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From 3,3,4,4-Tetraethoxybut-1-yne to furan derivatives

TESI DI LAUREA MAGISTRALE

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Francesco Livi

Bergen, June 2011

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Francesco Livi,

Bologna, February 2012

ABSTRACT

The starting material for this project was the highly functionalised compound 3,3,4,4-tetratethoxybut-1-yne (TEB) and it can be prepared from ethyl vinyl ether by a 4-steps synthesis. The third and the fourth step in TEB synthesis were sensitive to reaction condition, so it was developed a strategy to try to optimize the third step and obtain TEB with higher yields. An approach, which tries to optimize also the fourth step, will be developed in further works.

Several γ-hydroxy-α,β-unsaturated acetylenic ketones can be prepared from 3,3,4,4-tetratethoxybut-1-yne. TEB and γ-hydroxy-α,β-unsaturated acetylenic ketones have been previously synthesized in good yields using various reaction routes.

In this work will be shown the synthesis of 1,1-Diethoxy-5-hydroxyhex-3-yn-2-one, 1,1-Diethoxy-5-hydroxyundec-3-yn-2-one and 1,1-Diethoxy-5-hydroxydodec-3-yn-2-one, which will react with ethyl acetoacetate to give, respectively, 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate, 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-hexyl-3-carboxylate and 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-octyl-3-carboxylate furan derivatives.

This thesis project was carried out during the year 2011.

SOMMARIO

Il materiale di partenza per questo progetto è il 3,3,4,4,-tetraetossibut-1-ino (TEB), composto altamente funzionalizzato, che può essere preparato a partire dall'etil-vinil etere attraverso una sintesi di 4 stadi. Il terzo ed il quarto passaggio della sintesi del TEB sono risultati sensibili alle condizioni di reazione, quindi è stata sviluppata una strategia per cercare di ottimizzare il terzo step ed ottenere il TEB con rese più elevate. Un simile approccio, attraverso il quale si cerca di ottimizzare anche il quarto step, verrà sviluppato nei lavori futuri.

A partire dal TEB, posso essere sintetizzati vari chetoni acetilenici γ-idrossi-α,β-insaturi funzionalizzati; sia il TEB sia questi ultimi sono stati precedentemente sintetizzati ottenendo buone rese e seguendo varie strategie di sintesi.

In questo lavoro è presentata la sintesi di tre chetoni acetilenici γ-idrossi-α,β-insaturi quali: 1,1-dietossi-5-idrossi-3-esin-2-one, 1,1-dietossi-5-idrossi-3-undecin-2-one, 1,1-dietossi-5-idrossi-3-dodecin-2-one. Questi composti reagiscono con acetoacetato di etile per dare, rispettivamente, i derivati furanici 4-(3,3-dietossi-2-ossopropil)-2,5-dimetilfurano-3-etilcarbossilato, 4-(3,3-dietossi-2-ossopropil)-2-metilfurano-5-esil-3-etilcarbossilato e 4-(3,3-dietossi-2-ossopropil)-2-metilfurano-5-octil-3-etilcarbossilato.

Questo progetto di tesi è stato svolto durante l'anno 2011.

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ABBREVIATIONS

^{1}H	Hydrogen-1 nucleus
^{13}C	Carbon-13 nucleus
DCM	Dichloromethane
EtOAc	Ethyl Acetate
Hex	Hexanes
IR	Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
PTC	Phase-Transfer Catalysis / Condition
PTSA	*para*-Toluensulfonic Acid
r.t.	Room Temperature
TEB	3,3,4,4,-Tetraethoxybut-1-yne
TEBA	Triethylbenzylammonium chloride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Tetramethylsilan

1. INTRODUCTION

1.1 Carbohydrates[1 2]

Monosaccharides are the elementary units of the carbohydrates. Generally, these molecules are formed by a saturated chain of five or six carbon atoms and every carbon atom is linked to an hydroxyl group. One carbon of the chain is linked to an aldehyde or ketone group instead of an hydroxyl group.

Monosaccharides are classified according to the number of carbon atoms in their skeleton (pentoses, hexoses, heptoses, etc.,) and they are called aldoses if they contain an aldehyde group, or ketoses if they have got a ketone group.

A monosaccharides contains at least carbon, hydrogen and oxygen; its general formula is $C_nH_{2n}O_n$, or $C_n(H_{2n}O)_n$. Obviously monosaccharides could have a different number of hydrogen and oxygen atoms than those required in the general formula and therefore other elements could be present such as nitrogen, sulphur, halogen or other R-group linked to a carbon atom of the skeleton.

In 1891 Emil Fischer proposed a method to represent in a plane the three-dimensional structure of a monosaccharide molecule. The chiral carbon atom, which is in the plane of the observer, must be placed in the centre with the two neighboring carbon atoms projected on a vertical line, which are out of the plane of the observer and directed in the opposite direction of the observer. The hydrogen atoms and the hydroxyl group, linked to the same chiral carbon atom, are projected on a horizontal line. They are out of the plane of the observer and directed in the same direction of the observer.

It was evident that sugars was supposed to exist in a cyclic form, as some chemical behaviour of the open-chain structure could not be explained.

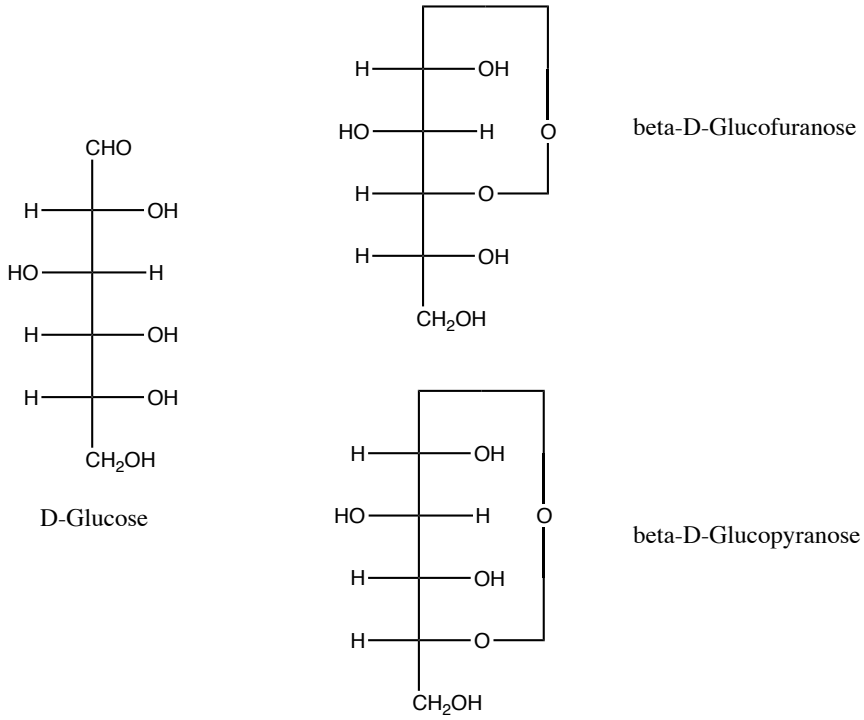


Figure 1: Fisher's projection of furanosic and pyranosic form of β-D-glucose.

Haworth proposed the terms furanoses and pyranoses for the two monosaccharide forms in the figure above and introduced a different way to represent the structure of monosaccharides; the name furanoses and pyranoses are related to the structure, similar to furan and pyran.

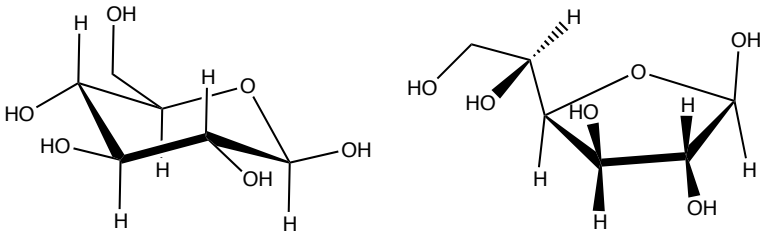


Figure 2: β-D-glucose pyranose form and β-D furanose form.

In the cyclic form of a sugar, the achiral carbonyl carbon has become a chiral lactol carbon and this transformation produces two more stereoisomers. These two stereoisomers are called anomers and are referred to as α and β isomers. In the anomer α, the-OH in place of the anomeric carbon is on the opposite side (trans) ring (second CH_2OH). The alternative form gives the anomeric β.

The deoxy sugars are interesting for this work: they are sugars that have had one or more hydroxyl groups replaced with an hydrogen atom or a non-O-linked functional group. This substitution changes the chemical properties of the carbohydrate, which could be exploited to design new drugs. For these reasons deoxy sugars are of interest for medicinal chemistry.[3]

1.2 Modified carbohydrate analogues in medicine

Bacteria can develop resistance to drugs. Antibiotic resistance is becoming a big problem for modern society because the number of the bacteria strains resistance to known antibiotics is growing. The investigation of new antibiotics, for these reasons, is a priority of pharmacological research.

To design new antibiotics we have to consider that these molecules could contain a large variety of chemical functionalities. For example, few antibiotics contain a core, where one or more modified carbohydrate units could be attached.

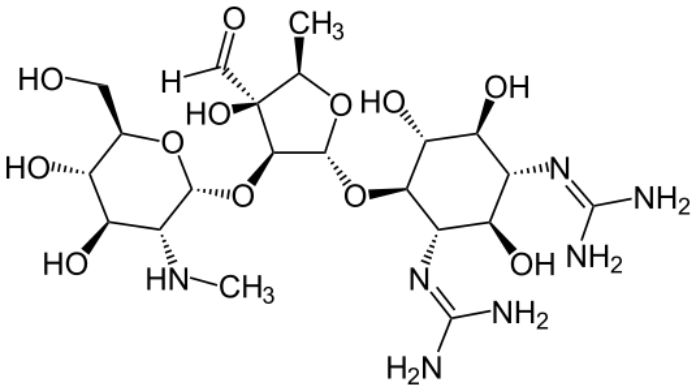
Interactions between the modified carbohydrates attached to the core and active sites of the bacteria[4] could change according to the carbohydrate analogues structure. For these reasons, sugar analogues are important for the antibiotics' efficacy.[5]

If we take as example a simple monosaccharide, few transformations can modify the nature of the carbohydrate:

- Alkylation and deoxygenation influence the polarity;
- Amination makes the sugar pH sensitive;
- Amination and deoxygenation change the ability to form hydrogen-bonds.

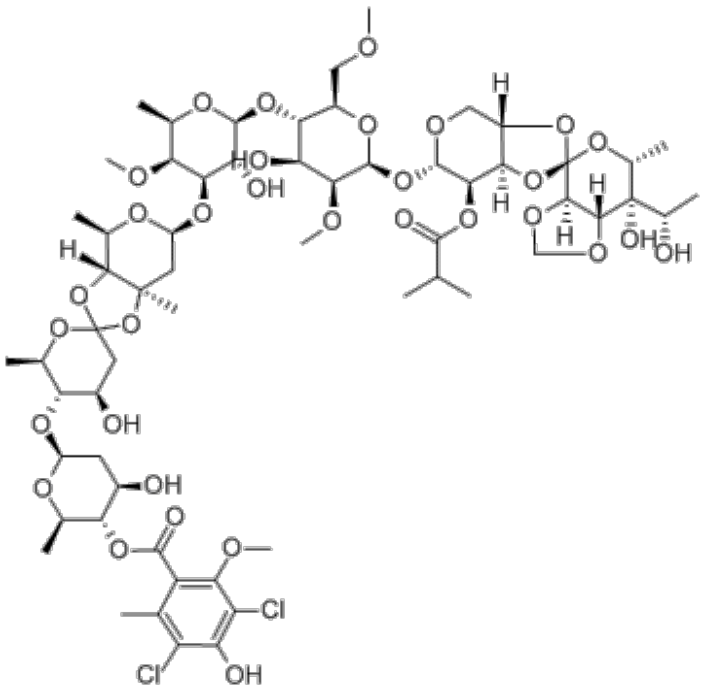
We can classify carbohydrates derivatives antibiotics into three groups[2]:

- Antibiotics in which the carbohydrates are glycosidically linked to a cyclitol or an amminocyclitol. One example is streptomycin.



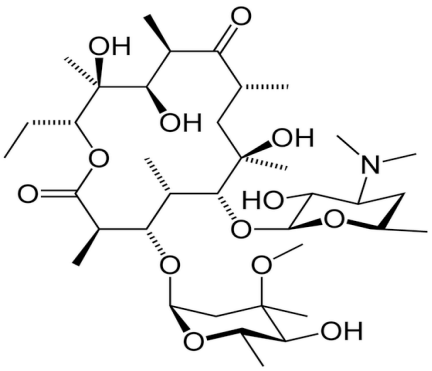
Streptomycin[6]

- Oligosaccharides in which the individual monosaccharides are linked both glycosidically and also with one or more orthoester linkages. A typical example is avilamycin.



Avilamycin[7]

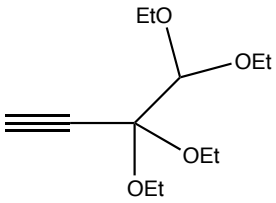
- Carbohydrates may be glicosidically linked to a noncarbohydrate part of an antibiotic. One example is erythromycin.



Erythromycin[8]

1.3 TEB as starting material for modified carbohydrate's synthesis

In order to synthesize carbohydrate analogues we need a stable but reactive compound that can be easily converted to some key intermediates, from which a large number of carbohydrate analogues could be synthesized.[9] One compound with those characteristics is 3,3,4,4,tetraethoxy-but-1-yne, TEB, that can be prepared from ethyl vinyl ether by a 4-step synthesis (see chap. 2.1.).



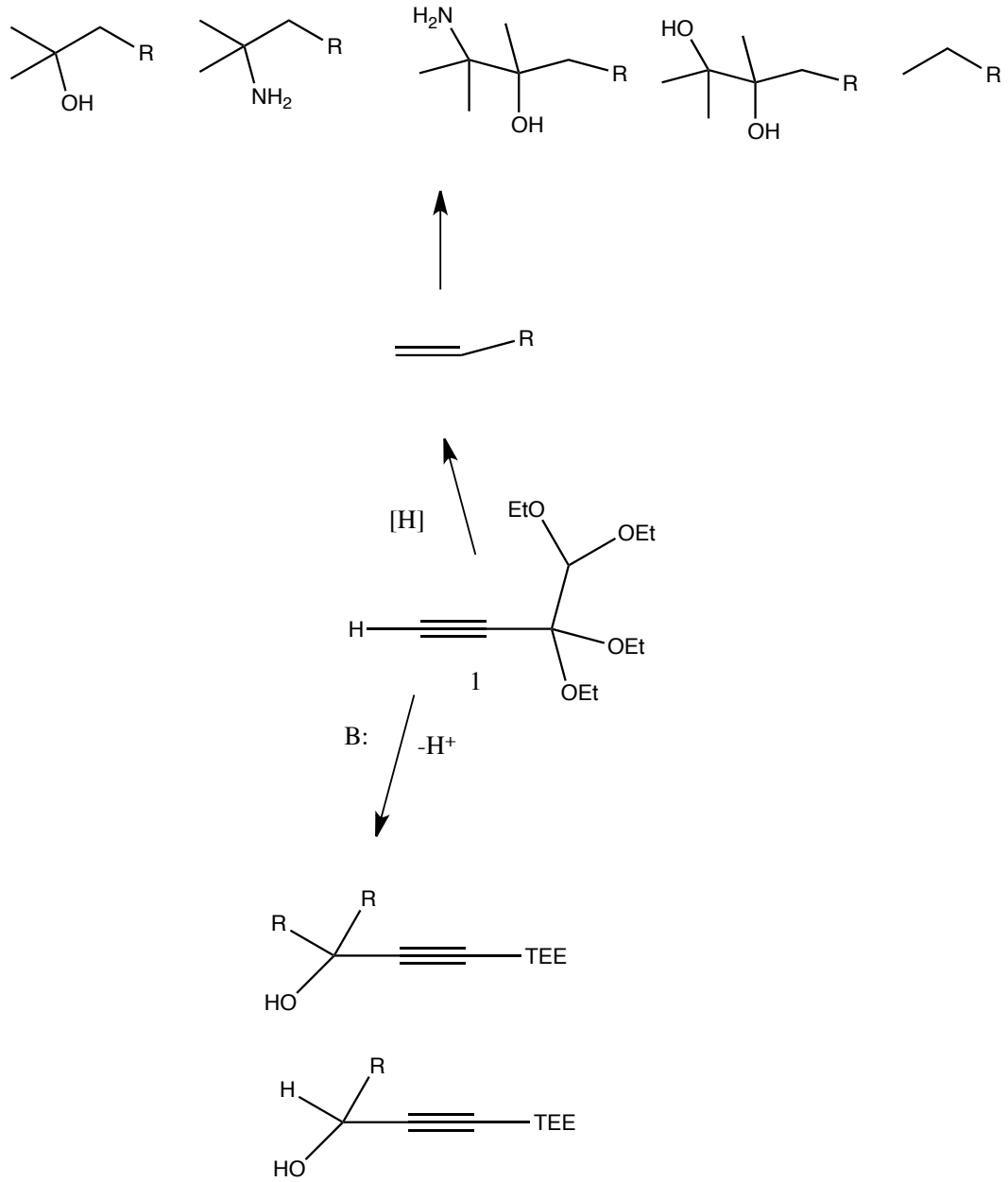
1, TEB

TEB is a thermally stable compund and it can be easily prepared as reported in previous works. [10]

The compound is stable under basic and neutral conditions but unstable under acidic conditions.

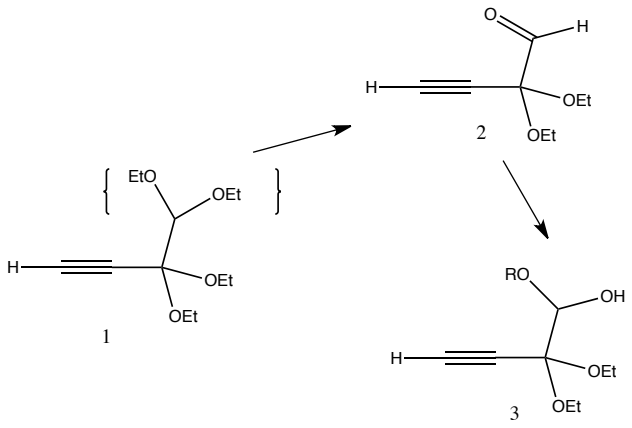
The chemical potential of TEB is significant. The triple bond has one acidic proton that it is a good starting point for a chain elongation. By deprotonation, TEB becomes reactive toward aldehydes and ketones to give the corresponding alcohols. On the other hand, the

triple bond can be converted in a C-C double bound that subsequently can take part in hydrogenation, hydration, amination, dihydroxylation and hydroxyamination processes.



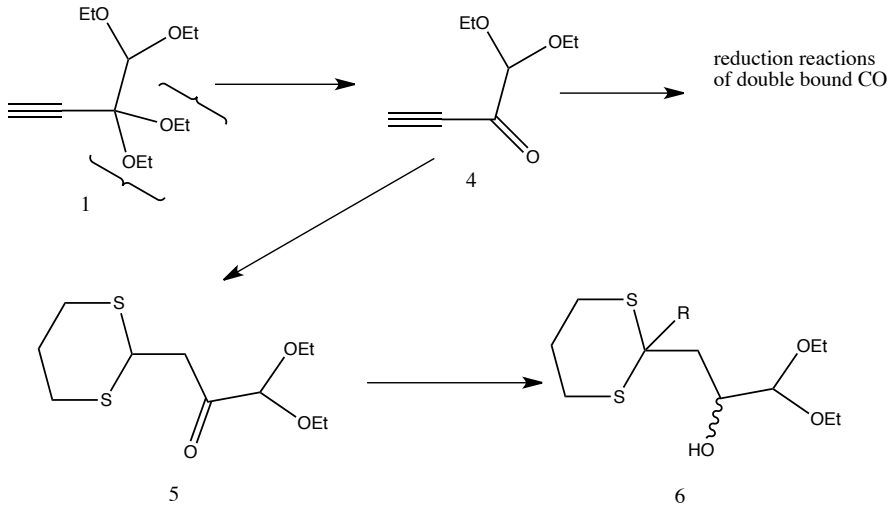
Scheme 1: reactivity of the triple bond of TEB

In addition, there is an acetal moiety that can be deprotected to give **2** and this can form hemiacetal **3** under the right conditions.



Scheme 2: reactivity of the acetal group of TEB

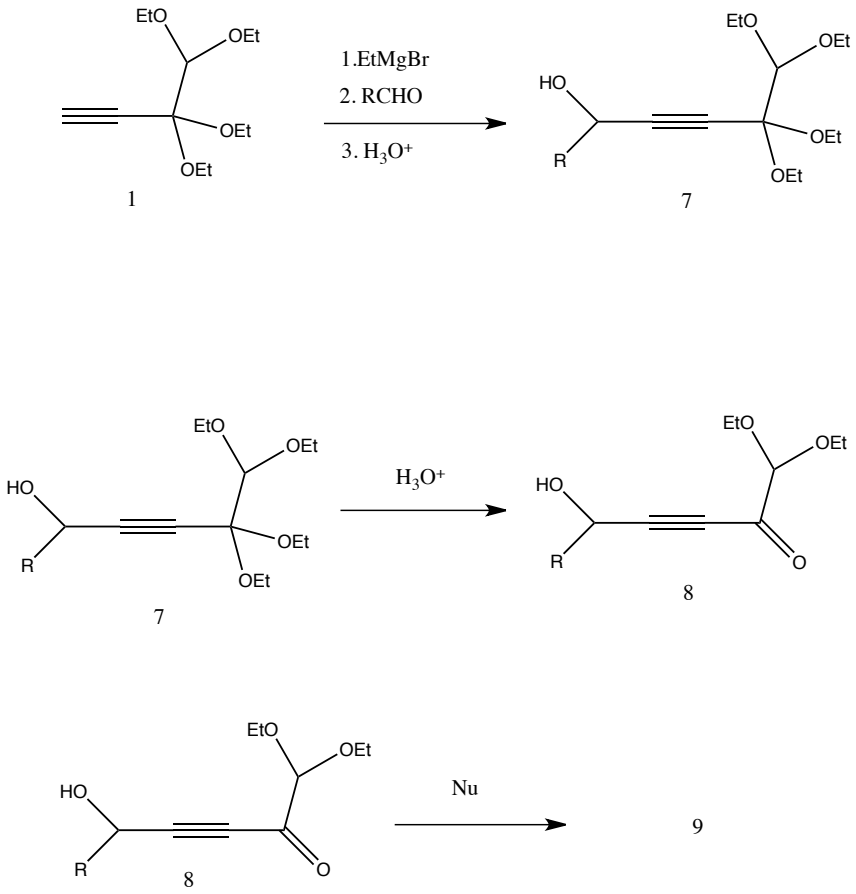
There is also a ketal group that can also be deprotected to give **4**, which can react, for example, through reduction reactions and nucleophilic additions. **4** is an α,β unsaturated ketone, which can react with a nucleophile in a Michael addition; one example of these nucleophiles could be propane-1,3-dithiol, that, under basic conditions, gives a 2-substituted 1,3-dithiane **5**.[11]-[12] If desired, **5** could react with an electrophilic agent to give **6** through an addition reaction, after reduction of the carbonyl group.[13]-[14]–[15] This could be a possible route to obtain modified carbohydrates.



Scheme 3: reactivity of the ketal group of TEB

Another route to make a starting material for modified carbohydrates from TEB could be a Grignard reaction to obtain the corresponding propargylic alcohols **7**: in spite of the compound's polar and bulky 1,1,2,2-tetraethoxyethyl group (TEE) the corresponding propargylic alcohols are obtained when TEB acetylide is generated with a base and

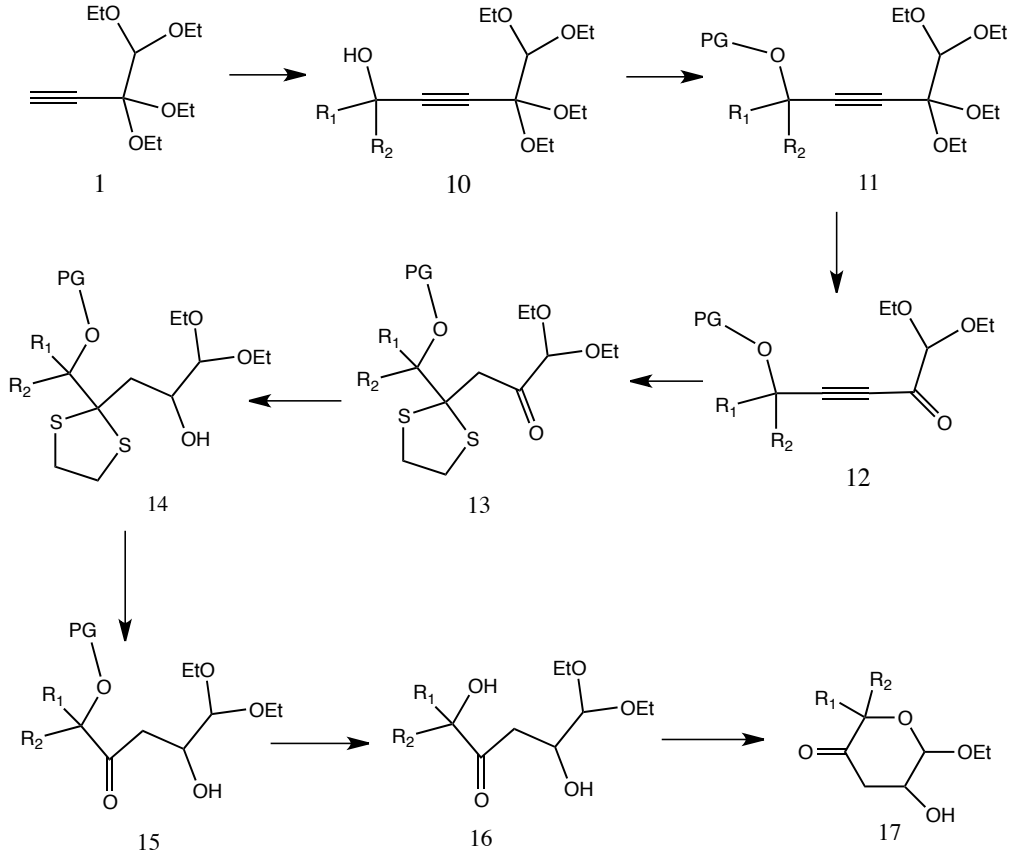
subsequently treated with an aldehyde or a ketone.[16] Generally the alcohols are formed in good to excellent yields. Then, the ketal group of **7** can be deprotected to give the ketone **8** that could react with a nucleophile, linked to the triple bond. The final product **9** depends from the nucleophile used, but the aim is producing a substituted heterocyclic compound, like substituted pyran or a substituted furan.



Scheme 4: from TEB to substituted pyran or furan

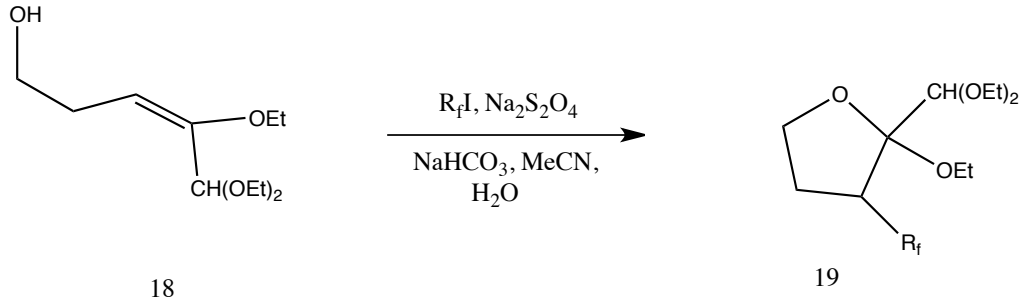
1.4 Previous works

Valdersnes has synthesized carbohydrate analogues from TEB.[13] The route consists first of chain elongation of **1**, producing different analogues **10**, then protection of the hydroxyl group and deprotection of the ketal moiety give **12**. Then, addition of dithiol to the triple bond gives **13** and its reduction gives **14**. Deprotection of the masked carbonyl moiety of **14** gives **15**, deprotection of the protected hydroxyl group and cyclization give the carbohydrate analogue **17**.[13]



Scheme 5: from TEB to carbohydrate anologues[13]

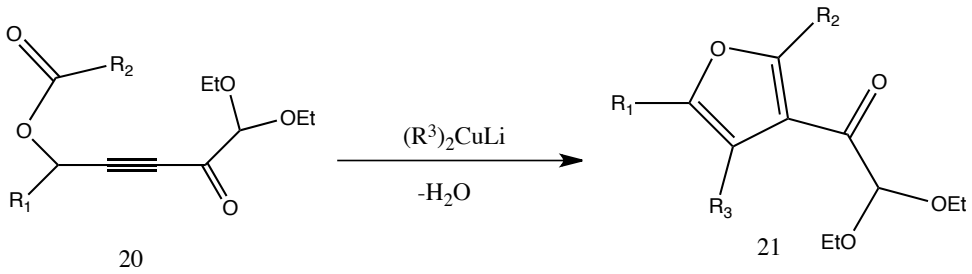
Another work regarding carbohydrates analogue synthesis published by Valdersnes and Sydnes is about conversion of 1-substituted and 1,1-disubstituted (*E*)-4,5,5-triethoxypent-3-en-1-ols **18** to perfluoroalkylated tetrahydrofuran **19** and tetrahydropyran in a selective fashion by 1-iodoperfluoroalkane attion under radical conditions using sodium dithionite ($Na_2S_2O_4$) as radical initiator[17].



Scheme 6: from 1-substituted-4,5,5-triethoxypent-3-en-1-ol to perfluoroalkylated tetrahydrofuran[17]

There are other works on the synthesis of precursors of carbohydrate analogues from TEB, for example a nucleophilic attack to the triple bond of ketoesters **20**, obtained from

TEB.[18] γ-acyloxy α,β-unsaturated acetylenic ketones **20** have shown to react with organocuprate reagents and undergo cyclization followed by dehydration to give substituted furans as the final product **21**. The transformation appeared to be versatile, and tri- and tetra-substituted furans were obtained with regiochemical control in moderate to good yields.[18]

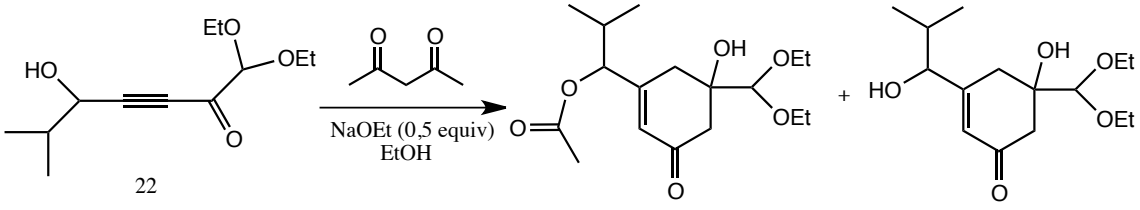


20 21

Scheme 7: from ketoester to substituted furan[18]

In my thesis I have investigated the reactivity of the ketone **8**, made from the propargylic alcohol **7,** with enolates of active methylene compounds such as 1,3 dicarbonyl compounds.

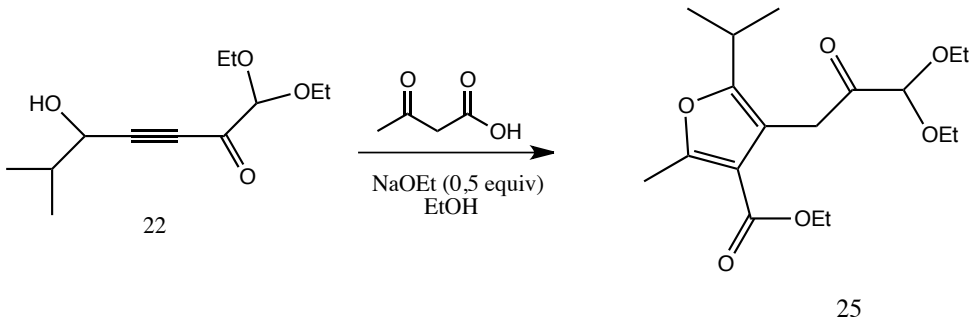
The ketone 1,1-Diethoxy-5-hydroxy-6-methylhept-3-yn-2-one **22** was already treated with the enolate of pentane-2,4-dione generated by 50 mole% sodium ethoxide in ethanol. Two products were isolated and subsequent IR and NMR spectroscopic analysis confirmed that 1-(5-(diethoxymethyl)-5-hydroxy-3-oxocyclohex-1-enyl)-2-methylpropyl acetate **23** and 5-(diethoxymethyl)-5-hydroxy-3-(1-hydroxy-2-methylpropyl)cycloex-2-enone **24** had been formed both as 3:2 mixture of diastereomers in 48% and 22% yields, respectively.[19]



Scheme 8: reactivity of the ketone, made from the propargylic alcohol, with the enolate of pentane-2,4-dione[19]

The same ketone **22**, made from the the propargylic alcohol, generated by TEB with isobutyl aldehyde (see Scheme 4), was also treated with the enolate of ethyl

acetoacetate. The crude product NMR analysis showed that only one product had been formed and cromatographic purification yielded 4-(3,3-diethoxy-2-oxopropyl)-2-isopropyil-5-methylfuran-3-carboxylate **25** in 90 % yield.[19]



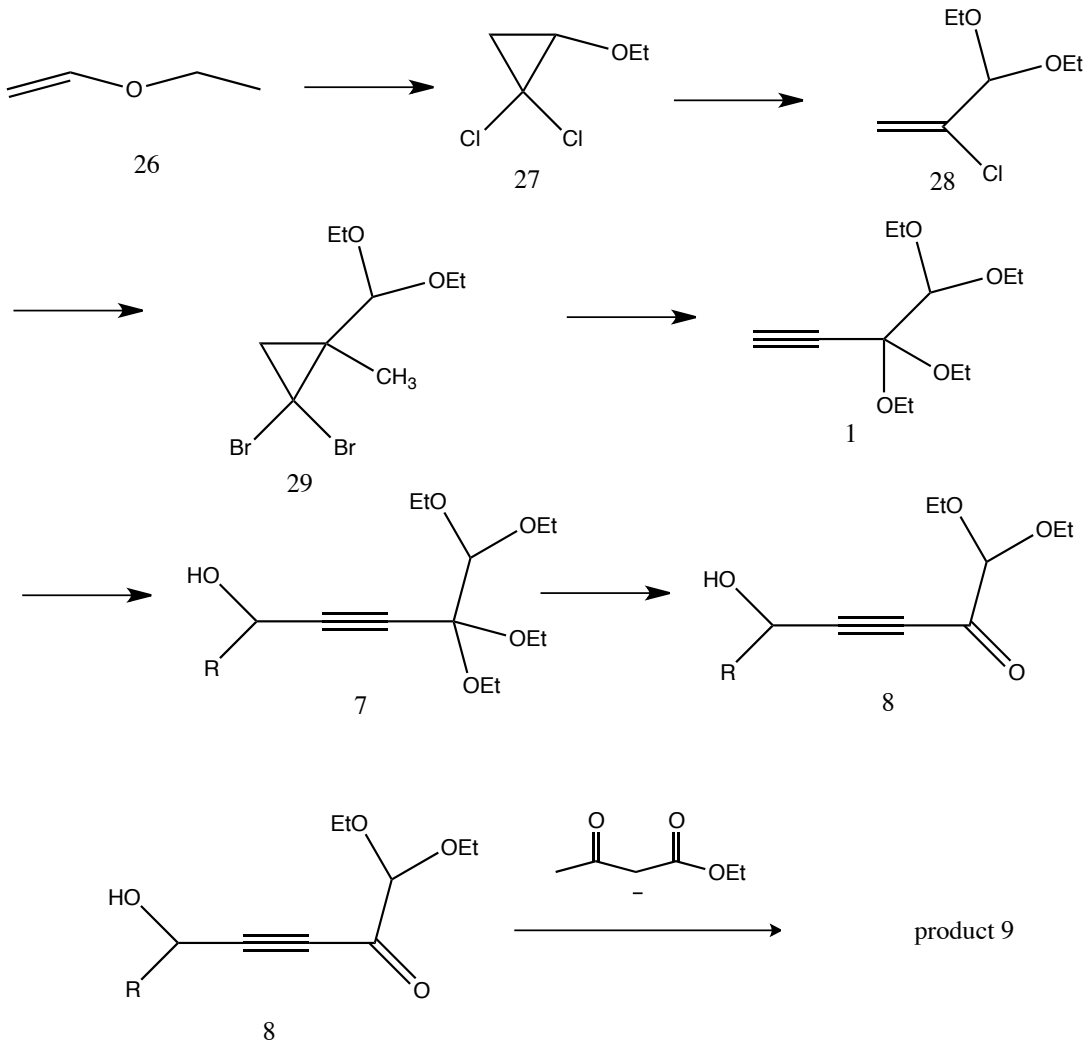
Scheme 9: reactivity of ketone, made from the propargylic alcohol, with the enolate of ethyl acetoacetate[19]

1.5 Aim of the project

The aim of this project is twofold.

- Synthesizing TEB as starting material for a lot of intersting chemistry and, especially, for modified carbohydrate analogues. Sytnthesis of TEB is a 4-step synthesis and the last 2 steps are very sensitive to reaction conditions and yields aren't so high as those of the first two steps. As I used TEB as starting material, I partecipated in ideation of a project in which it was thought how to carry out the optimization of the third step of the synthesis of TEB. I took part in the selection of operating conditions and how and which parameters can be changed even if I didn't make any experiment and data analysis;
- Then, continue with the synthesis with the aim to obtain an α,β-unsaturated compound derivatives of TEB on which try a new reaction that consists of a nucleophilic attack with ethyl acetoacetate to the triple bound through Michael's addition reaction and observe which product it could be possible to obtain, hoping to have an interest route to make modified carbohydrates analogues or other interesting chemist compounds. It was already observed that the addition of ethyl acetoacetate to 1,1-diethoxy-5-hydroxy-6-methylhept-3-yn-2-one **22** gave the

substituted furan ethyl 4-(3,3-diethoxy-2-oxopropyl)-2-methyl-5-isopropylfuran-3-carboxylate 25,[19] so I will try the same reaction with another γ-hydroxy-α,β-unsaturated acetylenic ketone, 1,1-diethoxy-5-hydroxyhex-3-yn-2-one **8** (R = Me), and I will check if the reactivity will be the same. If the reactivity will be the same, I will investigate two others γ-hydroxy-α,β-unsaturated acetylenic ketones with a longer aliphatic chain as R group and several others would be investigated, in order to confirm a route to synthesize substituted furan from TEB.



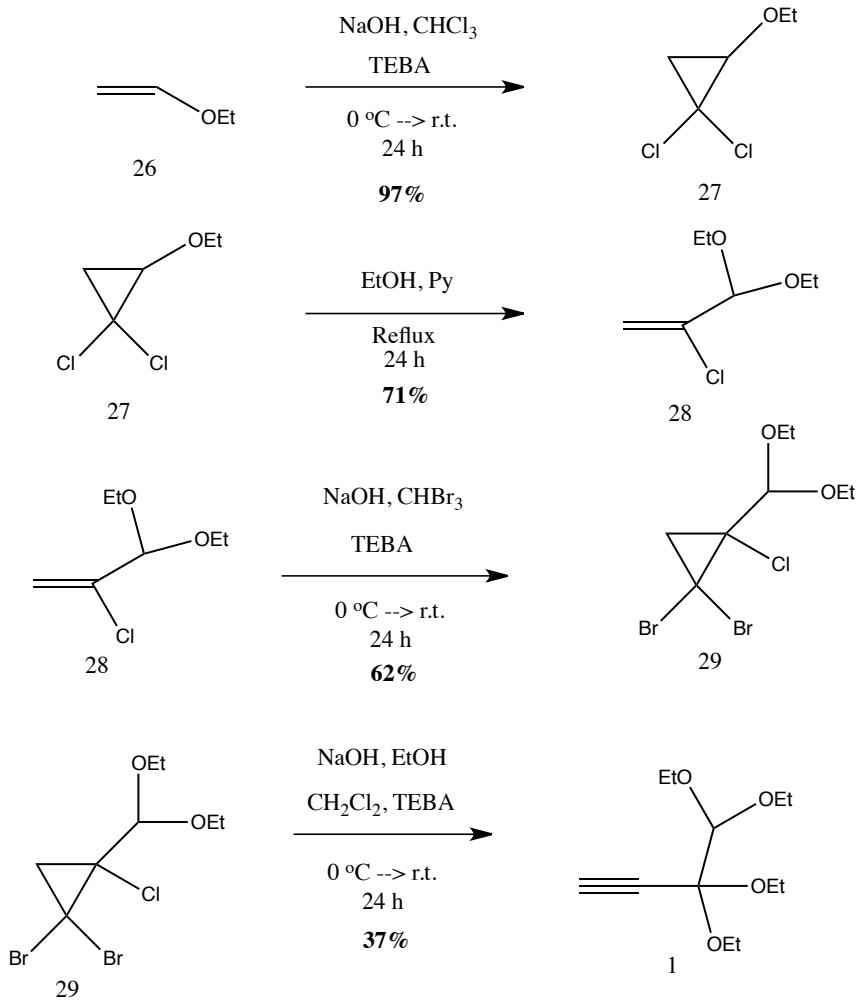
26 27 28 29 1 7 8 8

Scheme 10: my aim

2. RESULTS AND DISCUSSION

2.1. Preparation of TEB[20]

TEB synthesis starts from the cyclopropanation of ethyl vinyl ether **26**, then opening of the ring gives the alkene **28**. The synthesis proceeds with the cyclopropanation of this alkene under similar condition to the first step and TEB **1** is obtained with a regioselective ring opening of the ring of this substituted cyclopropane **29**.



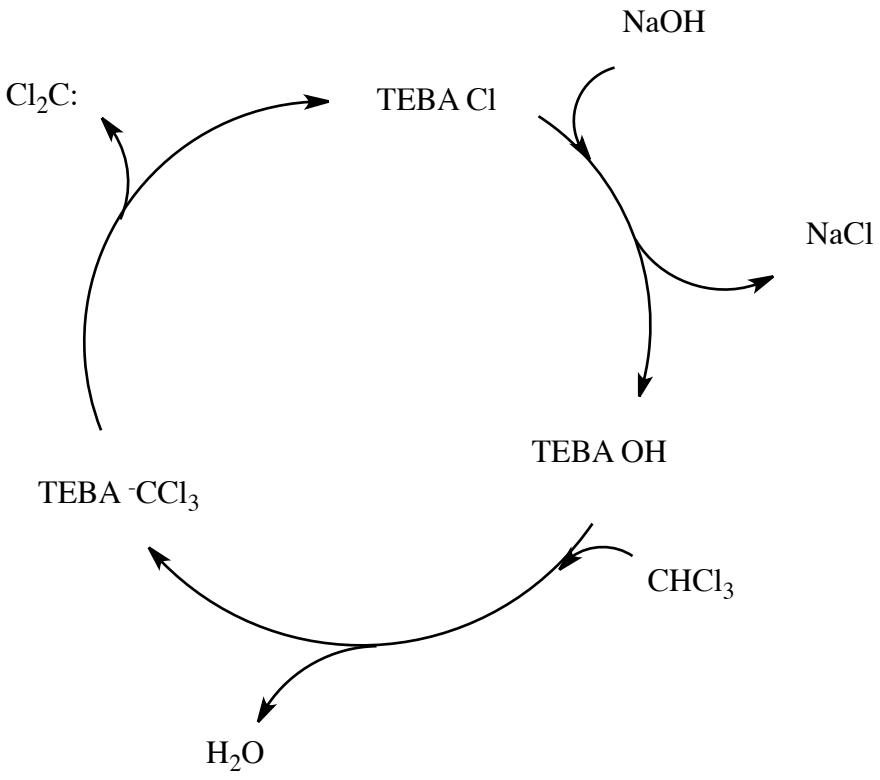
Scheme 11: the synthesis of TEB: 4-steps from ethyl vinyl ether[9]

Synthesis of 1,1-Dichloro-2-ethoxycyclopropane **27**

The first step of TEB synthesis is the cyclopropanation of ethyl vinyl ether with Makosza's method[21], scaled up by Kvernenes[22]. This yielded 97% of the crude product of 1,1-dichloro-2- ethoxycyclopropane **27** on a 0.35 mole scale.

The starting material, ethyl vinyl ether, is reacting with four equivalent of dichlorocarbene, which is generated by treating chloroform with six equivalents of a 50% aqueous solution of sodium hydroxide, and a phase transfer catalyst (triethylbenzylammonium chloride, TEBA). This is a two-phases system with the aqueous solution of base soluble in water, the starting and the product soluble in organic phase and the catalyst soluble in both phases.

TEBA is the catalyst of the reaction and we can see in the following scheme how the reaction starts and how catalyst takes place in the reaction to be regenerated in the end.



Scheme 12: catalyst's reaction

TEBA OH is insoluble in both phases and we can see it on the interface, then TEBA becomes soluble in organic phases and it can react with $CHCl_3$ to give a carbene and in the end catalyst is regenerated and Cl_2C: is formed as a very reactive species.

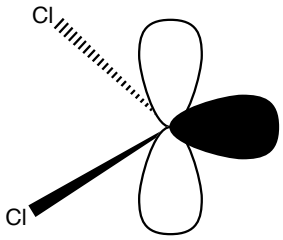
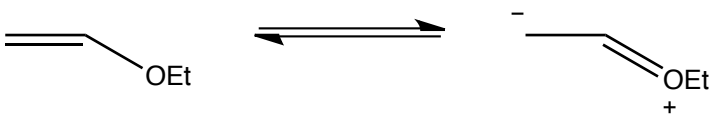


Figure 4: orbital of Cl_2C:

Dichlorocarbene is a singlet species, which means that it contains an empty *p* orbital and a filled sp^2 orbital.

Ethyl vinyl ether is an electron-rich alkene, as we can see from the resonance structures:



Scheme 13: resonance structures of ethyl vinyl ether

So, it is easy to understand the reaction mechanism: the carbene electron pair attacks electropositive carbon atom of ethyl vinyl ether and electrons pair on electronegative carbon of ethyl vinyl ether attach empty p orbital of carbene.

This mechanism is showed in Figure 5:

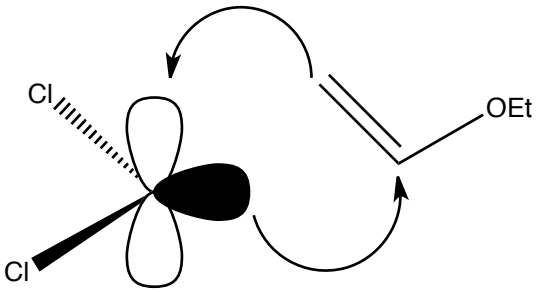


Figure 5: reaction mechanism

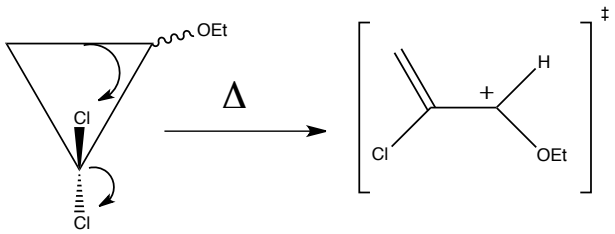
Cheletropic reactions are a type of pericyclic reaction. A pericyclic reaction is one that involves a transition state with a cyclic array of atoms and an associated cyclic array of interacting orbitals. A reorganization of σ and π bonds occurs in this cyclic array.

Specifically, cheletropic reactions are a subclass of cycloadditions.

Synthesis of 2-Chloro-3,3-diethoxyprop-1-ene **28**

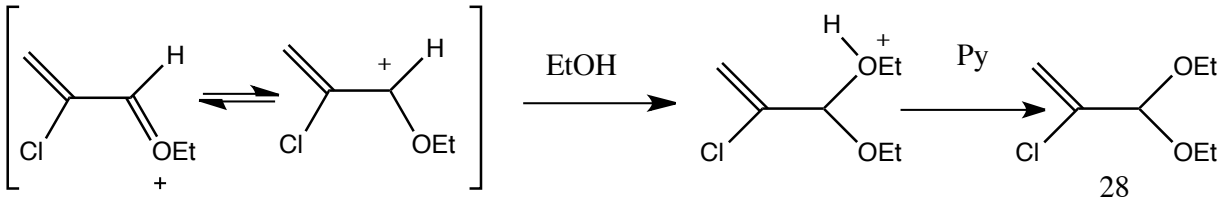
The second step is a thermally induced ring opening of **27**, which gave **28** with a 71 % yield, using a procedure developed by Skattebøl.[23] In this procedure either sodium ethoxide or pyridine as base was used. Kvernenes used commercial absolute ethanol and commercial pyridine simplifying reaction conditions.[22]

The reaction starts because heat induces ring opening with loss of chloride to give an allylic cation as intermediate, as shown in Scheme 14.



Scheme 14: formation of the intermediate

Ethanol then attacks the intermediate, on the positively charged carbon atom, to give the final product as showed in Scheme 15.



Scheme 15: reaction mechanism

The role of pyridine is to neutralise the acid formed during the reaction. The easiest way to remove pyridine is add a salt of a metal that may form a complex with that base.

We washed the organic layer extracted with an aqueous copper sulphate solution that complexes the pyridine. For being sure that this complex could be removed it's necessary filter the extracts though a small plug of alumina.[22]

Synthesis of 1,1-Dibromo-2-chloro-2-diethoxymethylcyclopropane **29**

TEB synthesis continues with a cyclopropanation by Makosza's method[21]. This method is similar to the first step, but here bromoform is used instead of chloroform. A clear difference between these two compounds is that the proton in bromoform is less acidic than that in chloroform. The yield of the crude product of 1,1-dibromo-2-chloro-2-diethoxymethylcyclopropane **29** was 62%.

The reaction conditions are similar to the first step and the reaction mechanism is in essence identical. This reaction is a cycloaddition, too. A carbene is formed and we are in presence of a transition state with a cyclic array of atoms and an associated cyclic array of interacting orbitals, as it is showed in Figure 6:

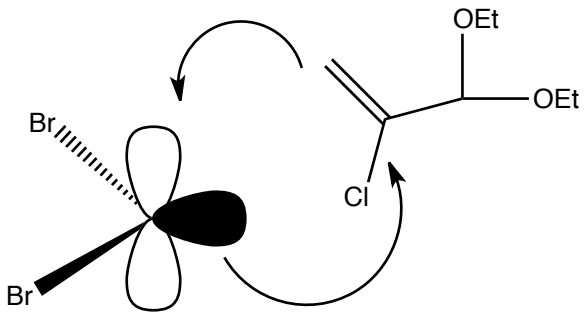


Figure 6: reaction mechanism

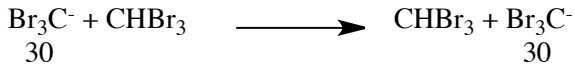
This reaction appears to be sensitive to the reaction conditions like temperature, amount of reagents, time and catalyst. The reason of this sensitively is not full understood.
During the carbene formation, some side reactions can occur. In fact 30 can act as a base towards bromoform to regenerate itself, or it can perform a nucleophilic attack on bromoform to give CBr_4 and others by product.

Formation of carbene:

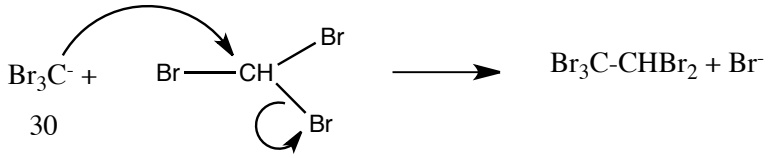
$$CHBr_3 + OH^- \rightleftharpoons \underset{30}{Br_3C^-} + H_2O$$

$$\underset{30}{Br_3C^-} \longrightarrow \underset{31}{:CBr_2} + Br^-$$

Acting as a base:



Acting as a nucleophile:



Due to multiple behaviour of bromoform we can use a large amount of this compound, but a lot of CBr_4 and polymeric by-products could be formed; we decided to use about 6 equivalent of bromoform to find a compromise between the large amount required and the risk of using too much reagent.

When the reaction is finished, we have to do a first distillation with a water pump to remove bromoform and a second distillation with an oil pump (if the product isn't clean) to obtain the product.

The excess of bromoform is recycled after the reaction by distilling it off before the product because the yield could be higher when recycled bromoform is used in the reaction.[13]

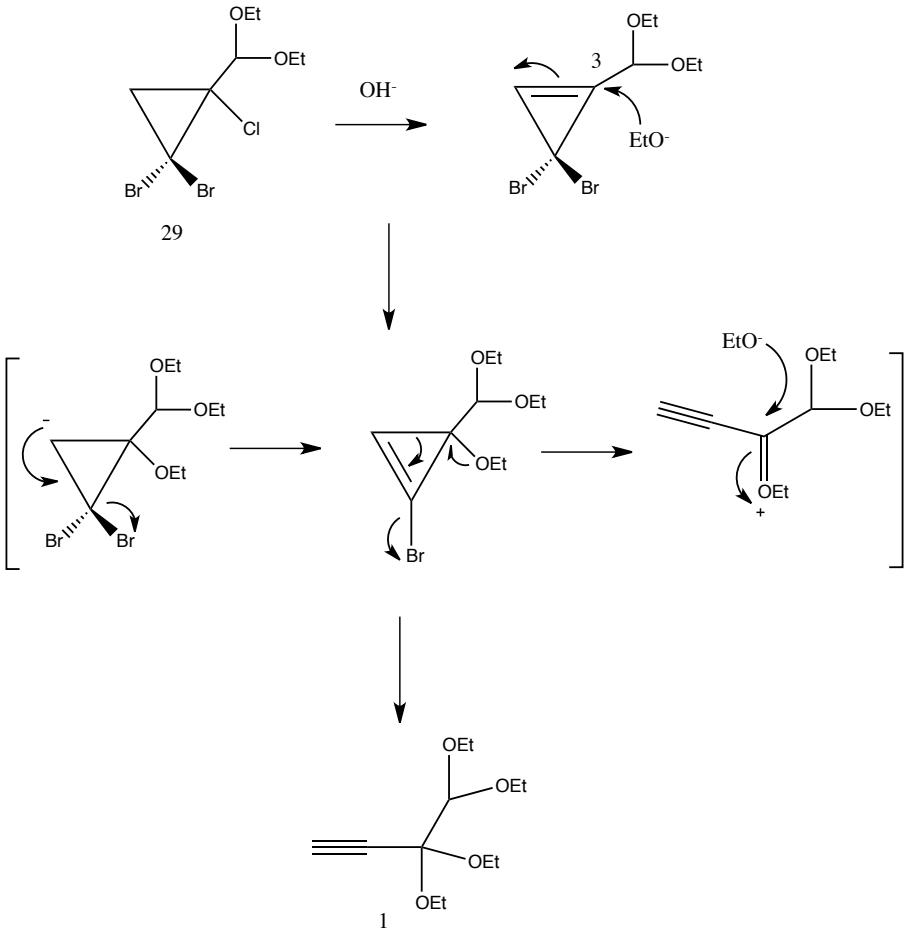
We can see, sometimes, at the end of the distillation, some polymeric residue derived from radical side reactions and CBr_4.

Synthesis of 3,3,4,4,-Tetraethoxybut-1-yne (TEB) **1**

The last step in the TEB synthesis is a regioselective ring opening of **29**, following a procedure published by Sydnes and Bakstad[24-25]. This reaction gave a yield of 37% for the product of 3,3,4,4,-tetraethoxybut-1-yne **1** after distillation, even if the yield was supposed to be higher, between 60-90%.[13_19_26]

In this reaction the product depends on the R-group linked to carbon 3 (see the reaction mechanism). In fact, ring opening of trihalocyclopropanes under PTC may give a mixture of products, but the reaction conditions can be modified to obtain a regiospecific ring opening of the cyclopropane. The R-group presents in 3 is diethoxymethyl: it is a bulky substituent and it has enough polarity to form hydrogen bond that redirects the ethanol attack and then gives only the ketal product[9-27-28].

It's now showed the reaction mechanism:



Scheme 16: reaction mechanism

Product of the 4rd step has to be distilled to obtain quite pure TEB.

Distillation is carried out with an oil pump. During the distillation is possible that some bromoform and CBr_4, not removed from 3rd step, is distilled at lower temperature than TEB (bromoform is distilled just while we made vacuum, without heating) and is also possible that some amount of the unreacted starting is distilling with TEB, cause its boiling temperature, not very higher than the product.

For every distillation we have made, we checked the boiling point of every compound on literature and, while we carried out distillations we checked the boiling point of the compounds at the operative pressure by using this following pressure-temperature monograph.

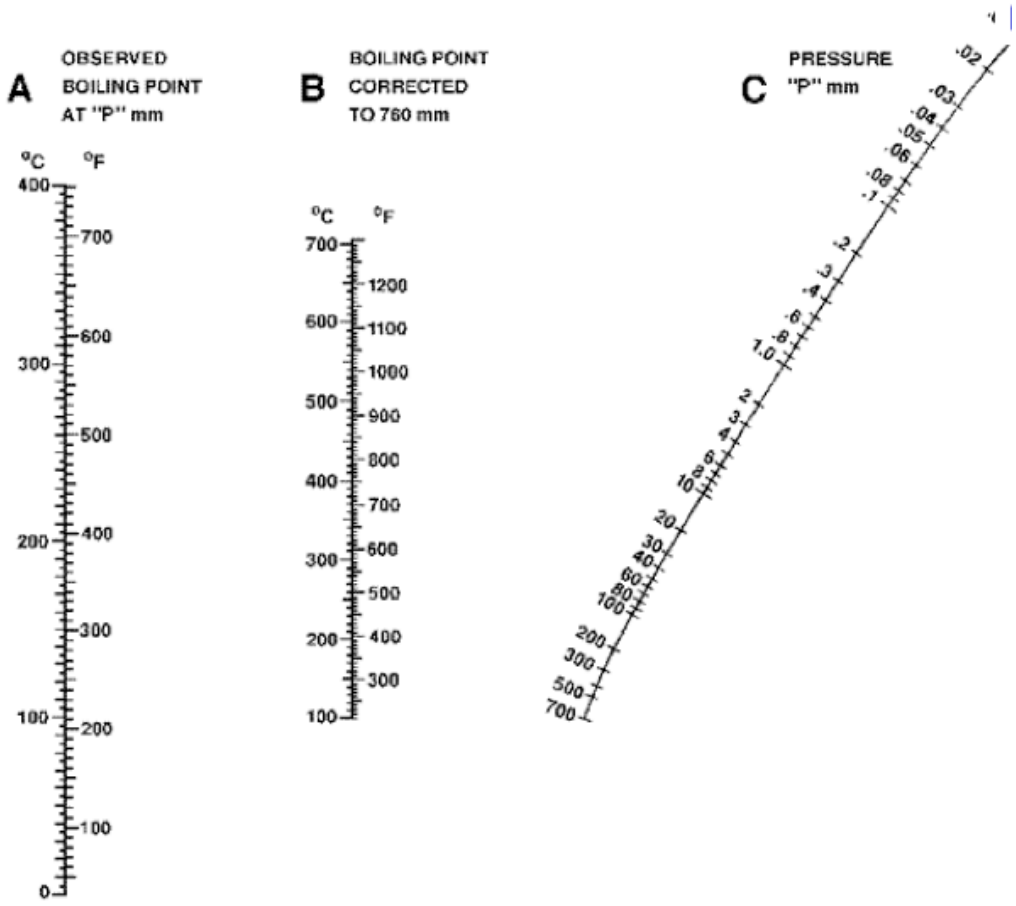


Figure 7: pressure-temperature monograph

In the next table, it's showed all the boiling temperature of the product or solvent distilled during the synthesis of TEB.

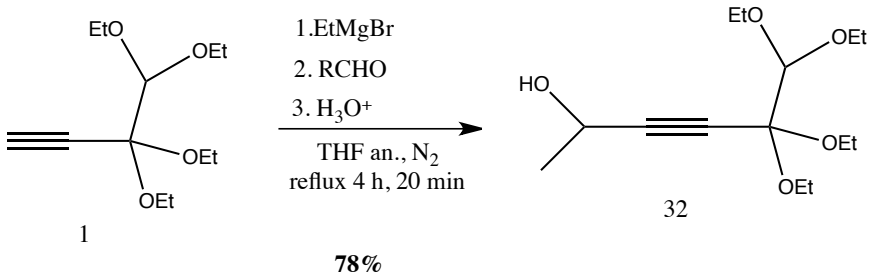
COMPOUND	T_{eb} at 760 mmHg	T_{eb} at 15 mmHg	T_{eb} at 0,15 mmHg
1,1-dichloro-2-ethoxycyclopropane	150 °C[a]	30-35 ˚C (53 ˚C, 28 mmHg[29])	r.t.
2-chloro-3,3-diethoxyprop-1-ene	180 °C[a]	70-78 ˚C (25 mmHg[23])	r.t.
1,1-dibromo-2-chloro-2-diethoxymethylcyclopropane	300 °C[a]	165 °C[a]	80-82 ˚C (lit[25])
3,3,4,4,-tetraethoxybut-1-yne	250 °C[a]	95 °C[a]	53-58 ˚C (lit[25]) (0,2 mmHg)
$CHBr_3$	149,5 °C (lit[30])	35 °C[a]	r.t.
CBr_4	179,5 °C (lit[21])	80 °C[a]	r.t.

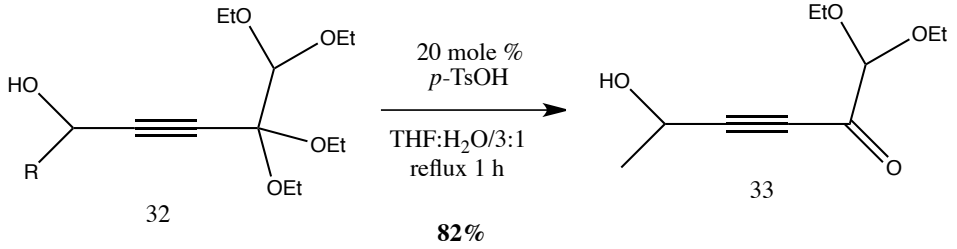
[a] Based on the nomograph shown in Figure 7.

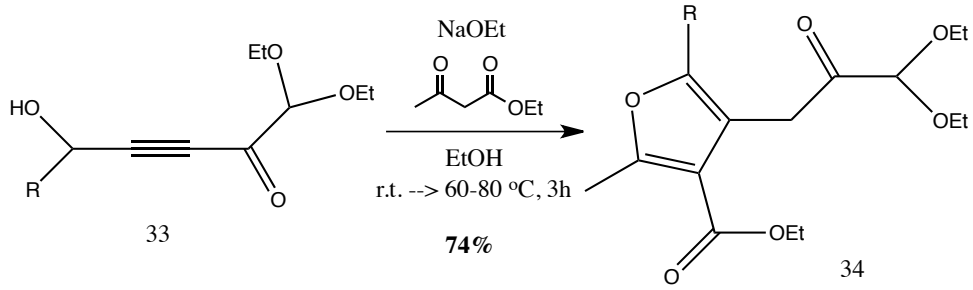
Table 1: T_{eb} of the compounds and solvents distilled during the synthesis of TEB

2.2. Synthesis of substituted furan from TEB

Furan derivative **34** is obtained following the route described in the introduction, adding ethyl acetoacetate to **33**.







Synthesis of 5,5,6,6-Tetraethoxyhex-3-yn-2-ol **32**

TEB has a terminal triple bond and therefore an acetylenic hydrogen atom. The presence of this hydrogen, pK_a approximately 23-27, depending on the substituents, allows the synthesis of propargylic alcohols.[26]

Propargylic alcohols are made by treating a terminal acetylene with a strong organic base, such as alkyllithium bases, sodium amide, lithium diisopropyl amide (LDA) or Grignard reagents followed by the addition of an aldehyde or a ketone.[31]

Exploratory experiments have been carried out with TEB using various bases and these experiments revealed that alcohol formation was sensitive to the base employed in the deprotonation of TEB and the best results were obtained when the acetylide was generated *in situ*, for example with ethylmagnesium bromide.[13–22]

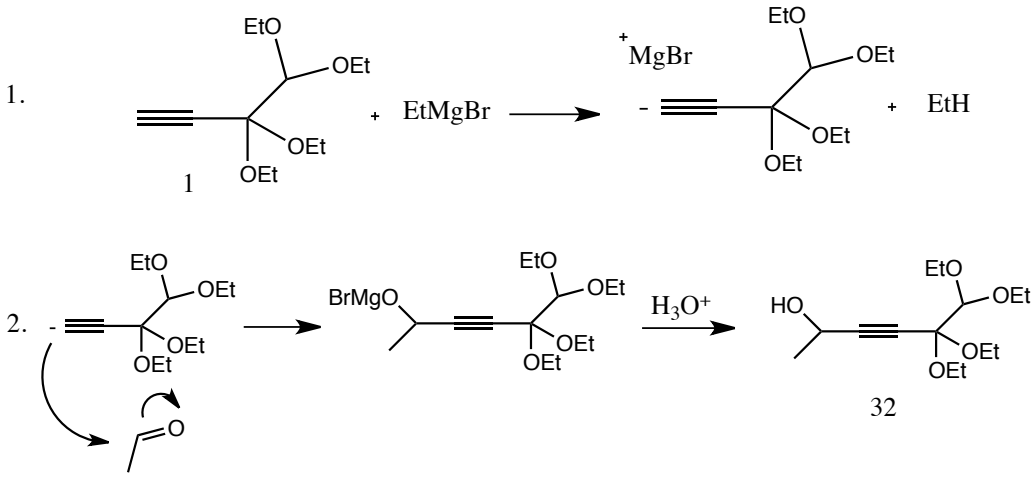
There are three general procedures to sytnhesize propargylic alcohols from TEB:

1. The reaction can be carried out with $NaNH_2$ generated *in situ* and was performed following the procedure described by Furniss *et al*[32];
2. The reaction can be performed with commercially available butyllithium as base and was carried out following a procedure published by Brandsma[31];
3. The reaction can be carried out with ethylmagnesium bromide as base.[16]

The base used for this synthesis was a solution of ethylmagnesium bromide 3M in Et_2O and after 80 min. reflux, acetalaldehyde was added to the reaction mixture.

The reaction has to be carried out on a inert atmosphere with anhydrous THF as solvent.

The mechanism is showed in Scheme 17:



Scheme 17: Reaction mechanism

As we can see from Scheme 17, the nucleophilic carbon of the triple bound attacks the elettrophilic carbon of the aldehyde and a new C-C bond it's formed.

The reaction is quenched by adding an acid: we used a saturated solution of ammonium chloride. In the end of the work-up the product has to be purified with flash chromatography.

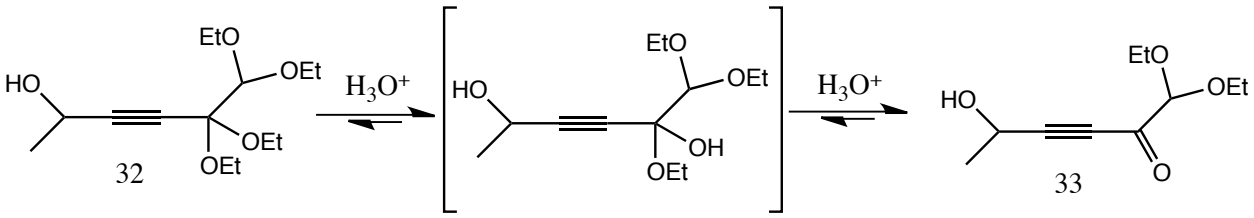
Synthesis of 1,1-Diethoxy-5-hydroxyhex-3-yn-2-one **33**

The propargylic alcohol from TEB undergo selectively ketal deprotection when treated under acidic condition giving γ-hydroxy-α,β-unsaturated acetylenic ketones.

The reaction can be carried out with Dowex 50W in moist acetone or with a solution of *p*-TsOH in a 3:1 mixture of THF and water.

The reaction was carried out with a solution of *p*-TsOH in a 3:1 mixture of THF and water because the yield is supposed to be higher.[19]

The reaction consists in a simple deprotection of the ketal moiety, which exploits its instability under acidic conditions.



Scheme 18: Deprotection of ketal function

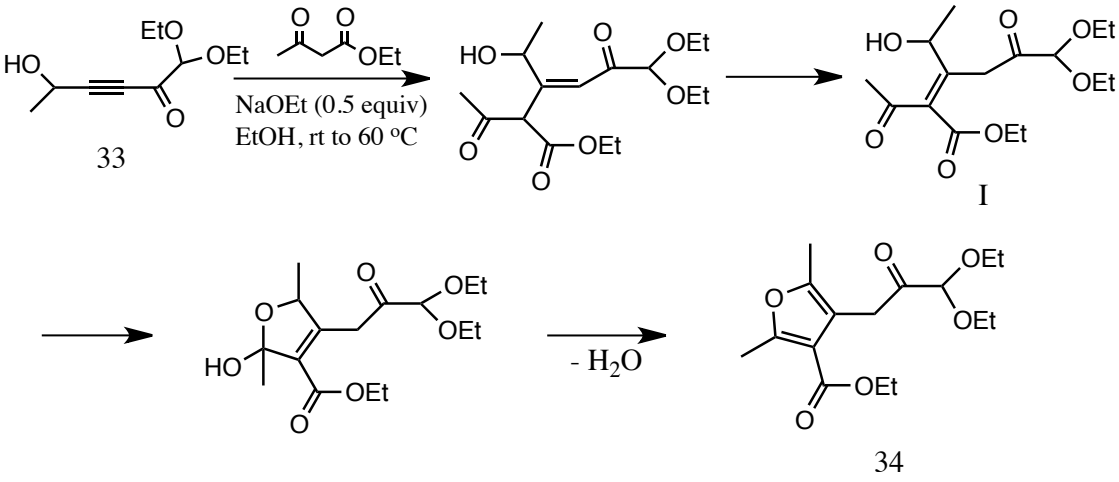
The crude product gave ^{1}H-NMR spectra that showed that the ketone was pure enough to be used in next reaction without purification.

Synthesis of 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate **34**

For the last step a procedure developed from Sengee M. was followed.[19]

The reaction starts with the formation of the adduct between the starting **33** and the enolate of ethyl acetoacetate**. T**he enolate of ethyl acetoacetate is formed with half equivalent of sodium ethoxyde in ethanol and then ketone was added. The reaction is left stirring 1h and then temperature was increased to 60-80 ^{o}C. The consumption of the starting was confirmed by TLC and the mixture was allowed to cool and was worked up. Cromatographic purification yielded 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate in 74% yield.

The initial Michael adduct underwent an attack of the hydroxyl group on the carbonyl group derivated from ethyl acetoacetate. Before the attack of the hydroxyl group took place, the other acidic methylene proton in the initial Michael adduct can be abstracted and intermediate I can be formed. In the end, after cyclization and elimination of water, the product was formed.



Scheme 20: Reaction mechanism[19]

The determinat factor in the regioselectivity is probably the stability of the keto-enol forms of intermediate I,[19] the most important forms are illustrated in the Table 2.

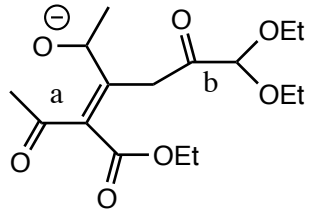
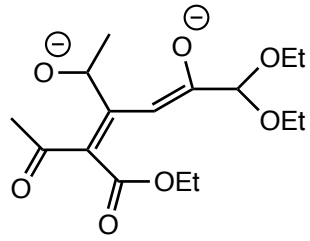
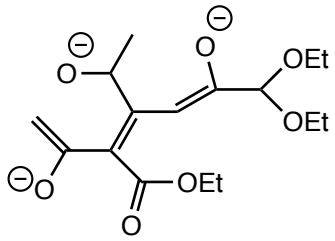
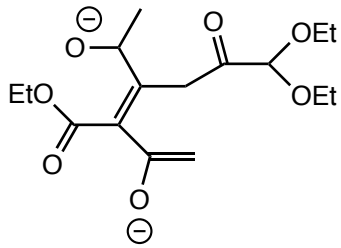
Intermediate	Tautomeric form	Possible attacks
	Keto-Keto	The electron pair on the oxygen of the hydroxyl group could attck both carbonyl groups *a* and *b.*
	Keto-Enolate	The elctron pair on the oxygen of the hydroxyl group could attack carbonyl group *a.*
	Enolate-Enolate	No possible attacks.
	Enolate-Keto	Both the electronegative carbon of the enolate *a* and the elctron pair on the oxygen of the hydroxyl group could attack carbonyl group *b.*

Table 2: keto-enol form of intermendiate I

The base is not present in excess, so only the protons from the most enolizable position would be abstracted: carbonyl *b* converts more easily to enolate than carbonyl *a* due to the formation of terminal C-C double bond in the enolate of carbonyl *a.* So, keto-enolate form is more favourable than enolate-keto form, and enolate-enolate form is the less favourable. The possible product derived from the attack of the hydroxyl group on the carbonyl group *b* is not observed; for these reasons the most stable tautomeric form is supposed to be the keto-enolate form and so it is explained the regioselectivity leading to the formation of the product.[19]

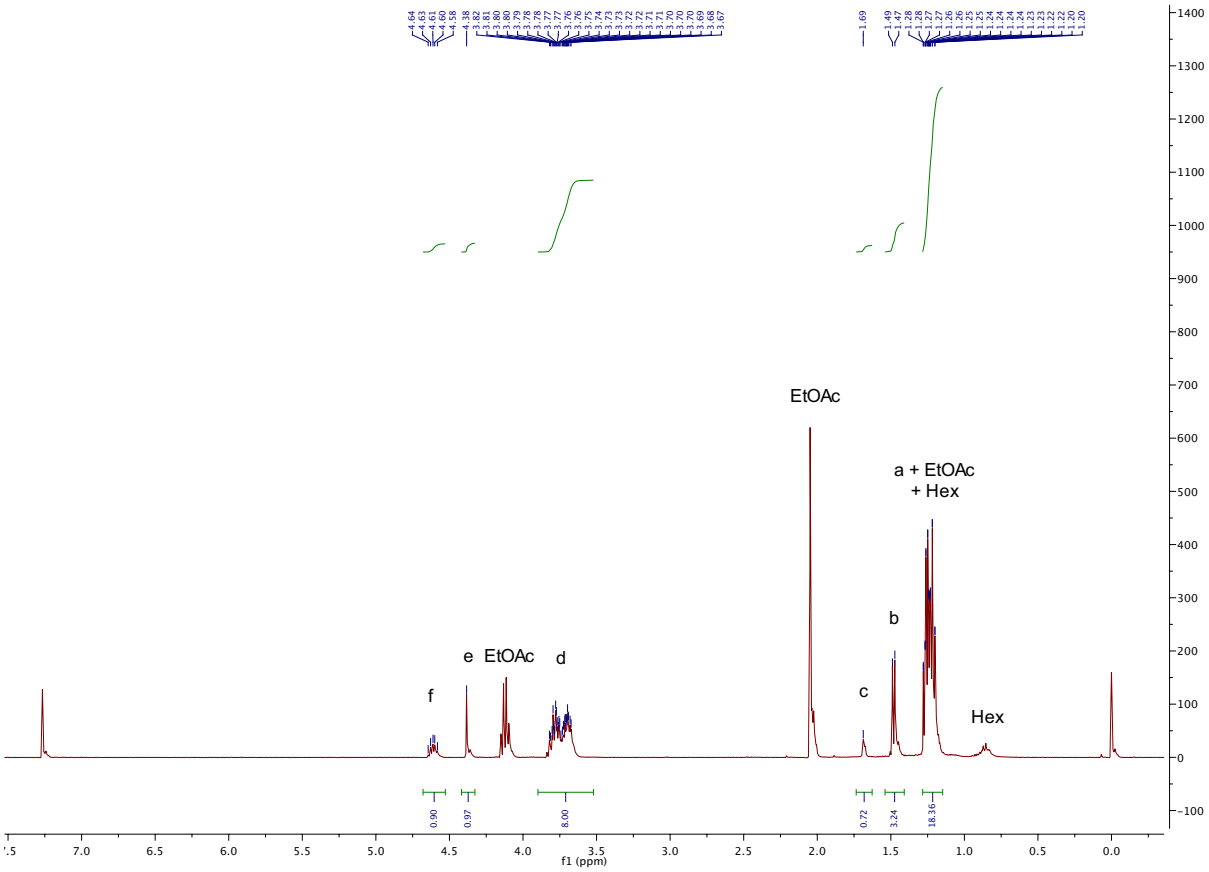
2.2.1. Assignment of NMR spectra

(see appendix for a view of all the spectra)

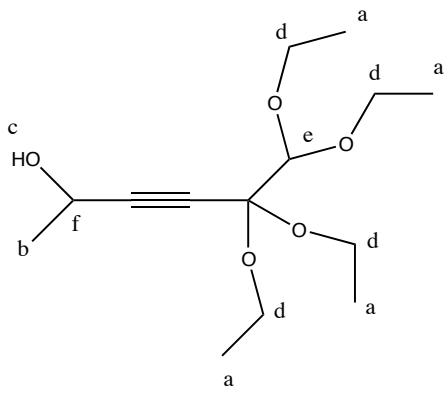
Assignment of NMR spectra might be verified with NOE, COSY and NOESY experiments

5,5,6,6-Tetraethoxyhex-3-yn-2-ol **32**

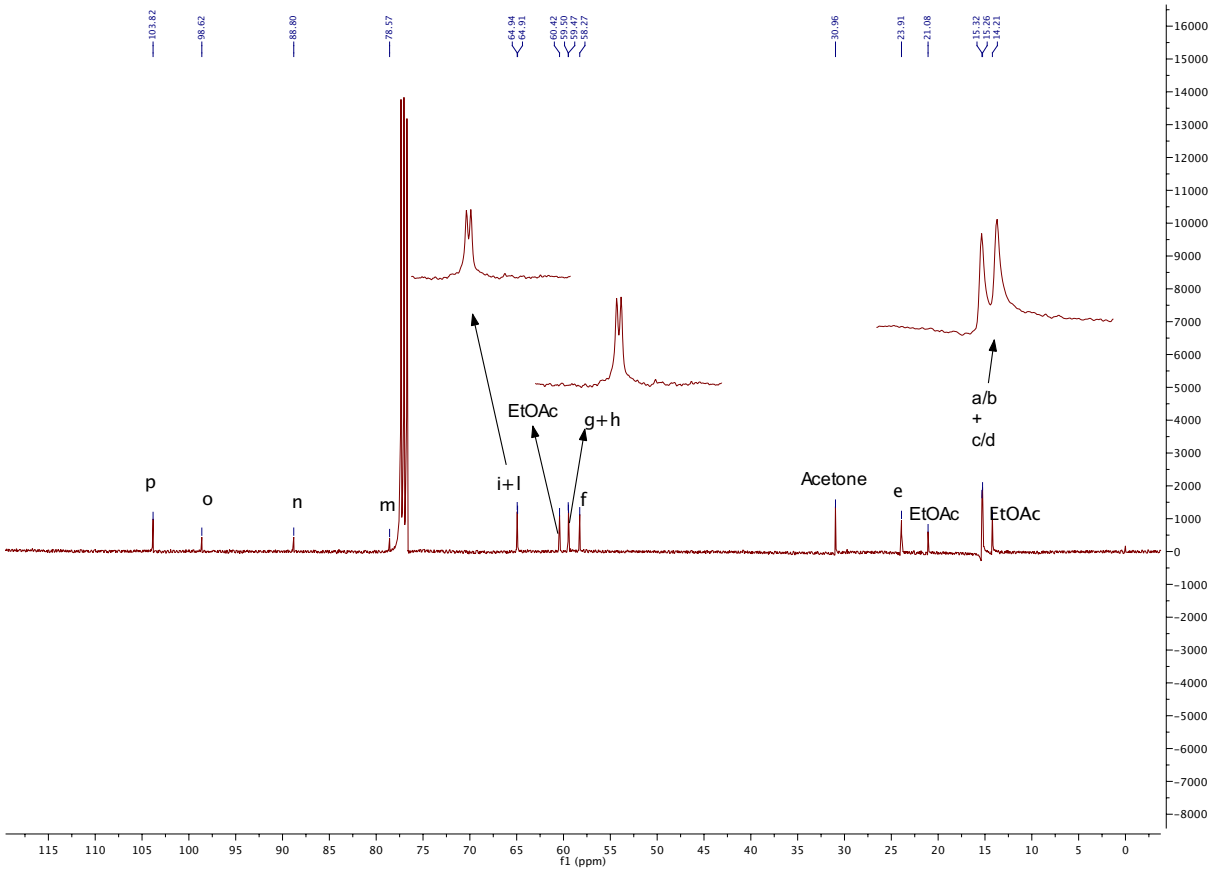
^{1}H



As shown in the spectra, the sample contains some solvent from the flash column, ethyl acetate and hexane. We note, except the solvents, the presence of two multiplets, one quintet, one doublet, one singlet and one mobile proton signal.

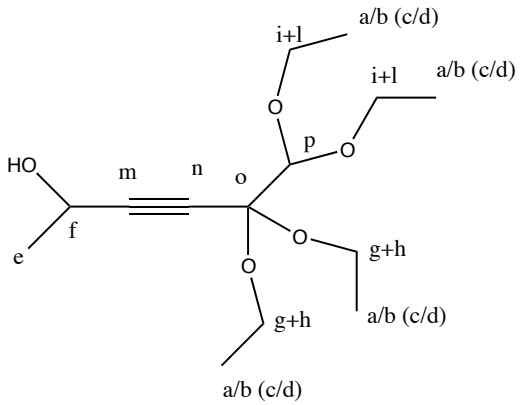


^{13}C



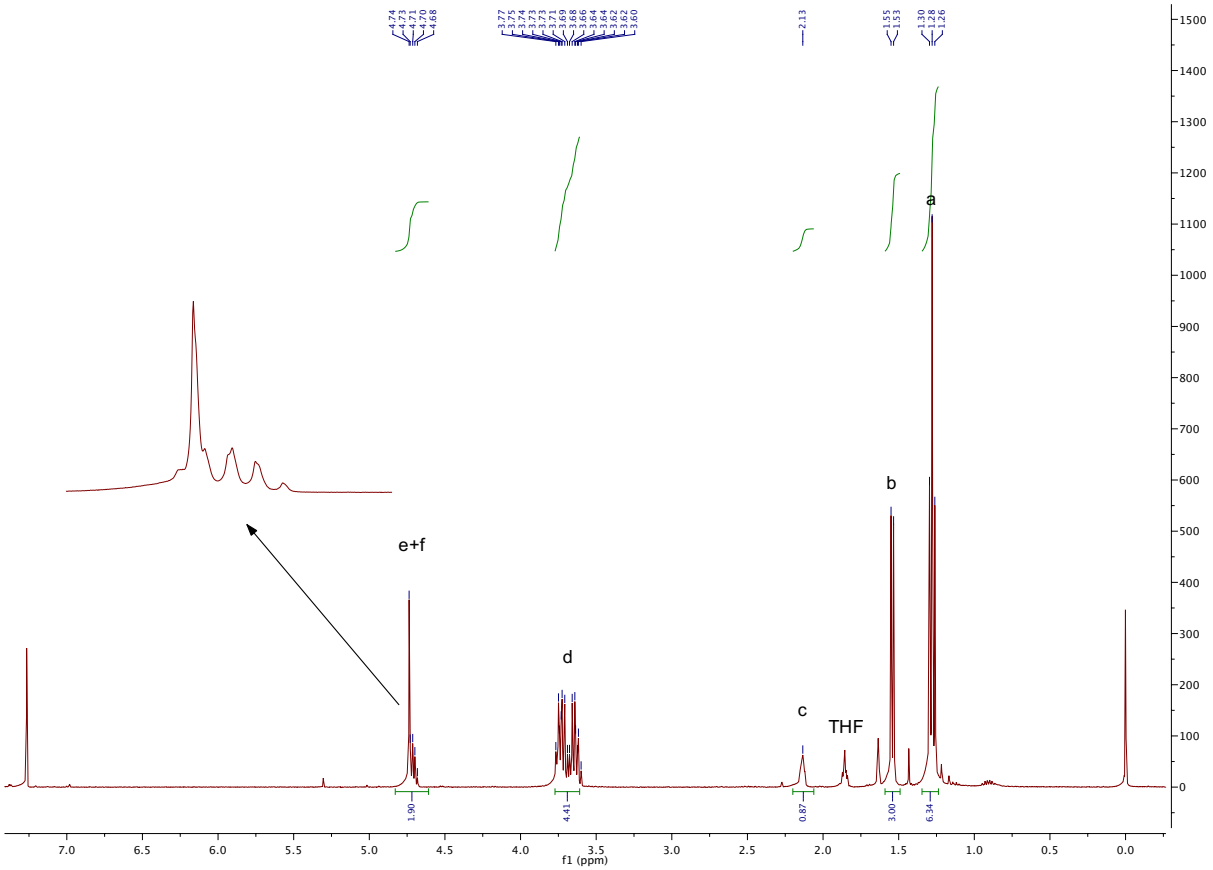
The carbon spectrum reveals the presence of, except the solvents, 12 peaks for 14 carbons. It means that the methyls of the ethoxy groups are equivalent to each other. The four CH_2 groups of the ethoxy groups are all different, but similar pairwise.

Carbon spectrum shows also the presence of three quaternary carbon, two CH groups and one methyl.



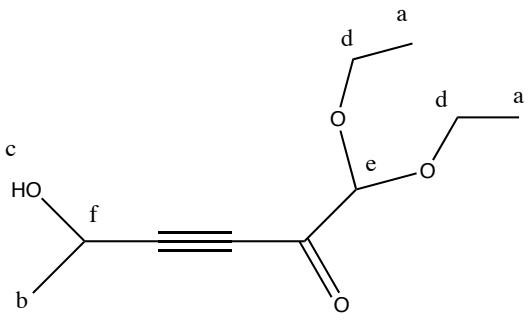
1,1-Diethoxy-5-hydroxyhex-3-yn-2-one **33**

^1H

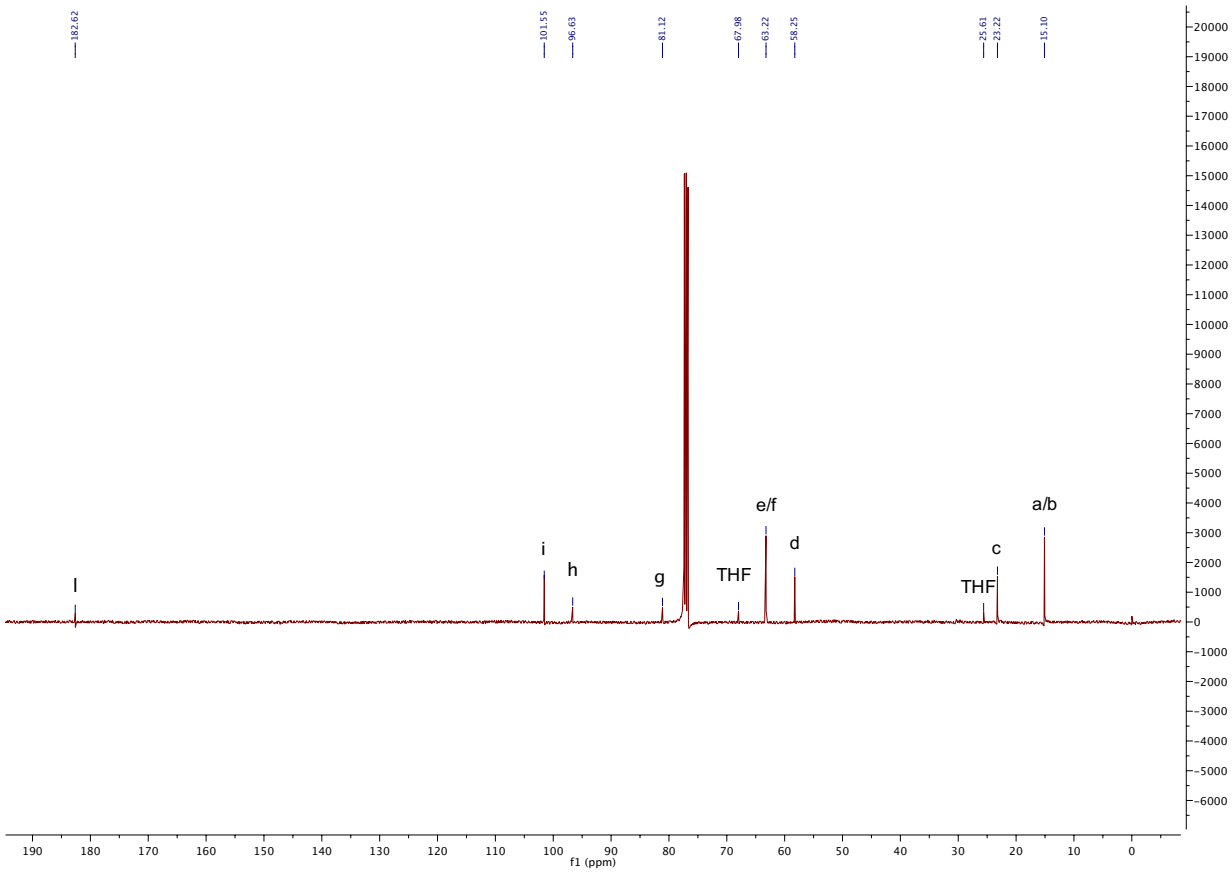


The sample contains some solvent and some very little impurities, due to that it wasn't purified after the work up, but, as we can see, was enough clean to go on with the synthesis.

The product shows one multiplet, one quintet, one triplet, one doublet, one singlet and one mobile proton signal. The quintet and one singlet are overlapped, the singlet is now a lower field than the starting, so it means that we have now the ketone moiety. Another test that we have the ketone is the value of the integral of the protons of ethyl group and the multiplicity of signal a.

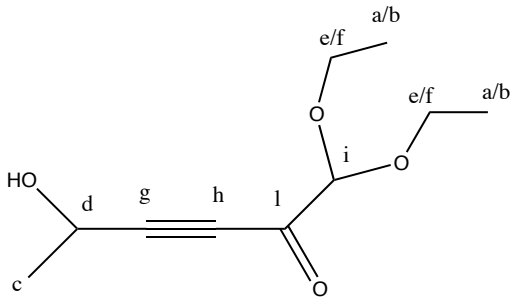


^{13}C



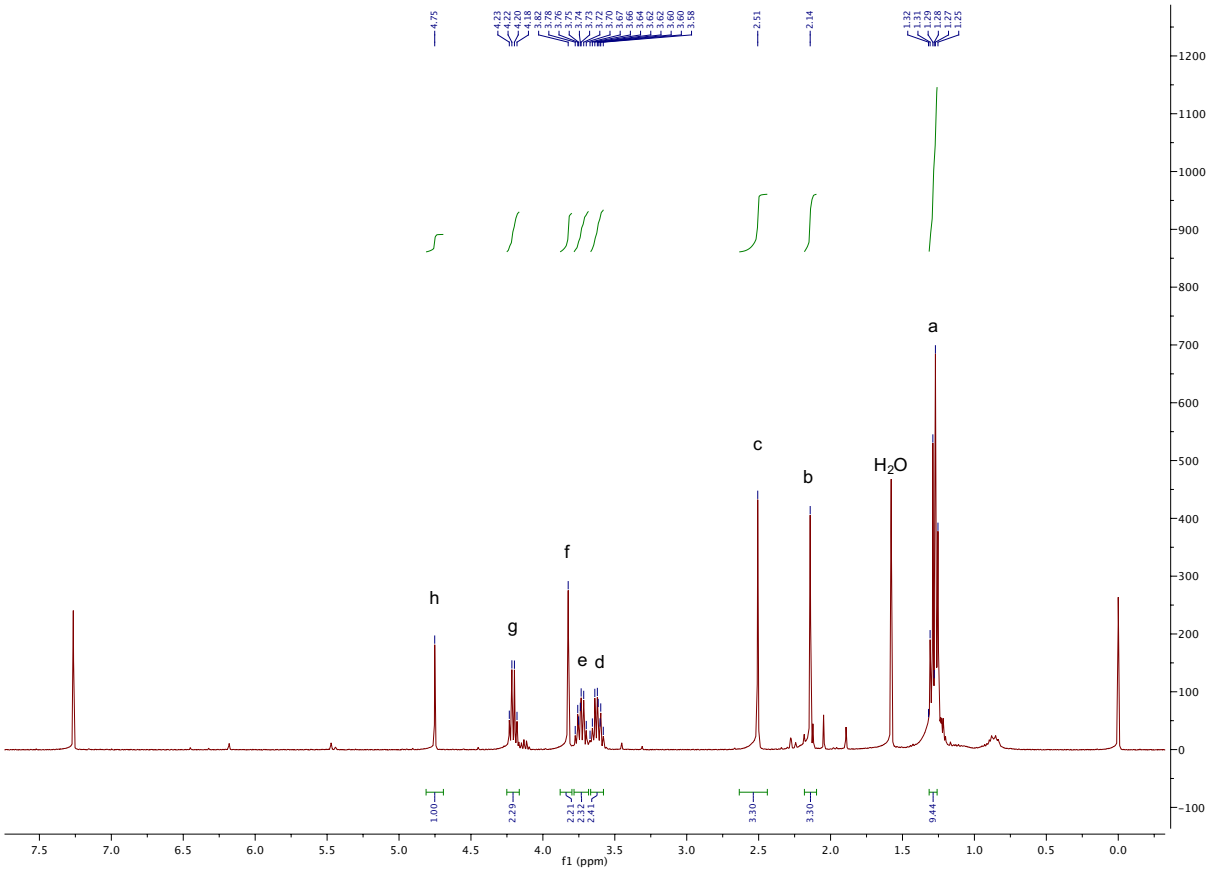
There are 8 peaks for 10 carbon.

CH_3 and CH_2 of the ethoxy groups are equivalent each others. Then, we can see 3 quaternary carbon, of which one shows the typical signal of a ketone around 180 ppm. In the end, the spectrum shows the presence of other three peaks, that are the remaining two CH groups and one CH_3 group.



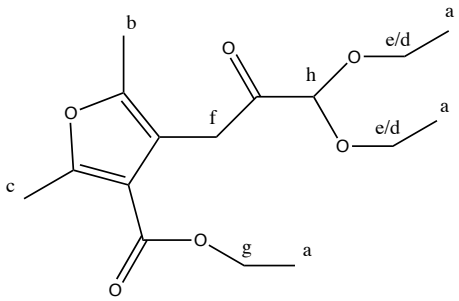
4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate **34**

^1H

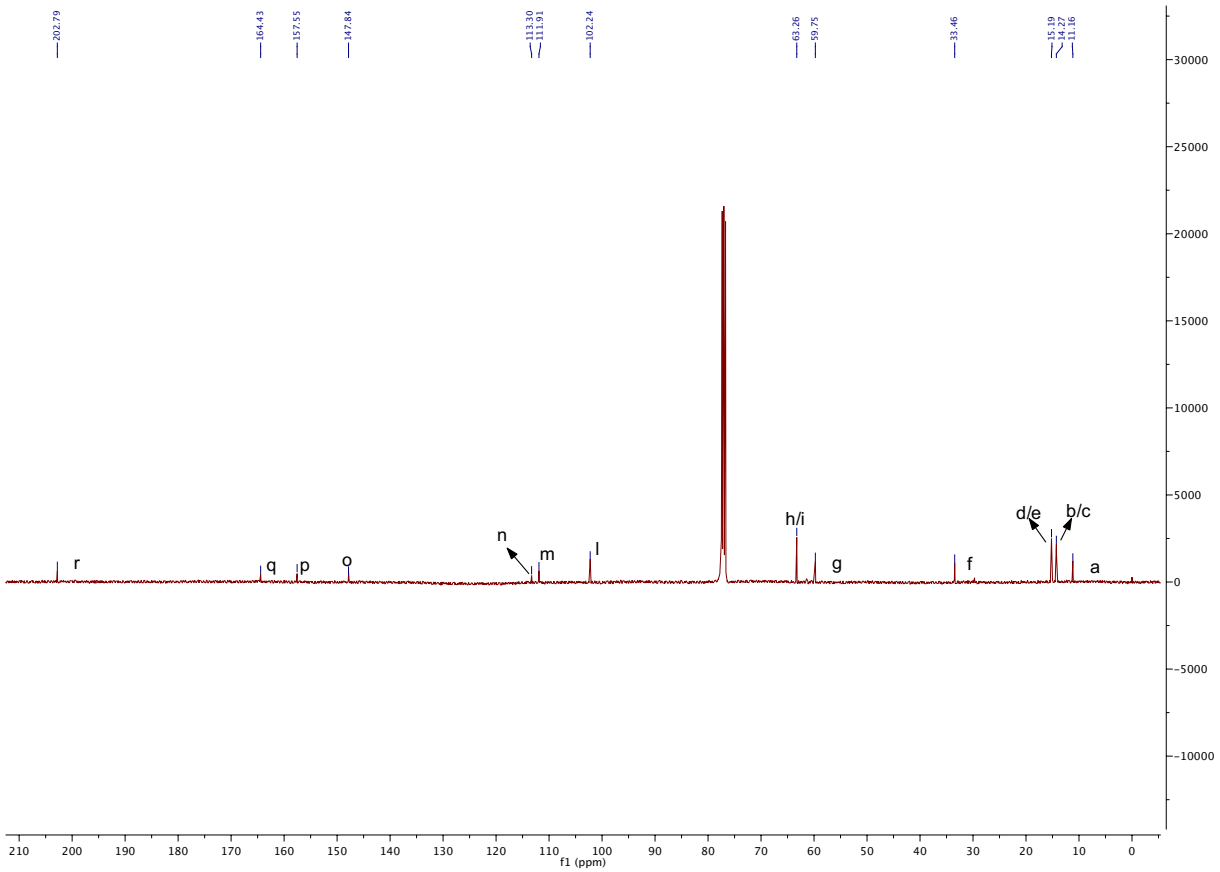


The sample is quite pure, except for the water present in chloroform and traces of solvent like hexane and ethyl acetate used for purify the product with flash chromatography.

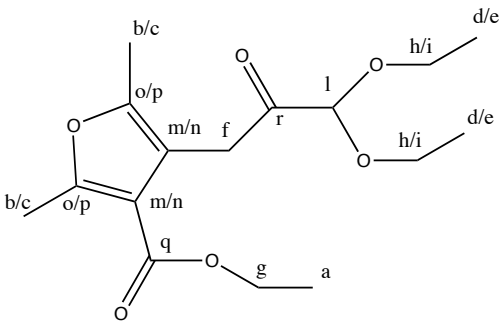
There are two multiplets, one quartet and four singlets. All proton can be easily assignet, since we can observe the presence of four singlets that are: the six proton of the two CH_3 bounded to furan, two proton of CH_2 between the furan and the ketone and the same one proton of CH, that we had also in the previous compounds, between the ketone and the two ethoxy groups. Then the assignment of the other signals is immediate.



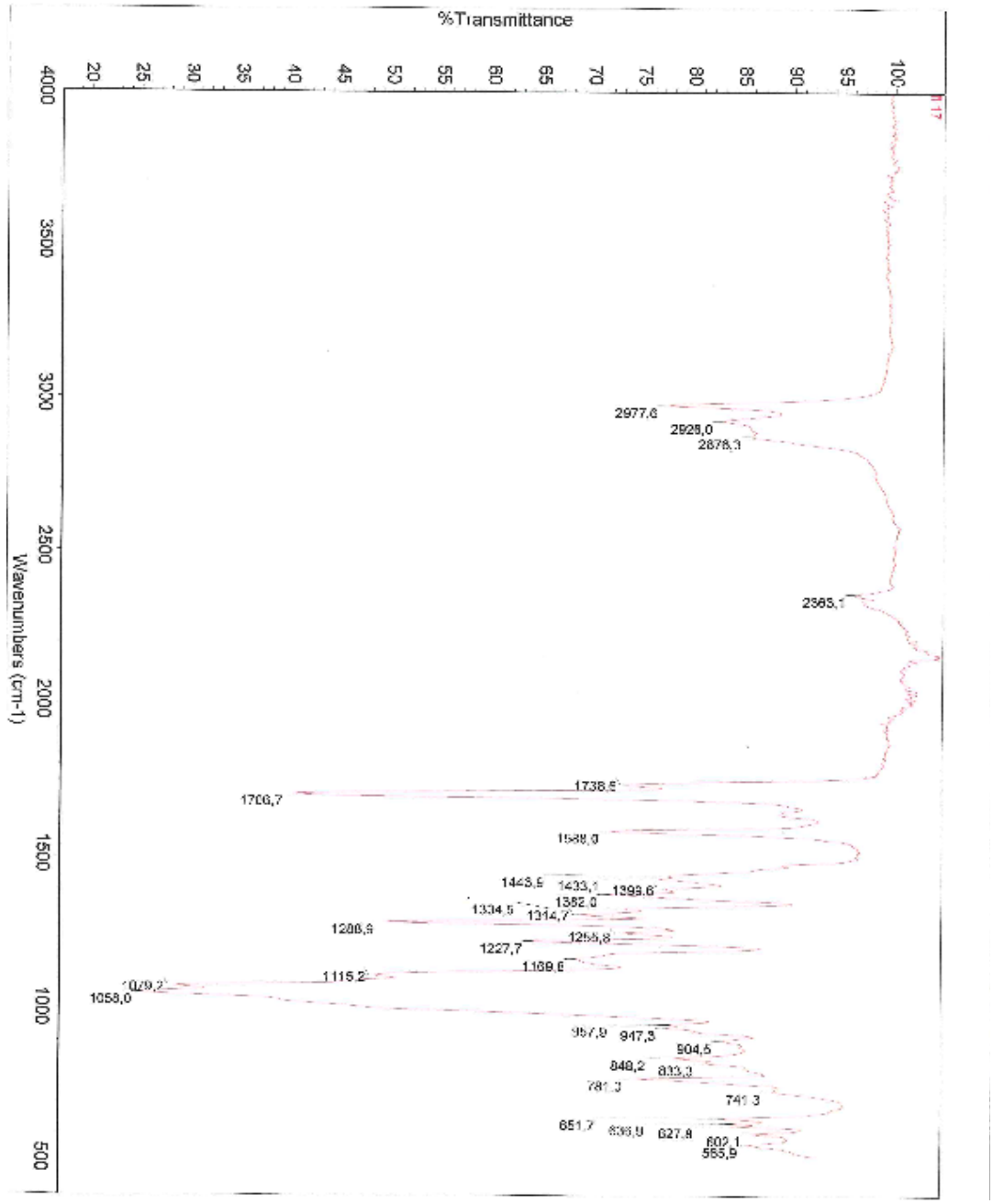
^{13}C



The carbon spectrum shows the presence of 13 peaks for 16 carbons, it means that three couple of carbon are equivalent each other. At high fields we can find ethylic carbon of the ethoxy groups, methyl groups linked to furan and the CH_2 group between the furan and the ketone moiety. At lower fields than chloroform we can find all the quaternary carbon and the CH group between the ketone moiety and the two ethoxy groups.

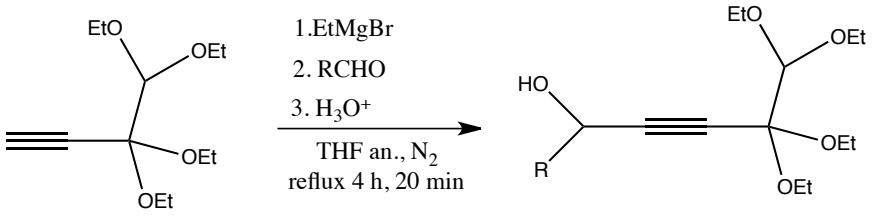


2.2.2. Assignment of IR spectrum of 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate **34**



Relevant signals for the identify the compound are: 1738.6, 1706.7, 1588.0. C=O ketone stretching is at 1706.7, C=O ester stretching is at 1738.6 and C=C furan stretching are at 1588.0.

2.3. Synthesis of other substituted furan with a longer aliphatic chain as R group from TEB

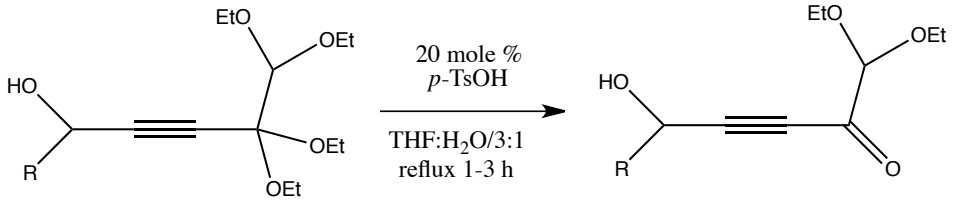


1

$R = C_6H_{13}, C_7H_{15}$

79%, R = C_6H_{13}
61%, R = C_7H_{15}

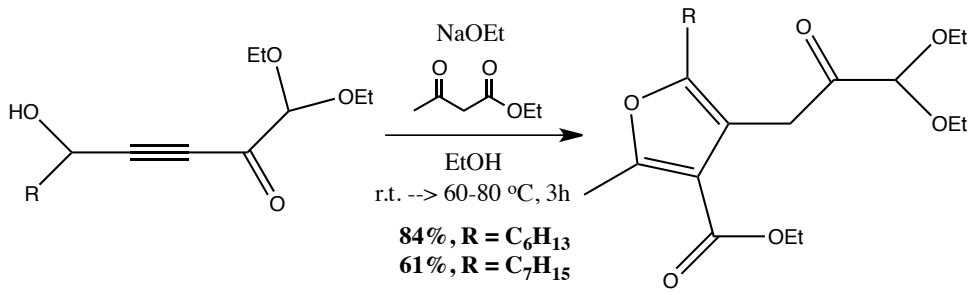
35, R = C_6H_{13}
36, R = C_7H_{15}



35, R = C_6H_{13}
36, R = C_7H_{15}

91%, R = C_6H_{13}
95%, R = C_7H_{15}

37, R = C_6H_{13}
38, R = C_7H_{15}



37, R = C_6H_{13}
38, R = C_7H_{15}

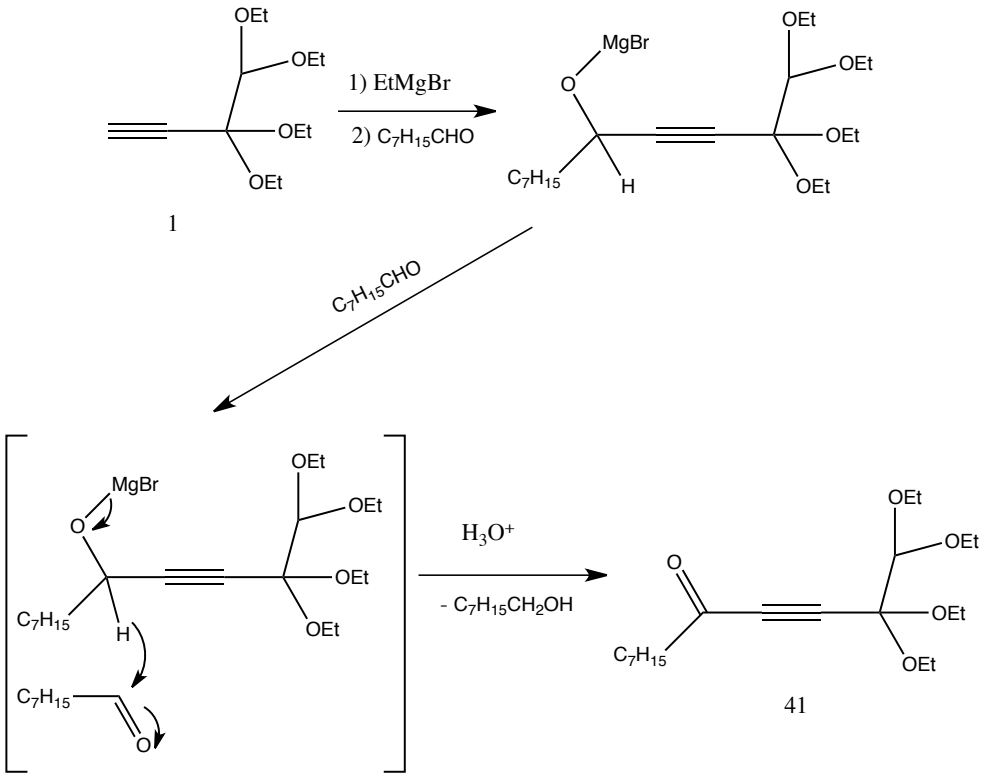
84%, R = C_6H_{13}
61%, R = C_7H_{15}

39, R = C_6H_{13}
40, R = C_7H_{15}

Reactions described in Chapter 2.2. were carried out again to obtain different furan derivatives.

Reactivity and yields were approximately the same, but for the reactions with R = C_7H_{15} yields were lower and for the reactions with R = C_6H_{13} were higher than the reactions described in Chapter 2.2., however more than 60 %. Also the spectra are approximately the same, the only differences are due to the presence of longer aliphatic chain, so we can see more peaks and a greater number of hydrogen atoms or carbon atoms at high fields. In particular, in the ^1H spectra, different multiplicities are observed.

However, a side reaction was observed when octanal reacted with magnesium bromide acetylide of TEB. The yield of propargylic alcohol **36** was lower than that of the other alcohols due to the formation of 4,4,5,5,-tetraethoxy-1-heptylpent-2-yn-1-one **41** as a by-product caused by Cannizzaro-type reaction. This reaction is believed to occur when alkoxymagnesium bromide generated in the reaction mixture functions as a hydride source and attacks unreacted aldehyde as shown in Scheme 22.[26]



Scheme 22

The analysis of the ^{1}H and ^{13}C spectra of the product and observation of the TLC plates confirm also the presence of octanol with the product.

4,4,5,5,-tetraethoxy-1-heptylpent-2-yn-1-ol with octanol and 4,4,5,5,-tetraethoxy-1-heptylpent-2-yn-1-one were isolated in 61% and 8% yields, respectively. The yields of the ketone and octanol are supposed to be equal.

In the figure 7, TLC plates of the crude product and of the mixture from the flash column (when product was eluting) are shown. As we can see, in the crude product, there are:

- the spot of the by-product, the less polar ketone;
- the spot of unreacted TEB;
- a large spot that actually contains two smaller spot, the product and octanol, the most polar compound in the mixture.

The desired product **36** eluted from the flash column together with octanol.

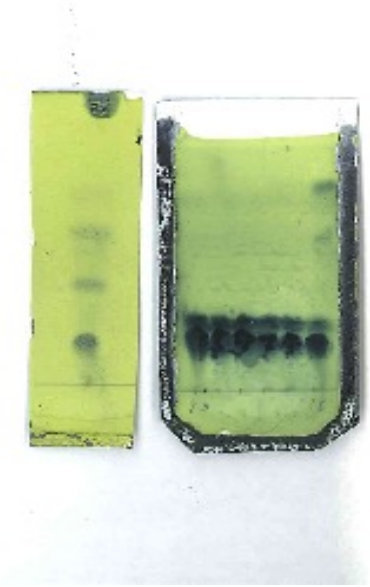


Figure 7

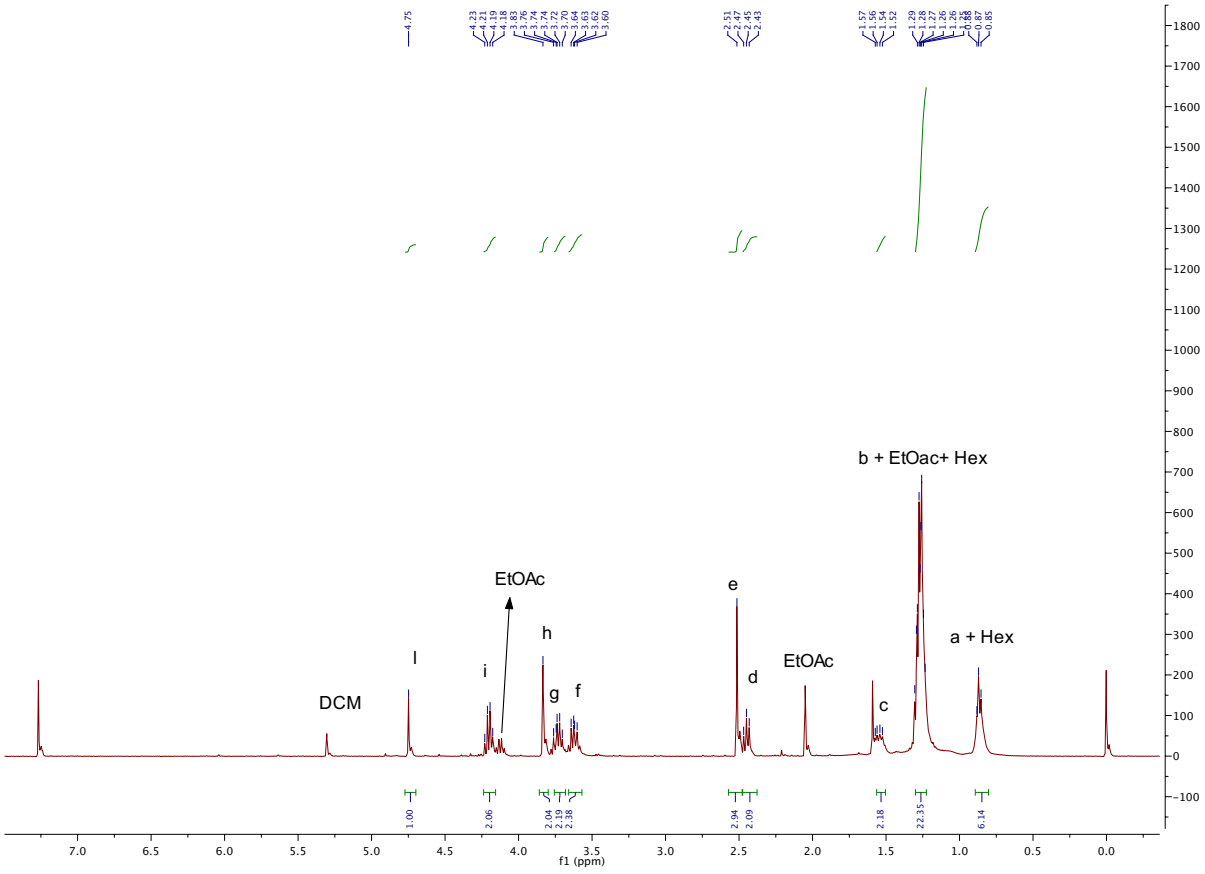
2.3.1. Characterization of the furan derivatives 39 and 40

Assignment of NMR spectra might be verified with NOE, COSY and NOESY experiments

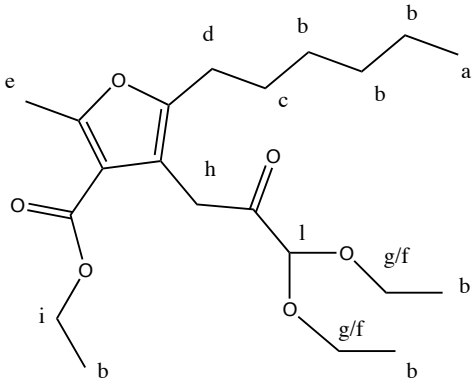
The assignment of NMR spectra of the synthesized furan derivatives **39** and **40** are now exposed. The other spectra, of the compounds shown in this chapter 2.3., are located only in appendix, due them similarity with the previous spectra explained in chap. 2.2.1.

4-(3,3-diethoxy-2-oxopropyl)-2-methyl-5hexylfuran-3-carboxylate **39**

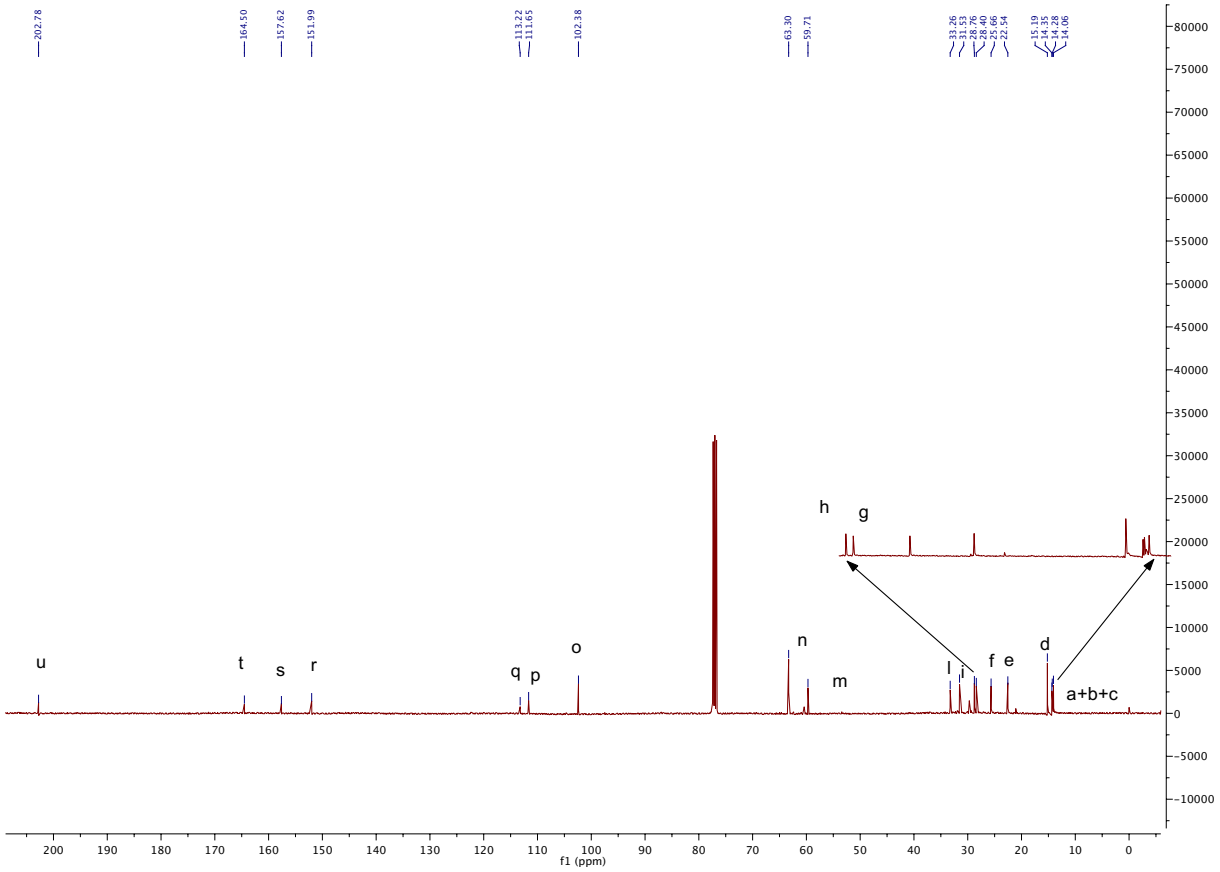
^{1}H



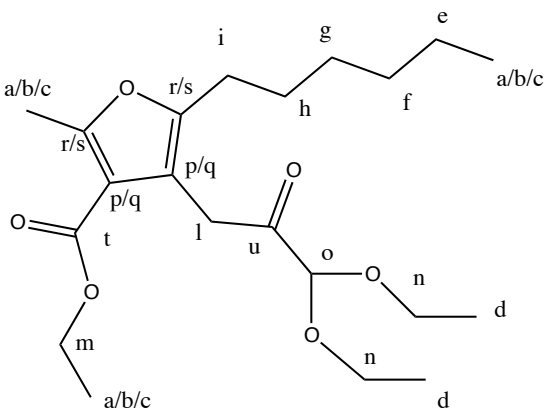
Sample is pure, there are only some solvents and water. The same considerations made for the furan derivative with R = Me are valid.



^{13}C

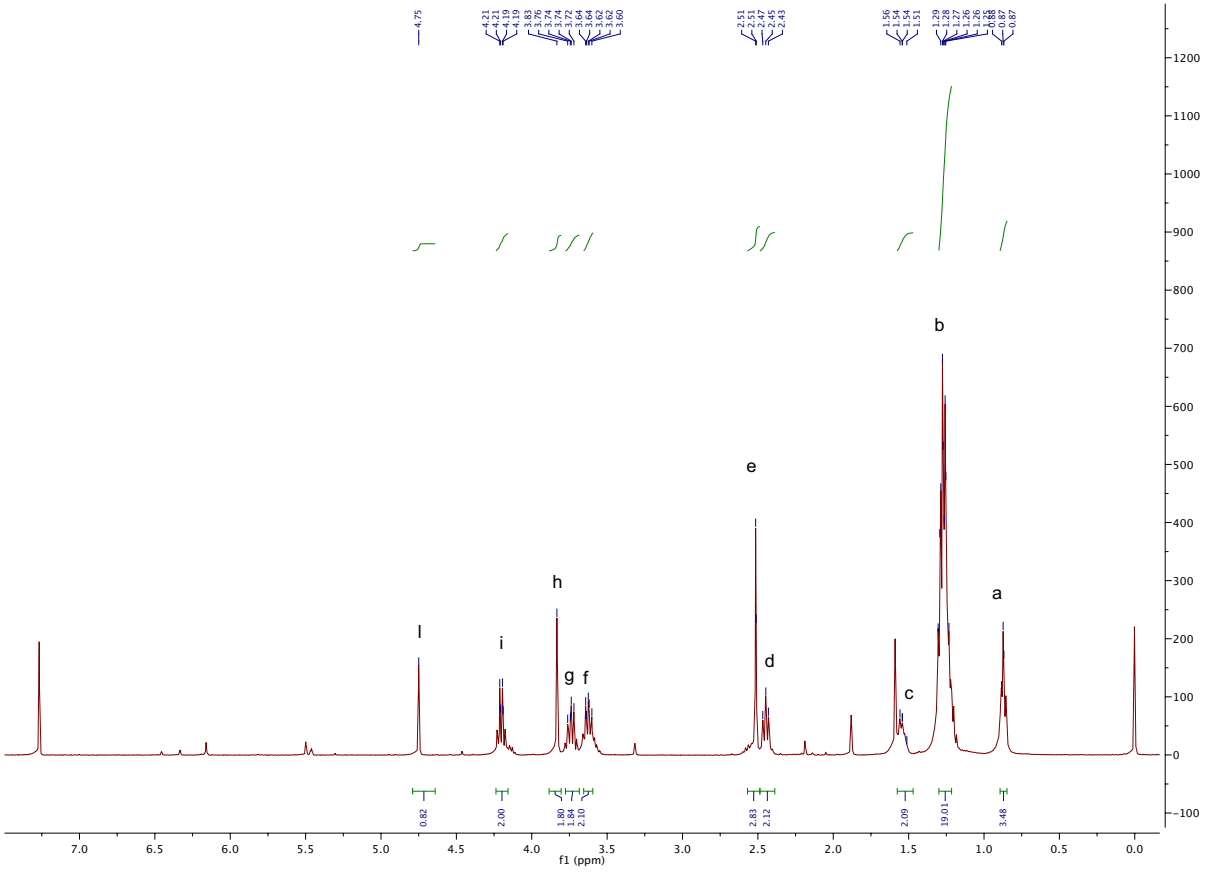


The carbon spectrum shows the presence of 19 peaks for 21 carbons: it means that two couple of carbon are equivalent to each other. Chemical shift of the carbon are approximately the same of 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate, the only difference is the presence of more carbon of the aliphatic chain at high fields.

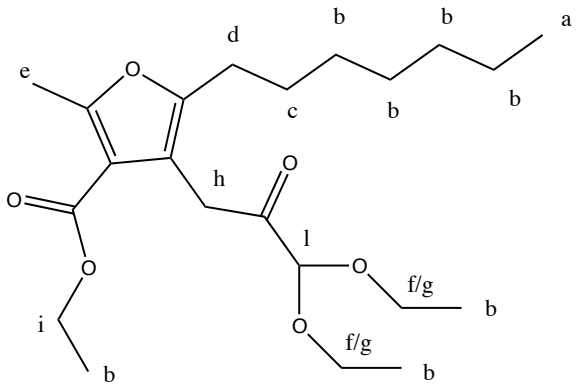


4-(3,3-diethoxy-2-oxopropyl)-2-methyl-5heptylfuran-3-carboxylate **40**

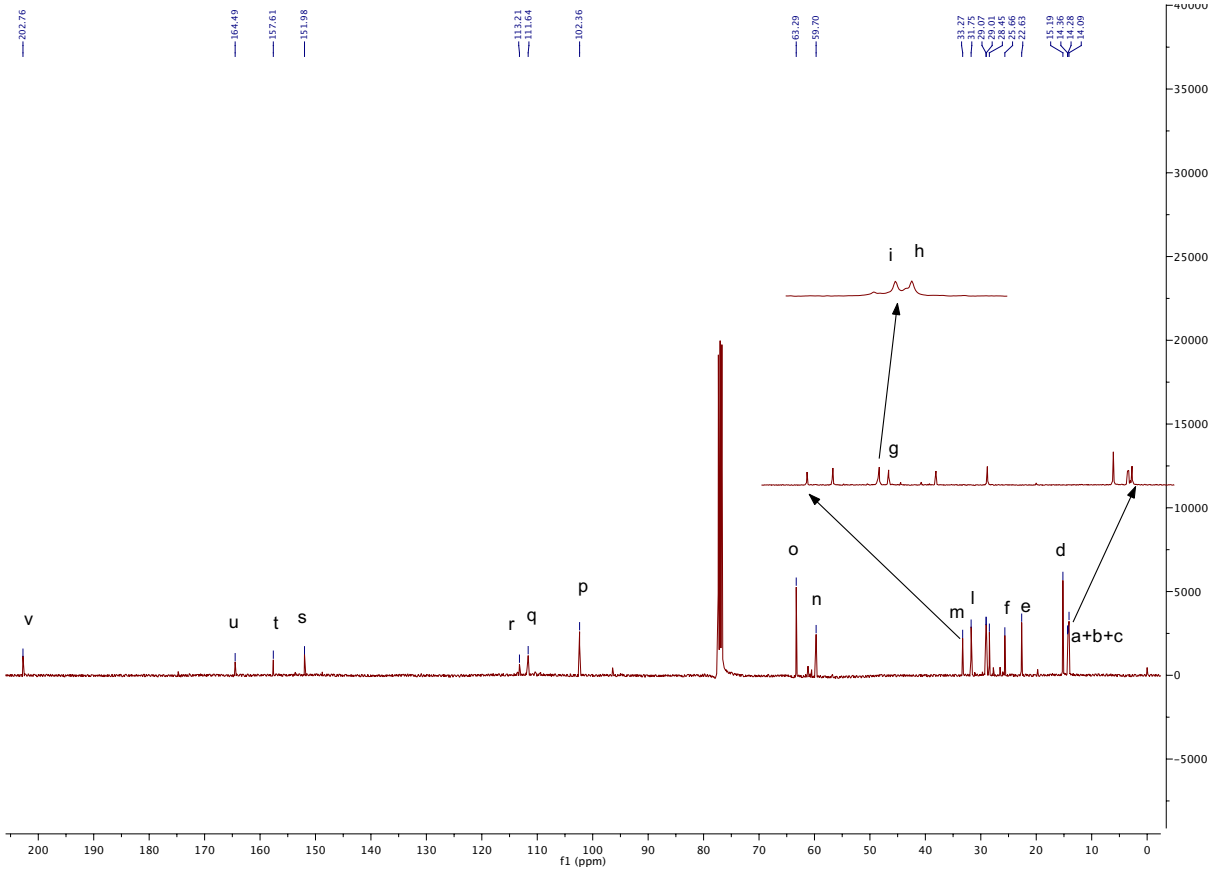
^{1}H



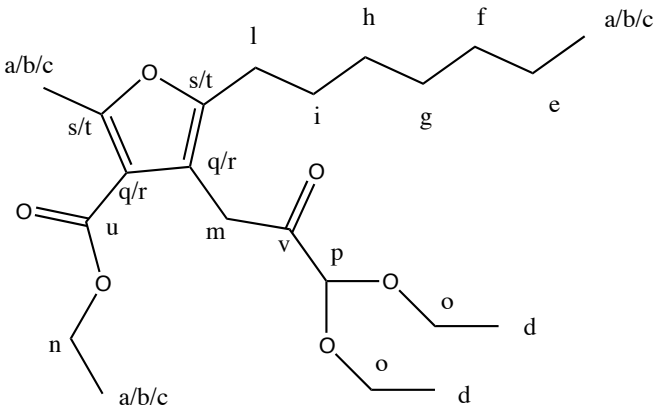
The sample is quite clean even if less clean than the previous furan derivative. There are not solvent residues, only the water present in chloroform.



^{13}C



The spectrum is very similar to 4-(3,3-diethoxy-2-oxopropyl)-2-methyl-5hexylfuran-3-carboxylate, here we can see the presence of 20 peaks for 22 carbons, it means that two couple of carbon are equivalent each other.



2.4. Further works

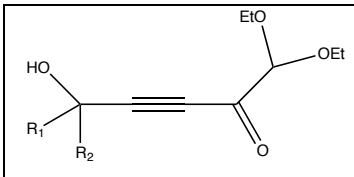
2.3.1. Reaction scale-up

The reactions after TEB have only been run on a 1 mmol, 10 mmol and 20 mmol scale for the synthesis of propargylic alcohol, 10 mmol scale for the synthesis of γ-hydroxy-α,β-unsaturated acetylenic ketone and 1 mmol scale for the synthesis of the substituted furan. Reaction scale-up should be performed both to ascertain whether the outcomes would be similar on a larger scale.

Reaction scale-up should be performed also for the chance to run further reactions on the final compound and evaluate its possible conversion on modified carbohydrate analogues or study its applications in organic synthesis.

2.3.2. Investigation of the reaction with ethyl acetoacetate on different γ-hydroxy-α,β-unsaturated acetylenic ketones

Addition of ethyl acetoacetate was investigated on 1,1-Diethoxy-5-hydroxy-6-methylhept-3-yn-2-one[19], 1,1-Diethoxy-5-hydroxyhex-3-yn-2-one, 1,1-Diethoxy-5-hydroxyundec-3-yn-2-one and 1,1-Diethoxy-5-hydroxydodec-3-yn-2-one. The reaction should be carried out on a larger number of γ-hydroxy-α,β-unsaturated acetylenic ketones with different R groups and check if they will react with the same reactivity and estimate the different yields.

	R_1	R_2
1	H	H
2	H	Ethyl
3	H	Propyl
4	H	Butyl
5...	Me, Et, Pr, Bu	Me, Et, Pr, Bu

2.3.3. Investigation on the addition of more nucleophilic compounds to γ-hydroxy-α,β-unsaturated acetylenic ketones

As already written in the introduction, TEB is a very good starting material for a lot of synthesis.

This work entered in detail about the availability to synthesize γ-hydroxy-α,β-unsaturated acetylenic ketones from TEB. Several routes could be taken from these compounds to synthesize carbohydrate modified analogues and other chemical compounds. So, one future employment could be to try nucleophilic addition reactions with more carbon and heteronucleophilic reagents.

2.3.4. Optimization of the 3rd step of TEB synthesis

It has been designed a 6-variables model for the optimization of this step. All the variables will be simultaneously varied randomly, because we want to follow the method "one variable at a time" that can be used only if the variables are indipendent of each other. It has been thought to vary reaction temperature, equivalents of bromoform, sodium hydroxide and catalyst, reaction time and addition time of sodium hydroxide.

In the end of this work probably the best reaction conditions will be found, reaction mechanism will be clearer and a lower amount of by-product will be observed.

It's now shown in the following table the ideation of the project about the optimization of the 3rd step.

A similar project could be done for the 4th step.

	X_1	X_2	X_3	X_4	X_5	X_6
Exp. n.	T, ^{o}C	eq. $CHBr_r$	eq. NaOH	eq. cat.	t, h	$t_{add\ NaOH}$, min
1	20	6	8	0,1	12	5
2	0	6	12	0,1	12	5
3	20	12	8	0,2	12	5
4	0	12	8	0,2	12	5
5	20	6	12	0,2	36	5
6	0	6	8	0,2	36	5
7	20	12	8	0,1	36	5
8	0	12	12	0,1	36	5
9	20	6	8	0,2	12	15
10	0	6	12	0,2	12	15
11	20	12	12	0,1	12	15
12	0	12	8	0,1	12	15
13	20	6	12	0,1	36	15
14	0	6	8	0,1	36	15
15	20	12	8	0,2	36	15
16	0	12	12	0,2	36	15

Table 3: experiments that will be carried out for the optimization of the 3rd step of TEB synthesis

3. EXPERIMENTAL

Most solvents and reagents were of puriss grade, and used as received from Sigma-Aldrich, Norway. Dichloromethane was of technical grade. Dry THF was preparated by distillation from sodium/benzophenone under nitrogen atmosfere. Anhydrous reactions were carried out under inert atmosphere, done using nitrogen gas passed through a container with sodium hydroxide pellets.

Flash chromatography was carried out with Silica gel as stationary phase and mixtures of hexanes/ethyl acetate as the mobile phase. TLC analyses were performed with silica gel 60 with fluorescent indicator UV254 and visualised through an ethanolic acidic phosphomolymdic acid solution.

IR spectra were obtained on a Nicolet 380 FT-IR spectrometer. The samples were analysed as a liquid film between sodium chloride plates. Absorptions are given in wave numbers (cm^{-1}), and intensities are given as (s) for strong, (m) for medium, (w) for weak.

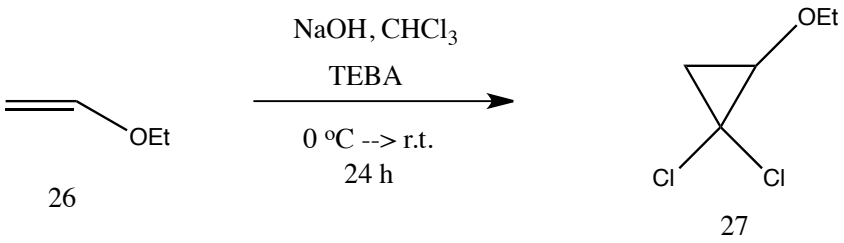
^{1}H-NMR spectra were recorded at ambient temperatures on a Bruker Spectrospin DMX 400 at 400 MHz. Chemical shifts are reported downfield from the reference standard (TMS), and the coupling constants are given in Hertz. Multiplicity is given as (s) for singlet, (d) for doublet, (t) for triplet, (dd) for doublet of doublets, and (m) for multiplet. ^{13}C-NMR spectra were recorded at ambient temperatures on the same spectrometer at 100 MHz with the central peak of the $CDCl_3$ triplet as the internal reference.

TEB was synthesized twice.

The first time was synthesized in small scale, from 0.10 mol of ethyl vinyl ether and the second time in big scale, from 0.35 mol of ethyl vinyl ether.

Here are shown big scale data, but the yields of the various steps are similar.

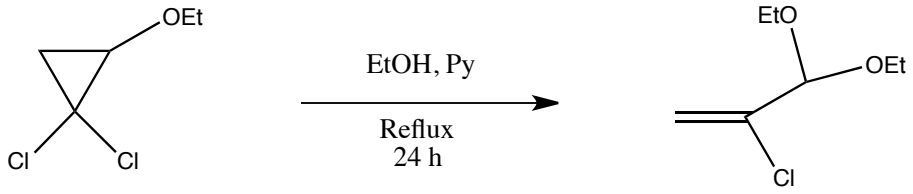
Synthesis of 1,1-dichloro-2-ethoxycyclopropane **27**



26 27

A 500 mL three-necked, round-bottom flask equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with ethyl vinyl ether (25.20 g, 0.35 mol), chloroform (167.30 g, 1.40 mol) and TEBA (0.18 g) and placed in an ice bath. After the reaction flask had been cooled for 10 min, the mixture was stirred vigorously and a 50% solution of NaOH (41.60 g, 1.50 mol, in 42.00 g H_2O) was added dropwise (45 min) to the reaction mixture. The reaction mixture was left stirring for 24 h at bath temperature (0 ^{o}C to r.t.) and was subsequently quenched by adding 3.00 M HCl. The solution was transferred to a separatory funnel, and the reaction flask was washed with CH_2Cl_2 and H_2O, which were also transferred to the funnel. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The combined extracts were dried (MgSO4), filtered and concentrated on a rotary evaporator to give 52.54 g (97% yield) of the title compound as a clear, colourless liquid, which was essentially pure according to ^{1}H-NMR spectrum. The crude product can however be distilled under reduced pressure to give the purified title compound at b.p. 53.5-53.6 ^{o}C/28 mmHg (although this might reduce the yield). The ^{1}H-NMR spectrum was in agreement of those published in the literature.[25_33]

Synthesis of 2-chloro-3,3-diethoxyprop-1-ene **28**

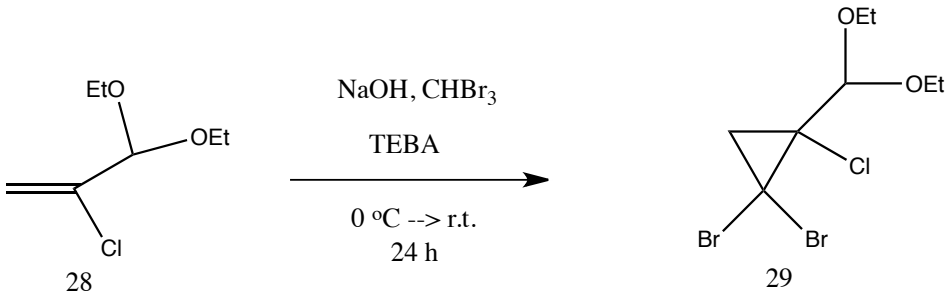


27 28

A 500 mL, single-necked, round-bottomed flask, equipped with a magnetic stirrer and a condenser, was charged with absolute ethanol (250 mL), pyridine (34.69 g, 0.44 mol) and **27** (52.54 g, 0.34 mol). The mixture was stirred at reflux for 48 h. The reaction mixture was concentrated under reduced pressure on a rotary evaporator, after it has been cooled. The residue was transferred to a separatory funnel, and the reaction flask washed with H_2O and CH_2Cl_2, which were also added to the separatory funnel. The organic layer was separated from the aqueous layer, and the aqueous phase extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with 0.70 M aqueous solution (3 x 70 mL) of copper sulphate ($CuSO_4$), then dried with magnesium sulphate ($MgSO_4$), and filtered through a plug of aluminium oxide. The resulting mixture was concentrated under reduced pressure on a rotary evaporator to give 39.98 g of the title compound **28** (71% yield) as a clear yellow liquid, which was essentially pure according to ^{1}H-NMR spectrum, that was in agreement of those published in the literature. [25_33]

(The product can however be obtained even purer by distillation under reduced pressure, b.p. 70-78 ^oC/25 mmHg).

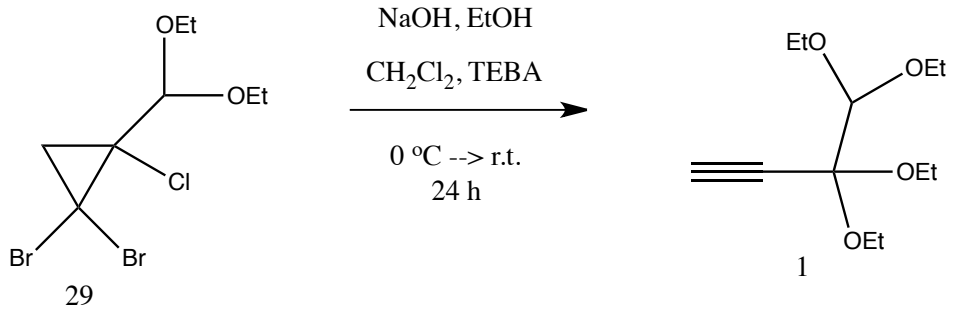
Synthesis of 1,1-dibromo-2-chloro-2-diethoxymethylcyclopropane **29**



A 1 L three-necked, round-bottom flask, equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with **28** (39.98 g, 0.24 mol), bromoform (364.00 g, 1.44 mol) and TEBA (0.6 g). After the reaction flask has been cooled for 10 min, the mixture was stirred vigorously and a 50% solution of NaOH (76.80 g, 1.92 mol, in 77.00 g H_2O) was added dropwise (45 min) to the reaction mixture. The reaction mixture was left stirring for 24 h at bath temperature (0 ^{o}C to r.t.) and then water was added. During the reaction, the mixture gradually changed colour from yellow to orange to dark brown. The reaction mixture was then transferred to a separatory funnel and the organic phases were separated from the water phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried overnight with magnesium sulphate (MgSO4), filtered, and concentrated under reduced pressure on a rotary evaporator.

The crude product was distilled to recycle the bromoform, at ca. b.p. 30 ^{o}C/ 15 mmHg (lit. b.p. 149.5 ^{o}C, 760 mmHg). Then, upon more heating, tetrabromomethane, a by-product of the reaction, came at ca. b.p. 75 ^{o}C/ 15 mmHg; the residue 50.99 g of title compound **29**, dark liquid (62% yield) were essentially pure according to ^{1}H-NMR spectrum. (The product can however be obtained even purer by distillation under reduced pressure, b.p. 80-82 ^{o}C/0.15 mmHg). The ^{1}H-NMR spectrum was in agreement of those published in the literature. [25]

Synthesis of 3,3,4,4-tetraethoxybut-1-yne TEB **1**

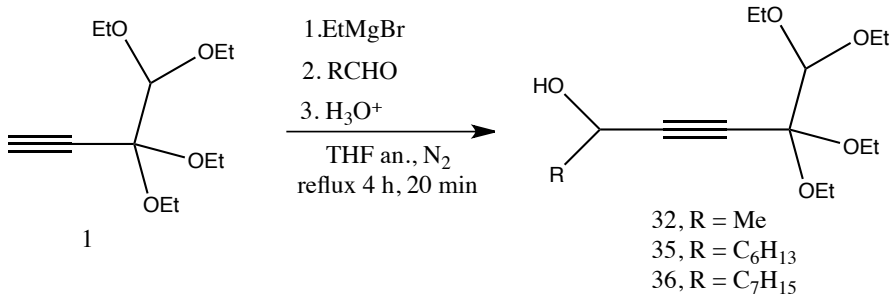


29 1

A 1 L three-necked, round-bottomed flask, equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with **29** (50.99 g, 0.15 mol), ethanol (41.40 g, 0.90 mol), TEBA (0.30 g) and CH_2Cl_2 (200 mL). After the reaction flask has been cooled for 10 min, the mixture was stirred vigorously and a 50% solution of NaOH (24.00 g, 0.60 mol, in 24.50 g H_2O) was added dropwise (45 min) to the reaction mixture. The reaction mixture was left stirring for 24 h at bath temperature (0 ^{o}C to r.t.) and then water was added and the reaction mixture was transferred to a separatory funnel. The reaction flask was washed with CH_2Cl_2 and H_2O. H_2O was also added to the funnel, the phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried overnight ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator. Distillation of the crude residue (dark brown colour) gave the title compound **1** (12.69 g, 37% yield) as a clear, slightly yellow, liquid, at b.p. 53-58 ^{o}C/0.2 mmHg. The ^{1}H-NMR spectrum was in agreement of those published in the literature. [25]

Synthesis of

- 5,5,6,6-Tetraethoxyhex-3-yn-2-ol **32**
- 1,1,2,2-Tetraethoxyundec-3-yn-5-ol **35**
- 1,1,2,2-Tetraethoxydodec-3-yn-5-ol **36**



General procedure:

An ether solution of ethylmagnesium bromide 3 M (1.2 eq.) was added dropwise to a stirred solution of 3,3,4,4-tetraethoxybut-1-yne (TEB) (1.0 eq.) in anhydrous THF. When the addition was complete, the reaction mixture was stirred at reflux for 80 min and cooled to r.t. before aldehyde (1.2 eq.) was added dropwise. The resulting mixture was stirred at reflux for 3 h before it was cooled to r.t. and quenched by adding a saturated aqueous solution of NH_4Cl (approximately 0.5 mL/mmol TEB). The mixture was extracted with dichloromethane (3 x 10 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator. Finally, the product was isolated by flash chromatography.

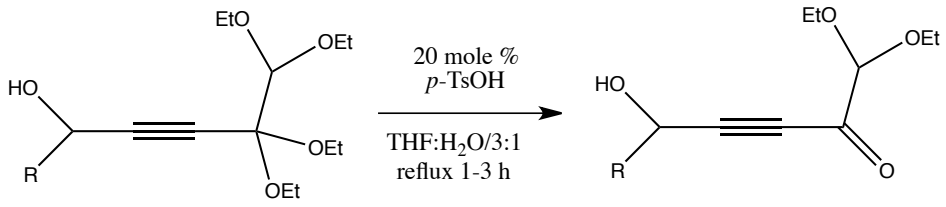
Compound **32** was synthesized in small scale, with 0.23 g of **1** (1.0 mmol), 0.40 mL of a solution 3.00 M of EtMgBr in Et_2O (1.2 mmol), 0.05 g of acetaldehyde (1.2 mmol) and 8 mL of anhydrous THF. The product was isolated by flash chromatography (hexanes-ethyl acetate = 70:30) to obtain 0.07 g (26% yield). Compound **5** was then synthesized in bigger scale, with 4.60 g of **4** (20.0 mmol), 8 mL of a solution 3.00 M of EtMgBr in Et_2O (2.4 mmol), 1.06 g of acetaldehyde (2.4 mmol) and 150 mL of anhydrous THF. The product **32** was isolated by flash chromatography (hexanes-ethyl acetate = 70:30), to obtain 4.28 g (78% yield) of it as a clear, yellow liquid. The ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[16–19]

Compound **35** was synthesized with 2.30 g of **4** (10.0 mmol), 4.00 mL of a solution 3.00 M of EtMgBr in Et_2O (10.2 mmol), 1.37 g of heptaldehyde (10.2 mmol) and 75 mL of anhydrous THF. The product was isolated by flash chromatography (hexanes-ethyl acetate = 80:20) to obtain 2.72 g (79% yield) of it as a clear, yellow liquid. The ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[16_19]

Compound **36** was synthesized with 2.30 g of **4** (10.0 mmol), 4.00 mL of a solution 3.00 M of EtMgBr in Et_2O (10.2 mmol), 1.54 g of octylaldehyde (10.2 mmol) and 75 mL of anhydrous THF. The product was isolated by flash chromatography (hexanes-ethyl acetate = 80:20) to obtain 2.19 g (61% yield) of it as as a clear, yellow liquid.

Synthesis of

- 1,1-Diethoxy-5-hydroxyhex-3-yn-2-one **33**
- 1,1-Diethoxy-5-hydroxyundec-3-yn-2-one **37**
- 1,1-Diethoxy-5-hydroxydodec-3-yn-2-one **38**



32, R = Me
35, R = C_6H_{13}
36, R = C_7H_{15}

33, R = Me
37, R = C_6H_{13}
38, R = C_7H_{15}

General procedure:

The propargylic alcohols were dissolved in 3:1 mixture of THF and H_2O. *p*-Toluensulfonic acid monohydrate (20 mole%) was added and the mixture was refluxed for 1-3 h, until all the starting material was consumed (followed by TLC examination). The mixture was then concentrated under reduced pressure on a rotary evaporator and, after, a saturated solution of NaCl and CH_2Cl_2 were added to the residue. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The extracts were washed with a saturated

aqueous solution of $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator to give a crude product that was pure enough for further reactions.

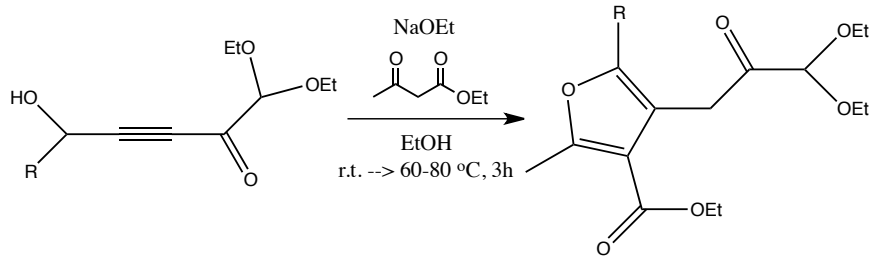
Compound **33** was synthesized with 1.10 g of **32** (4.0 mmol), in a 40 mL 3:1 mixture of THF and H_2O and 0.16 g of *p*-Toluensulfonic acid monohydrate (0.8 mmol). Then, after concentration of the mixture on a rotary evaporator, a saturated solution of NaCl (12 mL), CH_2Cl_2 (12 mL) and then 50 mL of $NaHCO_3$ were added. Work-up gave 0.66 g of **33** as a clear, yellow liquid (82% yield). The ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[16–19]

Compound **37** was synthesized with 1.25 g of **35** (3.63 mmol), in a 40 mL 3:1 mixture of THF and H_2O and 0.14 g of *p*-Toluensulfonic acid monohydrate (0.73 mmol). Then, after concentration of the mixture on a rotary evaporator, a saturated solution of NaCl (12 mL), CH_2Cl_2 (12 mL) and then 50 mL of $NaHCO_3$ were added. Work-up gave 0.90 g of **37** as a clear, yellow liquid (91% yield). The ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[16–19]

Compound **38** was synthesized with 1.25 g of **36** (3.49 mmol), in a 40 mL 3:1 mixture of THF and H_2O and 0.13 g of *p*-Toluensulfonic acid monohydrate (0.70 mmol). Then, after concentration of the mixture on a rotary evaporator, a saturated solution of NaCl (12 mL), CH_2Cl_2 (12 mL) and then 50 mL of $NaHCO_3$ were added. Work-up gave 0.94 g of **38** as a clear, yellow liquid (95% yield).

Synthesis of

- 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate **34**
- 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-hexyl-3-carboxylate **39**
- 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-octyl-3-carboxylate **40**



33, R = Me
37, R = C_6H_{13}
38, R = C_7H_{15}

34, R = Me
39, R = C_6H_{13}
40, R = C_7H_{15}

General procedure:

Ethyl acetoacetate (1.0 eq.) was added to a solution of sodium ethoxide (0.5 eq.) in ethanol (10 mL). The reaction mixture was stirred at room temperature for 30 minutes. Into this mixture, a solution the γ-hydroxy-α,β-unsaturated acetylenic ketones (1.0 eq.) in ethanol (5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 1 h and at 60-80 ^{o}C for additional 2 h before it was allowed to cool down to room temperature. Water and dichloromethane were added and the phases were separated. The aqueous phase was extracted with dichloromethane and the combined organic phases were dried ($MgSO_4$), filtered and concentrated on a rotary evaporator. The crude product was further purified by flash chromatography.

Compound **34** was synthesized with 0.13 g of ethyl acetoacetate (1.0 mmol), 0.03 g of sodium ethoxyde (0.5 mmol) in ethanol (10 mL) and 0.20 g (1.0 mmol) of **33** in ethanol (5 mL). Then 30 mL of water and 30 mL of dichloromethane were added to separate the phases. The crude product was further purified by flash chromatography, (hexanes-ethyl acetate, 80:20) which yielded **34** (0.23 g, 74%) as a colourless liquid.

IR (film): 2978(m), 2926(w), 2876(w), 2363(w), 1739(s), 1708(s), 1588(s), 1444(m), 1433(m), 1400(m), 1382(m), 1335(m), 1315(m), 1289(s), 1256(m), 1228(m), 1170(m), 1115(s), 1079(s), 1058(s), 958(w), 947(m), 905(w), 848(m), 833(w), 781(m), 741(w), 652(w), 637(w), 628(w), 602(w), 566(w) cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.75 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 2H), 3.75-3.69 (m, 2H), 3.68-3.58 (m, 2H), 2.51 (s, 3H), 2.14 (s, 3H), 1.30-1.24 (m, 9H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.8, 164.4, 157.6, 147.8, 113.3, 111.9, 102.2, 63.3, 59.8, 33.5, 15.2, 14.3, 11.2.

Compound **39** was synthesized with 0.13 g of ethyl acetoacetate (1.0 mmol), 0.03 g of sodium ethoxyde (0.5 mmol) in ethanol (10 mL) and 0.27 g (1.0 mmol) of **37** in ethanol (5 mL). Then 30 mL of water and 30 mL of dichloromethane were added to separate the phases. The crude product was further purified by flash chromatography, (hexanes-ethyl acetate, 80:20) which yielded **39** (0.32 g, 84%) as a colourless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.75 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 2H), 3.76-3.70 (m, 2H), 3.64-3.60 (m, 2H), 2.51 (s, 3H), 2.45 (t, *J* = 7.6 Hz, 2H) , 1.57-1.52 (m, 2H), 1.30-1.25 (m, 17H), 0.87 (t, *J* = 5.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.8, 164.5, 157.6, 152.0, 113.2, 111.7, 102.4, 63.3, 59.7, 33.3, 31.5, 28.8, 28.4, 25.7, 22.5, 15.2, 14.4, 14.3, 14.1.

Compound **40** was synthesized with 0.13 g of ethyl acetoacetate (1.0 mmol), 0.03 g of sodium ethoxyde (0.5 mmol) in ethanol (10 mL) and 0.28 g (1.0 mmol) of **38** in ethanol (5 mL). Then 30 mL of water and 30 mL of dichloromethane were added to separate the phases. The crude product was further purified by flash chromatography, (hexanes-ethyl acetate, 80:20) which yielded **40** (0.24 g, 61%) as a colourless liquid.

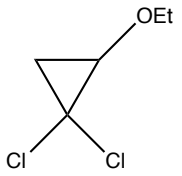
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.75 (s, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 2H), 3.76-3.72 (m, 2H), 3.64-3.60 (m, 2H), 2.51 (s, 3H), 2.45 (t, *J* = 7.5 Hz, 2H) , 1.56-1.51 (m, 2H), 1.29-1.25 (m, 19H), 0.87 (t, *J* = 5.3 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.8, 164.5, 157.6, 152.0, 113.2, 111.6, 102.4, 63.3, 59.7, 33.3, 31.8, 29.1, 29.0, 28.5, 25.7, 22.6, 15.2, 14.4, 14.3, 14.1.

CONCLUSION

At the end of this work three new furan derivatives have been synthesized from TEB: 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate; 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-hexyl-3-carboxylate and 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-octyl-3-carboxylate with satisfactory yields. The present syntheses represent a generalization of the protocol set up by M. Sengee[19] for the synthesis of furan derivatives from TEB. Other similar compounds are now under investigation.

APPENDIX



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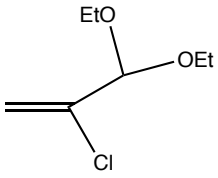

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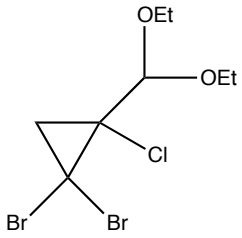

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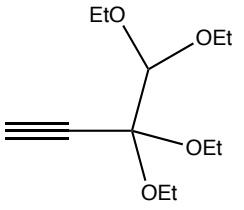

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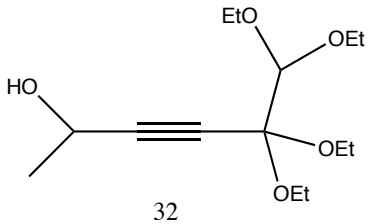

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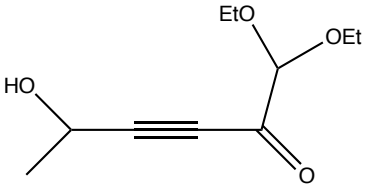

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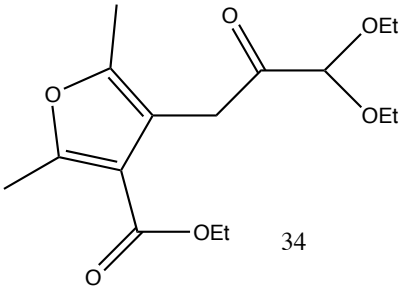

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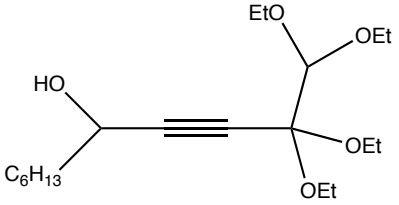

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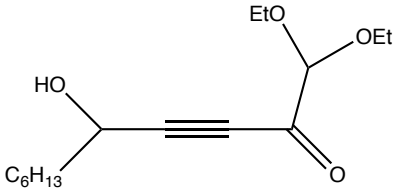

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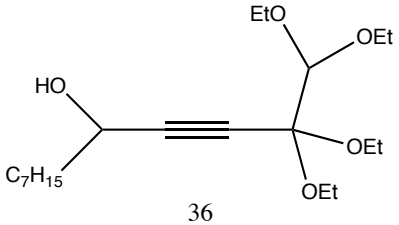

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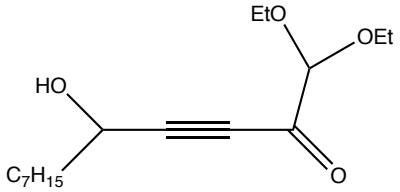

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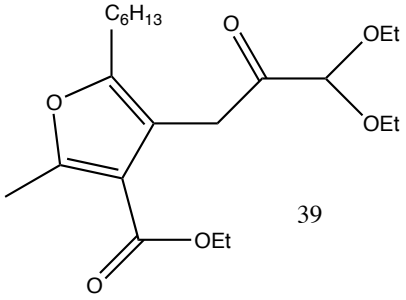

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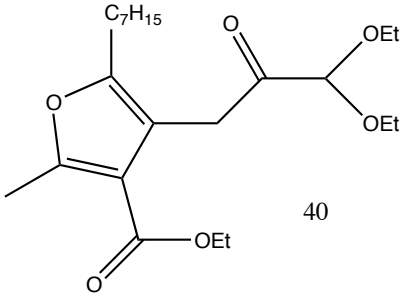
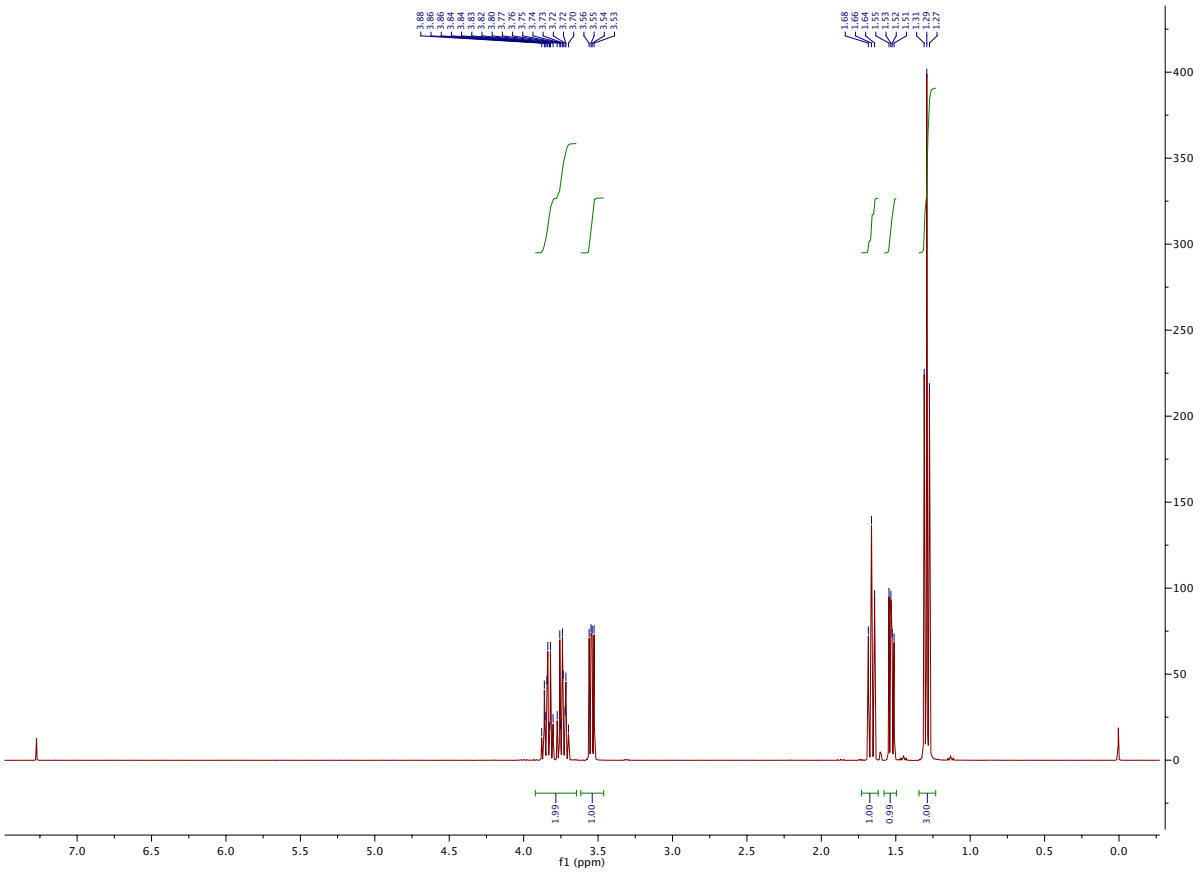
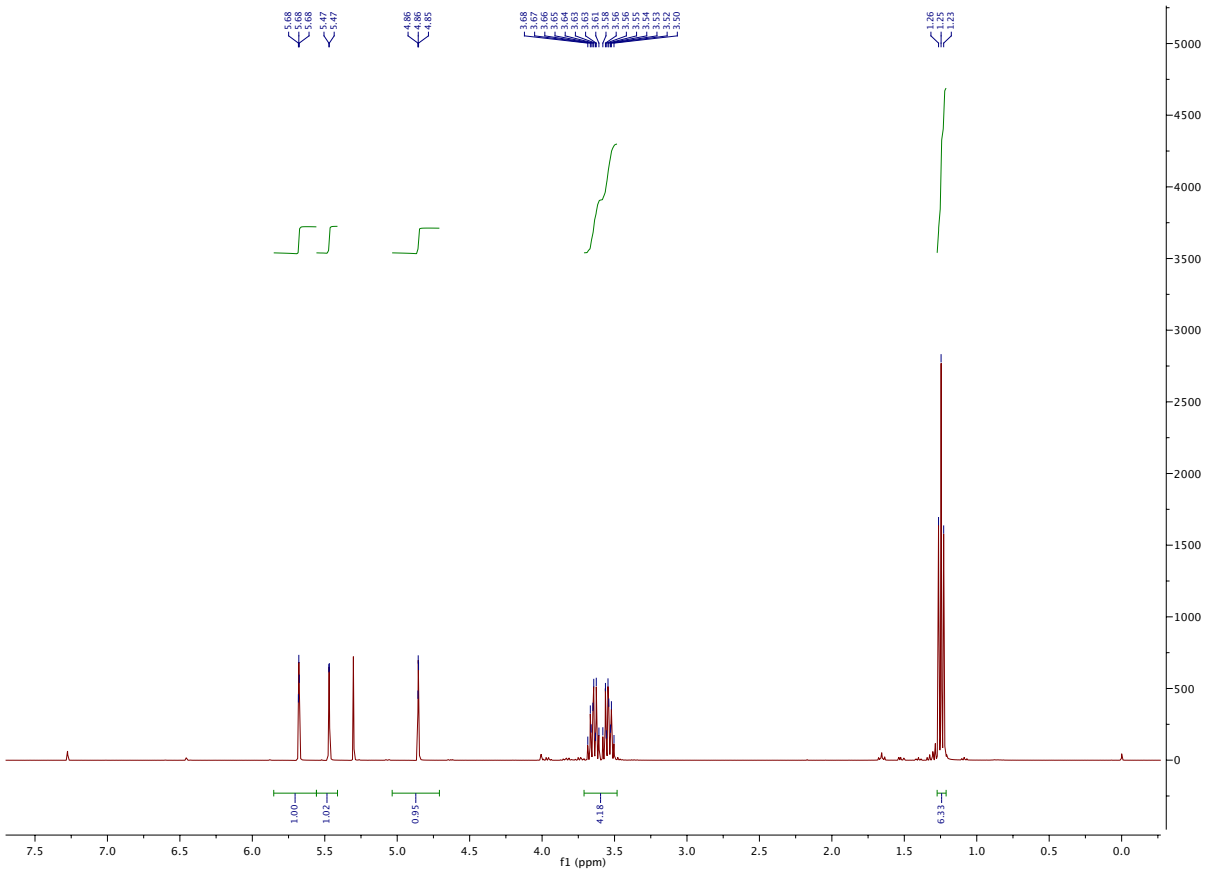


40

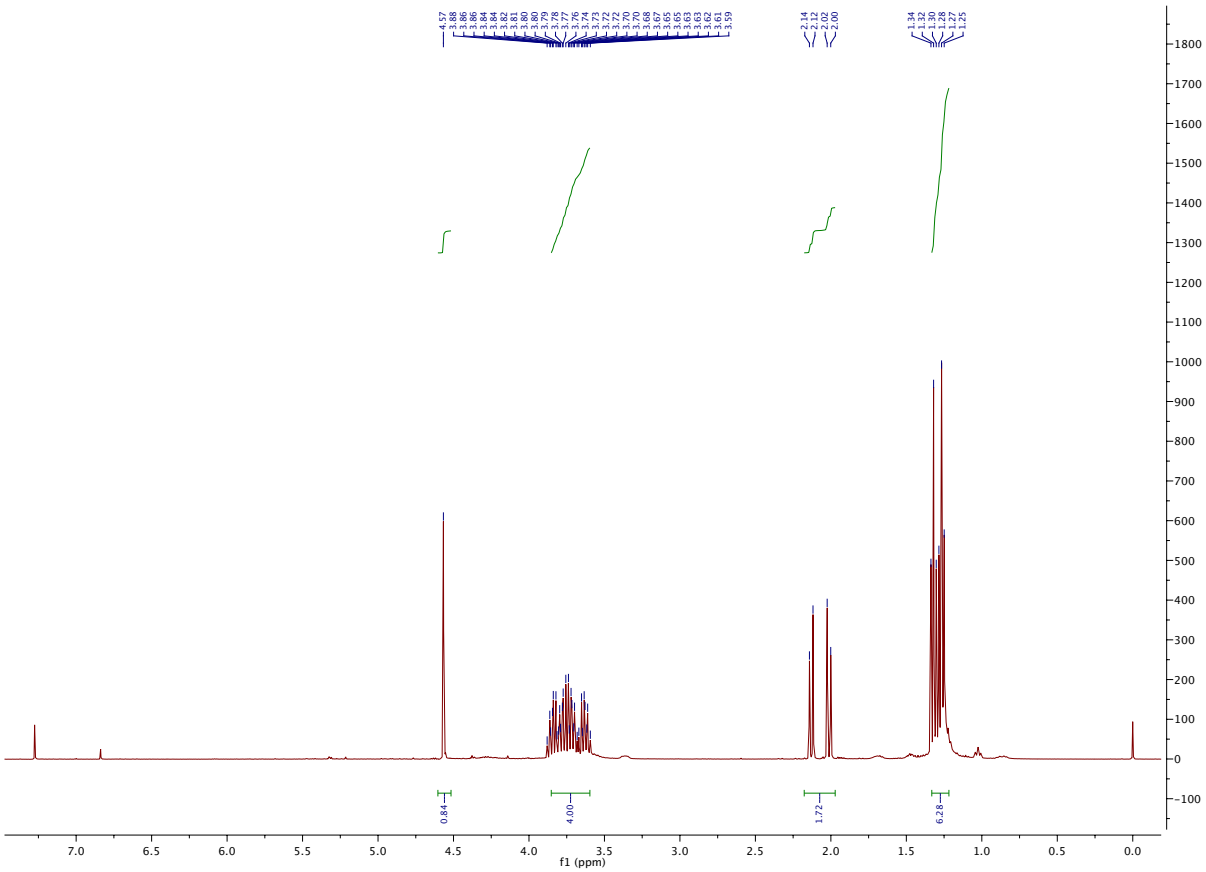
Scheme A.1: the compounds relevant for this project



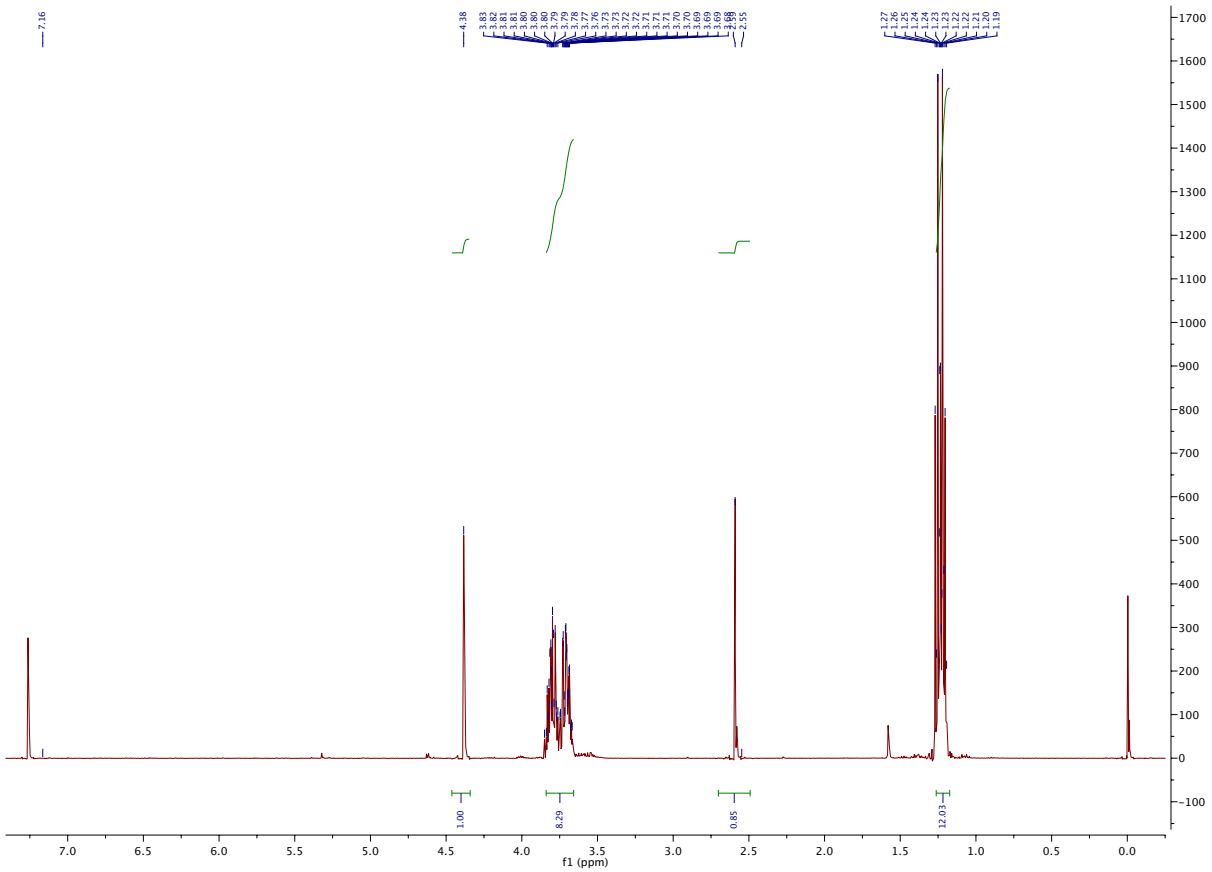
Scheme A.2: *^{1}H-NMR spectrum of* 1,1-Dichloro-2-ethoxycyclopropane **27**.



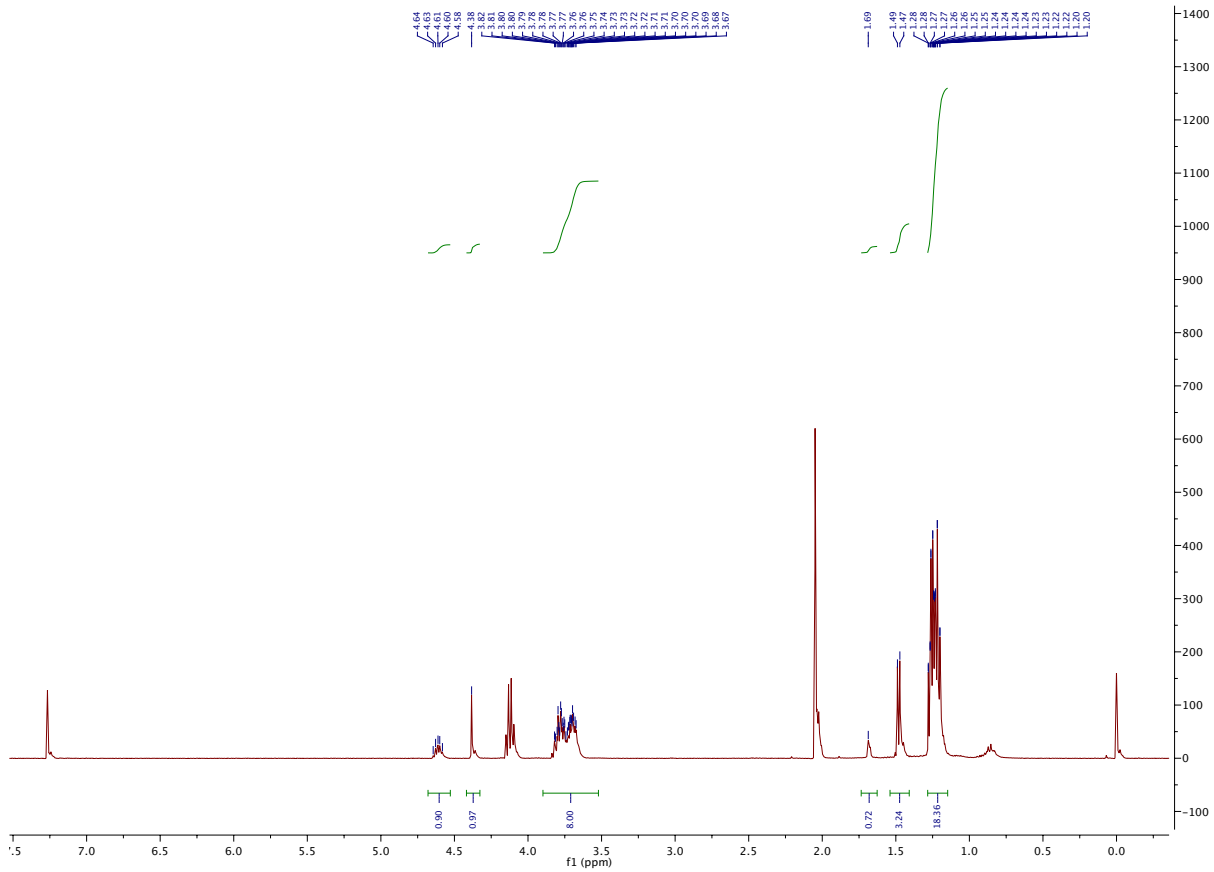
Scheme A.2: *^{1}H-NMR spectrum of* 2-Chloro-3,3-diethoxyprop-1-ene **28**.



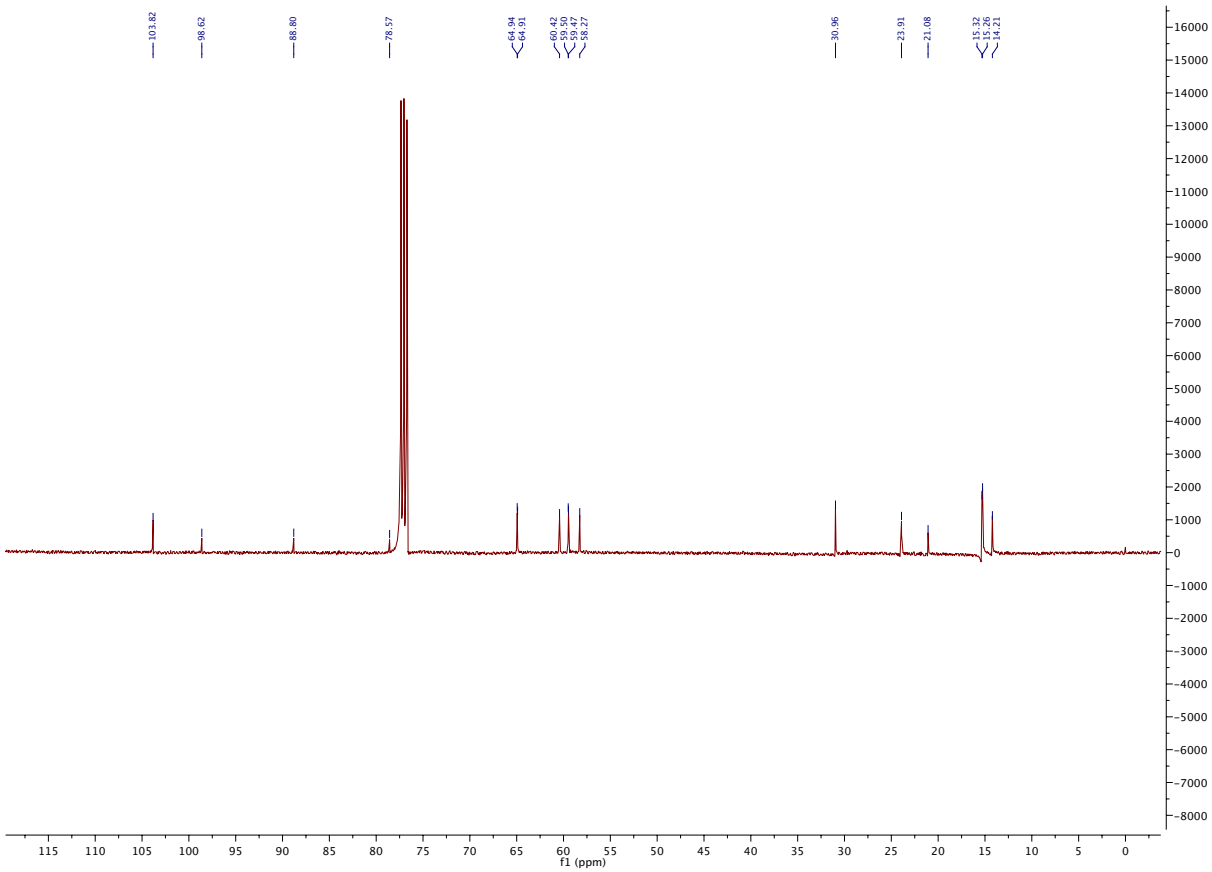
Scheme A.4: *^{1}H-NMR spectrum of* 1,1-Dibromo-2-chloro-2-diethoxymethylcyclopropane **29**.



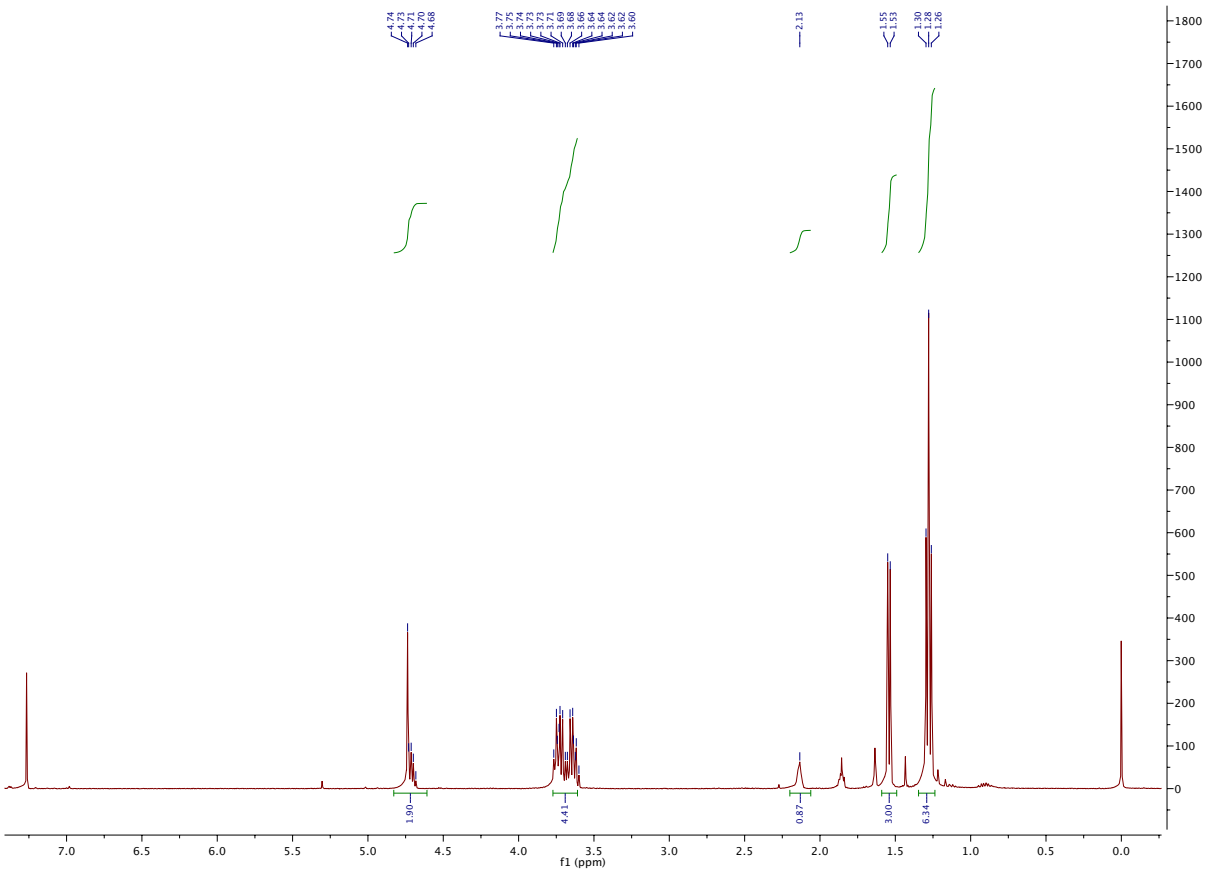
Scheme A.5: *^{1}H-NMR spectrum of* 3,3,4,4,-Tetraethoxybut-1-yne **1**.



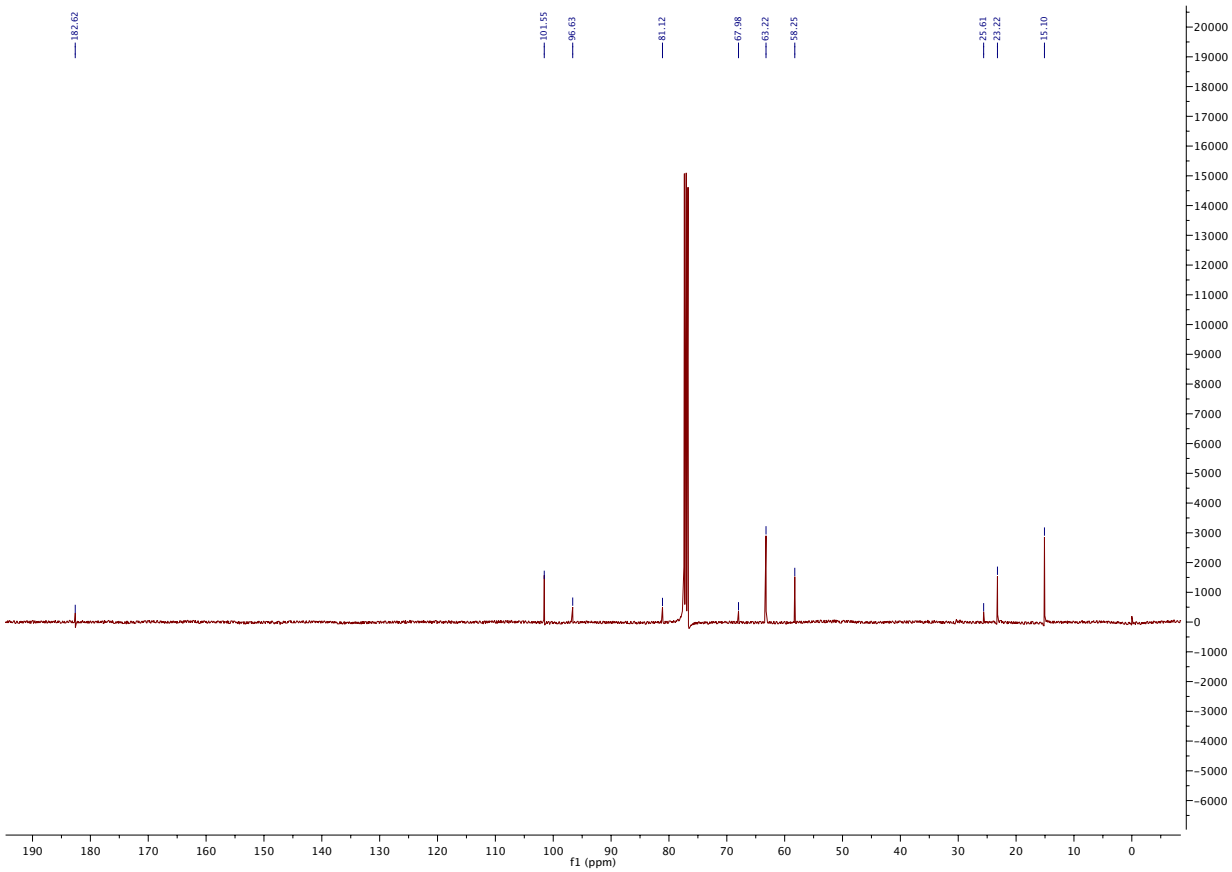
Scheme A.6: *^{1}H-NMR spectrum of* 5,5,6,6-Tetraethoxyhex-3-yn-2-ol **32**.



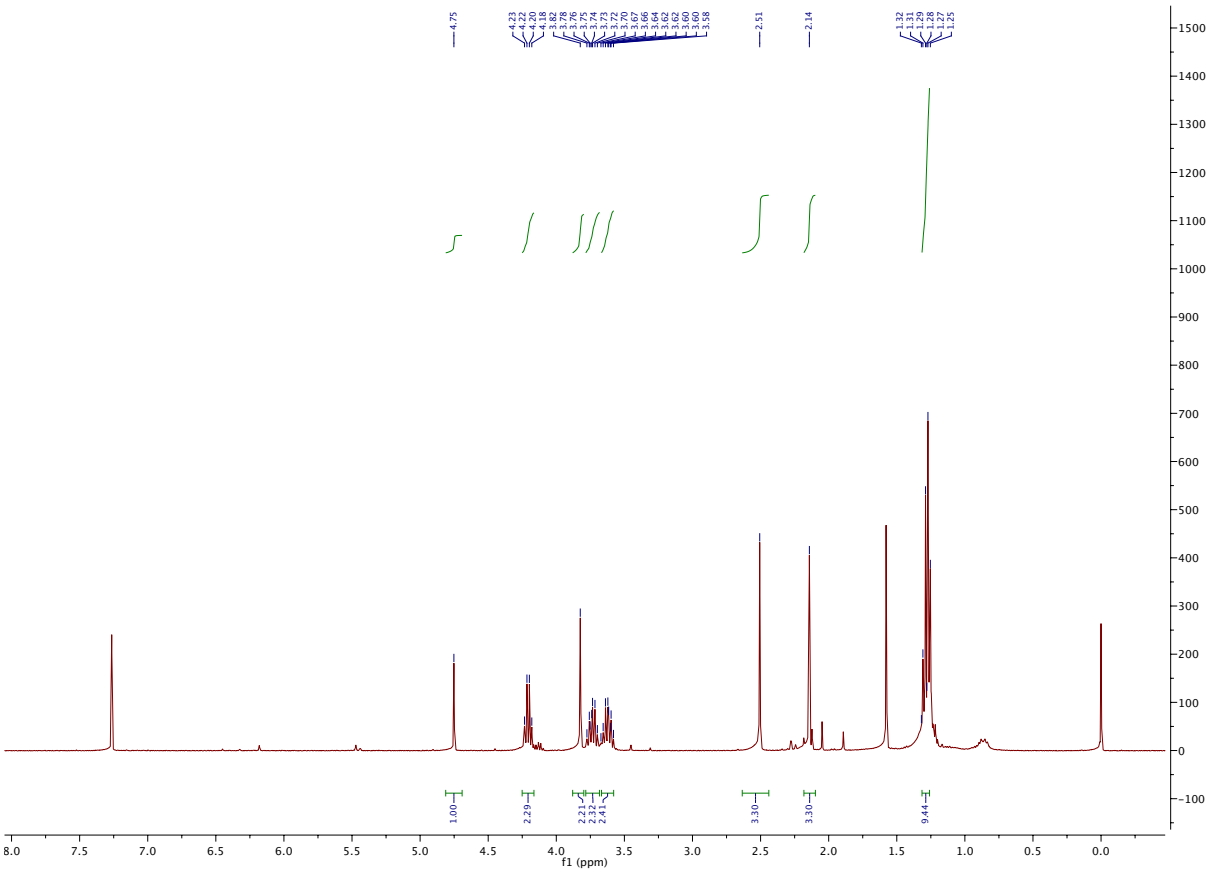
Scheme A.7: *^{13}C-NMR spectrum of* 5,5,6,6-Tetraethoxyhex-3-yn-2-ol **32**.



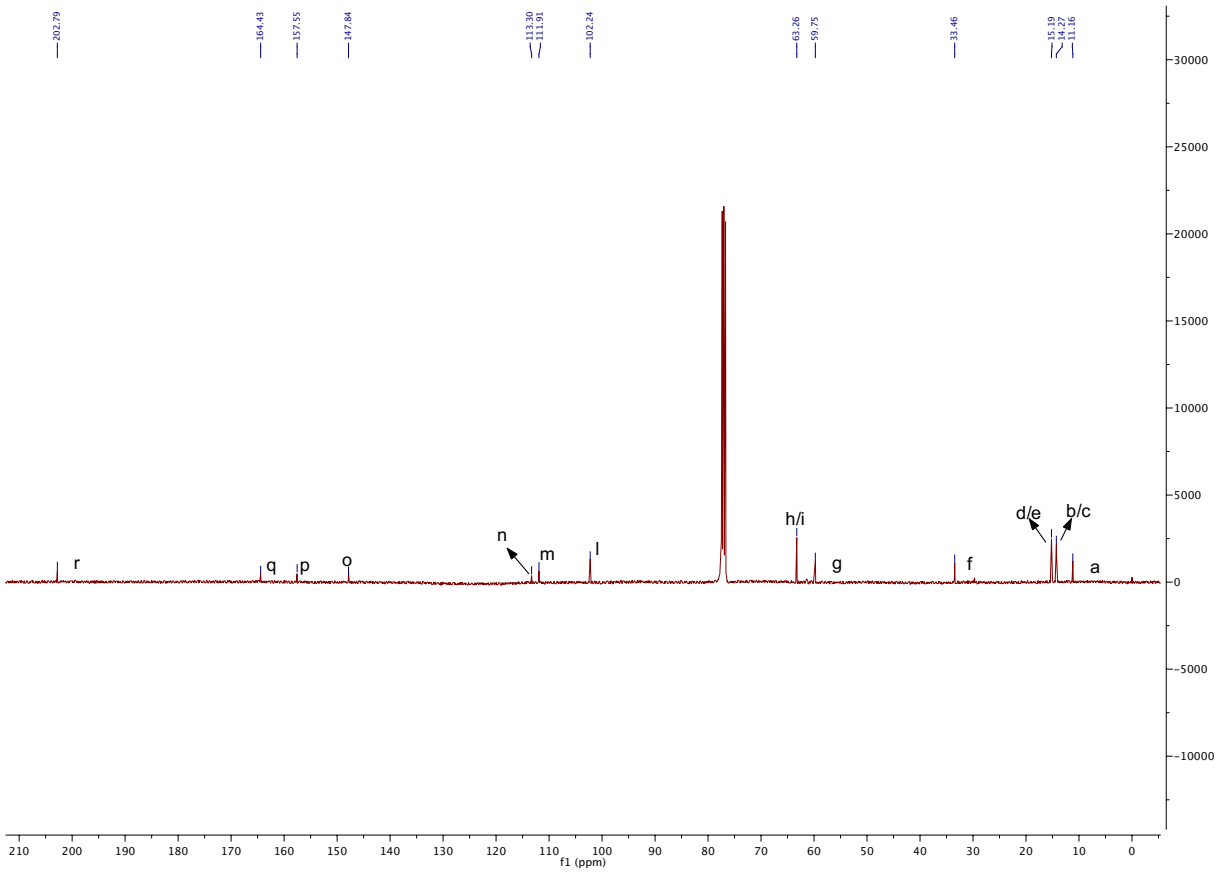
Scheme A.8: *^{1}H-NMR spectrum of* 1,1-Diethoxy-5-hydroxyhex-3-yn-2-one **33**.



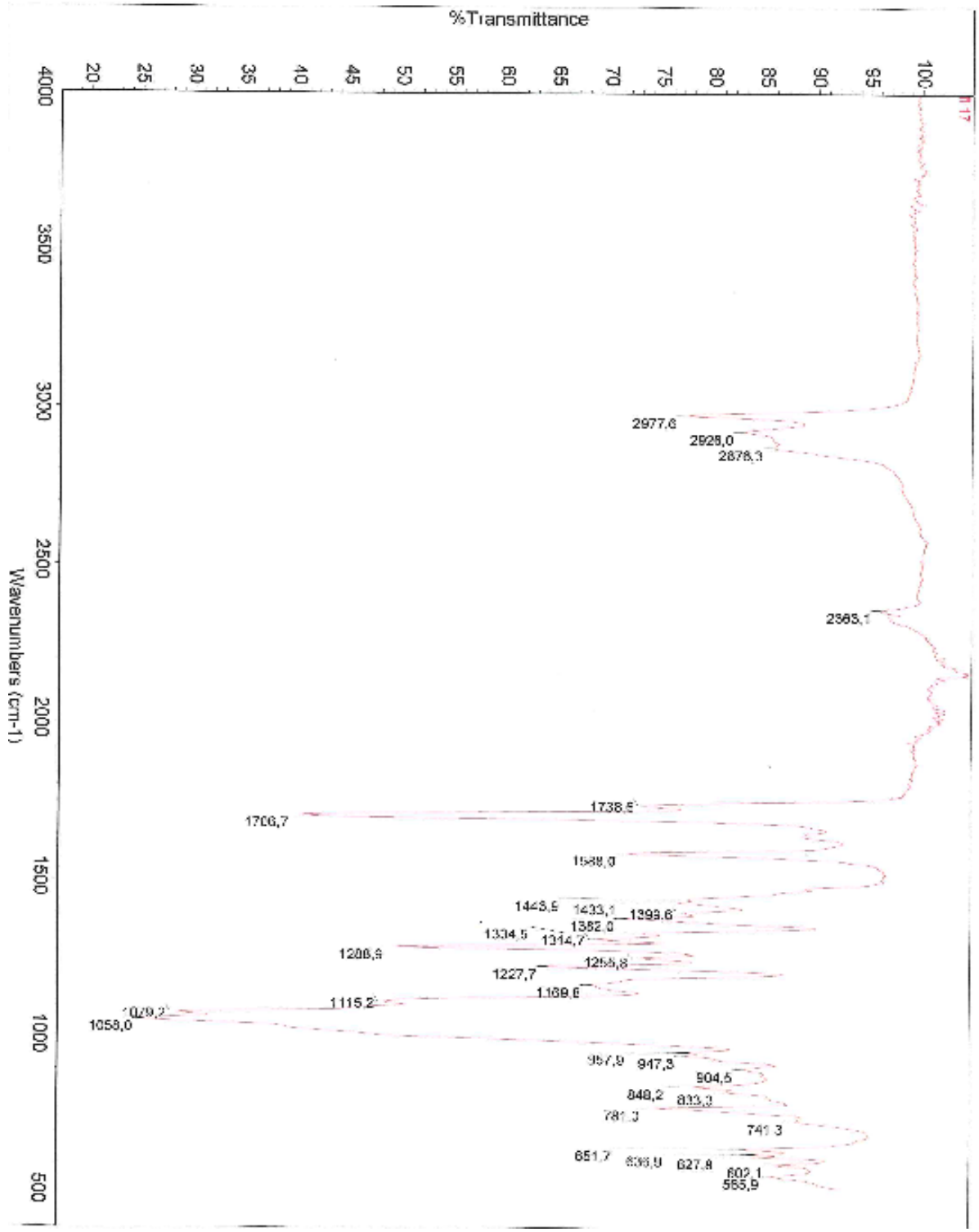
Scheme A.9: *^{13}C-NMR spectrum of* 1,1-Diethoxy-5-hydroxyhex-3-yn-2-one **33**.



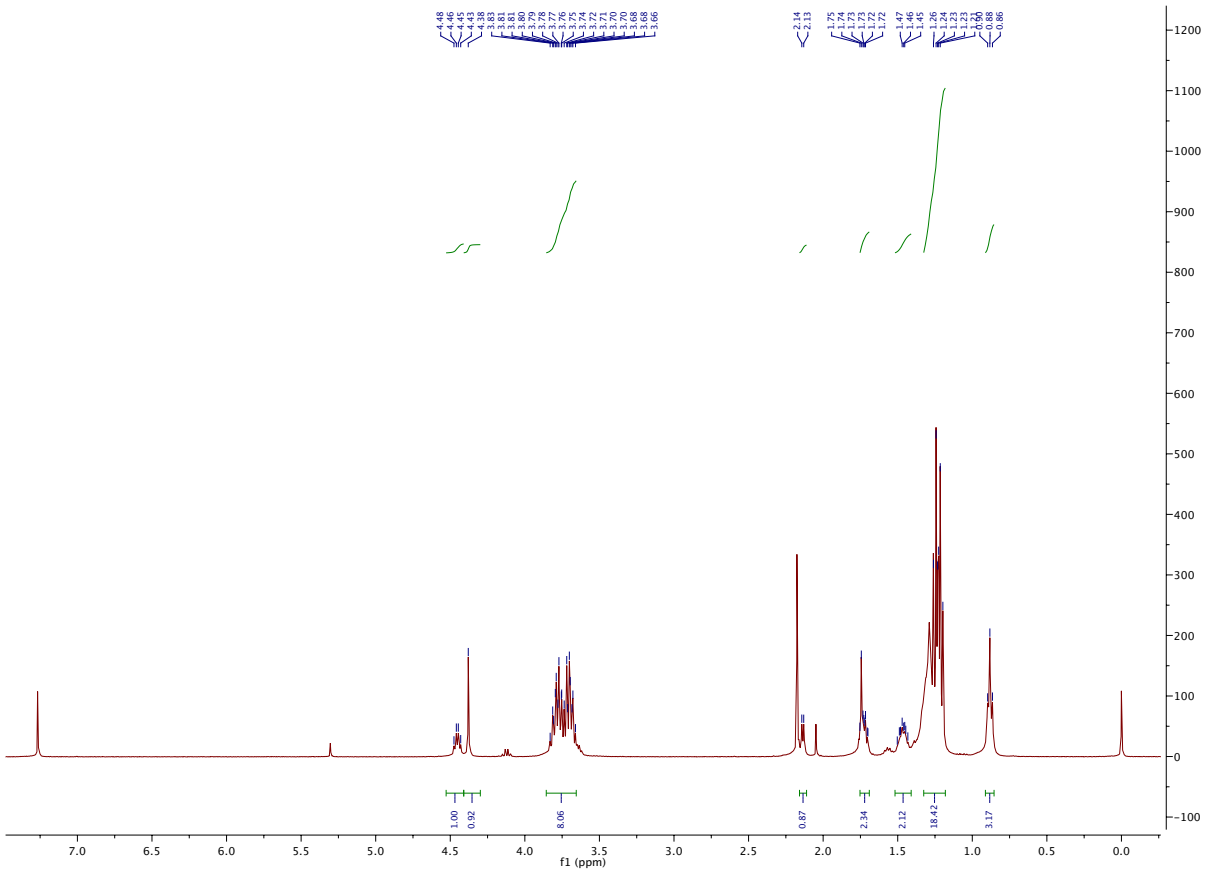
Scheme A.10: *^{1}H-NMR spectrum of* 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate **34**.



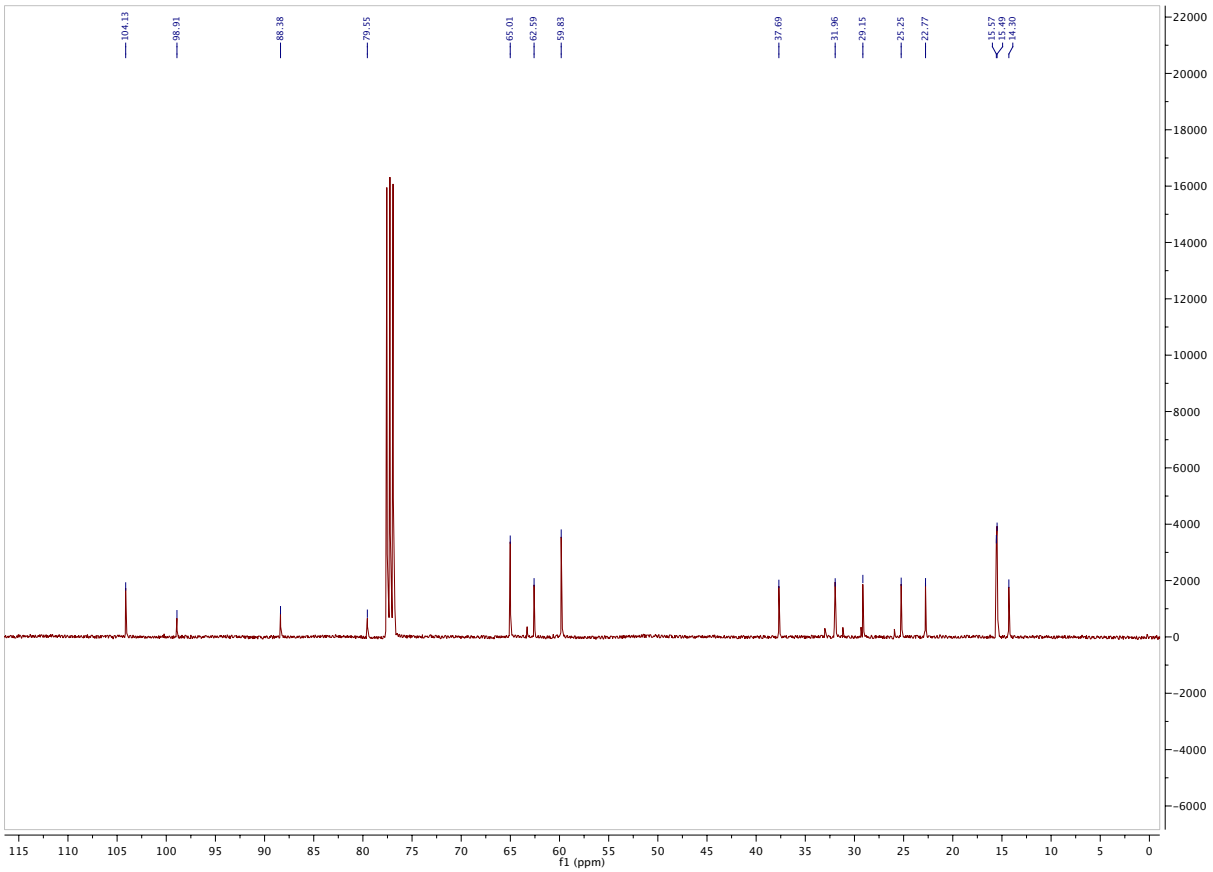
Scheme A.11: *^{13}C-NMR spectrum of* 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate **34**.



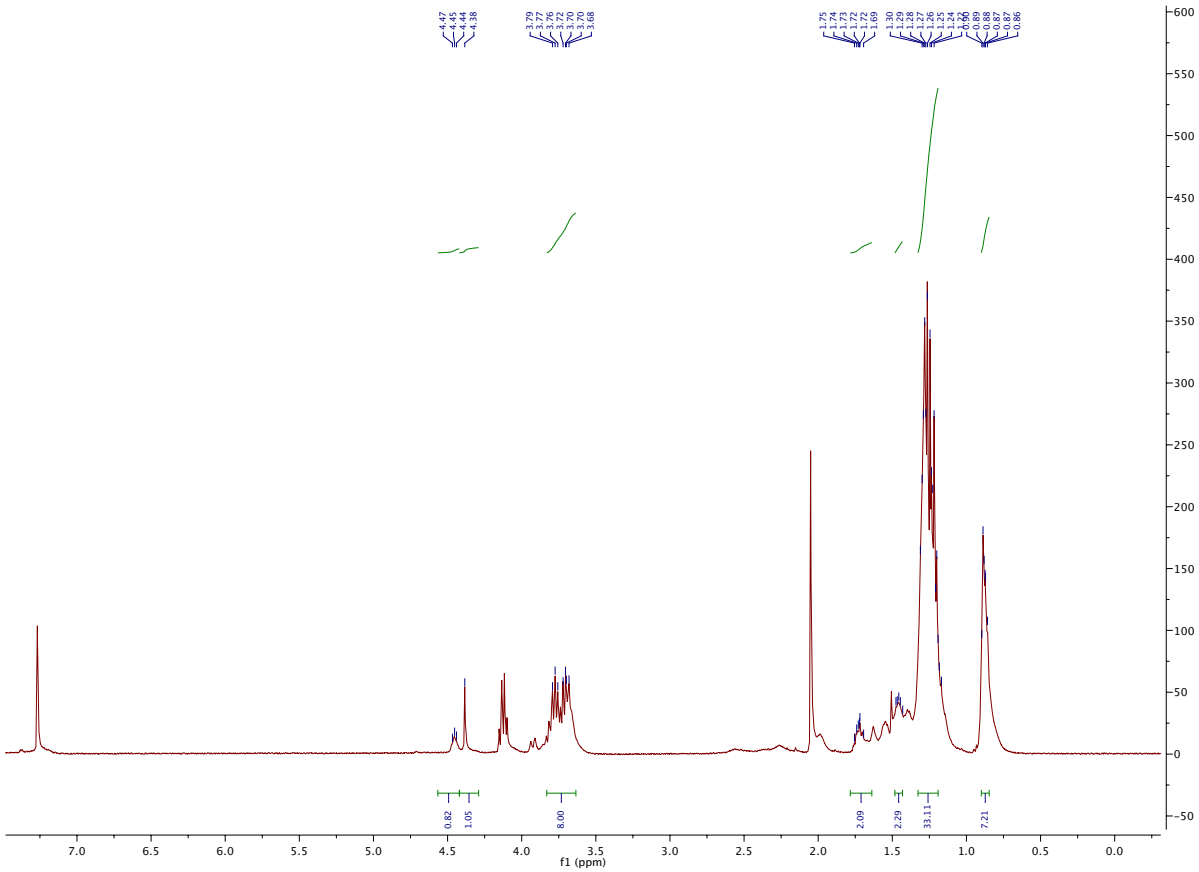
Scheme A.12: *IR spectrum of* 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate **34**.



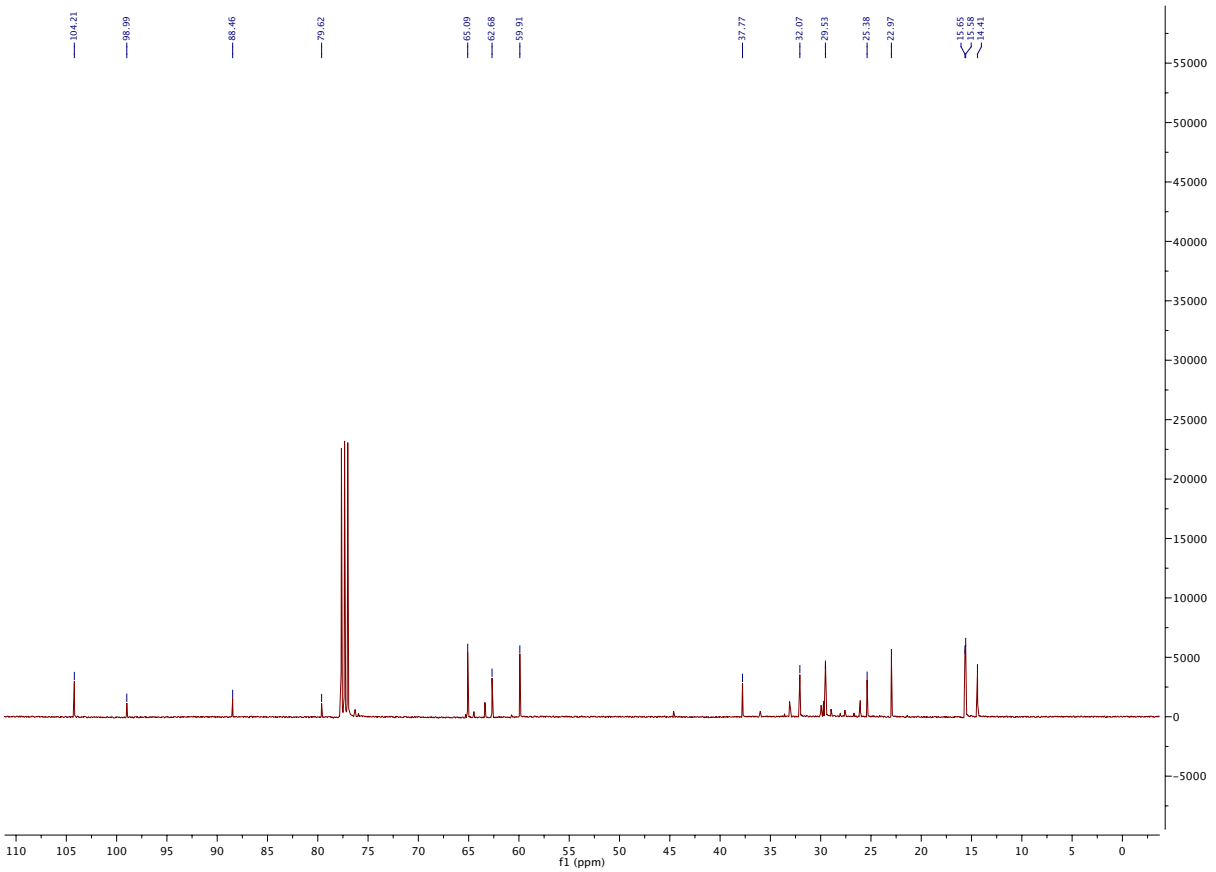
Scheme A.13: *^{1}H-NMR spectrum of* 1,1,2,2-Tetraethoxyundec-3-yn-5-ol **35**.



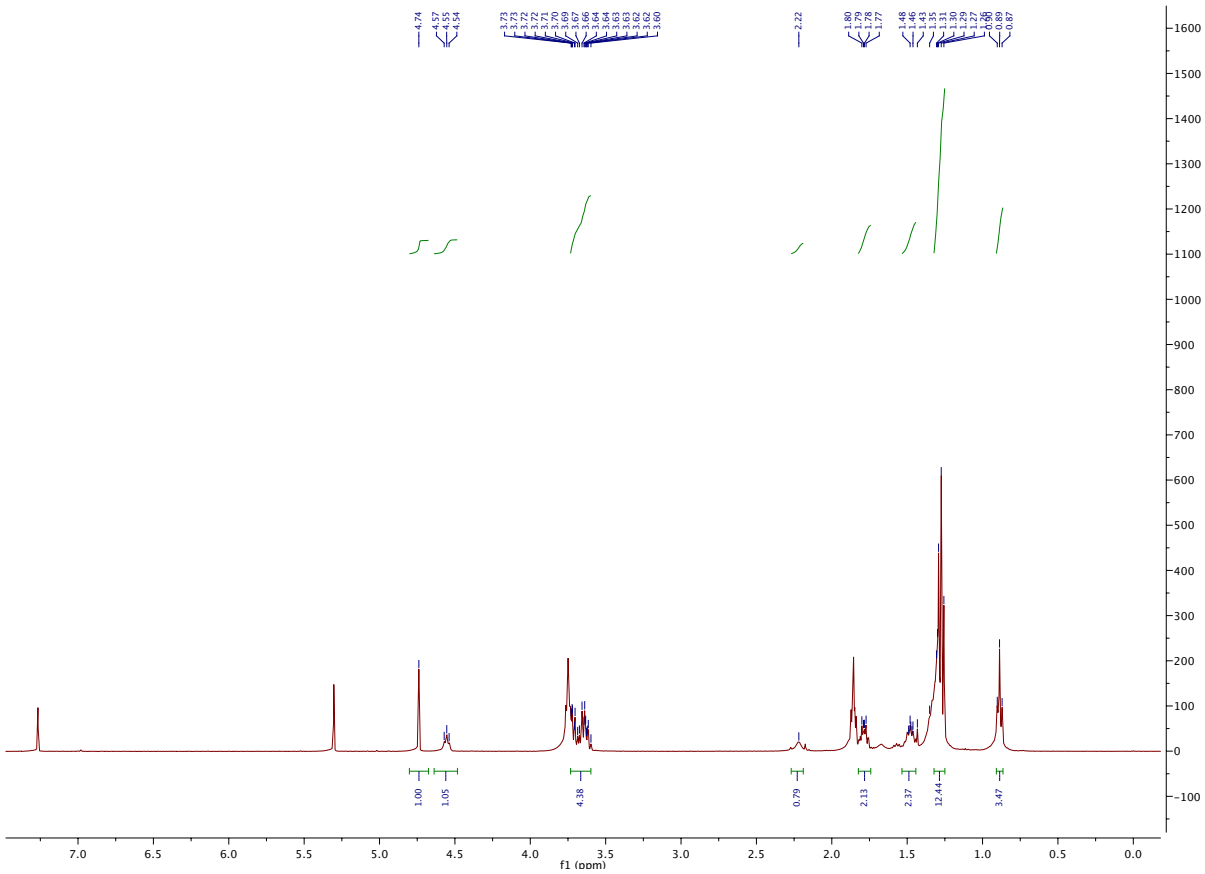
Scheme A.14: *^{13}C-NMR spectrum of* 1,1,2,2-Tetraethoxyundec-3-yn-5-ol **35**.



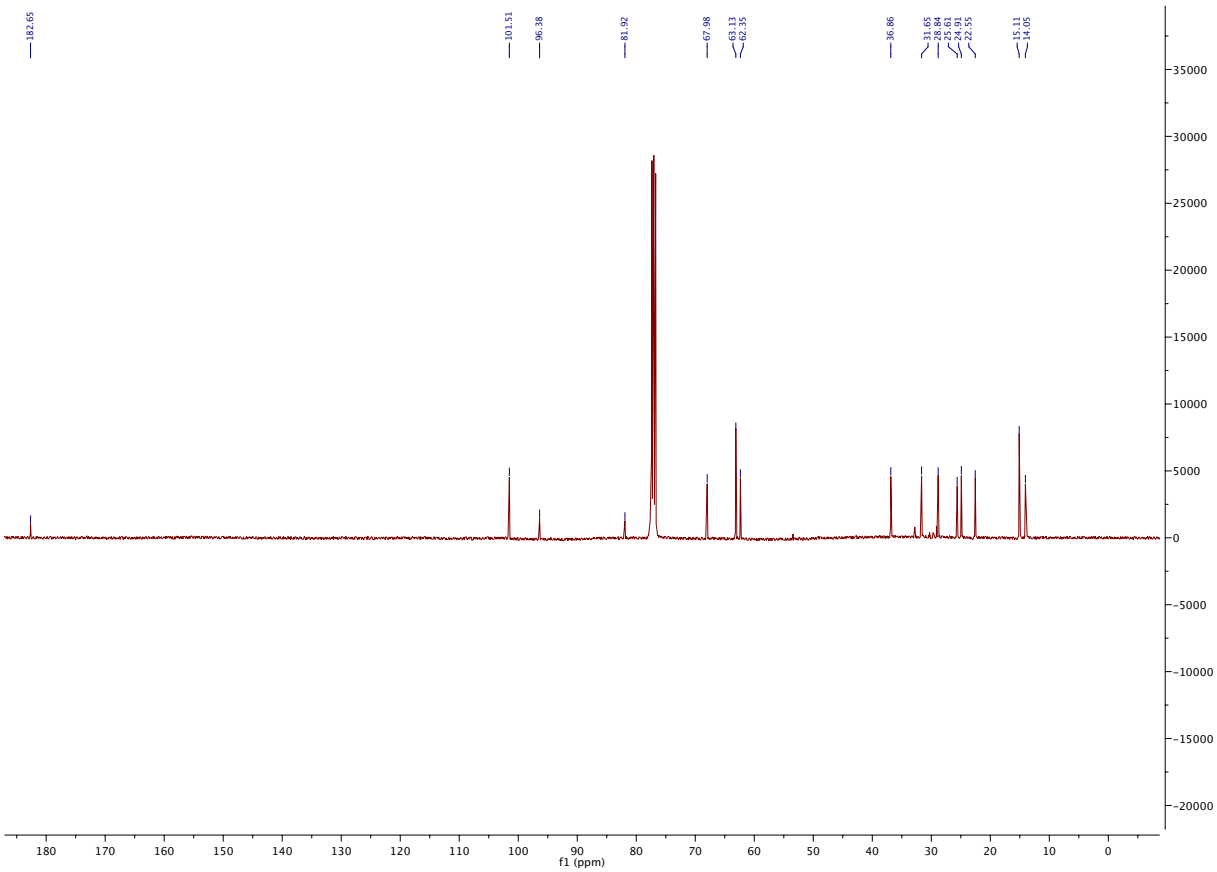
Scheme A.15: *^{1}H-NMR spectrum of* 1,1,2,2-Tetraethoxydodec-3-yn-5-ol **36**.



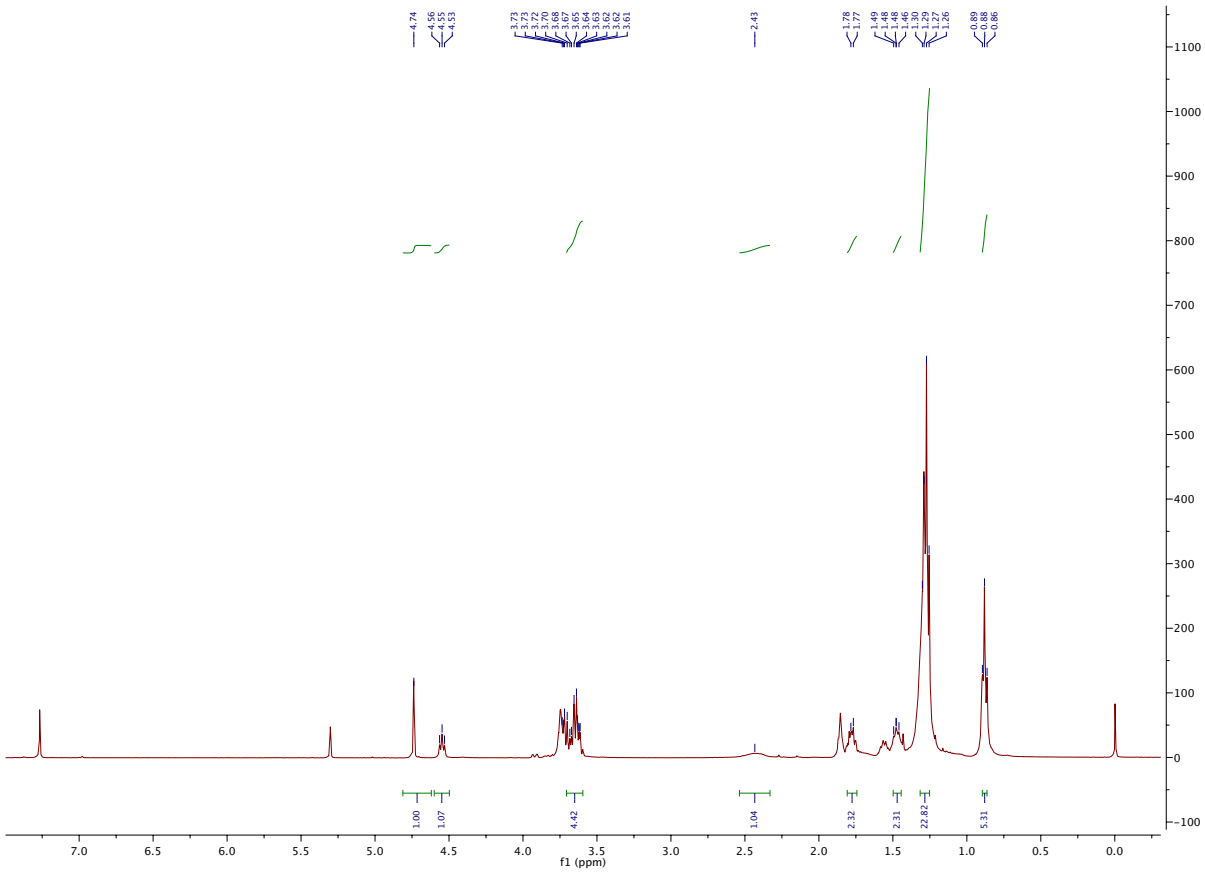
Scheme A.16: *^{13}C-NMR spectrum of* 1,1,2,2-Tetraethoxydodec-3-yn-5-ol **36**.



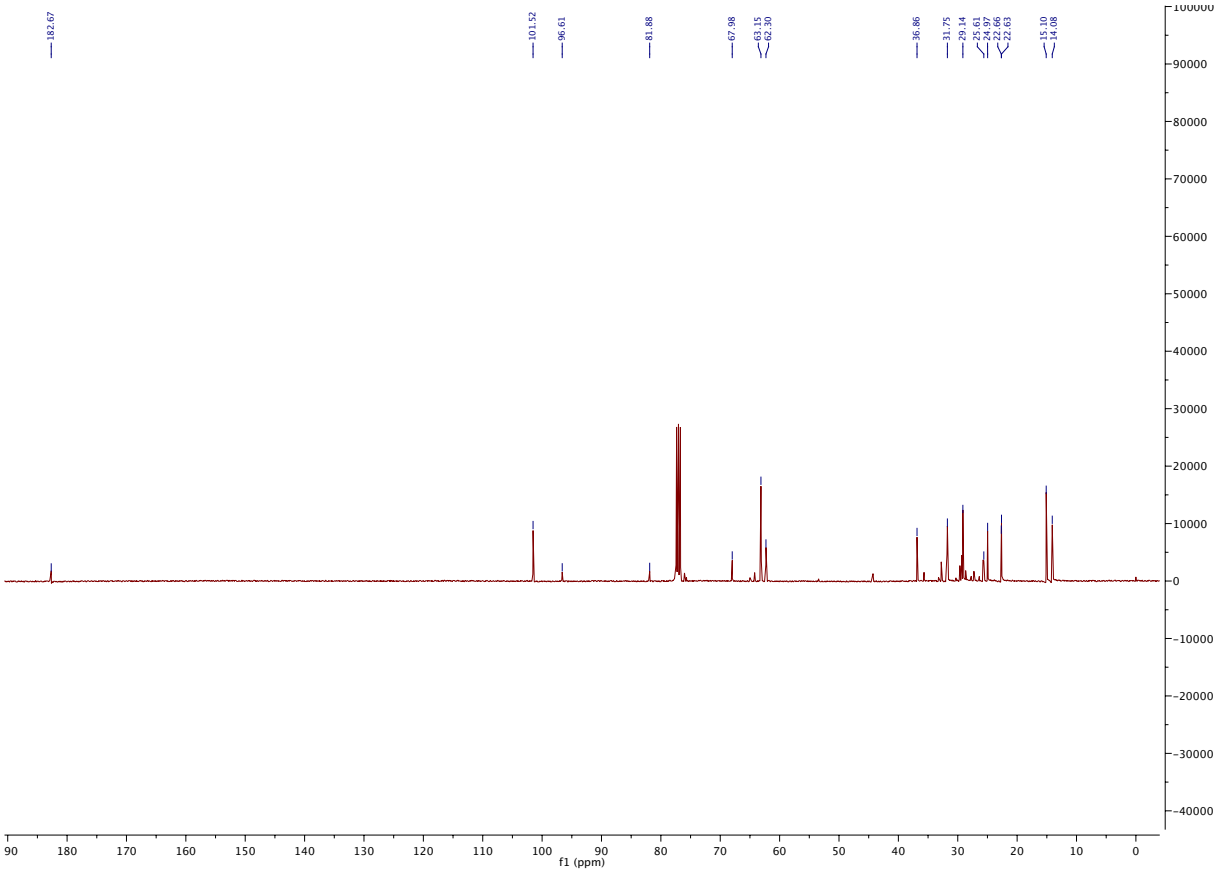
Scheme A.17: *^{1}H-NMR spectrum of* 1,1-Diethoxy-5-hydroxyundec-3-yn-2-one **37**.



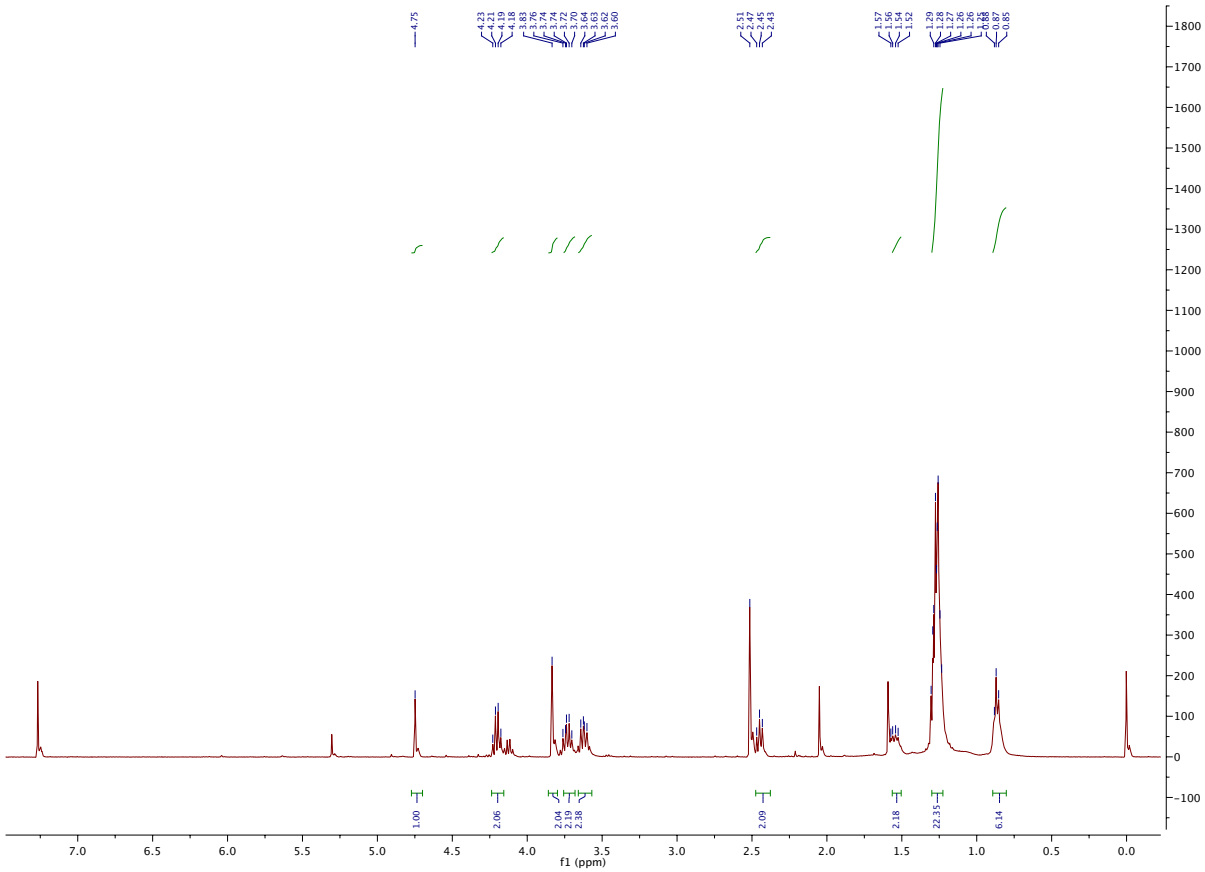
Scheme A.18: *^{13}C-NMR spectrum of* 1,1-Diethoxy-5-hydroxyundec-3-yn-2-one **37**.



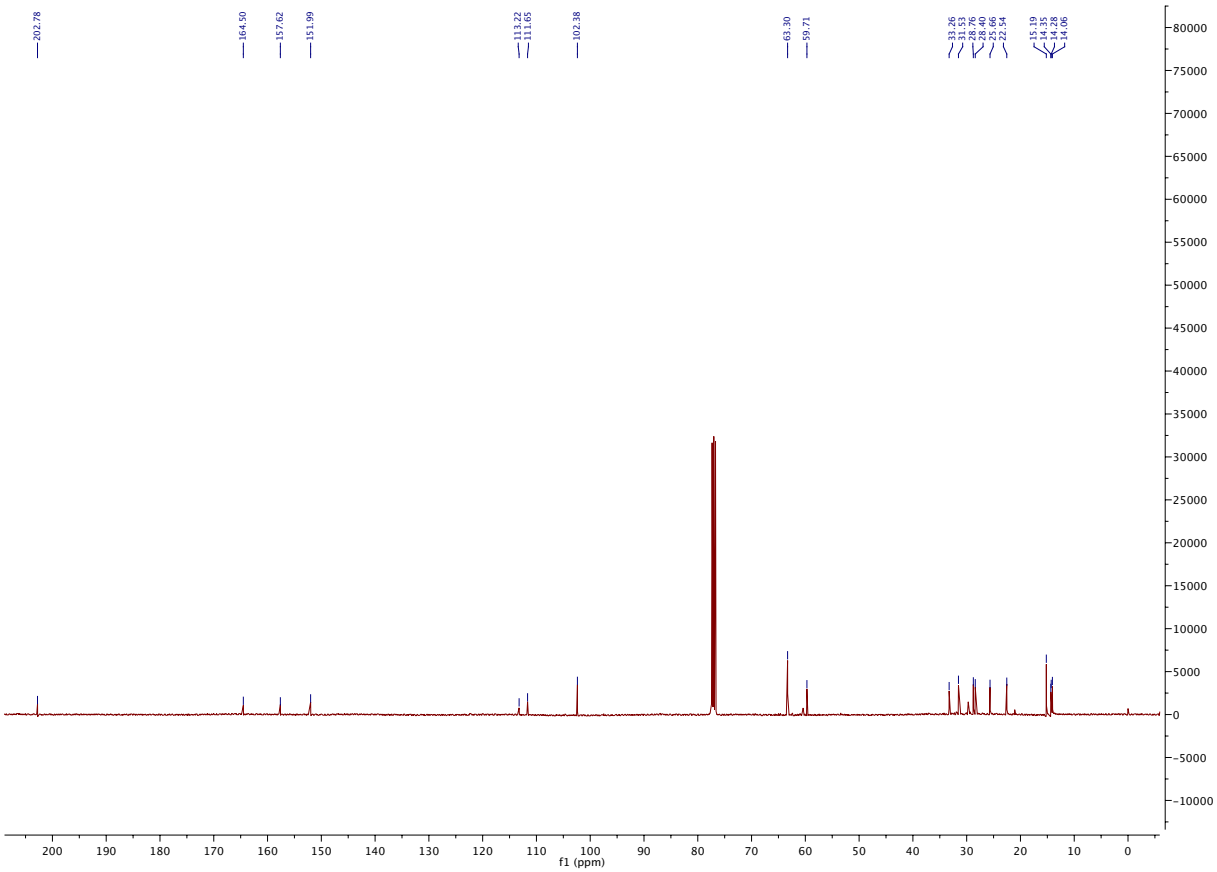
Scheme A.19: *^{1}H-NMR spectrum of* 1,1-Diethoxy-5-hydroxydodec-3-yn-2-one **38**.



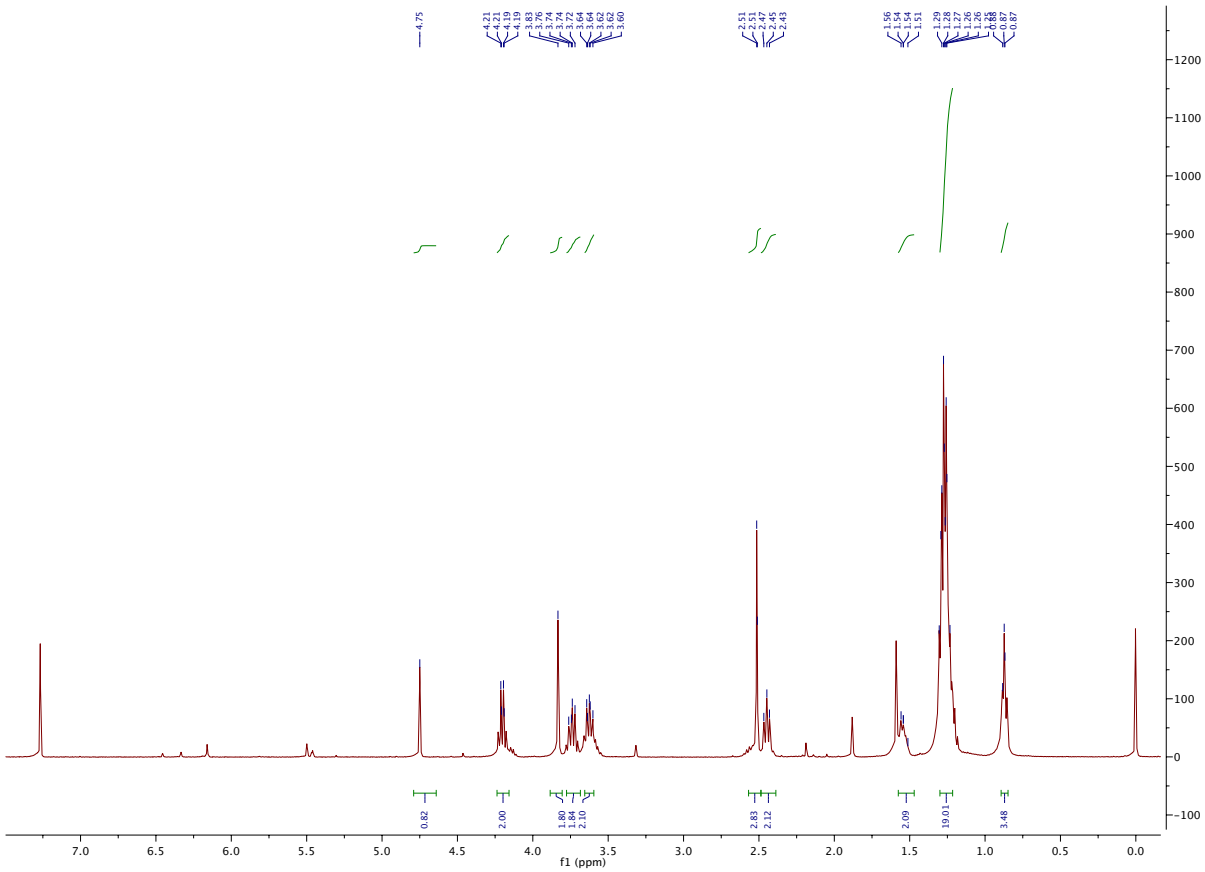
Scheme A.20: *^{13}C-NMR spectrum of* 1,1-Diethoxy-5-hydroxydodec-3-yn-2-one **38**.



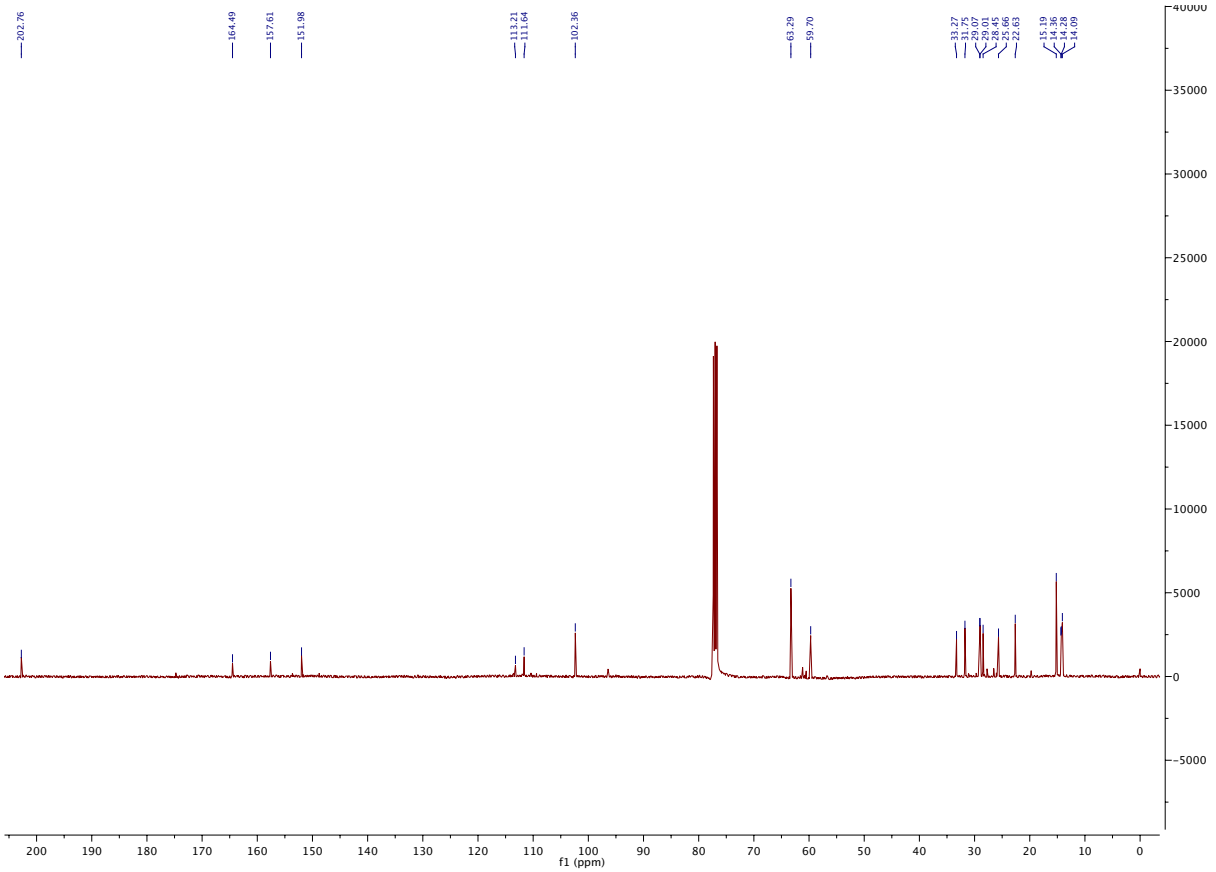
Scheme A.21: *^{1}H-NMR spectrum of* 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-hexyl-3-carboxylate **39**.



Scheme A.22: *^{13}C-NMR spectrum of* 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-hexyl-3-carboxylate **39**.



Scheme A.23: *^{1}H-NMR spectrum of* 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-octyl-3-carboxylate **40**.



Scheme A.24: *^{13}C-NMR spectrum of* 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-octyl-3-carboxylate **40**.

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ERRATA (ERRATA CORRIGE)

- Pag 5 (Abstract)

The correct names of 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate, 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-hexyl-3-carboxylate and 4-(3,3-diethoxy-2-oxopropyl)-2-methylfuran-5-octyl-3-carboxylate are, respectively, ethyl 4-(3,3-diethoxy-2-oxopropyl)-2,5-dimethylfuran-3-carboxylate, ethyl 4-(3,3-diethoxy-2-oxopropyl)-5-hexyl-2-methylfuran-3-carboxylate and ethyl 4-(3,3-diethoxy-2-oxopropyl)-5-heptyl-2-methylfuran-3-carboxylate. These names are repeated various times in the thesis.

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"Cheletropic reactions are a type of pericyclic reaction. A pericyclic reaction is one that involves a transition state with a cyclic array of atoms and an associated cyclic array of interacting orbitals. A reorganization of σ and π bonds occurs in this cyclic array. Specifically, cheletropic reactions are a subclass of cycloadditions."

It's a definition taken from: "Eric V. Anslyn and Dennis A. Dougherty *Modern Physical Organic Chemistry* University Science Books, 2006" and cited in Wikipedia.

- Bibliography

ref. 1: Date and publishing company are missing. The correct reference is: "Carbohydrates"; A. F. Bochkov, G. E. Zaikov and V. A. Afanasiev, **1991**, *VSP*, Utrecht

ref. 2: Date and publishing company are missing. The correct reference is: "Carbohydrates: Synthesis, Mechanisms, and Stereoelectronic Effects", Momcilo Miljkovic, **2009**, *Springer*, New York