Master's Thesis in Organic Chemistry

ON THE SYNTHESIS OF A FIMBROLIDE

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June, 2008

Faculty of Science
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To my 'girls', Anastassia and Valentine

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Acknowledgements

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LIST OF ABBRVIATIONS AND SYMBOLS

α	*alpha*
β	*beta*
δ	gamma
$^{s}O_2$	singlet oxygen
$^{t}O_2$	triplet oxygen
^{13}C	carbon 13
^{1}H	proton
t-BuOK	potassium tert-Butoxide
t-BuOH	potassium tert-alkoxy
BuLi	Butyllithium
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMSO	Dimethyl Sulfoxide
$CDCl_3$	Chloroform-*d*
CH_2Cl_2	dichloromethane
Et_2O	Diethyl ether
GC	Gas Chromatography
HMPA	Hexamethylphosphoramide
$MgSO_4$	Magnesium sulfate
NMR	Nuclear Magnetic resonance
R.T.	Retention Time
THF	Tetrahydrofuran

SUMMARY

The present work is on the total synthesis of a natural compound found in a mixture of secondary metabolite produced by an alga nearby the cost of Australia. The target molecule, the 4-bromo-3-butyl-5-(dibromomethylene)furan-2(5H)-one, has not previously been proposed. The synthetic route described in this thesis uses cheap and readily available starting materials and the target is reached after six synthetic steps. Several new results have been obtained: selective monolithiation of a dibromofuran; Suzuki coupling with butyl boronic acid; a regioselective photo-oxidation of furan.

The final step of the synthesis, a dibromoolefination, has not yet been accomplished.

Keys words: Fimbrolide, singlet oxygen, Suzuki coupling, halogen-metal exchange, Wittig reaction, total synthesis, retro-analysis, alkylation of furan, regioisomere, monolithiation.

CHAPTER 1

INTRODUCTION: some personal reflexions

1. Statement of the project

In January 2006 when I started my master program in organic chemistry my Supervisor Rolf Carlson introduced a project to me : the total synthesis of a natural compound which is made up of a tribrominated furanone with a butyl chain and two double bonds. Chemically it was the "4-bromo-3-butyl-5-(dibromomethylene)furan-2(5H)-one"

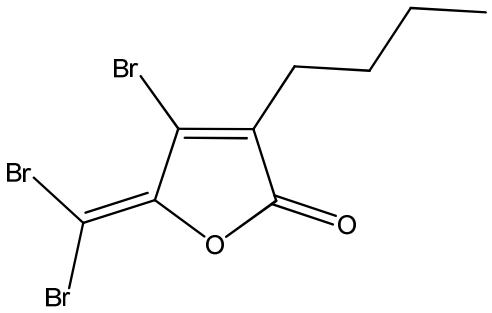


fig 1.1: My target molecule

The first step was to develop a retro synthesis using available and, if possible, cheap starting material. For my retro synthesis I had to look for another attempts to synthesize the given molecule to be sure to have an original and new route.

My retro-analysis was approved by my supervisor I could start the laboratory work.

The goal was of course not to discover a "new reaction", which could be anyway something nice…, but to find out a sequence of known and available reactions which might lead to my target molecule

2. Methodology

This was the first time for me to start such challenging task. In order to develop a proper and scientifically decent route a thorough literature work and "checking my organic knowledge" had to be done. To describe this intellectual and creative process is difficult, and I will just make a short overview. The retrosynthesis can be defined as *"a problem solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively materials along a pathway which ultimately leads to a simple or commercially available starting material or chemical synthesis"* *corey definition*

Literature search in the chemical abstract's data-base by the software *SciFinder Scholar* ^{TM} was an indispensable tool in this process. Thanks to this program I could explore some options for possible intermediates and or synthons allowing my attempted pathway. Of course, and unfortunately, some of them had not yet been synthesized or very poorly documented. Therefore I had to consider the possibility of carrying out some reaction on analogous substrates by adjusting the reaction condition to fit my objective. My knowledge of what can be available as staring compound was, however, limited when I started and lot of hypothetic routes were dead ends due to the impossibility to purchase the necessary chemicals. Another problem was to judge whether or not published procedures were trustworthy and reliable. When an attempted reaction failed I asked myself many times: "Is the failure my fault, i.e. I 'm not skilled enough or is my experiment based on an unreliable published method?". All this detail (I assume all chemists have been through them a least once …) make, of course, the whole project even more challenging. A total synthesis means also to be confronted with new types of reactions, some of them less "common" and gave me an opportunity to learn many techniques and manipulations.

CHAPTER 2

BACKGROUND INFORMATION

1. Some biology

Bacteria adhere to surfaces and organize themselves in matrix-enclosed biofilm structures. The biofilm mode of growth considerably increases resistance to antibacterial agents. It has been proposed that diffusion barriers and the physiological condition of cells in biofilms contribute to the increased resistance[1]. In the process of surface colonization and biofilm formation, certain bacteria exhibit a primitive form of multicellularity which leads to co-ordinate behavioral patterns by a sort of chemical language called quorum sensing * (QS). An example of this is *swarming motility*, which is viewed as organized bacterial behavior in which cell differentiation and expression of a range of extracellular[2] activities play a fundamental role.

Some molecules have the faculty to disturb this sort of "communication" by acting as an antagonist of this QS[3]. The target molecule of this thesis is one among them.

2. About the objective

The 4-bromo-3-butyl-5-(dibromomethylene)furan-2(5H)-one, my target is one of a halogenated secondary metabolite which has been isolated from a red alga nearby Sydney called *Delisea pulchra* [4](Bonnemaisonaceae) now synonymous of fimbriata. The interest was stimulated by the significant in vivo antifungal activity of this alga. After freeze-drying of freshly collected material R. Kazlauskas and his team obtained about 5% (dry weight) of a complex mixture of dichloromethane soluble material[4].

*__Quorum sensing__ is a type of decision-making process used by decentralized groups to coordinate behavior. Many species of bacteria use quorum sensing to coordinate their gene expression according to the local density of their population Wikipedia

G.C. /M.S. data has revealed that each component of this mixture could be rationalized by the general formula **$C_9H_9O_2BrRXY$** were X, Y are either hydrogen or halogen and R= OAc, OH or H.

R. Kazlauskas and his co-worker have proposed the generic name "fimbrolide" for this new family of compound according to one of the name of the alga.

My target is one of the most biologically active of this family and so far has been the target of several attempted, but unsuccessful syntheses, see below [7,9,10,11,12].

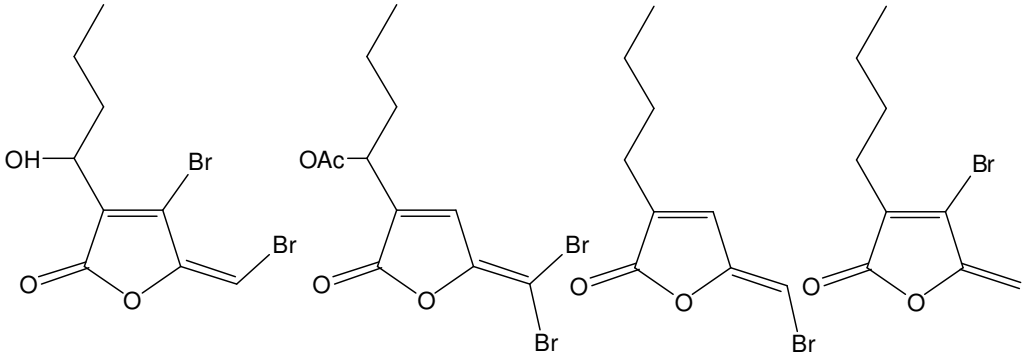


Fig. 2.1: examples of secondary metabolites *"fimbrolide"* from *Delisea pulchra*

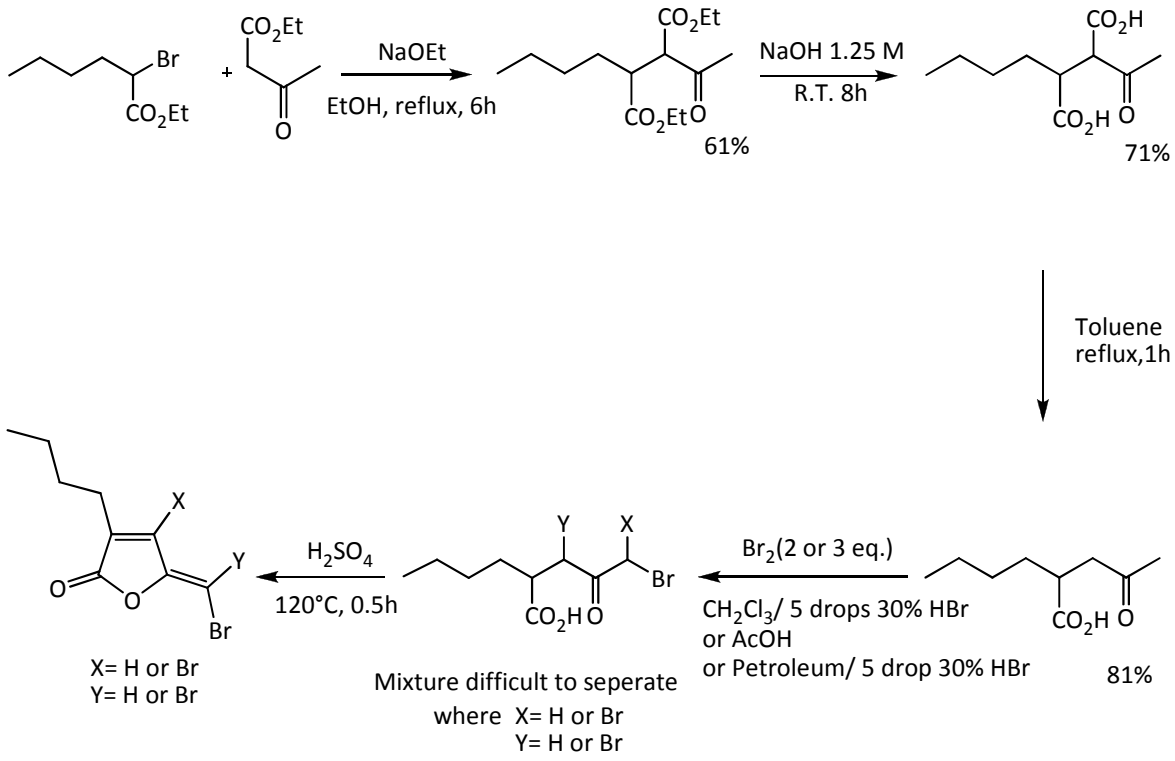
The possible use of such molecules can be of great benefit in many fields of action. They can be good alternatives to classical antibacterial since it is not likely that bacteria will develop resistance against it[5]. They can also be used as an efficient and environmental friendly antifouling agents(several patents have been already given)[6].

3. Previous attempts of synthesis

As mentioned above this new family of compounds has a large potential and the pharmaceutical world has been very interested to synthesize some of them. The synthesis of fimbrolides is challenging and many attempts have been made. Here below I will present the most interesting of them to show how different the strategies can be and how many attempts failed to yield my molecule.

a. The First attempt

The first attempted was carried out in 1979 by Sims Beechan [7]. The key step of this route was a sulfuric acid-catalyzed cyclisation in the last reaction



Schema 2.1: The first attempted synthesis of a fimbrolide

step. According to Wells [8] the sulfuric acid serves as both an oxidizing agent and as dehydrating agent giving a cyclisation of the keto-acid. Other steps are: an alkylation of ethyl-acetoacetate with ethyl-2-bromohexanoate. Hydrolysis of the diester to yield the diacid which has undergone a rapid decarboxylation. The next step was a bromination and this is a difficult reaction since the keto-acid had to undergo a tribromination yielding a complex mixtures of mono, di and tribrominated keto-acid very difficult to separate. A reinvestigation of this delicate reaction was done by Manny and his team in 1998[9]. The results were confusing and had shown some real difficulties as to the reproducibility of the bromination. Even if this synthesis route seems feasible, giving moderated to high yield for each step; it is not ideally suited for the specific synthesis of my target molecule.

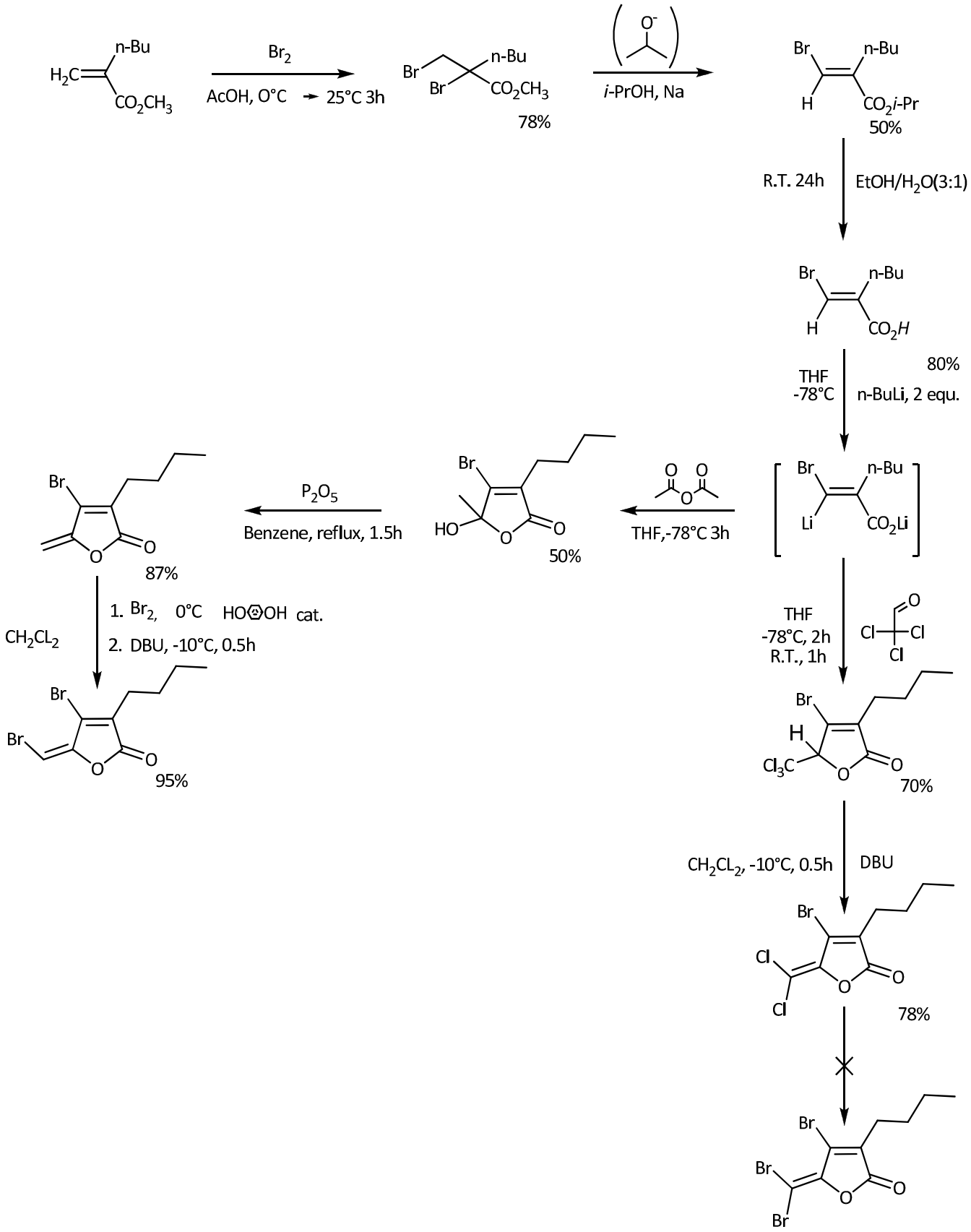
b. Trough a β-lithio carboxylate

An interesting and original synthesis was proposed by Caine and Ukachukwu in 1984[10].It is summarize on the next page The route involved a cyclisation reaction of a substituted β-lithio carboxylate with either trichloroacetaldehyde to form a substituted γ-(trichloromethyl)-butenolide (the originally plan with a tribromoacetaldehyde failed to react as they wished) or with acetic anhydride to form a γ-hydroxybutenolide. In order to obtain the correctly substituted β-lithio carboxylate they carried out an addition of bromine to the methyl 2-n-butylpropenoate to give a γ,β-dibromoderivative which was then converted by dehydrobromination and transesterification with an isopropoxide ion (the only base working with a n-butyl as a substituent) into the (E)-bromoester. This one underwent a hydrolysis and the (E)-bromoacid finally reacted with two equivalent of n-butyllithium to yield the β-lithio carboxylate.

-The γ-(trichloromethyl)-butenolide was treated with DBU to yield the dichlorobromo butenolide by dehydrochlorination but the next step, a halogen exchange reaction failed. The authors explained this failure due to *"the greater strength of the sp^2 carbon-chlorine bond than the sp^2 carbon-bromine bond preventing the exchange from being favorable".*

-The γ-hydroxybutenolide was dehydrated with phosphorus pentoxide to give a γ-methylene butenolide derivative which was followed by a bromination and dehydrobromination of the adduct with DBU to yield the 3-n-butyl-4-bromo-5(Z)-(bromomethyldiene)-2-(5H)-furanone.

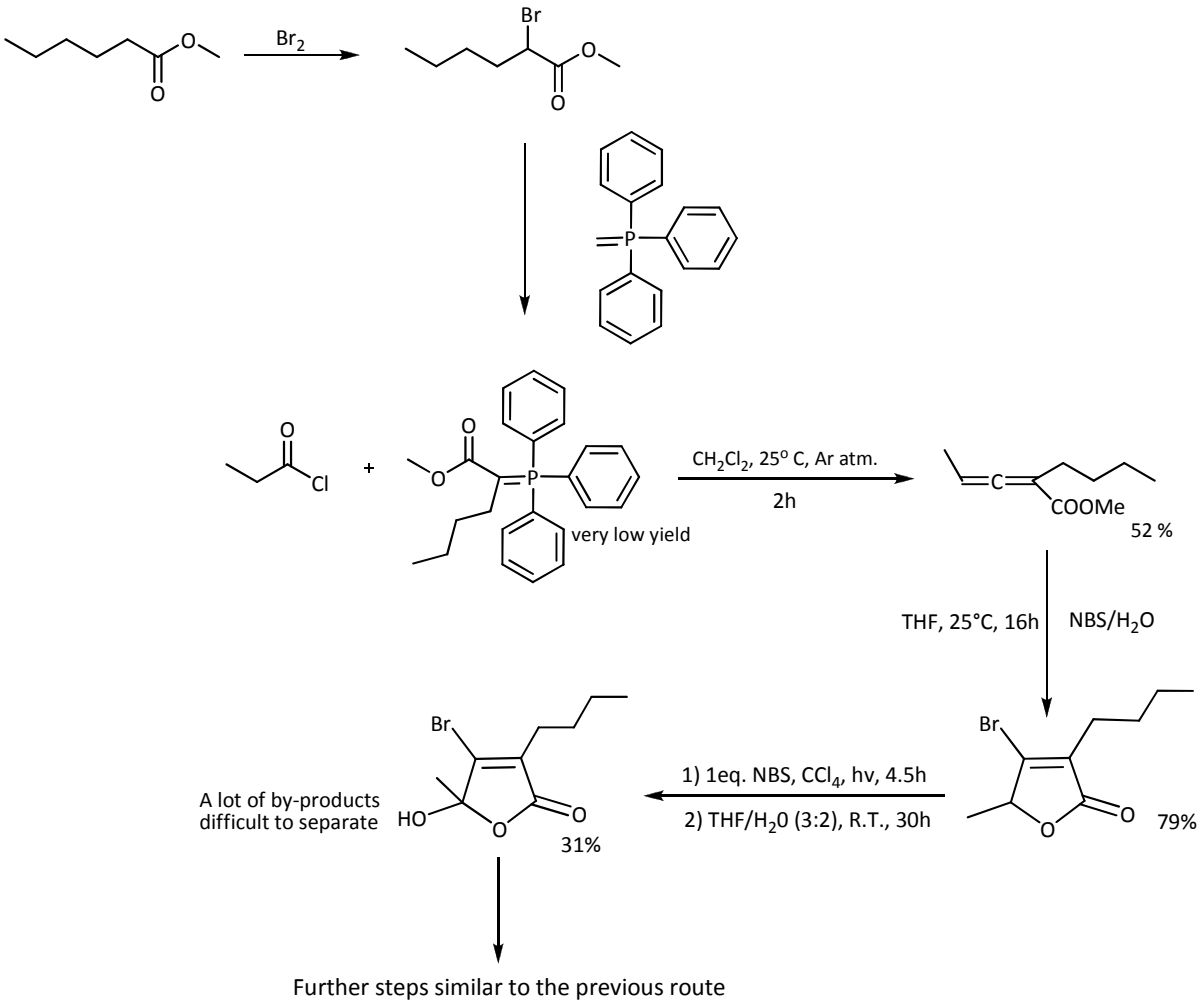
Even if this molecule is among the secondary metabolite synthesized by the *Delisea pulchra* there is one atom of bromine missing in comparison with my target. The authors decided to stop at this point their research and named their publication in accordance with their success.



Schema 2.2: Synthesis of 3-n-butyl-4-bromo-5(Z)(bromomethyldiene)2(5H)-furanone

c. Bromolactonisation of the 2-butyl-2, 3-pentadienoate

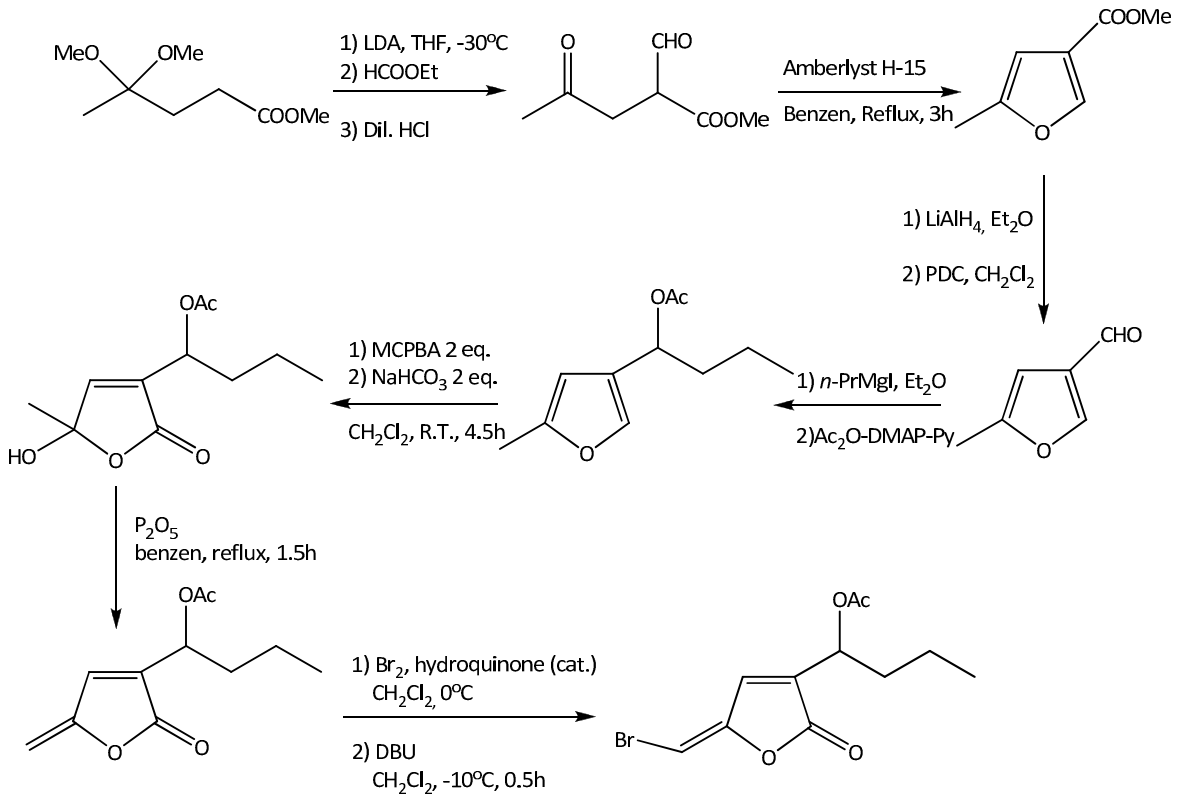
For this synthetic route, March, Font and Garcia have used an allenic ester in a bromolactonisation reaction[11] using N-bromosuccinimide as a brominating agent. The allenic ester was obtained through a Wittig reaction between propionyl chloride and [1-(methoxycarbonyl)pentylidiene]-triphenylphosphorane. The major problem is the step following the cyclisation reaction. The last hydrolysis produced manyof by-products that were difficult to separate and a low yield of final product was obtained. Furthermore as we saw in the previous route the final product is not suitable to further transformation to my target.



Schema 2.3: Bromolactonisation of allenic ester

d. Synthesis of Acetoxyfimbrolide

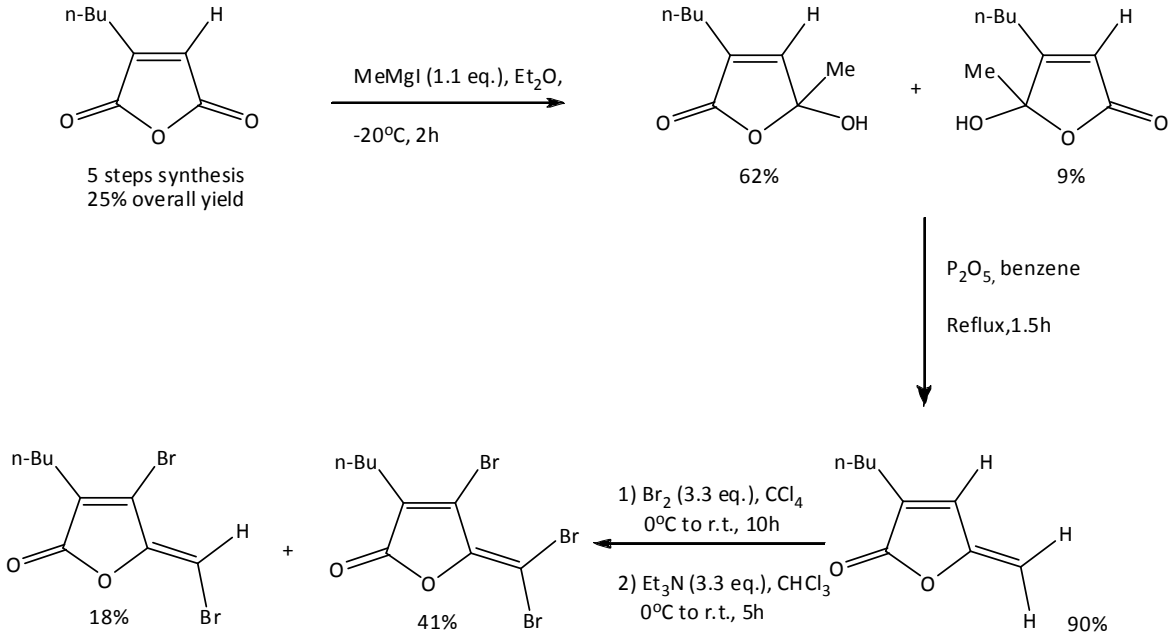
Even if the target molecule of this synthesis lacks of two atoms of bromine compared with my target and has an additional acetoxy function in the side chain, the carbon framework is similar. This makes this route very interesting[12] in and it also shows how different the routes leading to this type of structure can be. We can observe that the cyclisation which follows the formylation and the hydrolysis of the starting material does not yield a butenolide structure but a furan. The furan is then highly oxidized with *m*-chloroperbenzoic acid in presence of sodium bicarbonate. Further steps are similar to the previous route.



Schema 2.4: Synthesis of Acetoxyfimbrolide

e. With the butylmaleic acid as a precursor

The starting material was butylmaleic anhydride, which was synthesized over five steps[13]. The key step is a weakly regioselective nucleophilic addition of methylmagnesium iodide to one of the carbonyl groups. Dehydratation with phosphorus pentoxide gives the *exo*-methylenebutenoide, which upon bromination was converted to a mixture of di and tri brominated fimbrolides



Schema 2.5: With butylmaleic acid as a precursor

4. Some conclusions

As seen above, several approaches to the synthesis of fimbrolides have been presented over the last three decades.

The first one [7] is for me the most beautiful "state of the art" of pure organic chemistry.

However, it used harsh acid condition and a non reliable bromination step (mixture of brominated product were obtained.)

The other examples show, [9, 10, 11, 12, 13] nice and specific reactions, for example halolactonisation of an allenic acid[11] and dehydratation of the lactol to give the exo-methylenebutenolid[12].

Some main common features can be seen in these syntheses. The importance of the cyclisation step in the synthetic route to form the carbon framework of the molecule and the importance of the lactol dehydratation with phosphorus pentoxide meaning this lactol formation is a necessary step.

The last but not the least my target molecule has been isolated from mixtures of analogues fimbrolides. The molecule is stable and can survive in acidic as well as in basic media. Some reaches have been carried out either in concentrated sulfuric acid and other in the presence of triethylamine.

It`s in a way natural and expected that the nature often produces chemically stable molecules!

With this in mind I could start to think about my own strategy.

5. References

[1] O'Toole, George; Kaplan, Heidi B.; Kolter, Roberto. Biofilm formation as microbial development. Annual Review of Microbiology, (2000), 54 49-79.

[2] Fraser G M; Hughes C Swarming motility. Current opinion in microbiology, (1999), 630-5.

[3]Gram, Lone; De Nys, Rocky; Maximilien, Ria; Givskov, Michael; Steinberg, Peter; Kjelleberg, Staffan. Inhibitory effects of secondary metabolites from the red alga Delisea pulchra on swarming motility of Proteus mirabilis. Applied and Environmental Microbiology, (1996), 62(11), 4284-4287

[4]Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. A new class of halogenated lactones from the red alga Delisea fimbriata (Bonnemaisoniaceae). Tetrahedron Letters, (1977), (1), 37-40.

[5]Manefield, Michael; De Nys, Rocky; Kumar, Naresh; Read, Roger; Givskov, Michael; Steinberg, Peter; Kjelleberg, Staffan. Evidence that halogenated furanones from Delisea pulchra inhibit acylated homoserine lactone (AHL)-mediated gene expression by displacing the AHL signal from its receptor protein. Microbiology (Reading, United Kingdom) (1999), 145(2), 283-291

[6]Dworjanyn, S. A.; de Nys, R.; Steinberg, P. D. Chemically mediated antifouling in the red alga Delisea pulchra. Marine Ecology: Progress Series, (2006), 318

[7]Beechan, Curtis M.; Sims, James J. The first synthesis of fimbrolides, a novel class of halogenated lactones naturally occurring in the red seaweed Delisea fimbriata (Bonnemaisoniaceae). Tetrahedron Letters (1979), 1649-52.

[8]Wells, P. R. Enol lactones of dibromoacetylacrylic acid, Australian Journal of Chemistry, (1963), 16 165-9.

[9]J. Kjelleberg, Staffan; Kumar, Naresh; de Nys, Rocky; Read, Roger W.; Steinberg, Peter, Reinvestigation of the sulfuric acid-catalyzed cyclisation. Tetrahedron, (1997), 53, 15813-15826

[10]Caine, Drury; Procter, Katherine; Cassell, Roger A. A facile synthesis of (-)-R-5-methyl-2-cyclohexen-1-one and related 2-substituted enones from (+)-pulegone. Journal of Organic Chemistry, (1984)

[11]de March, Pedro; Font, Josep; Gracia, Antonio; Qingying, Zheng, Easy Access to 5-Alkyl-4-bromo-2(5H)-furanones: Synthesis of a Fimbrolide, an Acetoxyfimbrolide, and Bromobeckerelide. Journal of Organic Chemistry, (1995), 60, 1814-22.

[12]Kotsuki, Hiyoshizo; Monden, Mitsugu; Ochi, Masamitsu. Efficient synthesis of acetoxyfimbrolides and beckerelide analogs, Chemistry Letters, (1983), (7), 1007-8

[13] Haval, Kishan P.; Argade, Narshinha, Synthesis of natural fimbrolides. P. Synthesis, (2007), (14), 2198-2202.

[14] Baag, Md. Merajuddin; Sahoo, Manoj Kumar; Puranik, Vedavati G.; Argade, Narshinha P. Reactions of o-aminothiophenol and o-aminophenyl disulfide with itaconic anhydride and (-)-dimenthyl itaconate: access to enantiomerically pure 1,5-benzothiazepines and benzothiazolyl-2-methylacrylic acid. Synthesis, (2007),

[15]a)Haval, Kishan P.; Argade, Narshinha P. Haval-Argade contrathermodynamic rearrangement of alkylidenesuccinimides to alkylmaleimides via the corresponding isoimides: a general approach to alkyl and dialkyl substituted maleimides. Tetrahedron, (2006), 62

b) Haval, Kishan P.; Mhaske, Santosh B.; Argade, Narshinha P., Cyanuric chloride: decent dehydrating agent for an exclusive and efficient synthesis of kinetically controlled isomaleimides. Tetrahedron, (2006), 62-942.

CHAPTER 3

THEORETICAL PART

1. Description of the molecule

The name according the IUPAC rules is: *4-bromo-3-butyl-5-(dibromomethylene)furan-2(5H)-one*

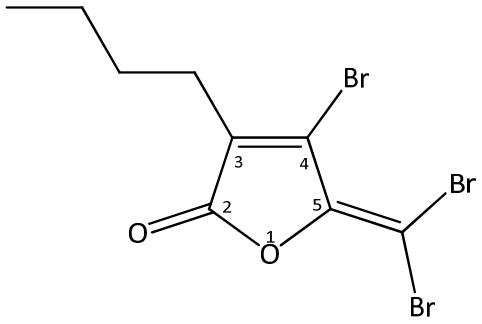
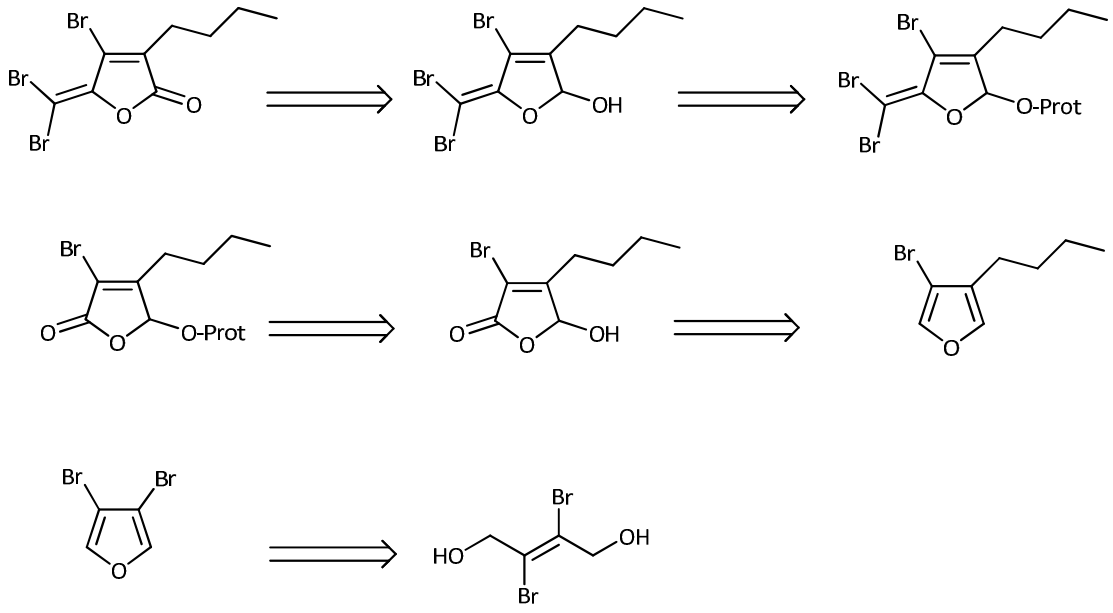


fig. 3.1

There are two C-C double bonds, a butyl chain and three bromo substituent, two of them bonded to an exocycle double bond to the five member heterocycle.

There is one nucleophilic site, the carbonyl oxygen and three positions which can undergo nucleophilic attacks: the carbonyl carbon (2), the brominated internal carbon (4) and the dibrominated allenic exocycle carbon. The molecule seems to be stable in acidic media and should protonated on the carbonyl oxygen in position 2. In the presence of nucleophiles, the protonated fimbrolide may undergo a ring opening and perhaps also a fast decomposition or polymerization.

2. Retrosynthetic strategy



My first layout of the retrosynthesis contained five steps which was shorter than previously described routes. Later, it was obvious that additional protection steps were needed to protect the hydroxyl function, increasing the total number steps to seven. This is a linear retrosynthesis. Of the retrosynthetic step only the final one had been carried out to give the specific molecule needed. To the best of my knowledge, the others had no exact precedence in the literature. A difference in the suggested synthetic route compared with other described syntheses is that the formation of the heterocyclic ring is the very first step. The reason for preparing the ring first was that the difficult step is likely to be the creation of the dibromostyrene function and that should be made late in the sequence of reactions. The question was how and when this functionality should be introduced.

The first step is an oxidative cyclisation of 2,3-dibromo-1,4-3butendiol to yield 3,4-dibromofuran. The starting material is commercially available. The next step is the replacement of one bromine in the furan with a butyl group to yield 3-brom-4-butylfuran. This bromoalkylated furan will undergo a regioisomeric photooxidation with singlet oxygen to yield a hydroxybutenolide which will be protected. Then the carbonyl function is converted to the dibromoalkene.

Deprotection followed by an oxidation of the hydroxyl function to yield the missing carbonyl function should give my target molecule.

3. Description of the possible reactions available

a. Formation of the 3,4-dibromofuran

An γ-Hydroxy-α,β-unsaturated carbonyl compounds can be dehydrate, using mineral or Lewis acids.

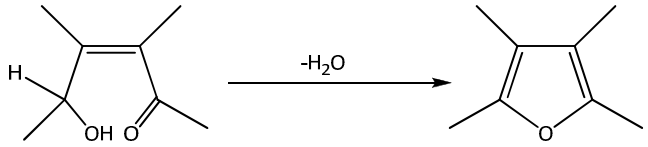
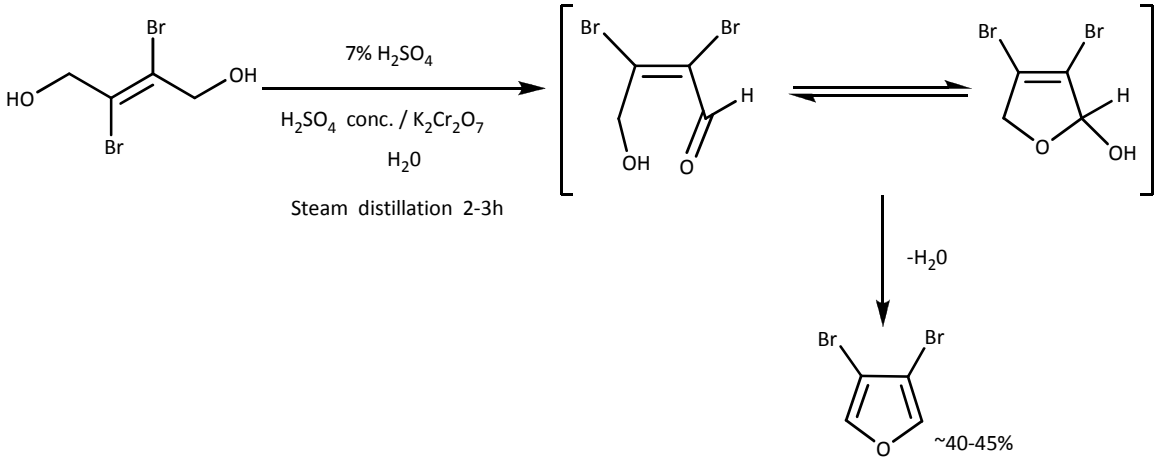


Fig. 3.2 γ-Hydroxy-α,β-unsaturated carbonyl

In order to synthesize the 3,4-dibromofuran, an oxidative cyclisation of the *trans*-2,3-dibromo-2-buten-1,4diol can be perform using aqueous potassium dichromate and sulfuric acid followed by steam distillation [1]. The reaction goes through a hydroxyl-aldehyde, (*Z*)-2,3-dibromo-4-hydroxybut-2-enal. The yield reported is about 55% which is modest, with evidence of byproducts due to over-oxidation.



Schema 3.2 oxidative cyclisation of the *trans*-2,3-dibromo-2-buten-1,4diol

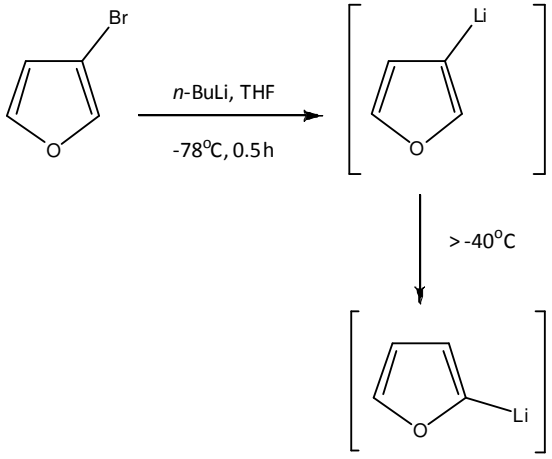
The positive feature of this method is the possibility to synthesize the product in a rather large scale (100 grams of reactant) without decrease in yield. Like most of the halogenofuran the 3,4-dibromofuran is quite unstable and should be kept in freezer under argon. Nevertheless, a slow decomposition occurs and it is necessary to use the product within a week. The pure slightly yellowish viscous oil crystallizes spontaneously at temperature below -10° C.

A modified procedure[2] using a mixture of hexane/water as solvent affords higher yields is also available. The acid-sensitive 3,4-dibromofuran is separated from the oxidant as soon as is formed by migrating into the hexane phase and this avoids over-oxidation. However due to the high temperature (100°C) the reaction must be run in a sealed tube. Small quantities can be made by using a small-scall microwave reactor.

b. The 3-Alkylation of the furan

Traditional Friedel-Crafts alkylation is not generally practicable to furan partly because of catalyzed-caused polymerization and partly due to polyalkylation. To prepare the butylfuran, the best way is likely to go via the correspondences lithiofuran and a butylating agent. The lithiofurans can be obtained from the bromofuran via halogen-metal exchange.

The preference for α-deprotonation of furan is nicely illustrated by the demonstration that 3-lithiofuran, produced from 3-bromofuran by metal/halogen exchange at -78^{o}C, equilibrates to the more stable 2-lithiofuran if the temperature rise to > -40^{o}C[3] by transmetallation.



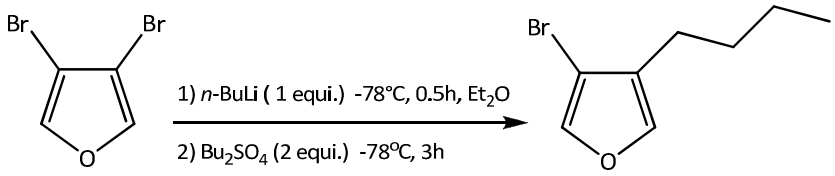
The regiospecific mono-*ipso*-substitution is not very well described in the literature in comparison with the 2-alkylation. The remarkably lower acidity of the furan β-protons as compared to the α-position affects both reaction types, so the conditions had to be changed in order to meet the different requirements.

The propensity of these 3-bromofuran derivatives to undergo the *ortho*-metallation and subsequent electrophilic reaction at the carbon C2 as well as a second metal-bromine exchange reaction.

Two obvious electrophilic butylating agents are: dibutylsulfate (Bu_2SO_4) and butyliodide (BuI). Both are commercially available or easily synthesizable.

i. With Me_2SO_4

The first reference is a publication written in 1996[4] where the author realized a 3-methylation of the 3-4,dibromofuran with Me_2SO_4 as an electrophile trough a mono-*ortho*-metallation with *n*-BuLi. The yield with dimethyl sulfate was approximately 76% but the problem concerning Bu_2SO_4 could be a lower electrophilicity of the butyl group. Reaction of the lithiofuran has mainly been made with very reactive electrophiles such as aldehydes or allylic halides.

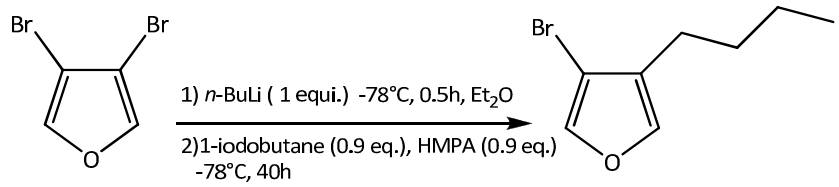


Scheme 3.4

ii. With 1-iodobutane and HMPA

To facilitate the electrophilic substitution of the 3-lithifuran with a primary alkyl halide a procedure[5] using hexamethylphosphoric acid triamide (HMPA) has been developed. The HMPA act as a cation-complexing solvating agent to avoid the competitive elimination reaction on *n*-butyl iodide. The main inconveniency of this procedure is the very long reaction time at -78°C which oblige the chemist to check the temperature carefully. But the publication did not describe the reaction with a dibromofuran. It was therefore an open

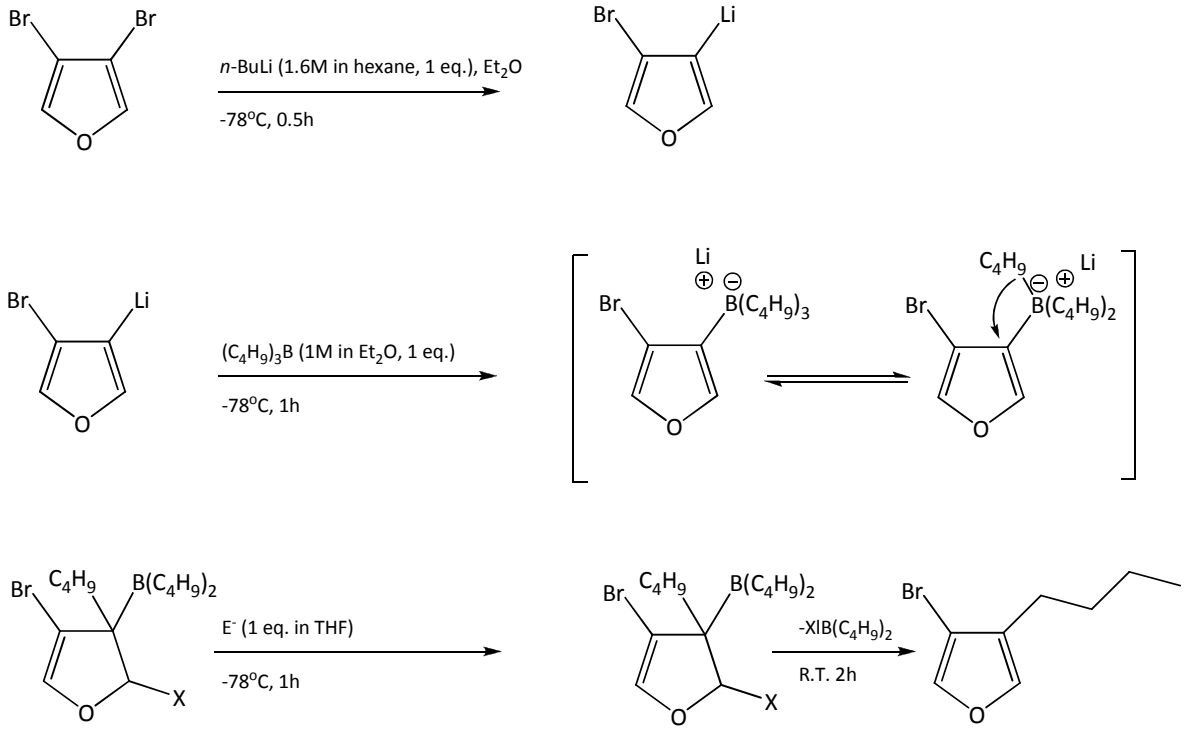
question whether or not this procedure could be used with the 3,4-dibromofuran and especially whether or not a mono-lithiation could be carried out in HMPA



Scheme 3.5

iii. With organoborane chemistry

Another possible reaction available is to react the lithiofuran with tributylborane in a non-catalyzed reaction. This was described in a paper by Suzuki in 1980[6] (one year after his first famous publication on coupling with palladium catalyst).



Schema 3.6: Alkylation of 3,4-dibromofuran via organoborane

According to the paper, the initial complexation leads to an"*ate*"complex which is thermally unstable. The ate complex is then reacted with an electrophile (mainly halogen or a source of molecular halogen like N-chlorosuccinimide or N-bromosuccinimide) the reaction is then

a migration of the *n*-butyl group on the β-carbon of the furan and the expulsion of dibutylhalogenoborane.

This one pot procedure involving several steps had, however, only been carried out with a mono 3-bromofuran. The electronic effect of the second bromine in the α position could be a major factors that can determine the course of the reaction.

c. Regioselective photooxidation

The photooxidation can give two products, 4-bromo-3-butyl-5-hydroxyfuran-2(5H)-one and the 3-bromo-4-butyl-5-hydroxyfuran-2(5H)-one.

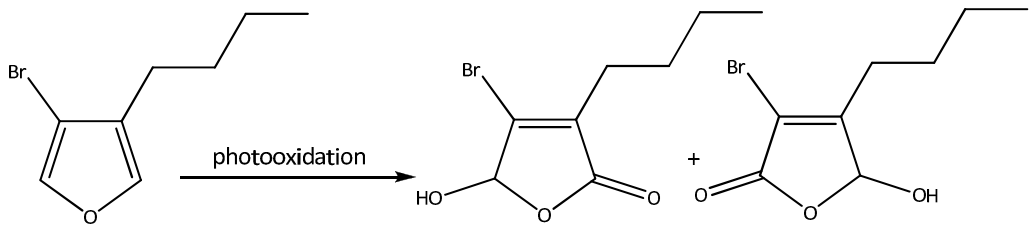


Fig 3.3: possible products of the photooxidation

For this type of reaction, the literature is more abundant than with the previous step. However, the product I wanted to synthesize was not found in these publications. So the result was still hypothetical even if it on paper seems to work.

-*Singlet oxygen*

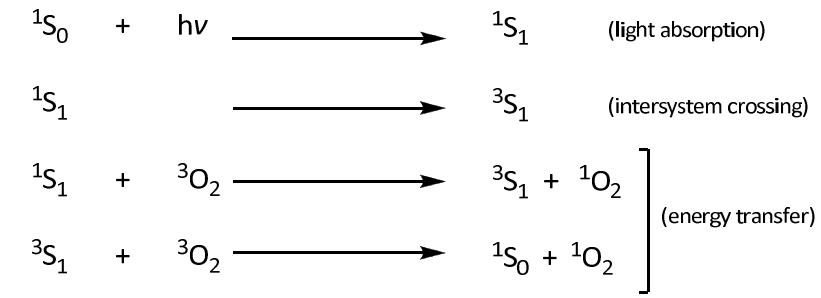
The singlet oxygen is an electrophilic species and isoelectronic with ethylene. The addition of $^1O_2$ to dienes generating endoperoxide may be viewed as a Diels-Alder reaction with $^1O_2$ as dienophile.

Singlet oxygen is the common name used for one of the two metastable states of molecular oxygen (O_2) with higher energy than the ground state triplet oxygen. The energy difference between the lowest energy of O_2 in the singlet state and the lowest energy in the triplet state is about 3625 Kelvin (T_e ($a^1\Delta_g$ <- $X^3\Sigma_g^-$) = 7918.1 cm^{-1}.)

Molecular oxygen differs from most molecules in having an open-shell triplet ground state, $O_2(X^3\Sigma_g^-)$. Molecular orbital theory predicts two low-lying excited singlet states O_2 ($a^1\Delta_g$) and $O_2(b^1\Sigma g)$. These electronic states differ only in the spin and the occupancy of oxygen's two

degenerate antibonding π_g-orbitals (see degenerate energy level). The $O_2(b^1\Sigma_g^+)$-state is very short lived and relaxes quickly to the lowest lying excited state, $O_2(a^1\Delta_g)$. Thus, the $O_2(a^1\Delta_g)$-state is commonly referred to as singlet oxygen.

The photosensitized generation of singlet oxygen is shown in the scheme below



schema 3.7 : photosensitized generation of Singlet Oxygen

The sensitizer commonly use for the generation of the Singlet Oxygen is 4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein or the Rose Bengal.

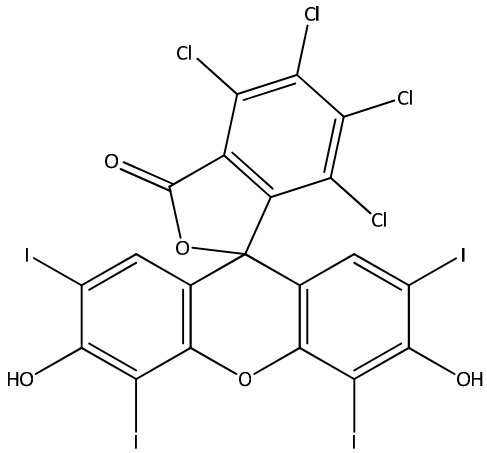


fig 3.4: Rose Bengal

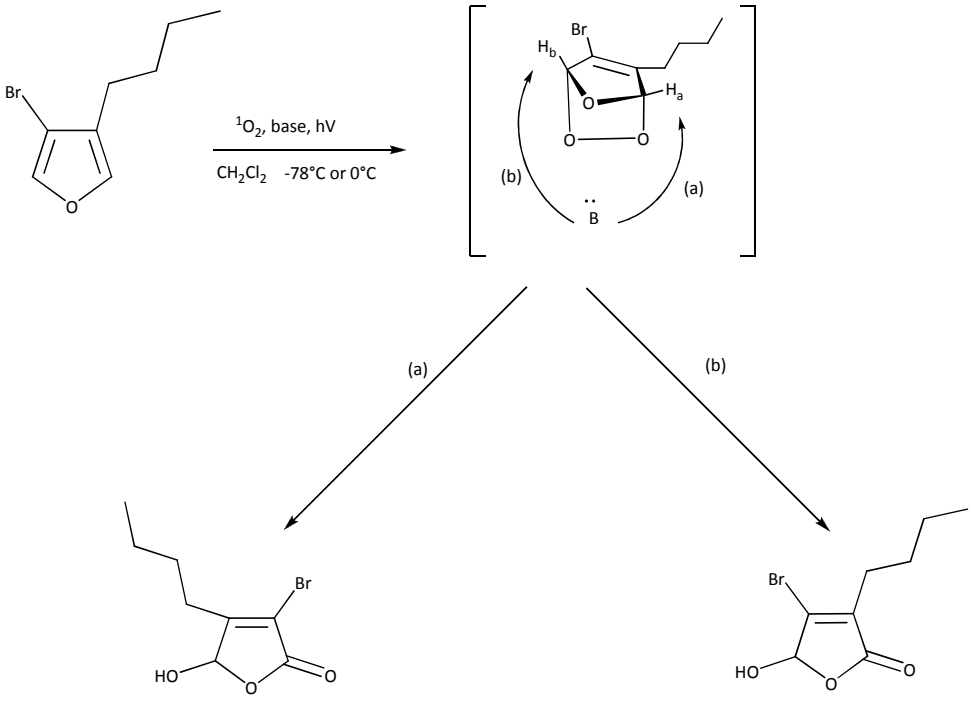
Rose Bengal is a dye with a beautiful pink color.

The absorption wavelength of Rose Bengal is between 480 and 620nm. In the CH_2Cl_2 the λ_{max1} is 562nm and λ_{max2} is 523nm. Even if most of the publication use a classical 200W tungsten filament lamp it should be more appropriate to use a medium pressure mercury vapor lamp since one of its emissions ray in this domain.

The simple one-pot, singlet-oxygen photooxidation of furans to γ-hydroxybutenolides in the presence of Rose Bengal photosensitizer, is known to suffer from relatively low chemical yield and is limited by the access to 4-substitued butenolides. The reaction was also known to produce many products including 1,3-diepoxides, epoxylactones and sometimes solvent addition products[7]. Most of these products are formed by thermal decomposition of the unstable *endo*-peroxides.

However, Faulkner and his co-worker have developed a base-promoted method[8] that improves the formation of γ-hydroxybutenolides and that give a better control of the regioselectivity by the proper choice of the base (mostly empirical). The base-catalyzed decomposition of the *endo*-peroxide is favored over the thermal decomposition.

In 2006, an article which reviewed this procedure[9] as their first step was published. Six different bases ($(TMS)_3N$, 2,6-di-*tert*-Bu-puy, pempidine, DIPEA, phosphazene and DBU) were described and these could be used to influence the ratio of the regioisomeric products. They explained this selectivity by a steric effect of these bulky bases. I decided to explore this way to find out if one of these bases could yield to a total selectivity in favor of my product.



Schema 3.8: Base promoted photooxidation

This synthesis arise another problem: How to determine the exact structure if the product is not a crystal.

In that case the method will be to compare the ^{13}C NMR with a reference molecule to : The Mucobromic (see paragraph f) acid and also to compare the theoretical displacement shift (ChemNMR ^{13}C Estimation) of the C2 and C3 of the two regioisomeric furanones which should exhibit a great difference.

d. Protection step.

A good protection is of course a protection which can tolerate the future reactions. It should be easy to put on and easy to remove. It should also have a high yield not to interfere too much with the total synthesis yield. It should not complicate the spectra of the molecule. There are useful handbooks available so it is easy to find a suitable protection group.

For the protection of the hydroxyl function, I decided to try two of them. The first one is the tetrahydropyranyl group. It is suitable under strong basic condition and it is easy to remove

by mild acid hydrolysis. The second one was to block the alcohol by a methyl group. The reason was to have a model compound that gives easily interpreted spectra.

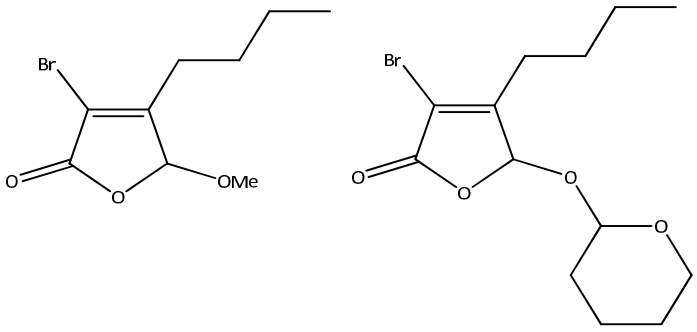
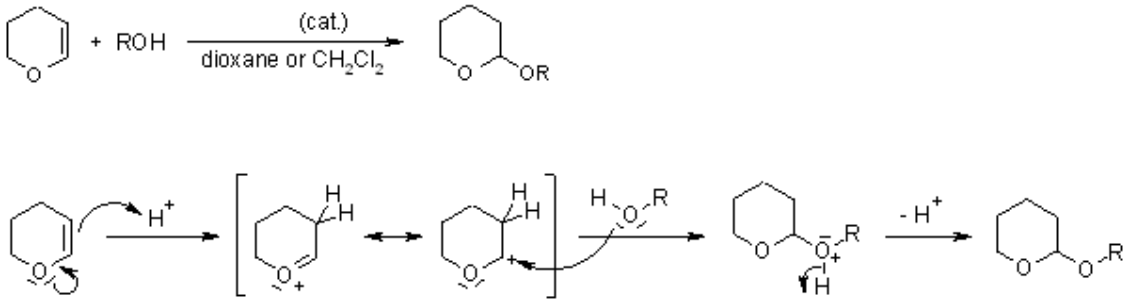


fig 3.5: The two protections choosed

The THP protection is a reaction between the hydroxyl group and the 3,4-dihydro-2H-pyran with an acid catalyst. In one publication [10] Nafion-H© was used. The advantages compare to a common acid (for THP protection the acid catalyst widely used is the *p*-toluensulfonic acid monohydrate) are: the high catalytic activity, the possibility to regenerate the catalyst, a significant decrease of by-product since the reaction can be carried out at room temperature and an easy work-up.



Scheme 3.9: mechanism of the THP protection of an hydroxyl group

The deprotection should not be a problem since the THP group can be removed by dilute acid and water.

This step should be carried out after the dibromoolefination and the deprotected molecule should be stable under acidic condition as was shown above.

For the methoxy protection, a very simple procedure[11] was found. It uses MeOH as a solvent containing 0.5% of sulfuric acid. For my project I wished to try Nafion-H© as the acid catalyst instead of sulfuric acid. Nafion-H© could act as a catalyst as well as a dehydrating agent. I did not plan to remove the methoxy protection. The methoxy derivative was used as a model compound to make my spectra easier to interpret.

e. Dibromoolefination.

Phosphonium ylid chemistry

An ylid[2] can be defined as a substance in which a carbanion is attached directly to a heteroatom carrying a high degree of positive charge. Phosphorus ylids have a general structure often written as a resonance hybrid.

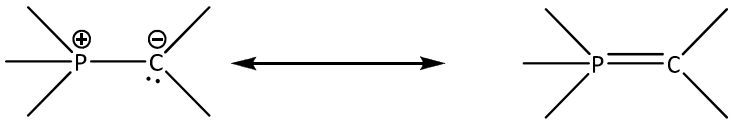


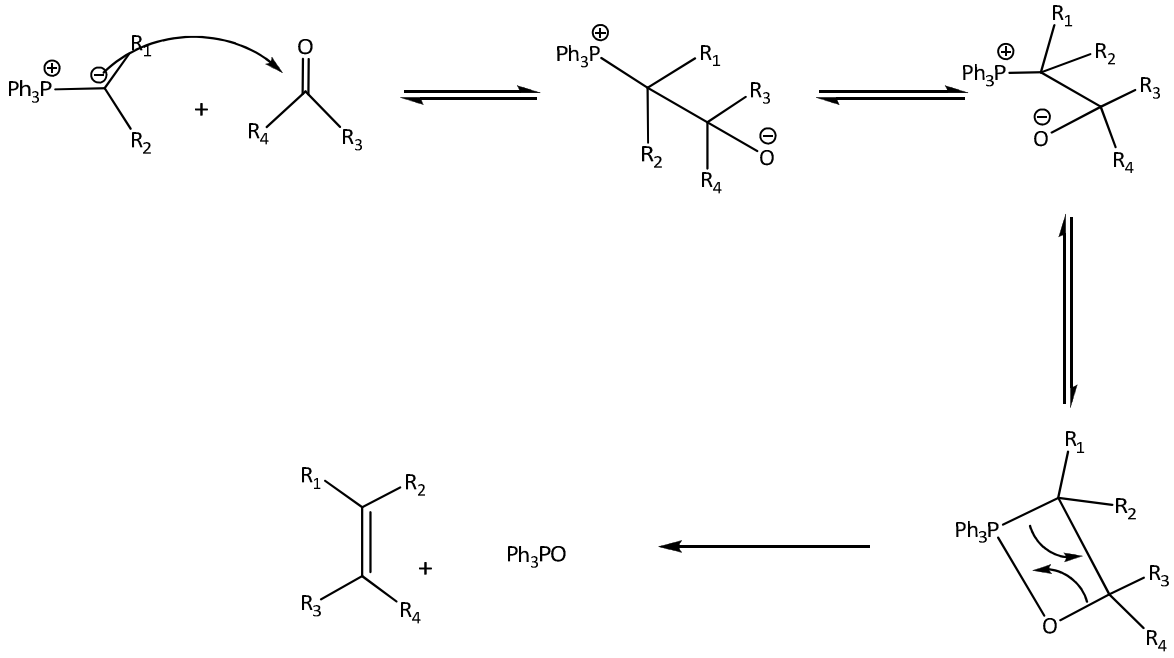
fig 3.6. : resonance hybrid of a phosphorus ylid

First seen as a chemical curiosity, it took years before chemists realized the great potentiality of such compound as a chemical tool. Whereas the first condensation-elimination reaction between a carbonyl compound and a phosphonium ylid, was reported in 1919 by Staudinger and Meyer[12] the real "birth" of this reaction was in 1953[13] when Wittig converted benzophenone to diphenylethylene by reacting methyltriphenylphosphonium iodide with phenyllithium. Later on G. Wittig developed and

[2] Phosphonium ylids have been named as phosphoniumalkylides, phosphine-methylenes and, more recently, as phosphoranes

elaborated this into a general method for the synthesis of alkenes. He also proposed a mechanism which involved the formation of a betaine and a four-membered intermediate. This mechanism is now generaly accepted by most of the people working in this field.

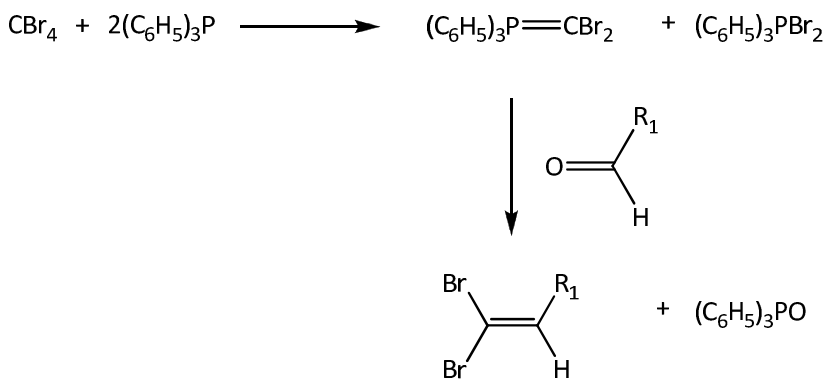
The steric bulk of the ylid influences the stereochemical outcome of the nucleophilic addition to give a conformation of the betaine in which the phosphorus and oxygen are anti to each other. Carbon-carbon bond rotation gives the betaine with the *syn*-conformation, which then forms the oxaphosphatane. Elimination gives the alkene and triphenylphosphine oxide.



Schema 3.10: Wittig reaction mechanism

There are several ways to prepare an ylid: Deprotonation of phosphonium salts; Synthesis via addition of carbenes to phosphines; phosphinazines; nucleophilic addition to vinylphosphonium salts; addition to benzyne; addition of phosphorus to olefins and alkynes or, among several others from phosphonium salts.

In order to produce the dibromomethylenetriphenylphosphorane ylid which will lead to a dibromoolefin product, the synthesis of a phosphonium salt is the most common.



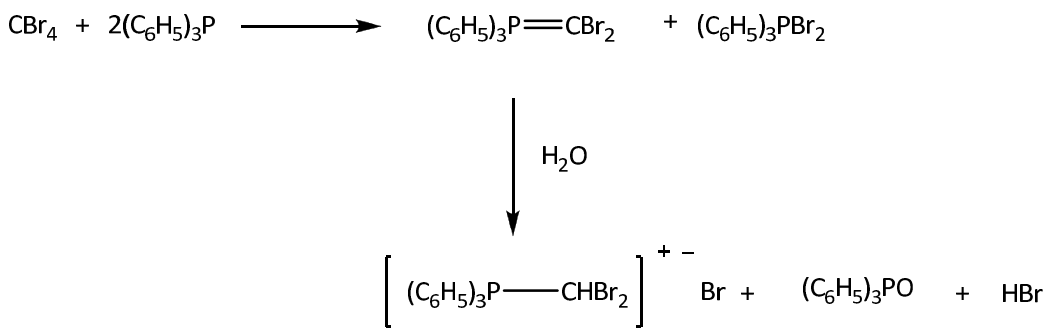
schema 3.11: Dibromoolefination with a Wittig-type reaction

The most common Wittig-type reaction for this purpose is the Ramirez method which produces the dibromomethylenetriphenylphosphorane in situ from dibromethylentriphenylphosphonium bromide[14].

It has been well established that this Wittig-type olefination is unsuited or give poor results with carbonyl groups of esters since these are much less reactive than those of aldehydes or ketones.

The experimental conditions with esters therefore need to be more drastic to allow them to react. However, the mixture of carbon tetrabromide, triphenylphosphine and carbonyl reagent turns black at temperature above 0°C. The reagent has been used to convert aldehyde and ketones to dibromoolefins at low temperature. The thermal instability prohibited the use of higher temperature that might be necessary for reactions with esters. Maybe, it was the procedure that gave a thermally unstable reaction mixture. Three others methods for the generation of the dibromophosphorane have been described. It was hoped that at least one of them could give a reagent that could be used at elevated temperature. However the use was only demonstrated with aldehydes or ketones, with an exception for the last one.

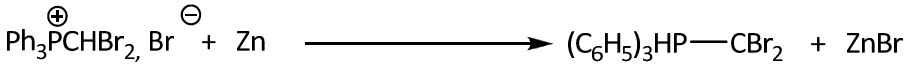
-The first one [15]uses the dibromotrimethylphosphonium bromide reagent, which is synthesized by adding water into the Ramirez procedure instead of a carbonyl reagent.



Scheme 3.12: Modification of the Ramirez procedure

The dibromotrimethylphosphonium bromide is treated with *t*-BuOK to generate the dibromomethylenetriphenylphosphorane by deprotonation. This ylid react at room temperature without any problem according the original publication[15] and in works subsequent to this paper. This may give opportunity to use the ylid at high temperature.

-The second one[16] is slightly similar but instead of using a very strong base the authors used activated zinc[17].



Scheme 3.13: Formation of the ylid by the zinc

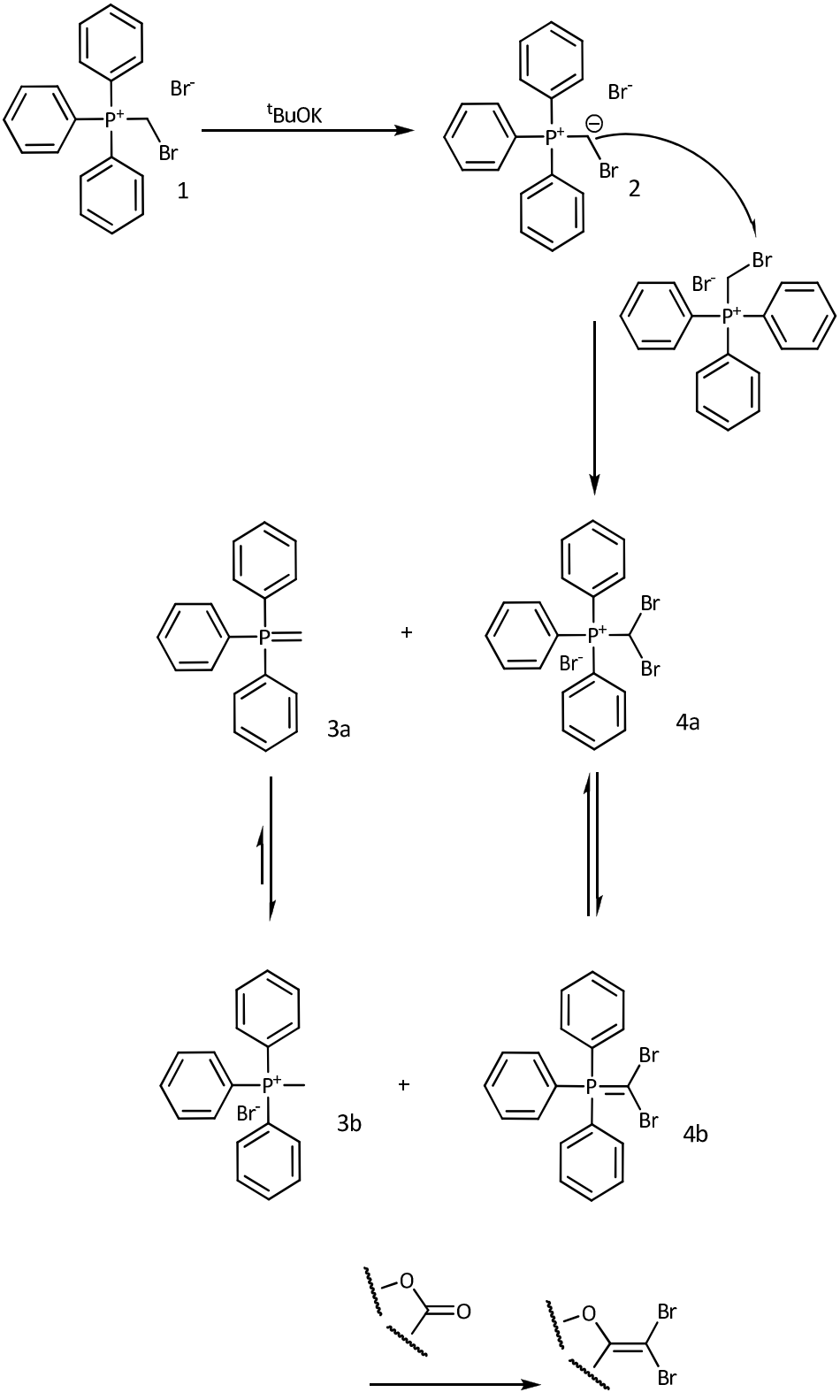
After the rapid formation of the ylid the experimental conditions for the reaction with carbonyl compound were refluxing dioxalane. This might be suitable for my reaction.

-The third one, and the most promising, is described in a publication[18] from Chapleur et al. They have carried out a number lot of dichloroolefination of lactones[19, 20, 21] which is now well documented and well cited. They give an example which is a beautiful illustration of the concept “serendipity”. They wanted to synthesize a monobromoolefin from lactone by using the bromomethyltriphenylphosphonium bromide with a strong base (mainly *t*-BuOK) at very low temperature. The reaction was slow and the mixture was heated. The product obtained was a dibromoolefin!

They explained that by the two different following mechanisms.

"On the one hand, dibromomethylenetriphenylphosphorane 4b should be formed from 2 under the reaction conditions and reacts with the lactone. Thus, according to Schema 1, deprotonation of 1 with t-BuOK leads to phosphorane 2 in equilibrium with 1. Thus, ylid 2 could react with the phosphonium salt 1 to give the dibromomethylenephosphoniumbromide 4a and the phosphorane 3a. Subsequent transylidation between 3a and 4a or deprotonation of the latter by t-BuOK, would afford the phosphorane 4b and then the dibromoolefin. On the other hand, the expected monobromoolefin would be formed and undergo electrophilic bromination and subsequent elimination to afford the dibromoolefin."

However there are problems: the high basicity of the media and, the reaction between *t*-BuOH and the in-situ formed ylid if the reaction is carried out at temperature above -78^{0}C. This obliges to have the addition of the base as the last constituent of the reaction



Schema 3.14: Possible mechanism for dibromomethylation

f. The Mucobromic acid route.

The proposed synthetic route is a linear synthesis plan. The inconvenience is that the accessibility at each step reduced accessible starting material. Since almost each step had to create a new molecule never published or referenced, a lot of work was necessary to set up useful procedures. Explorative experiments consume starting material and for this reason, fairly large amounts were needed. The question of the purity was also a problem. It was time consuming to repeat the previous step when more material was needed and it was also frustrating.

As said above to my surprise and joy I found a compound, Mucobromic acid, in the Aldrich catalogue when I was looking for a reference compound to solve the problem concerning the determination of configuration of the third step.

The mucobromic acid has the desired molecular framework and if one bromine could be selectively replaced by a butyl group it would give a short-cut of the route described above.

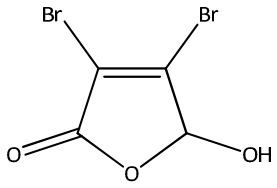


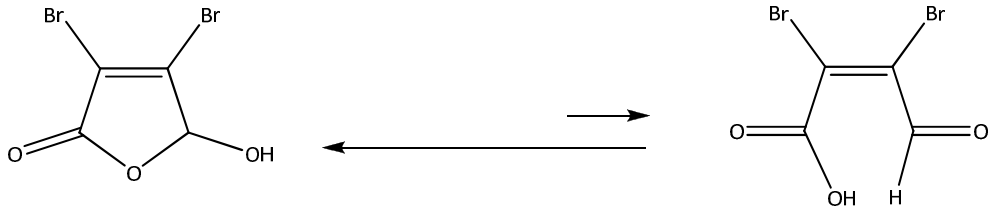
fig 3.7: Mucobromic acid

The Mucobromic acid is a small molecule difficult to work with for three reasons:

-It contains several functional groups so selective manipulations are difficult.

-It has poor stability under basic conditions.[22]

-The tautomeric equilibrium between enol and keto.



Scheme 3.15: Tautomeric equilibrium of the mucobromic acid

With this molecule I could try all the protections reaction, the dibromoolefination reactions and finally the deprotection reaction before to try on the *3-bromo-4-butyl-5-hydroxyfuran-2(5H)-one.*

After careful reading of the literature I also found out that it could perhaps be possible to make a regiospecific Suzuki coupling with an n-butyl boronic acid to yield directly acid the molecule of my fourth step: the *3-bromo-4-butyl-5-methoxyfuran-2(5H)-one* from protected Mucobromic.

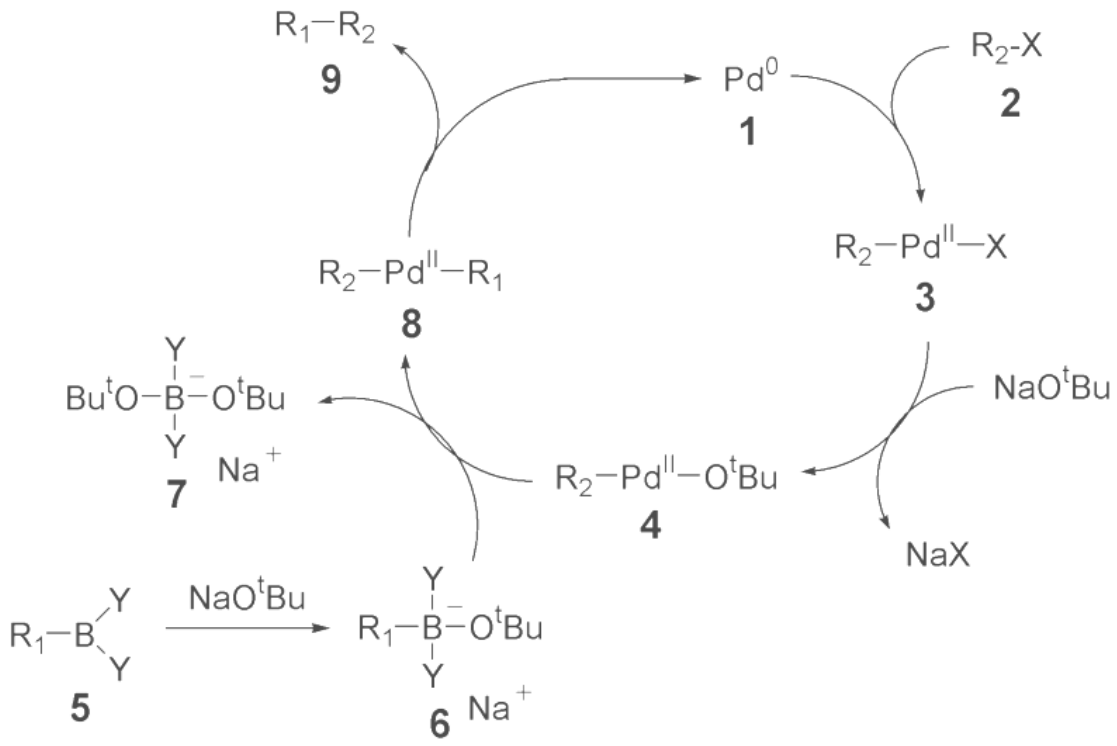
The hypothesis was based on two facts.

-Whenever Suzuki coupling has been realized on mucobromic[9] acid with aryl- or vinyl-boronic acid the coupling always occurred on the carbon adjacent to the carbon wearing the hydroxyl function and never on the other.

-Protocol for the Suzuki coupling with alkyl boronic acid has been improved in recent years.

Suzuki coupling, named after his discover Akira Suzuki, is a reaction in which aryl- or vinyl-boronic acid coupled to an aryl- or vinyl-halide using a palladium(0) catalyst in the presence of a base.

The mechanism of the Suzuki reaction is best viewed from the perspective of the palladium catalyst. The first step is the oxidative insertion of palladium on the halide 2 to form the organo-palladium species 3. Reaction with base gives intermediate 4, which via transmetallation reaction with the boron-ate complex 6 forms the organopalladium species 8. Reductive elimination gives the desired product 9 and restores the original palladium(0) catalyst 1.



Scheme 3.16: mechanism of the Suzuki reaction

Since its discovery many attempts have been made to use it with alkyl boronic acids.

However, they are not very efficient in the reaction and to overcome this, several modifications have been suggested:

with respect to the base used and the nature of the palladium catalyst has been reported that cesium bases are efficient[22]. It has been also reported that silver oxide, Ag_2O, rapidly increase the race of the reactions[23]. There is a large variation in the choice of the palladium catalyst.

The palladium catalyst has been varied in different attempts and there is no general procedure but mainly specific procedure for a given reaction.

After careful reading of the literature of the many attempts described, especially the work of Bellina and Balazecka[24, 25, 26, 27, 28] three different palladium catalysts (Bis(acetonitrile)dichloropalladium(II), Bis(triphenylphosphine)palladium(II)dichloride, palladium(II)acetate , three different bases (cesium fluoride, potassium carbonate and

tripotassium phosphate) one additional ligand (triphenylarsine) and two solvents (THF, dioxane) and the use of addition of silver oxide.

The objective was to run small scale experiments in the microwave reactor to see if this coupling could be realized and to which carbon the n-butyl chain would be coupled.

If the *3-bromo-4-butyl-5-hydroxyfuran-2(5H)-one* is not a crystalline compound for which the structure can be determined by crystallography, the differentiation between *3-bromo-4-butyl-5-hydroxyfuran-2(5H)-one* and *4-bromo-3-butyl-5-hydroxyfuran-2(5H)-one* can be made by comparison of their ^{13}C NMR spectra in the same way of analyze as described above.

The experiments will be run with the methoxy protected substrate.

g. Oxidation of the hydroxyl group.

The last step is an oxidation of a hydroxyl group. The main problem can arise from the fact that the substrate contains two double bonds that may interfere.

However, some oxidizing reagents only oxidize unsaturated bonds. Two among them were chosen for the oxidation.

The Jones reagent[29]:

This a solution of chromium trioxide diluted in sulphuric acid that can be used safely for oxidations of organic substrates in acetone. Although the reagent is very acidic, the substrate in acetone is essentially titrated with the oxidant solution and only very acid-sensitive groups are incompatible. The drawback is that the chromium residue is very toxic, and care must be taken to dispose it properly.

Pyridinium Chlorochromate (PCC) or Corey-Suggs Reagent[30] :

Chlorochromic acid can by prepared by the dissolution of chromium trioxide in 6 M aq. hydrochloric acid. Addition of pyridine gives pyridinium chlorochromate as orange crystals. The drawback is the formation of viscous materials that complicate product isolation.

4. References

[1]Gorzynski, Marek; Rewicki, Dieter. Synthesis of alkyl-2,3-dihydrothieno[2,3-c]furans. Aromatic compounds of coffee. Inst. Org. Chem., Freie Univ. Berlin, Berlin, Fed. Rep. Ger. Liebigs Annalen der Chemie, (1986)

[2]Kraus, George A.; Wang, Xuemei. An improved synthesis of 3-substituted furans from substituted butene-1,4-diols. Department of Chemistry, Iowa State University, Ames, IA, USA. Synthetic Communications, (1998), 28, 1093-1096.

[3]Bock, Inge; Bornowski, Hans; Ranft, Andreas; Theis, Heinz. New aspects in the synthesis of mono- and dialkylfurans. Tetrahedron, (1990), 46, 1199-210

[4]Alvarez-Ibarra, Carlos; Quiroga, Maria L.; Toledano, Emilio. Synthesis of polysubstituted 3-thiofurans by regiospecific mono-ipso-substitution and ortho-metalation from 3,4-dibromofuran Tetrahedron, (1996), 52, 4065-78.

[5]New aspects in the synthesis of mono- and dialkylfurans. Bock, Inge; Bornowski, Hans; Ranft, Andreas; Theis, Heinz. Tetrahedron, (1990), 46, 1199-210.

[6]Akimoto, Itaru; Sano, Masahiro; Suzuki, Akira. Regiospecific synthesis of 3-alkylfurans and 3-alkylthiophenes via organoboranes. Bulletin of the Chemical Society of Japan, (1981), 54.

[7]Graziano, M. Liliana; Iesce, M. Rosaria; Cinotti, Angela; Scarpati, Rachele. Photosensitized oxidation of furans. Part 12. Solvent effects in thermal rearrangement of the 2,5-peroxides of 2,5-unsubstituted furans. Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972--1999)

[8]Kernan, Michael R.; Faulkner, D. John. Regioselective oxidation of 3-alkylfurans to 3-alkyl-4-hydroxybutenolides. Journal of Organic Chemistry, (1988), 53(12), 2773-6.

[9]Quino, M.; Bruno, I.; Riccio, R.; Gomez-Paloma, L. Regioselective Entry to Bromo-□ -hydroxybutenolides: Useful Building Blocks for Assemblying Natural Product-Like Libraries. Organic Letters, (2006), 8, 4831-4834

[10]Olah, George A.; Husain, Altaf; Singh, Brij P. Catalysis by solid superacids ; 19. Simplified and improved polymeric perfluorinated resin sulfonic acid (Nafion-H) catalyzed protection-deprotection reactions. Synthesis, (1983), (11), 892-5.

[11]Lattmann Eric; Sattayasai Nison; Schwalbe Carl S; Niamsanit Suwanna; Billington David C; Lattmann Pornthip; Langley Christopher A; Singh Harjit; Dunn Simon Novel anti-bacterials against MRSA: synthesis of focussed combinatorial libraries of tri-substituted 2(5H)-furanones. Current drug discovery technologies, (2006), 3(2), 125-34.

[12] Staudinger, H.; Meyer, Jules. New organic compounds of phosphorus. III. Phosphinemethylene derivatives and phosphinimines. Helvetica Chimica Acta, (1919), 2 635-46.

[13]Wittig, Georg; Geissler, Georg. Course of reactions of pentaphenylphosphorus and certain derivatives. Justus Liebigs Annalen der Chemie, (1953), 580 44-57.

[14]Ramirez, Fausto; Desai, N. B.; McKelvie, N. New synthesis of 1,1-dibromoolefins via phosphinedi-bromomethylenes. The reaction of triphenylphosphine with carbon tetrabromide. Journal of the American Chemical Society, (1962), 84, 1745-7.

[15]Michel, Patrick; Gennet, Dominique; Rassat, Andre. A one-pot procedure for the synthesis of alkynes and bromoalkynes from aldehydes. Tetrahedron Letters, (1999), 40(49), 8575-8578.

[16]Dolhem, Franck; Lievre, Catherine; Demailly, Gilles. Synthesis of 1,1-dibromo-1-alkenes from partially protected and unprotected aldoses. Tetrahedron Letters, (2002), 43(10), 1847-1849.

[17]Bouhlel, Ezzeddine; Rathke, Michael W. A convenient procedure for the preparation of reactive zinc for the Reformatskii reaction. Synthetic Communications, (1991), 21(1), 133-6.

[18]Lakhrissi, Y.; Taillefumier, C.; Chretien, F.; Chapleur, Y. Facile dibromoolefination of lactones using (bromomethylene)triphenylphosphorane. Tetrahedron Letters, (2001), 42.

[19]Lakhrissi, Mohammed; Chapleur, Yves. Wittig olefination of lactones. Angewandte Chemie, International Edition in English, (1996), 35, 750-2.

[20]Lakhrissi, Mohamed; Chapleur, Yves. Dichloromethylenation of Lactones. 6. Efficient Synthesis of Dichloroolefins from Lactones and Acetates Using Triphenylphosphine and Tetrachloromethane. Journal of Organic Chemistry, (1994), 59(19), 5752-7.

[20]Lakhrissi, M.; Chapleur, Y.Triphenylphosphine and tetrachloromethane: an efficient reagent for the dichloromethylenation of lactones and acetates. Synlett (1991), (8), 583-5.

[21]Zhang Ji; Sarma Koushik Das; Curran Timothy T; Belmont Daniel T; Davidson James G Efficient synthesis of novel gamma-substituted gamma-butenolides by Lewis acid catalyzed addition of metal enolates of active methylene compounds to mucohalic acids. The Journal of organic chemistry, (2005), 70(15), 5890-5.

[22]Duan, Xin-Fang; Zhang, Zhan-Bin. Organic reactions promoted by cesium salts. Youji Huaxue (2006), 26.

[23] Zou, G.; Reddy, Y. K.; Falck, J. R. Ag(I)-promoted Suzuki-Miyaura cross-couplings of n-alkylboronic acids. Tetrahedron Letters, (2001), 42, 7213-7215.

[24]Bellina, Fabio; Anselmi, Chiara; Martina, Francesca; Rossi, Renzo. Mucochloric acid: A useful synthon for the selective synthesis of 4-aryl-3-chloro-2(5H)-furanones, (Z)-4-aryl-5-[1-

(aryl)methylidene]- 3-chloro-2(5H)-furanones and 3,4-diaryl-2(5H)-furanones. European Journal of Organic Chemistry, (2003).

[25]Bellina, Fabio; Rossi, Renzo. Mucochloric and mucobromic acids: Inexpensive, highly functionalized starting materials for the selective synthesis of variously substituted 2(5H)-furanone derivatives, sulfur- or nitrogen-containing heterocycles and stereodefined acyclic unsaturated dihalogenated compounds. Current Organic Chemistry, (2004), 8.

[26]Bellina, F.; Anselmi, C.; Rossi, R. Synthesis of 4-alkyl-3-bromo-2(5H)-furanones and unsymmetrically disubstituted 3,4-dialkyl-2(5H)-furanones by palladium-catalyzed cross-coupling reactions. Tetrahedron Letters, (2001), 42(23), 3851--3854.

[27]Doucet, Henri. Suzuki-Miyaura cross-coupling reactions of alkylboronic acid derivatives or alkyitrifluoroborates with aryl, alkenyl or alkyl halides and triflates. European Journal of Organic Chemistry, (2008), (12), 2013--2030.

[28]Zhang, Ji; Blazecka, Peter G.; Belmont, Daniel; Davidson, James G. Reinvestigation of mucohalic acids, versatile and useful building blocks for highly functionalized □ ,□ -unsaturated □ -butyrolactones. Organic Letters, (2002), 4(25), 4559--4561.

[29]Jones, E. R. H. *et al. J. Chem. Soc.* 1953, 457 & 2548 & 3019.

*[30]*Corey, E.J.; Suggs, W. (1975). "Pyridinium Chlorochromate. An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds". *Tetrahedron Letters* .16: 2647–2650.

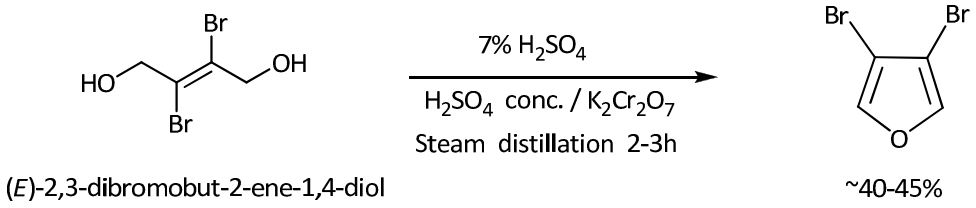
CHAPTER 4

RESULTS AND DISCUSSIONS

1. Synthesis of the 3,4-dibromofuran

The attempts to reproduce the procedure in the publication of Gorzynski[1] have been successful without any complication regardless of the scal of the synthesis (from 10 to 50 gr). The reaction yields were in the range 40-45%.

The yields are not too impressive mainly due to the over oxidation of the product in the reaction medium. I did not make any modification of this water steam distillation procedure or of the extraction work-up. The slightly yellowish odorous oil which was extracted from the water with petroleum ether is subject to a rapid decomposition if kept at room temperature. This dibromofuran has to be stored under argon at low temperature.



(*E*)-2,3-dibromobut-2-ene-1,4-diol ~40-45%

Schema 4.1: Cyclooxidation

The possibility to run the reaction at large scale is an advantage in a total synthesis. The chemist must not repeat the synthesis too often. The problem is more ecological since the chromic waste are environmental hazardous.

Another procedure[2] increased dramatically the yield to 80% by using a two phase solvent system.

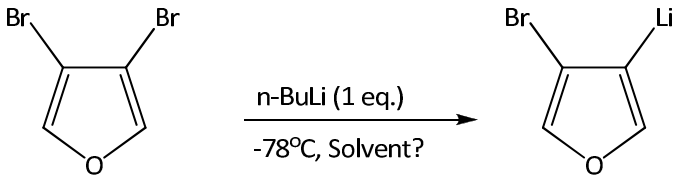
This procedure has to be run at 140°C and since one of the solvent is hexane this requires special high pressure equipments. Thanks to this two phases system the product formed is

extracted into the hexane phase and is protected from over-oxidation. To validate this procedure I have run small batches (20mmol) with a microwave reactor which can support such pressure. The yields were as the published value. However due to the small amount of product synthesized each time the water steam distillation has been the recurrent method for this first step.

The product was purified by flash column chromatography on silica with hexane as eluent and pushed by argon to yield at 45% of the pure product as colorless oil.

2. Synthesis of the 3-bromo-4-butylfuran

The common step of the three procedures selected from the literature for the synthesis of 3-bromo-butylfuran is a bromine lithium exchange.

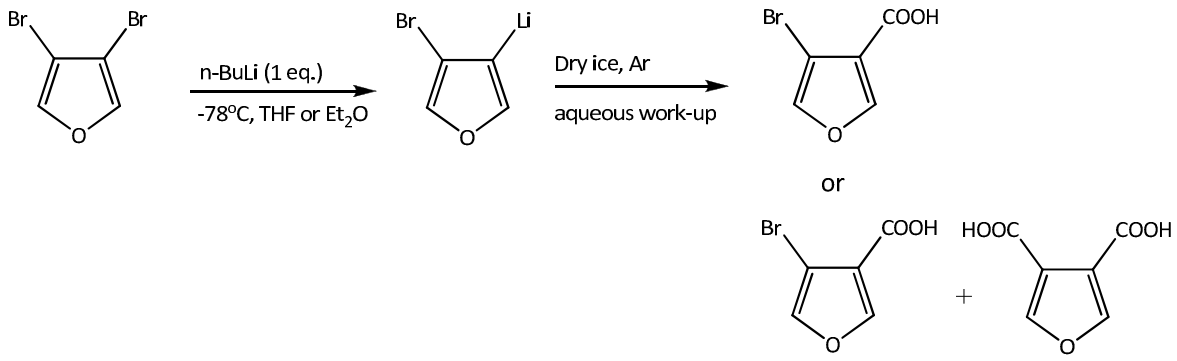


Schema 4.2: Bromine-lithium exchange reaction

This reaction is temperature dependent and may also be solvent dependant. To find out if a single bromine lithium exchange occurs, experiments were run in two different solvents: THF and Et_2O

After addition of one equivalent of n-butyllithium at -78°C under argon atmosphere and after complete consummation of the 3,4-dibromofuran as monitored by GC the reaction mixture was rapidly poured into a batch of dry ice under argon followed by an aqueous workup and extraction in order to determine which carboxylic acids that were formed. ^{13}C NMR spectra were recorded in order to determine how many different products were obtained. If there are five peaks present it means a single bromine-lithium exchange had

occurred. If there are more than five it means that some molecules undergone a double bromine-lithium exchange.



Schema 4.3:Test for an appropriate solvent

The results were without ambiguities. The use of Et_2O as solvent leads to a single bromine-lithium exchange. Careful precautions were made to have dry Et_2O and to run the experiment under inert atmosphere (argon in most of the cases.)

With this important factor under control I could start the alkylation experiments.

A careful monitoring of the reaction by GC after the addition of 2 equivalents of Bu_2SO_4 after monolithiation of the furan at -78°C in Et_2O shows that there is no reaction occurring. A work-up confirm it since the only recovered material was the unchanged Bu_2SO_4.

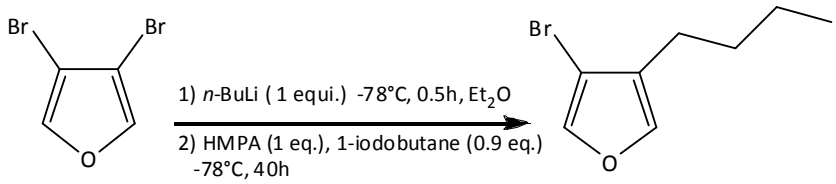
That the reaction failed is perhaps due to the low electrophilicity of the reagent. The reaction might have been forced to work at higher temperature but as mentioned in the Theoretical part this would affect the β-position of the lithium by transmetallation. Still at -40°C which is the minimum requirement to avoid transmetallation no electrophilic substitution occurred.

The reaction between 1-iodobutane and 3,4-dibromofuran in presence of hexamethylphosphoric acid triamide (HMPA) was successful.

The Inge Bock procedure[3] was used.

One equivalent of HMPA was slowly added at -78°C to one equivalent of (4-bromofuran-3-yl)lithium previously obtained with the reaction of one equivalent of BuLi (1.6M in hexane)

with one equivalent of 3,4-dibromofuran in dry Et_2O under argon. Then 0.8 equivalent of 1-iodobutane in Et_2O was added.



Schema 4.4: Alkylation of 3,4-dibromofuran with iodobutane and HMPA

The reaction time is about 40 h at -78°C for achieving the complete conversion.

The course of the reaction is easy to follow even without GC since a highly viscous complex is formed and the viscosity is progressively reduced = after the addition of the electrophile and disappears when the reaction is complete.

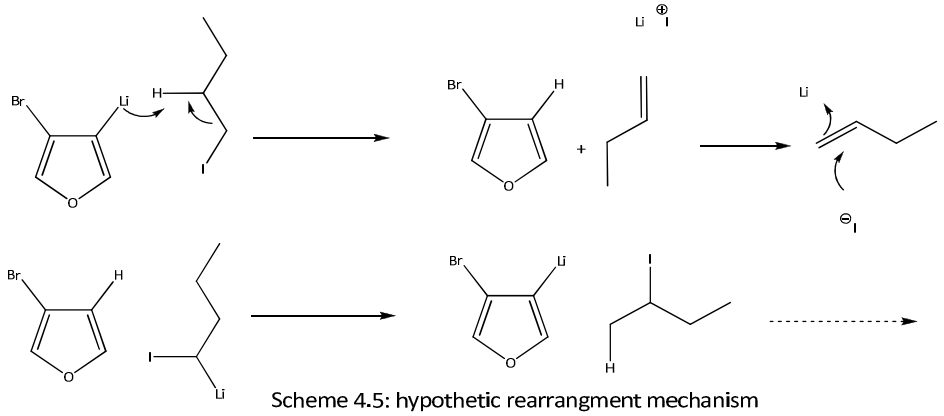
This complexation is the result on the action of HMPA since the basic oxygen atom in HMPA coordinates strongly to lithium cation.[4]

However the G.C. shows the formation of four products each time the experiment has been run. The ^1H NMR was also quite complex but shows clearly a mixture of four products.

However, all attempts to separate the products by column chromatography failed showing the close nature or the similar molecular mass of these different products.

Competing reaction in-situ may explain this result.

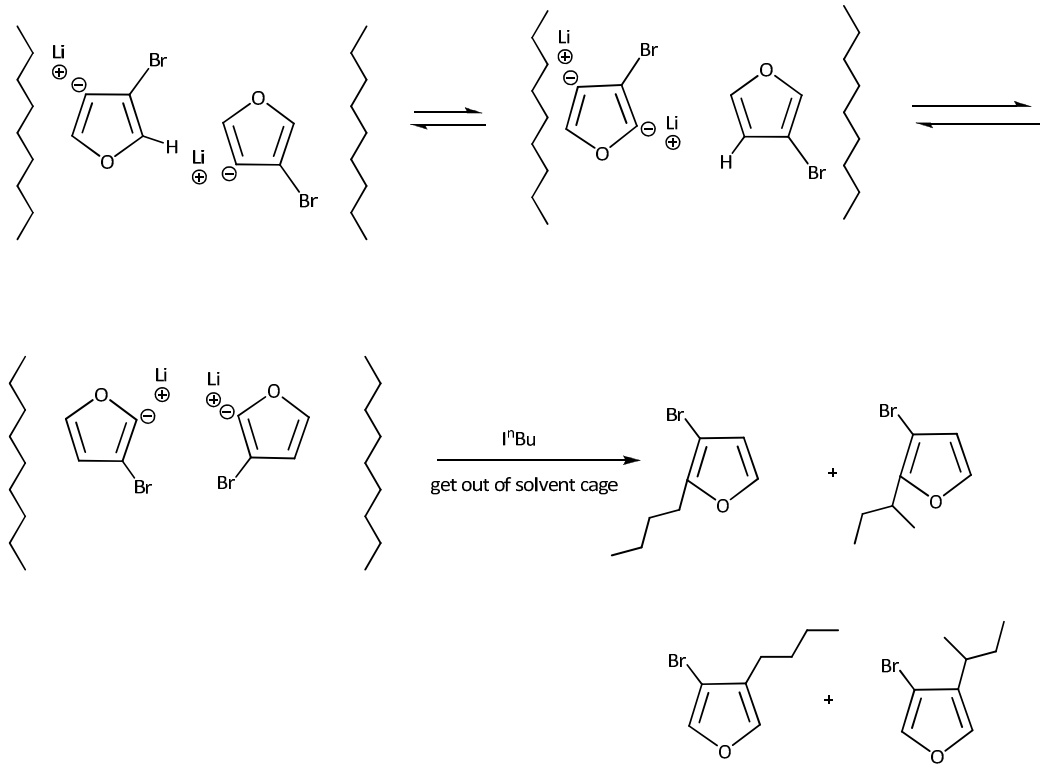
The first is a hypothetic rearrangement of primary butyl iodide into the secondary isobutyl iodide. A possible mechanism is shown below. The formation of the 2-iodobutan is evidenced by the sextuplet of the ^1H NMR spectra.



Scheme 4.5: hypothetic rearrangment mechanism

The second one has been proposed by Carlos Alvarez-Ibarra and his team[5].

"In fact, the HMPA is a polar solvent which enhances the reactivity of carbanion species as a consequence of the formation of solvent-separated ionic pairs. Thus, fast and consecutive acid-base bimolecular reactions could occur before the nucleophile reagent escapes from the solvent cage so leading to the isomerization of 3-lithio-4-n-butylbromofuran or 3-lithio-4-isobutylbromofuran. The regioselectivity of subsequent alkylation reaction is directed by the greater acidity of the H-atom bound at C2 position."



Schema 4.6: Solvent cage reaction

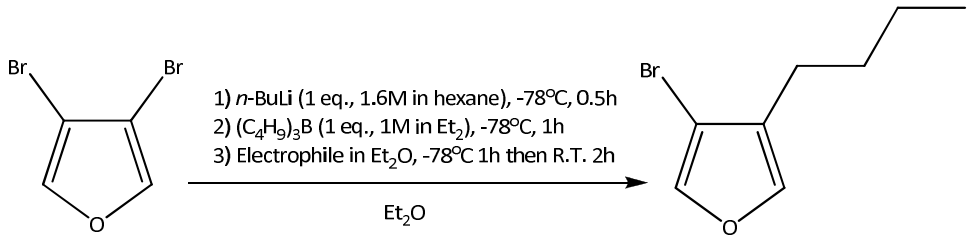
To summarize there are three factors to take in consideration. The temperature which can lead to either a transmetallation or a elimination reaction E_2, the time which can lead to the hypothetical rearrangement of the butyl chain and the complexing agent which slowly releases the (4-bromofuran-3-yl)lithium in the mixture.

It was, however, not possible to control all these parameters and I had to find another method.

The third method was the object of a small publication[6] with few references and which has nearly never been cited. But the name of the authors and the kind of chemistry was a good sign.

The reaction was an alkylation of furan via organoborane.

It took me a long time to set up a proper procedure for the reaction to obtain decent result with my molecule. But at least it was possible to yield a single product in 60-65% yield.



Schema 4.7: Alkylation of 3,4-dibromofuran via organoborane chemistry

The authors using the 3-bromofuran instead of 3,4-dibromofuran. This was evident that the bromine atom of my molecule will make a change in the condition to use. Since bromine is more electronegative than hydrogen I supposed that the ate-complex should be more stabilized allowing the second step reaction to occur more easily and perhaps at lower temperature.

The main problem was to set up a good temperature and a good timing for each step of the reaction so that a single product is formed without any byproducts and permitting an easy work-up procedure. In the publication, the authors let the reaction reaches room temperature before injecting the electrophile (third step). In my case I found out that this was not necessary and it was even better to run the reaction for longer time at -78°C.

The use of Et_2O instead of THF might have outcome on the course of the reaction but in order to obtain a mono-lithiation by halogen-metal exchange, Et_2O is the only appropriate solvent.

I also tried different electrophiles for the third step: Iodine; bromine; N-bromosuccinimide and N-chlorosuccinimide electrophile

For both an easier work-up and a higher yield N-chlorosuccinimide was the most suitable.
The last problem met was the work-up. The solution after adding the electrophile is very thick and attempts to extract the product by direct solvent extraction were not appropriate.

Subsequent to adding aqueous NaOH and 30% H_2O_2[7] to remove the residual organoborane the solution was poured into pentane and then ethanolamine (3 mol%) used as a scrubbing agent[8]. The solution could then be easily gravity filtered and the solvent removed in vacuum to yield dark odorous oil of 80% purity according the GC:
The *3-bromo-4-butylfuran.*
Further purification of this compound is difficult since it is unstable and decomposes rapidly. For this reason I decided to run the next step without further purification.
The spectra of the product shown in the appendix have been obtained from a flash chromatography purified compound.

3. Synthesis of the 3-bromo-4-butyl-5-hydroxyfuran-2(5H)-one

It was a challenge to set up an apparatus for the photooxidation with the material available in the laboratory. I had at disposition a photoreactor and a mercury lamp without any specification about the power (I found it in the store-room…). I decided to mount on it a homemade tube to introduce pure O_2 to the bottom of the reactor. The reaction tube was immersed in a long Dewar vase with dry ice and acetone to reach the -78^{o}C required.
Constant checking of the cooling bath was necessary to ensure the good temperature since the lamp develops a lot of heat which was aggravated because of the reflexion of the mirror inside of the Dewar vase.
One equivalent of alkylated bromofuran dissolved in the dichloromethane to prevent decomposition was introduced in the reactor. Then a catalytic amount of polystyrene bounded Rose Bengal and finally two equivalent of base. The oxygen flow was started to obtain a fine stream of bubble. The reactor was placed the Dewar vase. The cooling water was put on and the lamp lighted. To follow the reaction by GC I have to turn off the lamp, cut off the oxygen flow and remove the cooling system of the reactor in order to get out a

sample. After that it was necessary to wait for at least ten minutes to cool down the mercury lamp before it can be turn on again otherwise it will not work.

My first experiences were unsuccessful due the unusual difficulty of the manipulation. I from time to time, forgot either to turn on the oxygen flow or the cooling system, I several times burnt myself on the lamp, I poured out the content of the Dewar vase while trying to insert the reactor. I plugged out the water tube or the oxygen one etc…

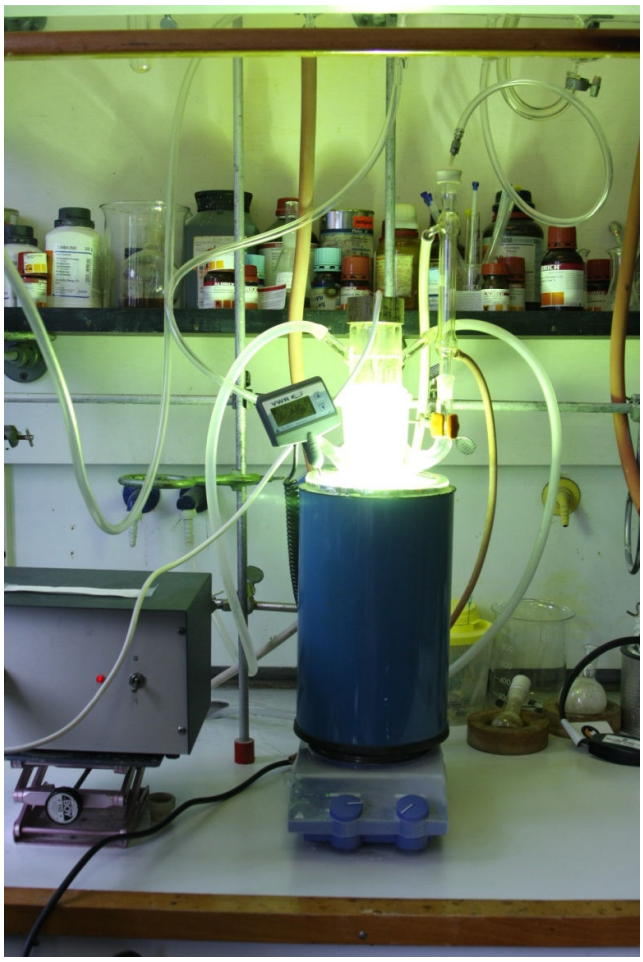


Fig. 4.1: Picture of the photoreactor in action

After getting used to the apparatus I could start the real experimental study of the effect of using different bases.

The first successful experiment was obtained with triethylamine as the base and the outcome was promising.

The first major remark is the diminution of the necessary reaction time in comparison with the other procedure[9,10]. Indeed, a careful GC to follow the course of the reaction shows a total disappearance of the starting material within an hour. I may think that this is due to the high power and the correct wavelength (in accordance with the absorption spectra of polystyrene bounded Rose Bengal) of the mercury lamp used since I have the same catalytic amount of Rose Bengal.

The second major remark is the formation of two products with close retention times in GC in unequal rate and having the same expected molecular mass of 234g.mol^{-1} according to GC/MS/MS.

A series of experiments were using different bases to observe any variation of the ratio of these two products. Of the base, D.B.U. yielded a final mixture with a ratio of approximately 80:20. My immediate reaction to this result was to try to separate the products by HPLC. Before this was made, an idea came to my mind: "Why not ran the experiment at higher temperature?" This one was motivated by the following:

There is no explanation in the literature for the reason of such a low temperature. Maybe It was used to prevent the degradation of the endoperoxide to a lot of by-products but since the experiment is run in presence of a base which efficiently prevent this there is no reason for using such a low temperature. Maybe, a low temperature was used to practical reason, i.e. to cool the lamp or maybe for the reason that someone in the past run the reaction at -78^{o}C.

Anyway running this reaction with D.B.U. at 0^{o}C gave one single regioisomeric product.

The reaction is thus dependent on the reaction temperature and the nature of the base used.

The bad side is the formation of more by-products which make the purification very difficult.

Unfortunately, the product is an oil that could not be crystallized and it was therefore not possible to determine the structure by X-ray crystallography.

The ^{13}C NMR was then the only way to determinate which regioisomere it was.

The conclusion was: the product is the 3-bromo-4-butyl-5-hydroxyfuran-2(5H)-one and yield after incomplete purification are in the range 50%--65%

4. Protection of the hydroxyl group

All the protection reactions have been carried out using the Mucobromic acid.

a. The THP protection

The procedure performed as expected with the mucobromic acid in CH_2Cl_2.The reaction time were three hs. Thanks to the use of Nafion-H©, as the acid catalyst, the production of by-product was limited and only one equivalent of dihydro-4H-pyran was needed, to compare with the three or even more equivalent in a standard procedure. The course of the reaction was easy to follow since the mucobromic is only slightly soluble in CH_2Cl_2 while the product is fully soluble.

This experiment showed that it's the lactol form of the Mucobromic acid which is protected.

The reaction with the butylated hydroxyl butenolide can so be assumed to work in the same way.

After the protection, tautomerisation is not possible anymore.

The final product, the 3,4-dibromo-5-(tetrahydro-2H-pyran-2-yloxy)furan-2(5H)-one, is a highly viscous colorless oil with a strong odor of pear! The yield after aqueous work-up, evaporation under vacuum and flash column chromatography with Hexane/Et_2O (90:10) was ca. 90%.

b. The methoxy protection

The tentatives of using Nafion-H© instead of sulfuric acid in the normal procedure was successful. The Nafion-H© absorbed the all water formed in the reaction. The reaction time can be slightly longer or shorter in comparisons with the normal procedure depending on the quantity of Nafion-H© used. Filtration of the solution and a simple evaporation of the solvent is sufficient for obtaining the pure crystalline product in >95% yield.

5. Dibromoolefination

All the reactions described in this part have been carried out with the methoxy-protected substrate.

a. Attempts with Dibromotriphenylphosphine bromide and t-BuOK

The preparation of dibromotriphenylphosphine bromide salt was performed according the procedure found in the literature since neither Aldrich nor VWR have this compound in their catalogues. No difficulties have been met. The NMR spectrum was in accordance with the reported one. The yield was about 65% after the third recrystallisation in acetonitrile (a very pure salt was a necessary requirement for making this reaction).

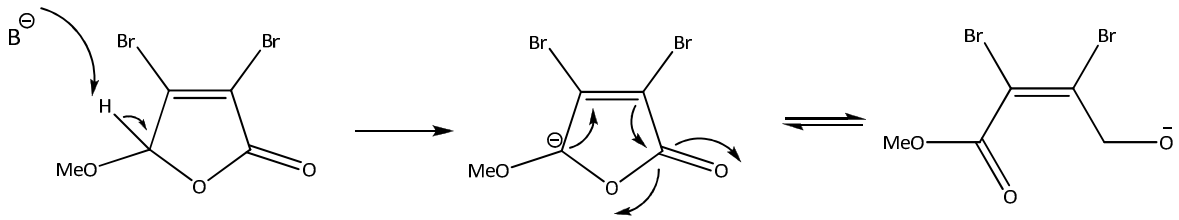
The ylid chemistry requires most of the time a large excess of reactant to perform a good conversion and so a fairly large quantity of salt had to be synthesized.

The salt has been reported to be stable for at least six months if stored at -20^{o}C under an inert atmosphere it have been thus prepared in large quantities (50 mmol of reagent).

Even when protected, the substrate is base sensitive. Direct contact with any mild or strong base gives an instantaneous decomposition.

This is due to the proton of the molecule which is in a conjugate position, making it more acidic.

A mild and strong base can deprotonate it which result of a ring opening leading to a enolate highly reactive and prone to polymerization.



Schema 4.8: Formation of the enolate

The addition of the substrate should be done after the addition of 3.9 eq. Of *t*-BuOK to 4 eq. of the phosphonium salt. Small excess of salt is required to ensure the all full consumption of the base.

The addition of the base to the salt at room temperature and under inert atmosphere leads to formation of the ylid which is characterised by an intense yellow/brown colour. This ylid is stable at room temperature and in refluxing dioxane.

However, once the substrate is injected to the solution it turned into deep black in a few minutes. The GC shows each time that the substrate has been consumed but the desired product was not formed according to the GC.

Many attempts made with different work-up procedure, distillations under vacuum (fractioned, Kugelrohr), chromatography to head on this black and viscous residue.

Attempts to change the procedure:

-change the solvent (THF, Toluene), special care for using dry one

- change the relative amounts of reagent (mainly reduce the amount of base used)

-change the temperature

-change the base

-temperature, rate and dilution of addition of the substrate

led to the same black residue.

During the period when these experiments were run, I did not have access to a mass-spectrometer. This made the evaluation of the experiment very difficult and time consuming.

b. Attempts with dibromotriphenylphosphonium bromide and activated zinc

The activated zinc should be freshly made in order to perform the reaction. Normal zinc powder, even when taken from a new box, did not react with the salt. The reaction between the activated zinc and the salt took place at around 60-70^{o}C. As for the previous reaction, a deep yellow/brown color was formed indicating the presence of the ylid and It remained stable even in refluxing dioxane.

Unfortunately, the result of the addition of the substrate was similar to the previous reaction.

The cause, this time, could have been the highly reactive activated zinc which reacted with the bromine in the substrate. However, a large excess of salt (one equivalent of activated zinc for three equivalent of salt) led to the same result.

A long reaction time between the activated zinc and the salt before injection of the substrate (more than two hour in refluxing dioxane which is the maximum before the total color vanishing of the reaction.) could not thus be a solution.

Once again a lot of variations of the procedure have be made.

However no desired product could be yielded.

c. Attempts with (bromomethyl)triphenylphosphonium bromide and *t*-BuOk

It was the most promising among them all since this dibromoolefination procedure was set up above all for lactone. Being a tetrahedron letter publication[11] no experimental part was described. However, after a short while of reflexion and failures in the first attempts some conclusions were evident.

The first and the most characteristic conclusion was that the different species were poorly soluble in THF (Et_2O and dioxalane did not even allowed the salt to react with the base). The only solvent which can efficiently solubilise the species was DMSO but according the publication[11] this was reactive under the reaction condition. Analogous reduction of DMSO by triphenylphosphine and carbon tetrachloride by a yet unknown mechanism has been already described[12].

The medium is well too basic for the base sensitive substrate and obviously the *t*-BuOH formed by the protonation of the base reacted with the ylid formed in situ since the yellow characteristic ylid colour disappeared after 30 min in the refluxing system. The only possibility would have been (probably what was done in the paper) is to inject the base as the last constituent. In this manner the in situ formed ylid can react directly and specifically with the already present lactone. This assumption is confirmed by the fact that the reaction times indicated in the publication are around 30 min which show a rapid reaction between the species.

Thus even a slow excess of salt compare to the base cannot be

However attempts have been made to determine if the disappearance of the yellow colour was correlated with the impossibility of the dibromoolefin formation. After one day at reflux temperature, the lactone remained unconsumed as shown by GC.

Different types of bases have been also tried. If some strong one (BuLi, Lithiumdiisopropylamide,...,) could in a certain measure produce the ylid ,after injection of this one it was either impossible to have a stabilised solution (very short time life of the in-situ formed ylid) or violent reaction when the substrate was injected.

In the long process of trying solvents I have found only toluene to be useful which is actually the same solvent in which the salt was synthesized.

The small excess of salt in toluene, in presence of 18-crown-6 ether, can yield the ylid which did not react with *t*-BuOH.

This ylid was stable until 90°C. Higher temperature led to black mixture. Unfortunately the lactone remained unconsumed at 90°C.

This last failure concludes all the attempts to synthesize the dibromoolefin.

6. Suzuki compling on protected Mucobromic acid

All the reactions mentioned in this part have been carried out on the methoxy protected substrate. Special care were been made to have dry solvent, dry microwave tube and each tube was filled with argon.

It has been a long time of trial and error.

With Three catalysts, three base, a complementary catalytic base (two possibilities: use or not use), two solvents and another ligand (two possibilities: use or not use) the number of experiment to run was: 3x3x2x2x2=48.

After it has been set up the reaction stoichiometry of each reagent according to the literature:

-5% equivalent of catalyst

-1.1 equivalent of N-butylboronic acid

-2 or 3 equivalent of base

-3 equivalent of silver oxide

-20% equivalent of additional ligand

The orders of the experiments have been set up according the following order.

*First try all the 24 first experiments with silver oxide and one solvent: THF.

*Use one catalyst at a time and try the different bases on it.

*Never use additional ligand for the first 12 experiments.

All the experiments showed that after 3 hours in the microwave reactor the n-butylboronic acid was not consumed at all and that the substrate disappeared without the formation of new product.

The next has been to:

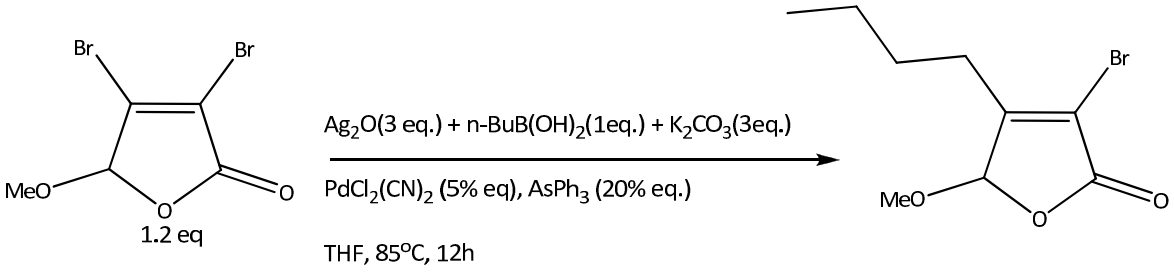
*Repeat the same experiments with the additional ligand.

Of these experiments only one showed the apparition of a new single product, quasi complete consummation of the substrate and total consummation of the n-butylboronic acid after 12 hours.

After extraction and analysis of this new single product it has been demonstrated that it was the ***3-bromo-4-butyl-5-methoxyfuran-2(5H)-one***

Besides to be an efficient shortcut to the original route, this reaction leads to a much less contaminated product than the photooxidation reaction. The purification was also much easier and yields a clean product. The yield was about 55%.

The good procedure for this reaction has been:



Schema 4.9: The good procedure for the Suzuki coupling

No other combinations have been successful.

Further experiments of the reaction showed that for a complete consummation of the n-butylboronic acid it was necessary to use an excess of substrate (1.2 equivalents). This is may be due to the fact that the substrate is base sensitive and undergone also a slow decomposition during the reaction. The same reaction run in dioxane at higher temperature was unsuccessful.

7. References

[1]Gorzynski, Marek; Rewicki, Dieter. Synthesis of alkyl-2,3-dihydrothieno[2,3-c]furans. Aromatic compounds of coffee. Inst. Org. Chem., Freie Univ. Berlin, Berlin, Fed. Rep. Ger. Liebigs Annalen der Chemie, (1986), 625-37.

[2] Kraus, George A.; Wang, Xuemei. An improved synthesis of 3-substituted furans from substituted butene-1,4-diols. Department of Chemistry, Iowa State University, Ames, IA, USA. Synthetic Communications (1998), 28(6), 1093-1096. .

[3]Alvarez-Ibarra, Carlos; Quiroga, Maria L.; Toledano, Emilio. Synthesis of polysubstituted 3-thiofurans by regiospecific mono-ipso-substitution and ortho-metalation from 3,4-dibromofuran. Tetrahedron, (1996), 52.

[4]Dykstra, R. R. "Hexamethylphosphoric Triamide" Encyclopedia of Reagents for Organic Synthesis, 2001 John Wiley & Sons, Ltd

[5]Bock, Inge; Bornowski, Hans; Ranft, Andreas; Theis, Heinz. New aspects in the synthesis of mono- and dialkylfurans. Tetrahedron, (1990), 46, 1199--210.

[6]Akimoto, Itaru; Sano, Masahiro; Suzuki, Akira. Regiospecific synthesis of 3-alkylfurans and 3-alkylthiophenes via organoboranes. Bulletin of the Chemical Society of Japan, (1981), 54(5), 1587

[7]Marinelli, Edmund R.; Levy, Alan B. Aromatic substitution via organoboranes. 2. Regiospecific alkylation of the furan and pyrrole nucleus. Tetrahedron Letters, (1979), (25), 2313-16

[8]Levy, Alan B. Aromatic substitution via organoboranes. Regiospecific formation of 2-alkylindoles. Journal of Organic Chemistry, (1978), 43(24), 4684-5

[9]Kernan, Michael R.; Faulkner, D. John. Regioselective oxidation of 3-alkylfurans to 3-alkyl-4-hydroxybutenolides. Journal of Organic Chemistry, (1988), 53(12), 2773-6.

[10]Quino, M.; Bruno, I.; Riccio, R.; Gomez-Paloma, L. Regioselective Entry to Bromo-□ -hydroxybutenolides: Useful Building Blocks for Assemblying Natural Product-Like Libraries. Organic Letters (2006), 8(21), 4831-4834.

[11]Lakhrissi, Y.; Taillefumier, C.; Chretien, F.; Chapleur, Y. Facile dibromoolefination of lactones using (bromomethylene)triphenylphosphorane. Tetrahedron Letters, (2001), 42.

[12]Astrillon, Jose P. A.; Szmant, H. Harry. Reduction of sulfoxides by triphenylphosphine and carbon tetrachloride. Journal of Organic Chemistry, (1965), 30.

CHAPTER 5

SOME KIND OF CONCLUSIONS

To summarize:

- Was the retro-analysis suitable for the synthesis of the target molecules?

After reading this thesis the answer is no. The target was not reach.

- Was the effort worthwhile?

The answer is yes, but some arguments are needed

-The time for achieving the goal was too short for such a project.

-I did not have much experience when the project started, but the project gave me an opportunity to learn a lot; learning by doing.

-My knowledge of advanced organic chemistry was limited when the project started and it was difficult to evaluate published methods.

-During the course of the project, unforeseen difficulties arisen: tautomery, unusual base-sensitivity, unstable compound.

- The retro-analysis and synthetic roads attempted are original and to the best of my Knowledge, not previously attempted.

-the key feature is that starting materials are cheap and easily available.

-There was a small change in the course of the project: The furan tactic was replaced by using mucobromic acid which gave a short-cut of the route. Maybe, I was too stubborn and reluctant to change my ideas so that the mucobromic route was attempted too late.

- The final step, dibromoolefination, has not yet been successful. There is nothing that rules out the possibilities, this is probably a question of finding suitable experimental conditions.

- With the exception of the last step, the attempted routes afforded the desired results. This demonstrates that the retro-analysis was reasonable.

- As a pedagogical project, this study has been very rewarding.

-It forced me to read between the lines to reveal hidden difficulties in published procedures.

-It forced me to use techniques unfamiliar to me: photo-oxidation, micro-wave, ultra-dry conditions and equipments.

- Chemicals results:

-Mono-lithiation of 3,,4-dibromofuran can be made in diethyl ether.

-3,4-dibromofuran can be mono-butylated.

-A regioselective Suzuki coupling has been form using butyl boronic acid and mucobromic acid.

-Regioselective photo-oxidation of 3-bromo-4-butylfuran can be achieved at $0^{o}C$ with DBU.

-A simple procedure has been found for methyl protection of alcohols using Nafion-H® as acid catalyst and water scavenger.

- The most important experience for me was that I should trust and respect the experimental results: Often the intended chemistry is reluctant and this is not my fault.

Molecules can be very mean and nasty.

CHAPTER 6

EXPERIMENTAL PART

1. Materials

All glassware used to air sensitive experiments were oven-dried at least 1hr before use.
All reaction s were carried out either under argon or nitrogen atmosphere.
Molecular sieves (4 A, 4-8 mesh) purchased from Aldrich have activated by heating in an oven at 400°C for at least 2 days.
Flash Chromatography was performed using granular silica gel (60 A/35-70qm) purchased from matrex.

Solvents

Prior to use, THF and Et_2O were pre-dried over anhydrous $CaCl_2$ and then reflux over sodium benzophenone ketyl under nitrogen atmosphere.
Dioxane was distilled under reduced pressure over anhydrous $CaCl_2$ and stored over molecular sieves.
Toluene, CH_2Cl_2, pentane and methanol were used as delivered.

Reagents

All reagents were used as purchased from the manufactures.

-Reagents purchased from *Aldrich* were: trans-2,3-dibromo-2-butene-1,4-diol, 97%; n-Butyllithium (1.6M in hexane); tributylborane (1M in ether); D.B.U.; Nafion©NR50; 1-Iodobutane, 99%; Mucobromic Acid, 99%; Triphenylarsine, 97%; butylboronic acid, 97%; Cesiumfluoride, 99%; tetrabromomethane, 99%; dibromomethane, 99%; Silver(I) oxide, 99%; Potassium tert-butoxide, 95%; hexamethylphosphoramide, 99%.

-Reagents purchased from *FULKA* were: Triphenylphosphine, 95%; Potassumdichromate, Dibutyl Sulfate; Bengal Rose B Bound to polystyrene; All the palladium catalyst, 18-Crown-6,
-Reagents purchased from *Merck* were: 3,4-Dihydro-2H-pyran, 99%; Lithium in oil suspension;
All other reagents used in the experimental were available in house.

2. Substance Identification/specific equipment

-The following spectroscopic techniques were used to identify reactants and products:

Gas-Liquid Chromatography (GC): GC was performed on two Varian 3300 instruments equipped with a mediumpolar or unpolar Supelco columns and a flame ionization detector.

NMR Spectroscopy: NMR spectra were recorded on a Mercury-Varian Plus spectrometer (400MHz for ^{1}H, 100MHz for ^{13}C) at room temperature. Chemical shifts (δ) are reported in parts per million (ppm). ^{1}H shifts are referenced to chloroform-d(δ = 7.26), acetone-*d6* (δ =2.05) or Dimethyl-*d6* Sulfoxide (δ = 2.5)
^{13}C shifts are referenced to chloroform-d(δ = 77.16), acetone-*d6* (δ =19.84 and 206.26) or Dimethyl-*d6* Sulfoxide (δ = 39.52).
Splitting patterns were represented as follow: s for singlet; d for doublet; t for triplet; q for quartet and m for multiplet.

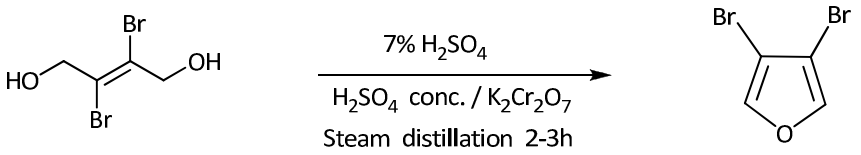
GC/MS/MS: GC/MS/MS were recorded at the pharmacy department.

-Specific equipment:

Microwave: Microwave experiments have carried out on an Initiator EXP EU from Biotage.

3. Generals Procedures

a. Synthesis of the 3,4-dibromofuran



Steam distillation method :

(*E*)\-2,3-Dibromo-2-butene-1,4-diol (20.0 g, 81.3 mmol) and 7% aqueous H_2SO_4 (50 mL) was added to a flask with steam distillation apparatus attached. The mixture was rapidly stirred at 110 °C to begin distillation. A solution of $K_2Cr_2O_7$ (25.1 g, 85.4 mmol) and H_2SO_4 (16.1 mL, 300.4 mmol) in water (160 mL) was then added over 1 h using a dropping funnel while distillation continued. After the chromic acid solution had been added, the mixture was further distilled for two, three hours more. The 3,4-dibromofuran was extracted from the distillate with hexane (2×100 mL) and the organic layers were washed with sat. Na_2CO_3 solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash column chromatography using hexane gave (9.2 g, 45%) as a colorless liquid

Two phase solvent method:

To a solution of (*E*)-2,3-Dibromo-2-butene-1,4-diol (1.23 g, 5 mmol) in 3 mL of 7% H_2SO_4 and 10 mL of hexane in a 20 mL sealed microwave reactor tube at 85^{o}C (oil bath), was added carefully trough a syringe a solution of potassium dichromate (1.47g, 5.0 mmol in 1.8g of concentred sulfuric acid and 5 mL of water) over 10min. The tube was placed in the microwave cavity and was heated at 110^{o}C for six hours. The reaction was cooled to room temperature and separated. The aqueous solution was extracted twice with 50mL of hexane

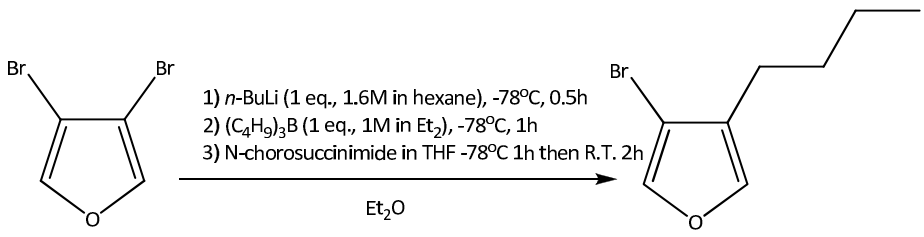
and the combined organic layers were washed with sat. Na_2CO_3 solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash column chromatography using hexane gave (0.94 g, 85%) as a colorless liquid

Analytical Data:

^{1}H NMR ($CDCl_3$): δ 7.48 (s, 2H)

^{13}C NMR ($CDCl_3$): δ 104 (C-Br); 141.6 (C-O)

b. Synthesis of the 3-bromo-4-butylfuran



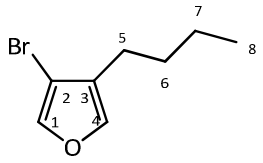
A dry 250 mL round-bottomed flask with a magnetic stirring bar was flushed with argon.
In the flask was placed 3,4-dibromofuran (3.39g, 15 mmol) and anhydrous ether (30ml). Then butyllithium (15 mmol, 9.37ml of a 1.6M solution in hexane) was added dropwise at -78°C to form 4-bromo,3-lithiofuran. The mixture was stirred for 30min. After the metallation was complete, tributylborane (15 mmol, 15mL of a 1M solution in ether) was added to the mixture at -78°C, followed by stirring for one hour. Finally a solution of N-chlorosuccinimide (3mmol, 2gr in 30 ml of THF) was fed in at -78°C. The reaction was allowed to warm to room temperature after one hour and stirred for two hours more. In order to remove the residual organoborane, the mixture was treated with 3 M aqueous hydroxide (10ml), followed by a dropwise addition of 30% of hydrogen peroxide (5ml).

The solution was poured into an Erlenmeyer containing 300ml of pentane and 10 ml of ethanolamine was added. The mixture was vigorously stirred for 30 min. Finally the precipitate is gravity filtered and concentred *in vacuo* to yield 1.97 g (65%)

Observations:

Sometimes, 30 min after injection of the tributylborane the solution turns into a cream like mixture. If it happens the solution should be warmed at room temperature until the clear liquid solution appears again and then cooled to -78^{o}C. The N-chlorosuccinimide has to be injected when the solution is liquid to get a better yield and transformation. The solution after injection of The N-chlorosuccinimide turns deep yellow. This color is partly disappears when is mixture is allowed to warm at room temperature. The N-chlorosuccinimide should be solved in THF since it no soluble in diethyl ether.

Analytical Data:

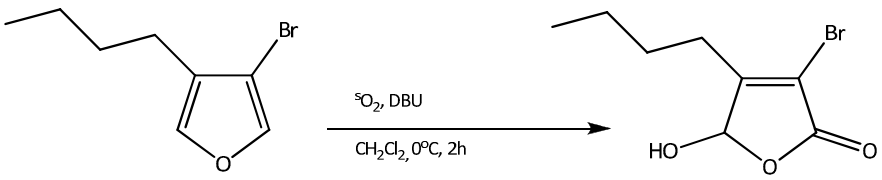


^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, 8); 1.3 (m, 2H, 7); 1.47 (m, 2H, 6), 2.28 (t, 2H, 5); 7.08 (s, 1H, 4); 7.30 (s, 1H, 1)

^{13}C NMR ($CDCl_3$): δ 13.8(8); 22.3(7); 23.48 (5); 31.09 (6); 102.7(2); 125.5 (5); 139.4 (4), 140.8 (1)

GC/MS/MS: calc. for $C_8H_{11}OBr$: 203; found 202.73, 204.73 (ratio 1 :1)

c. Synthesis of the 3-bromo-4-butyl-5-hydroxyfuran-2(5H)-one

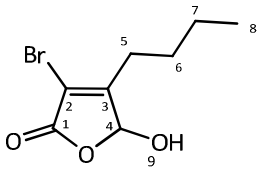


A photoreactor charged with 150 mL of dry dichloromethane was cooled at 0^{o}C. 3-bromo-4-butylfuran (1.38 g, 6.8 mmol) and finely powdered polystyrene-bounded rose Bengal catalyst (150 mg) were added. Then the D.B.U. (2.07 g, 13.2 mmol, 2 eq.) was introduced, the reactor was closed and the oxygen bubbled for 15 min. Then the medium pressure mercury lamp was turned on. The solution was in a continuous flow of oxygen for two hours until the reaction was complete. The catalyst was filtered off and the solution was washed with an aqueous solution of HCl 1M (100mL). The aqueous layer was extracted with dichloromethane twice (100mL). The combined organics layers were washed with water, dried with $MgSO_4$, filtered and concentred *in vacuo*. The residue was purified by column chromatography and gave a sweet acidic odorous yellowish oil. (1.05g ,65%)

Observation:

The residue was very complex and difficult to purify. Many attempts to obtain a pure product by column chromatography have failed and changing the experimental conditions to avoid it led to the formation of the two regioisomeres. The maximum purity reached, according the GC was 85%.

Analytical Data:

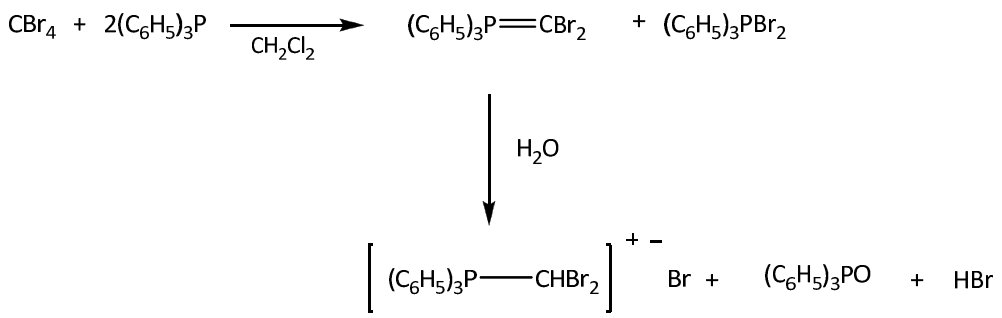


^{1}H NMR ($CDCl_3$): δ 0.80 (t, 3H,8); 1.25 (m, 2H, 7); 1.50 (m, 2H,6), 2.35 (2m, 2H, 5); 3.70 (s, OH, 9), 6 (2s, 1H, 4)

^{13}C NMR ($CDCl_3$): δ 13.62 (8); 22.71 (7); 27.58 (5); 28.51 (6); 98.90 (d, 4); 111.87 (3), 164.33 (2); 167.38 (1)

GC/MS/MS: calc. for $C_8H_{10}O_3Br$: 235; found 233.09, 235.07 ratio (1:1)

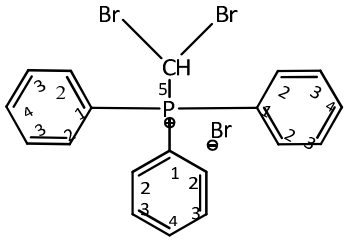
d. Synthesis of the dibromotriphenylphosphonium bromide



Carbon tetrabromide (it must be a colourless solid) (16.4 g, 49.4 mmol) was added to a solution of triphenylphosphine (26 g, 99.1 mmol) in methylene chloride (240 mL). The solution was stirred for 15 min at room temperature. Water (8 mL) was added to this resulting red reaction mixture. After 15 min of vigorous magnetic stirring, the aqueous layer was separated with $MgSO_4$. The organic layer was dried and evaporated under reduced pressure to syrup. The salt was precipitated by trituration with acetonitrile. The yellow powder obtained was filtered, dried under vacuum and resolubilised in CH_2Cl_2 (500 mL) and re-evaporated to syrup and reprecipitated by addition of acetonitrile. The white powder

obtained was filtered, concentred *in vacuo* and recrystallised from dry acetonitrile from the solvent disposable. The solution was filtered hot and the recrystalysed dibromomethyl-triphenylphosphonium bromide recrystallised was filtered. The recrystallisation was repeated twice and then the crystals were in a oven at 200^0C.

Analytical Data:



^{13}C NMR ($CDCl_3$): δ 29.7 (d, 5); 115.9 (s,1); 130.3 (d,2); 135 (d,3); 135.6 (s,4).

e. Synthesis of activated zinc

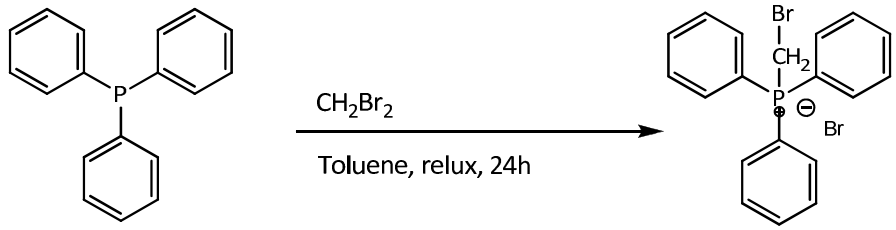
The lithium dispersion (30 wt% in mineral oil, sodium content, 0.5%) (1.388 g, 60 mmol) was weighed directly into a 250 mL round two-necked flask. This flask was then fitted with a magnetic stirrer, rubber septum and reflux condenser attached to a balloon of argon gas. To the lithium was added 10 mL of dry Et_2O. The mixture was stirred and the flask was immersed in a water bath. $ZnCl_2$, 1.0 M solution in Et_2O (30 mL, 30 mmol) was added dropwise by a syringe through the septum. The mixture was stirred for 5 h at room temperature. The flask was then immersed in an ice-water bath and the mixture was quenched with absolute ethanol and filtered. The zinc was washed successively with water (2 L), acetone (200 mL) then Et_2O (100 mL). The zinc was dried 100^OC under vacuum over night. It must be used quickly by using sodium: the sodium dispersion (40 wt% in mineral oil) must be used instead of the lithium. The activation's procedure was the same, only the solvent was modified: using ethylene glycol dimethylether instead of ethyl ether.

Observation:

When the zinc was filtered, before the addition of water, the ethanol must be completely removed, and addition of n-hexane is needed. During water washing, it is essential to remove the suspension.

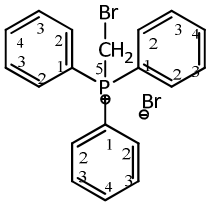
No Analytical Data available

f. Synthesis of (bromomethyl)triphenylphosphonium bromide



A solution of triphenylphosphine (10.0 g, 38.0 mmol) and dibromomethane (15.0 g, 85.5 mmol) in 90 mL of toluene was refluxed for 24h. After cooling to 0^{o}C, the phosphonium salt was collected as a white precipitate and washed three times with 200mL of hot toluene. The filtrate was heated further at reflux for 24h, affording an additional amount of phosphonium salt. The total yield was 75% (12.4 gr of bromomethyltriphenylphosphonium bromide)

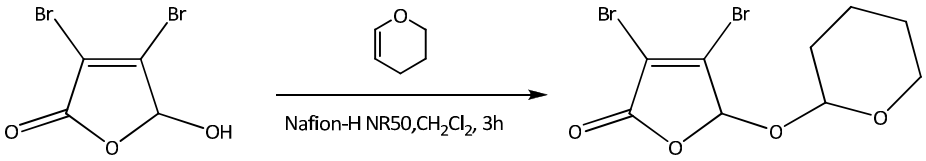
Analytical Data:



^{1}H NMR (DMSO): δ 5.81 (d, 2H,5); ≈7.9 (m, 15H, 1,2,3,4)

^{13}C NMR (DMSO): δ 16.75(d,5); 117.45(d,1); 130.7(2); 134.5(3); 136.04(4)

g. Synthesis of the O-Tetrahydropanyl Mucobromic acid derivative

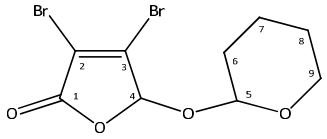


To a stirred solution of the mucobromic acid (2.58g 10 mmol) in dry dichloromethane (15mL) containing Nafion-H NR50 (200mg), a solution of dihydro-4H-pyran (0.84g, 10 mmol) in dry dichloromethane (10ml) was added over a period of one hour under argon. After completation of the addition, stirring was continued for three hours more. When the reaction was complete, Nafion-H NR50 was removed by filtration. Evaporation of the solvent gave the crude product which was purified by flash column chromatography on silica gel eluting with 10%Et_2O/hexane. The yield was 2.92g (87%)

Observation:

An increase of temperature, even of 10^0C, increased significally the production of by-products and a decrease of temperature increase the reaction time dramatically.

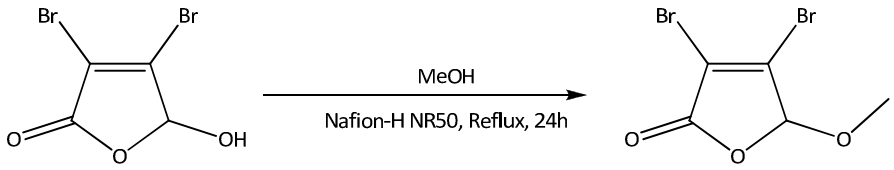
Analytical Data:



^{1}H NMR ($CDCl_3$): δ 1.70 (m, 6H, 7-8-9); 3.65 (m, 1H);

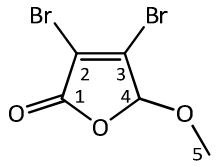
^{13}C NMR ($CDCl_3$): δ 17.71/17.89-19.75 (t, 7); 24.84/25.01 (d, 8); 29.37/29.45-30.69 (t, 6); 61.90/62.16 (d, 9); 96.70/98.55 (d, 4); 100.31/102.05 (d, 5); 117.85/118.28 (d, 2); 143.70/144.25 (d, 3); 164.35 (1)

h. Synthesis of the methoxy protected Mucobromic acid



A solution of the mucobromic acid (2.58g 10 mmol) in methanol (30 mL) containing Nafion-H NR50 (200 mg) was stirred at reflux temperature for 12h. The Nafion-H NR50 was removed by filtration. Evaporation of the solvent gave pure white crystals which according GC are pure at 95%. The yield was 2.56 g (95%)

Analytical Data:



^{1}H NMR ($CDCl_3$): δ 3.59 (s, 3H, 5); 5.80 (s, 1H, 4)

^{13}C NMR ($CDCl_3$): δ 56.16/56.29 (d, 5); 103.67/103.83 (d, 2); 118.95 (4); 143.07 (3); 164.00 (1)

GC/MS/MS: calc. for $C_4H_2O_3Br_2$: 272; found 270, 272, 274 (ratio 1:2:1)

i. Synthesis of 3-bromo-4-butyl-5-methoxyfuran-2(5H)-one

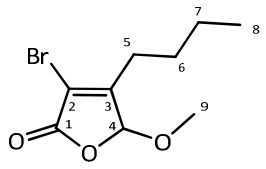
To a 20ml microwave reactor tube charged with 15 ml of dry and degassed THF was poured successively:

Butylboronic acid (0.18g, 1.84 mmol), methoxy protected mucobromic acid (0.60 gr, 2.2 mmol, 1.2eq.), silver oxide (1.27g, 5.52 mmol, 3eq.), potassium carbonate (0.76g, 5.52 mmol, 3eq.), triphenylarsine (0.11 ,0.38 mmol, 20% wt eq.) and Bis(acetonitrile)dichloropalladium(II) (0.023gr ,0.092mmol, 5% wt eq.).

The tube was filled with argon prior to be sealed and was inserted into the microwave apparatus. The reaction mixture was heated at 85^{o}C for 12h.

The tube was opened and the mixture was filtered and poured into 20 ml of dichloromethane. In order to remove the residual organoborane, the mixture was treated with 3 M aqueous hydroxide (2ml), followed by a dropwise addition of 30% of hydrogen peroxide (1ml). The solution was washed with 20mL of HCl 1M aqueous solution. The aqueous layer was extracted twice with 30 mL of dichloromethane. The combined organic layers were dried with $MgSO_4$, filtered and concentred in vacuo. The brown residual oil was diluted into 30ml pentane to precipitate the triphenylarsine, filtered and concentred vacuo. The oil was purified by flash chromatography (1:4 CH_2Cl_2, Pentane) to yield a slightly yellow/orange oil (0.30 g ,56%).

Analytical Data:



^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H, 8); 1.40 (m, 2H,7); 1.60 (m, 2H,6); 2.45 (2xm, 2H, 5); 3.57 (s, 3H, 9); 5.71 (s,1H, 4)

^{13}C NMR ($CDCl_3$): δ 13.67 (8); 22.65 (7); 27.50 (5); 28.46 (6); 59.93 (9); 103.87 (2); 112.89 (4); 161.94 (3); 166.30 (1)

GC/MS/MS: calc. for $C_8H_{11}O_3Br$: 248; found 247.1, 249.1 ratio (1:1)

j. THF versus Et_2O

A dry 100 mL round-bottomed flask with a magnetic stirring bar was flushed with argon.

In the flask was placed 3,4-dibromofuran (1.13 g, 5 mmol) and anhydrous ether or anhydrous THF (10ml). Then butyllithium (5 mmol, 3.12 mL of a 1.6M solution in hexane) was added dropwise at -78^{o}C to form 4-bromo,3-lithiofuran. The mixture was stirred for 30min. After the metallation was complete the mixture was siphonated into a closed and argon filled round-bottomed flask containing dry-ice and a magnetic stirring bar. The mixture was vigorously stirred until the dry-ice was evaporated. Then distillated water was added into the flask and vigorous stirred.

The organic layer of the experiment with Et_2O as solvent was extracted with ethyl acetate, dried with $MgSO_4$, filtered and evaporated in vacuo. The crystal residue (not weighted) was analyzed as it was by ^{13}C NMR

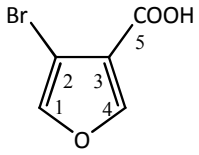
The mixture of the experiment with THF as solvent was mixed with saturated brine and extracted with ethyl acetate, dried with $MgSO_4$, filtered and evaporated in vacuo. The crystal residue (not weighted) was analyzed as it was by ^{13}C NMR

Observation:

No acid have been added for the protonation (considering the risk of incomplete reaction) to ensure the only carboxilation of the compound and no other side reactions.

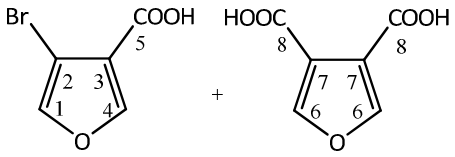
Analytical Data:

With Et_2O



^{13}C NMR ($CDCl_3$): δ 99.82 (2); 117.69 (3); 143.46 (1); 150.50 (4); 166.68 (5)

With THF



^{13}C NMR ($CDCl_3$): δ 99.80 (2); 117.72 (3-7); 143.40 (1); 143.56 (1); 150.52 (4); 150.61 (6); 166.63 (5-8)

CHAPITRE 7

FURTHER PROSPECTS

As a continuation of my work, an obvious choice is to use the mucobromic route and an optimization of each successful step.

By this way the method could become more viable.

The present work did not present any procedures of deprotection and even if theoretically it seems feasible it has to be tested.

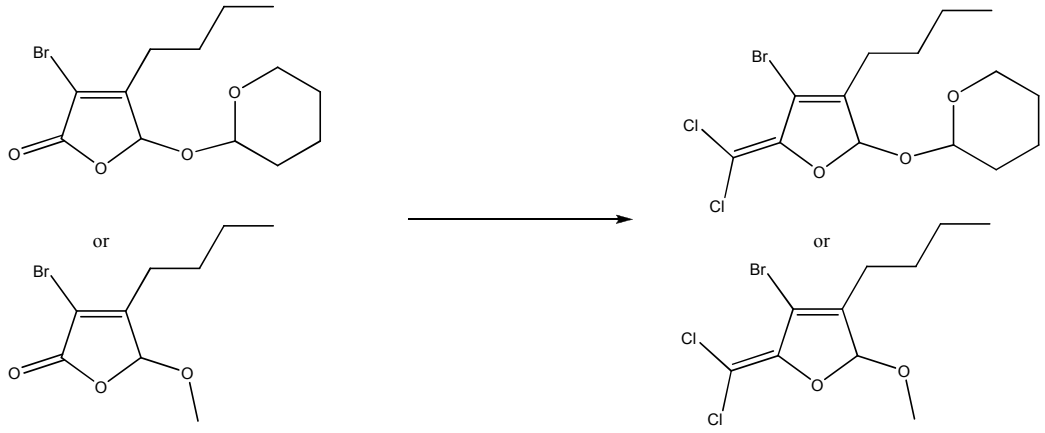
Besides no protection, or other type of reactions, has been realized on the product from the photooxidation. Maybe, this mixture is not appropriate for further reaction since some by-product are found.

The Suzuki coupling has only been carried out on one protected substrate. The outcome with other types of protective group can may give a mixture of products of the other isomer. This should be investigate

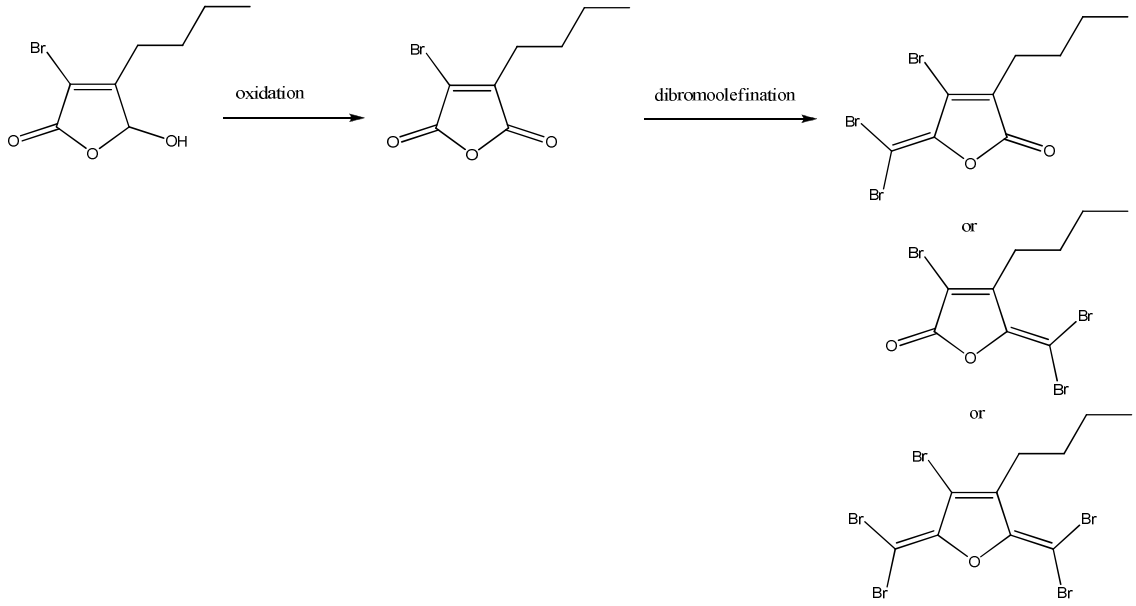
Of course to validate the retrosynthesis the dibromoolefination must work.

For this purpose additional reaction can be suggested.

A dichloroolefination of the lactone followed by a halogen exchange could be a suitable solution, even if this includes one more step, since this type of reaction seems more documented and widely used on lactone.



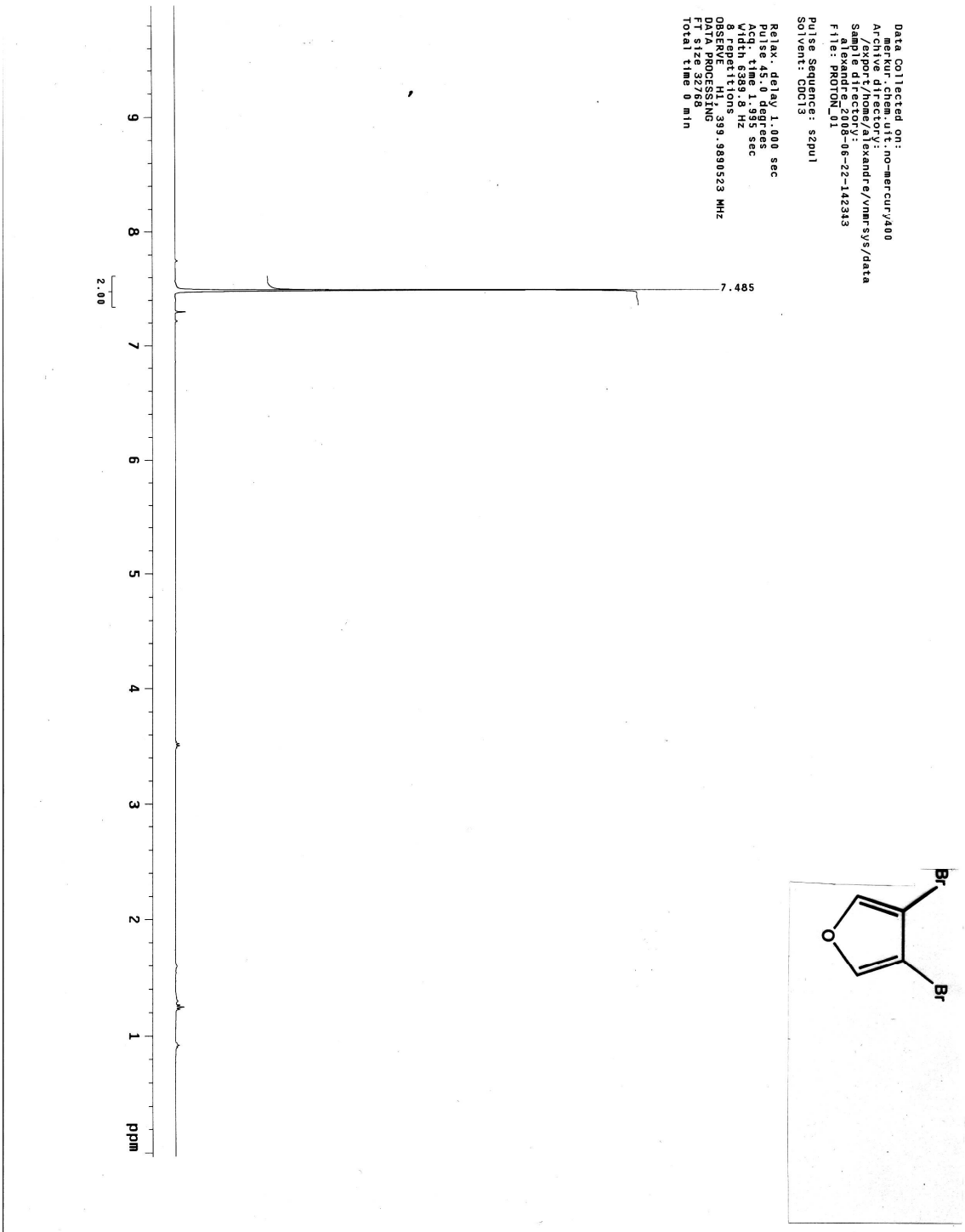
In order to make the hydoxy butenolide less base sensitive a oxidation of the hydroxyl group can be realized. It should be investigate to know if this substrate can react with the dibromoolefination reaction available.



At last start to think that these dibromoolefins are too unstable and cannot be synthesized!

CHAPTER 8

APPENDICES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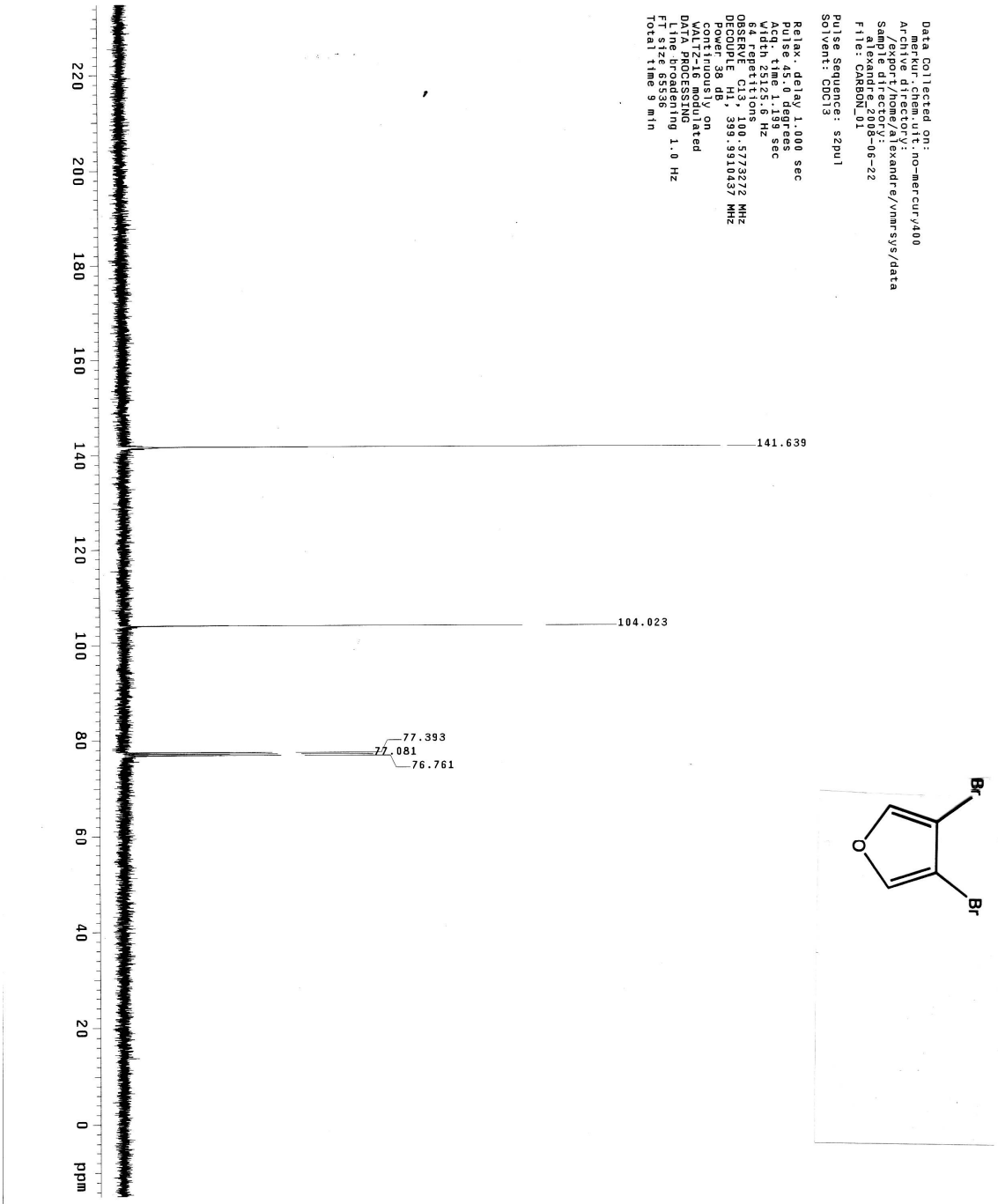
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
width 6389.8 Hz
8 repetitions
OBSERVE H1, 399.9895523 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
7.485
2.00
9
8
7
6
5
4
3
2
1
ppm
Br
O
Br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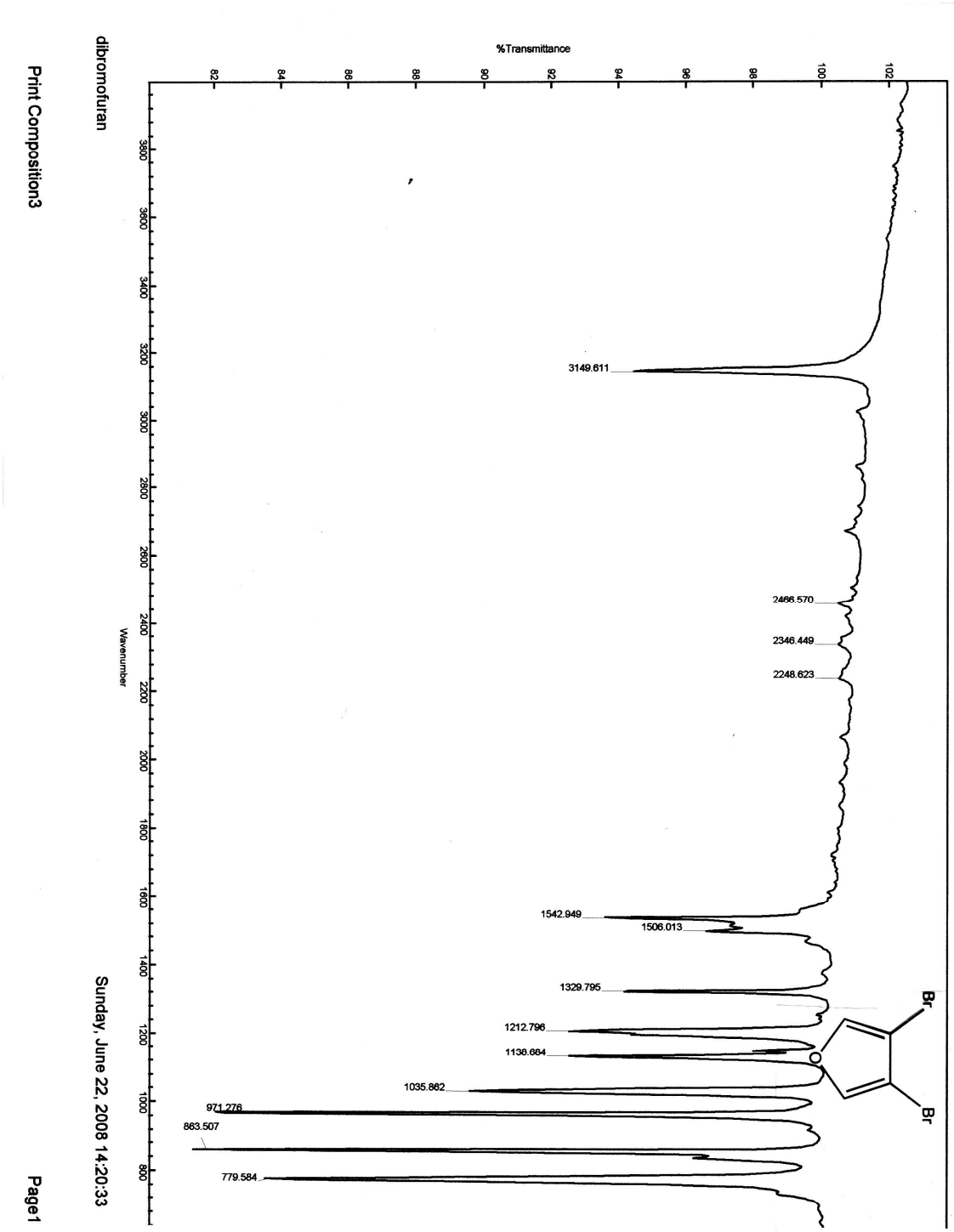
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.139 sec
Width 15151.5 Hz
64 repetitions
OBSERVE C13, 100.5773272 MHz
DECOUPLE H1, 399.9910437 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 9 min
141.639
104.023
77.393
77.081
76.761
220
200
180
160
140
120
100
80
60
40
20
0
ppm
Br
O
Br


dibromofuran
%Transmittance
Wavenumber
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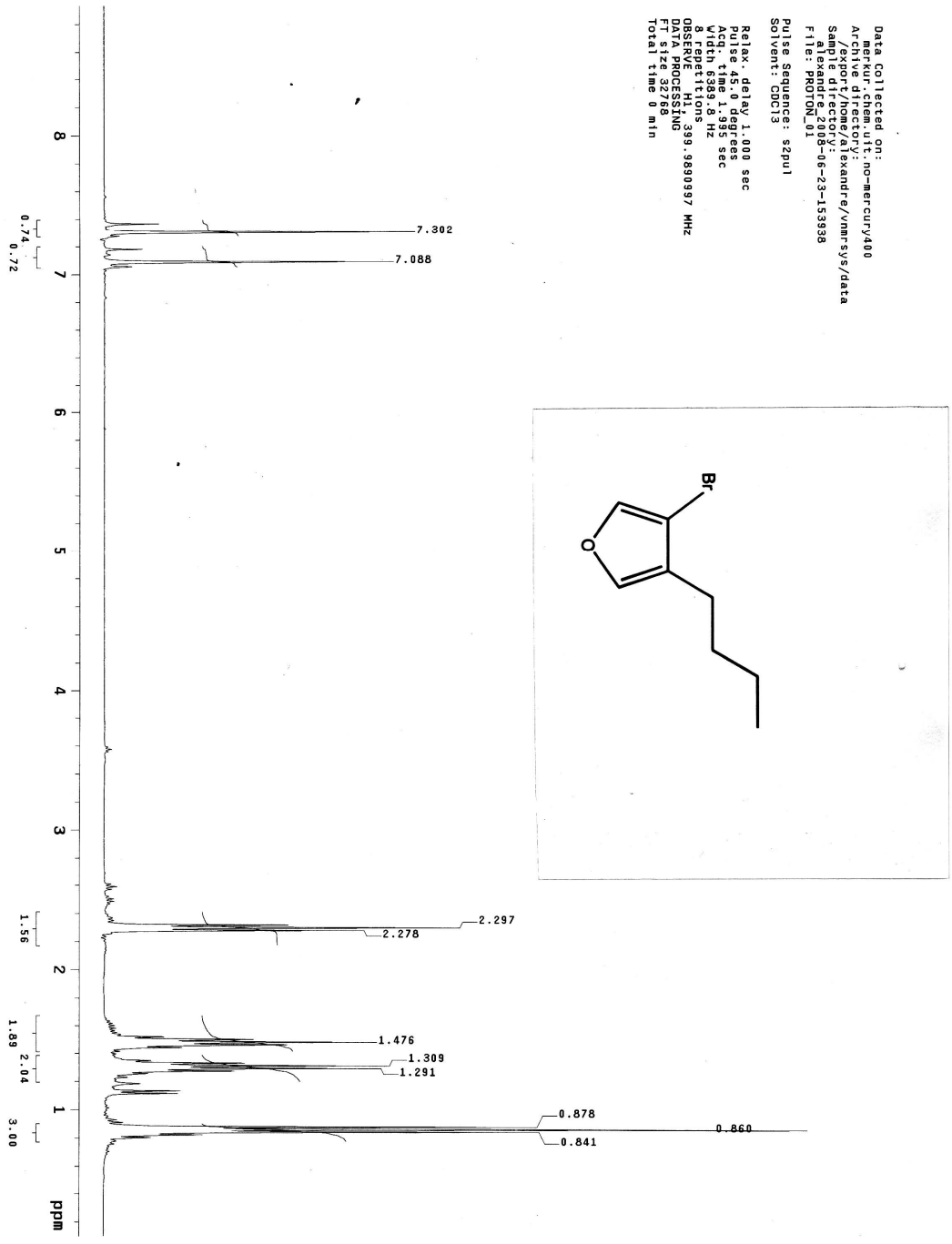
2466.570
2346.449
2248.623
1542.949
1506.013
1329.795
1212.796
1138.684
1035.862
971.276
863.507
779.584
Br
Br
Sunday, June 22, 2008 14:20:33
Print Composition3
Page1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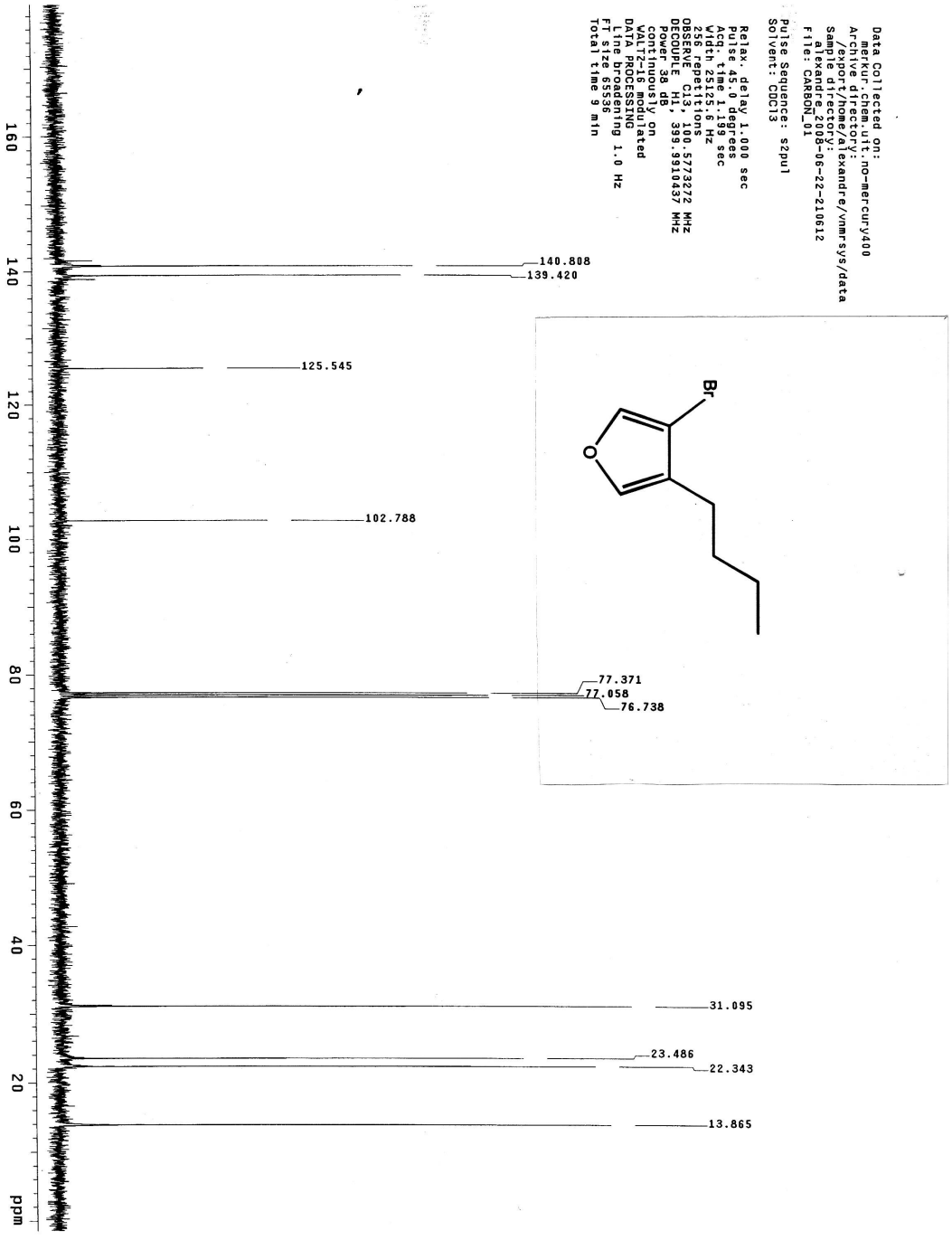
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 6389.8 Hz
8 repetitions
OBSERVE H1, 399.9899997 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
Br
O
7.302
7.088
2.297
2.278
1.476
1.309
1.291
0.878
0.860
0.841
0.74
0.72
1.56
1.89
2.04
3.00
ppm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Sample directory:
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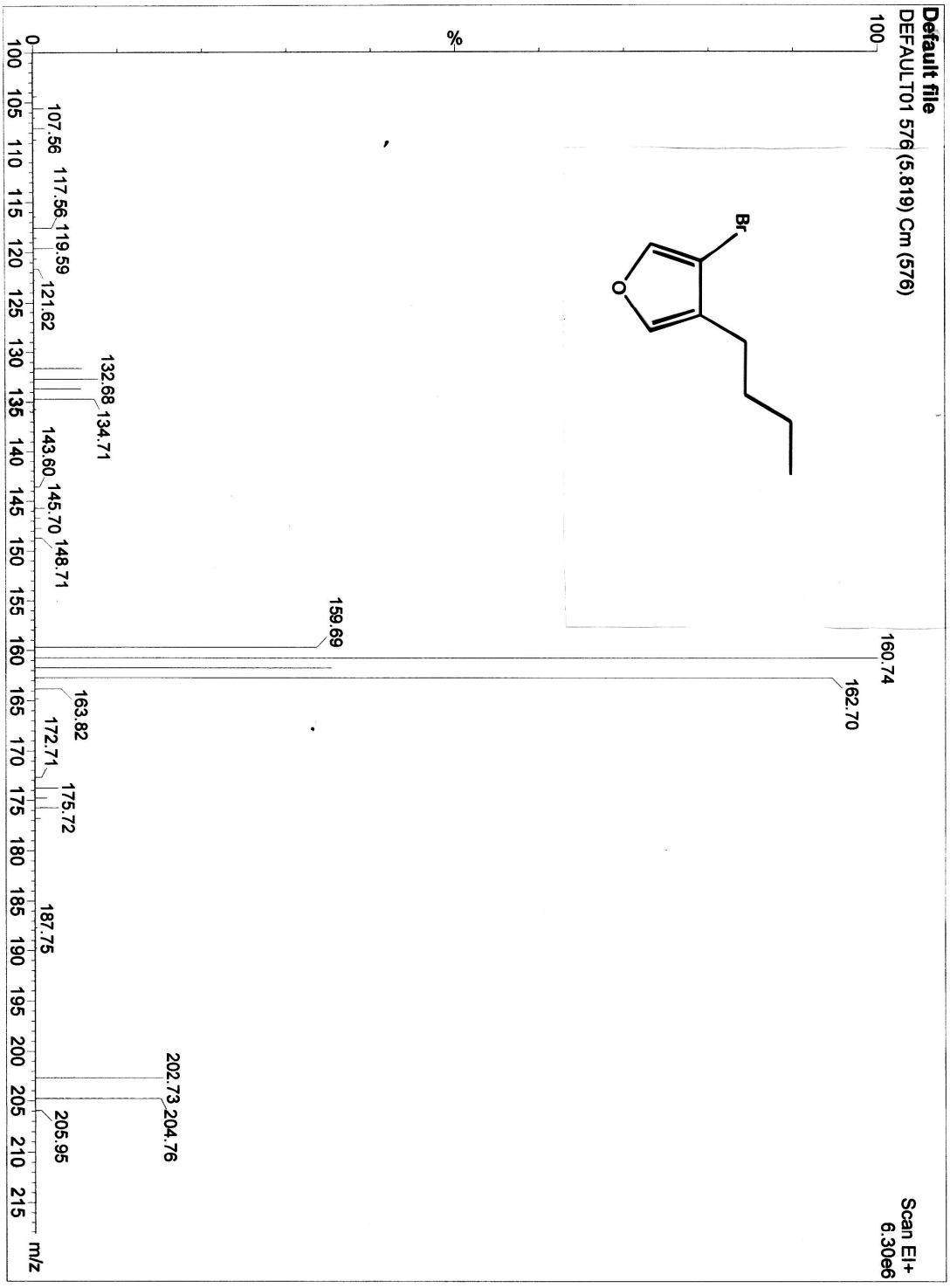
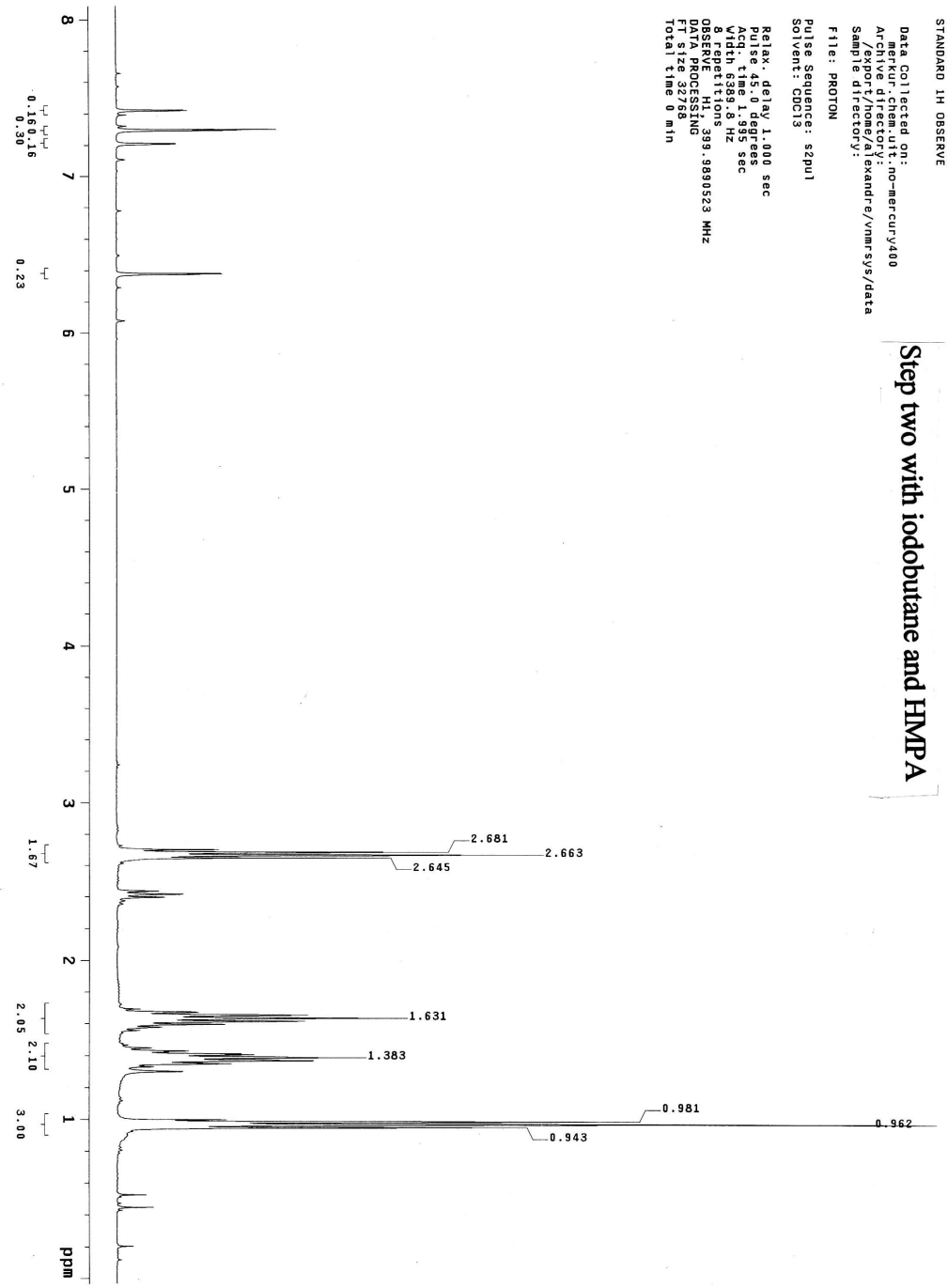
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.191 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.5773272 MHz
DECOUPLE H1, 399.9910437 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 9 min
140.808
139.420
125.545
102.788
77.371
77.058
76.738
31.095
23.486
22.343
13.865
Br
O
160
140
120
100
80
60
40
20
ppm


Default file
DEFAULT01 576 (5.819) Cm (576)
Scan EI+
6.30e6
%
Br
O
107.56
117.56
119.59
121.62
132.68
134.71
143.60
145.70
148.71
159.69
160.74
162.70
163.82
172.71
175.72
187.75
202.73
204.76
205.95
m/z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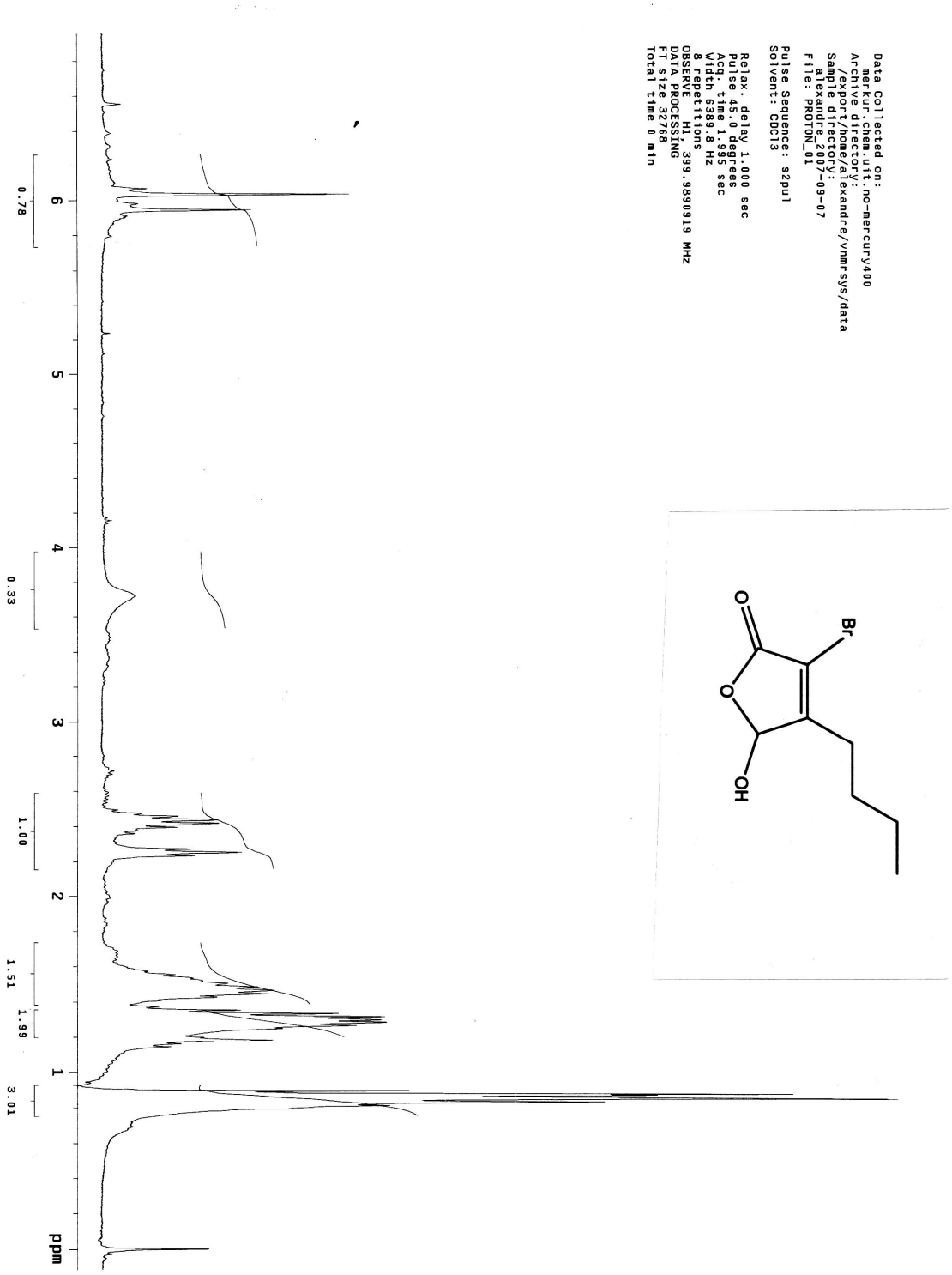
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 6389.8 Hz
8 repetitions
OBSERVE H1, 399.9890523 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
Step two with iodobutane and HMPA
2.681
2.663
2.645
1.631
1.383
0.981
0.962
0.943
0.16
0.16
0.30
0.23
1.67
2.05
2.10
3.00
ppm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Sample directory:
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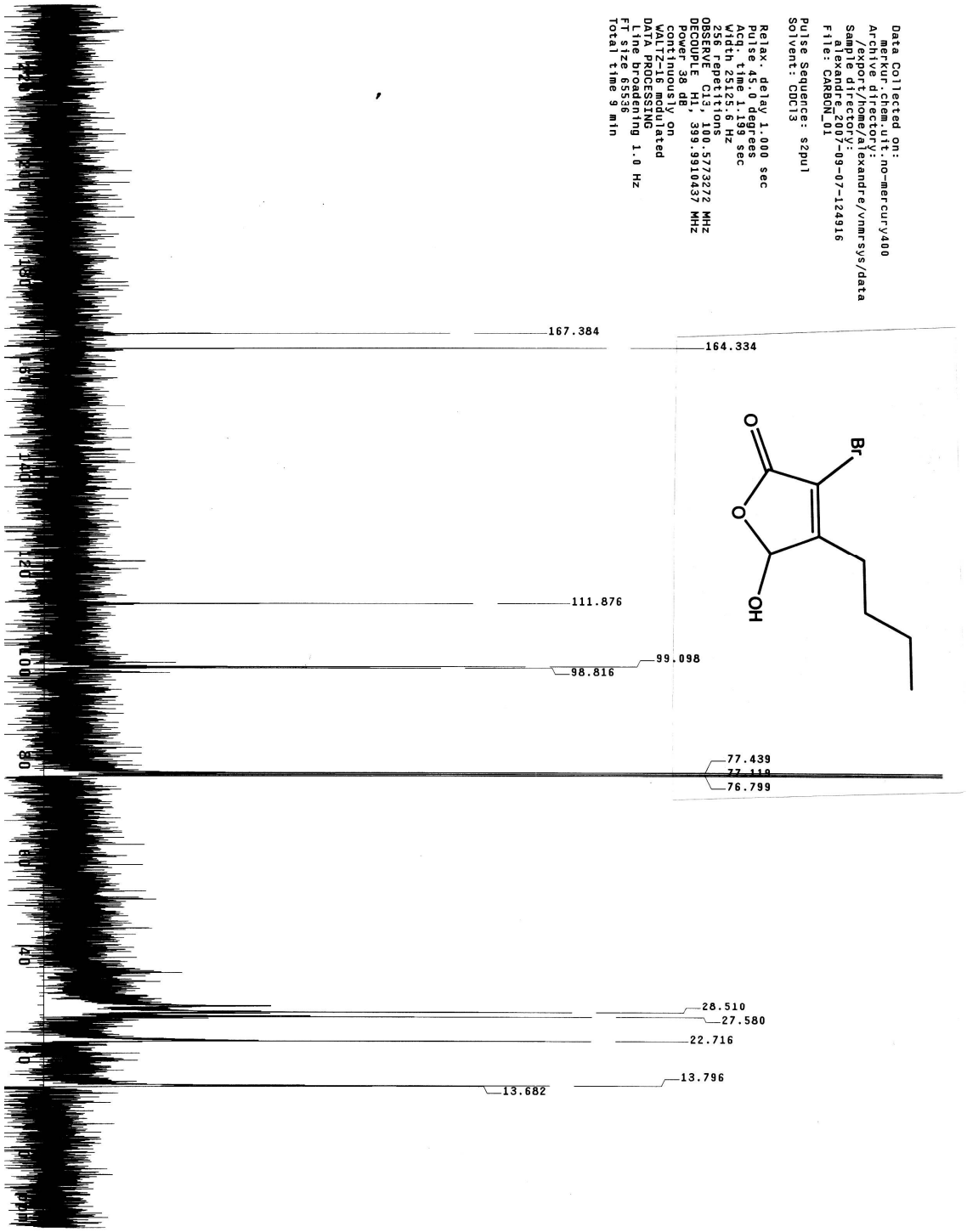
File: PROTON_01
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 6389.8 Hz
8 repetitions
OBSERVE H1, 399.9890919 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
Br
O
O
OH
ppm
0.78
0.33
1.00
1.51
1.99
3.01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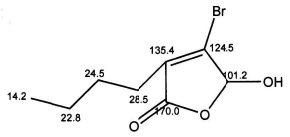
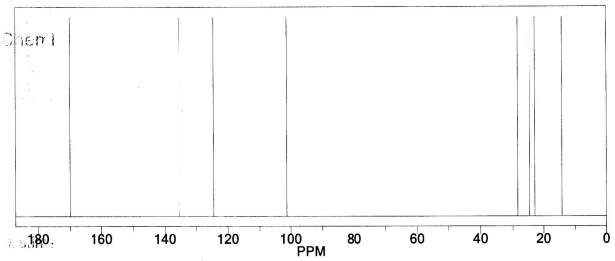
File: CARBON_01
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.5773272 MHz
DECOUPLE H1, 399.9910437 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 9 min
167.384
164.334
111.876
99.098
98.816
77.439
77.119
76.799
28.510
27.580
22.716
13.796
13.682
O
Br
O
OH

ChemNMR ^{13}C Estimation



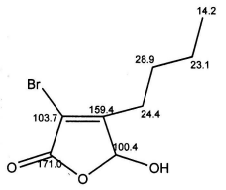
Estimation quality is indicated by color: good, medium, rough



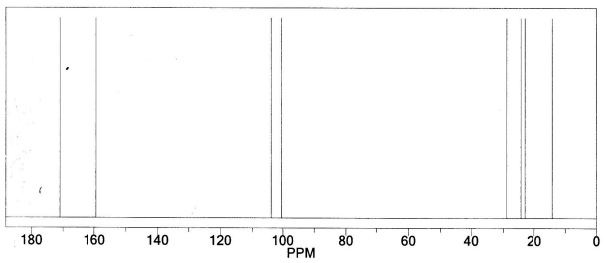
Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
C	124.5	123.3	1-ethylene
		14.2	1 -C-O
		-9.6	1 -Br
		-8.9	1 -C-C-C-C
		5.5	1 -C(=O)OC
C	170.0	165.0	1-carboxyl
		4.0	1 -C=C-C
		-5.0	1 -C from O-carboxyl
		5.0	general corrections
CH	101.2	-2.3	aliphatic
		19.5	1 alpha -C=C
		54.9	1 alpha -O-C=O
		49.0	1 alpha -O
		11.0	1 beta -Br
		-2.5	1 gamma -C
		0.3	1 delta -C
		-28.7	general corrections
C	135.4	123.3	1-ethylene
		-8.2	1 -C-O
		-0.9	1 -Br
		17.3	1 -C-C-C-C
		7.1	1 -C(=O)OC
		-3.2	general corrections
CH2	28.5	-2.3	aliphatic
		19.5	1 alpha -C=C
		9.1	1 alpha -C
		2.0	1 beta -C(=O)-O
		9.4	1 beta -C
		-5.0	2 gamma -C
		-3.8	1 gamma -Br
		0.3	1 delta -O

ChemNMR ^{13}C Estimation

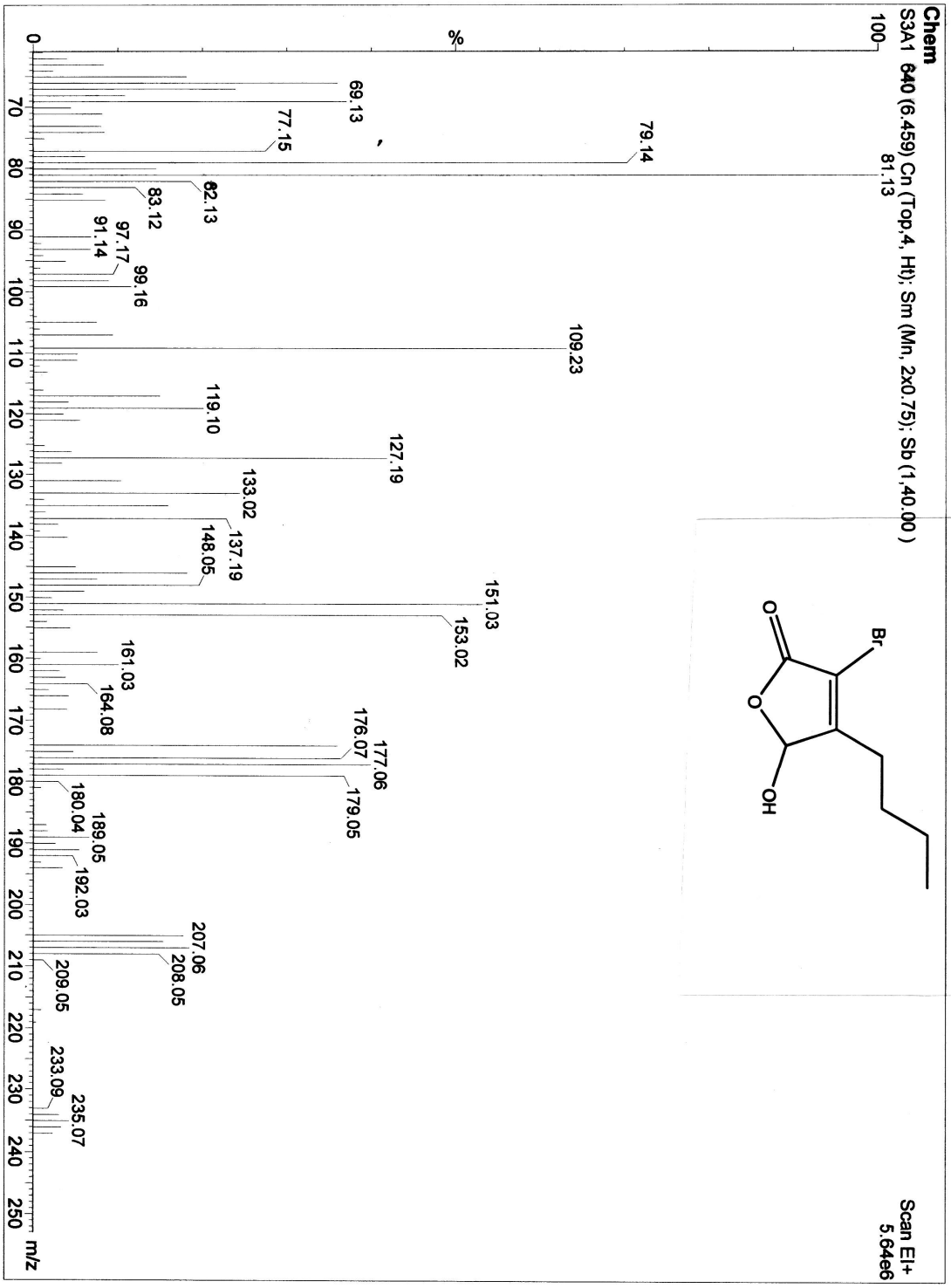


Estimation quality is indicated by color: good, medium, rough



Protocol of the C-13 NMR Prediction:

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
C	103.7	123.3	1-ethylene
		7.1	1 -C(=O)OC
		-9.6	1 -Br
		-8.9	1 -C-C-C-C
		-8.2	1 -C-O
C	171.0	166.0	1-carboxyl
		10.0	1 -C=C(C)C
		-5.0	1 -C from O-carboxyl
CH	100.4	-2.3	aliphatic
		19.5	1 alpha -C=C
		54.9	1 alpha -O-C=O
		49.0	1 alpha -O
		9.4	1 beta -C
		-2.5	1 gamma -C
		-3.8	1 gamma -Br
		0.3	1 delta -C
		-24.1	general corrections
C	159.4	123.3	1-ethylene
		5.5	1 -C(=O)OC
		-0.9	1 -Br
		17.3	1 -C-C-C-C
		14.2	1 -C-O
CH2	24.4	-2.3	aliphatic
		19.5	1 alpha -C=C
		9.1	1 alpha -C
		18.8	2 beta -C
		-2.8	1 gamma -C(=O)-O


Chem
S3A1 640 (6.459) Cn (Top,4, Ht); Sm (Mn, 2x0.75); Sb (1,40.00)
Scan EI+
5.64e6
100
%
0
Br
O
O
OH
69.13
77.15
79.14
81.13
82.13
83.12
91.14
97.17
99.16
109.23
119.10
127.19
133.02
137.19
148.05
151.03
153.02
161.03
164.08
176.07
177.06
179.05
180.04
189.05
192.03
207.06
208.05
209.05
233.09
235.07
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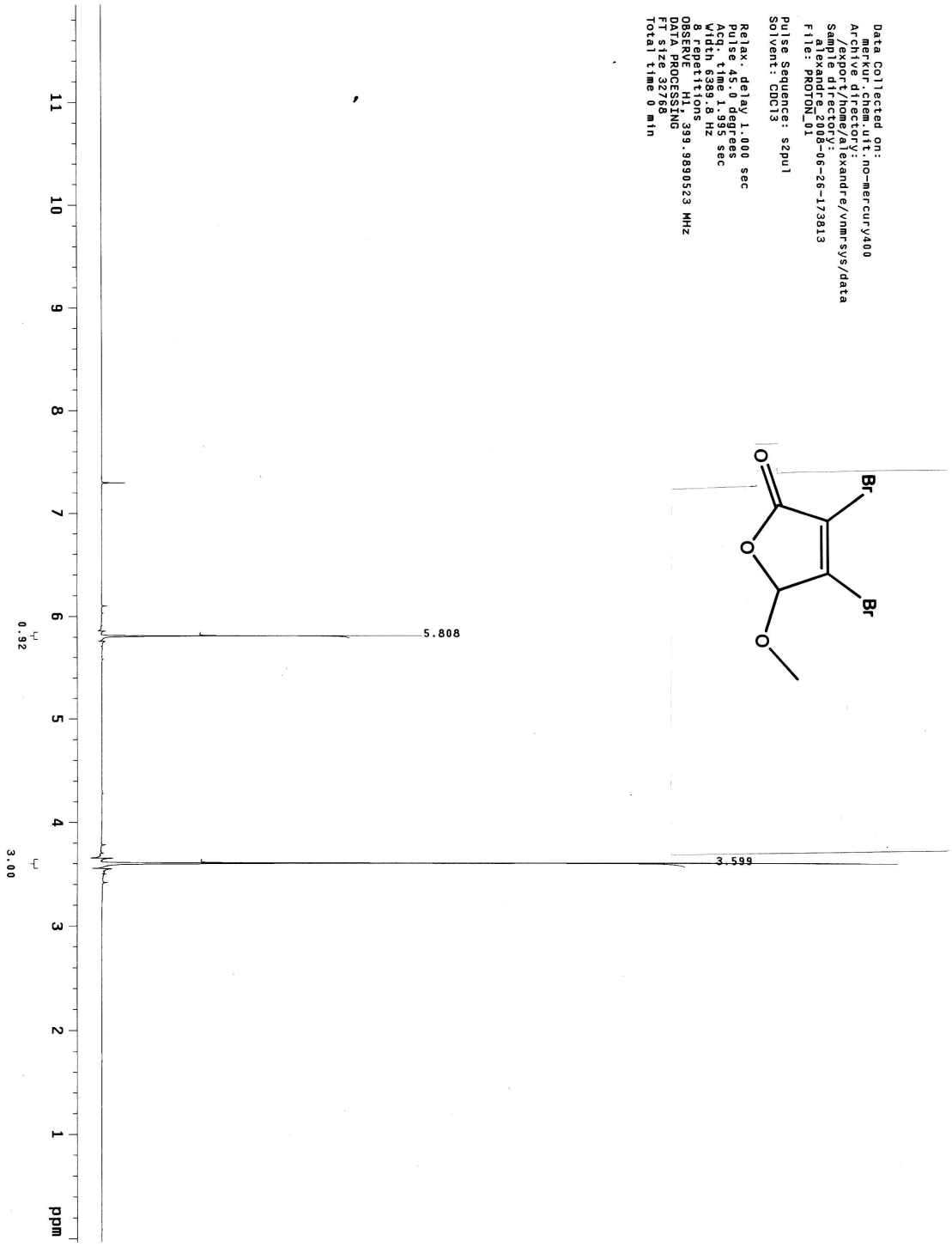
180
190
200
210
220
230
240
250
m/z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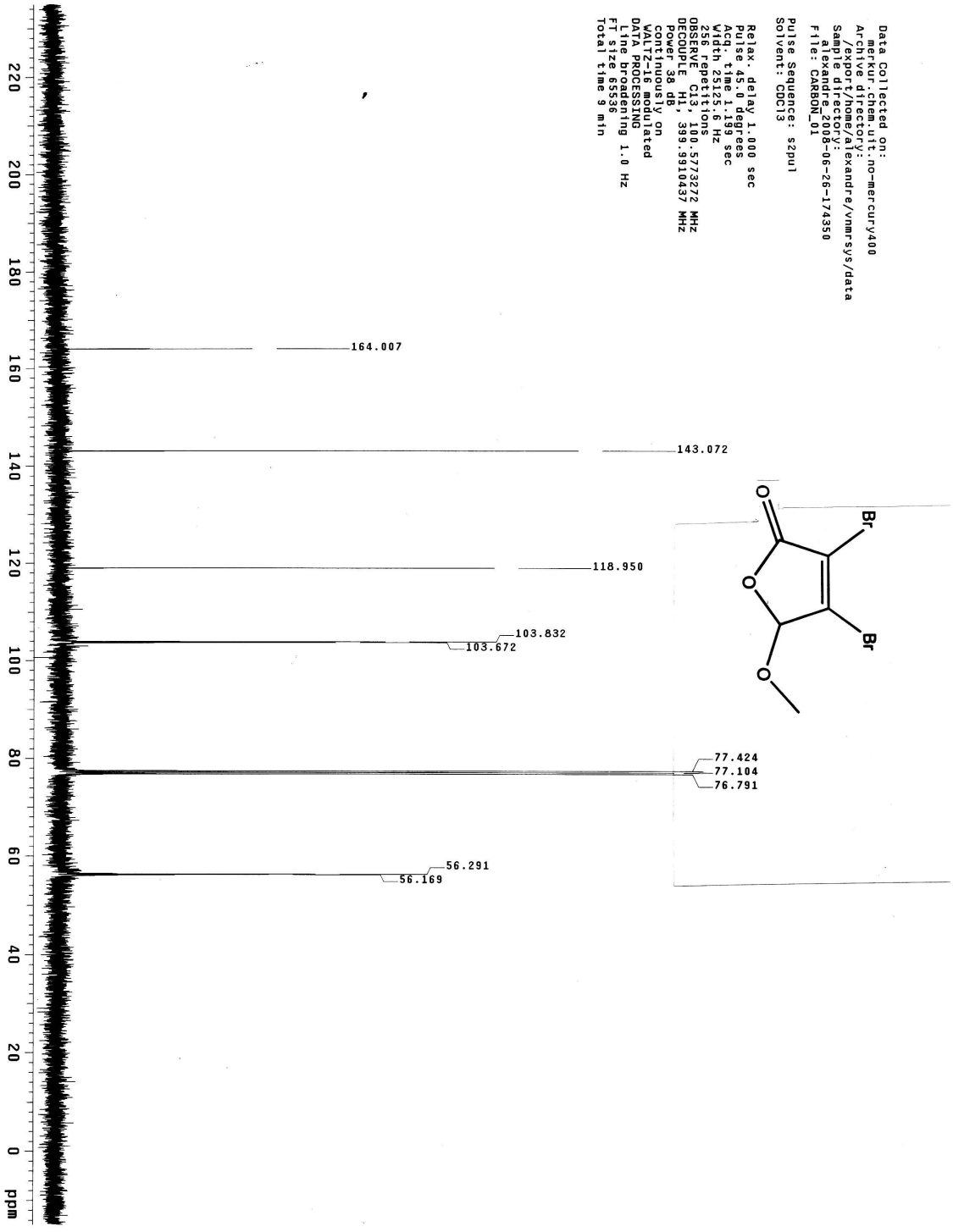
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 6389.8 Hz
8 repetitions
OBSERVE H1, 399.9890523 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
Br
Br
O
O
O
5.808
3.599
0.92
3.00
11
10
9
8
7
6
5
4
3
2
1
ppm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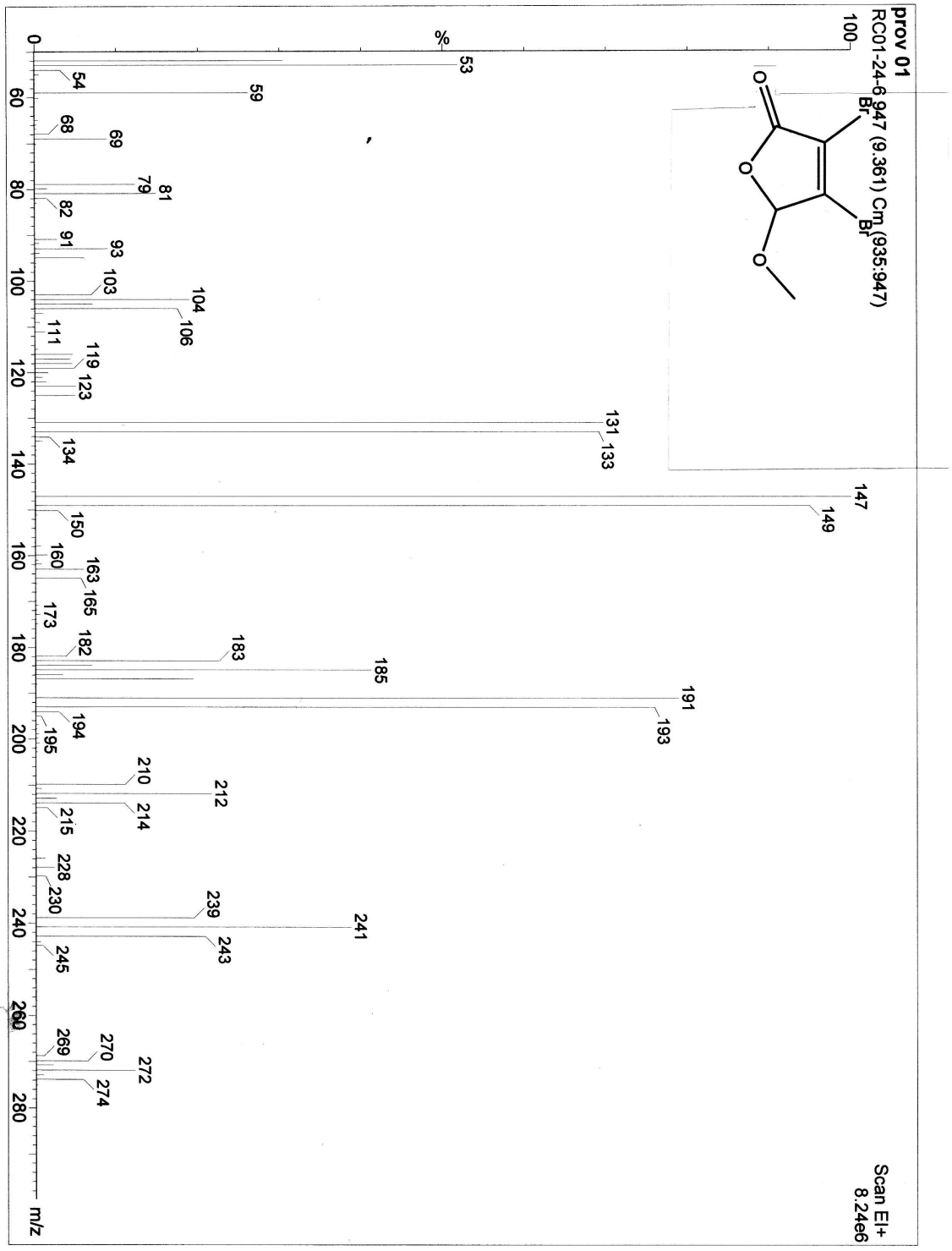
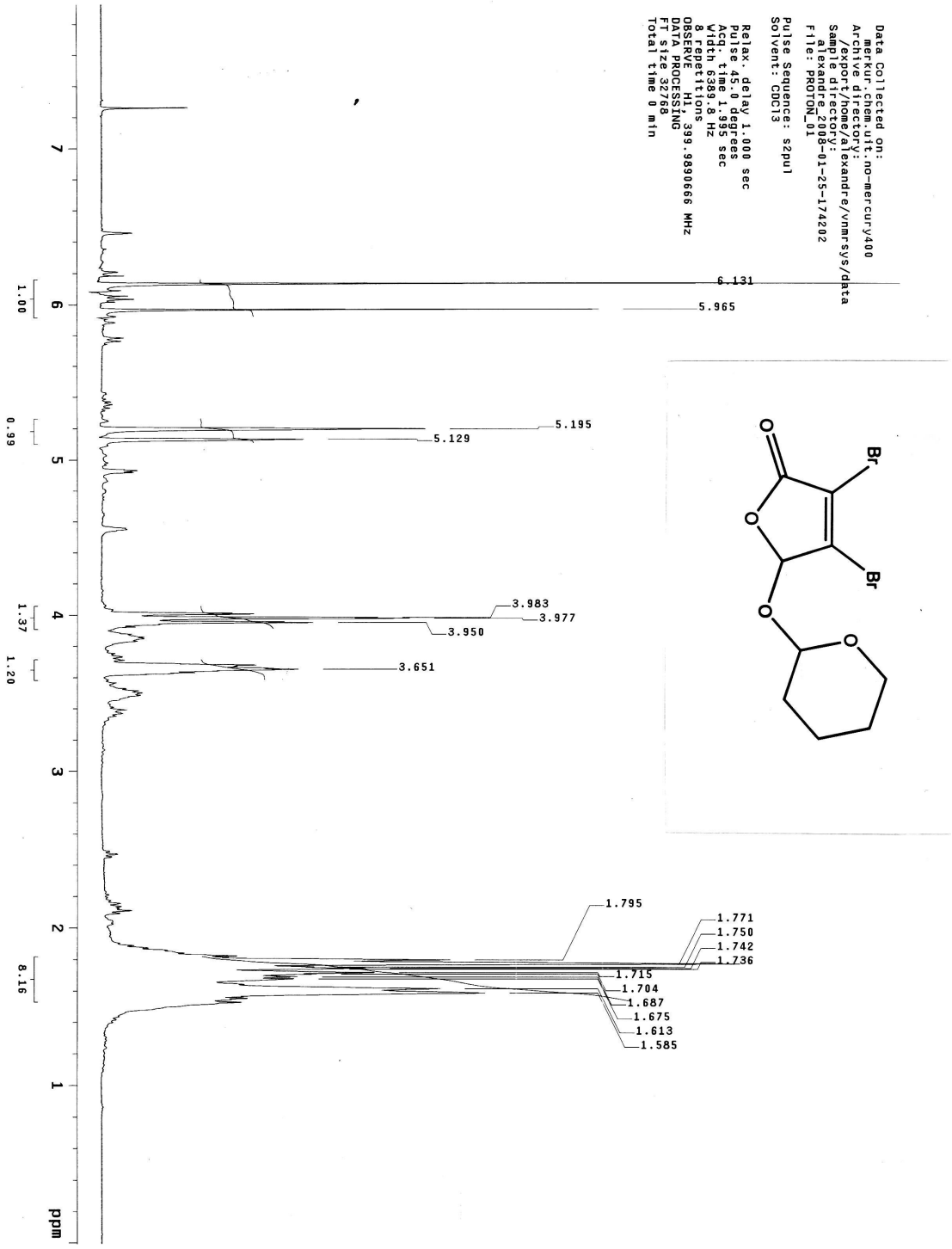
File: CARBON_01
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.5773272 MHz
DECOUPLE H1, 399.9910437 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 9 min
164.007
143.072
118.950
103.832
103.672
77.424
77.104
76.791
56.291
56.169
Br
Br
O
O
O
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm


prov 01
RC01-24-6 947 (9.361) Cm (935:947)
Scan EI+
8.24e6
%
m/z
Br
Br
O
O
O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alexandre_2008-01-25-174202
File: PROTON_01
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 6389.8 Hz
8 repetitions
OBSERVE H1, 399.9899666 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
6.131
5.965
5.195
5.129
3.983
3.977
3.950
3.651
1.795
1.771
1.750
1.742
1.736
1.715
1.704
1.687
1.675
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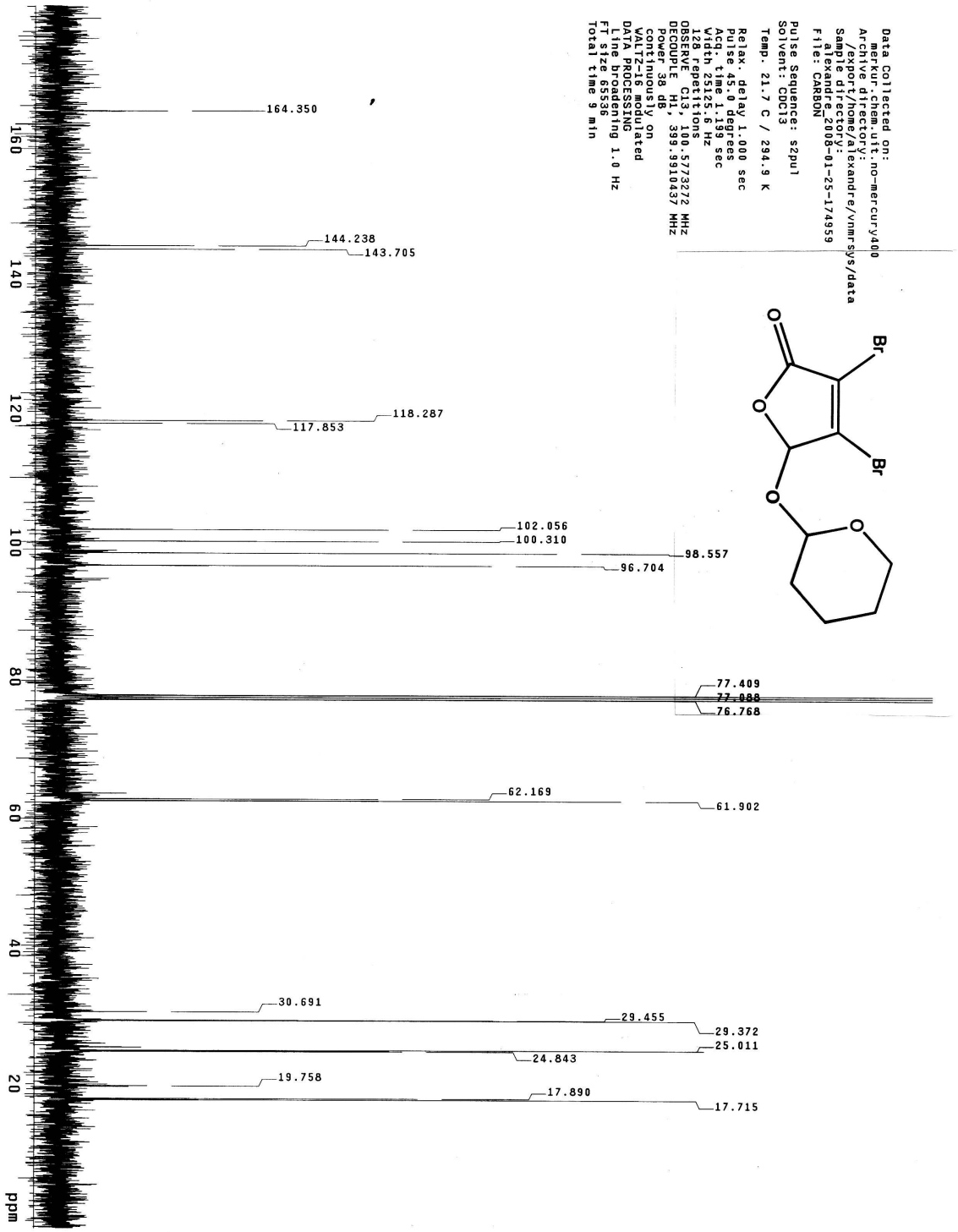
1.37
1.20
8.16
Br
Br
O
O
O
O
ppm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merkur.chem.uit.no-mercury400
Archive directory:
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Sample directory:
alexandre_2008-01-25-174959
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 21.7 C / 294.9 K
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
128 repetitions
OBSERVE C13, 100.5773272 MHz
DECOUPLE H1, 399.9910437 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 9 min
Br
Br
O
O
O
O
164.350
144.238
143.705
118.287
117.853
102.056
100.310
98.557
96.704
77.409
77.088
76.768
62.169
61.902
30.691
29.455
29.372
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19.758
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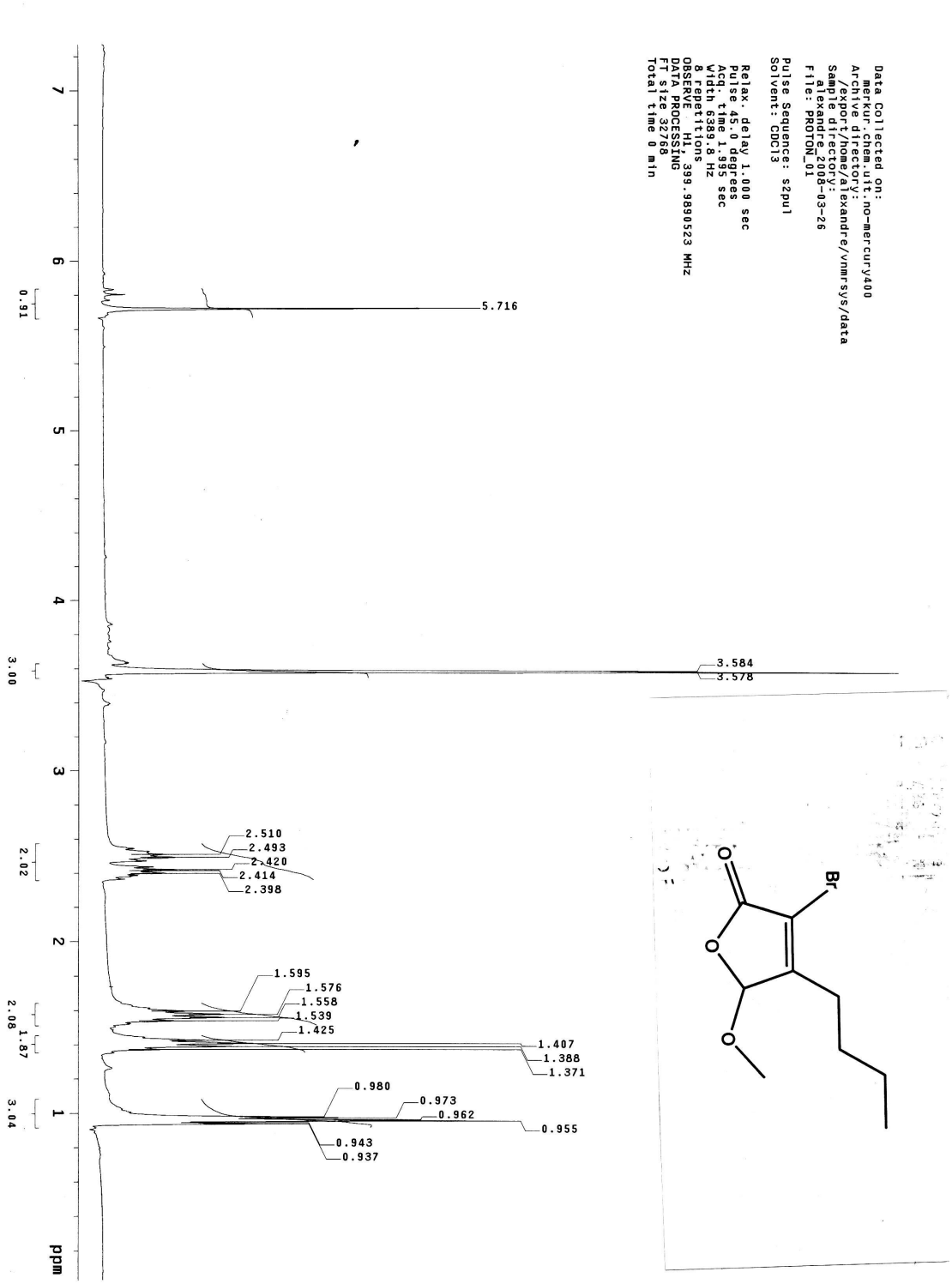
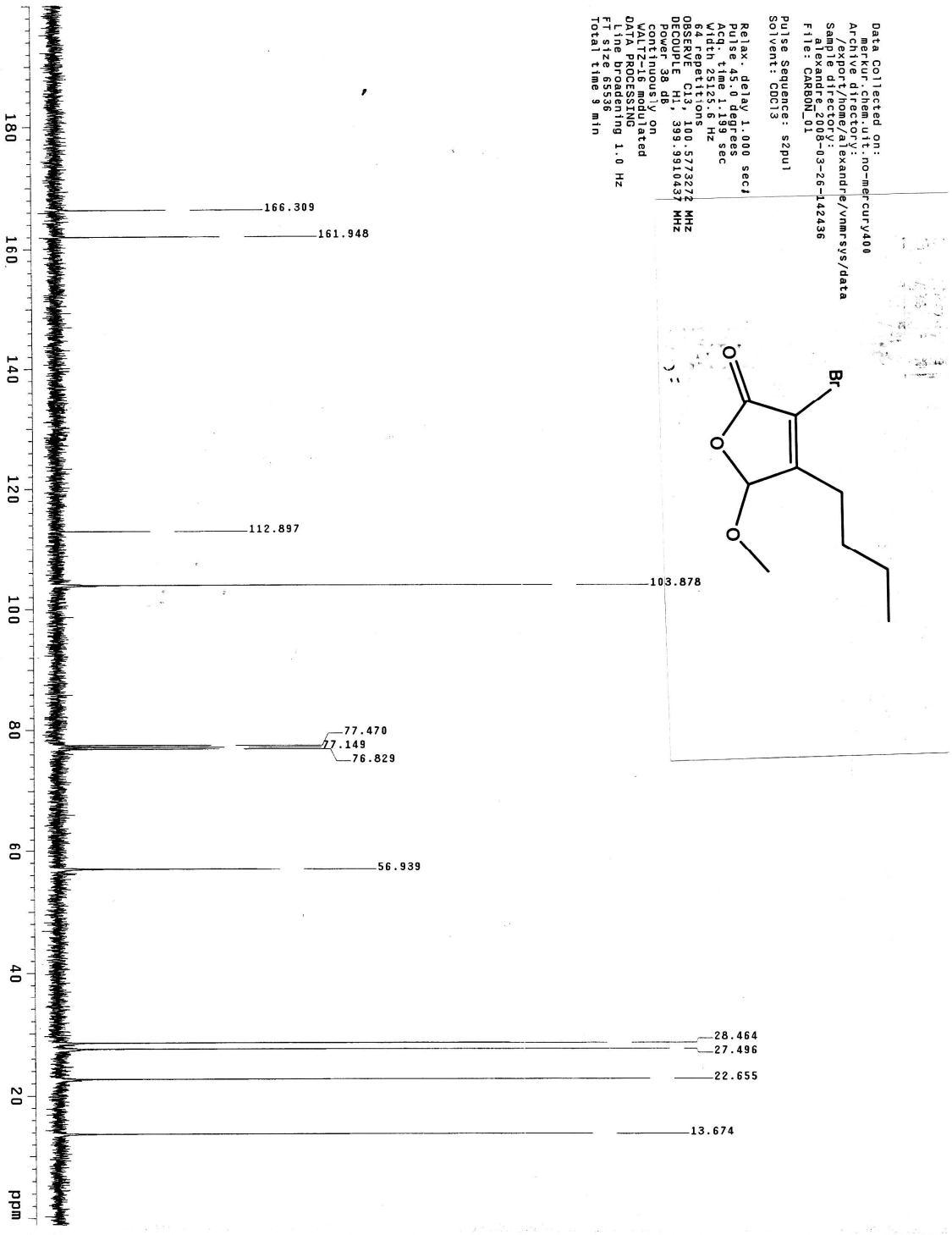
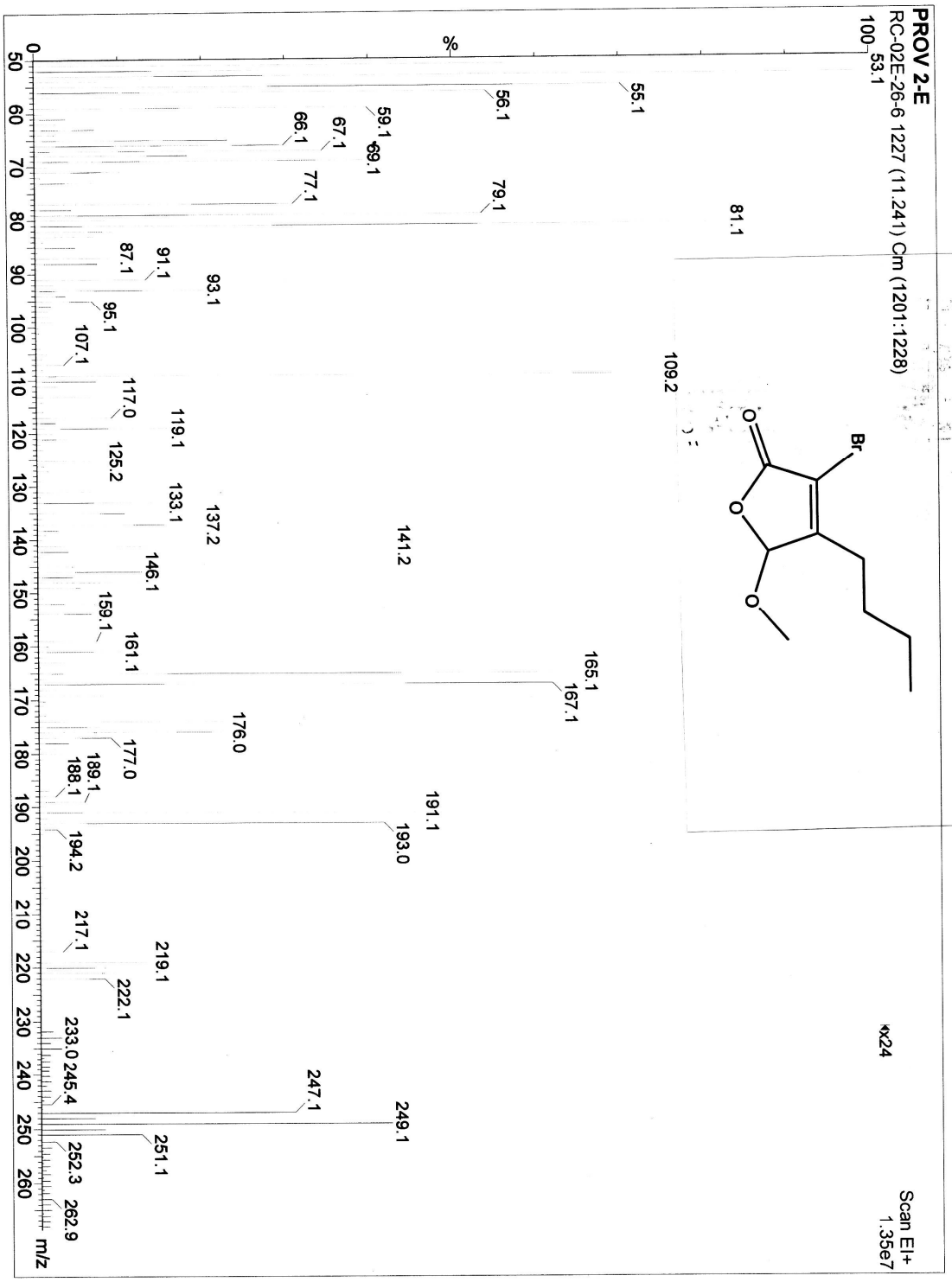
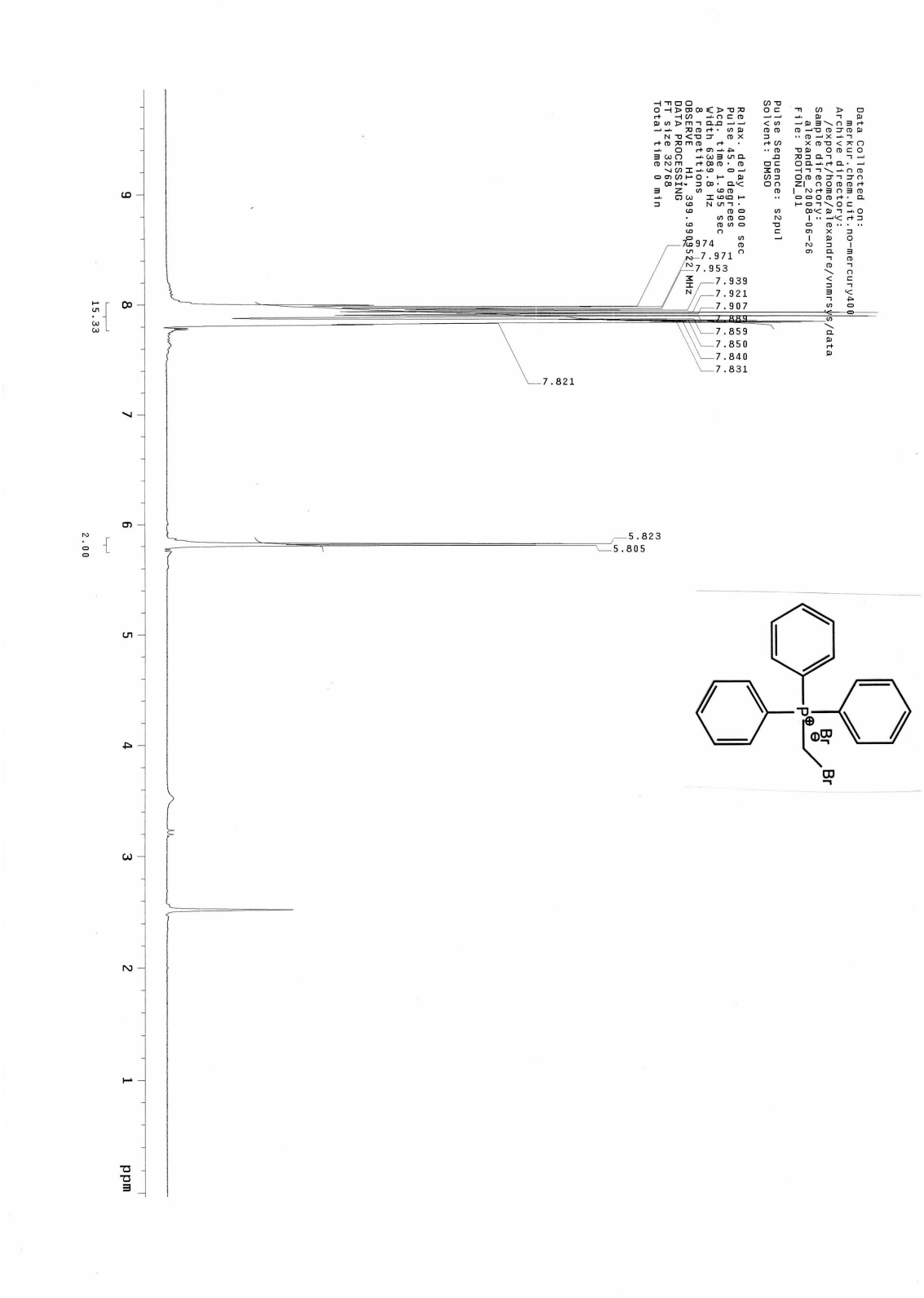
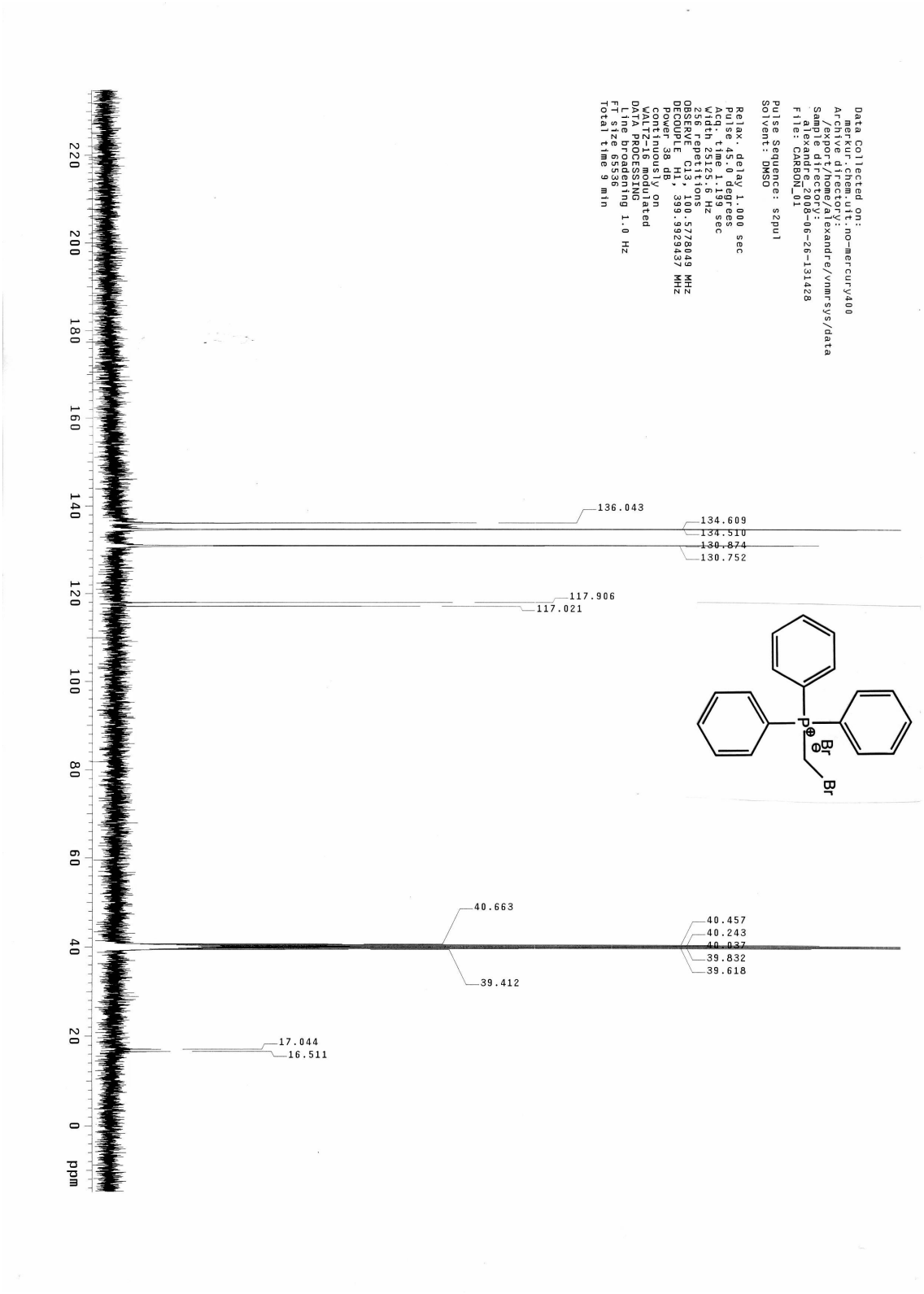
17.715
160
140
120
100
80
60
40
20
ppm

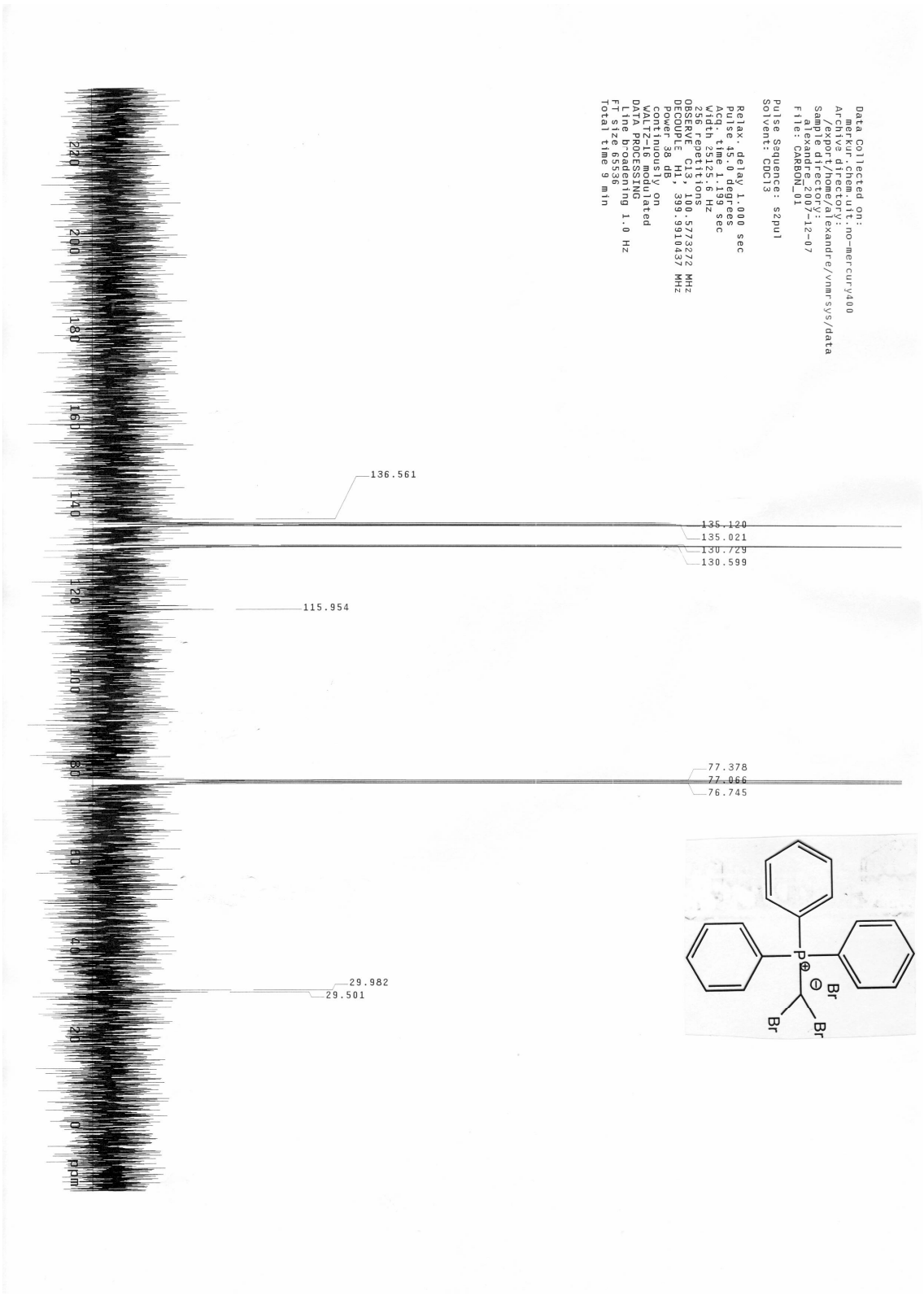

Data Collected on:
merkur.chem.uit.no-mercury400
Archive directory:
/export/home/alexandre/vnmrsys/data
Sample directory:
alexandre_2008-03-26
File: PROTON_01
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 6389.8 Hz
8 repetitions
OBSERVE H1, 399.9890523 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
5.716
3.584
3.578
2.510
2.493
2.420
2.414
2.398
1.595
1.576
1.558
1.539
1.425
1.407
1.388
1.371
0.980
0.973
0.962
0.955
0.943
0.937
0.91
3.00
2.02
2.08
1.87
3.04
ppm
Br
O
O
O

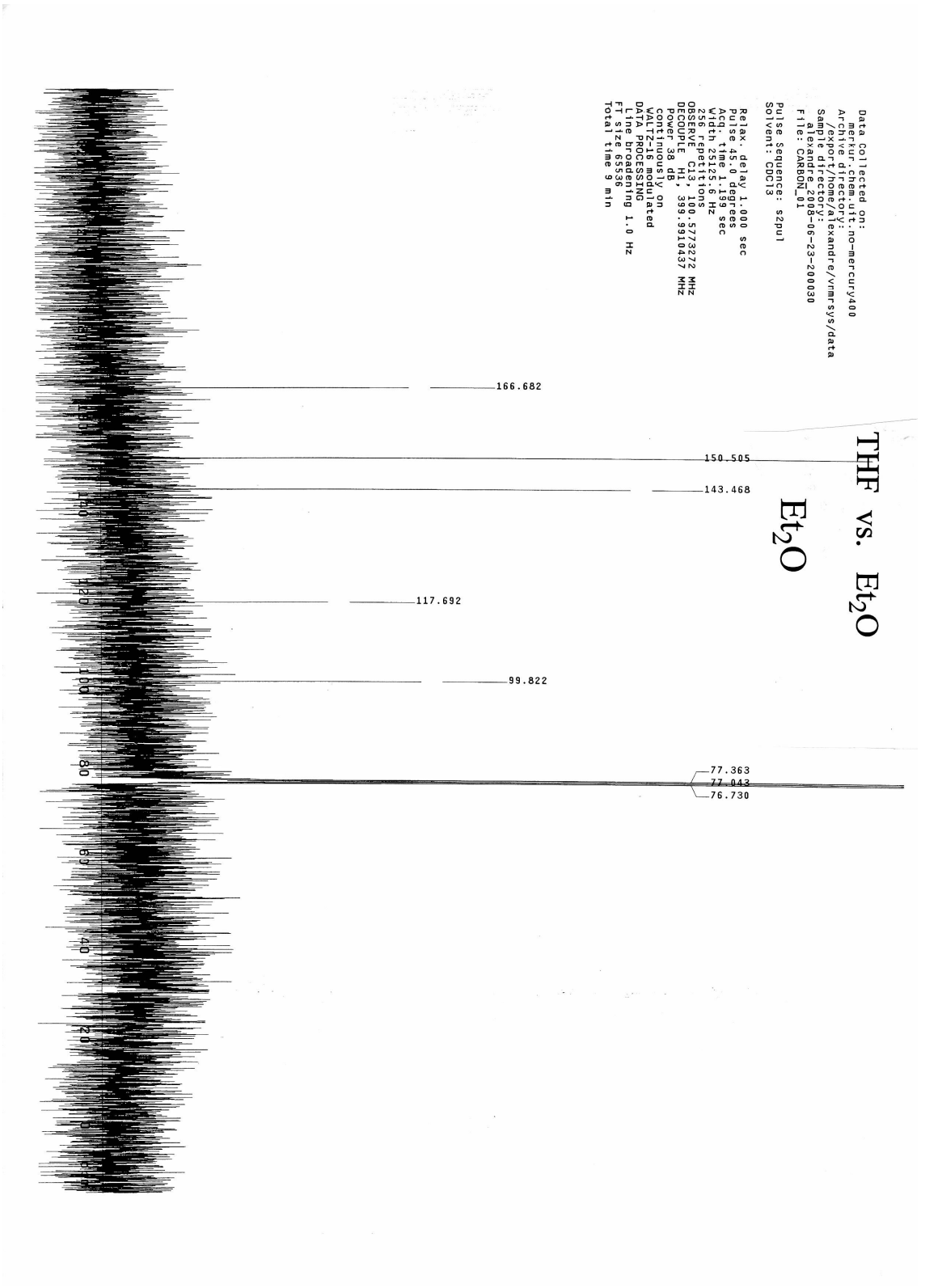

Data Collected on: nmr-kur.chemuit.no-mercury400
Archive directory: /export/home/alexandre/vnmrsys/data
Sample directory: alexandre_2008-03-26_142436
File: CARBON_01
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.295 sec
Width 24125.6 Hz
64 repetitions
OBSERVE C13, 100.5773272 MHz
DECOUPLE H1, 399.9910437 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 9 min
Br
166.309
161.948
112.897
103.878
77.470
77.149
76.829
56.939
28.464
27.496
22.655
13.674
180
160
140
120
100
80
60
40
20
ppm

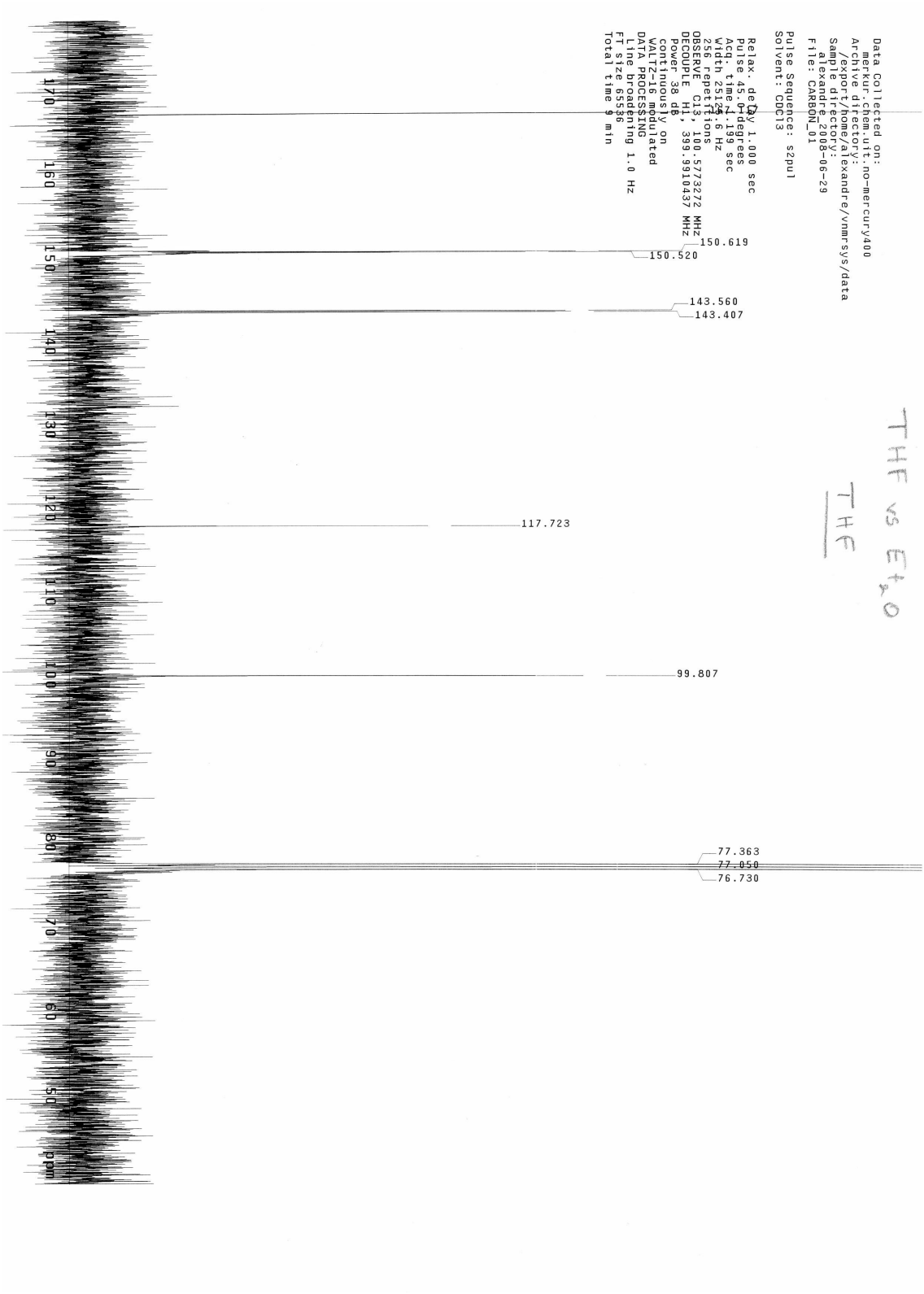

PROV 2-E
RC-02E-26-6 1227 (11.241) Cm (1201:1228)
Scan EI+
1.35e7
x24
Br
%
m/z
53.1
55.1
56.1
59.1
69.1
66.1
67.1
77.1
79.1
81.1
87.1
91.1
93.1
95.1
107.1
109.2
117.0
119.1
125.2
133.1
137.2
141.2
146.1
159.1
161.1
165.1
167.1
176.0
177.0
188.1
189.1
191.1
193.0
194.2
217.1
219.1
222.1
233.0
245.4
247.1
249.1
251.1
252.3
262.9


Data Collected on:
merkur.chem.uit.no-mercury400
Archive directory:
/export/home/alexandre/vnmrsys/data
Sample directory:
alexandre_2008-06-26
File: PROTON_01
Pulse Sequence: s2pul
Solvent: DMSO
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.995 sec
Width 6389.8 Hz
8 repetitions
OBSERVE H1, 399.9909522 MHz
DATA PROCESSING
FT size 32768
Total time 0 min
7.974
7.971
7.953
7.939
7.921
7.907
7.889
7.859
7.850
7.840
7.831
7.821
5.823
5.805
15.33
2.00
ppm
Br
Br


Data Collected on:
merkur.chem.uit.no-mercury400
Archive directory:
/export/home/alexandre/vnmrsys/data
Sample directory:
alexandre_2008-06-26-131428
File: CARBON_01
Pulse Sequence: s2pul
Solvent: DMSO
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.5778049 MHz
DECOUPLE H1, 399.9929437 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 9 min
136.043
134.609
134.510
130.874
130.752
117.906
117.021
40.663
40.457
40.243
40.037
39.832
39.618
39.412
17.044
16.511
220
200
180
160
140
120
100
80
60
40
20
0
ppm
P
Br
Br


Data Collected on:
merkur.chem.uit.no-mercury400
Archive directory:
/export/home/alexandre/vnmrsys/data
Sample directory:
Experiment:
File: CARBON_01
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.5773272 MHz
DECOUPLE H1, 399.991043 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
LB 1.0 Hz
FT size 65536
Total time 9 min
136.561
135.120
135.021
130.729
130.599
115.954
77.378
77.066
76.745
29.982
29.501
220
200
180
160
140
120
100
80
60
40
20
0
ppm
P
Br
Br
Br


Data collected on:
merkur.chem.uit.no-mercury400
Archive directory:
/export/home/alexandre/vnmrsys/data
Sample directory:
alexandre_2008-06-23-200030
File: CARBON_01
Pulse sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 24154.8 Hz
256 repetitions
OBSERVE C13, 100.5773272 MHz
DECOUPLE H1, 399.9910437 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 9 min
THF vs. Et2O
Et2O
166.682
150.505
143.468
117.692
99.822
77.363
77.043
76.730


Data Collected on:
merkur.chem.uit.no-mercury400
Archive directory:
/export/home/alexandre/vnmrsys/data
Sample directory:
alexandre_2008-06-29
File: CARBON_01
Pulse Sequence: s2pul
Solvent: CDCl3
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.199 sec
Width 25125.6 Hz
256 repetitions
OBSERVE C13, 100.5773272 MHz
DECOUPLE H1, 399.9910437 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 9 min
150.619
150.520
143.560
143.407
117.723
99.807
77.363
77.050
76.730
THF vs Et2O
THF
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm