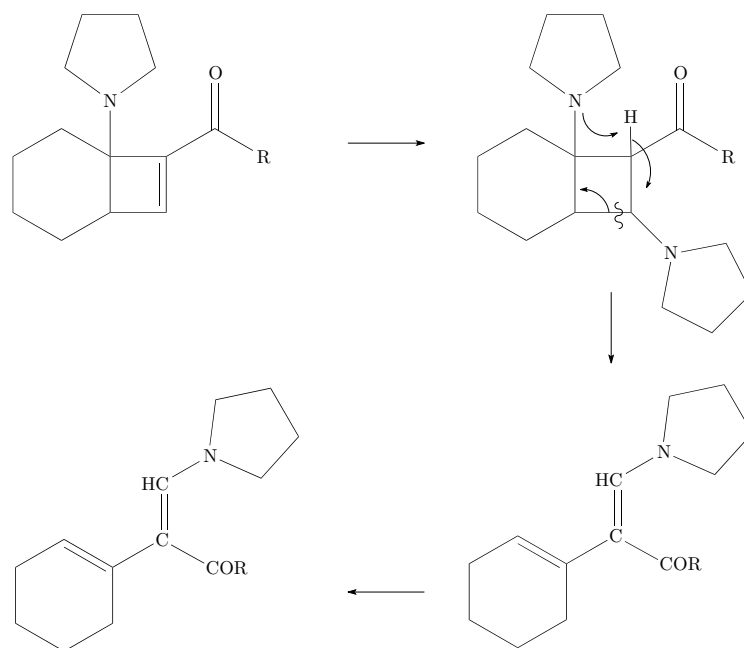
Scheme 2.7 Proposed mechanism by Branncock et al.[68]

Morpholine being less basic than pyrrolidine could explain why, under mild acidic condition, it is first the double bound that is hydrolysed. It could also explain why this reaction gives satisfactory results with morpholine as substituent and not with the others.

The experience was repeated with enamines from cycloheptanone and cyclooctanone. In the case of cycloheptanone derivative the reaction proceed in the same way to give a 3-(2H)-furanon-yl substitute link on a cycloheptene (**13**). The resolved NMR pattern from the first reaction was present as the major produc.This molecule was very sensitive, prone to fast decomposition with no possiblities of purification. A problem since the product was also polluted with some cycloheptanone and a third product which gives two doublets in the NMR spectrum, one at 7.64ppm and one at 5.51 ppm (j=12.7 Hz) which was attributed to 1-bromo-4-hydroxybut-3-en-2-one. The former was <u>not</u> coming from the hydrolysis of uncomsumed starting material

since great care has been made to monitor the reaction. Up to now all the efforts to avoid this contamination were unsuccessful and the reason why it appears during the hydrolysis is obscure. The latter one was also reported (albeit with other substituent) as a by-product in similar reaction when morpholinyl cyclique enamine was used at low to room temperature. Again attempts to perform the ring expansion or avoiding by-products by heating the intermediate led to the destruction of the adduct. Moreover, the outcome of this reaction suggests that the reaction goes via the mechanism proposed in this work.

With the cyclooctanone enamine derivative the reaction procceeds in two different ways depending to the solvent, but in both case the products are +2 C ring enlargement.

In Et$_2$O at room temperature it undergoes the expected +2 C ring enlargement plus subsequent ring closure under acidic condition to generate in average yield the 3-(2H)-furanon-yl substitutent link to a cyclodeca-1,3-diene (Scheme 2.8).
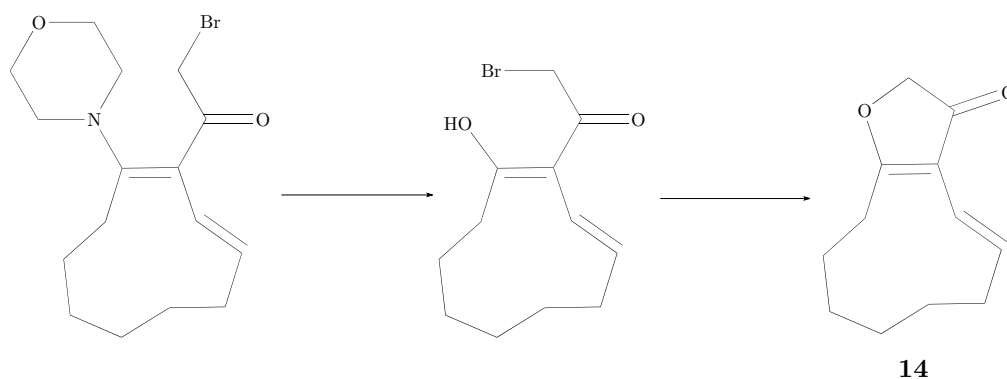
*Scheme 2.8 Formation of **14***

In THF at room temperature the +2 C ring enlargement does not undergo subsequent ring closure (Scheme 2.9). The possible conformation of the intermediate must have a direct implication is those contrasted outcomes.
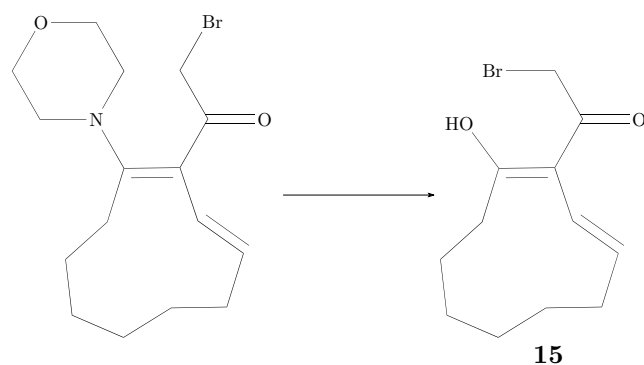
Scheme 2.9 Hydrolysis of the morpholinyl moiety

It may also be that in THF the keto-enol equilibrium shifts (Scheme 2.10) towards the keto form, avoiding the ring closure. But in CDCl$_3$ the ^{1}H NMR shows that the enolic modification is dominating as revealed olefinic by proton resonances at 6.01 ppm as a doublet of doublet and at 5.65 ppm as a multiplet.

The cyclodeca-1,3-diene 3-(2H)-furanon-yl was not soluble in CDCl$_3$ and the NMR set of data was recorded in the slighly more acidic DMSO-d_6.
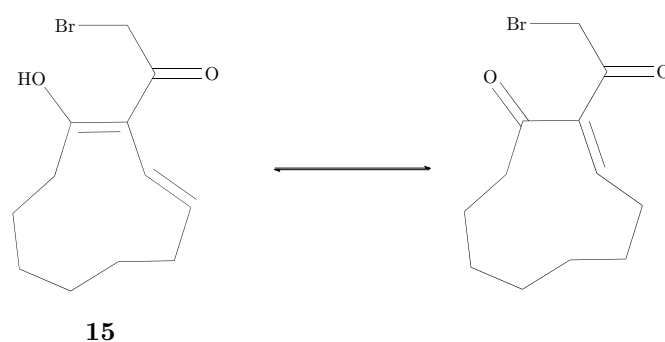
*Scheme 2.10 Tautomerism of **15***

Additional experiments with enamines from cyclopentanone could not give satisfactory results and the structure of the products couldn't be resolved.

III. Design and optimization

1. About optimization

When a chemical reaction is to be developed into a useful synthetic procedure, an early and important step is to identify which experimental variables have a real influence on the outcome and those variables that have no or negligible influence. This chapter describes different approaches to this problem.

2 Background

The outcome of a synthetic reaction depends on the energetics of the reaction system. The substrate (the compound to be converted into the product) is treated with a reagent (or a combination of agents), commonly in a solvent. The substrate interacts with the reagent and the product is formed. The substrate and the product are stable molecules and are present around in the reaction mixture. They are not stiff molecules; their bonds stretch, twist and vibrate. The substrates and reagents collide and interact with each other and with solvent molecules. Any such interaction involves energy: the stretching or bending of a bond increases the energy of a molecule; the solvation of a molecule may stabilize the molecule and decrease the energy. All these interactions will describe a potential energy surface on which the substrate interacting with its surroundings defines a minimum on the potential energy surface. The same holds for the reaction product. The substrate and the product define different minima on the potential energy surface. For a reaction to occur, the substrate and the reagents must encounter each other and collide with the correct geometry and with sufficient energy to surmount the energy barrier that separates the minima in the potential energy surface, i.e. to pass over the transition

state. The thermal motion, stretching and bending of bonds, the interaction with solvent molecules are dependent of the reaction temperature. The frequencies of the collision between molecules are dependent on the concentrations of the various species. Thus, we can say that the shape of the potential energy surface, i.e. how shallow the energy minima are and how high the energy barrier of the transition state is all depend on the experimental conditions.

In synthetic chemistry the yield of the product is an important result.
The yield can be described as an integral of the rate of the reaction over time:

$$Yield = \int_0^t (Rate) dt \qquad (1)$$

The energy barrier of the transition state determines the rate. Thus, it is determined by the experimental conditions. Consequently, it is reasonable to assume that the yield is a function of the experimental condition:

Yield = f (Experimental conditions).

Let η be the true yield obtained. It can, however, not be determined as such. Instead, we will use the experimentally determined yield, y, as an estimate of η.

The experimental conditions are defined by the settings; x_i, of the variables "I" and the yield function can be expressed as:

$$y = f (x_1, x_2, x_3 \dots x_k) \qquad (2)$$

It will be very difficult to derive an analytical expression of the function f but we can make certain assumption. It is a smooth and continuous function that is several times differentiable.

Provided that the range spanned by the variables x_i is limited, the general features of f can be portrayed by a truncated Taylor expansion around the centre point of the experimental domain, $x_1 = x_2 = ... x_i = 0$, i.e.

$$y = f(\mathbf{0}) + \sum_{i=1}^{k} \frac{\partial f(\mathbf{0})}{\partial x_i} \cdot x_i + \frac{1}{2!} \sum_{i=1}^{k} \sum_{j=1}^{k} \frac{\partial^2 f(\mathbf{0})}{\partial x_i \partial x_j} \cdot x_i x_j \qquad (3)$$

$$+ \, higher \, order \, terms + R(\mathbf{0}) + e$$

Where $R(\mathbf{0})$ is a residual term containing the left-out higher order terms of the Taylor expansion and it will contain the model error. The Taylor expansion is a polynomial of the experimental variables and the coefficients are partial derivatives of f. This function is written as:

$$y = \beta_o + \beta_1 x_1 + ... + \beta_i x_i + ... \beta_k x_k + \beta_{12} x_1 x_2 + ... \beta_{ij} x_i x_j + \beta_{11} \qquad (4)$$
$$x_1^2 + \, ... \, \beta_{kk} x_k^2 + e.$$

In which e is an error term containing the random experimental error and the deviation between the "true" response and the response predicted by the model. The coefficients of the model can be estimated by multiple linear regression /least squares fit) using a proper experimental design. Such a model is called a response surface because it describes a surface in the multi dimensional space spanned by $\{y, x1, x2, ... , xk\}$

3. Fitting the model by multiple linear regression

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In a screening experiment it will usually be sufficient to include the linear terms, describing the slope of the response surface along the different variable axes, and the cross-product terms, $x_i \, x_j$, describing the interactions between the corresponding variables. It is not necessary to include the quadratic terms in a screening model. Those terms describe the curvatures of the surface in the different variable directions and for an optimisation such features of the response surface will be important. For screening models, linear and cross-product terms, it is sufficient to analyse the variations of the experimental variables on only two levels, high and low. The "natural" experimental variable is usually scaled so that the low level is set to -1 and the high level is set to $+1$. This means that the coefficients of the model will describe how the variation of the experimental variables will influence the result. This is exactly what is wanted. An experimental design is a scheme that describes the variation of the experimental variables over a set of experiment. A factorial design[73] comprises all variation of the variable settings of all variables included. Such designs with k variables and two levels of the variable settings will contain 2^k individual experiments. With many variables it will give a prohibitively large number of runs. Their designs matrices specify the designs, i.e. the variation of the experimental variables over the set of experiments. For two variables on two levels, the design matrix will be as specified by $\mathbf{x}_1$ and $\mathbf{x}_{2..}$ (fig. 3.1)

Exp no	$\mathbf{x}_1$	$\mathbf{x}_2$
1	-1	-1
2	1	-1
3	-1	1
4	1	1

Fig. 3.1 Design matrix fro two variables.

An interaction model with two variables will be

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + e \tag{5}$$

In which e is an error term. From the terms in the model, a model matrix, $\mathbf{X}$, is constructed by appending columns of the cross-product variable $x_1 x_2.$, and a column of ones (corresponding to the constant β_0). (Fig. 3.2)

$$\begin{bmatrix} 1 & -1 & -1 & 1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & 1 & -1 \\ 1 & 1 & 1 & 1 \\ 1 & 0 & 0 & 0 \end{bmatrix}$$

Fig 3.2 Model matrix, $\mathbf{X}$, for two variables.

The experiments are then run to yield the responses. The responses define the response vector.

$$\mathbf{y} = [\ y_1 \quad y_2 \quad y_3 \quad y_4]^{\mathrm{T}}. \tag{6}$$

The Taylor coefficients are expressed as the vector.

$$\boldsymbol{\beta} = [\beta_0 \quad \beta_1 \quad \beta_2 \quad \beta_{12}]^{\mathrm{T}} \tag{7}$$

i.e. the partial derivatives of the Taylor polynomial cannot be determined experimentally due to the presence of an experimental error, but a least squares estimate $\mathbf{b} = [b_0 \ b_1 \ b_2 \ b_{12}]^{\mathrm{T}}$ is obtained by multiple linear regression.

$$\mathbf{b} = (\mathbf{X}^{\mathrm{T}} \, \mathbf{X})^{-1} \, \mathbf{X}^{\mathrm{T}} \, \mathbf{y}. \tag{8}$$

This can be extended to any design but the qualities of it will depend on *how* the experiments have been conducted.

The quality of the estimated coefficients is determined by the properties of the dispersion matrix $(\mathbf{X}^{\mathrm{T}} \, \mathbf{X})^{-1}$. The columns of the model matrix in a two-level factorial design are mutually orthogonal and the information matrix $(\mathbf{X}^{\mathrm{T}} \, \mathbf{X})$ is a diagonal matrix in which the diagonal elements, n, equal the number of experimental runs in the design. Hence, the dispersion matrix is also a diagonal matrix with the diagonal elements $1/n$. A design for which the columns in the model matrix are orthogonal is called an *orthogonal design*:

The experimental error variance, σ^2, is not known but an estimate, s^2, can be obtained by replication of one or more experiments.

The variance-covariance matrix $(\mathbf{X}^{\mathrm{T}} \, \mathbf{X})^{-1} \, s^2$, in which the diagonal elements show the error variance of the estimated model parameters,

$$V(b_0) = V(b_1) = V(b_2) = V(b_{12}) = s^2/n. \tag{9}$$

The coefficients are estimated with the same precision. Since $(\mathbf{X}^{\mathrm{T}} \, \mathbf{X})^{-1}$ is a diagonal matrix, the covariances are all zero and there are no correlations between the estimated coefficients, they are independently estimated. The square-root of the error variance, $s \, /\sqrt{n}$ is the standard error, S.E, of the coefficients which can be used to compute confidence limits for the estimated coefficients by using the t distribution. A significant variable will have its coefficient distinctively different from zero.

The value zero should be outside the confidence limits.

However, sometimes an estimate of the error variance is not available, and in such a

case a plot of the estimates as a cumulative Normal probability distribution can be used to distinguish the important variables. Thorough accounts of experimental designs are given in the book by Box, Hunter, and Hunter[74] and the book by Box and Draper.[75] The use of experimental design in organic synthesis is presented in the book by Carlson, and Carlson.[76]

4. Normal probability plots

The experimental error in synthetic experiments can safely be assumed to have a Normal probability distribution for the following reasons. The result of a synthetic reaction depends of the energy of the interacting molecules, cf. discussion above. The result recorded is not the individual reaction product molecule; it is an average property of a large number of molecules acting together. It is not likely that a random perturbation of the experimental condition will give a single molecule infinite energy. Thus, the energy distribution of the molecules in the reaction mixture will have a limited variance. The Avogadro number $6.023 \bullet 10^{23}$ is tremendously large and in any tiny sample of the reaction mixture there will be a very large number of individual molecules. Since the response observed is an average property, we can apply the Central limit theorem.

> *"If a population has a finite variance of σ^2 and a mean μ, then the distribution of the sample mean approaches the normal distribution with the variance σ^2 / n and the mean μ as the sample size n increase."*[77]

If it is assumed that none of the variations of the experimental variables in the designs have no influence on the response, i.e. the response is constant in the experimental domain and that the true values of the coefficients in the Taylor model are all zero. Due to the presence of the experimental error the recorded responses will

show a variation and the estimated value of the coefficients will be different summations of the error terms. If the error is normally distributed, the sums of errors terms will also have a normal distribution. Stipulated that the experiments have been randomised, we can consider the estimated coefficients as a random sample of a population of normally distributed errors. Since random sample is representative for the population from which it has been drawn we can assume the sample is normally distributed. By plotting the estimated coefficient as a cumulative normal distribution the coefficients that are nothing but summations of errors will be portrayed as a straight line in the plot. Fig. 4.3 shows an example.
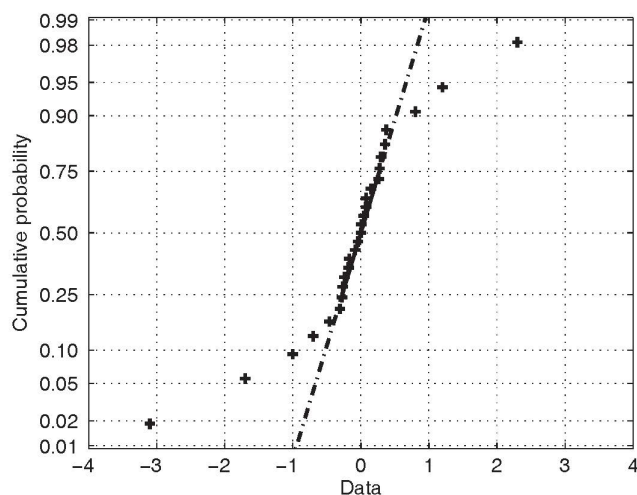
Fig 4.3 Cumulative normal probability plot of estimated coefficient.
The figure is taken from Carlson, Carlson, Design and Optimisation in Organic Synthesis, 2nd Edition with permission from the publisher.

The straight line of normally distributed noise is clearly seen but there are outliers from the line, in the upper right and the lower left part. These outliers represent something else than a normally distributed error and they are likely to represent

significant coefficients. Such plots can therefore be used to evaluate screening experiments and to distinguish significant coefficients from random noise.[78]

5. Some classical designs for screening experiments

5.1 Fractional Factorial design

A full two-level factorial design with k variables contains 2^k individual experimental runs. When k is large, this will rapidly lead to a prohibitively large number of experiments. When there are four or more experimental variables to consider, a two-level fractional factorial design is convenient for screening experiment. Such designs are fractions of the full factorial design with k variables to consider a fractional factorial design can be constructed in the following way. Select a full factorial design with n runs so that $n > k$. Use the columns the model matrix $\mathbf{X}$ of the smaller factorial design to define the setting of the k variables in n experiments. The principle is illustrated with seven variables in eight runs in Fig. 5.1

		2^{7-4} fractional factorial design							Model matrix for a complete 2^3 factorial design
		X_1	X_2	X_3	X_4	X_5	X_6	X_7	
Exp. no.	I	1	2	3	12	13	23	123	
1	1	-1	-1	-1	1	1	1	-1	
2	1	1	-1	-1	-1	-1	1	1	
3	1	-1	1	-1	-1	1	-1	1	
4	1	1	1	-1	1	-1	-1	-1	
5	1	-1	-1	1	1	-1	-1	1	
6	1	1	-1	1	-1	-1	1	-1	
7	1	-1	1	1	-1	-1	1	-1	
8	1	1	1	1	1	1	1	1	

Fig. 5.1 Construction of a fractional factorial design

Box and Hunter have given excellent accounts of fractional factorial designs.[79]

5.2 Plackett-Burman designs

Other two-level designs that can be used for screening are the Plackett-Burman designs. These designs are based upon Hadamard matrices, $\mathbf{H}_n$, i.e. $n \times n$ matrices in which the matrix element are 1 or -1 and for which $\mathbf{H}^T\mathbf{H}$, and $\mathbf{H}\mathbf{H}^T$ is a diagonal matrix with the diagonal elements are n. They can be used to test $(n-1)$ variables in n runs. Plackett and Burman have described designs in which n is a multiple of four up to $n = 100$.[80]

5.3 D-Optimal designs

The joint confidence region of the estimated response surface model parameters is proportional to the square root of the determinant of the dispersion matrix,

$$(|(\mathbf{X}^T\,\mathbf{X})^{-1\cdot}|)^{1/2}. \tag{9}$$

Since $|(\mathbf{X}^T\,\mathbf{X})^{-1\cdot}| = 1/|\mathbf{X}^T\,\mathbf{X}|$ this is equivalent to say that the determinant $\mathbf{X}^T\,\mathbf{X}|$ should be as large as possible. Designs for which this criterion is fulfilled are called D-Optimal designs (D stands for Determinant). A general reference to D-optimal designs is the book by Fedorov.[81] It should be noted that factorial designs, fractional factorial designs, and Plackett-Burman designs are D-optimal designs. In the general case, computers must be used for the construction of D-optimal designs and algorithms for the construction have been presented.[81] [82]

5.4 A new principle: Designs from near-orthogonal experiments. (Paper IV)

These designs are based upon *Singular Value Decomposition*, SVD, of the model matrix constructed from a set of candidate experiments. A good description of SVD decomposition is found in the book by Strang.[83]

Any matrix $\mathbf{M}$ can be factorised as:

$$\mathbf{U} \; \mathbf{S} \; \mathbf{V}^{\mathrm{T}} \tag{10}$$

The matrix $\mathbf{U}$ is defined by the normalised eigenvectors of the correlation matrix $\mathbf{M} \; \mathbf{M}^{\mathrm{T}}$ and the matrix $\mathbf{V}$ by the normalised eigenvectors of the variance-covariance matrix $\mathbf{M}^{\mathrm{T}} \; \mathbf{M}$ The matrix. $\mathbf{S}$ is a diagonal matrix of the singular values $\sigma_1, \; \sigma_2, ..., \; \sigma_{\mathrm{k}}$ The squared singular values, σ_{i}^2 are the eigenvalues, λ_i of the correlation matrix $\mathbf{M} \; \mathbf{M}^{\mathrm{T}}$, and σ_{i}^2 are the eigenvalues of the variance-covariance matrix $\mathbf{M}^{\mathrm{T}} \; \mathbf{M}$.

6. The model space

The model space is spanned by the variables in the Taylor expansion model. For an interaction model with two variables, the design space is spanned by x_1, and x_2, and the model space is spanned by x_1, x_2, and x_1x_2, (Fig. 6.1)
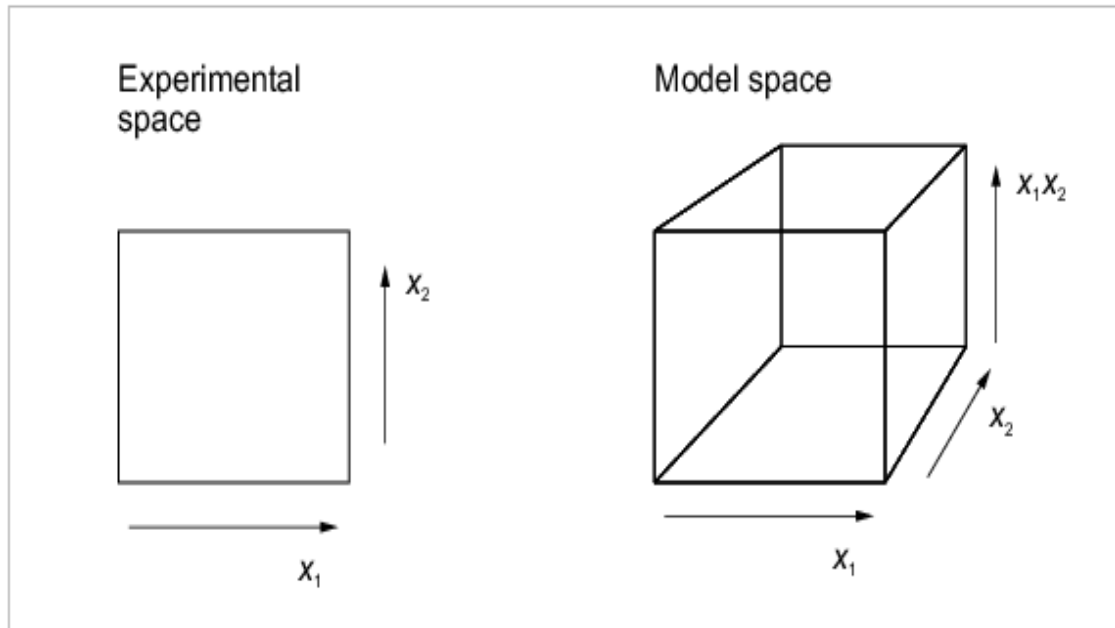
Fig. 6.1 Design space and model space for an interaction model

For three variables x_1, x_2, and x_3 the model space of the interaction model is spanned by x_1, x_2, x_3 , x_1x_2, x_1x_3, and x_2x_3. The space is six-dimensional. With for variables in an interaction model, the space is spanned by x_1, x_2, x_3, x_4, x_1x_2, x_1x_3, x_1x_4, x_2x_3, x_2x_4, and x_3x_4, a ten-dimensional space. The principle is to select experimental rows from the model matrix in such a way that these row vectors span the model space as efficiently as possible. This is accomplished in the following way:

7. Near-orthogonal experiments

The design is generated as followed.

First, select a set of candidate experiments, $\mathbf{D}_C$, that span the design space. Then, expand $\mathbf{D}_C$ to form the candidate model matrix, $\mathbf{X}_C$ and make a singular decomposition of $\mathbf{X}_C$:

i.e.

$$\mathbf{X}_C = \mathbf{U} \ \mathbf{S} \ \mathbf{V}^T. \qquad\qquad (11)$$

The first singular vector, $\mathbf{v}_1$ describes the direction through the model space and along which the projection of the experimental points have the largest variance. The number r of singular vectors, $\mathbf{v}_i$ ($i = 1, ..., r$) equals the dimensions of the model space, and the singular vectors will be an orthonormal base of the models space.

 The next step is to determine the experimental row $\mathbf{x}_i$ in $\mathbf{X}_C$. that is most parallel to the first singular vector. This, as evaluated from the absolute value of the scalar product $|\mathbf{x}_i \cdot \mathbf{v}_1|$ and the experiment that gives the largest scalar product, is selected. The corresponding experiment in the candidate design matrix $\mathbf{D}_C$ is selected as the first experiment. The principles are illustrated in Fig. 7.1
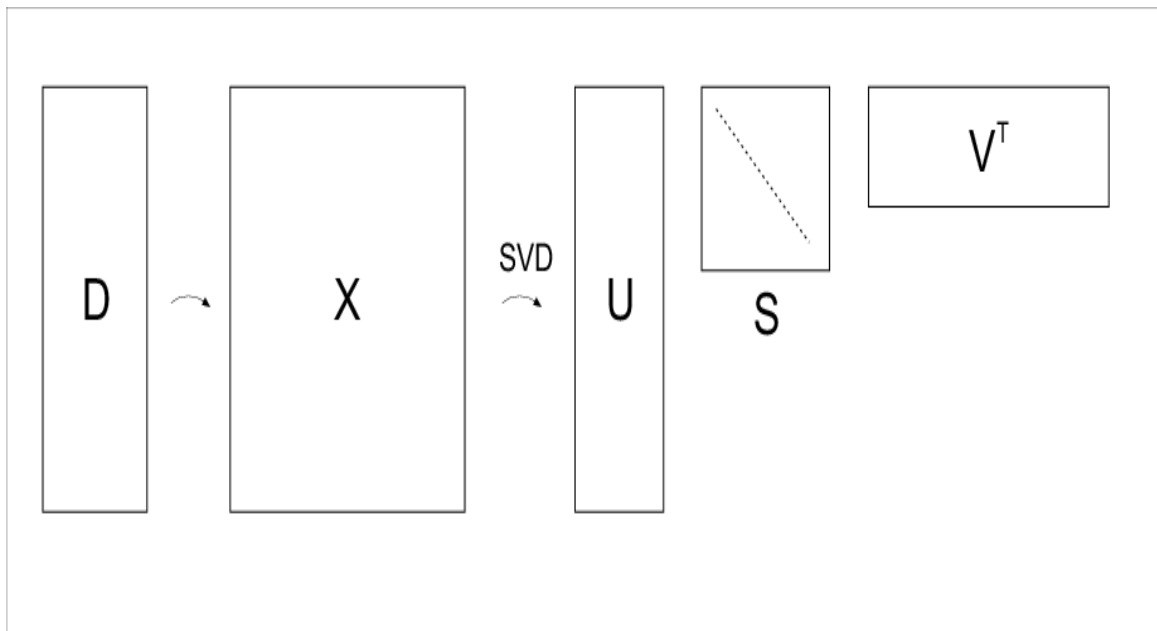
Fig. 7.1 Singular value decomposition of the candidate model matrix
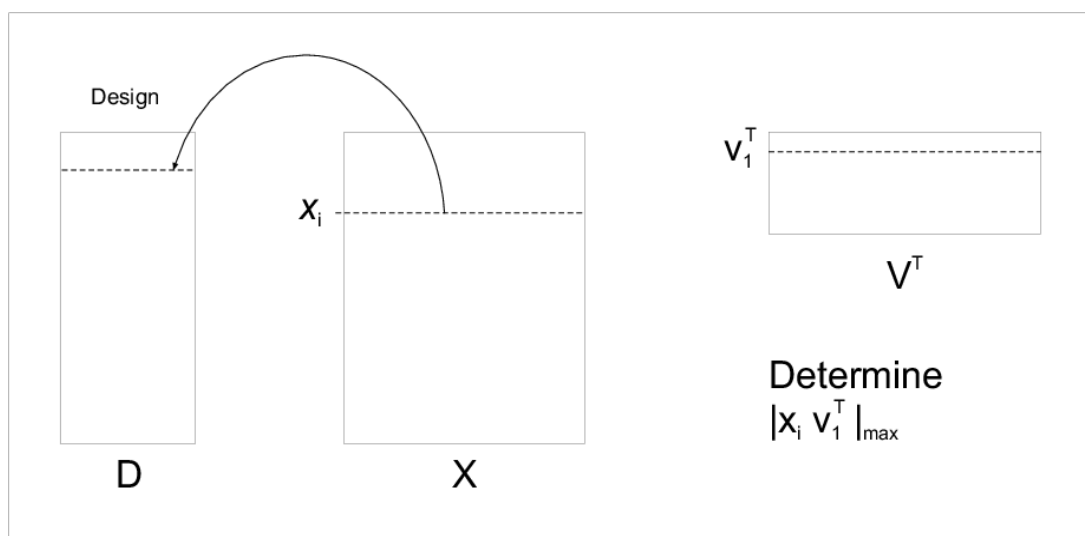
Fig. 7.2 Selection of experiments from the model matrix.

The next step is to remove the selected row, $\mathbf{x}_i$, from $\mathbf{X}_C$. The selected row will span one dimension of the model space. Then, the variation described by $\mathbf{x}_i$, is removed from all the remaining element by subtracting the projections of the remaining rows onto $\mathbf{x}_i$.

$$\mathbf{x}_k(\text{new}) \;=\; \mathbf{x}_k \;-\; \mathbf{x}_i\,\mathbf{x}_k^{\mathrm{T}} \,/\mathbf{x}_i\,\mathbf{x}_i^{\mathrm{T}} \cdot \mathbf{x}_i \tag{12}$$

Yielding the reduced model matrix $\mathbf{X}_{C-1}$.with the rank $r-1$.

The procedure is then repeated with $\mathbf{X}_{C-1}$ to select the second experiment and so on until the dimensions of the reaction space is spanned. Since the singular vectors are mutually orthogonal, the selected experimental rows will be near-orthogonal and span the model space, see Fig. 7.3.
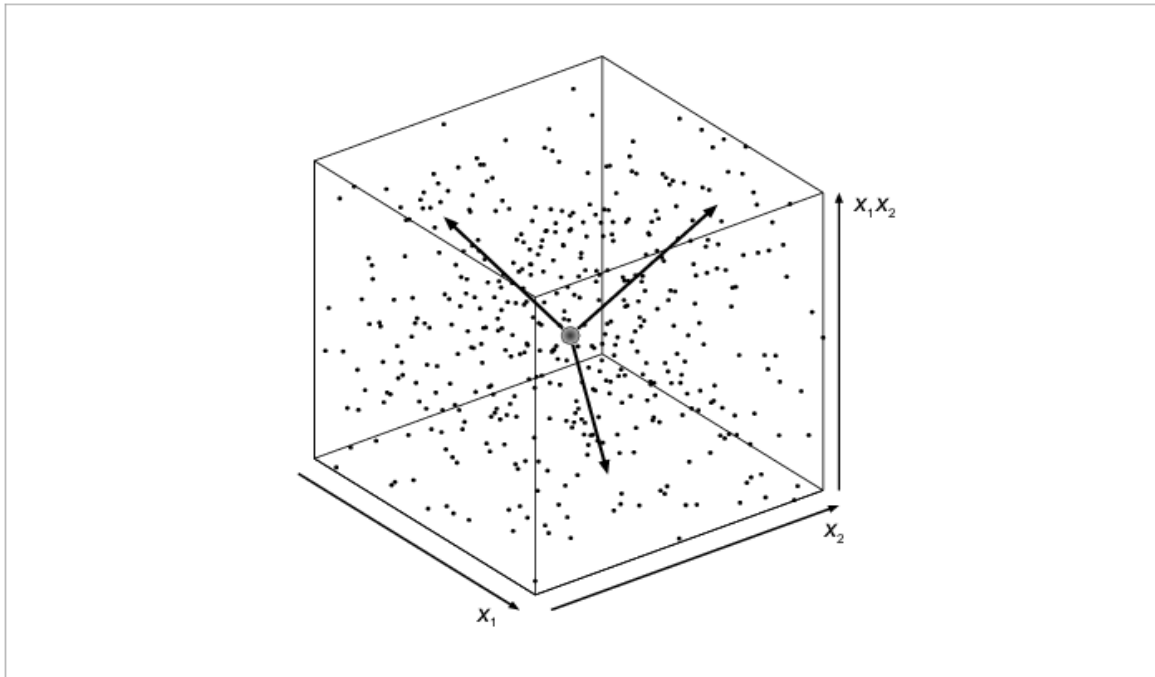
Fig. 7.3 Experimental vectors in the model space

These principles were used for the first time in a paper on the selection of test items in combinatorial libraries.[84] The paper gives a thorough mathematical derivation of the method. It was later realised that the procedure can be used for the experimental designs for fitting response surface models. An Appendix to Paper IV presents designs for fitting linear models, second order interaction models, and quadratic models for three up to five variables. The candidate designs were eleven-levels full factorial designs with 1331, 14641, and 161 051, experiments respectively. It was supposed that this would give a sufficient coverage of the corresponding model spaces. Figure 7.4 shows how the experimental point withe three variables are displaced in the design space for fitting a linear model, a second order interaction model, and a quadratic model.
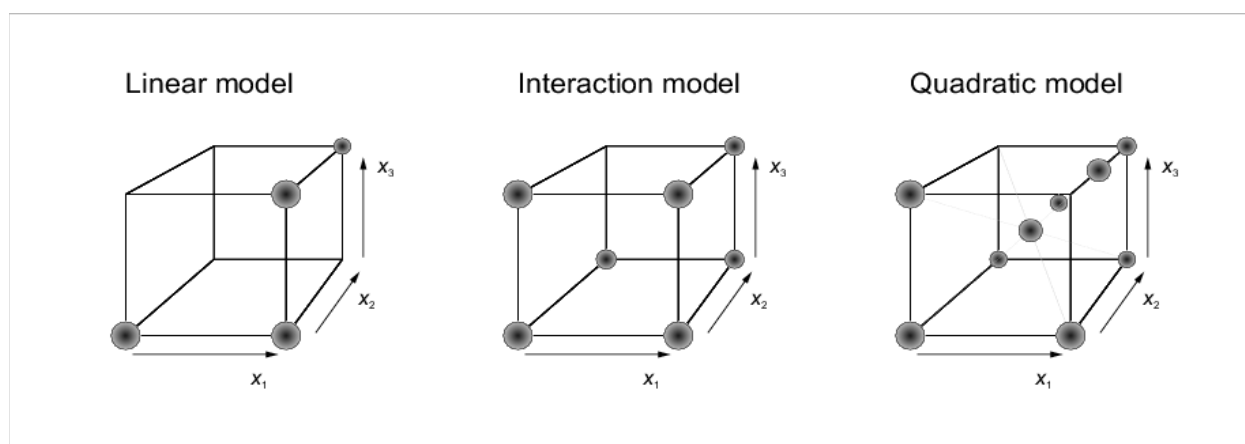
Fig. 7.4 Experimental points in SVD designs

8. Synthesis of 2-bromomethyl-2-(1-bromoethyl)-1,3-dioxolane
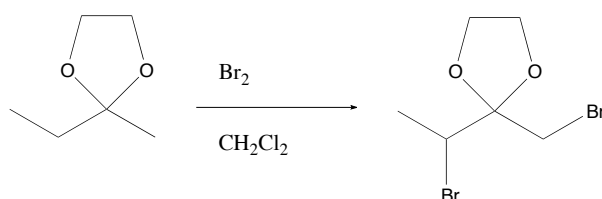
This dibromoacetal is a key intermediate in the synthesis of the unsaturated bromoketones **1**, **2** and **2** in this thesis. Laboratory scale (10 mmol) synthesis afforded 87% yield from the parent.[6] It was assumed that the yield could be improved and for this a SVD design was used.

The variables studied are specified in Table 8.1. The settings of the variables were chosen to embrace the hitherto best known conditions, the centre point.

Table 8.1: Experimental variables and the levels of their settings.in the SVD design

Variables	Levels of the settings		
	-1	0	$+1$
x_1: Reaction temperature/ $^{\mathrm{o}}$C	0	15	30
x_2: Concentration of acetal/M	0.2	0.3	0.4
x_3: Stirring rate/rpm	250	325	400
x_4: Rate of bromine addition/$\mathrm{m_{eq}}$ min^{-1}	20	50	70

The candidate experiments were the full three-level factorial design 3^4 and it was assumed that a second-order interaction model would be sufficient. The model contains eleven unknown parameters and the model space is eleven-dimensional. To span this space eleven experiments will be necessary. Table 8.1 and Table 8.2 show the design and the yields obtained.

Experiment #12 at the centre was added to the design to allow for a comparison with the previously known best experimental conditions. The estimated model was:

$$y = 77.71 + 8.92\ x_1\ -\ 0.71\ x_2\ -\ 3.11\ x_3\ -\ 0.18 x_4\ -\ 6.83\ x_1\ x_2\ -\ 1.24\ x_1$$

$$x_3\ +\ 2.66\ x_1\ x_4\ +\ 0.69\ x_2\ x_3\ +\ 6.27\ x_2\ x_4 + 1.64\ x_3\ x_4\ +\ e \qquad (13)$$

The model is interpreted as follows: The temperature, x_1, should be adjusted to its high level (30 $^{\mathrm{o}}$C; the concentration, x_2, should be low; the stirring rate, x_3 should be low; and the rate of bromine addition, x_4, should be low. With these settings, the interaction effects would have a maximum beneficial influence. The model can be understood as follows. The reaction is slightly exothermal, and to prevent unwanted temperature increase, bromine should be slowly added to the acetal at not a too high concentration rate. To dissipate heat from the reaction mixture, stirring is necessary, but it is probably sufficient at any level in the experimental domain. With a rapid

addition of bromine to a concentrated solution of the acetal, minor amounts $< 5\%$ of higher brominated products were observed. A response surface projection showing the variation in yield vs x_1 and x_2 when x_3 and x_4 were set to their low levels is seen in Fig. 8.1.

Table 8.2: Experimental design for the synthesis of 2-bromomethyl-2-(1-bromomethyl)-1,3-dioxolane and yields obtained.

	Design				Yield
Exp #	x_1	x_2	x_3	x_4	y
1	1.0	1.0	1.0	1.0	87.4
2	1.0	−1.0	−1.0	−1.0	95,8
3	−1.0	1.0	−1.0	1.0	79.5
4	−1.0	−1.0	1.0	−1.0	63.7
5	−1.0	−1.0	0.2	1.0	53.9
6	−1.0	1.0	1.0	−1.0	68.7
7	1.0	1.0	1.0	−1.0	58.8
8	1.0	−1.0	1.0	−1.0	93.5
9	1.0	−1.0	−1.0	1.0	94.0
10	−1.0	−1.0	−1.0	−1.0	77.1
11	1.0	−1.0	1.0	1.0	80.9
12	0	0	0	0	88.6
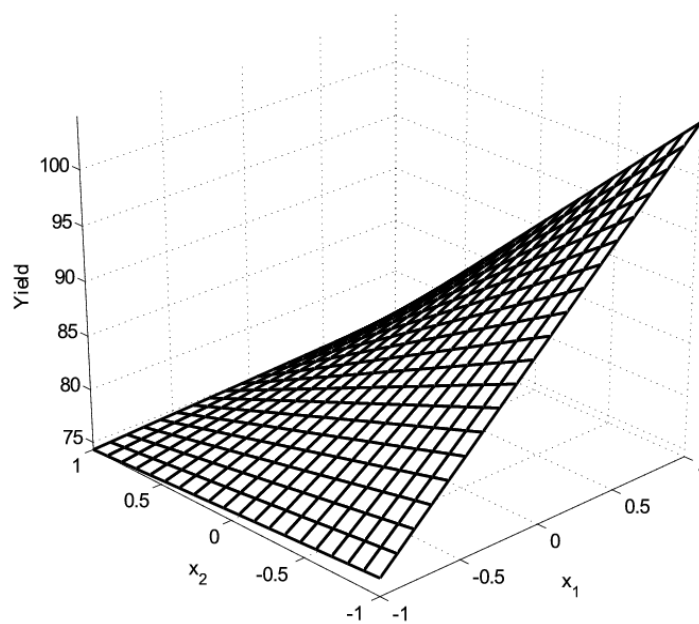
Fig. 8.1 Projection of the response surface model.

The suggested improved experimental conditions were applied in scale-up runs using 1 mol of the substrate.
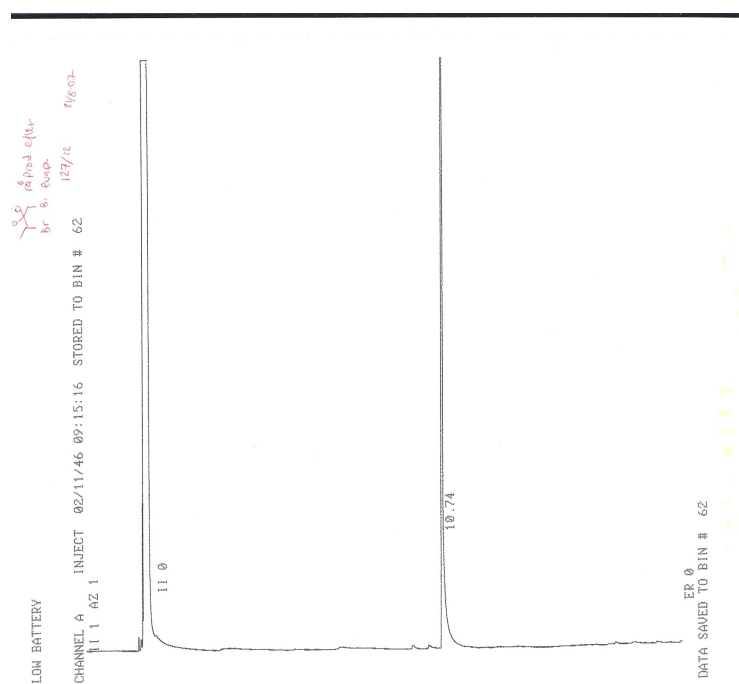
Fig.8.2 chromatogram of the isolated product.

The result were reproducible and the isolated yields was 98% with a purity > 97% (GC and ^{1}H NMR). Fig.8.2 shows a gas chromatogram of the isolated product. The product was sufficiently pure and could be taken to the next step without further purification.

9. Screening with near-orthogonal experiments, (Paper V).

There are situations in which severe time-constraints prevent any attempt to run a screening design with many experiments. Two examples are:

(1) A new compound turns out to have interesting pharmaceutical properties. For more testing, 200 g of the compound in needed within four weeks. Testings are expensive and no delay can be tolerated. The chemists have to produce the necessary quantity within the time limits.

(2) Outsourcing is nowadays very common for producing the active ingredients in drugs. A chemical company is contacted by the customer to make some test experiments of a given procedure, and to deliver 2 kg of the desired compound within six weeks.

Common to these problems is that the chemist should run a reaction that is known and has already been used to make smaller quantities of the desired compound. It can therefore be assumed that a useful experimental domain is known, (i.e. the possible variation of the experimental factors). It is also reasonable to assume that an improved result can be obtained in the vicinity of the known experimental conditions. A second-order interaction response surface model will probably be sufficient to describe the variation of the response in the experimental domain.

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In a screening experiment it is often found that out of many experimental variables initially considered only a few will have real influence on the response. For discussion of this, see[74-75, 85].

It was realised that the near-orthogonal experiments may be useful in this context. The very first near orthogonal experiment will span one dimension of the model space. The important variables will exert their influence in this first experiment. The second experiment is nearly orthogonal to the first, and the important variables will have their influence in tis experiment too, *but in different way.* It may well be that only a few experiments are necessary to span the important variation in the model space and, hence, that a handful of experiments will be sufficient to discern the important variables. This has been tested with two experimental systems. The first is the bromination of an acetal described above. The second is on the synthesis of an enamine from methyl isobutyl ketone and morpholine over molecular sieves.

10. Enamine synthesis

The following reaction was studied.
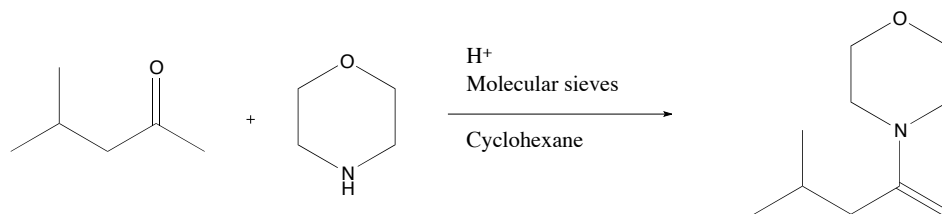
Table 10.1 Experimental variables and their settings in the enamine synthesis.

Variables	Settings				
	-1	-0.5	0	0.5	1
x_1: Type of acid	Nafion®				TFA
x_2: Temperature / ^{O}C	0	10	20	30	40
x_3: Type of molecular sieve 5A	Powder				Pellets
x_4: Stirring rate / rpm	None				300
x_5: Ratio morpholine/ketone/mol/mol	1.0	1.5	2.0	2.5	3.0
x_6: Ratio molecular sieves/ketone/g/mol	200	300	400	500	600
x_7: Molar concentration of ketone[a]	2.5	2.9	3.3	4.0	5.0

[a] Actually, the amount of solvent was varied and the concentration given are calculated from this.

A full factorial design with these settings contains $2^3 . 5^4 = 5000$ runs and this defines the candidate design matrix. A second order interaction model with 29 unknown parameters was assigned.

Table 10.2 shows the design with near-orthogonal experiments and the yield of enamine obtained.

Table 10.2 Experimental design and the yields obtained in the enamine synthesis.

	Variables							Yield
Exp. no.	x_1	x_2	x_3	x_4	x_5	x_6	x_7	y
1	−1	−1	−1	−1	−1	−1	1	0.4
2	1	1	1	1	1	1	1	44.2
3	−1	−1	−1	−1	1	1	1	0.9
4	−1	−1	−1	1	−1	1	1	1.7
5	1	1	1	−1	1	1	−1	51.9
6	1	0.5	1	−1	−1	−1	−1	27.0
7	1	1	1	1	−1	1	−1	30.9
8	1	1	1	−1	−1	1	1	26.3
9	−1	−1	−1	−1	1	−1	−1	0.2
10	−1	−1	−1	1	−1	−1	−1	0.2
11	−1	1	1	1	−1	−1	1	22.7
12	1	−1	−1	1	−1	−1	−1	5.2
13	−1	−1	−1	1	1	−1	1	0.8
14	−1	−1	1	−1	−1	1	−1	25.6
15	1	−1	−1	1	−1	−1	1	4.5
16	1	−1	−1	1	−1	−1	1	4.5
17	−1	1	−1	−1	−1	1	−1	4.8
18	1	−1	−1	−1	−1	1	−1	4.5
19	1	−1	−1	−1	1	−1	1	6.2
20	1	1	−1	1	1	−1	−1	27.4
21	−1	1	−1	1	−1	1	1	11.1
22	1	−1	−1	1	1	1	−1	5.6
23	−1	1	−1	1	1	1	−1	13.3
24	−1	1	1	−1	1	−1	−1	25.2
25	−1	−1	1	1	−1	−1	1	11.5
26	−1	1	1	−1	1	−1	−1	25.2
27	1	1	−1	−1	−1	−1	1	17.0
28	1	−1	1	1	1	1	1	25.4
29	−1	1	1	1	1	1	−1	43.6
30	−1	−1	−1	−1	−1	1	−1	0.4

10.1 Estimation of the Taylor polynomial coefficients using PLS

Least squares estimates of the vector of the coefficients, $\mathbf{b}$ is obtained by regression and

$$\mathbf{b} = (\mathbf{X}^{\mathrm{T}}\,\mathbf{X})^{-1}\,\mathbf{X}^{\mathrm{T}}\,\mathbf{y}. \qquad\qquad (8)$$

However, when there are fewer experiments (rows) in $\mathbf{X}$ than the number of variables (columns), the matrix $\mathbf{X}^{\mathrm{T}}\,\mathbf{X}$ is singular and the dispersion matrix $(\mathbf{X}^{\mathrm{T}}\,\mathbf{X})^{-1}$ does not exist. It is therefore not possible to estimate $\mathbf{b}$ by regression. Instead, the estimates can be obtained by using PLS, see below. PLS is an acronym for *P*rojected *L*atent *S*tructures. A good description of PLS is given in[86]. PLS is a computational method by which it is possible to obtain quantitative relations between a matrix of independent variables (X-block) and a matrix of dependent variables (Y-block). The columns of $\mathbf{X}$ define an X--pace and the columns of $\mathbf{Y}$ define a Y-space. The first step is to find a vector, i.e. a direction through the Y-space that describes the largest variation of the responses. The next step it to find a vector, i.e. a direction through the X-space so that the projections of the experimental points onto this vector have a maximum correlation to the projections on the vector of the Y-space. The principles are illustrated in Fig 10.1
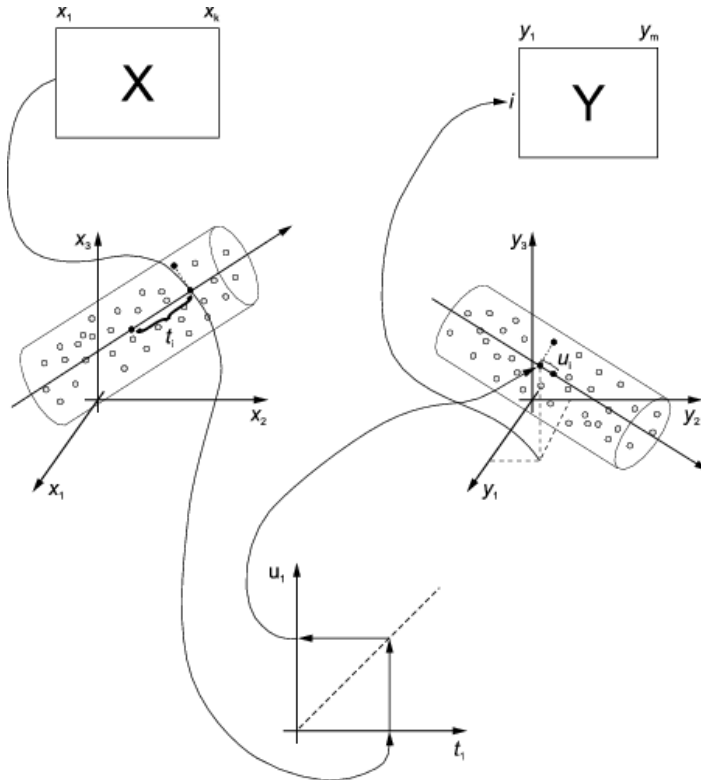
Fig 10.1 PLS modelling.

The computation are carried out as follows:

The first step is to calculate the cross-covariance matrix $\mathbf{C_{YX}}$ as

$$\mathbf{C_{YX}} = \mathbf{Y}^{\mathrm{T}} \mathbf{X} \tag{14}$$

Where $\mathbf{X}$ is an $N \times K$ matrix and $\mathbf{Y}$ is an $N \times L$ matrix.

Find the first principal component of $\mathbf{C_{YX}}$, (i.e. the eigenvector of $\mathbf{C_{YX}}^{\mathrm{T}}$) $\mathbf{C_{YX}}$ corresponding to the largest singular value of $\mathbf{C_{YX}}$. This vector, also called weight vector, is denoted $\mathbf{w}_1$. The first score vector of the X-block is then:

$$\mathbf{t}_1 = \mathbf{X}\mathbf{w}_1 \tag{15}$$

I.e. the projection of $\mathbf{X}$ onto $\mathbf{w}_1$. The corresponding loading vector, $\mathbf{p}_1$ of the X-block is then.

$$\mathbf{p}_1 = \mathbf{X}^T \mathbf{t}_1 / (\mathbf{t}_1^T \mathbf{t}_1) \tag{16}$$

For the Y block the first loading vector $\mathbf{q}_1$ is given by

$$\mathbf{q}_1 = \mathbf{Y}^T \mathbf{t}_1 / (\mathbf{t}_1^T \mathbf{t}_1) \tag{17}$$

The residuals of the first iteration, $\mathbf{E}_1$ and $\mathbf{F}_1$ for the X block and the Y block, respectively are then

$$\mathbf{E}_1 = \mathbf{X} - \mathbf{t}_1 \mathbf{p}_1^T \tag{18}$$

$$\mathbf{F}_1 = \mathbf{Y} - \mathbf{t}_1 \mathbf{q}_1^T \tag{19}$$

To find the next PLS component the steps above are repeated with $\mathbf{E}_1$ and $\mathbf{F}_1$ as new staring matrices. His procedure is then repeated until the desired number of components, A, has been determined. The scores and loadings of the X and Y blocks are then stored as columns in the matrices, $\mathbf{T}$, $\mathbf{P}$, and $\mathbf{Q}$.

$$
\begin{aligned}
\mathbf{T} &= [\mathbf{t}_1 \quad \mathbf{t}_2 \text{ .... } \mathbf{t}_A] \\
\mathbf{P} &= [\mathbf{p}_1 \quad \mathbf{p}_2 \text{ .... } \mathbf{p}_A] \\
\mathbf{Q} &= [\mathbf{q}_1 \quad \mathbf{q}_2 \text{ .... } \mathbf{q}_A]
\end{aligned}
\tag{20}
$$

The weight vectors from the different iterations are stored in the weight matrix ($K \times A$)

$$\mathbf{W} = [\mathbf{w}_1 \quad \mathbf{w}_2 \text{ .... } \mathbf{w}_A] \tag{21}$$

The original matrices $\mathbf{X}$ and $\mathbf{Y}$ can now be expressed inn terms of the PLS-components.

$$\mathbf{X} = \mathbf{T}\mathbf{P}^{\mathrm{T}} + \mathbf{E} \tag{22}$$

$$\mathbf{Y} = \mathbf{T}\mathbf{Q}^{\mathrm{T}} + \mathbf{F} \tag{23}$$

Where $\mathbf{E}$ and $\mathbf{F}$ are residual matrices of the X and Y blocks, respectively.

Prediction of $\mathbf{Y}$ from $\mathbf{X}$ is accomplished as:

$$\mathbf{Y}_{\mathrm{predicted}} = \mathbf{X}\mathbf{W}^{*}\mathbf{Q}^{\mathrm{T}} \tag{24}$$

Where

$$\mathbf{W}^{*} = \mathbf{W}(\mathbf{P}^{\mathrm{T}}\mathbf{W})^{-1} \tag{25}$$

The predicted responses, $\mathbf{y}_{\mathrm{Predicted}}$ from the model matrix by the Taylor model is :

$$\mathbf{y}_{\mathrm{Predicted}} = \mathbf{X}\,\mathbf{b} \tag{26}$$

Hence we see that an estimate of the Taylor parameters from a PLS model can be obtained as:

$$\mathbf{b} = \mathbf{W}^{*}\mathbf{Q}^{\mathrm{T}} \tag{27}$$

This relation has been used to predict the model parameters from the SVD experiments

11. Experimental Results

11.1 Acetal bromination

The experiments in Table 10.2 were used to fit PLA models from designs with five, six, and twelve experiments, respectively and the Taylor model coefficients were estimated. Cumulative normal probability plots are shown in Fig. 11.1.
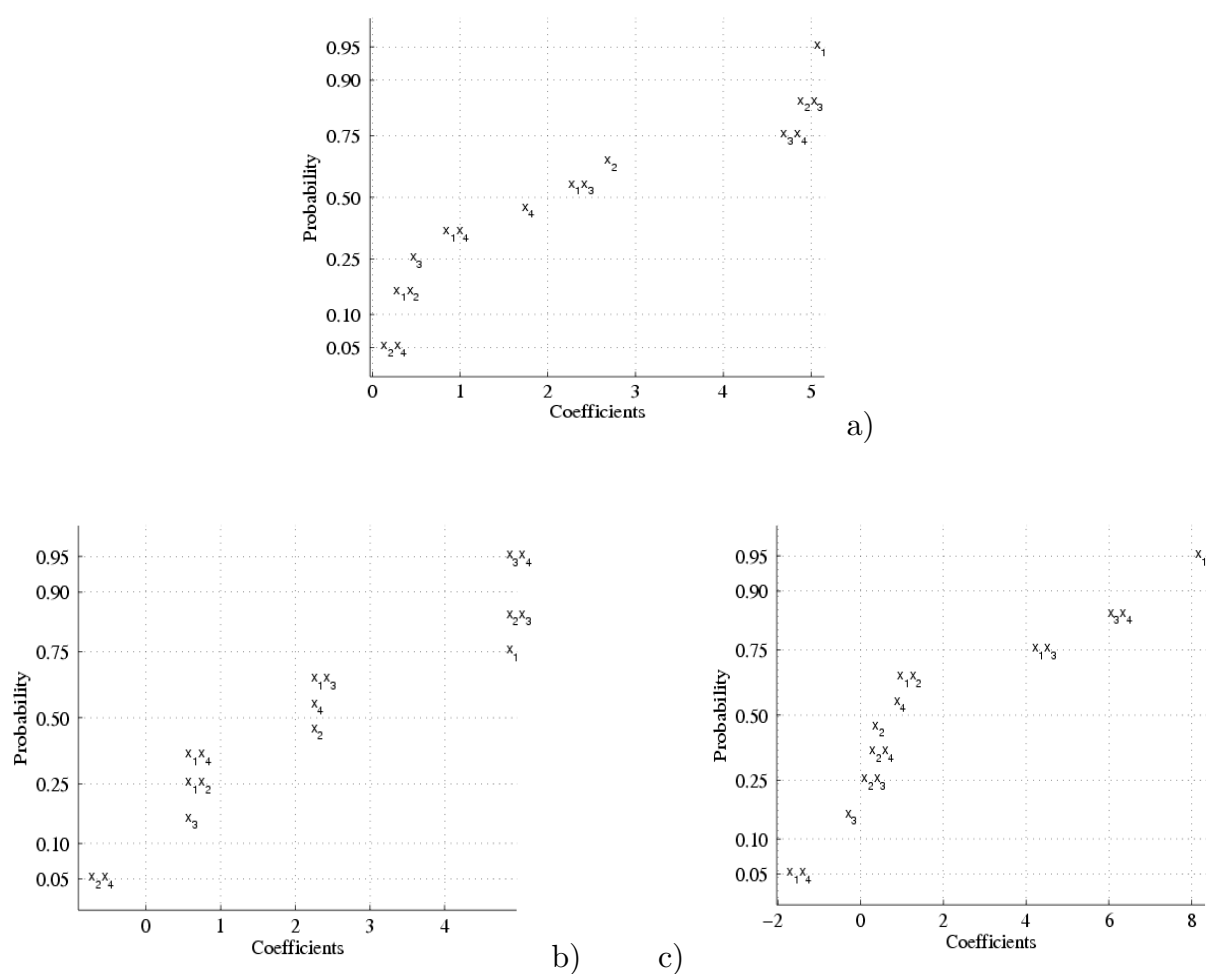
Fig 11.1 Cumulative normal probability plot with a) five, b) six and c) twelve experiments

It is seen that the temperature, $\mathbf{x}_1$ is indicated as a probably important variable together with some interactions. However, when few experiments are included the plots are not very lucid. There is another way to assess the importance of the variables in a PLS model, viz. the variable importance plots. The variable importance is computed from the weight vector, **w.**

Fig 11.2 show a weight vector in a hypothetical model space.
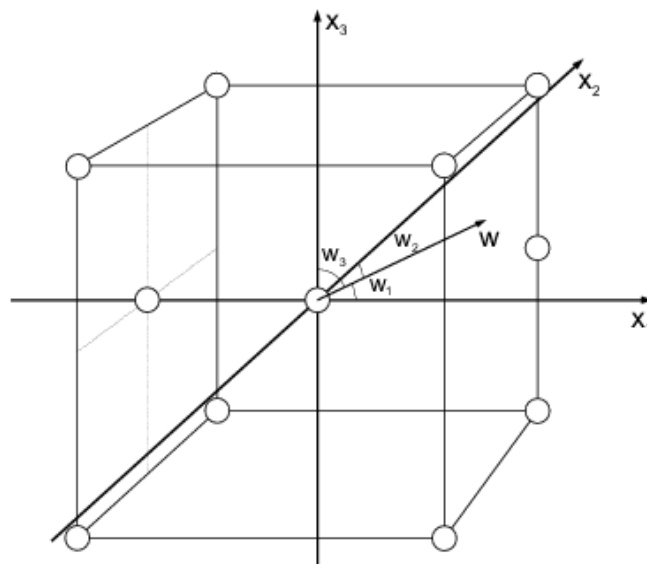
*Fig 11.2 Weight vector **w**.*

The weight vector is defined by the cosines of the angle between **w** and variable axes. With an angle 0, the cosine is 1 and the corresponding settings of the variable are fully correlated with the variation of the response. If the weight vector is perpendicular to the variable axis, $\cos(\pi/2)$ is zero and the corresponding variable is not correlated to the response. For a PLS model with one component, the variable importance, VIP, of a variable is computed from the weight of the variable, w_i, R^2 (the sum of squarest of he predicted responses $\Sigma\, y_{\text{Predicted}}{}^2$ divided by the sum of squares of the observed response $\Sigma\, y_{\text{Observed}}{}^2$, an the number, K, of terms in the response model,

$$VIP_i = [w_i^2 \bullet R^2 \bullet K]^{1/2} \qquad\qquad (28)$$

A $VIP > 1$ shows that the variables has a real influence on the response, and $VIP < 1$ indicates a negligible influence.

The VIP-plots in the acetal bromination are shown in Fig. 11.3
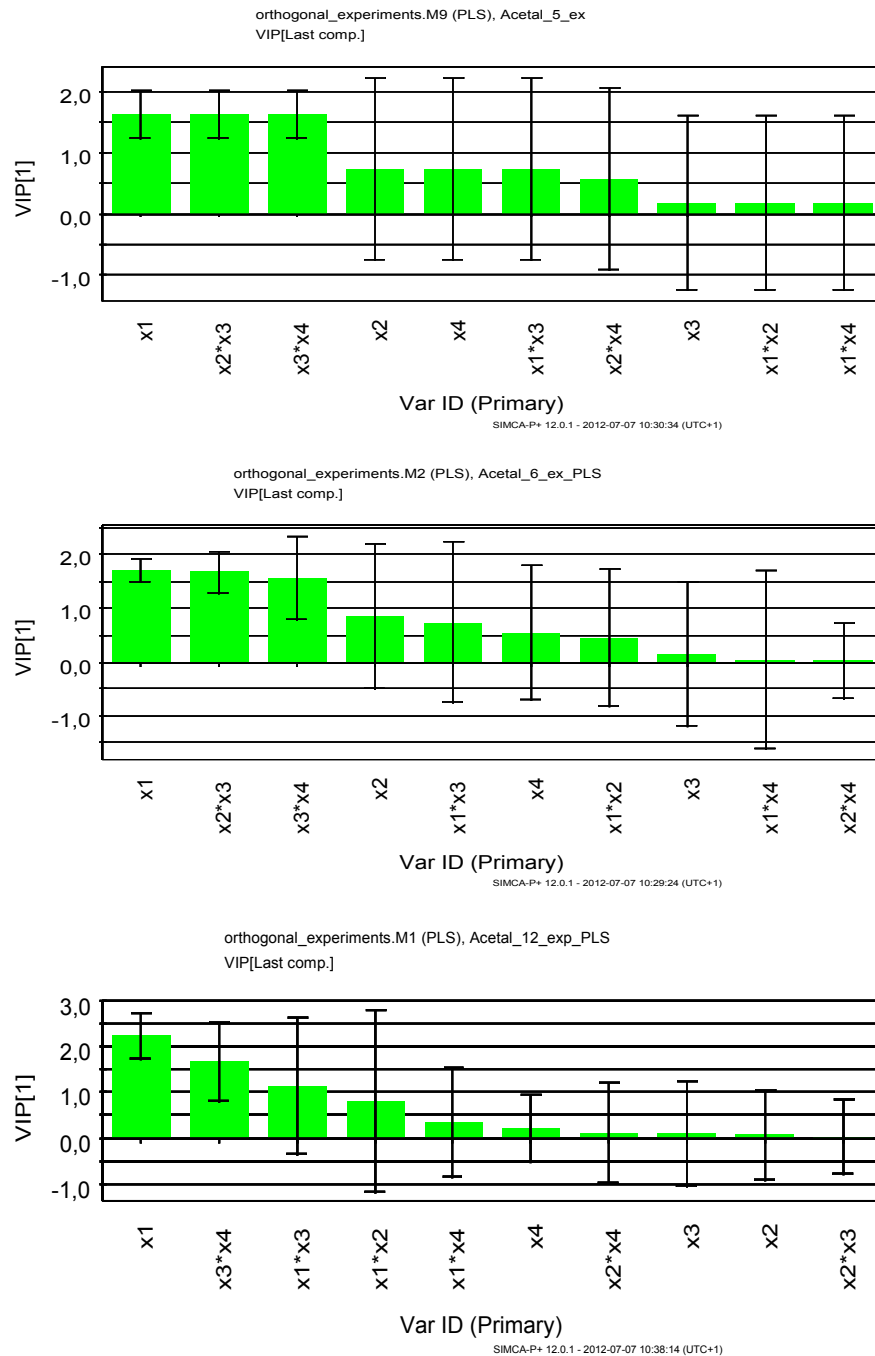
Fig.   11.3   VIP-plots   in   the   acetal   bromination

11.2 Enamine synthesis

The coefficient from least squares fitting of the Taylor polynomial. As shown in Fig. 11.3.
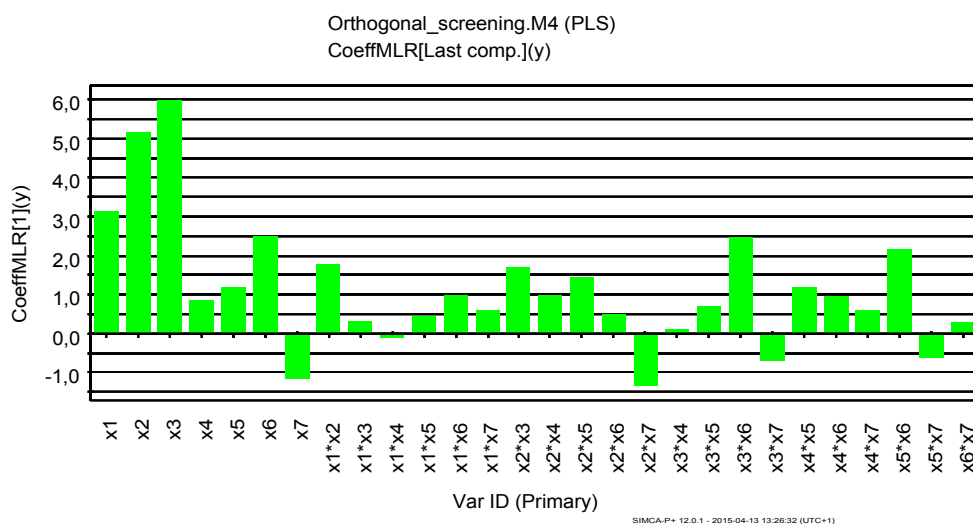
Fig. 11.3 The coefficient from least squares fitting of the Taylor polynomial

It is seen that the coefficients of x_1, x_2, and x_3 are clearly out side the noise level and these variables can be considered as significant

Cumulative normal probability plots obtained with after eight, twelve, sixteen, twenty, and thirty experiments are shown in Fig. 11.4.

Eight experiments
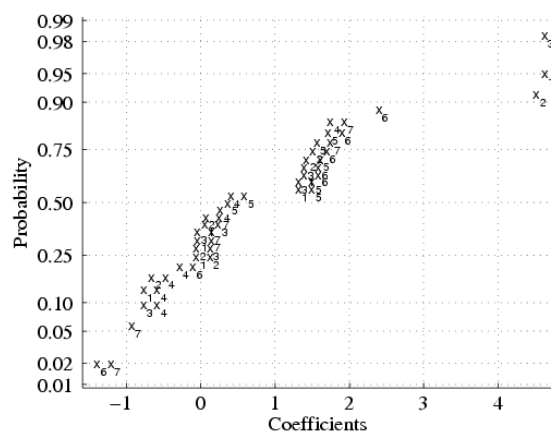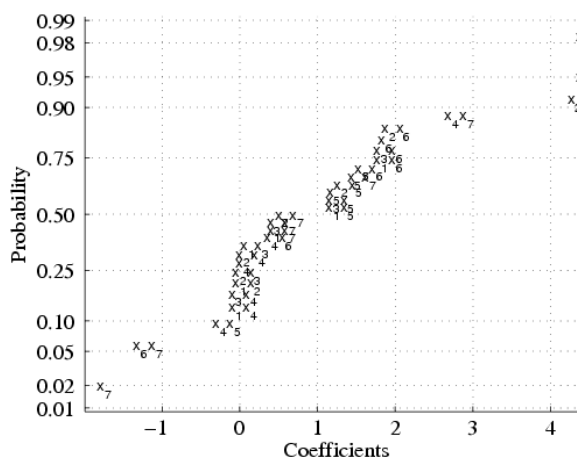
Twelve experiments
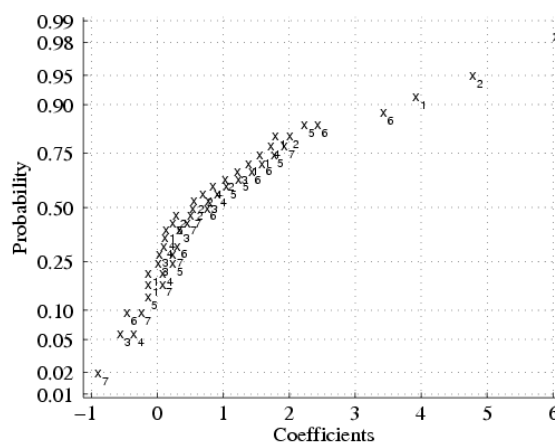
Twenty experiments
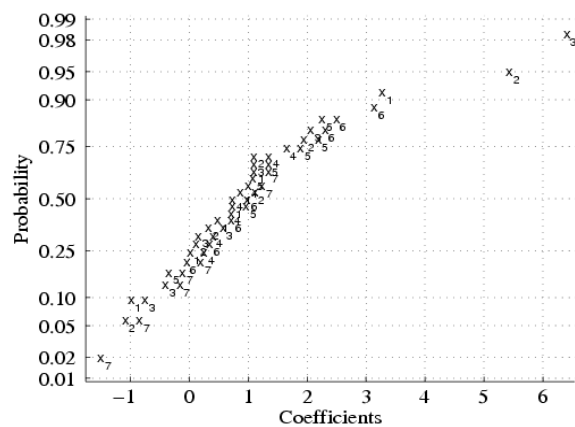
Thirty experiments

Fig. 11.4 Cumulative normal probability for the enamine synthesis.

Orthogonal_screening.M11 (PLS), Enamin_16_exp
VIP[Last comp.]

SIMCA-P+ 12.0.1 - 2012-07-07 10:23:56 (UTC+1)
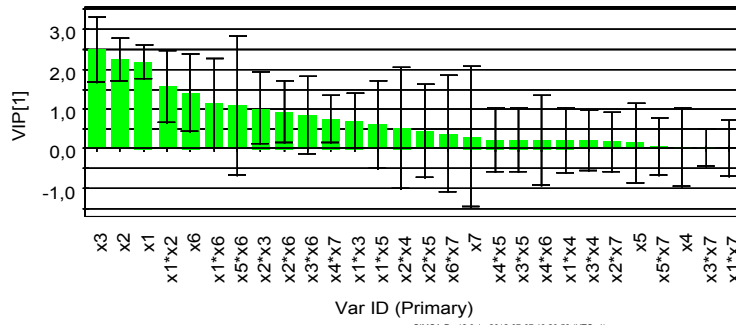
Orthogonal_screening.M10 (PLS), Enamin_12 exp
VIP[Last comp.]

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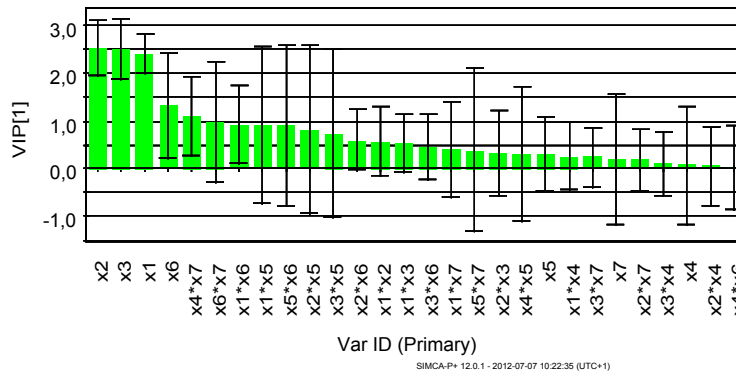
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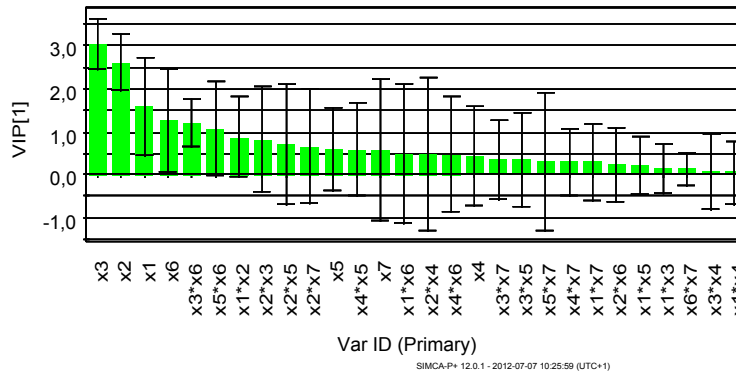
Orthogonal_screening.M7 (PLS), Enamin_8_exp
VIP[Last comp.]

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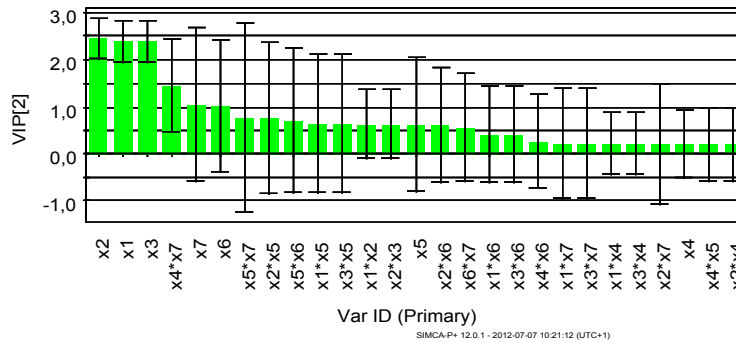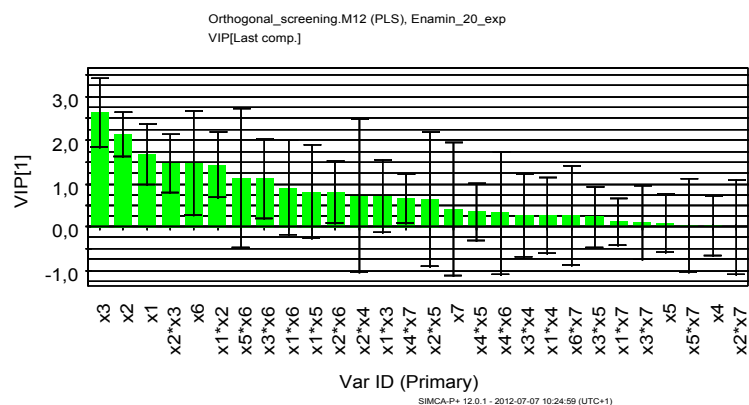
Fig. 11.6 VIP-plots in the Enamine Synthesis

From the plots it is seen that the important variables x_1, x_2, and x_3 point out both in the normal probability plots and the *VIP* plots and that this can be done already after eight experiments.

These results show that near-orthogonal experiments can be used for identifying the important experimental variable from a limited number of experimental runs.

The linear coefficient in the Taylor model shows the slopes (the gradients) of the response surface in the different directions of the experimental space. A possible extension, yet untested, would be to use estimates the linear coefficients and determine a set of new experiments along the direction of the steepest ascent [87] and this may lead to a near-optimum experimental domain.

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IV. Conclusion

All the target molecules could be isolated and characterized in pure form and all procedures were possible to perform without any distillation or chromatographic separation. The routes presented are convergent and highly efficient in terms of yield and reaction time and target compounds can easily be prepared on a large scale.

Several key steps of this procedure offer significant improvements over the earlier procedures, e.g. the new procedure developed to overcome the problem created by the formation of KBr. In addition, two robust transformations were setup to overcome a very long lasting problem concerning the last deprotection step by a microwave assisted procedure or reaction in a heterogeneous solvent system. Even if the target compounds are highly unstable they can be stored as their acetal precursors and deprotected prior to chemical investigation.

The problem regarding Chemoselectivity/regioselectivity could not be resolved concerning nucleophilic substitution of the bromine. It still remains to investigate whether the reaction chosen was the problem or if the selectivity of these highly functionalized brominated unsaturated methyl ketone is even possible to control.
Even though the synthesized target compounds are sensitive to work with, they allow access to new exotic molecules never synthesized before.

-Diels-Alder 4+2 cycloaddition between 1,3-butadiene and the target compounds could be achieved with the aid of a Lewis acid. This test reaction shows the possibility to use the target molecules to incorporate a bromomethyl ketone moiety in different unsaturated cyclic products.

-The heterocyclic 3-(2H)-furanone moiety can be easily synthezised using **3** and this one-pot procedure gives access to 3-(2H)-furanone derivatives that may be of great interest.

As future prospect it would be interesting to explore in depth the scope and limitation of the reaction between enamines and the target compounds.

Changing solvent from apolar to polar could lead to new mechanisms and could produce new interesting compounds via e.g. a Michael addition. Enamines synthesised from different functionalized cyclic ketone could also lead to other 3-(2H)-furanone derivatives and, hence, broading the scope of this reaction.

The availability of a slightly acidic proton in alpha position of the ketone of the 3-(2H)-furanone moiety could be interesting to explore as many reactions can link substituents at this position.

Surely many other types of reaction can be attempted on the target compounds.

Nevertheless the powerful lacrimogenous effect and instability can be penalizing for their use. Also, due to its very unstable nature **2** is maybe does not fulfill the criteria for a good synthon.

The optimisation part presents a new strategy for orthogonal experiments for the design of explorative experiments when the objective is to identify the important experimental variables as well as the development of a new Near-Orthogonal strategy for design when the objective is to identify the important variables from few experiments. Even with basic knowledge about optimization, chemists could simply implements and use the Design Matrices presented in their research. The possibility to stop the search when sufficiently good experimental conditions are found is a real improvement over classical orthogonal experiments.

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VII. Appendix

Experimental section

General procedure for the synthesis of the Diels-Alder products (9,10,11)

One equivalent of one the target compound (**1**, **2** or **3**) diluted in CH_2Cl_2 (2ml. per mmol. of reagent) and 10 Mol% of a solution of $SnCl_4$ (1.10^{-2} mol.L^{-1} in CH_2Cl_2) were added in a sealed round bottom flask. After 20 min, 3 equivalents of 1,3-Butadiene (15 wt. % in hexane) were injected drop wise by syringe. The reaction was stirred at room temperature until the total consumption of the reagent. After the end of the reaction time the crude reaction mixture was diluted in CH_2Cl_2 (3ml. per mmol. of reactant) and washed successively with brine and water. The organic layer was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent evaporated under reduced pressure to give the crude product that was analysed without purification.

Experimental procedure for the synthesis of 12

0,72 gr (4.8 mmol, 1.25 eq.) of 1-bromobut-3-yn-2-one in 10ml of dry Et_2O was transferred drop wise over 30 min to 0,65 gr (3.8 mmol, 1eq.) of 4-(cyclohex-1-en-1-yl)morpholine in 10ml of dry Et_2O in a sealed round bottom flask flush with argon at -10°C. The reaction was allowed to reach room temperature after 30 min. 5ml of 1N HCl solution was injected at once after 20 to 30 min. The mixture was stirred 1 h at room temperature. The reaction mixture was diluted with 10 ml saturated $NaHCO_3$ and extracted 4 times repeatedly with 10 ml CH_2Cl_2. The combined organic layers were washed with brine two times. The organic layer was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent carefully evaporated under reduced pressure at 10°C to give the crude product that was analyzed without purification.

Experimental procedure for the synthesis of 13

0,72 gr (4.8 mmol, 1.25 eq.) of 1-bromobut-3-yn-2-one in 10ml of dry Et$_2$O was transferred drop wise over 30 min to 0,68 gr (3.8 mmol, 1eq.) of 4-(cyclohep-1-en-1-yl)morpholine in 10ml of dry Et$_2$O in a sealed round bottom flask flush with argon at 0°C. The reaction was allowed to reach room temperature after 30 min. 5ml of 1N HCl solution was injected at once after 20 to 30 min. The mixture was stirred 1 h at room temperature. The reaction mixture was diluted with 10 ml saturated NaHCO$_3$ and extracted 4 times repeatedly with 10 ml CH$_2$Cl$_2$. The combined organic layers were washed with brine two times. The organic layer was dried over anhydrous MgSO$_4$. The drying agent was filtered off and the solvent carefully evaporated under reduced pressure at 10°C to give the crude product that was analyzed without purification.

Experimental procedure for the synthesis of 14

0,50 gr (3.3 mmol, 1 eq.) of 1-bromobut-3-yn-2-one in 5ml of dry Et$_2$O was transferred drop wise over 30 min to 0,64 gr (3.3 mmol, 1eq.) of 4-(cyclooct-1-en-1-yl)morpholine in 5ml of dry Et$_2$O in a sealed round bottom flask flush with argon at room temperature. The reaction was stirred for 5h. 5ml of 1N HCl solution was injected at once. The mixture was stirred 1 h at room temperature. The reaction mixture was diluted with 10 ml saturated NaHCO$_3$ and extracted 6 times repeatedly with 10 ml CH$_2$Cl$_2$. The combined organic layers were washed with brine two times. The organic layer was dried over anhydrous MgSO$_4$. The drying agent was filtered off and the solvent carefully evaporated under reduced pressure at 20°C to give the crude product that was analyzed without purification.

Experimental procedure for the synthesis of 15

0,50 gr (3.3 mmol, 1 eq.) of 1-bromobut-3-yn-2-one in 5ml of dry THF was transferred drop wise over 30 min to 0,71 gr (3.63 mmol, 1.1 eq.) of 4-(cyclooct-1-en-1-yl)morpholine in 5ml of dry THF in a sealed round bottom flask flush with argon at room temperature. The reaction was stirred for 1h. 5ml of 1N HCl solution was injected at once. The mixture was stirred 1 h at room temperature. The reaction mixture was diluted with 10 ml saturated $NaHCO_3$ and 5ml brine, the'n extracted 6 times repeatedly with 10 ml CH_2Cl_2. The combined organic layers were washed with brine two times. The organic layer was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent carefully evaporated under reduced pressure at 20°C to give the crude product that was analyzed without purification

NL:
4.34E7
TIC MS
mol01

2.22
3.18
3.26
3.30
4.12
4.62
4.79
5.50
6.56
6.62
7.09
7.30
8.09
8.21
8.68
9.75
9.83
10.60
11.22
11.79
12.01
12.56
12.93
13.47

Time (min)

Proton_cdcl3_T25_001
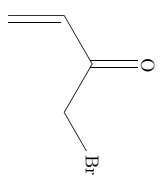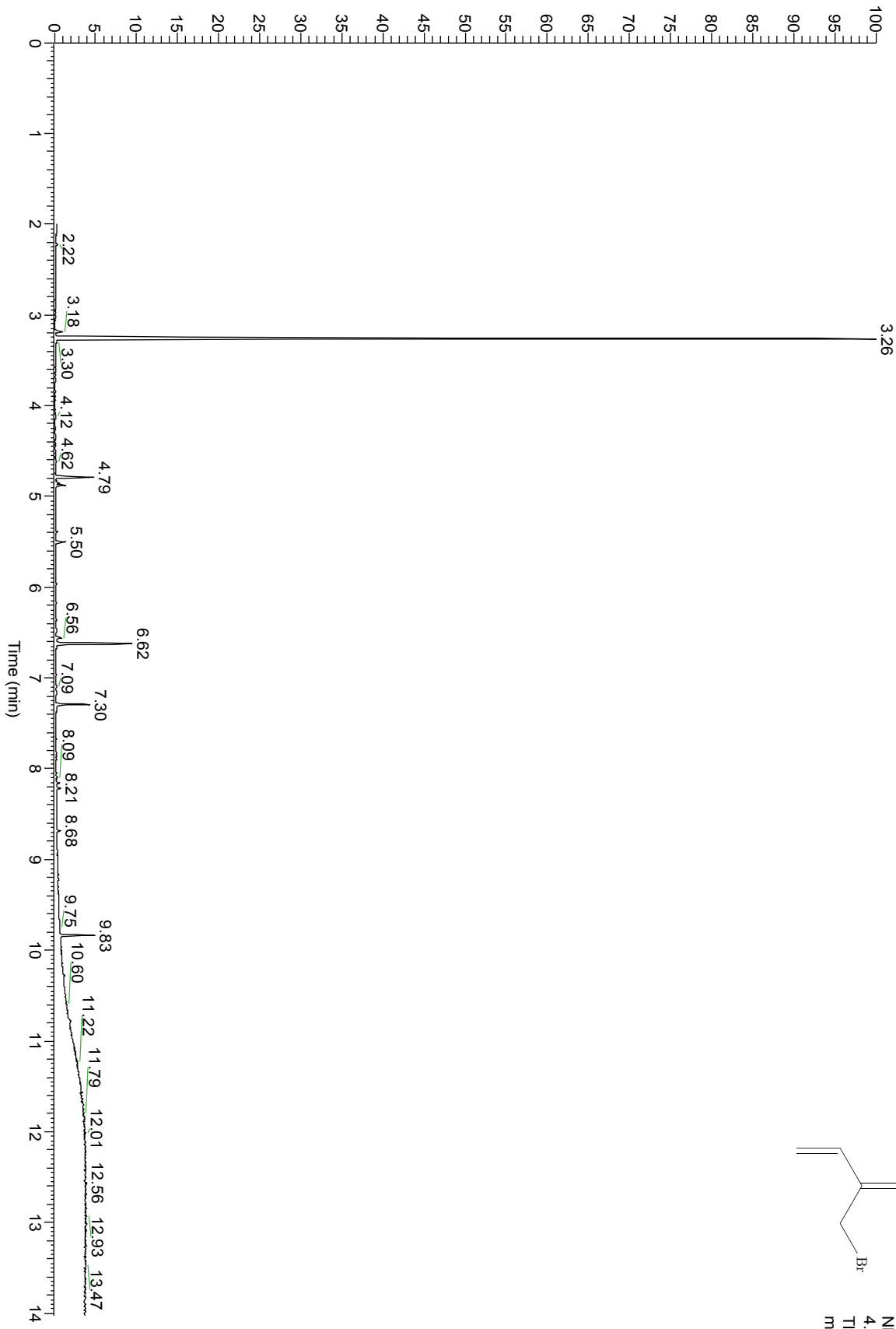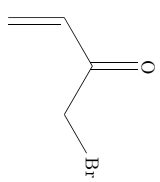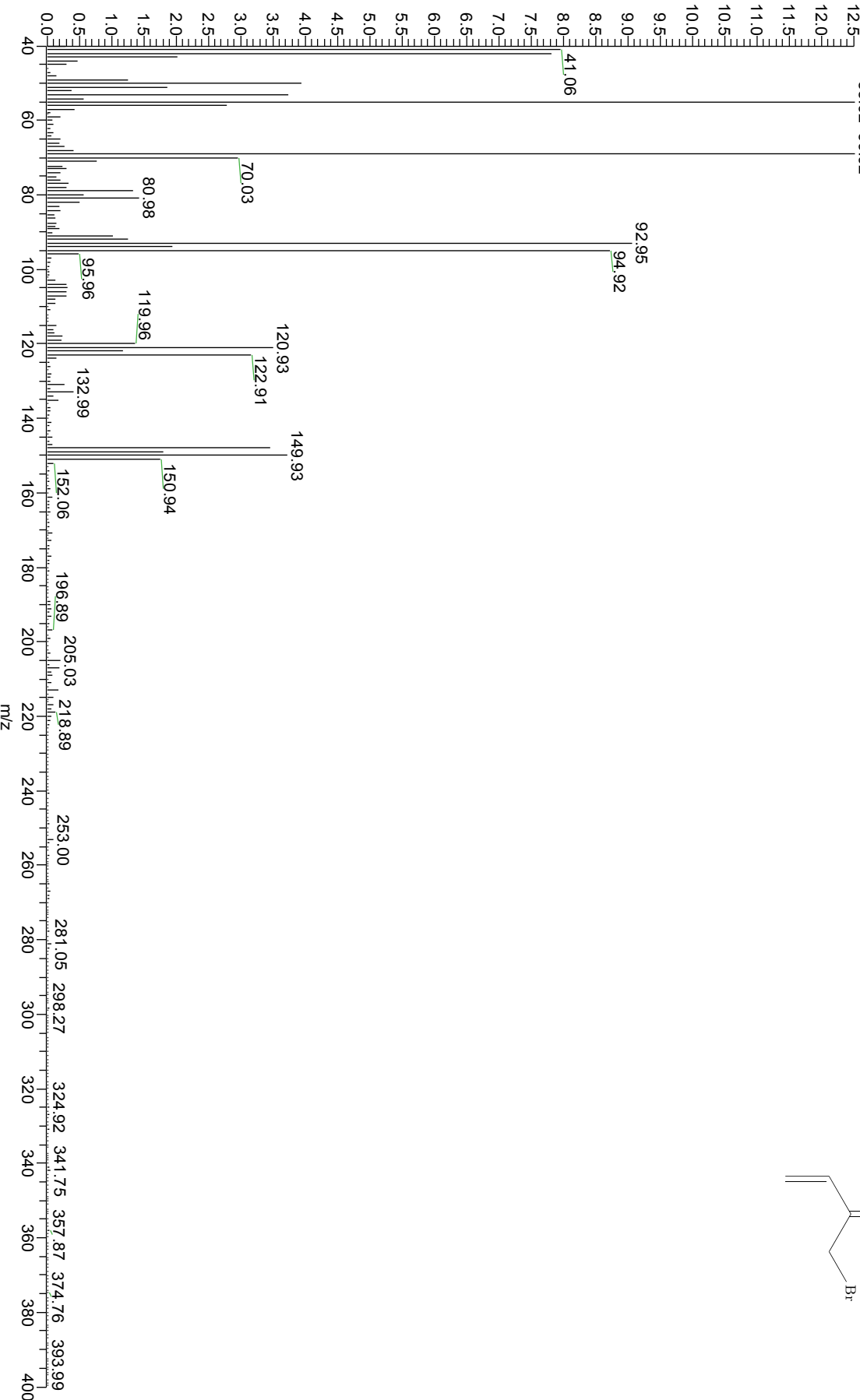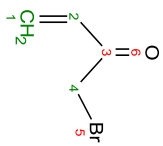
^{1}H NMR (400 MHz, Chloroform-d) δ 6.57 – 6.42 (m, 1H), 6.32 (dd, J = 12.8, 7.3 Hz, 1H), 5.90 (dd, J = 11.8, 4.5 Hz, 1H), 4.01 (s, 1H), 4.07 – 3.96 (m, 1H).
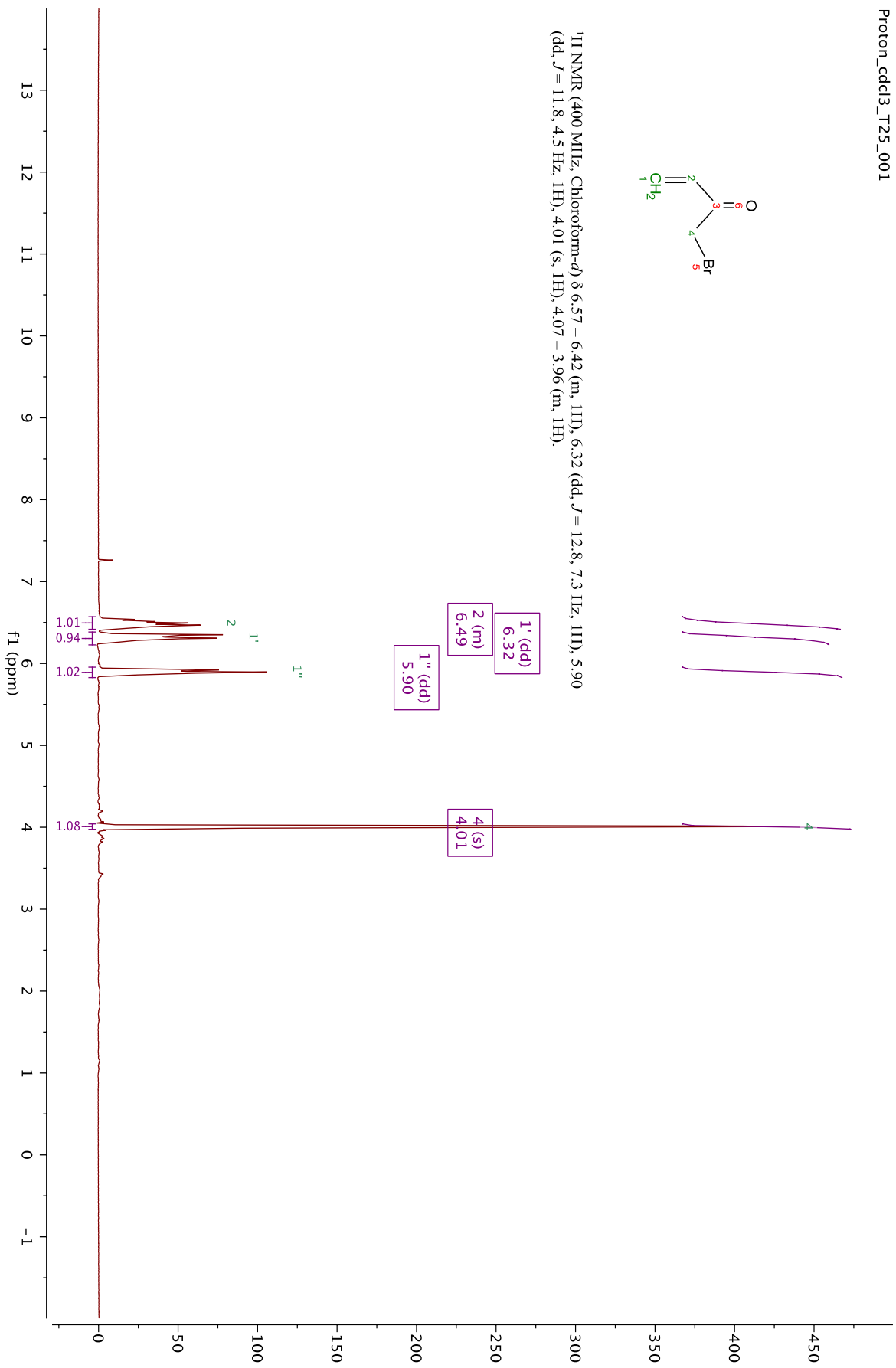
Carbon_cdcl3_T25_001
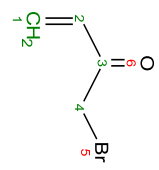
^{13}C NMR (101 MHz, cdcl$_3$) δ 191.17, 132.77, 130.89, 32.27, 32.19.
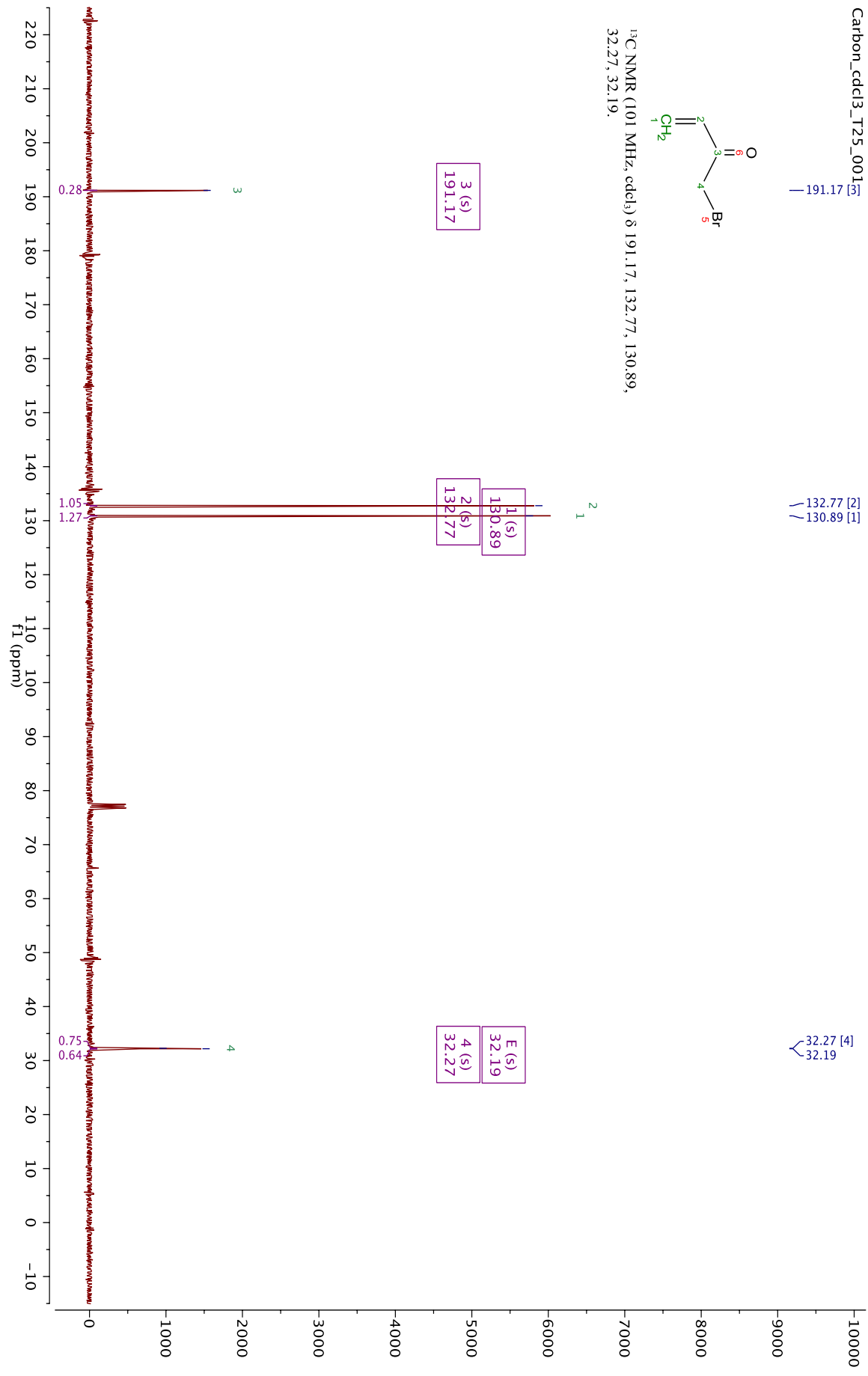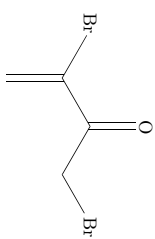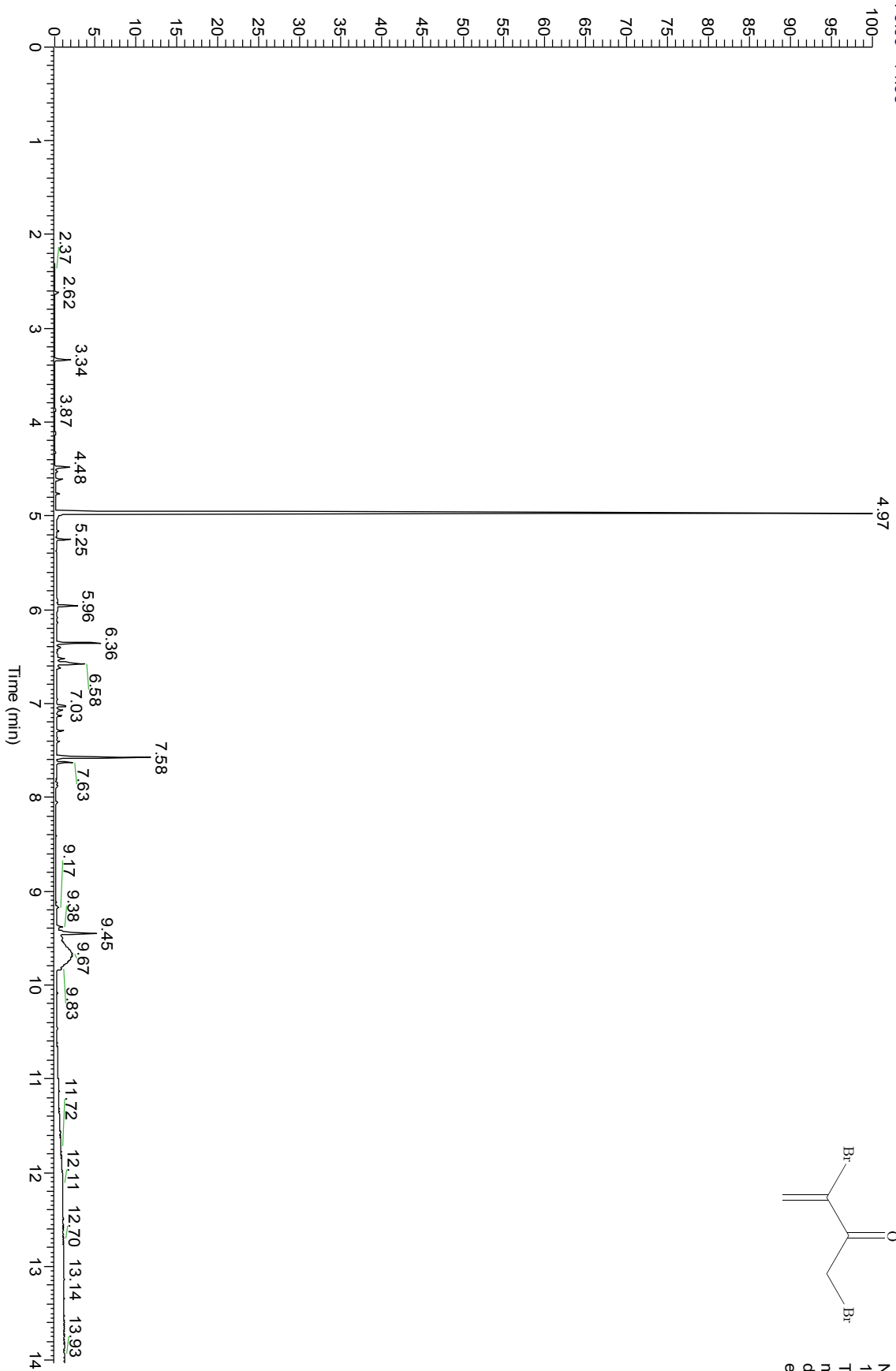
109
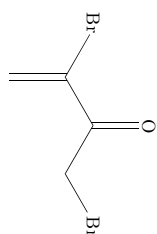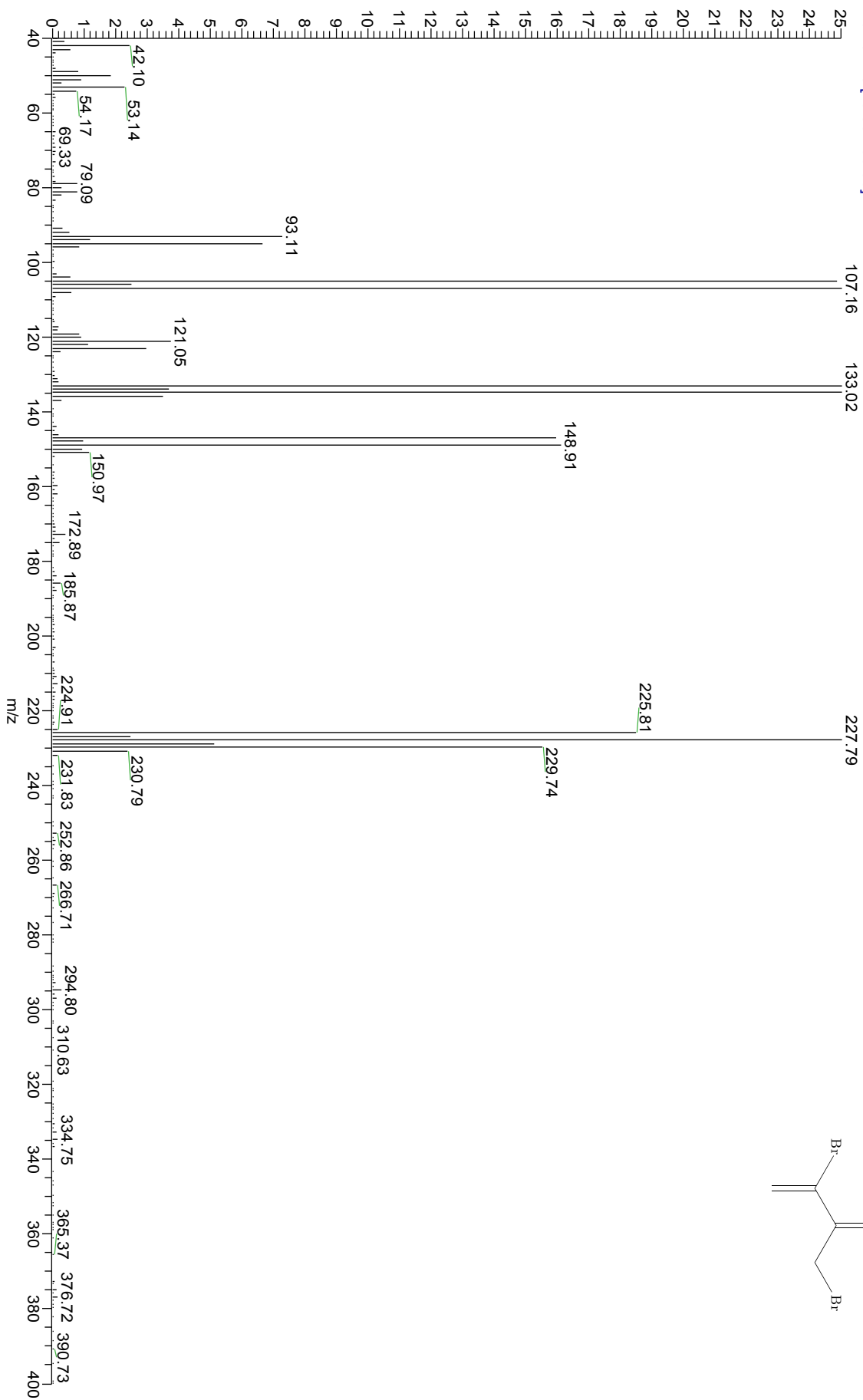
Proton_cdcl3_T25_001
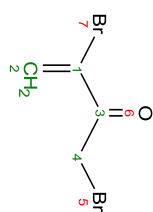
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.90 (d, *J* = 2.8 Hz, 1H), 6.44 (d, *J* = 2.8 Hz, 1H), 4.32 (s, 2H).

110
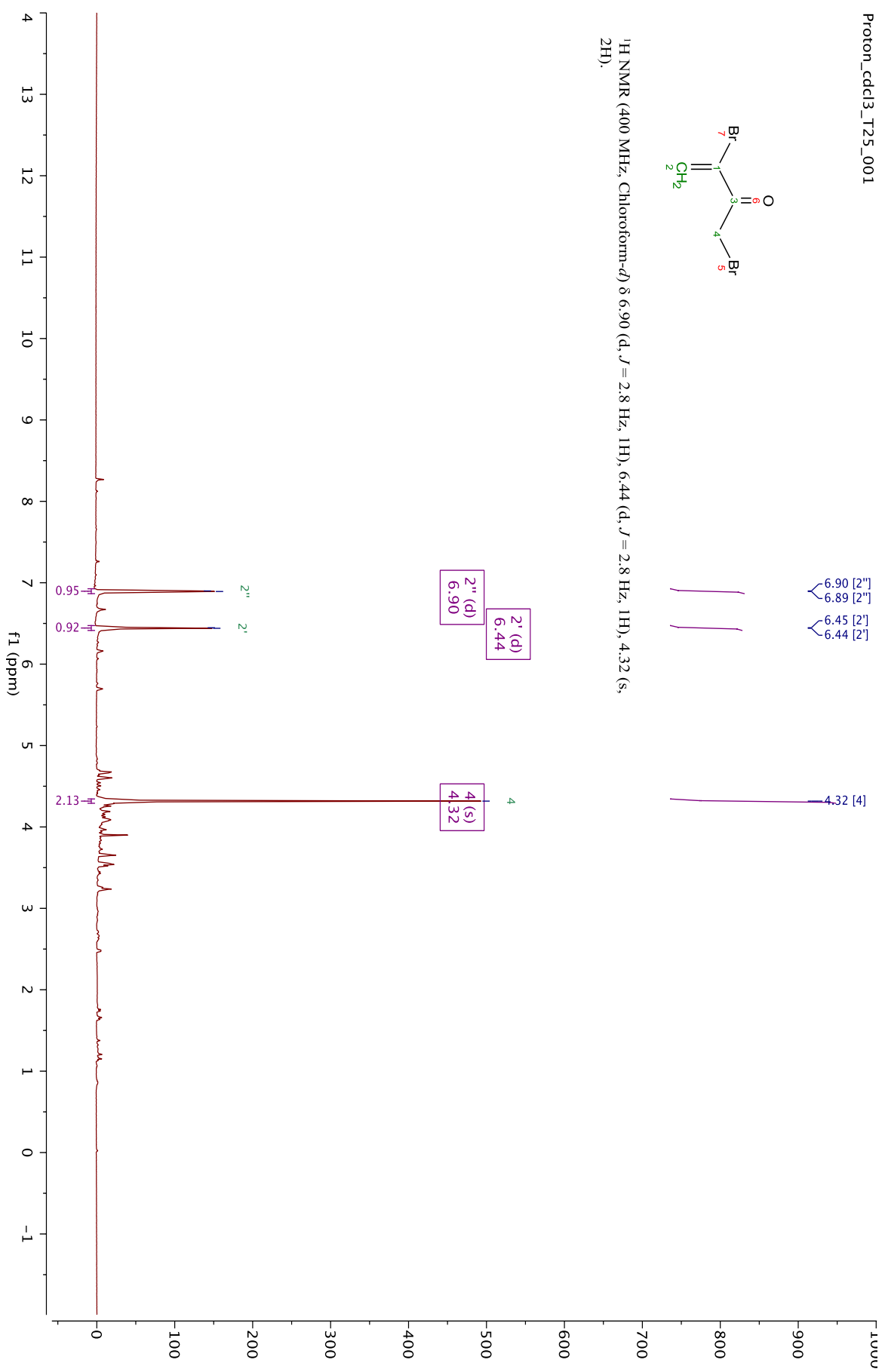
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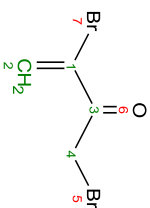
^{13}C NMR (101 MHz, cdcl$_3$) δ 185.97, 131.19, 127.12, 77.46, 77.15, 76.83, 30.18.

— 185.97 [3]

— 131.19 [2]
— 127.12 [1]

77.46 cdcl3
77.15 cdcl3
76.83 cdcl3

— 30.18 [4]

3 (s)
185.97

2 (s)
131.19

1 (s)
127.12

4 (s)
30.18

111

53.06

54.06

78.10

80.96

92.91

94.92

117.01

117.96

119.91

120.98

147.87

177.01

205.17

220.27

253.03

267.02

284.00

315.03

342.04

356.80

368.93

384.00

m/z

113
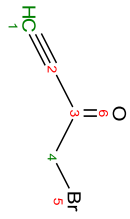
^{1}H NMR (400 MHz, cdcl$_3$) δ 4.05, 3.43.

4 (s)
4.05

1 (s)
3.43

—4.05 [4]

—3.43 [1]

2.02

0.98

f1 (ppm)

114
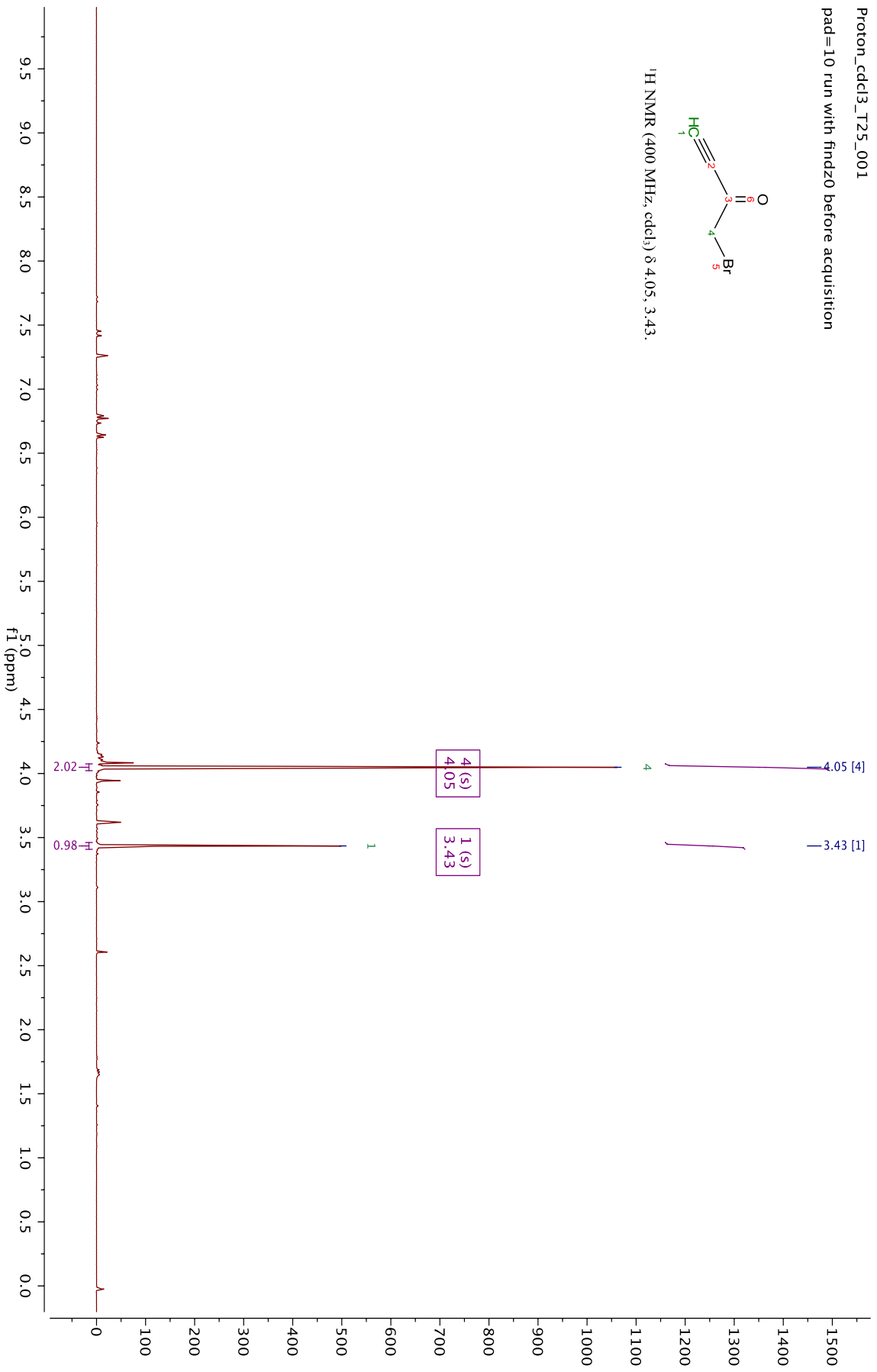
pad=10 run with findz0 before acquisition
pad=10 run with findz0 before acquisition
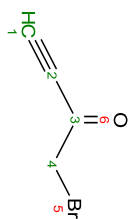
^{13}C NMR (101 MHz, cdcl$_3$) δ 177.53, 82.31, 82.30, 78.95, 77.38, 77.07, 76.75, 35.28.

3 (s)
177.53

C (s)
82.30

2 (s)
82.31

1 (s)
78.95

4 (s)
35.28

177.53 [3]

82.31 [2]
82.30
78.95 [1]
77.38 cdcl3
77.07 cdcl3
76.75 cdcl3

35.28 [4]

0.47

0.71
0.73
0.30

1.80

f1 (ppm)

115
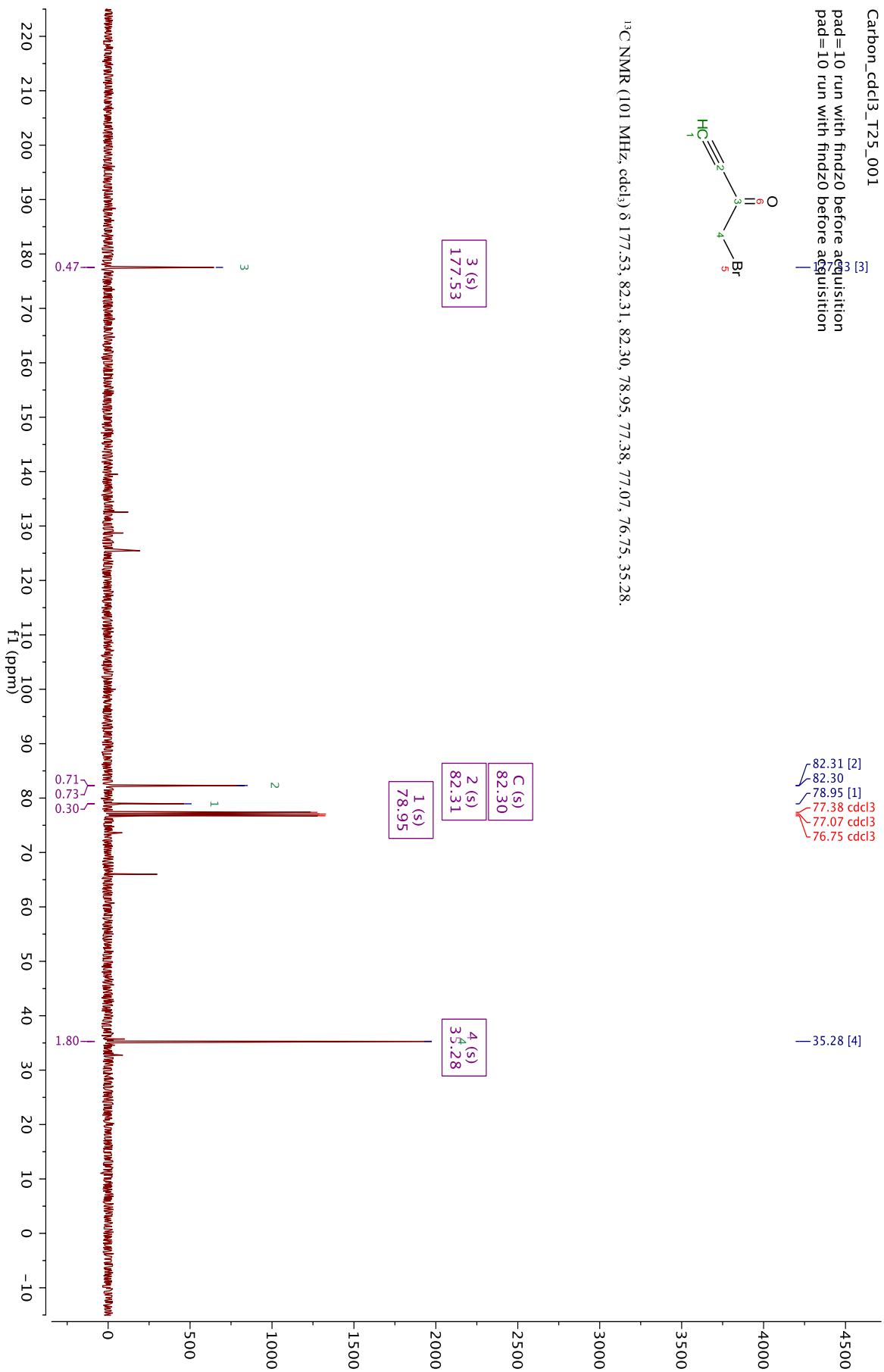
RT: 0.00 - 11.23

NL:
1.81E7
TIC MS
mol(4)

3.67
3.78
3.90
4.96
5.45
6.47
6.52
6.68
7.97
8.44
8.98
9.48
9.83
10.54
11.06

Time (min)

116
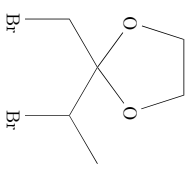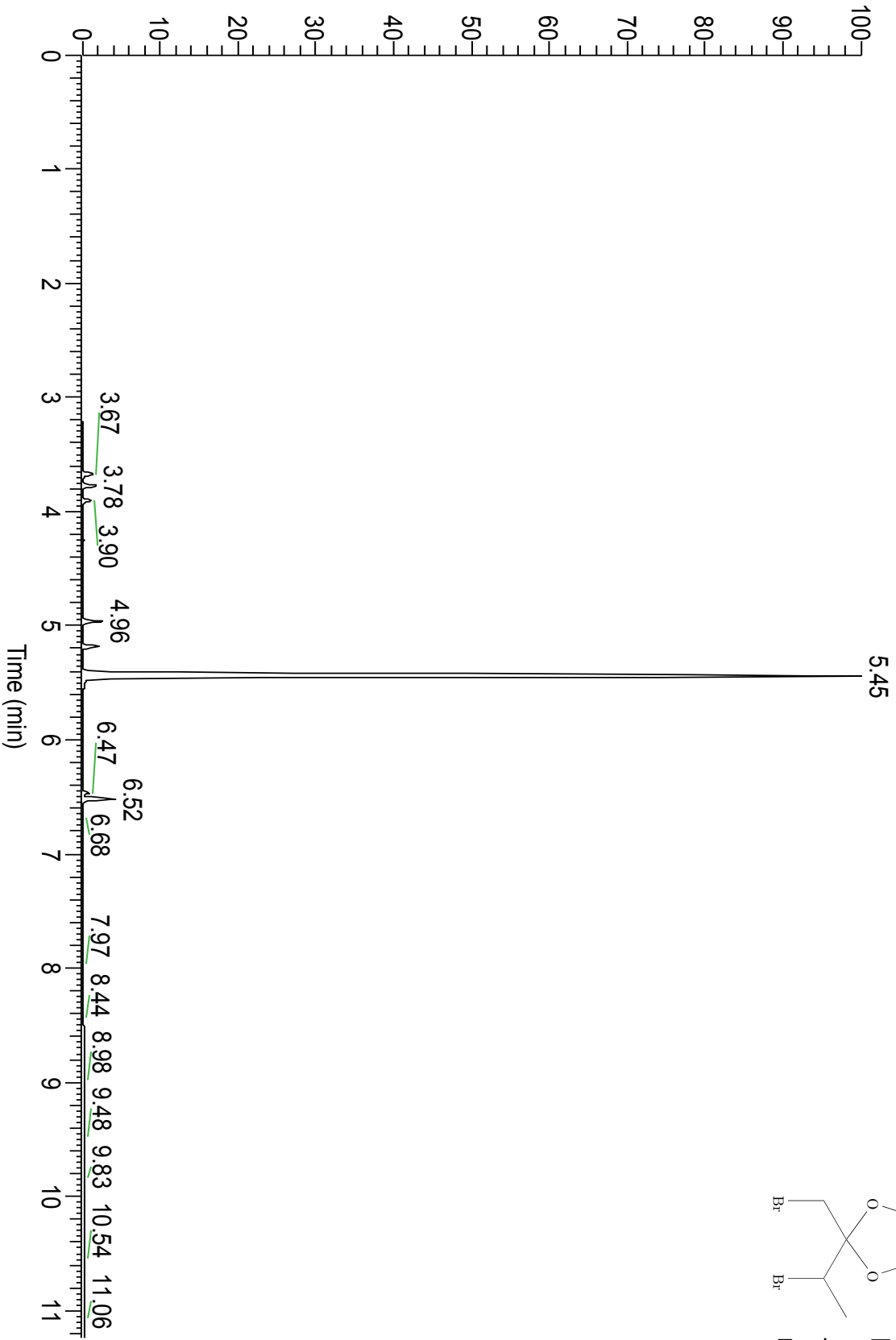
mol(4) #255-275 RT: 5.37-5.52 AV: 21 SB: 9   79, 3.86-3.90 NL: 5.43E5
T: + c Full ms [40.00-500.00]

m/z

53
56
69
83
86
100
121
135
137
149
165
179
195
273
275
277
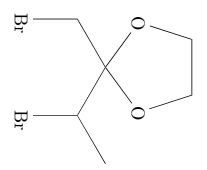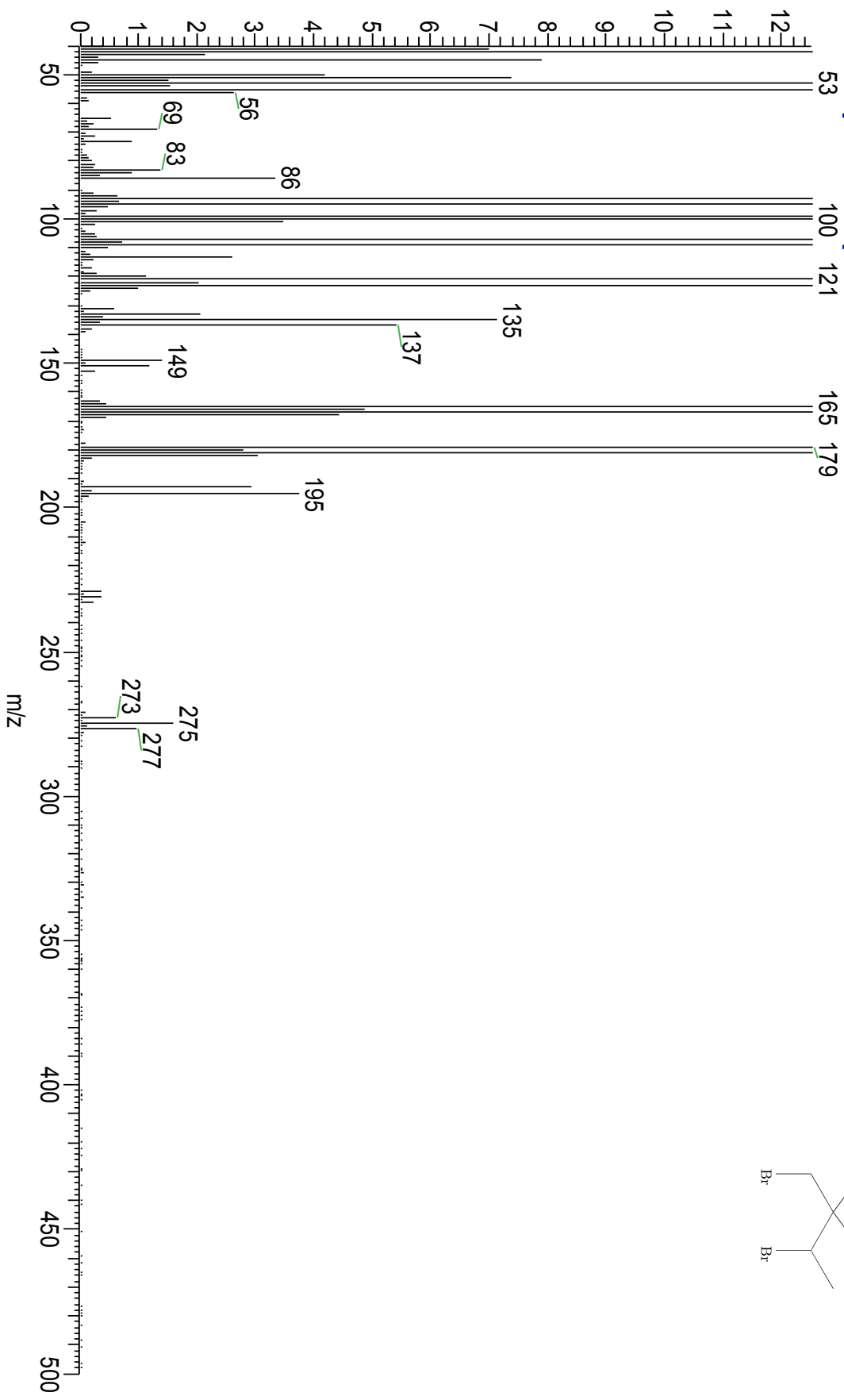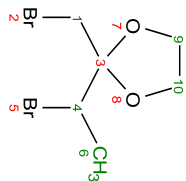
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.45 (q, *J* = 6.9 Hz, 1H), 4.25 – 4.07 (m, 3H), 3.79 (d, *J* = 11.2 Hz, 1H), 3.57 (d, *J* = 11.1 Hz, 1H), 1.69 (d, *J* = 6.9 Hz, 3H).

118
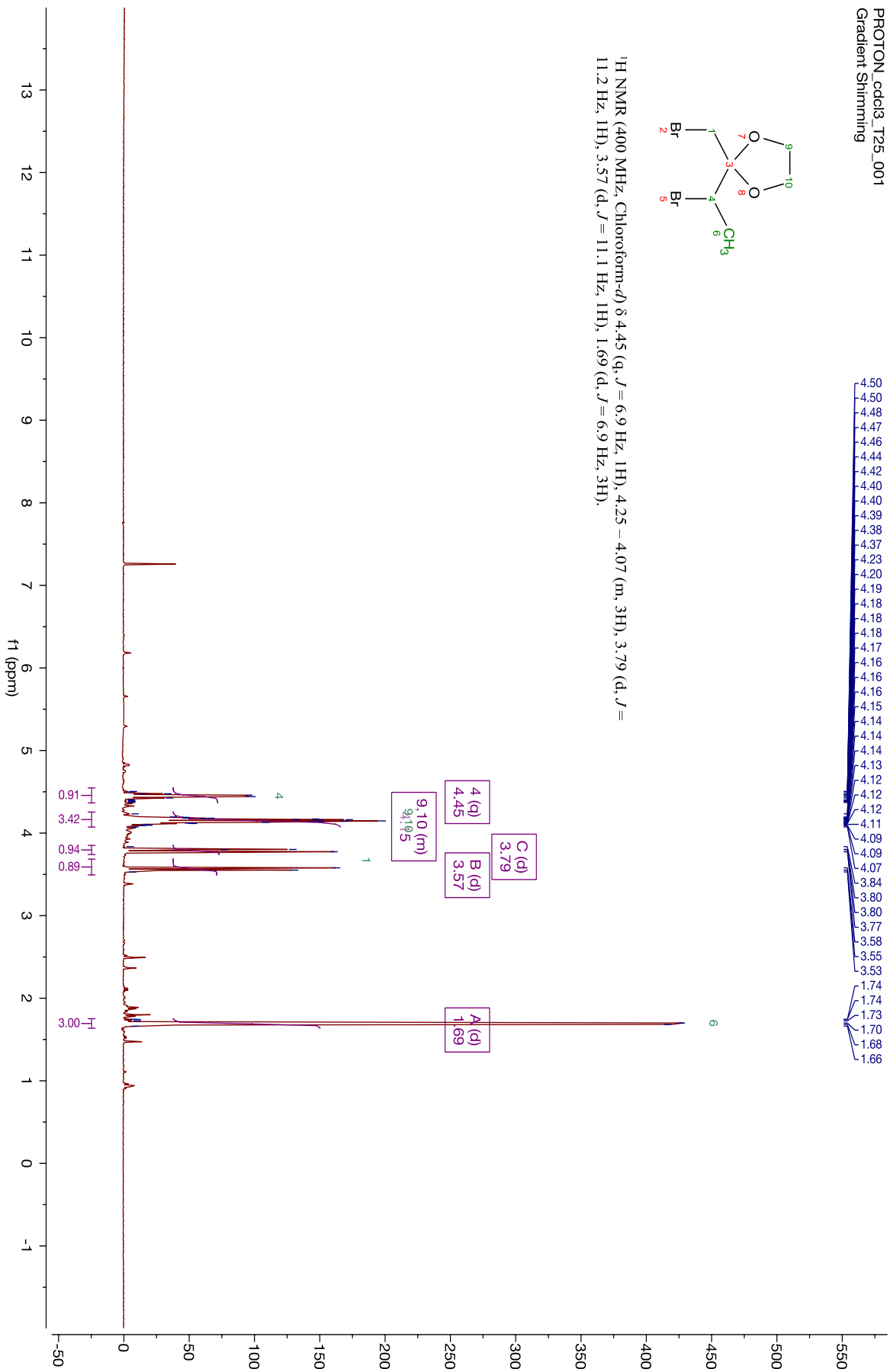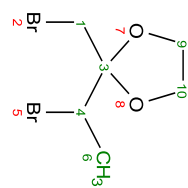
^{13}C NMR (101 MHz, cdcl$_3$) δ 108.58, 67.07, 67.04, 49.97, 34.40, 20.12.
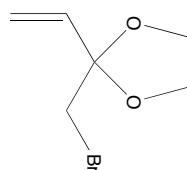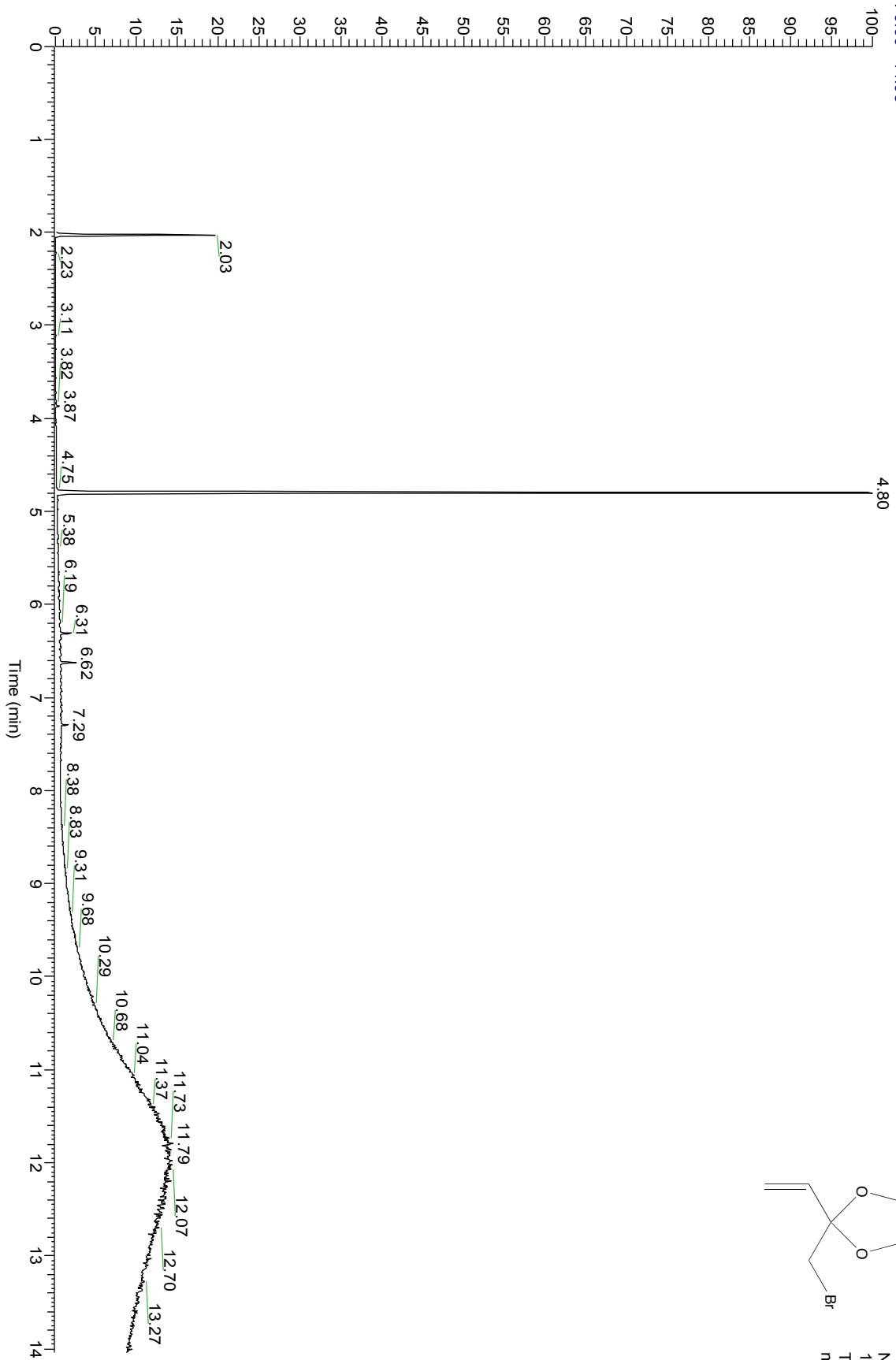
119

RT: 0.00 - 14.03

NL:
1.49E8
TIC MS
mol04

Time (min)

2.03
2.23
3.11
3.82
3.87
4.75
4.80
5.38
6.19
6.31
6.62
7.29
8.38
8.83
9.31
9.68
10.29
10.68
11.04
11.37
11.73
11.79
12.07
12.70
13.27

120

Proton_cdcl3_T25_002
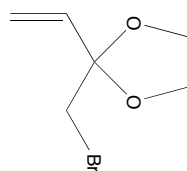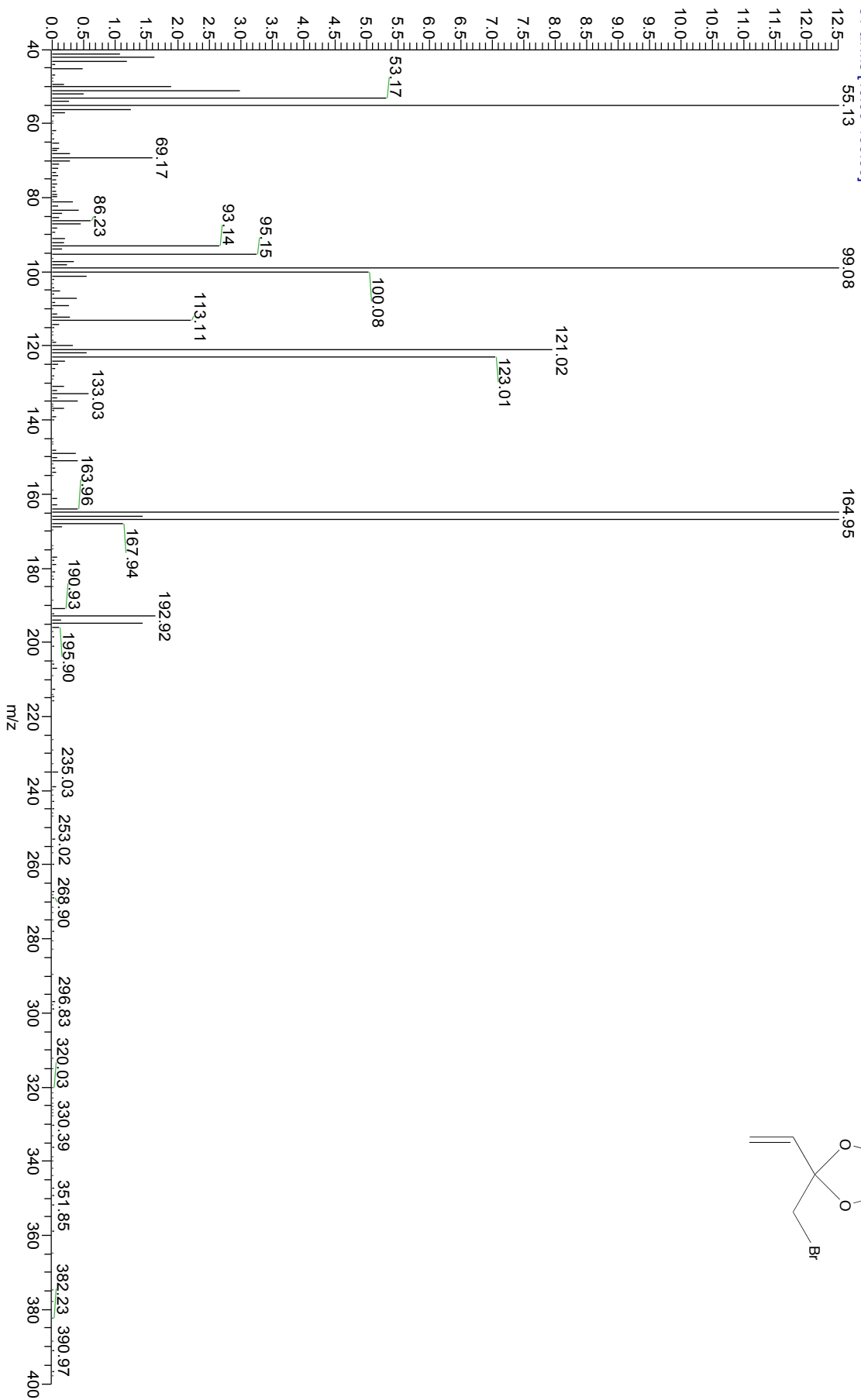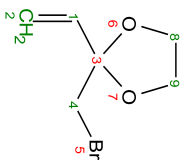
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.89 – 5.74 (m, 1H), 5.55 – 5.42 (m, 1H), 5.25 (dd, *J* = 10.6, 1.6 Hz, 1H), 4.15 – 3.98 (m, 2H), 4.00 – 3.85 (m, 2H), 3.45 (s, 2H).

122
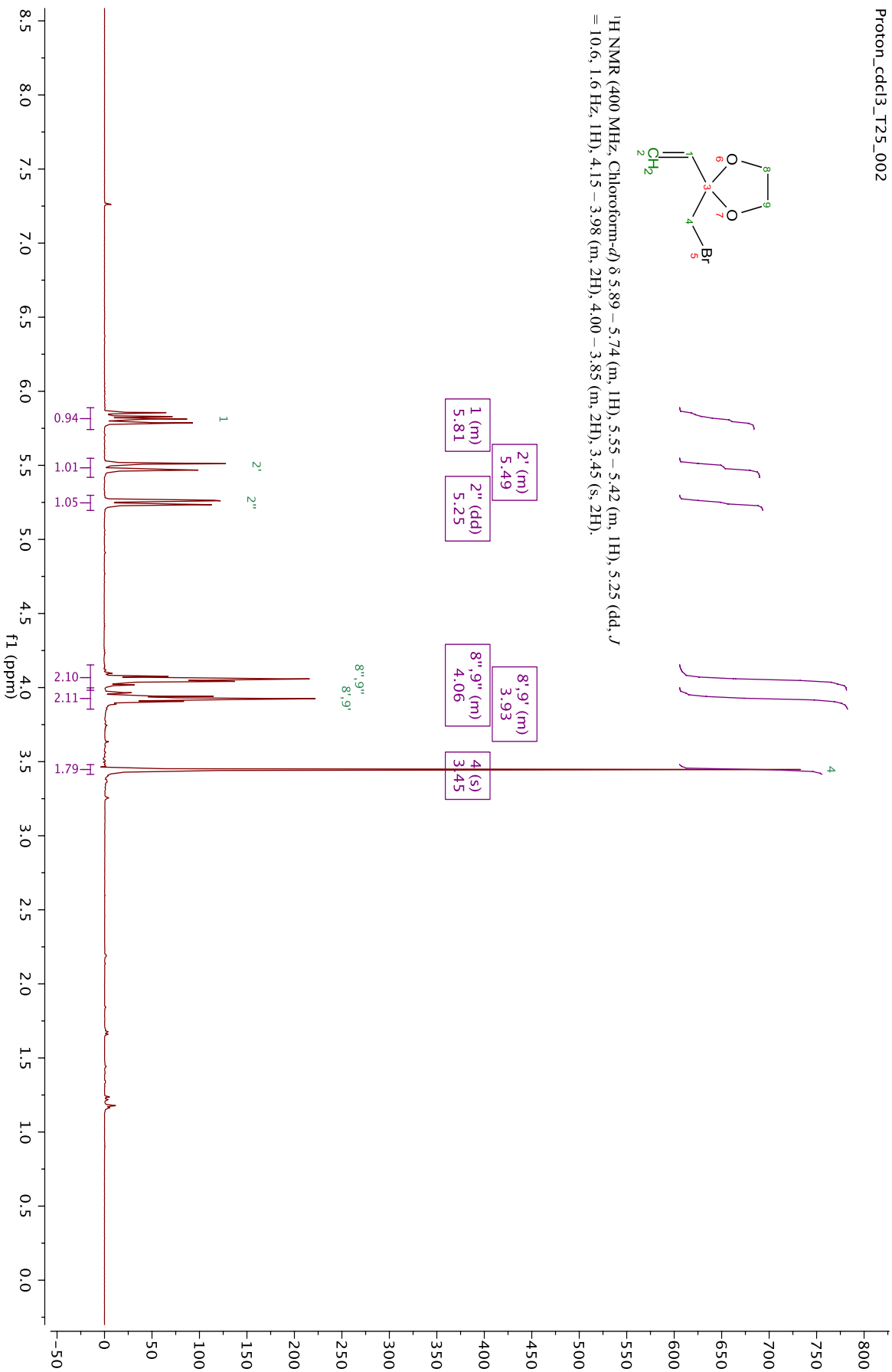
Carbon_cdcl3_T25_001
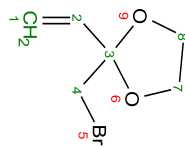
^{13}C NMR (101 MHz, cdcl$_3$) δ 134.87, 117.71, 106.02, 77.40, 77.08, 76.76, 65.65, 36.25.
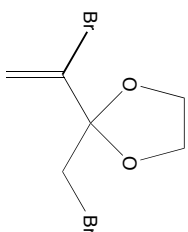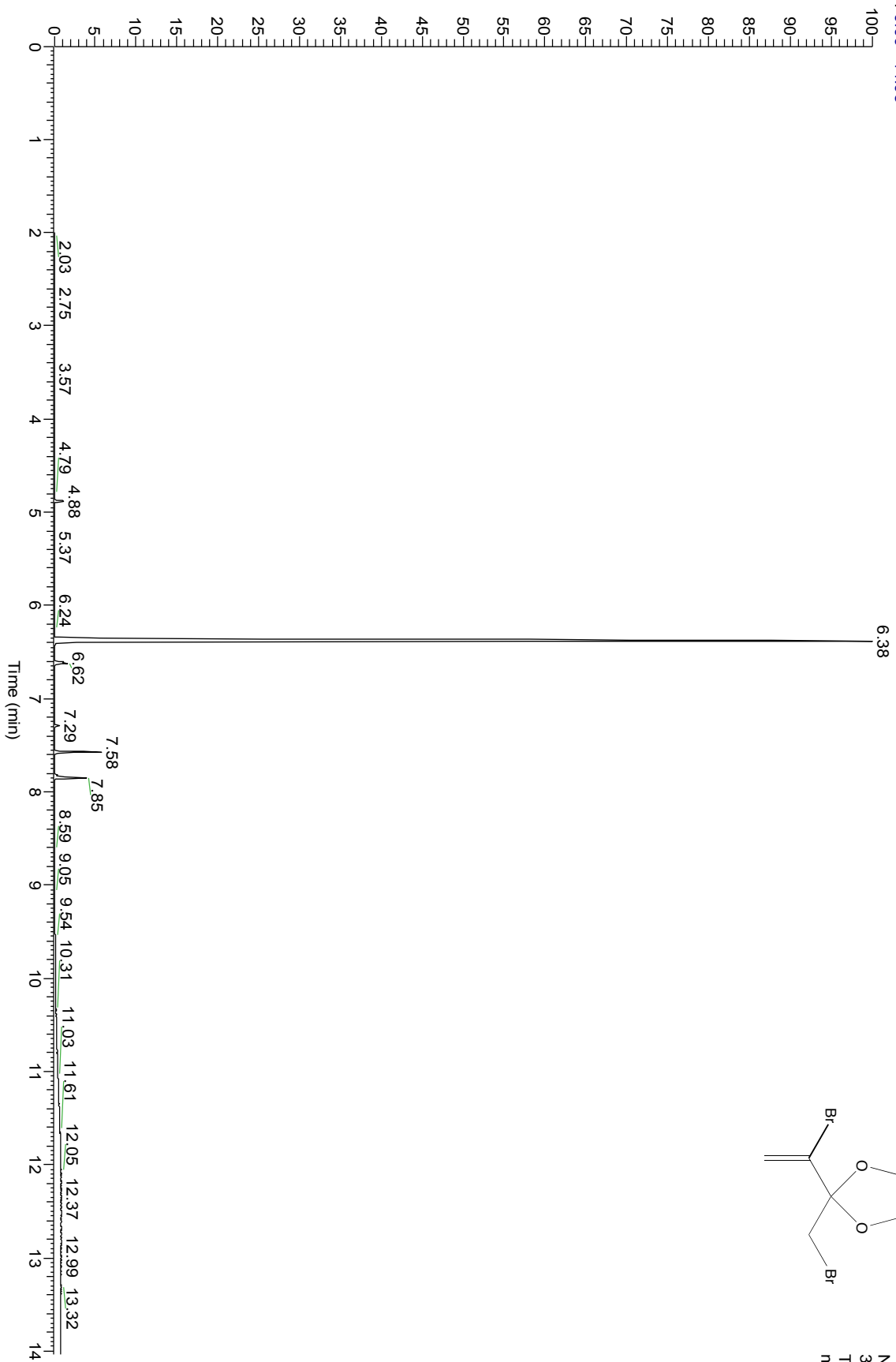
123

RT: 0.00 - 14.03

NL:
3.73E8
TIC MS
mol06

124

51.14
53.12
55.16
86.24
93.10
107.05
121.03
133.00
135.04
135.90
165.14
177.05
179.89
192.97
205.01
228.85
244.96
264.50
270.70
272.79
274.78
275.81
312.82
324.84
345.80
362.80
390.75

m/z

125
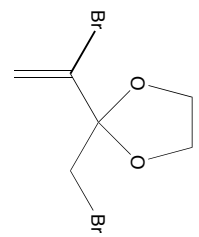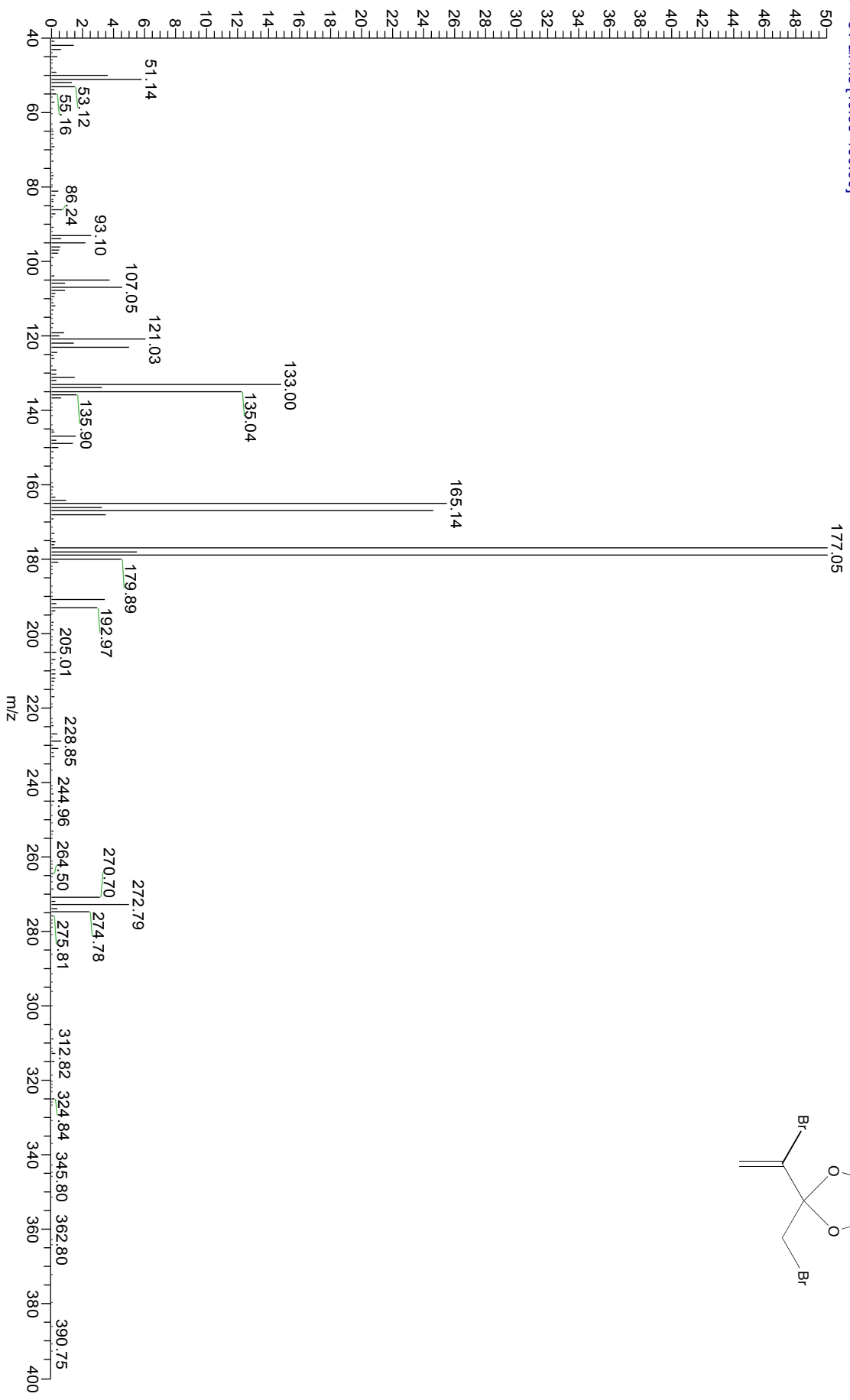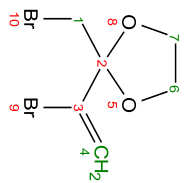
^{1}H NMR (400 MHz, Chloroform-d) δ 6.15 (d, J = 1.7 Hz, 1H), 5.68 (d, J = 1.8 Hz, 1H), 4.14 – 4.00 (m, 2H), 4.04 – 3.89 (m, 2H), 3.64 (d, J = 2.0 Hz, 2H).
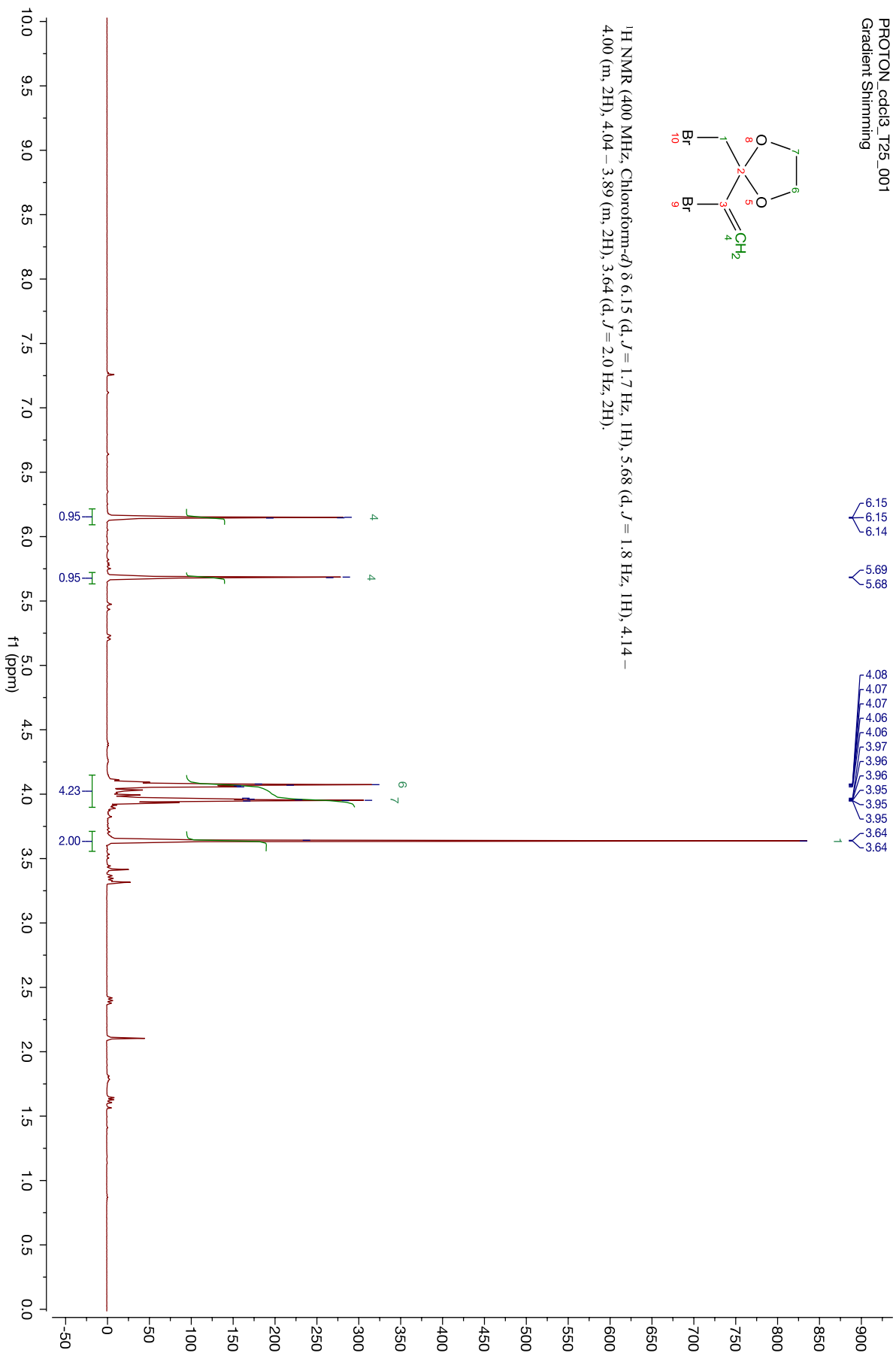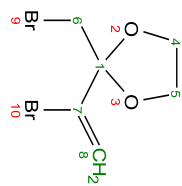
126

^{13}C NMR (101 MHz, cdcl$_3$) δ 129.07, 120.72, 120.69, 106.95, 66.06, 34.44, 34.41.

7 (s)
129.07

B (s)
120.72

8 (s)
120.69

1 (s)
106.95

4,5 (s)
66.06

6 (s)
34.41

F (s)
34.44

— 129.07

— 120.72
— 120.69

— 106.95

— 66.06

— 34.44
— 34.41

127

NL:
1.98E8
TIC MS
mol05

2.03
2.69 3.12
3.72
4.66
4.80
4.90
4.97
6.13
6.62
7.29
7.38
8.70 9.43
9.94 10.45
11.03
11.57 11.92 12.26 12.62 13.17

Time (min)

53.09
55.16
67.15
81.17
93.11
95.09
97.02
99.07
111.09
120.96
122.92
130.97
132.97
146.97
148.98
164.95
166.92
188.93
190.90
192.87
193.89
207.01
228.92
253.02
253.96
268.97
296.83
326.96
345.86
368.96
398.74

m/z

129
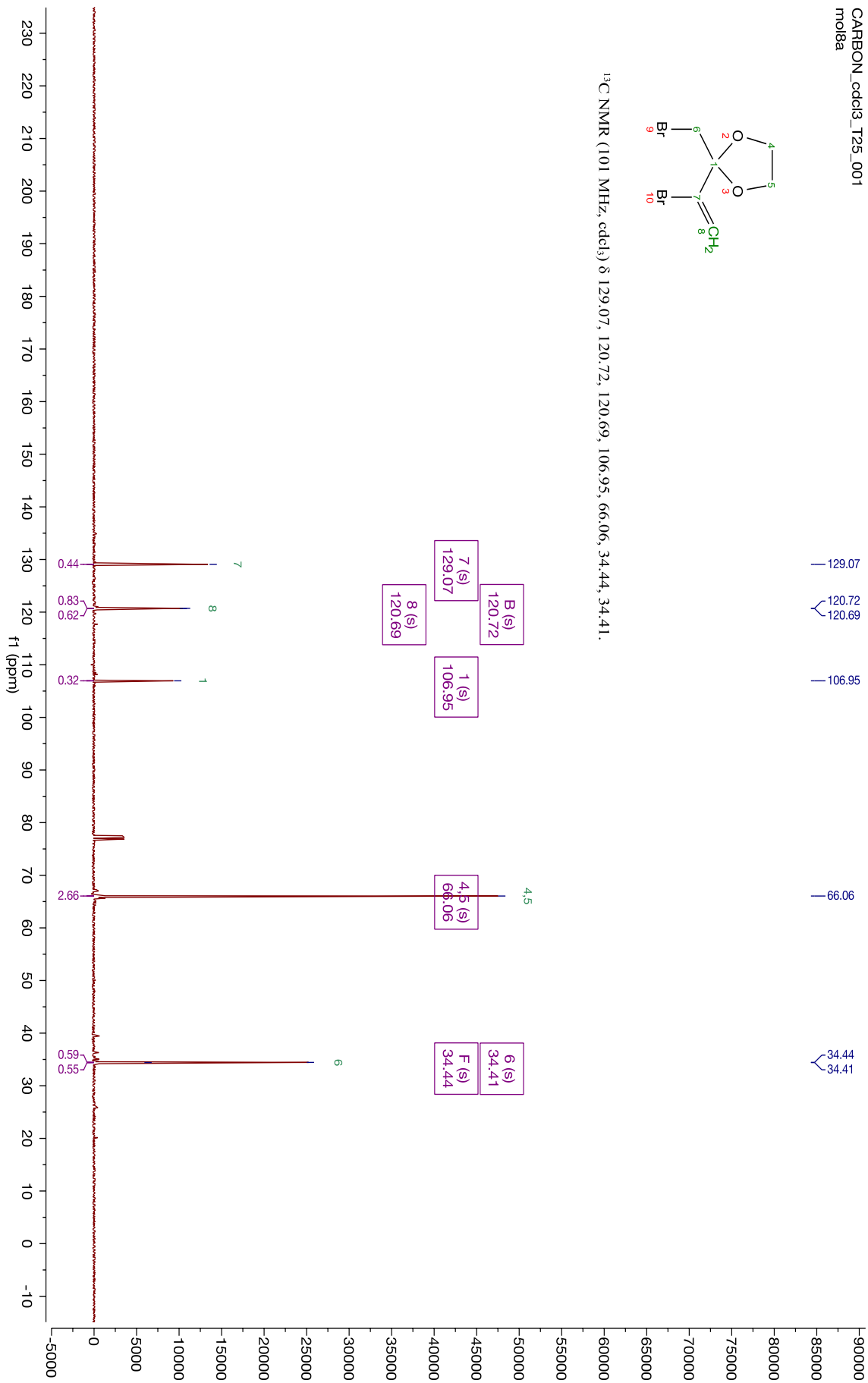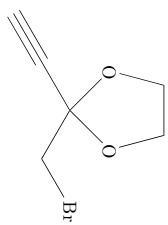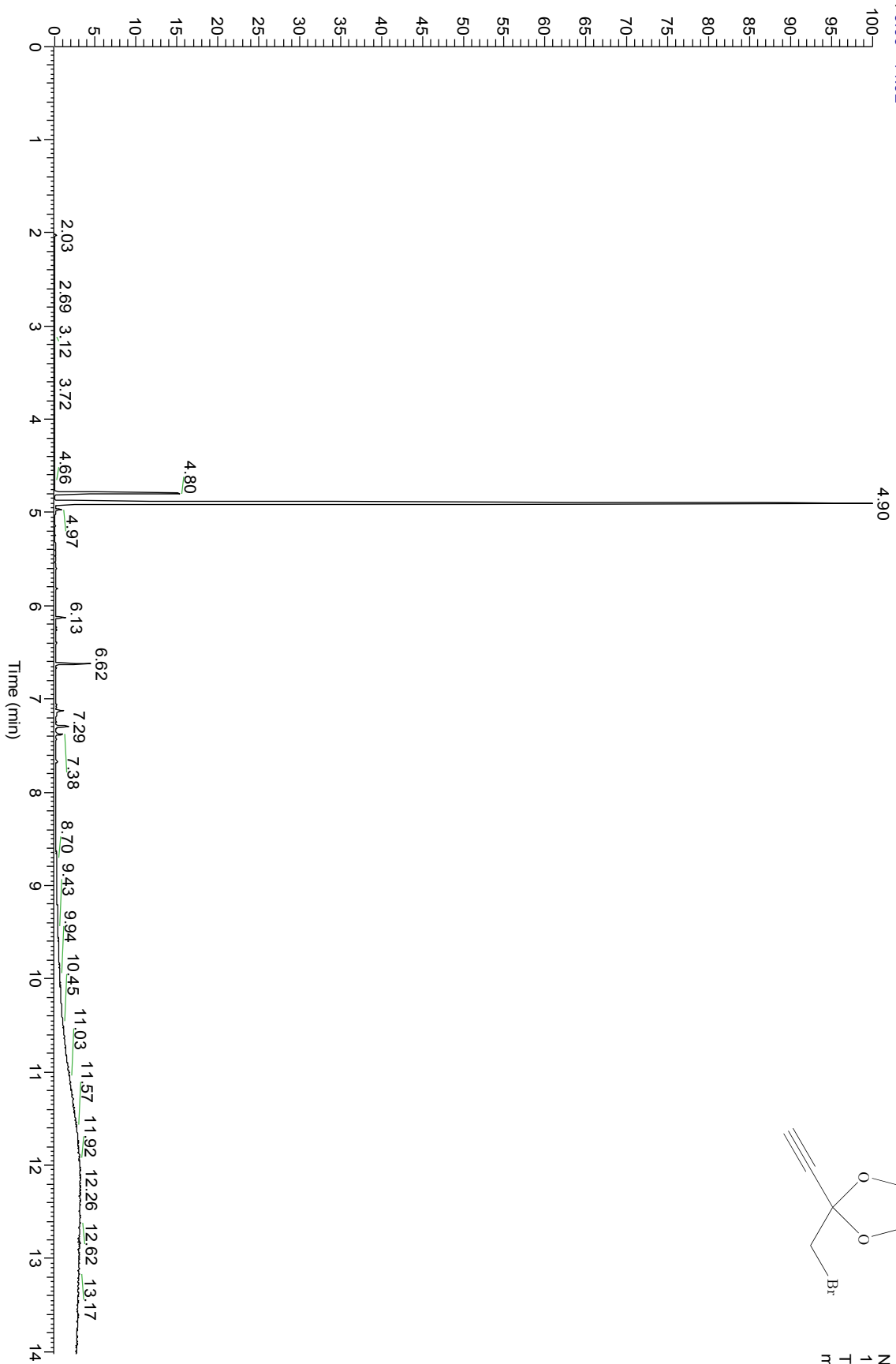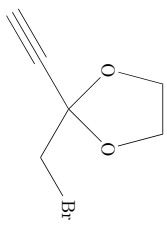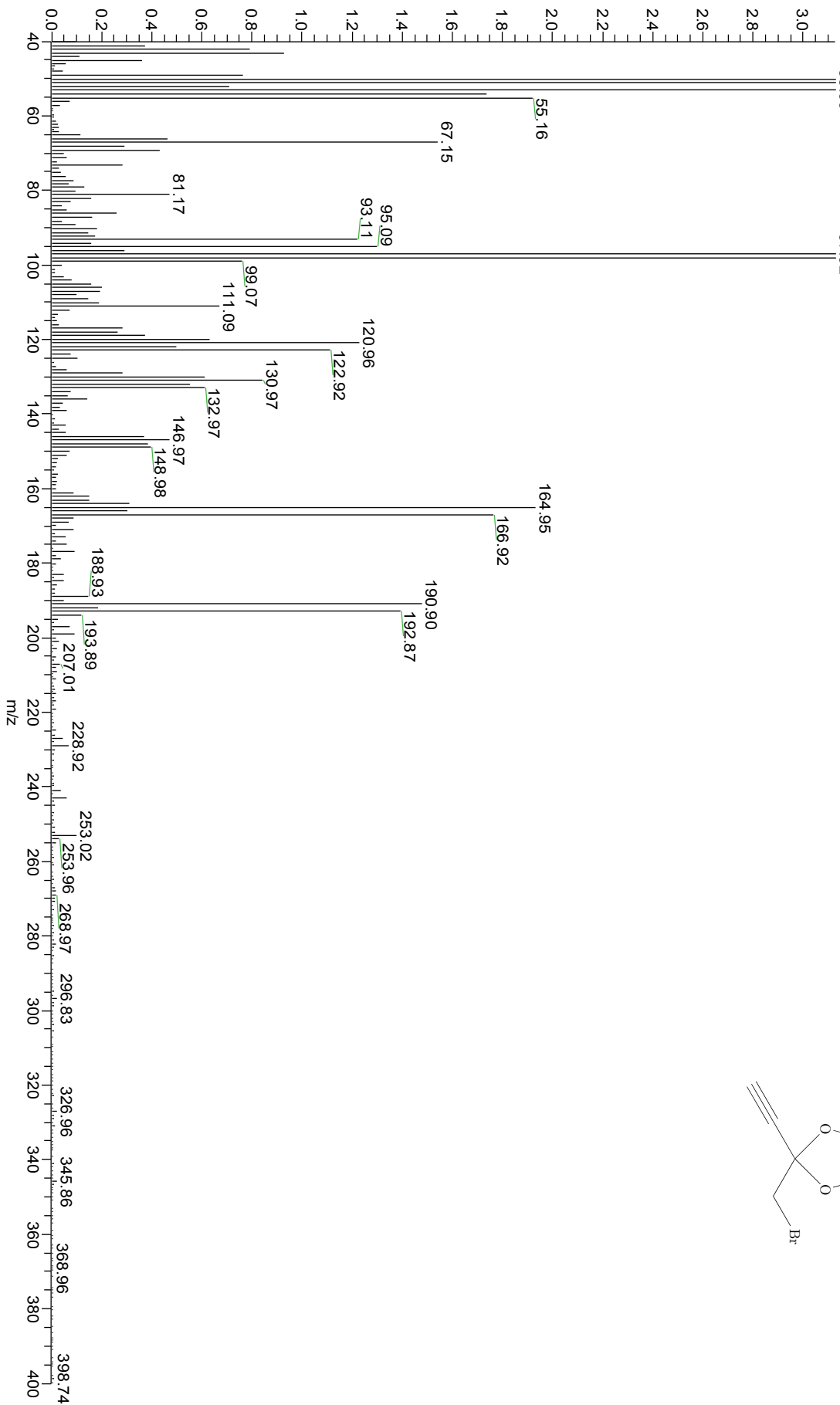
Proton_cdcl3_T25_001

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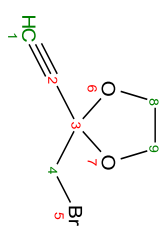
¹H NMR (400 MHz, Chloroform-*d*) δ 4.13 – 4.06 (m, 4H), 3.61 (d, *J* = 1.2 Hz, 2H), 2.60 (d, *J* = 1.1 Hz, 1H).
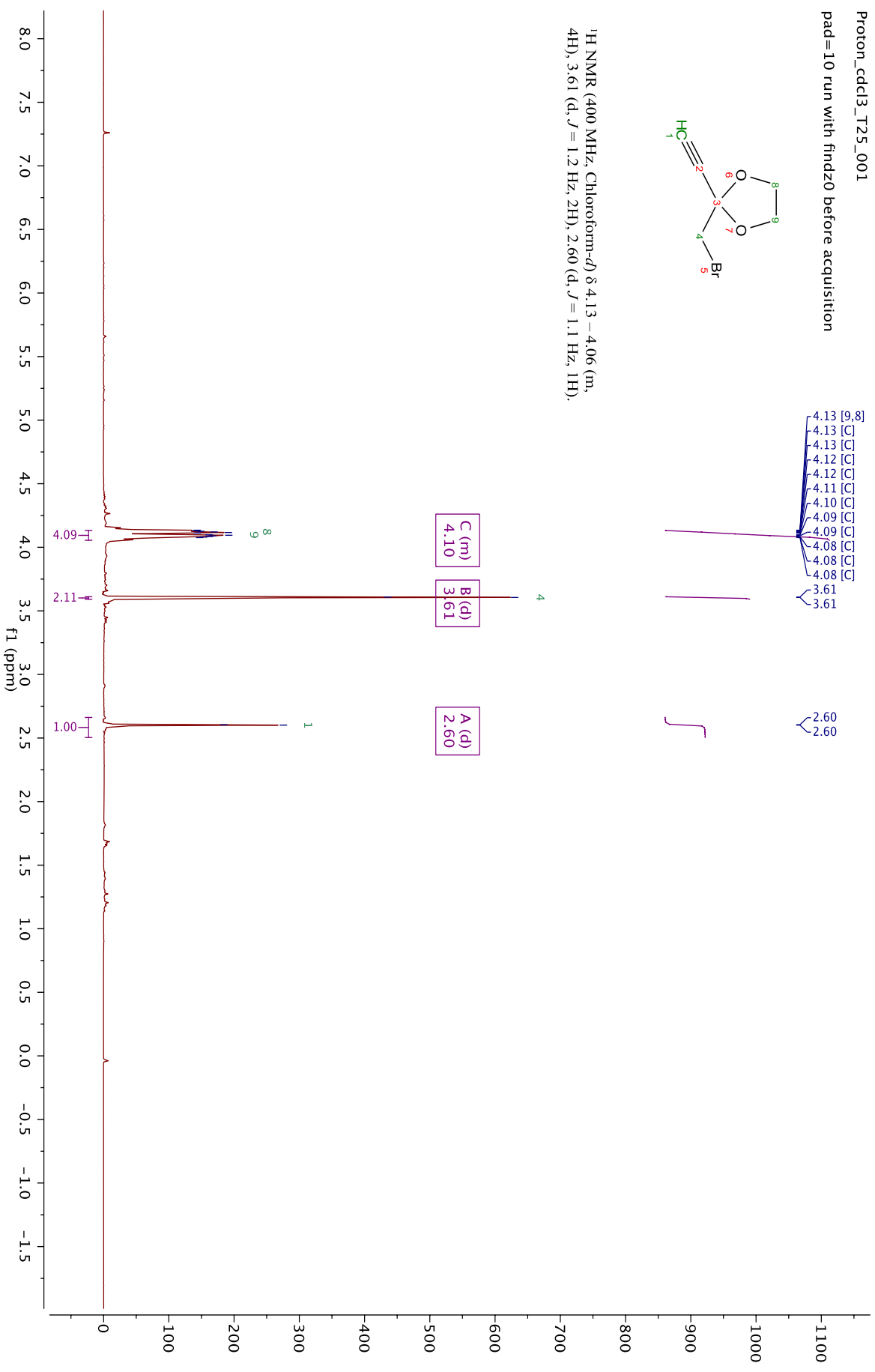
130

Carbon_cdcl3_T25_001

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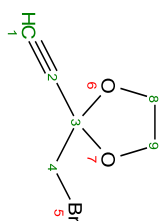
^{13}C NMR (101 MHz, Chloroform-d) δ 100.00, 79.15, 73.62, 65.99, 35.71.

3 (s)
100.00

1 (s)
79.15

2 (s)
73.62

8,9 (s)
65.99

4 (s)
35.71

— 100.00 [3]

— 79.15 [1]
— 77.43 cdcl3
— 77.11 cdcl3
— 76.79 cdcl3
— 73.62 [2]

— 65.99 [8,9]

— 35.71 [4]

0.27

0.25
1.19

2.81

1.48

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

131

RT: 0.00 - 14.00

Time (min)

2.04
2.24
3.19
3.26
4.32
4.54
4.79
4.83
5.83
6.33
6.62
6.84
7.29
8.15
8.21
9.79
9.83
11.23
11.32
12.25
12.62
13.29
13.92

NL:
2.22E8
TIC MS
mol07

132
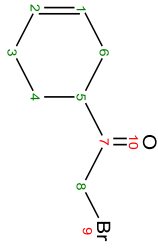
^{1}H NMR (400 MHz, Chloroform-d) δ 5.64 (s, 1H), 3.95 (s, 2H), 2.21 − 2.02 (m, 4H), 1.91 (dt, J = 12.1, 4.0 Hz, 1H), 1.65 − 1.51 (m, 1H).
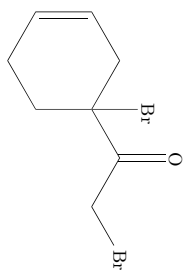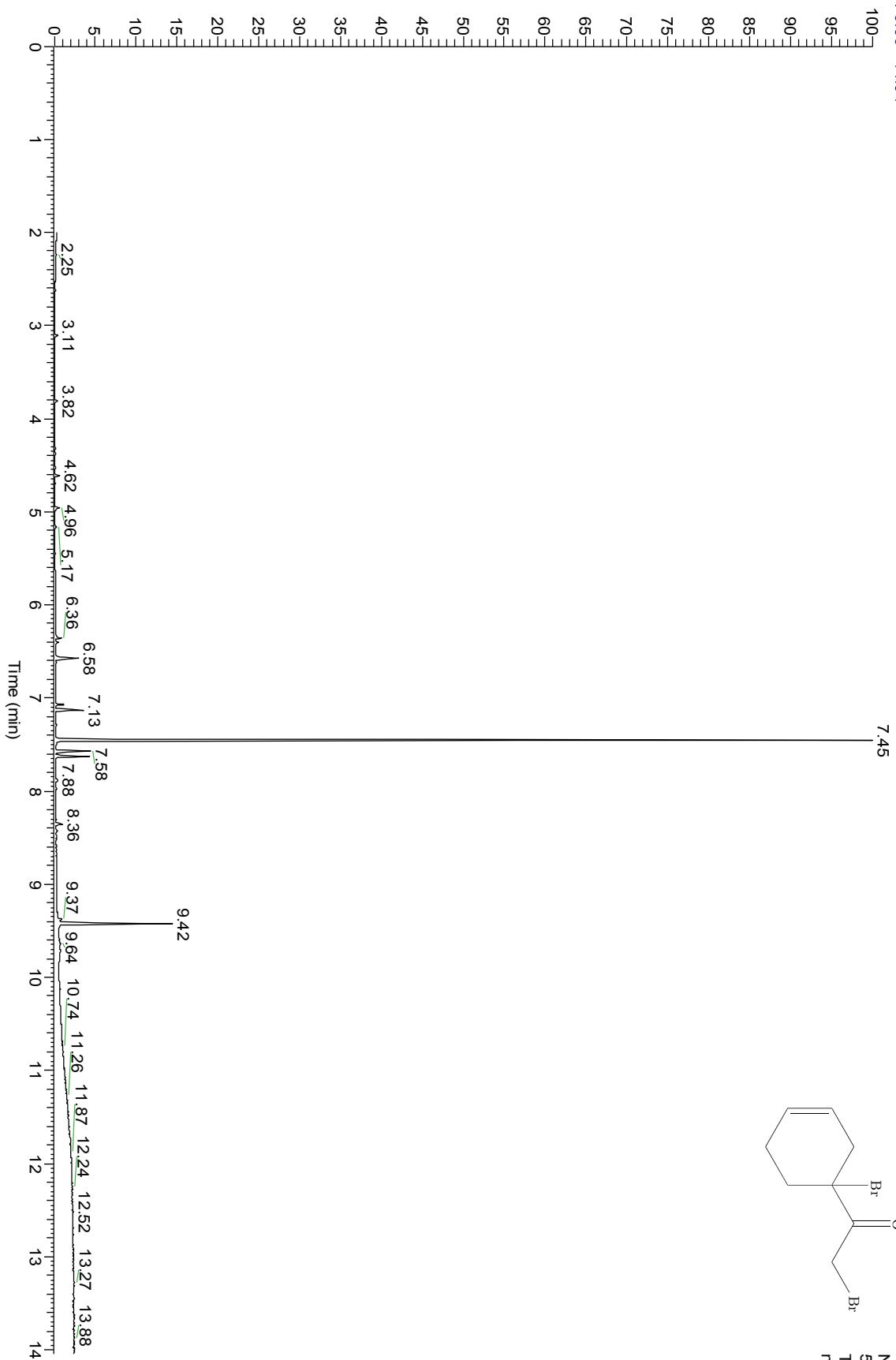
Carbon_cdcl3_T25_001

pad=10 run with findz0 before acquisition
pad=10 run with findz0 before acquisition

^{13}C NMR (101 MHz, cdcl₃) δ 204.30, 126.61, 124.88, 77.38, 77.06, 76.74, 43.90, 33.27, 27.05, 24.86, 24.49.

135

RT: 0.00 - 14.04

NL:
5.68E7
TIC MS
mol09

136

Proton_cdcl3_T25_002

138
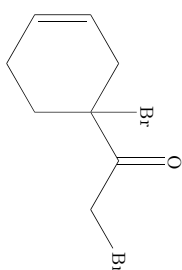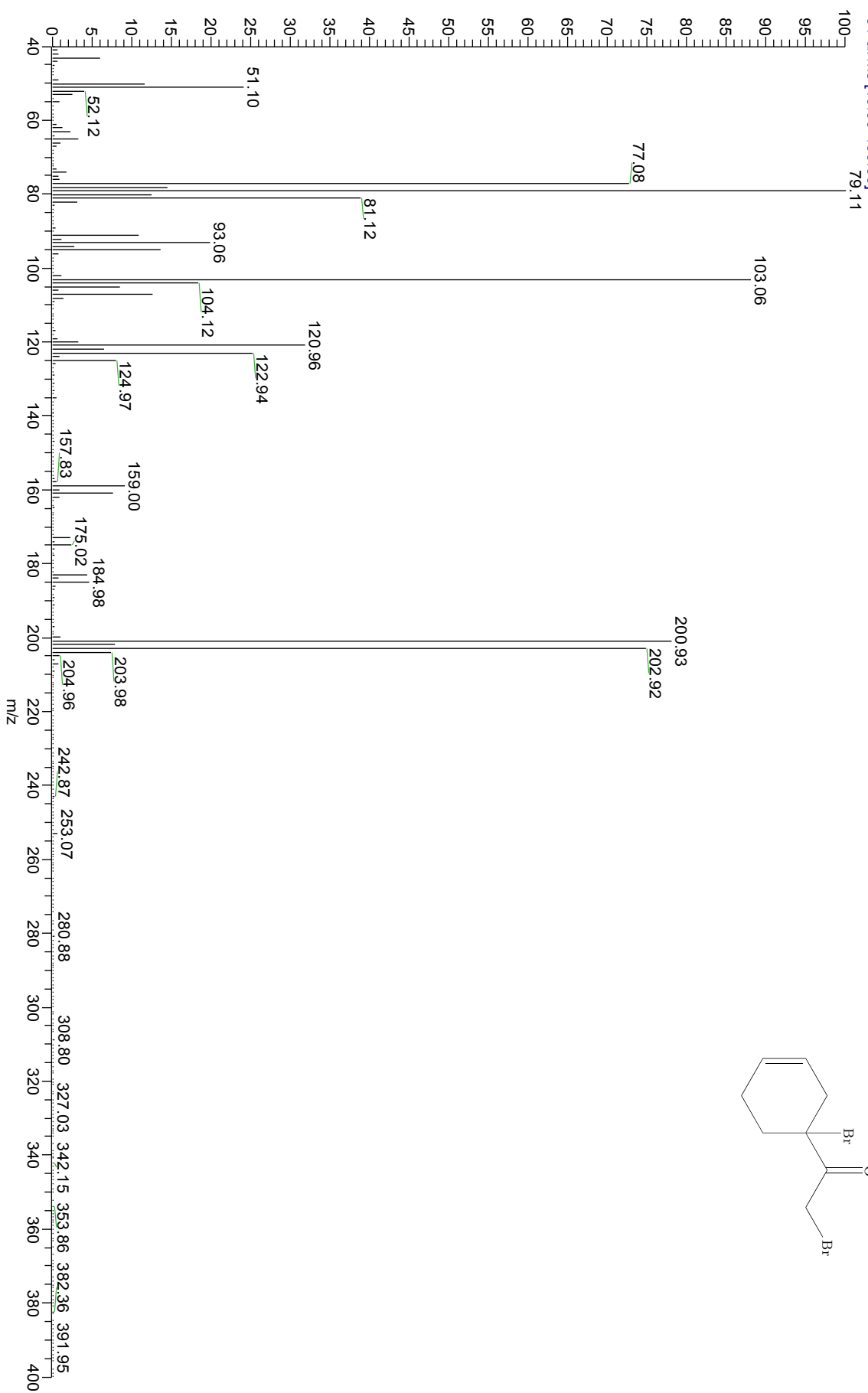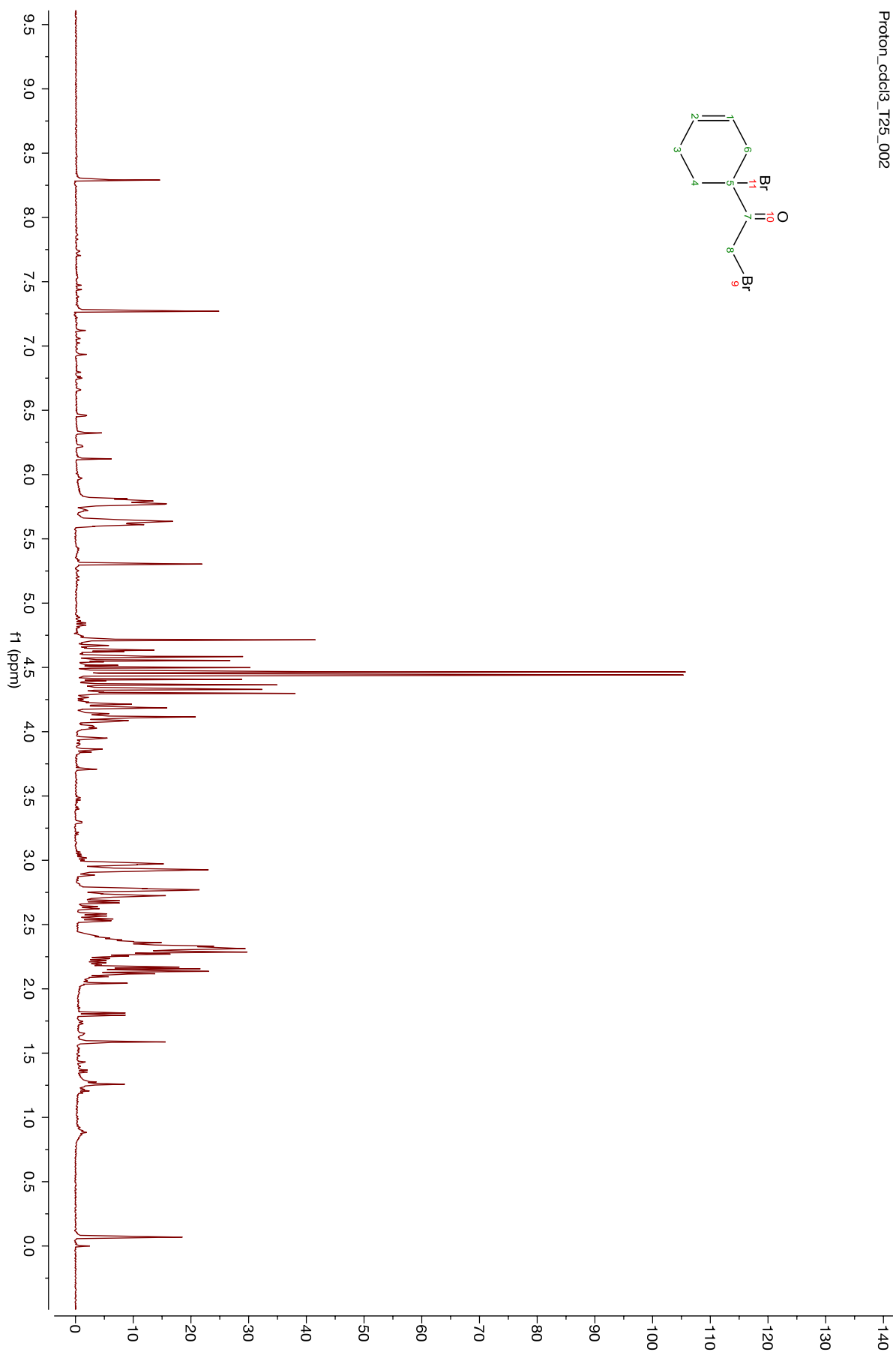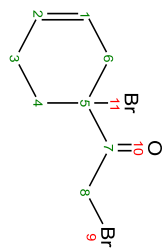
Carbon_cdcl3_T25_00
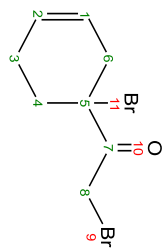
^{13}C NMR (101 MHz, cdcl$_3$) δ 195.60, 126.31, 122.30, 66.04, 36.41, 32.44, 29.70, 23.81.

139
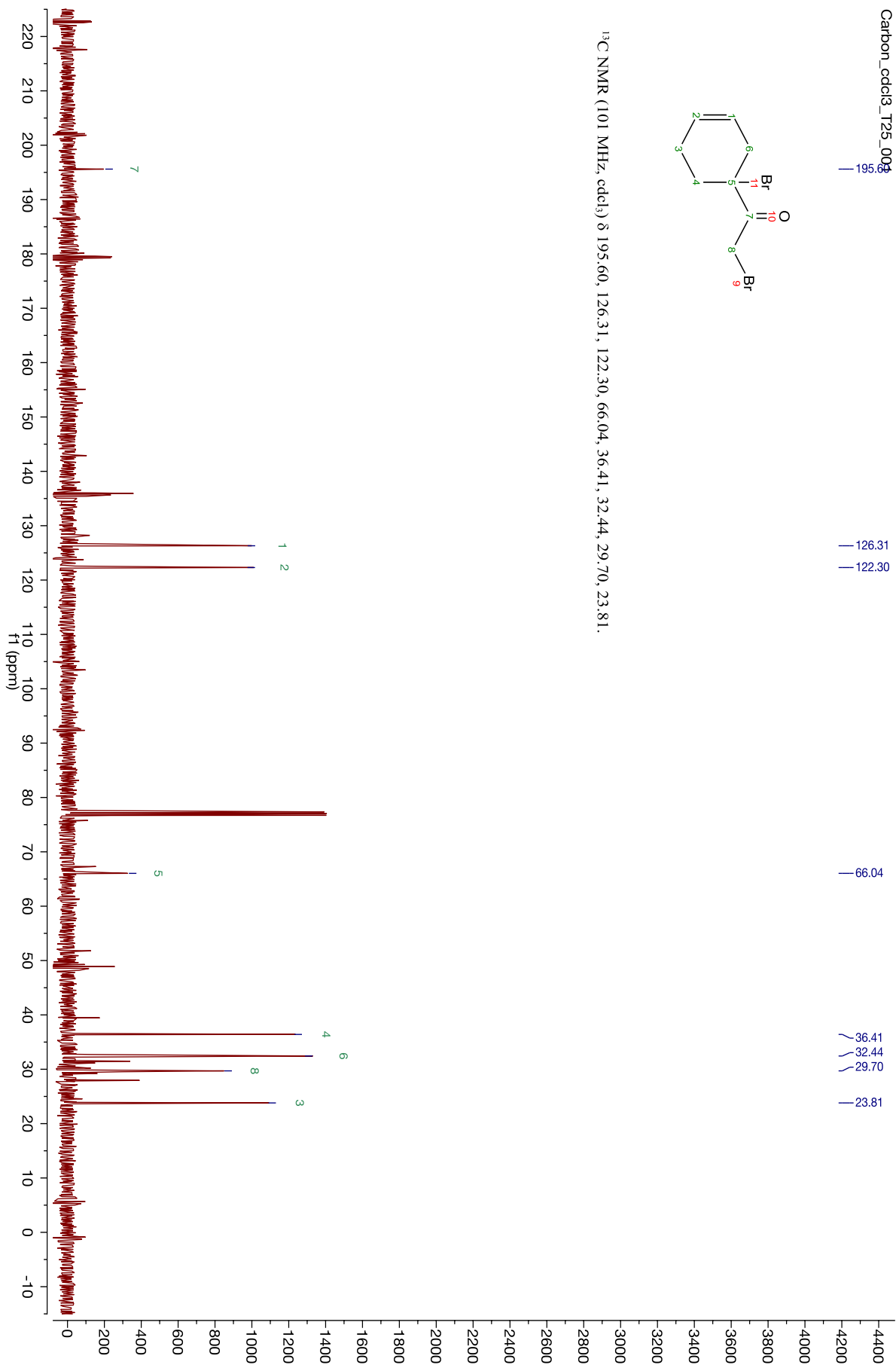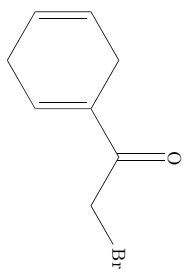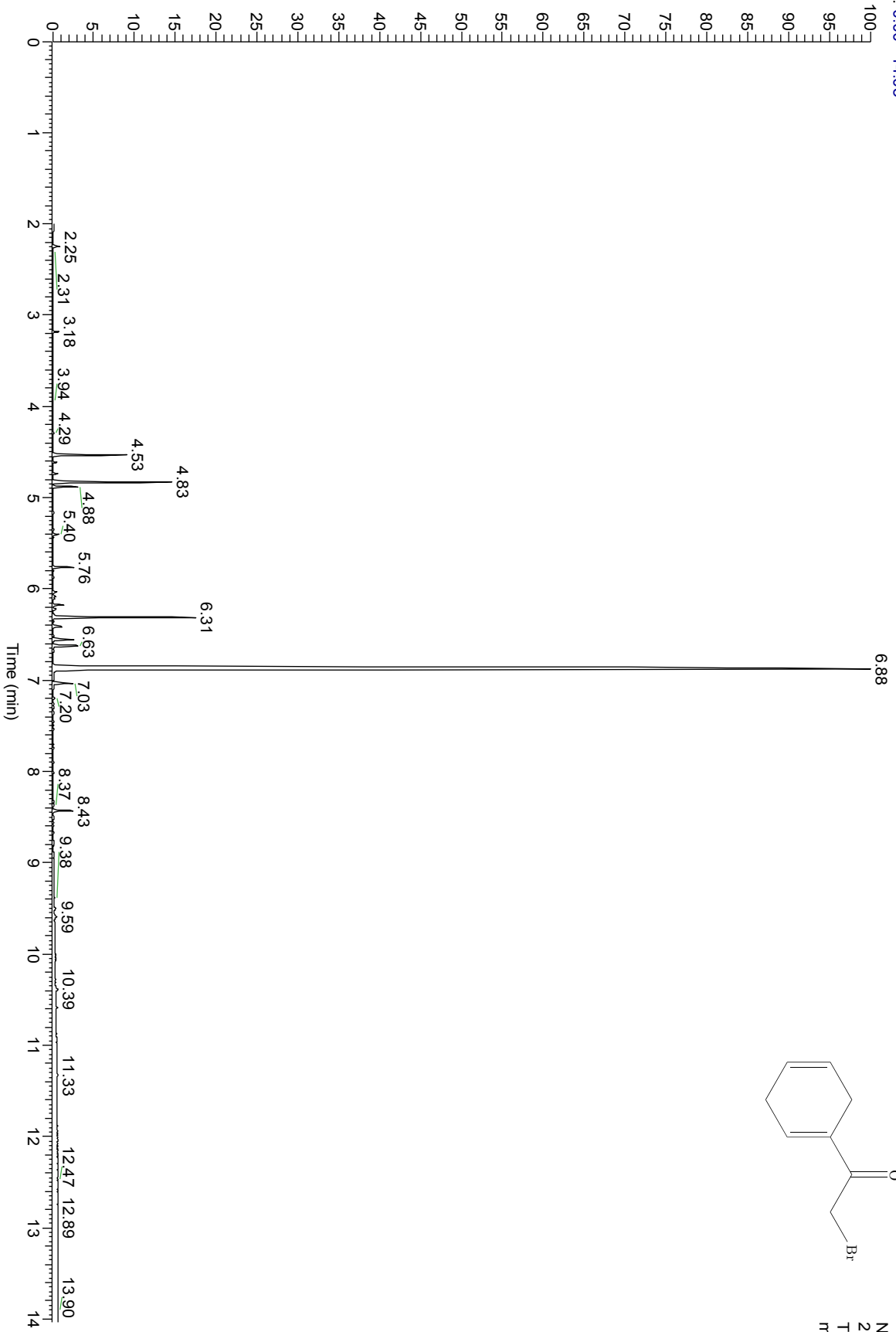
mol08 #702 RT: 6.88 AV: 1 NL: 7.24E7
T: + c Full ms [40.00-400.00]

51.21
52.20
77.22
79.29
91.19
103.11
105.06
107.09
121.00
123.04
124.11
157.02
169.06
183.00
200.97
203.97
240.80
258.89
275.62
302.97
322.55
336.06
354.99
373.03
398.91

m/z

141

Proton_cdcl3_T25.09.1

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.97 (tt, *J* = 3.8, 1.5 Hz, 1H), 5.88 – 5.62 (m, 2H), 4.20 (s, 2H), 3.08 – 2.84 (m, 4H).

D (tt)
6.97

C (m)
5.75

A (s)
4.20

B (m)
2.94

1.02
2.02
2.00
4.28

6.98 [D]
6.98 [D]
6.98 [D]
6.97 [D]
6.97 [D]
6.96 [D]
6.96 [D]
6.96 [D]
6.92 [D]
5.84 [C]
5.83 [C]
5.83 [C]
5.82 [C]
5.82 [C]
5.82 [C]
5.81 [C]
5.81 [C]
5.80 [C]
5.80 [C]
5.79 [C]
5.79 [C]
5.79 [C]
5.70 [C]
5.70 [C]
5.69 [C]
5.69 [C]
5.69 [C]
5.68 [C]
5.68 [C]
5.67 [C]
5.67 [C]
5.66 [C]
5.66 [C]
5.66 [C]
5.65 [C]
5.65 [C]
5.64 [C]

4.22
4.20
4.19
4.19

3.07 [B]
3.02 [B]
3.01 [B]
3.01 [B]
3.00 [B]
3.00 [B]
2.99 [B]
2.99 [B]
2.99 [B]
2.98 [B]
2.98 [B]
2.98 [B]
2.97 [B]
2.97 [B]
2.96 [B]
2.96 [B]
2.96 [B]
2.95 [B]
2.93
2.92
2.92
2.92
2.91 [B]
2.91 [B]
2.91 [B]
2.90 [B]
2.90 [B]
2.89 [B]
2.89 [B]
2.89 [B]
2.88 [B]
2.88 [B]
2.87 [B]
2.87 [B]

f1 (ppm)

142

Carbon_cdcl3_T25_001

^{13}C NMR (101 MHz, cdcl$_3$) δ 191.67, 139.47, 134.04, 124.44, 121.62, 77.35, 77.03, 76.71, 29.65, 27.36, 24.25.

—191.67

—139.47
—134.04

—124.44
—121.62

77.35 cdcl3
77.03 cdcl3
76.71 cdcl3

—29.65 [8]
27.36
—24.25

143
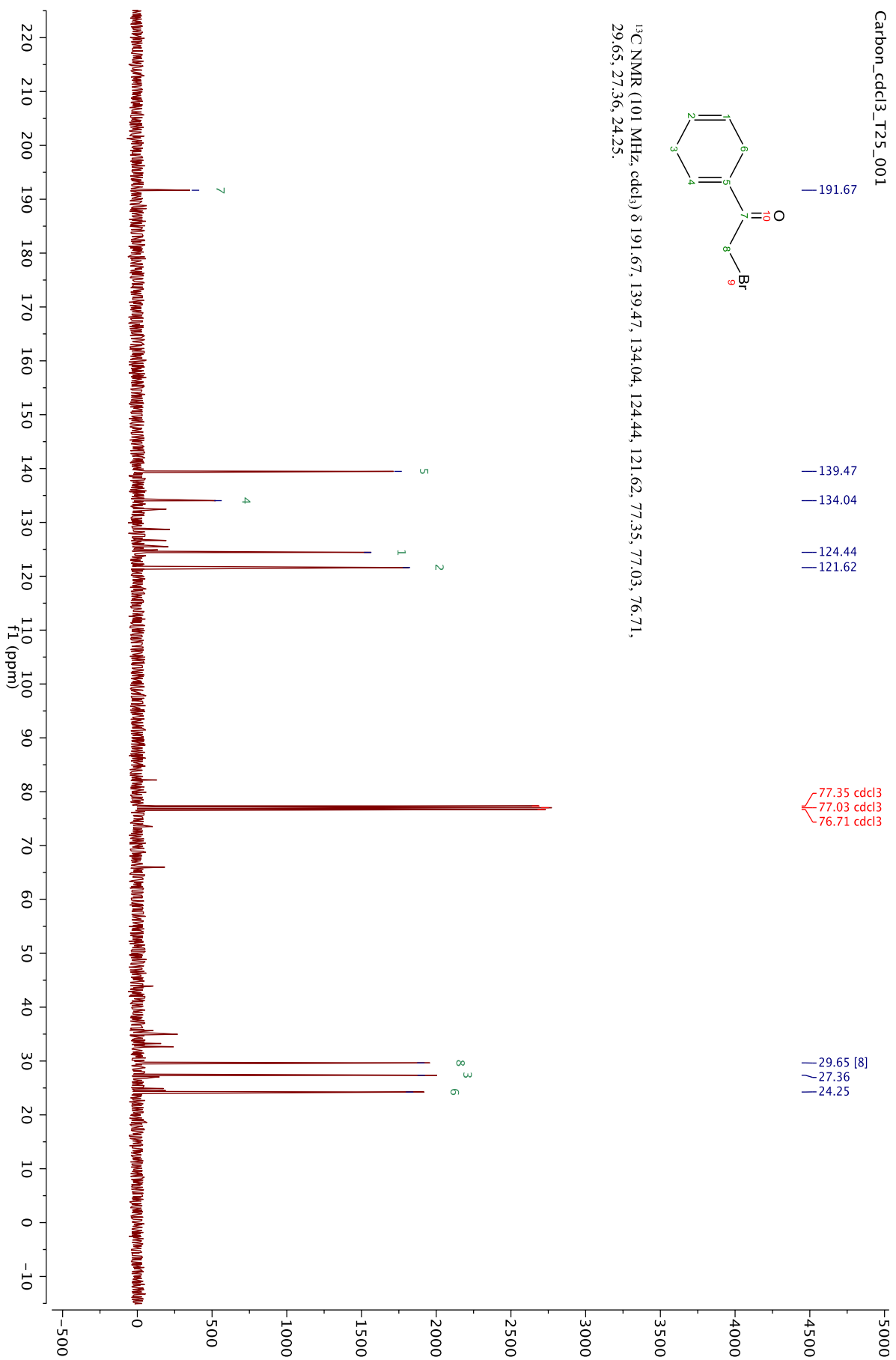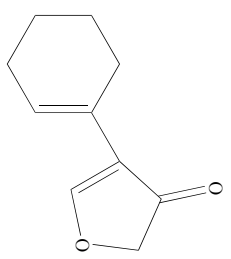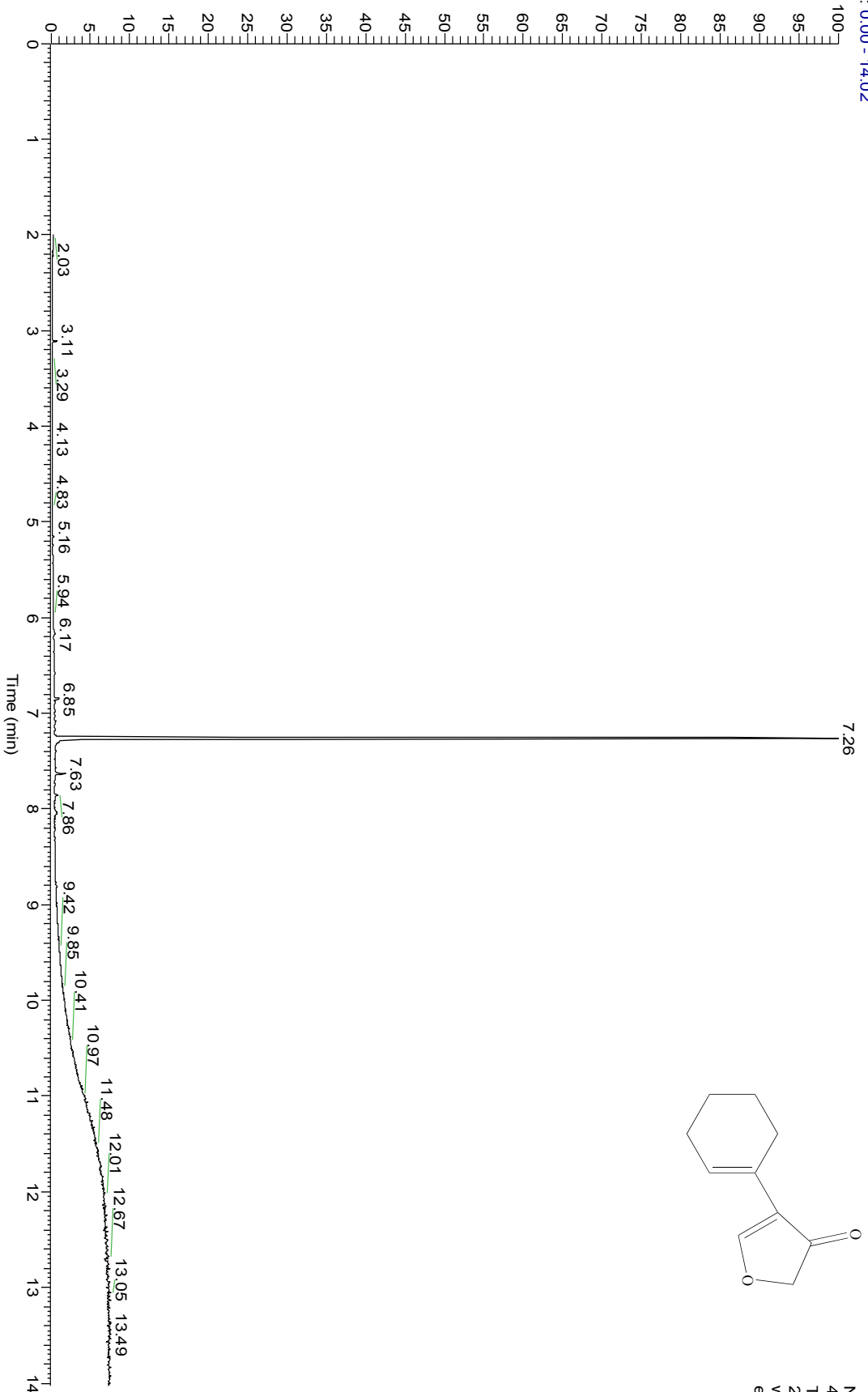
NL:
4.52E7
TIC MS
2+2 mol 3
with storck
enamine

2.03

3.11
3.29
4.13
4.83
5.16
5.94
6.17
6.85

7.26

7.63
7.86

9.42
9.85
10.41
10.97
11.48
12.01
12.67
13.05
13.49

Time (min)

Proton

295 K, CDCl$_3$

146
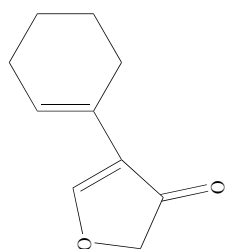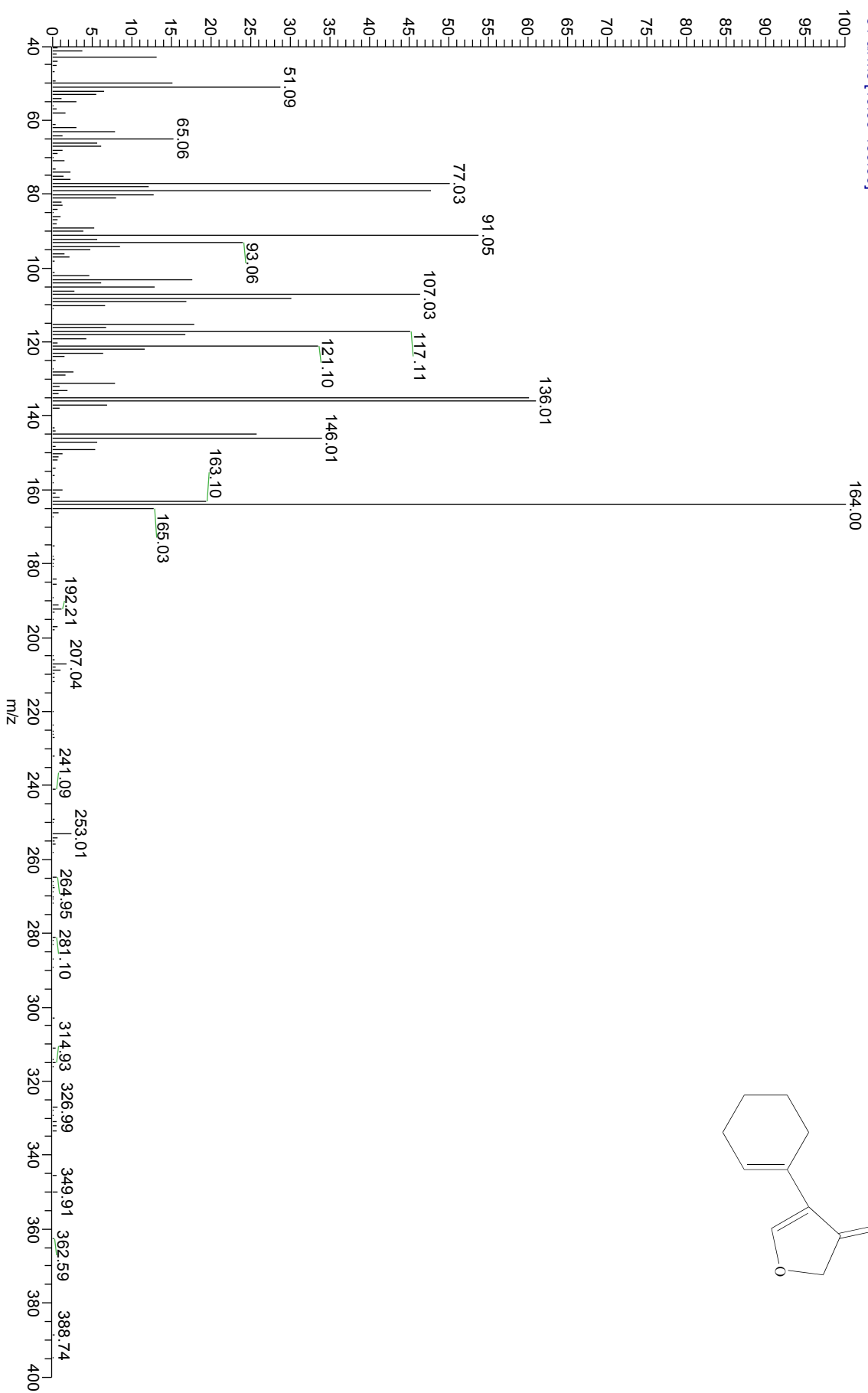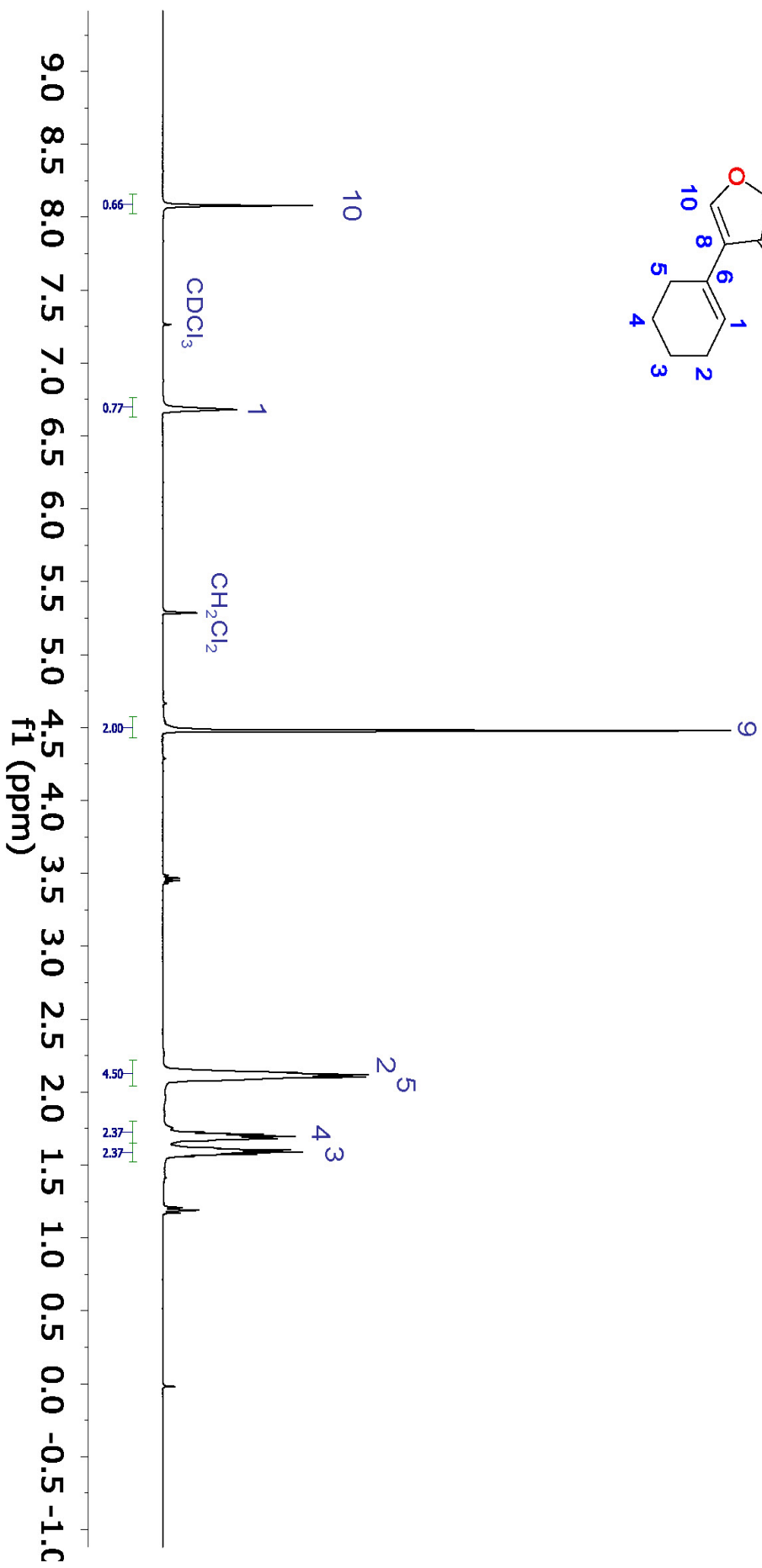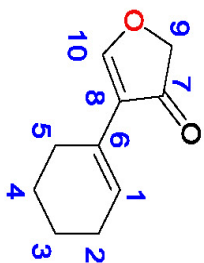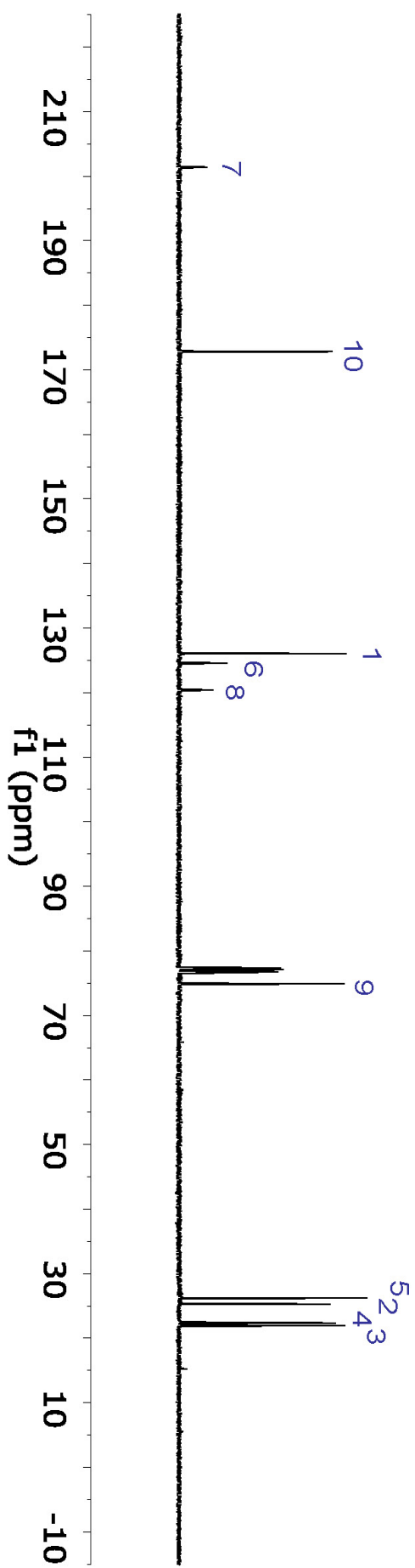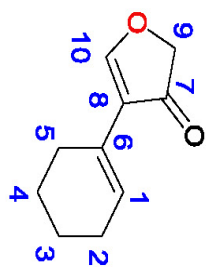
Carbon

295 K, CDCl$_3$

gHSQC+gHMBC 295 K, CDCl$_3$

148
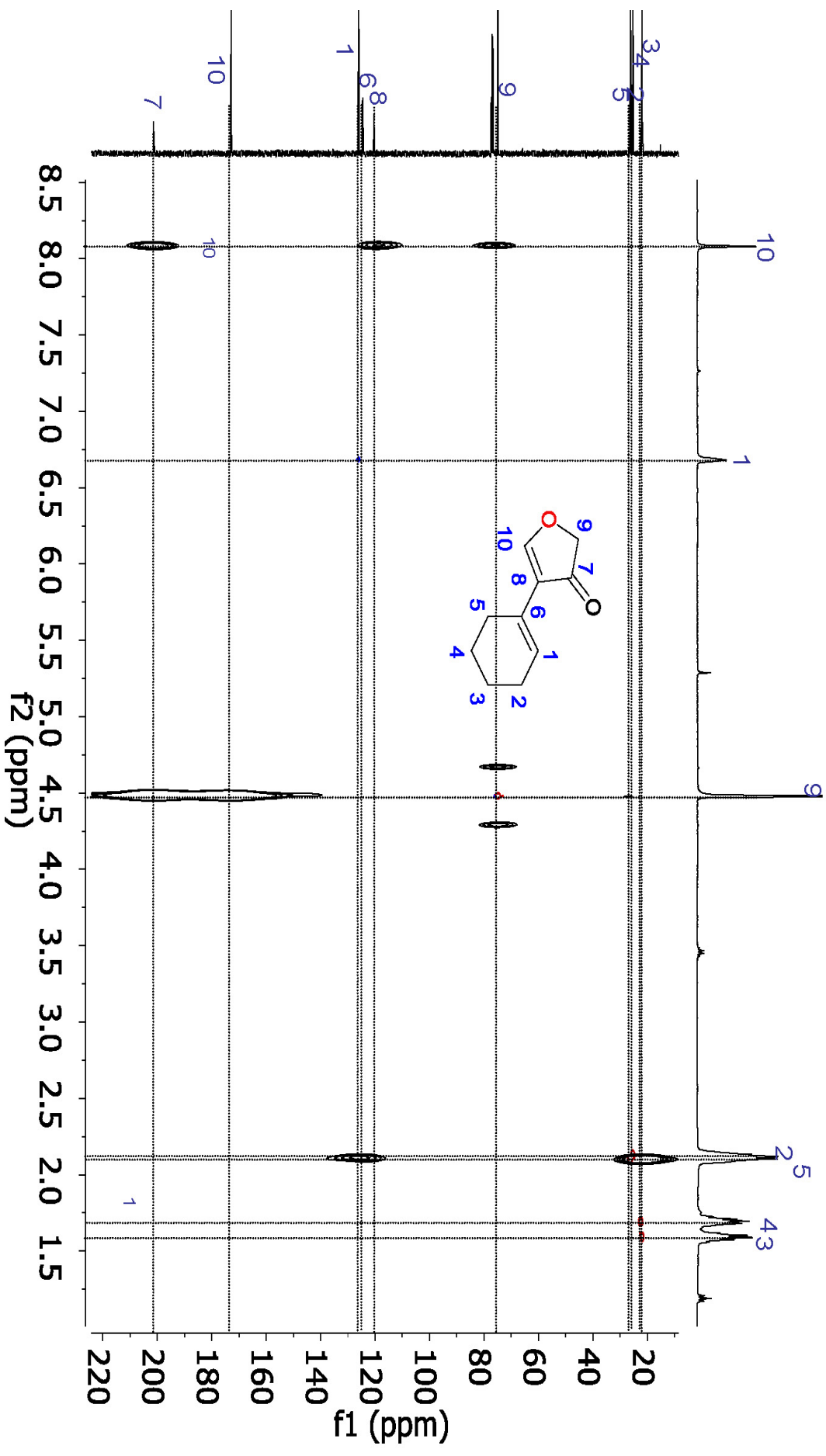
NOESY, 700ms
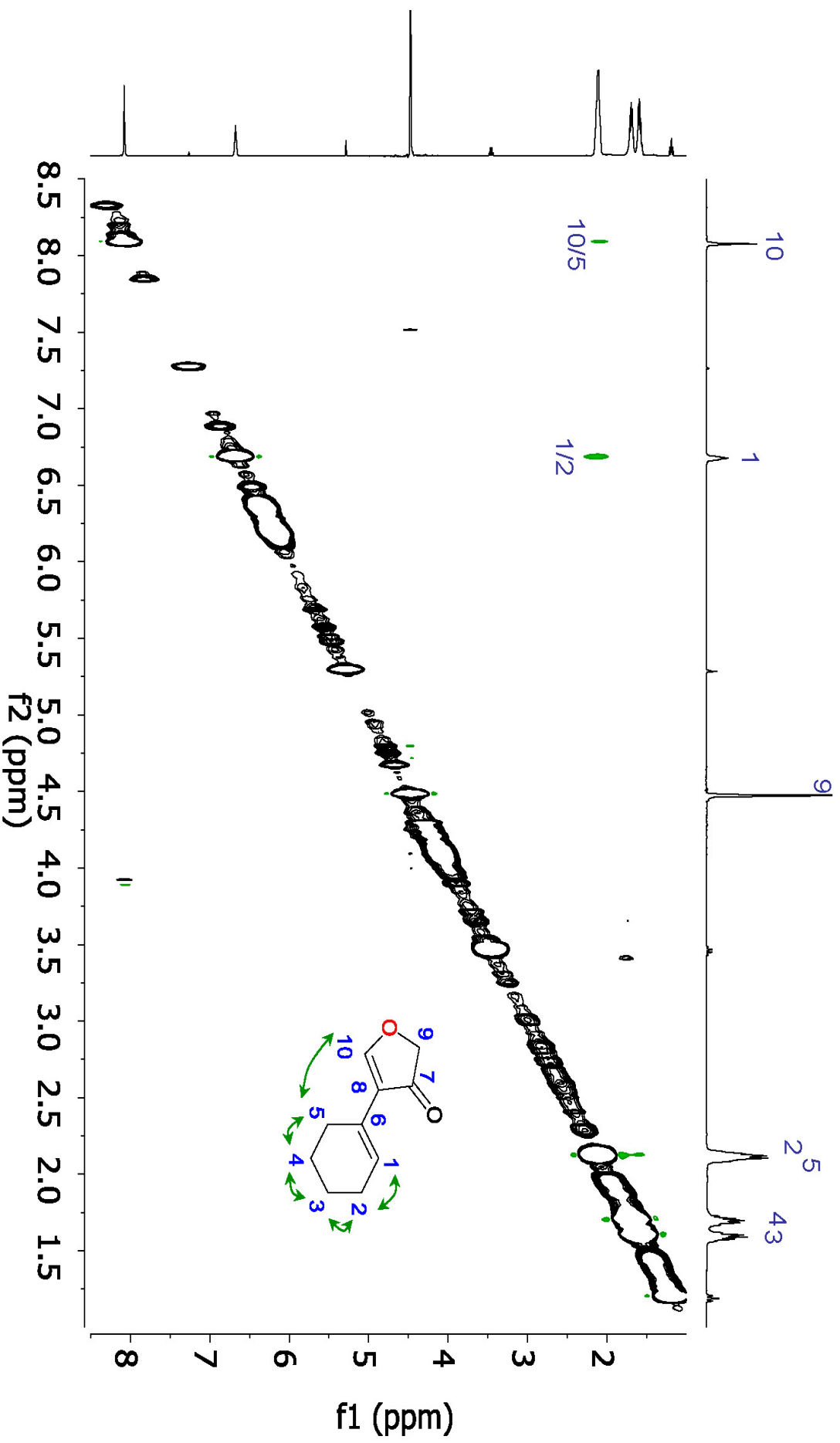
295 K, CDCl$_3$

Selective NOESY, 700ms

295 K, CDCl₃

150

3085.414 5.205
2932.143 12.644
2854.676 4.300
1677.097 48.976
1577.325 47.853
1417.715 21.039
1390.064 25.594
1328.677 20.167
1294.125 30.134
1161.109 41.869
1085.970 -0.206
956.007 38.692
924.707 22.456
846.479 24.838
815.650 11.616
729.709 16.001
675.457 19.244
626.293 10.614

%Transmittance

Wavenumber

Multi-Spectral Document(12)

TIC: Tore_syntese_11112206.D\data.ms

9.272

6.395

6.853

8.353   8.806   9.429
        8.858   9.800   10.121   11.387

4.50 5.00 5.50 6.00 6.50 7.00 7.50 8.00 8.50 9.00 9.50 10.00 10.50 11.00 11.50 12.00 12.50 13.00 13.50

Average of 9.264 to 9.281 min.: Tore_syntese_11112206.D\data.ms

178.1

135.1

149.1

91.1

79.1

107.1

122.1

163,1

115.1

51.0

65.0

57.2

73.0

98.0

129.1

143.1

155.9

171.1

18!

40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180

Proton_cdcl3_T25_002

¹H NMR (400 MHz, Chloroform-*d*) δ 7.64
(d, *J* = 12.6 Hz, 1H), 5.51 (d, *J* = 12.8 Hz,

A (d)
7.64

B (d)
5.51

C (s)
4.01

THF

153

Carbon_cdcl3_T25_001

154

Time (min)

3.81
4.04
4.90
5.08
5.42
6.07
6.68
7.05
7.52
7.87
8.84
9.23
9.60
9.83
10.52
10.78

NL:
1.90E7
TIC MS
2+2 with
S8 in Et2O

155

156
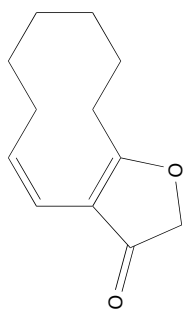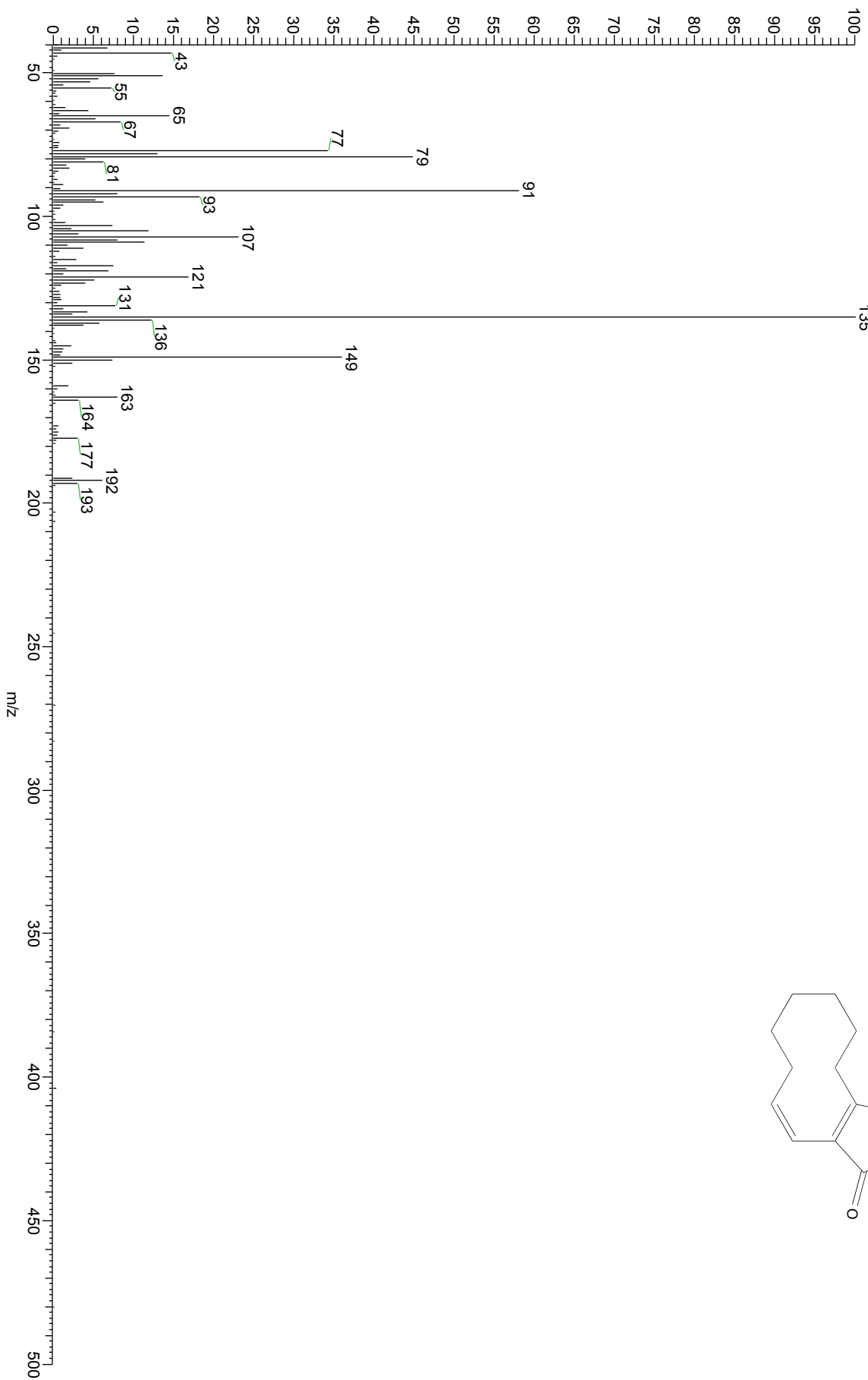
CARBON_dmso_T25_001
Gradient Shimming

158

gCOSY_dmso_T25_001
AD006_dmso_4th_ateempt

159

gHMQC_dmso_T25_001
ad006_2D_spectra

160

%Transmittance

2927.241 12.948
2854.847 6.079
1692.830 42.970
1587.427 34.066
1456.404 6.785
1417.361 2.445
1398.814 14.666
1336.888 9.985
1221.558 4.151
1176.765 6.507
1149.558 4.580
1114.342 6.833
1055.992 1.522
980.081 9.578
938.555 5.835
907.238 4.295
801.231 7.046

Wavenumber

Proton_cdcl3_T25_002

A (s)
4.19

B (d)
6.00

C (dt)
5.63

162

Carbon_cdcl3_T25_001

163

Carbon_cdcl3_T25_001