Master Thesis in Organic Chemistry

ATTEMPTED SYNTHESIS OF A 2,3,6-TRISUBSTITUTED 5-PYRANONE

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Abstract

Carbohydrate analogues are of great interest for the development of new pharmaceutical products. These compounds are attached to the macromolecule via glycosidic linkages, and then influence directly the overall biological activity.

The goal of this project was to synthesize 2,3,6-trisubstituted-5-pyranone (**10**) from 1,1-diethoxy-3-(1,3-dithian-2-yl)-prpan-2-ol (**7**) which can undergo further reaction to synthesize carbohydrate analogues and great interest in the development of new pharmaceutical drugs.

In this project, 3,3,4,4-tetraethoxy-1-butyne (TEB) was investigated as a starting material, further deprotection reaction and double Michael addition has also been carried out. Chain elongation of β-hydroxy dithiane has been also done to synthesize the target compound, which was prepared by treating compound 1,1-diethoxy-3-(1,3-dithan-2-yl)propan-2-ol with *n*-butyllithium followed by benzaldehyde. The target compound (**8**) has further been reacted to form carbohydrate analogues by cyclization and then hydrolysis of dithiane.

Preparation of compound 8-Oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**9**) in a satisfactory yield is an important step in this project. The yield of compound **9** could be increased by repeating the attempt, from 48% to 59% respectively, and then furnished 2,3,6-trisubstituted-5-pyranone as the main product in this study.

Acknowledgements

This project has been carried out at the University of Bergen, under supervision of Professor Leiv K. Sydnes. I would like to thank Professor Sydnes for all help and his guidance throughout the project.

A special thanks is in order to my laboratory colleagues Ingebjørg, Inger and Anne who great a fun and enjoyed a lab-day. They made an interesting and fun experience.

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Last but not least, I would also like to send a hug thank to my family who was very helpful to continue and choose my education which was based on interest. I just want to say sorry that I could not be there when they needed, and they had complained me because I spent most of my time at school.

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Abbreviation

^{1}H	Hydrogen-1 nucleus
^{13}C	Carbon-13 nucleus
COSY	Correlation Spectroscopy
DCM	Dichloromethane
DNA	Deoxyribonucleic acid
EtOAC	Ethyl acetate
HMPA	Hexamethylphosphoramide
IR	Infrared Spectroscopy
Mp	Melting point
MS	Mass Spectroscopy
n-BuLi	*n*-Butyllithium
NMR	Nuclear Magnetic Resonance
ppm	Parts per million
PTC	Phase-transfer catalysis/ conditions
p-TSA	*para*-Toluenesulfonic acide
r.t.	Room Temperature
t.BuLi	*tert*-Butyllithium
TBAH	Tetrabutylammonium hydrogensulphate
TEB	3,3,4,4-Tetra ethoxybut-1-yne
TEBA	Tetrabutylammonium iodide
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane

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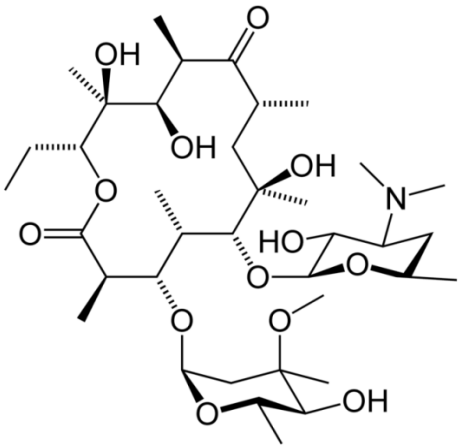
Chapter 1. Introduction

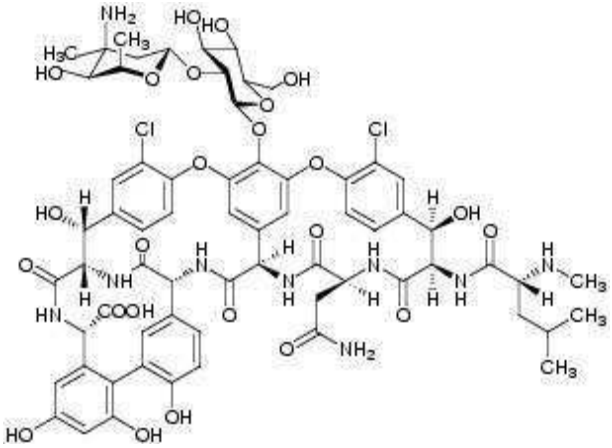
1.1 Carbohydrates

Carbohydrates play an important role for the biological activity of many natural products, they can participate in many physiological process, such as energy storage, target recognition in the immune system and cell-cell recognition.[22] Carbohydrates are the main molecular drug targets, which means by removing the carbohydrate moiety most of the drug, contains carbohydrates, will lose their biological activity.

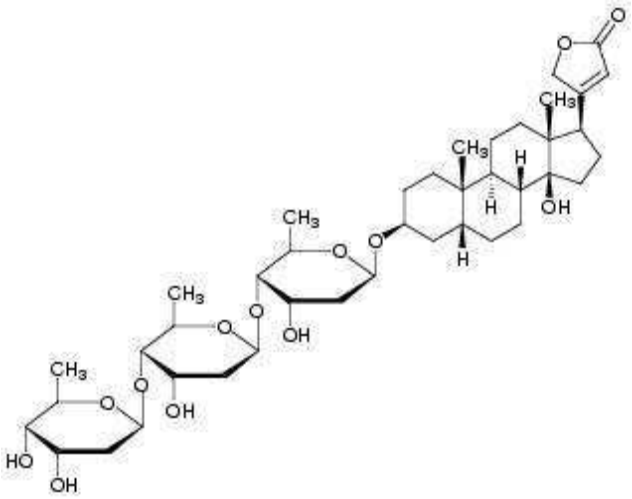
Carbohydrates are attached via glycosidic linkages to the macromolecule, and then influence directly the overall biological activity. Many of the drugs contain carbohydrate moiety. Good examples are antibiotic drugs vancomycin and erythromycin which are effective against Gram-positive bacteria, digitoxin which is used in cardiovascular medicine, and aciclovir effective against DNA viruses (Figure 1.1).



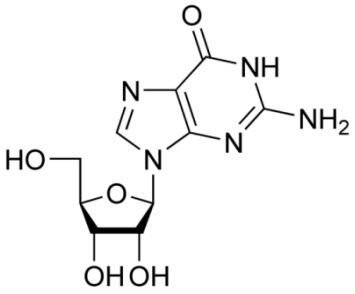
Erythromycin (antibacterial)



Vancomycin (antibacterial)



Digitoxin (Cardiac glycoside)



Aciclovir (antiviral)

Figure 1.1 Some drugs contain carbohydrate moieties.[9,44]

1.2 An example: Erythromycin

Macrolides are consisted a group of antimicrobial drugs which are characterized by different pharmacokinetic properties but similar in chemical structure, mechanism of action and resistance and antibacterial spectra. Macrolides are classified according to the size of lactone ring which usually contain 12 to 16 atoms, to which is attached to one or more sugars via glycoside bonds. The sugar residues are important against activity to Gram-positive bacteria.[25]

Erythromycin, is an antibiotic of the macrolide class, contains two carbohydrate derivatives attached to macrocylic lactone ring (Figure 1.2). It will lose antibacterial activity if one or both sugar groups, attached to the macrolide ring, are removed.

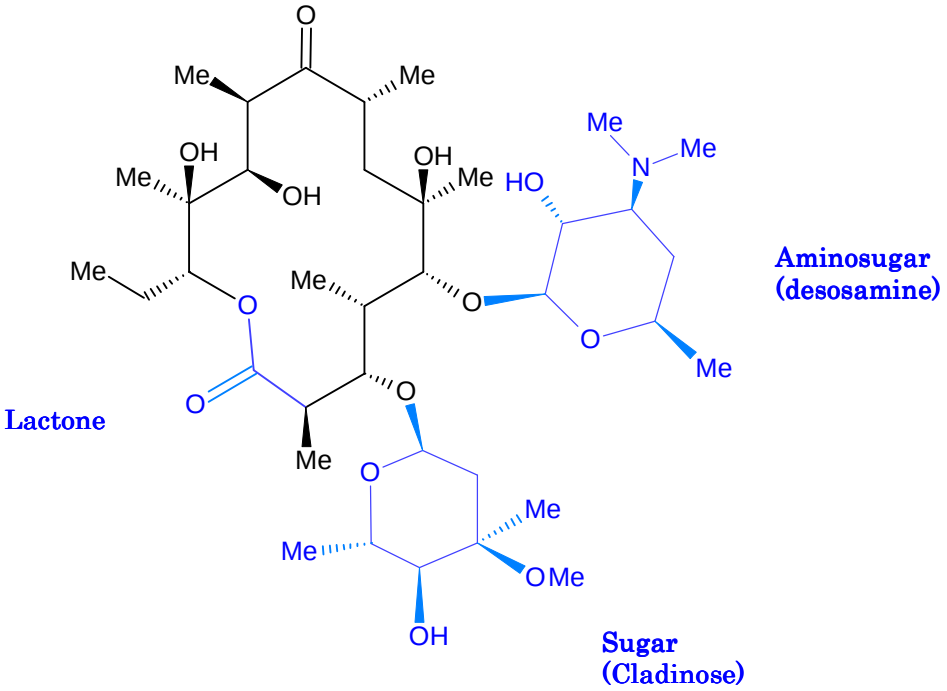


Figure 1.2 Erythromycin and their attachment.[28]

Carbohydrate derivatives are normally referred to as deoxy sugars which more of hydroxyl groups are replaced by another substituent, e.g. hydrogen, amino acid…etc. some studies found that removal of hydroxyl group in Erythromycin analogue will change the activity of the drug.[22]

Deoxy sugars play an important role in many antibiotic drugs, as they interact with targets on the cell surface of bacteria. These types of sugars also serve as important constituents of secondary metabolite in bacteria, including cardiac glycosides and macrolide antibiotic. Bacteria growing increasingly resistance to common antibiotics, therefore antibiotic drugs are always needed to treat infection.

The sugar moieties of the macrolides are essential for the microbial activity of the compound.[42] the sugar moieties have been linked with many pharmacological properties display by the macrolidies antibiotic.

The presence of the dimethylamino group in erythromycin will give dimerization and possibility of active transport of drug into the cell, while the ester group in the compound is preferred due to their favorable pharmacological and pharmacokinetic properties.[42]

The carbohydrate affects the orientation of aromatic ring with respect to the antibiotic backbone and influence the alignment of the amide protons. The carbohydrate substituents are believed to be responsible for a number of favorable interactions in the formation of dimer.

Carbohydrate moiety on erythromycin is quit important to study, which is created a large interest in the field of synthesizing new carbohydrate analogues and finding out a better antibiotic for the resistance of bacteria.

Carbohydrate modification has a greater complexity due to the densely functionalized molecules of hydroxyl groups with similar reactivity, and the other possibility during their synthesis.

Many of studies reported formation of carbohydrate by using different starting materials. A good starting material is needed to generate deoxygenated carbohydrate, and different sugar can be screened to for biological activity.

In this study, 3,3,4,4-tetraethoxybut-1-yne has been used as starting material for such synthesis, due to its functional groups and it can easily converted in to a various compounds or deoxy sugars.

1.3 TEB: Functional groups and their properties

TEB is a highly functionalized compound which is easily available, cheap and therefore effective as a starting material in synthesis of different carbohydrate analogues. TEB contains both an acetal and a ketal moiety which are useful as protecting groups for aldehydes and ketones, respectively.[7] The proton in C1, which is acidic, can be removed by a strong base, and generate an acetylide which is strongly nucleophilic and reacts with different electrophiles to generate a new carbon-carbon bond, leads to chain elongation (Figure 1.3). Triple bond can be used in addition reaction, or reduced to the corresponding alkene. Diethoxy groups in C_3 and C_4 can be deprotected and undergo a range of reactions.

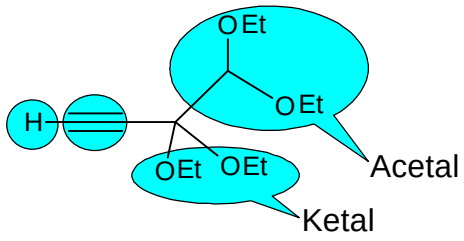
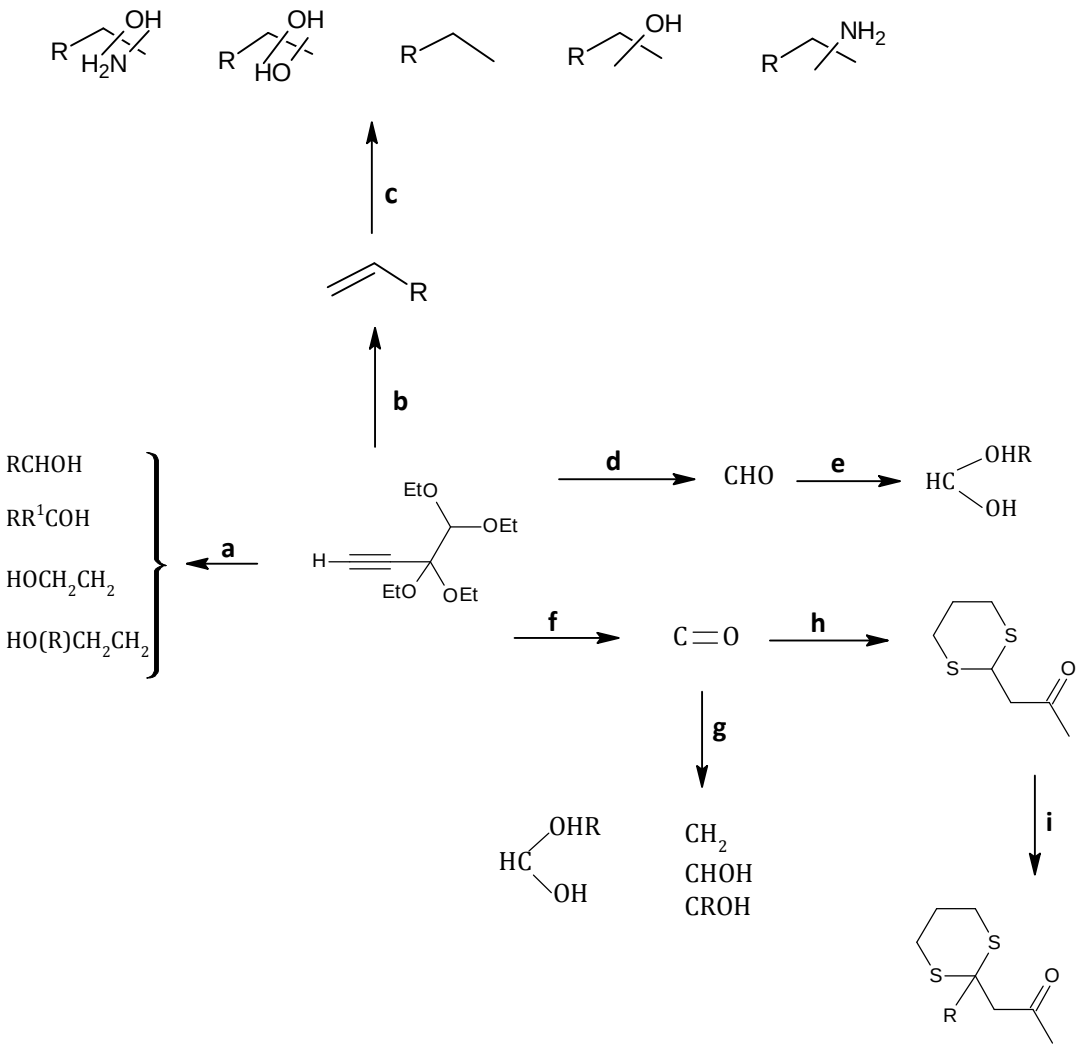


Figure 1.3 Functional groups of TEB

TEB as a high density of reactive functional groups can undergo a range of reactions, which are depicted in Scheme 1.1.

As mentioned above, the proton is acidic, and can generate an acetylide group under basic condition, the group is nucleophile and react with aldehydes or ketones to give a propargylic alcohols (**route a**). Reductions of triple bond can occur to give a double bond (**route b**). The unsaturated C-C bond can be reduced and undergo many reactions like dihydroxylation, epoxidation, hydration, hydroxyamination and so on (**route c**). An acetal group can undergo a range of reactions including hemeacetal formation as well as witting reaction (**route e**). Deprotection of the ketal moiety producing the conjugated acetylenic ketone (**route f**). Furthermore, the ketal group can be deprotected and selectively be reduced to a chiral alcohol (**route g**). An α,β-unsaturated system is present, and then can undergo 1,2-addition reaction. Addition of propan-1,3-ditiol will protect carbonyl group which is stable under acidic and basic conditions (**route h**). Addition to an electrophilic agent (**route i**).

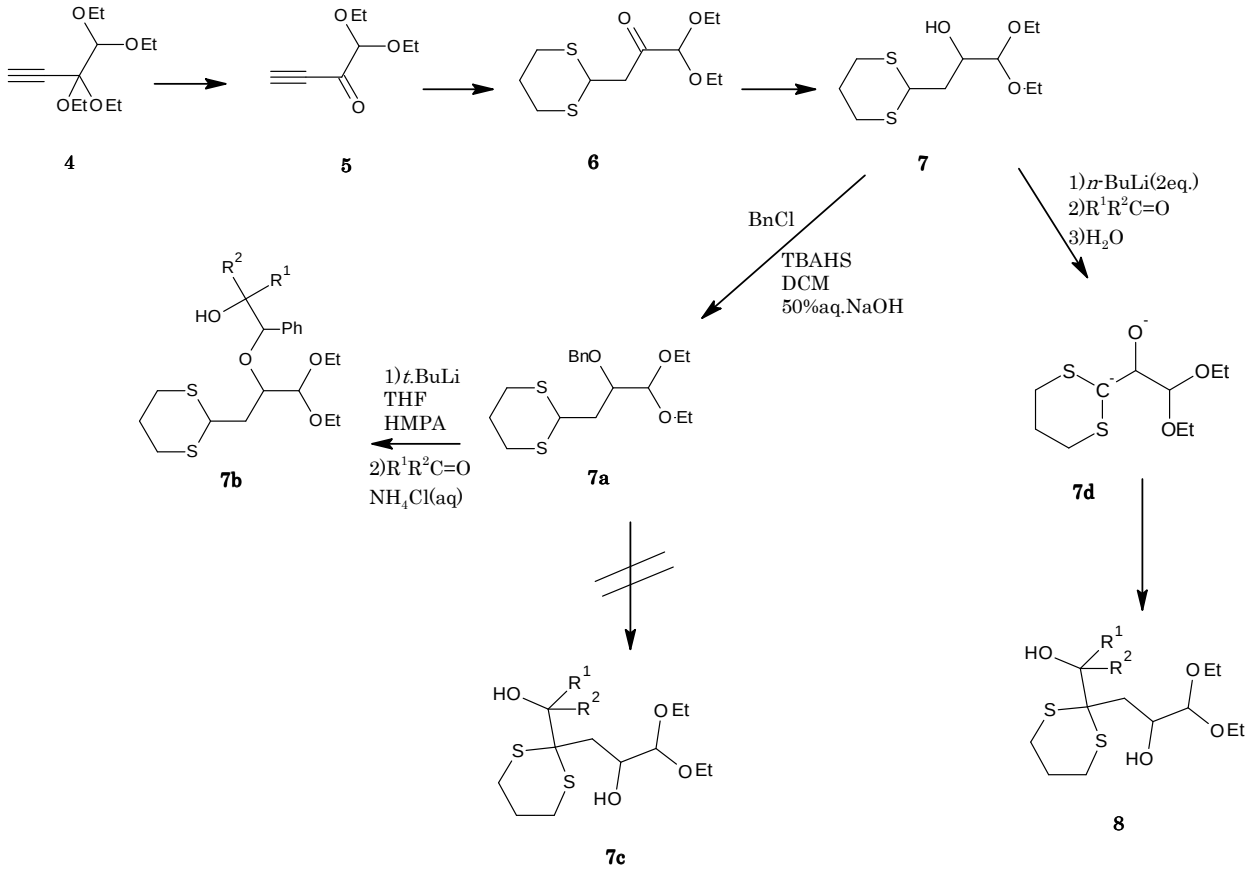


Scheme 1.1 Possible reaction of TEB.[22]

1.4 Previous work

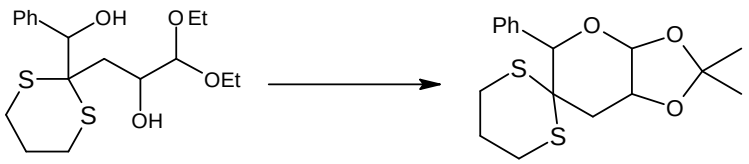
Valdersnes tried to synthesize carbohydrate analogues in several ways by using TEB as a starting material was tried. He started with deprotection of the ketal moiety, double Michael addition of propane-1,3-dithiane to ketone **6**, reduction of the ketone to the corresponding secondary alcohol **7**, then protection of hydroxyl group by reacting with benzyl chloride and TBAHS. This gave benzylprotected β-hydroxydithiane **7a** which was treated with 1 molar equivalent *t*-BuLi followed by benzylaldehyde. This did not give the expected product **7c** , but instead alcohol **7b** obtained in 24%.[38] Valdersnes tried also to use HMPA as a co-solvent, but the result was the same, **7b** was obtained rather than **7c** (Scheme 1.2).

A different strategy was chosen by Flemmen and Nilsen.[9,27] First Flemmen treated alcohol **7** with 2 molar equivalents of several strong bases to make dianion **7d** from **7** before treatment with various aldehydes and ketones. She worked on a small scale (0.8 mmol) and she got a various yield by using different methods.[9] the best results were obtained for preparing **8** when 2 molar equivalents of *n*-BuLi were used with addition of benzaldehyde (95%).



Scheme 1.2 Previous work done by Valdersnes and Flemmen for synthetic some carbohydrate analogues.[9,38] R^1= H or alkyl, R^2= phenyl or alkyl

Nilsen tried to scale up the chain-elongation reaction, in which *n*-butyllithium was added to the dianion followed by benzaldehyde, and then she attempted the cyclization reaction which furnished a carbohydrate analogue in reasonable yield (scheme 1.3).[27]



8 **9**

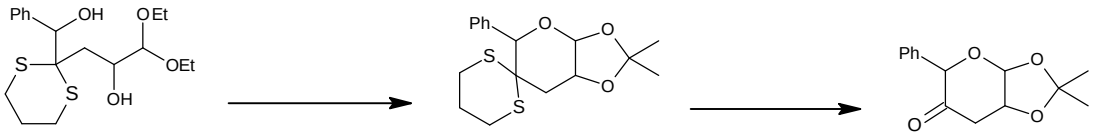
Scheme 1.3 previous attempts to furnish a carbohydrate analogues by Nilsen.[27]

This project is based on the Nilsen's work which attempted to obtain a good yield on further addition reaction of compound **7.** Then improve the synthesis of compound **9** and subsequently to remove the 1,3-dithiane protection to obtain the corresponding ketone which can be used to make a range of modified deoxygenated carbohydrate derivates.

1.5 Aim of project

In this project, it was important to continue the work started by Flemmen and further continued by Nilsen (Scheme 1.4).

The purpose of this investigation was to obtain a good yield of compound **9**, and then continues reaction by hydrolysis of dithiane to obtain the corresponding ketone **10** in a satisfactory yield.



8 **9** **10**

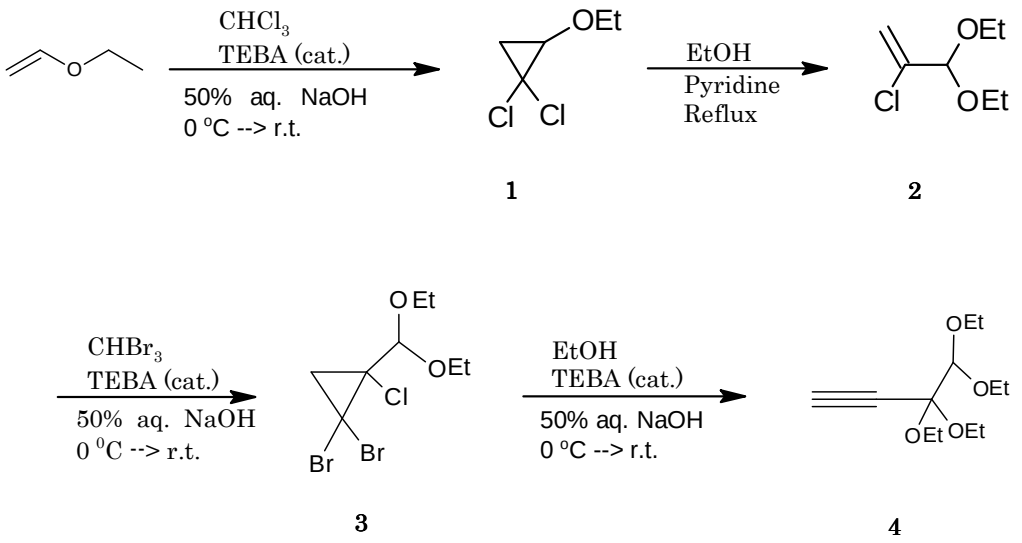
Scheme 1.4 Synthesis of compound **10** as a carbohydrate analogue.

If the reactions prove successful and ketone **10** is achieved in a reasonable yield, it would be possible to synthesize tertiary alcohol by treatment with Grignard reagents followed by water. These compounds would be a group of carbohydrate analogues which would be of interest to test as possible carbohydrate substituent for antibiotics, such as erythromycin.

Chapter 2. Results and discussion

2.1 Preparation of starting material

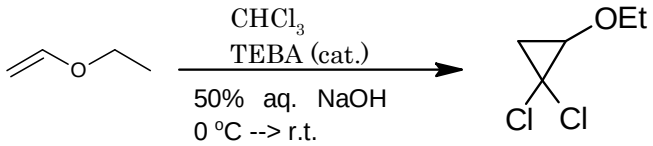
Preparation of 3,3,4,4-tetraethoxybut-1-yne **4** (TEB) was done following a synthesis developed by Sydnes *et al.* and resulted in scheme 2.1.[21,36] The starting material was ethyl vinyl ether, and all the reagents were stable and relatively very cheap chemicals.



Scheme 2.1 Synthesis of **4** (TEB) from ethyl vinyl.

Synthesis of TEB was started with cyclopropanation which was performed under two-phase condition using Makosza's method,[24] as described by Kvernenes.[22]

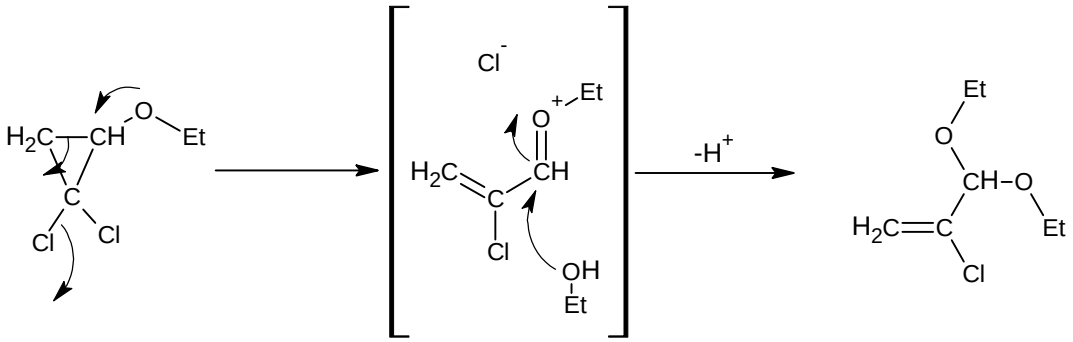
This reaction is exothermic, thus an ice-water bath was required during the addition of the base (NaOH), and for over 2 h before the reaction slowly reached r.t. In order to achieve satisfactory mixing of the two phases, vigorous stirring with a mechanical stirrer was applied. 1,1-dichloro-2-ethoxycyclopropane (**1**) was isolated in 89% yield.



1

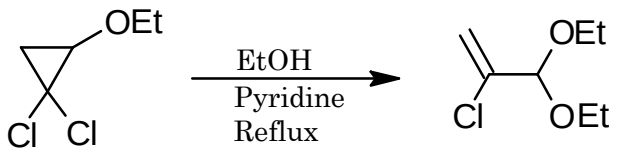
Scheme 2.2 Synthesis of cyclopropan.

The next reaction was ring opening of compound **1,** a reaction which was first observed by Skattebøl.[32] The reaction is facilitated by the non-bonding electrons of oxygen atom which attack the ring and help the cyclopropane to undergo ring opening and form a cationic intermediate (Scheme 2.3).



Scheme 2.3 Ring opening of 1,1-dichloro-2-ethoxycyclopropane.

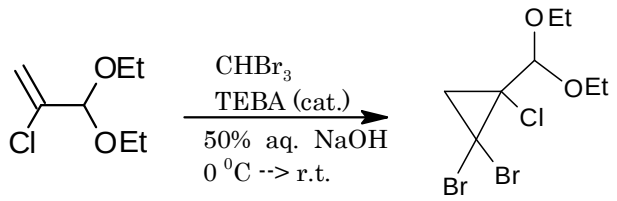
This intermediate was attacked by ethanol, and hydrogen chloride was thus formed (Scheme 2.4). Pyridine was used as a base to neutralize the generated hydrogen chloride from the reaction. Pure ethanol and pyridine was used without any purification in this reaction. The compounds were mixed and warmed to reflux with stirring for 48 h. Heat was necessary in this step of the reaction to induce the thermal ring opening reaction. Then the reaction was cooled down to room temperature and ethanol was removed by evaporation. Most of pyridine was removed by washing the organic phase with an aqueous solution of copper sulphate. The organic solution was filtered through a small plug of alumina to remove drying agent ($MgSO_4$) and all remaining pyridine complex in the solution. After evaporation of solvent in this step, distillation afforded (93%) yield of the compound.



1 **2**

Scheme 2.4 Ring opening of cyclopropan.

Cyclopropanation was done in the third step, which was performed by Makosza condition (Scheme 2.5)[24], and is similar to the first step in the reaction. Bromoform was used instead of chloroform.

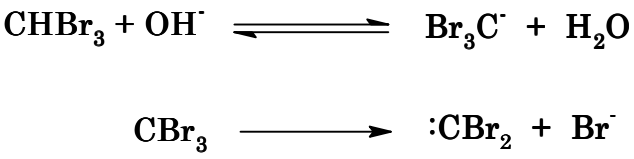


2 **3**

Scheme 2.5 Formation of cyclopropan.

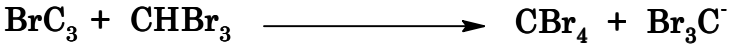
Kvernenes reported that a significant amount (10 equivalents) of bromoform is required to give a good yield of product in this step of reaction.[22] However, the formation of tetrabromomethane (CBr_4), as a by-product, can give a potential risk during the reaction. The problem is using of more bromoform in the reaction can facilitate the formation of CBr_4. The reason is appeared after the proton is extracted and anion formed, and it can react as a nucleophile and as a base. As a nucleophile, the anion reacts with another bromoform molecule, and abstracting a bromide atom instead of a proton, and then creates tetrabromomethane as a by-product. As a base, the anion reacts with another bromoform molecule, and then creates another anion while regenerating itself as a bromoform molecule again (Scheme 2.6).[27]

Reaction of bromoform in the third reaction



As a nucleophile

As a base:



Scheme 2.6 Formation of CBr_4 as a by-product.[27]

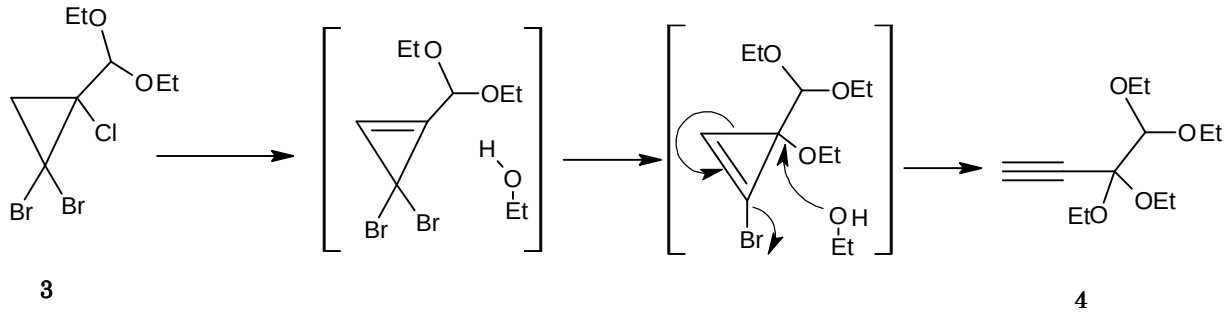
A large amount of tetrabromomethane as a by-product was formed when an excess amount (10 equivalents) of bromoform was used. An emulsion resulted and it was difficult to avoid by usual filtration. Less bromoform is required to reduce the problem with by-product and get a satisfactory yield of product.

Significant amount of bromoform (6 equivalents) is required to offer a good yield of cyclopropane.[31] Last attempt in formation of TEB shown that small amount of bromoform gave fewer by-products.

Unreacted bromoform was recovered by distillation. Valdersnes reported that the use of recycled bromoform can give a high yield of product in this step rather than the use of new bromoform.[38]

The product for this reaction could not be distilled off, and this was because of oil pump which was unstable. The crude product was black and tarries, and used in the next step, without any purification.

The last step in the preparation of TEB (**4**) was ring opening of trihalocyclopropane (**3**) (Scheme 2.7) as described in the procedure published by Sydnes and Bakstad.[35]



Scheme 2.7 Ring opening of the 1,1-dibromo-2-chloro-2-diethoxymetyl-cyclopropane.

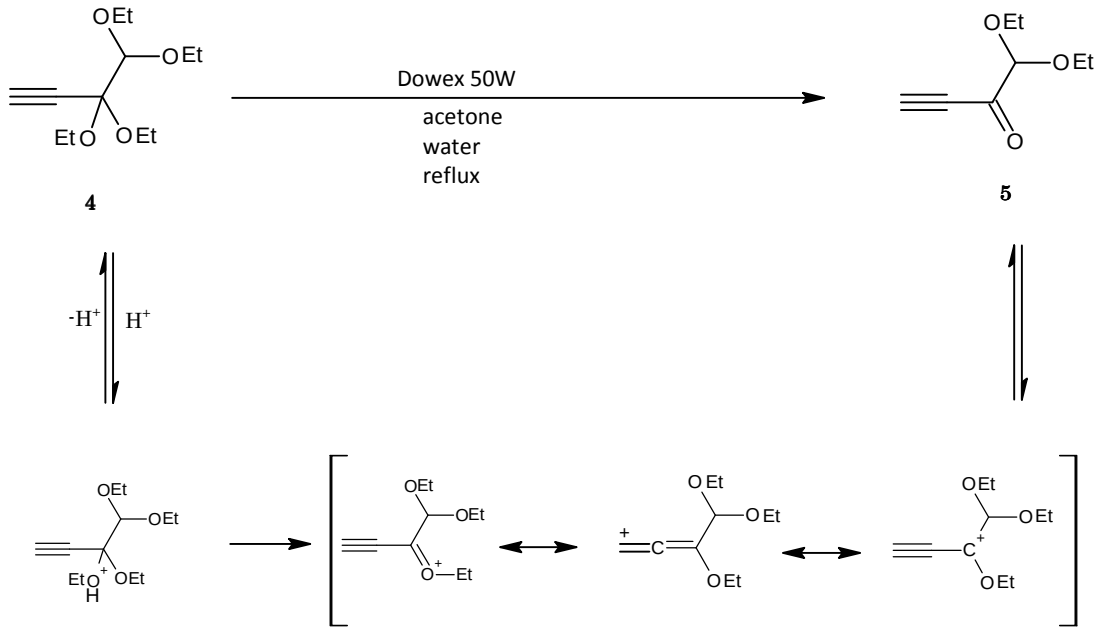
Intermediate in this step is occurred by alkoxide induced elimination. Ethanol is attacked to the acetal groups by hydrogen bonding, and this will be the reason to loss bromide, and gives the ketal product. Ring opening occur and 3,3,4,4- tetraethoxybut-1-yne **4** (TEB) will be afforded.

^{1}H-NMR and ^{13}C-NMR spectra of the product in this step have shown a pure compound of TEB and free from by-product. The two first fractions which were collected during distillation contain pure TEB, but the third one was TEB with some unknown impurities.

2.2 Deprotection of ketal group

1,1-Diethoxybut-3-yn-2-one (5)

Ketone preparation was done according to the procedure described by Leiren.[23] The reaction was started by adding Dowex 50W, a strong acidic catalyst, to compound **4** and mix it in a solution of aqueous acetone (Scheme 2.8). The use of Dowex resulted in selective deprotection of the ketal group, leaving the acetal group untouched. The reason for this regioselectivity is probably the electron contribution from the alkyne, which is capable of delocalizing the cationic intermediate formed in the reaction and also forms a stable product in form of a conjugated ketone.[22]



Scheme 2.8 Hydrolysis of ketal.[22]

Leiren compared using of Dowex 50W in a solution of aqueous acetone against the use of *p*-TSA in a solution of aqueous THF. She found that the yield was the best to be used for the reaction with Dowex 50W (80%) than *p*-TSA (49%).23 She concluded that the Dowex 50W method was the best to use for making ketone **5**.

Leiren also reported the importance of the reaction time and found that a shorter reaction time than 24 h was sufficient to convert most of the TEB into ketone **5**, and minimize the production of by-product. She compared two different reaction times for both Dowex 50W (24 h and 12 h) and *p*-TSA (10.5 h and 2 h). The longer reaction time gave a lower yield of product, and more by-products were formed. Kvernenes originally tried 8 h as a reaction time,[22] and Flemmen tried 24 h as a reaction time.[9] It seems therefore that the better results were obtained by reducing the reaction time and using a new batch of acid catalyst.

A new batch of Dowex 50W was used to deketalize **4,** with 12 h reaction time on a small scale. The yield was not good as it expected (56%). Therefore the reaction was tried again with the same batch of Dowex 50W, but with 8 h reaction time, and an excellent yield of ketone **5** was obtained (90%).

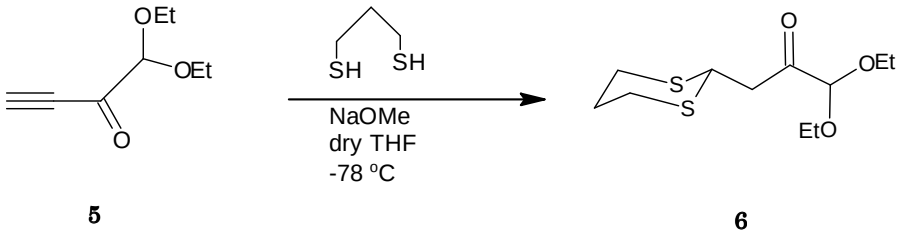
2.3 Double conjugate addition of propane-1,3-dithiol

1,1-Diethoxy-3-(1,3-dithan-2-yl)propan-2-one (6)

Generation of β-keto 1,3-dithiane can be achieved by double conjugate addition of dithiol to propargylic ketones, esters, and aldehydes in a good yield.[36] The compound is important because of its two differently protected aldehyde groups and one keto moiety in a four carbon structure.

The reaction was described in the literature by Ley and co-workers by using methanol as a solvent,[14] and then Valdersnes modified the reaction by using dry THF as a solvent to optimize the reaction condition,[33] with cooling (-78 ˚C) and nitrogen atmosphere flushing through to minimize the formation of dimer, sodium methoxide was used as a strong base to affect a double conjugate addition of dithiol (Scheme 2.9).

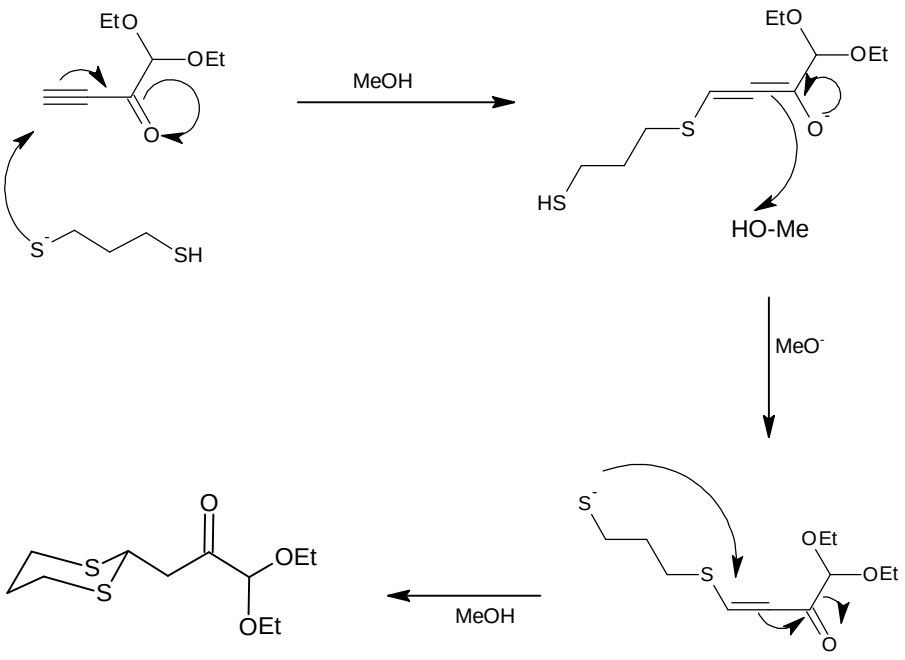
The reaction procedure was followed as described in the literature.[27,31] Purification of the product by flash chromatography gave 88% of compound **6**. A small amount of TEB which existed in the reaction did not complicate the reaction, since the ketal **4** does not react with the dithiol.



5 6

Scheme 2.9 Synthesis of compound **6.**

A double Michael addition of dithiol to the terminal carbon was involved in this step which is and depicted in Scheme 2.10 and described in the literature.[33] The methods of this reaction require a catalytic amount of a Lewis acid or a strong base, to activate the electrophile or nucleophile, respectively.[33]

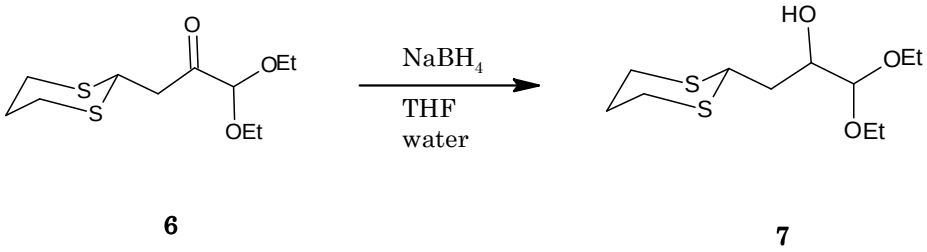


Scheme 2.10 Double Michael addition of propane-1,3-dithiol to a propargylic carbonyl system.[23]

2.4 Reduction of ketone

1,1-Diethoxy-3-(1,3-dithian-2-yl)-prpan-2-ol (7)

Reduction of ketone (**6**) was performed by sodium borohydride in aqueous THF. The product was isolated by flash chromatography and 1,1-diethoxy-3-(1,3-dithan-2-yl)propan-2-on (**7**) was obtained as a clear colorless, viscous liquid in excellent yield (97%). The reaction was fast; TLC showed that most of the starting material had been consumed within 15 min.

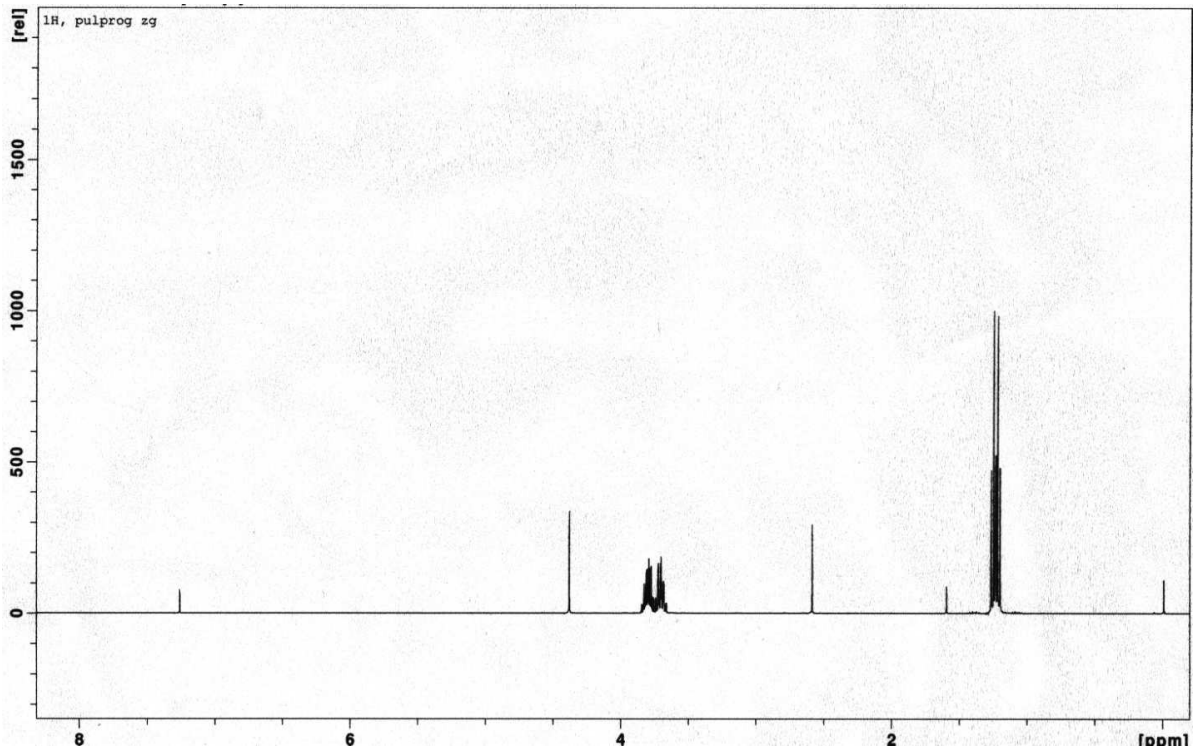


6 **7**

Scheme 2.11 Reduction of ketones.

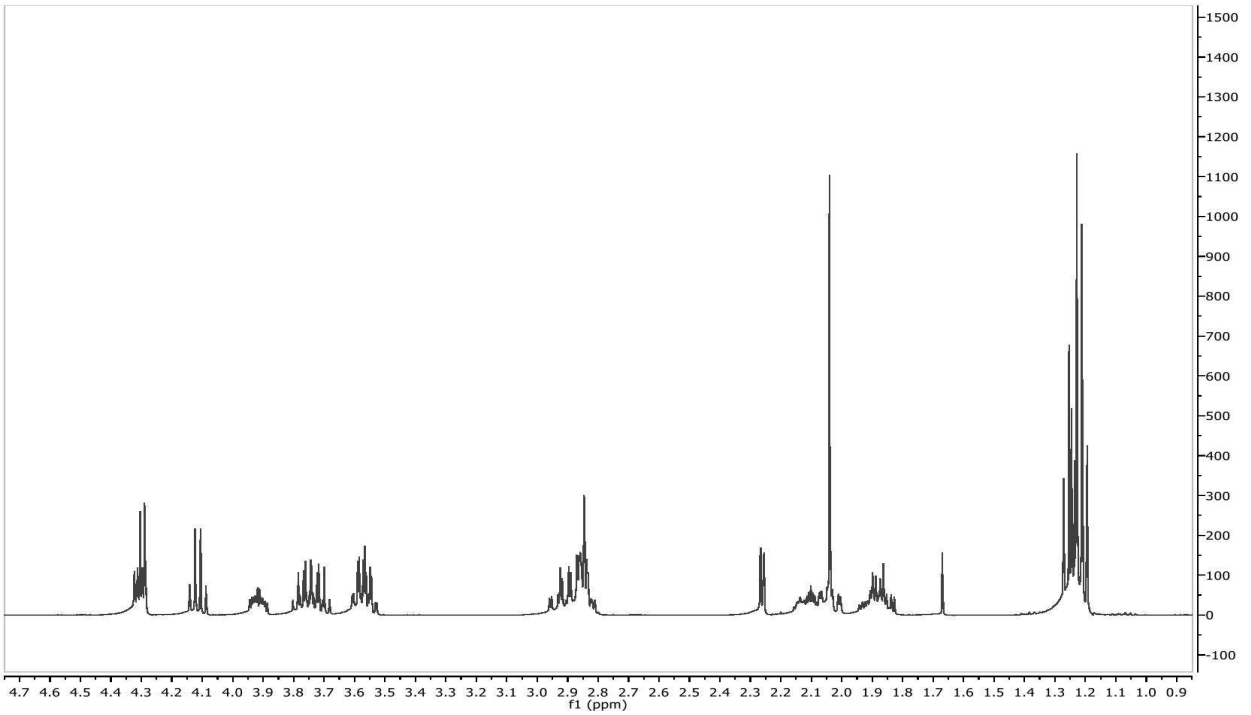
The original procedure was published by Zeynizadeh and Behyar,[43] and then modified by Valdersnes.[33] In this reaction 0.5 mol equivalent of sodium borohydride was used instead of 2 mol equivalents, and the reaction was run at 0 ˚C instead of reflux.

The rest of the reaction was collected in to fractions. The first sample collected was unreacted reactant. The second fraction had a light yellow color, and then it was changed to a dark yellow, after one day, when it saved at r.t. The sample was analyzed by ^{1}H-NMR experiment which confirmed purity of TEB (Figure 2.1). It is impossible to form TEB from compound **6** in this reaction, especially when ethanol is not present, so probably the starting material was contaminated with TEB (See Figure A6).

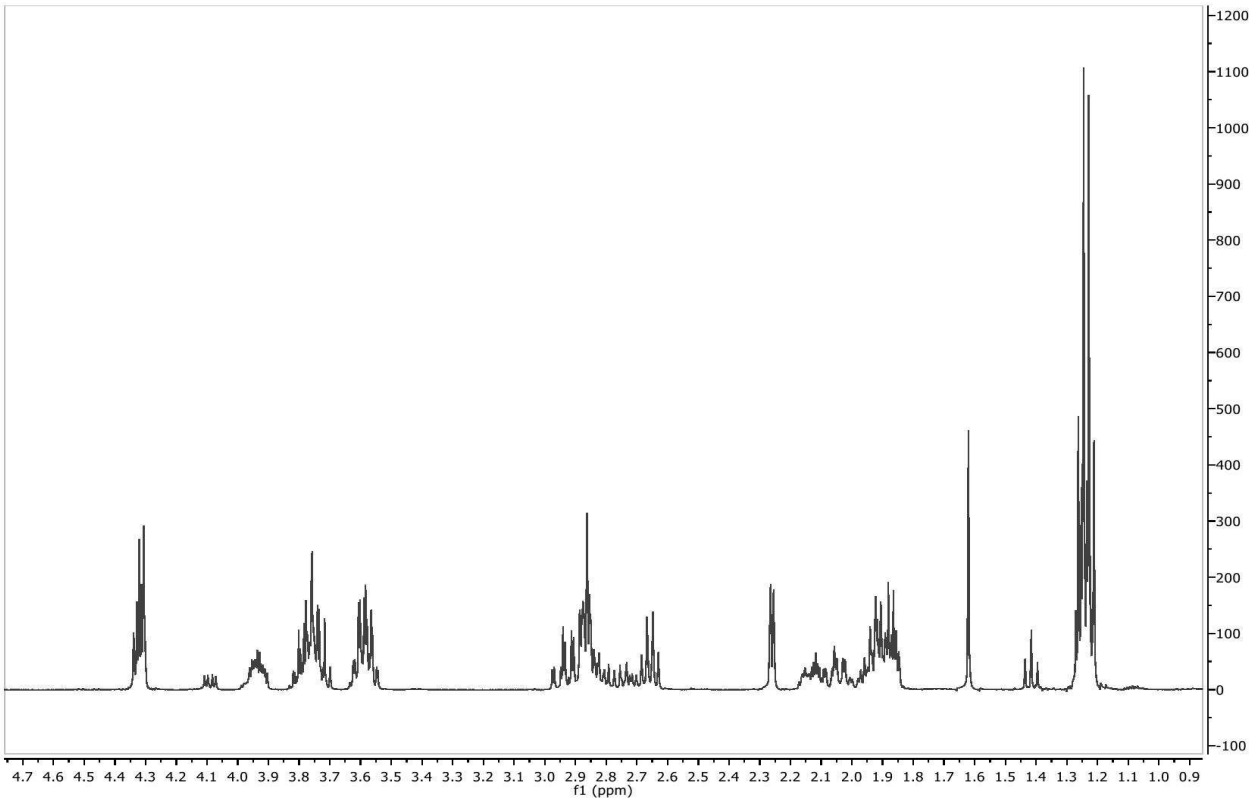


Spectrum 2.1 ^{1}H-NMR spectrum for the second fraction from flash chromatography.

Compound **7** was saved for 7 weeks in the refrigerator, and there was no change in color and viscosity for the freshly made and the 7 weeks of saving in refrigerator. ^{1}H-NMR spectra confirmed the stability of compound **7** and no by-product formed during one day and 7 weeks stored in refrigerator. Nilsen has reported that both color and viscosity for the compound did not change, while Flemmen has reported the change of both color and viscosity for the compound after storage 4 weeks in refrigerator.[9,27] This probably indicate a by-product is formed in Flemmen's sample, but caused this change is unclear.



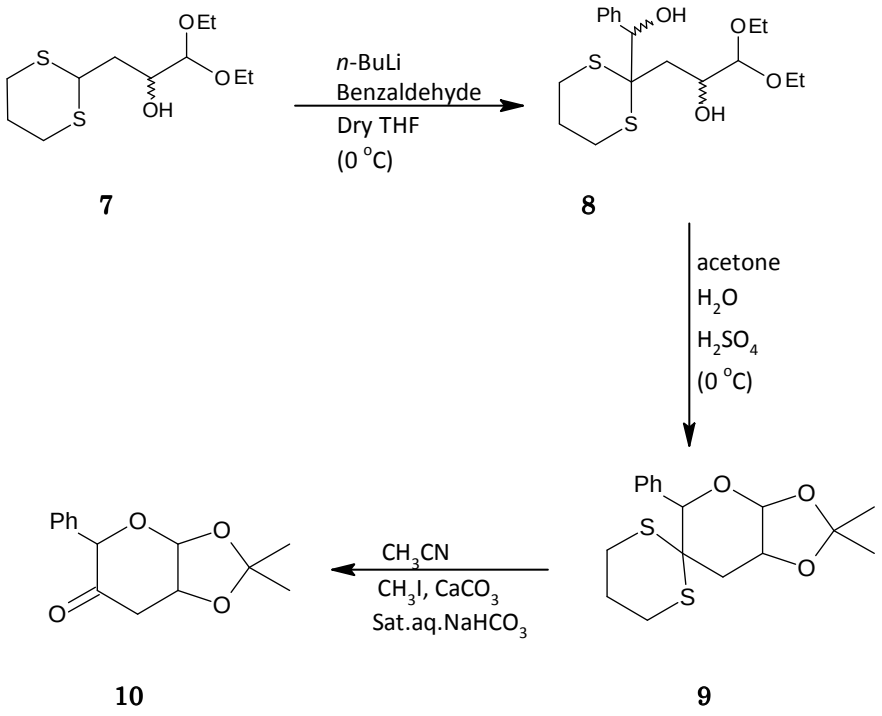
Spectrum 2.2 ^{1}H-NMR spectrum for compound **7** after 1 day in refrigerator.



Spectrum 2.3 ^{1}H-NMR spectrum for compound **7** after 7 weeks in refrigerator.

2.5 Chain elongation using β-hydroxydithiane 7

5,5-Diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**), 8-Oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**9**) and 2,3,6-trisubstituted 5-pyranone (**10**) were synthesized in this project following procedures which are described in Valdersnes and Nilsen.[27,38]

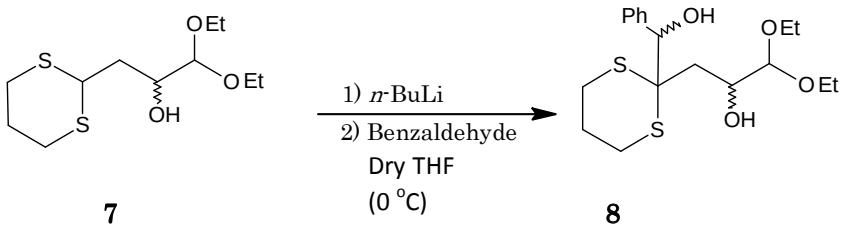


Scheme 2.12 Synthesis of compounds **8**, **9**, and **10.**

2.6 Chain elongation

5,5-Diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (8)

The reaction was done by addition of *n*-butyllithium to 1,1-diethoxy-3-(1,3-dithian-2-yl)-propan-2-ol (**7**), and then benzaldehyde as described by Nilsen.[27] The total yield was 71% for 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**) after flash chromatography (Scheme 2.14).



7 8

Scheme 2.13 Synthesis of compound **8.**

Valdersnes tried this reaction by using HMPA as a co-solvent, and *t*-BuLi in THF at -78˚C, but the reaction was unsuccessful or generated a product with coupling of carbonyl compound on protective alcohol group rather than at dithiane.[33] The reason was at lithiated dithiane was existed as a contact ion pair in THF, while the use of HMPA separates ion pair, and affect the reaction.[37]

The reaction requires two equivalents of *n*-BuLi was used, one to abstract the unprotected hydroxyl proton, and the other to abstract the proton at C-2 of the dithiane,[33]

Assignment of ^{1}H-NMR spectrum for compound 8

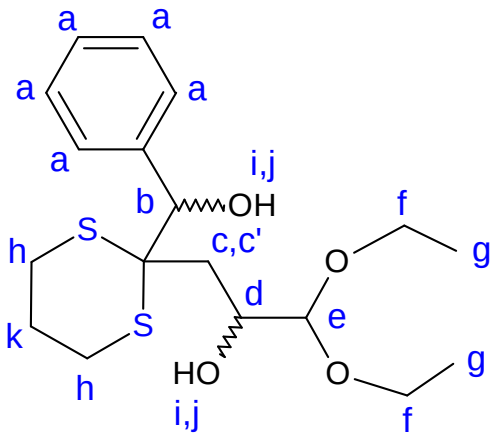
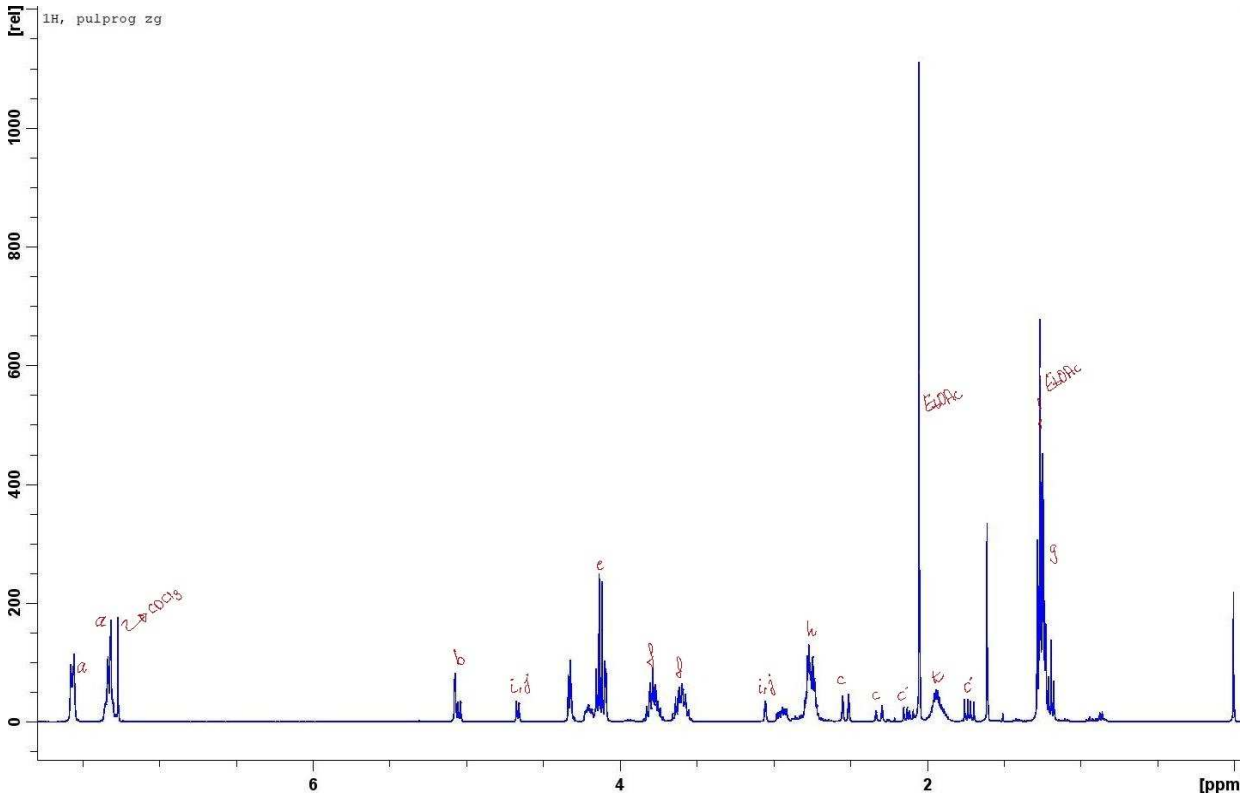


Figure 2.1 Hydrogen distributions for compound **8.**



Spectrum 2.4 ^{1}H-NMR spectrum for compound **8.**

The spectra of compound **8** were in agreement with the spectroscopical data presented by Nilsen and Flemmen (Spectrum 2.4).[9,27]

^{1}H-NMR spectra proves the presence of phenyl group with two peaks experience deshielding. All the five aromatic hydrogens has not the same chemical shift, since alkyl substituents on the ring tends to shift the hydrogens in the *para* and *ortho* positions further upfield than the hydrogens in the *meta* position,[9] it can be assumed that the two hydrogens giving the signals furthest downfield are hydrogens *a* in the meta position, and that the hydrogens *a* in the *para* and *ortho* positions give the signal upfield.

The hydrogens *c* and *c'* exhibit quit different chemical shift. These hydrogens appear as two sets of doublets upfield, and as two sets of doublets further downfield. The hydrogens *i* and *j* appear as a broad signals that do not couple with any other hydrogen.

The hydrogens at position *f, g*, *k*, *h, e* and *d* signals are previously known from the spectra for early compounds **5**-**7** (see appendix). Hydrogen at position *b* does not coupled to any other hydrogen, and the proximity to the aromatic ring gives the signal furthest downfield of the non-aromatic signals as two overlapping singlets.

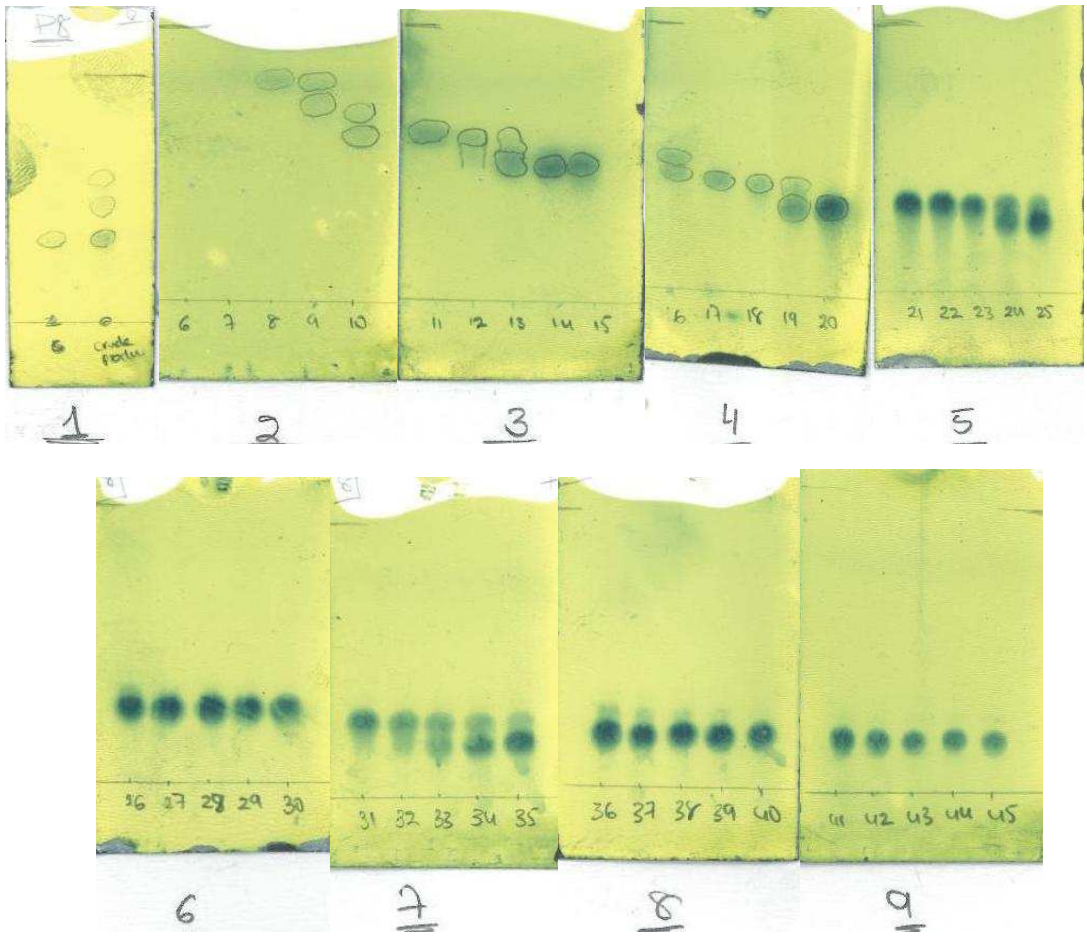


Figure 2.2 TLC plates from flash chromatography for compound **8**.

Plate 1 is for starting compound and crude product of this reaction. Start material consist of one spot, while the crude product contains three spots, as shown in the plate.

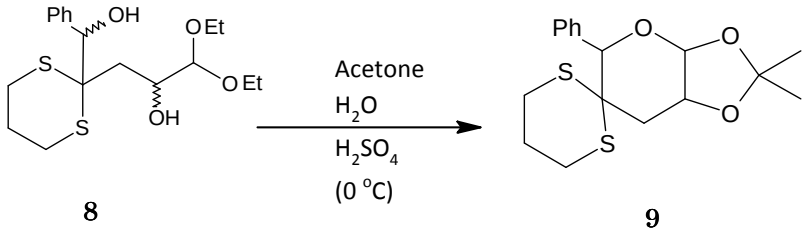
Plate 2, 3, 4, 5, 6, 7, 8 and 9 are for the collection of samples eluted from flash chromatography column. Total spots consist of nine spots which means nine different compounds was obtained in this reaction or another reason like column package, wrong diluents, TLC plate or so on. The reason for this is probably due to the different properties of TLC plates from different package. However, the first two plates were from an old package, while the others were taken from a new package.

^{1}H-NMR spectra was done for each similar spots from plat 2 to plate 7, and all of them indicated the unreacted compound of starting material. While the other spots from plate 8 indicates to compound **8**.

2.7 Cyclization

8-Oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (9)

Cyclization of compound **8** was carried out by using wet acetone at 0 ˚C and sulphuric acid as a catalyst (Scheme 2.16). The total yield of the product was 59% after purification by flash chromatography; the rest was unreacted reactant with some unknown impurities.



8 **9**

Scheme 2.14 Ring formation of compound **8.**

The reaction was done according to the procedure described by Valdersnes,[33] ring formation of compound **8** was tried before hydrolysis of dithiane reaction. Valdersnes tried the reaction when both substituent groups were hydrogen atom and he obtained 60% of the product. While in this study, the reaction tried with compound **8** when the substituted groups were phenyl group and hydrogen atom for hydroxyl group, total yield of compound **9** was 59%, the rest was unreacted starting material and mixing of product with unknown impurity, as shown in TLC plates (Figure 2.3). Spots from no. 3 to 5 indicate the product; spots from no.6 to 7 are for an impure product, while the spots from no.12 are for unreacted reagent.

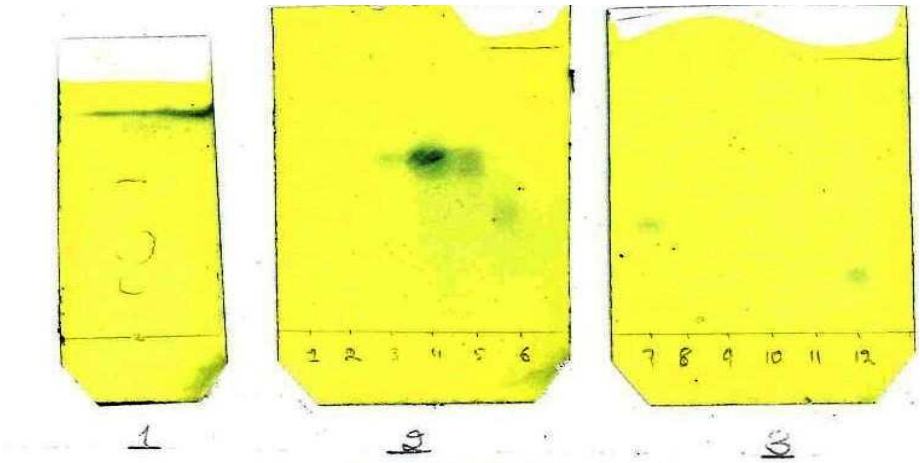
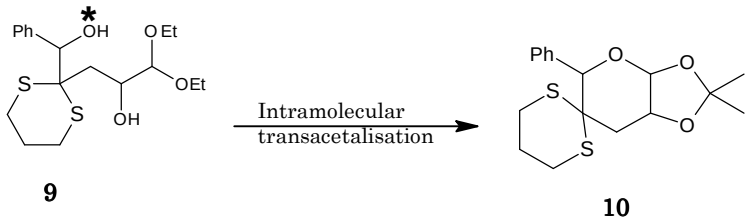


Figure 2.3 TLC plates from flash chromatography for compound **9**

The reaction occur via an intramolecular transacetalisation to furnish the protonation of hydroxyl group at position *, and then giving a desired product (Scheme 2.17). Valdersnes reported that the ring formation can be difficult, due to the different functional groups in compound.



9 **10**

Scheme 2.15 Protonation of hydroxyl group at position *.

Upon purification by flash chromatography, the reaction proved to give quite a pure sample of the wanted product, and spectroscopic data agreed with those reported in the literature.[27]

Assignment for ^{1}H-NMR spectrum for compound 9

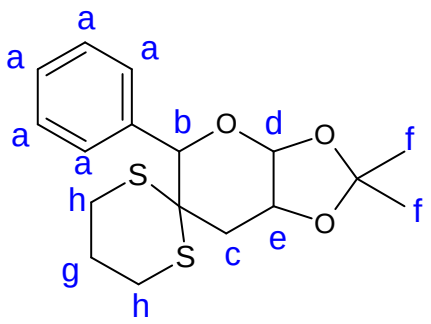
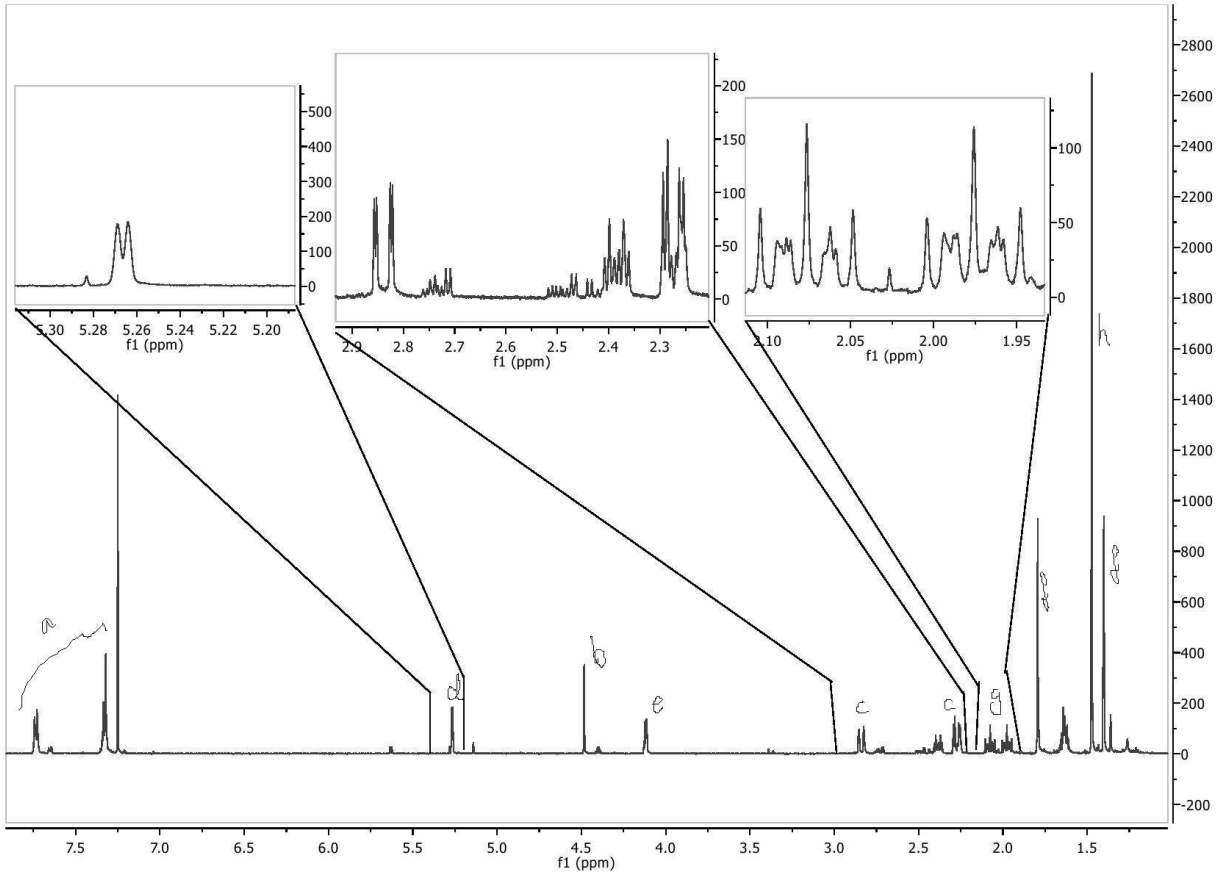


Figure 2.4 Hydrogen distributions for compound **9.**



Spectrum 2.5 ^{1}H-NMR spectra for compound **9.**

As shown in Spectrum 2.5, the signal of aromatic hydrogen atoms ***a*** does not changed, and appears at the same chemical shift as compound **8**. Hydrogen atom at position ***b*** does not couple to any other neighbor hydrogen, and it appears as a strong singlet and more downfield than the hydrogens ***b*** for compound **8**, because of phenyl group and oxygen as neighboring group. The signal for hydrogen ***d*** appears as a doublet and more downfield than the other hydrogen atoms, because of the two oxygen neighbor groups. The hydrogens *e* appears as a triplet and quite downfield in the spectrum.

Hydrogen atom ***c*** is quite upfield in the spectra and appears as a doublet at two positions.

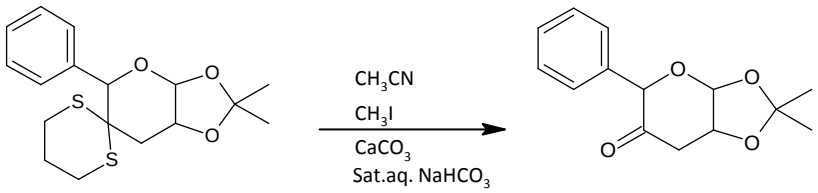
Hydrogens ***g*** and ***h*** is known from the previously spectra for compound **9** and it appears as a double multiplet at position (2.1 – 1.8 ppm) and a strong singlet at position 1.47 ppm, respectively.

Hydrogens ***f*** appears as a two strong singlets which are similar to the literature,[27,38] and both of them are integrate for three hydrogens each. The first region of ***f*** is more appears at 1.79 ppm, while the other appear at 1.40 ppm

2.8 Hydrolysis of dithiane

2,3,6-Trisubstituted-5-pyranone

Many different methods are available for the hydrolysis of dithiane, and conversion of dithiane **9** to the corresponding ketone **10**.



9 **10**

Scheme 2.16 Hydrolysis of dithiane.

Three general methods were commonly used for hydrolysis of dithiane: 1) metal coordination, 2) oxidation, and 3) alkylation.[4]

The different methods were used by Valdersnes to hydrolysis dithiane to the corresponding ketones.[33]

Method A: $NaNO_2$, AcCl, DCM

Method B: CH_3I, $CaCO_3$, CH_3CN, H_2O, THF

Method C: CH_3I, $CaCO_3$, H_2O

Method D: I_2, sat. $NaHCO_3$ (aq.), CH_3CN

He found that method A did not give any desired product, and mainly recovered starting material was obtained from the crude product. Method B gave a low yield. But it required a large excess of methyl iodide, heating, and long reaction time. Method C and D were the most successful ones and gave a satisfactory yield of product after purification.

In this study, we tried the reaction with methyl iodide and acetonitrile at r.t, followed by Valdersnes procedure (Method C) which gave the best yield according to this method.[33]

The reaction was carried out by using a small amount of methyl iodide and acetonitrile at room temperature (Scheme 2.17).

After purification by flash chromatography two fractions were obtained, as shown in figure 2.8. The first to spots from nr.4 to nr.5 which were just the unreacted starting material, and spot from nr.6 was the product with unreacted reactant and some impurities. But the collection from nr.7 did not give any amount of sample in the flask to be tested. The collected sample from nr.4 and 5 gave 0.031 g as a white, slightly yellow solid, and nr.6 gave 0.01 g as a slightly yellow solid. The second flash chromatography should have been probably run for the fraction, and obtain more pure compound. Purification for compound 10 could not be completed and analyzed further.

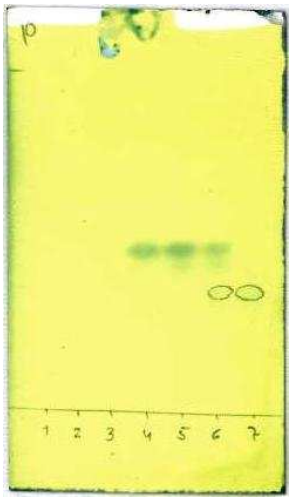
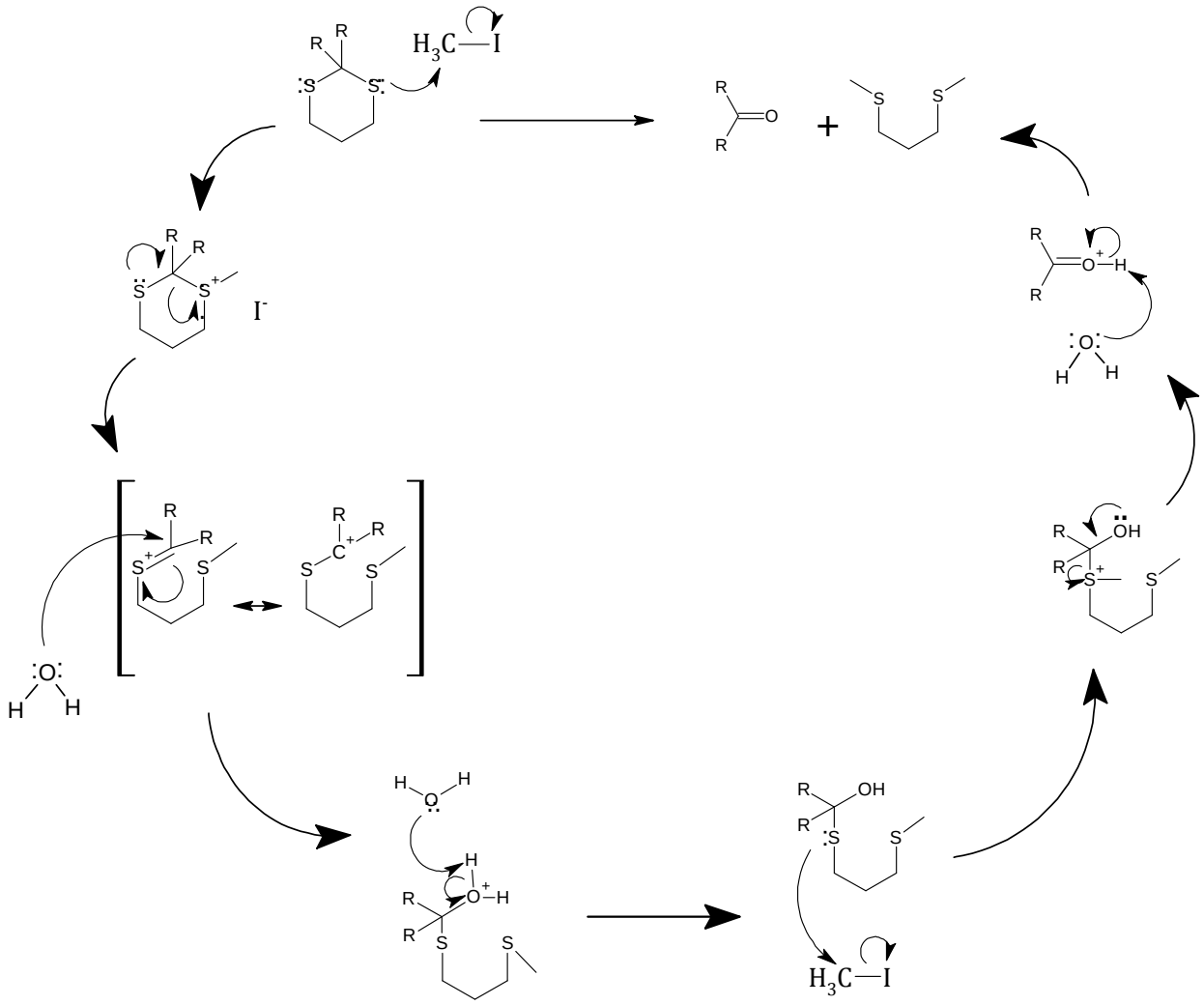


Figure 2.5 TLC plate from flash chromatography of compound 10.



Scheme 2.17 Mechanism of dithiane conversion to ketone.

Assignment for ^{1}H-NMR spectrum for compound 10

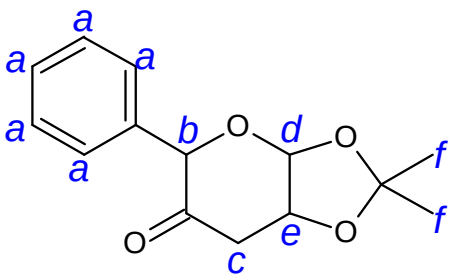
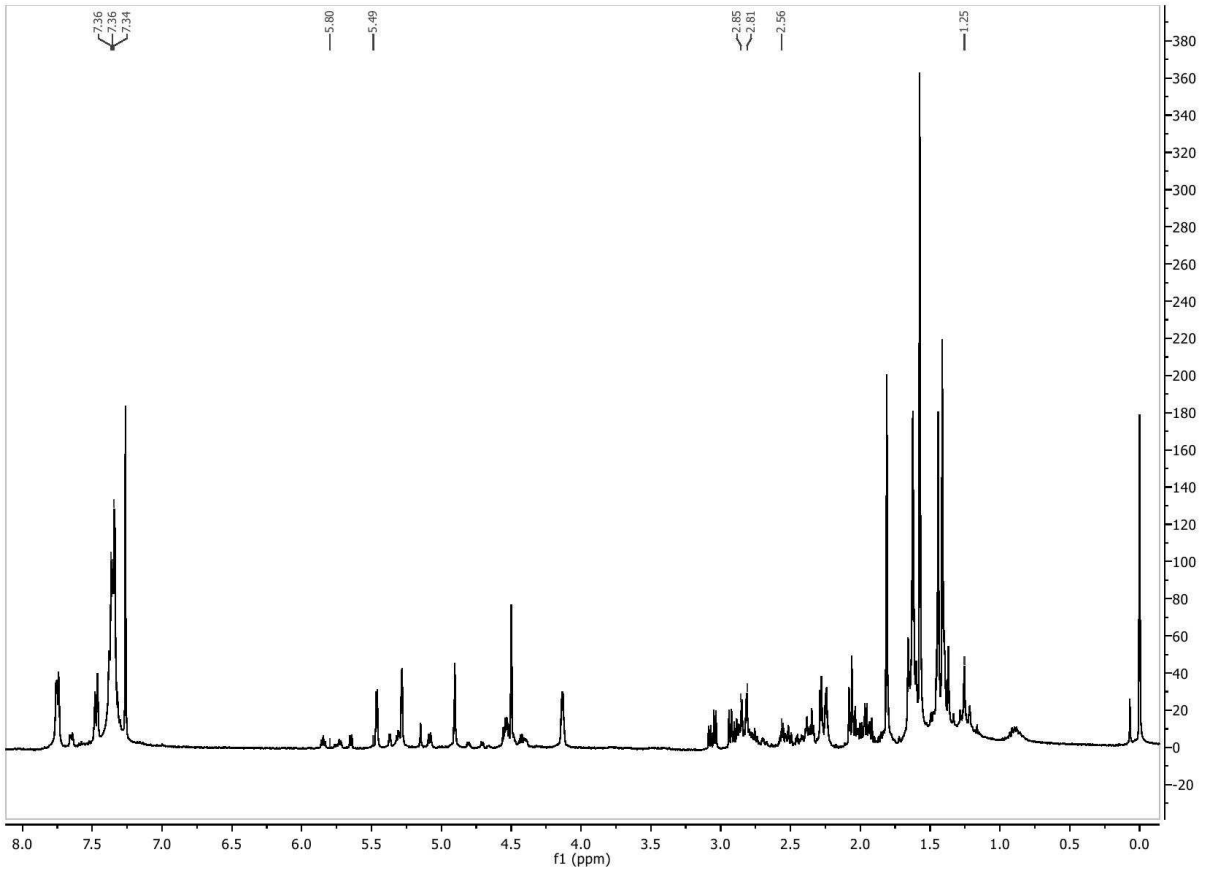
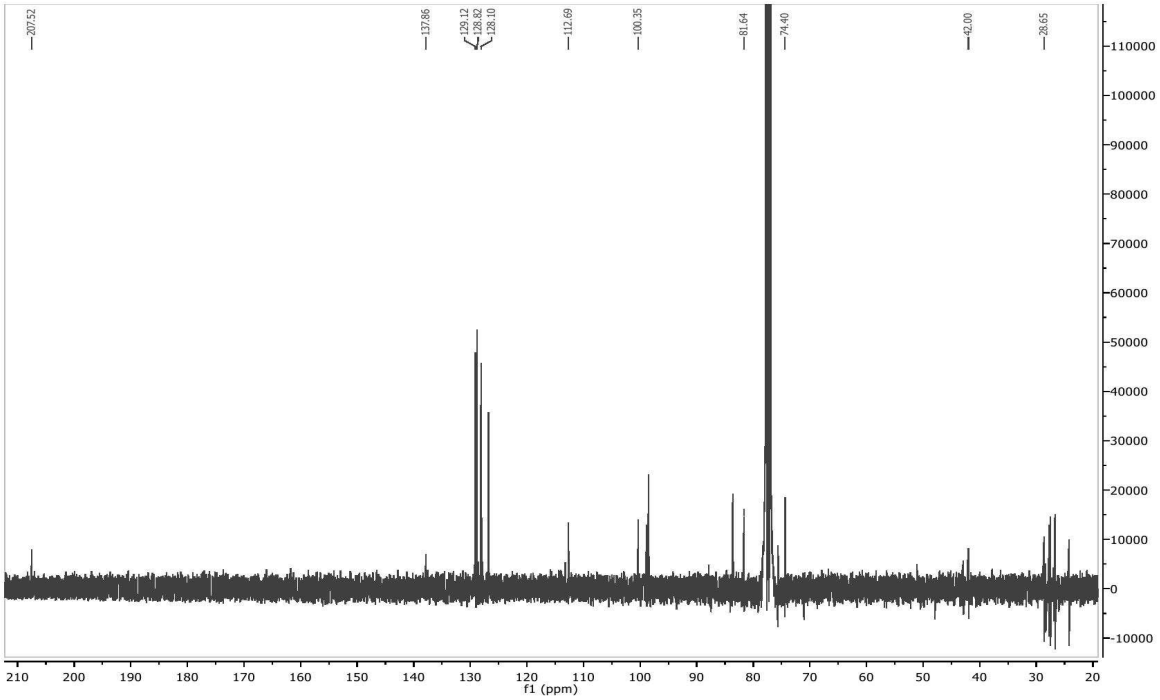


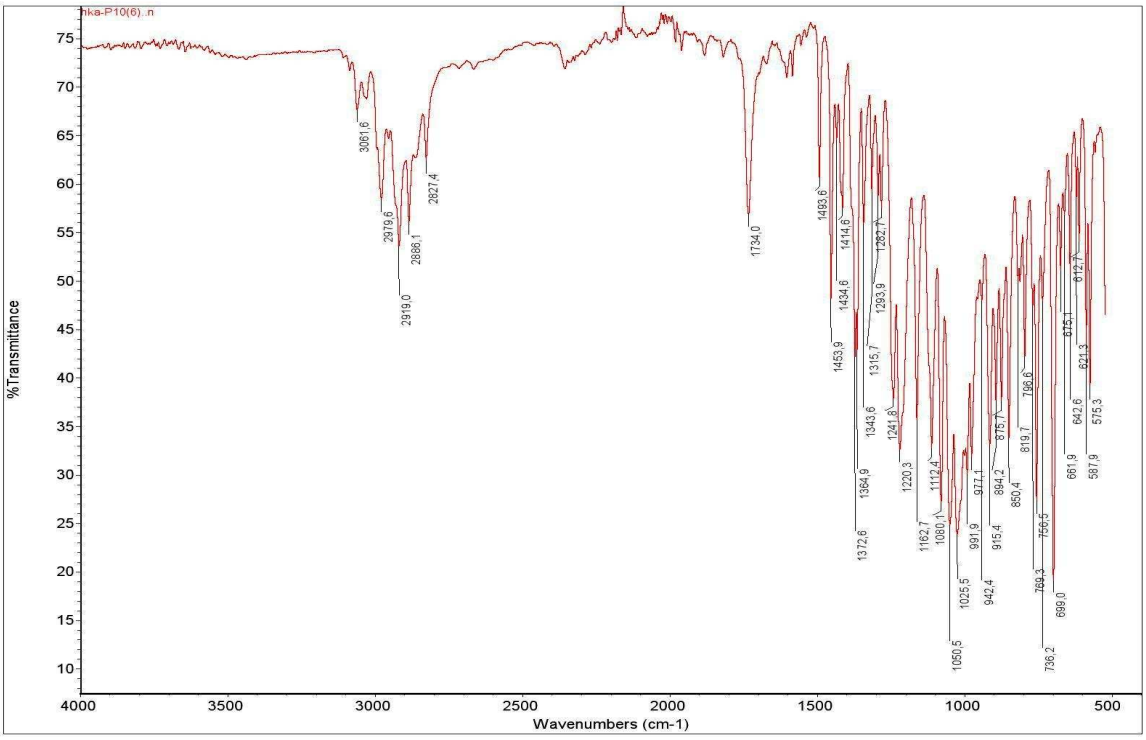
Figure 2.6 Hydrogen distributions for compound **10.**



Spectrum 2.6 ^{1}H-NMR spectrum for compound **10.**



Spectrum 2.7 ^{13}C-NMR spectrum of compound **10**



Spectrum 2.8 IR spectrum of compound **10**.

As shown in ^{1}H-NMR spectrum of **10** (Figure 2.9), the compound is not entirely pure and it is therefore difficult to analyze the ^{1}H NMR spectrum in detail. Peaks due to unreacted starting material and the product. The presence of a carbonyl group is substantiated by a clear signal at 207 ppm in the ^{13}C NMR spectrum and a sharp peak of 1734 cm^{-1} in the IR spectrum. This is the important observation that 2,3,6-trisubstituted-5-pyranone **10** has been obtained

2.9 Conclusion

One of the most important observations in this study is in the preparation of **4** (TEB). The use of tetrabutylammonium iodide as a catalyst make much more easily to done third step of TEB than to use triethylbenzylammonium chloride, and the separation of organic phase could be better during a short time.

A significant amount of bromoform (6 equivalents) is recommended to obtain a satisfactory yield of 1, 1-dibromo-2-chloro-2-diethoxymetylcyclopropane (**3**). Tetraboromethane as by-product can be formed by using large amount of bromoform in the third step of preparation TEB.

The successful preparation of compound 5,6, and 7 suggests that these compounds can be obtained in excellent yields when the reactions are scaled up. Chain-elongated reaction is also performed by adding aldehydes or ketones to β-hydroxydithiane **7**. Compound **9** was synthesized by cyclization of compound **8,** then **9** could be obtained in a satisfactory yield, which is a good useful compound to further reactions for the synthesis of a wide range of carbohydrate analogues.

Further work would be interesting to done based on this project.

There is a need to find good solvent system for purification and better separation of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**) by flash chromatography.

Preparation of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**9**) could be tried by more than two attempts to obtain a satisfactory yield.

Hydrolysis of dithiane reaction could be trying by different methods as Valdersnes tried and reported in his PhD project.[33] The presence of starting material in preparation of 2,3,6-trisubstituted-5-pyranone indicates that the reaction need the long reaction time than that attempted. An excess amount of reagents especially methyl iodide may be required to offer a significant yield of product. Purification of the compound by flash chromatography is needed to find a good solvent which could not be done in this project.

With a good synthesis of compound **10** a starting material is available for making a range of modified deoxygenated carbohydrate by reacting the carbonyl group with Grignard reagents.

Chapter 3. Experimental

3.1 Equipments, chemicals, and methods

From the beginning of this project, IR was recorded on a Nicolet impact 410 spectrometer with a product as a liquid film between NaCl-plates. Absorption of the product are given in wave-number (cm^{-1}) and intensities are characterized as strong (s), medium (m), weak (w), or broad (br).

^{1}H-NMR spectra were recorded on a Bruker spectrospin DXP 400 and AV 500, and TMS was used as the intern reference (δ_H = 0 ppm). The chemical shifts are given in ppm and the coupling constants *J* in Hertz (Hz). Multiplicity is given as single (s), doublet (d), triplet (t), quarter (q), or multiplett (m). The numbers of protons are reported according to the calculation of integral of each peak in the ^{1}H NMR spectrum. While in ^{13}C NMR spectra, the solvent ($CDCl_3$) peak was the reference.

Flash Column Chromatography was carried out in this project by using J.T. Baker Silica Gel as stationary phase, and a mixture of Hexane (containing a mixture of isomer) and ethyl acetate as mobil phase. Analytical TLC was performed on Macherney-Nagel pre-coated TLC-sheets with silica gel 60 with fluorescent indicator UV254 and visualised by staining using ethanolic acidic phosphomolymdic acid solution.

Mass Spectra were obtained on JEOL AccuTOF MS JMS-T100LC spectrometer operated in the DART/ESI+ mode.

Dry THF was obtained by distillation from sodium/benzophenone. The other solvents and reagents were purchased from Sigma-Aldrich Norway. Intern atmosphere was achieved with nitrogen gas.

The pressure from water aspirator pump was estimated between 10-15mmHg.

3.2 Preparation of TEB

1,1-Dichloro-2-ethoxycyclopropane (1)

A 500 mL three-necked round-bottom flask was equipped with a condenser and magnetic stirrer. The flask was charged with ethyl vinyl ether (36.0 g, 0.50 mol), chloroform (239 g, 2.00 mol), and TEBA (0,50 g). The flask was placed on an ice bath and stirred vigorously by a mechanical stirrer. After 10 min a 50% aqueous solution of NaOH (60 g, 1.50 mol in 60 mL water) was added dropwise in 25 min. The reaction mixture was stirred at bath temperature for 2 h and then at r.t. for 22 h to ensure proper mixing between the two phases. Hydrochloric acid (150 mL, 6M) was added carefully over 20 min on reduced stirring. The hydrolysate was transferred to a 1 L separatory funnel, and the flask was washed with water (2 x 50 mL) which is also added to a funnel. After addition of more water (300 mL) to the funnel, the mixture was shaken and the organic layer was separated. Dichloromethane (3 x 100 mL) was used to extract the aqueous phase, and the organic phases were collected, dried with $MgSO_4$, filtered and concentrated under reduced pressure on a rotary evaporator (40 ˚C/300 mmHg). The crude product was purified by distillation under reduced pressure and gave 70.03 g (89%) of 1,1-dichloro-2-ethoxycyclopropane as a clear liquid, b.p. 35 ˚C/7 mmHg (lit.[21] 55 ˚C/30 mmHg). Spectroscopic data were in agreement of those published in the literature. [21]

2-Chloro-3,3-diethoxyprop-1-ene (2)

A 500 mL one-necked round-bottom flask was equipped with a condenser and magnetic stirrer. The flask was charged with compound **1** (54.31 g, 0.35 mol), pyridine (36.01 g, 0.45 mol) and ethanol (250 mL). The solution was refluxed with stirring (700 turn/min) for 48 h. Ethanol was evaporated on a rotary evaporator (40 ˚C/90 mmHg) and the remained liquid was transferred to a separatory funnel. The flask was washed with H_2O (2 x 50 mL) and then with CH_2Cl_2 (3 x 50 mL) which were added to the separatory funnel. More H_2O was added to a funnel, and then the organic layer was separated. The aqueous layer washed with CH_2Cl_2 (3 x 70 mL). The organic phases were collected and washed again with 0.7M aqueous solution of $CuSO_4$ (2 x 100 mL) then (2 x 50 mL). The organic phases were collected, dried with dry $MgSO_4$ and filtered through an alumina-plug (Al_2O_3). The mixture was concentrated on a rotary evaporator (40 ˚C/375 mmHg). Distillation was run for the reaction to give 53.37 g (93%) of 2-Chloro-3,3-diethoxyprop-1-ene as a clear liquid, b.p. 60 ˚C/15 mmHg (lit.[21] 70-78 ˚C/19 mmHg). Spectroscopic data were in agreement of those published in the literature.[21]

1, 1-Dibromo-2-chloro-2-diethoxymetylcyclopropane (3)

A 500 mL three-necked round-bottom flask was equipped with a condenser, and mechanical stirrer. The flask was charged with compound **2** (31.08 g, 0.19 mol), bromoform (292.75 g, 1.6 mol), and TEBA (0.38 g). The flask was placed on an ice bath and stirred virgously (500 turns/min) for 10 min. 50% aqueous solution of NaOH (120.50 mL) was added dropwise over 30 min and the reaction mixture were left stirring for 24 h. H_2O (500 ml) was added in to the flask and was left stirred for 1 h. The mixture was transferred to a separatory funnel and the flask was washed with H_2O (3 x 50 mL). The phases were left over night to separate, and the aqueous phase was extracted with dichloromethane (3 x 250 mL). The combined organic phases were dried with drying $MgSO_4$ over night, filtered, and concentrated on rotary evaporation (40 ˚C/375 mmHg). Bromoform was recovered by distillation (40 ˚C/10 mmHg). The product and tarry residue was left in the distillation flask, and then was used to next step of preparing TEB, without distillation for purifying product. The reason is due to the unstable oil pump that should be used for product purification by distillation.

3,3,4,4-Tetraethoxybut-1-yne (4)

A three-necked round-bottom flask was equipped with a condenser, and mechanical stirrer. The flask was charged with compound **3** and black tarry residue which was left from a third step (66.78 g), ethanol (54.8 mL), and TEBA (0.398 g). The flask was placed on an ice-bath and stirred virgously. 50% aqueous solution of NaOH (127.2 g, 3.18 mol) was added dropwise. The mixture was stirred virgously (500 turns/min) for 24 min. Water (250 mL) was added and was left stirred for 1 h. The mixture was transferred to a separatory funnel, and the aqueous phases were washed with dichloromethane (3 x 250 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated. Distillation afforded 16.42 g of title compound **4** as a light yellow liquid, b.p. 50-60 ˚C/0.05-0.1 mmHg (lit.[36] 53-59 ˚C/0.2 mmHg).

3.2 Deprotection of ketal group

1,1-Diethoxy-but-3-yn-2-one (5)

A one-necked round-bottom flask was charged with compound **4** (1.11 g, 4.83 mmol), Dowex 50W (1.388 g), acetone (25 mL) and water (1.2 mL). The mixture was stirred at reflux for 9 h. After cooling, Dowex 50W was filtered off and washed with acetone. Acetone was removed under reduced pressure (40 ˚C/150 mmHg). The mixture was transferred to a separatory funnel, water (3 mL) and dichloromethane (10 mL) was added. The phases were separated and the aqueous phase was washed with dichloromethane (3 x 20 mL). The combined brown yellow liquid was collected and dried with $MgSO_4$, filtered and concentrated on a rotary evaporator. The title compound **5** (0.68 g, 90%) was obtained as a yellow liquid by flash chromatography (Hexanes: EtOAc, 90:10).

3.4 Double conjugated addition

1,1-Diethoxy-3-(1,3-dithan-2-yl)propan-2-one (6)

A one-necked round-bottom flask was equipped with a condenser and magnetic stirrer. The flask was charged with NaOMe (0.338 g, 6.26 mmol), propane-1,3-dithiol (0.63 mL, 6.27 mmol), and dry THF (85 mL), and the mixture was left stirring for 5 min at (-78 ˚C) while nitrogen gas was flashed through. Compound **5** (0.65 g, 4.16 mmol) was dissolved in dry THF (20.8 mL), and then added dropwise to the mixture over 30 min. The reaction was left stirring for 15 h. Saturated NH_4Cl (25 mL) was added to the solution, and a white precipitate formed. The mixture was transferred to a separatory funnel, and the flask was washed with CH_2Cl_2 (2 x 10 mL) and H_2O (2 x 10 mL). CH_2Cl_2 (30 mL) was added to the funnel. The phases were separated, and the aqueous phase was washed with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over night with $MgSO_4$, filtered and concentrated under reduced pressure on a rotary evaporator. Flash chromatography (Hexanes:EtOAc, 90:10) afforded 0.97 g (88%) of the title compound **6**.

3.4 Reduction of ketone

1,1-Diethoxy-3-(1,3-dithian-2-yl)-prpan-2-ol (7)

A one-necked round-bottom flask was equipped with a condenser and magnetic stirre. The flask was charged with compound **6** (0.95 g, 3.6 mmol), THF (14.0 mL) and H_2O (0.3 mL). The reaction was stirred for 45 min before more H_2O (4 mL) was added. The mixture was transferred to a separatory funnel, and the flask was washed with CH_2Cl_2 (3 x 5 mL) and H_2O (2 x 5 mL), and then transferred to the separatory funnel. The organic phase was collected and the aqeoues phase was washed with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated on a rotary evaporator (40 ˚C/300 mmHg). The title compound 0.93 g (97%) was obtained as a clear viscous liquid by flash chromatography (Hexanes: EtOAc, 80:20).

3.6 Chain elongation

5,5-Diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (8)

A 250mL one-necked round-bottom flask was equipped with a condenser, magnetic stirrer and septum, and nitrogen gas was flashed through. The flask was charged with compound **7** (1.70 g, 6.4 mmoL), and dry THF (50 mL). The flask was placed in an ice bath, and 3 equivalent of *n*-BuLi (12.2 mL, 19.2 mmol) was added dropwise (15 min) to the mixture. The solution left to stir for 60 min at 0 ˚C. Benzaldehyde (0.25 g, 2.35 mmol) was dissolved in THF (25 mL), and added dropwise to the solution (15 min). Then the mixture left to stir for 90 min. Saturated NH_4Cl (122 mL) was added to the solution, and then the mixture transferred to a separatory funnel, the flask was washed with CH_2Cl_2 (3 x 20 mL) and H_2O (2 x 20 mL), which were also transferred in to the funnel. More CH_2Cl_2 (50 mL) was added to the separatory funnel. The aqueous phases were washed with CH_2Cl_2 (3 x 50 mL). The combined organic phases was dried with dry $MgSO_4$, filtered and concentrated on a rotary evaporator (40 ˚C/375 mmHg). The title compound 1.71 g (71%) was obtained as a clear yellow, viscous liquid by flash chromatography (Hexanes: EtOAc, 70:30)

3.7 Ring formation

8-Oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (9)

A 100 mL round-bottom flask was equipped with a condenser and magnetic stirrer. Compound **8** (0.10 g, 0.27 mmol) was dissolved in acetone (33 mL) and H_2O (5 drops). The mixture was cooled in an ice bath, and H_2SO_4 (0.6 mL) was added to the mixture when the temperature of ice bath was reached 0 ˚C. The mixture left to stir for 1 h before adding H_2O (20 mL). The solution was transferred to a separatory funnel, and the flask was washed with DCM (3 x 5 mL) and H_2O (2 x 5 mL), followed by extracting with DCM three times. The combined organic phases were dried with $MgSO_4$, filtered and concentrated on a rotary evaporator (40 ˚C/300 mmHg) to give 1.23 g of the crude product as a white, yellow solid. Purification of the product by flash chromatography gave 0.053 g (59%) of compound **9** as a white solid.

IR (ATR), ν_{max} (cm^{-1}): 3061(w), 2978(m), 2919(m), 2886(m), 2827(m), 2357(w), 1493(m), 1454(w), 1414(w), 1372(m), 1364(w), 1343(m), 1315(w), 1293(m), 1282(w), 1242(m), 1220(m), 1162(m), 1112(s), 1079(s), 1050(s), 1027(s), 1050(s), 991(s), 977(s), 915(s), 894(s), 876(s), 850(s), 812(s), 796(m), 769(w), 756(s), 699(s), 674(m)

^{1}H-NMR (500 MHz; $CDCl_3$), δ (ppm): 7.74-7.31 (5H, m), 5.27-5.26 (1H, d), 4.48 (1H, s), 4.13-4.11 (1H, t), 2.86-2.85 and 2.83-2.82 (1H, two sets of dd), 2.29-2.25 (1H, two sets of dd), 2.10-2.05 (2H, m), 1.79 (3H, s), 1.47 (1H, s),1.40 (3H, s)

^{13}C-NMR (500 MHz; $CDCl_3$), δ (ppm): 138.73, 129.92, 129.36, 128.73, 113.41, 99.39, 84.50, 75.22, 49.13, 43.59, 29.34, 28.39, 28.17, 27.40, 25.00

3.8 Hydrolysis of dithiol

2,3,6-trisubstituted-5-pyranone

100 mL round bottom flask was charged with compound **9** (0.05 g, 0.15 mmol), which was dissolved in acetonitrile (6.5 mL), H_2O (1.5 mL) and $CaCO_3$ (0.037 g, 0.37 mmol), and then added CH_3I (0.32 mL, 5.10 mmol). The reaction mixture was stirred at room temperature for 47 h before quenching with saturated NH_4Cl (3 mL), followed by extraction with DCM three times. Collected organic phases were dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator to give 2.7 g of crude product as a yellow red liquid. Purification of the product by flash chromatography (Hexan: EtOAc, 70:30) gave 0.013g of compound 10 as a slightly yellow solid.

IR (ATR), ν_{max} (cm^{-1}): 3061 (w), 2979 (m), 2919 (m), 2886 (m), 2827 (w), 1734 (s), 1493 (m), 1453 (s), 1434 (w), 1414 (w), 1372 (s), 1364 (m), 1343 (m), 1315 (w), 1282 (w), 1241 (s), 1220 (s), 1162 (s), 1124 (s), 1080 (s), 1050 (s), 1025 (m), 991 (m), 977 (m), 942 (w), 915 (s), 894 (m9, 875 (w), 850 (m), 819 (w), 796 (s), 769 (w), 756 (s), 736 (w), 699 (s), 675 (w), 661 (w), 642 (w), 612 (w), 587 (m), 575 (s),

^{1}H-NMR (400 MHz; $CDCl_3$), δ (ppm): See Spectrum 2.6

^{13}C-NMR (100 MHz; $CDCl_3$), δ (ppm): 207.52, 137.86, 129.12, 128.82, 128,10, 112.69, 100.35, 81.64, 74.40, 42.00, 28.65

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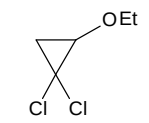
Appendix



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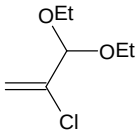

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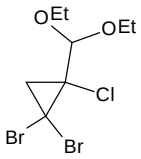

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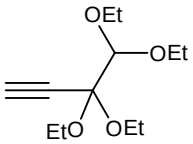

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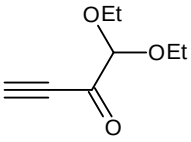

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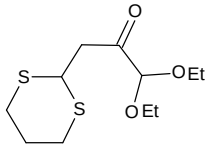

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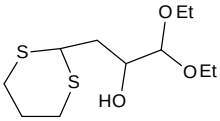

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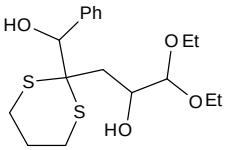

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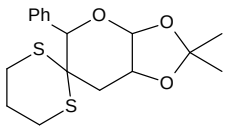

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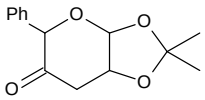
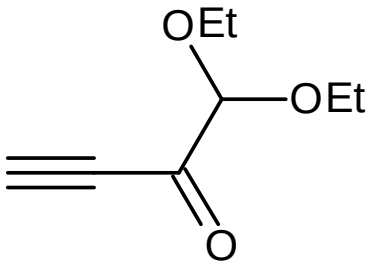


10

Figure A1 Overview chart of the isolated compound.

1,1-Diethoxybut-1-yn-2-on



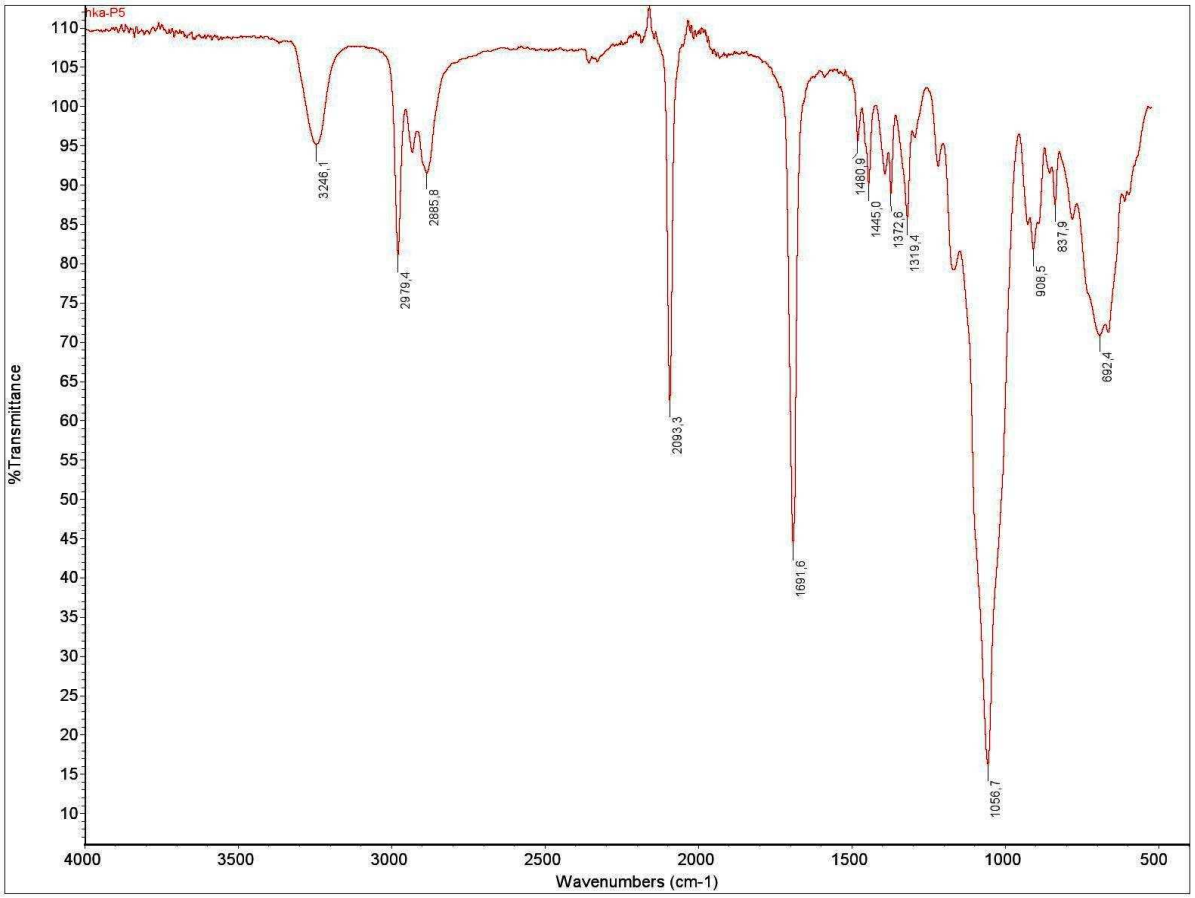


Figure A2 IR spectrum of 1,1-diethoxybut-1-yn-2-on (**5**).

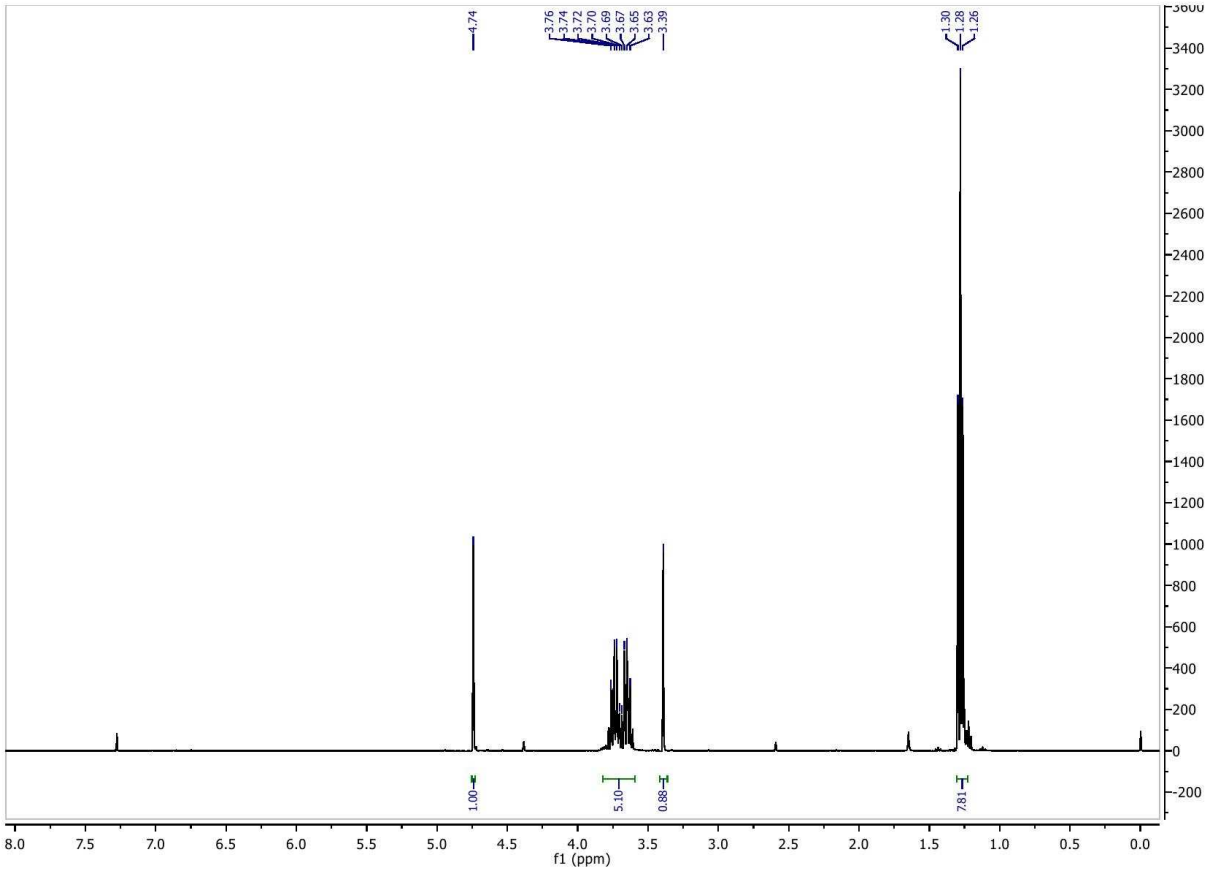


Figure A3 ^{1}H-NMR spectrum of 1,1-diethoxybut-1-yn-2-on (**5**).

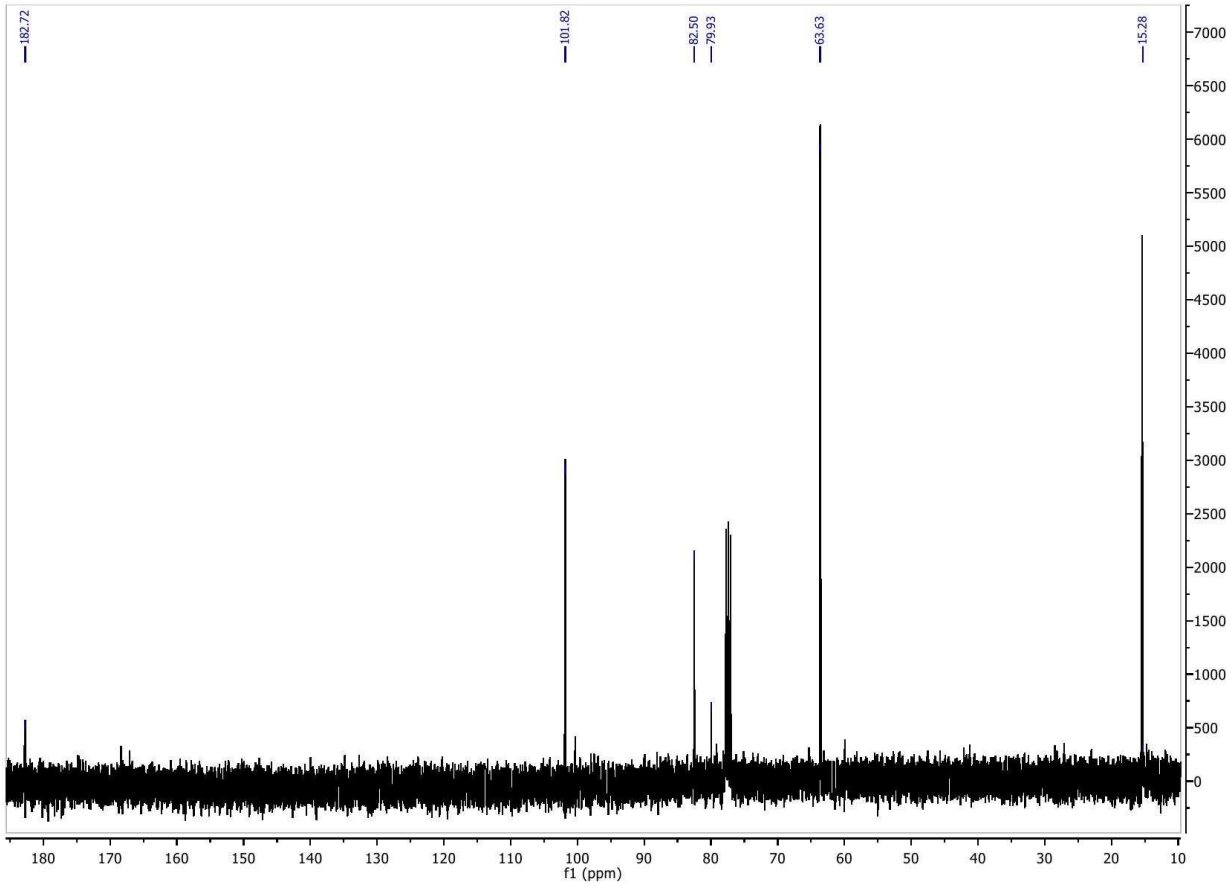
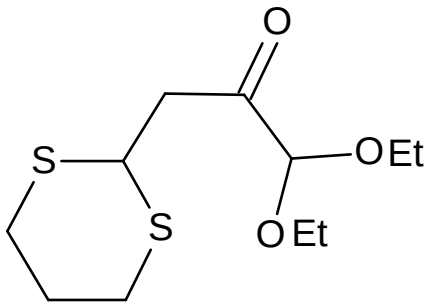


Figure A4 ^{13}C-NMR spectrum of 1,1-diethoxybut-1-yn-2-on (**5**).

1,1-Diethoxy-3-(1,3-dithan-2-yl)propan-2-on



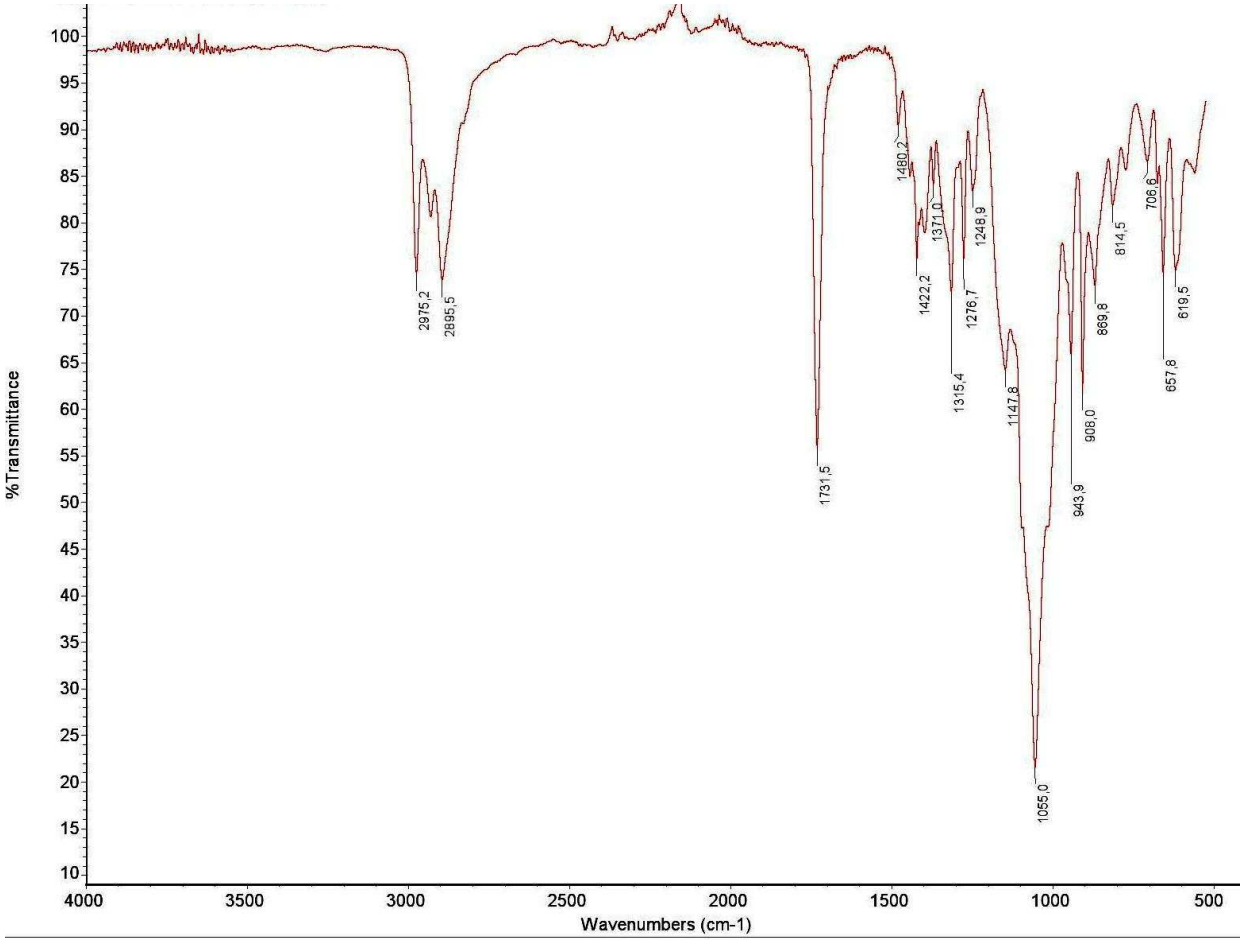


Figure A5 IR spectrum of 1,1-diethoxy-3-(1,3-dithan-2-yl)propan-2-one (**6**).

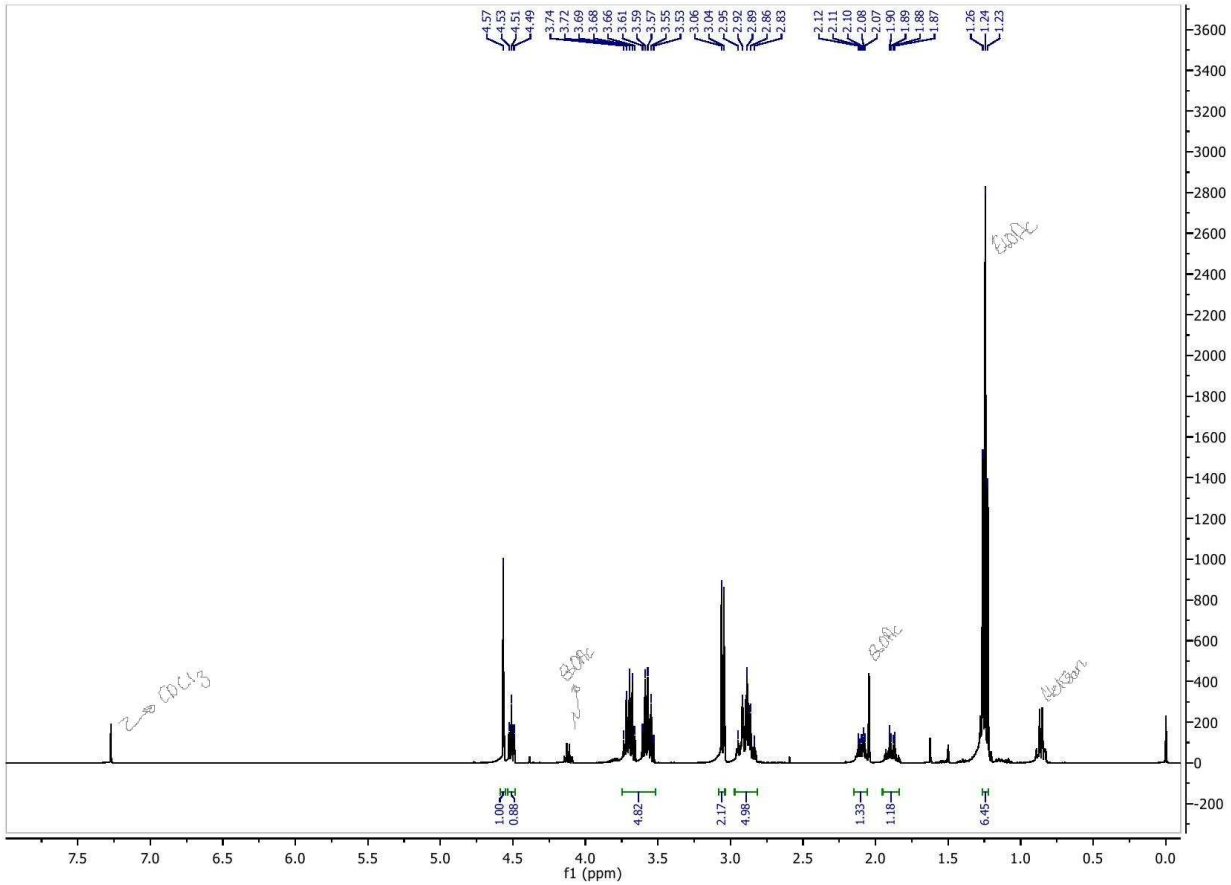


Figure A6 ^{1}H-NMR spectrum of 1,1-diethoxy-3-(1,3-dithan-2-yl)propan-2-one (**6**).

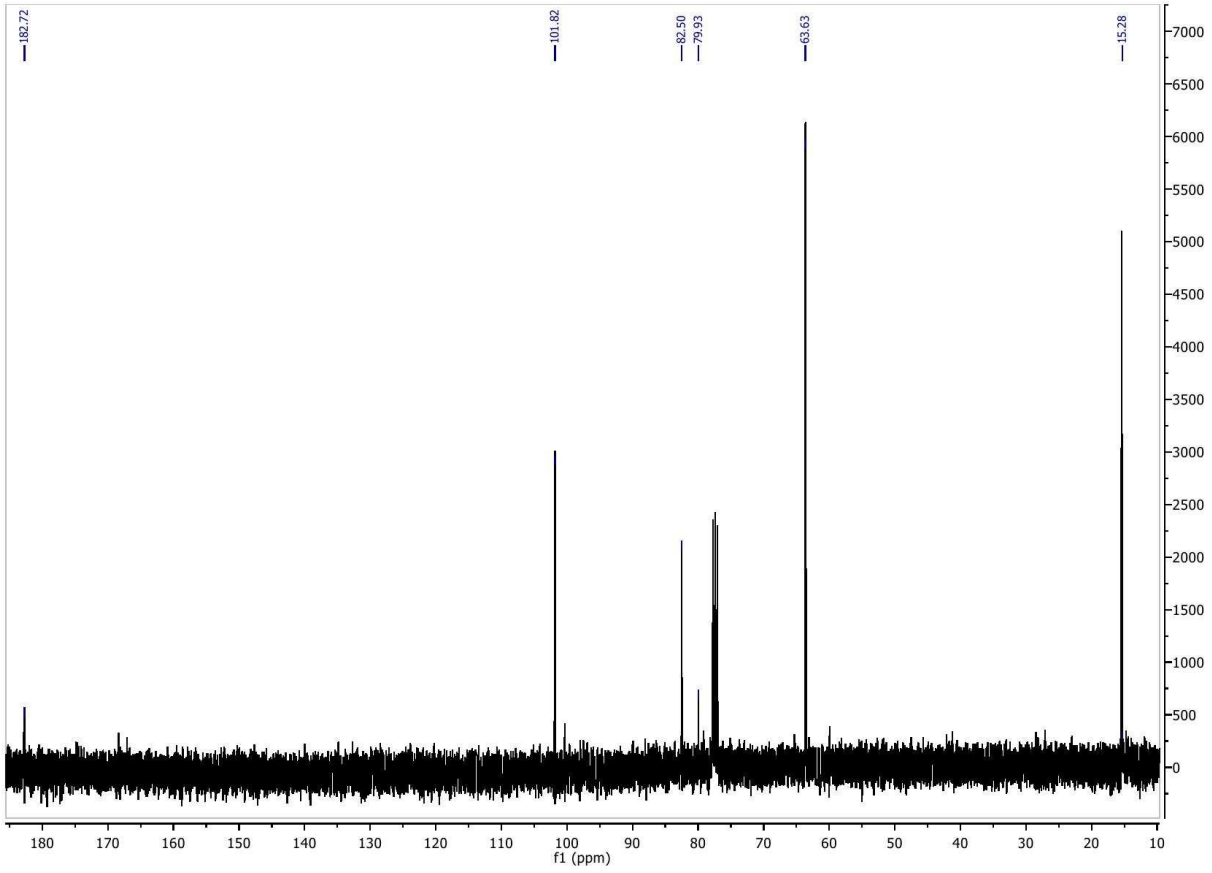
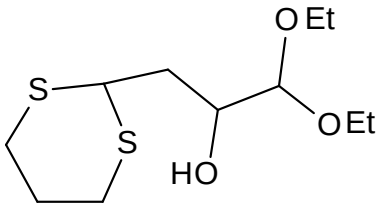


Figure A7 ^{13}C-NMR spectrum of 6 1,1-diethoxy-3-(1,3-dithan-2-yl)propan-2-one (**6**).

1,1-Diethoxy-3-(1,3-dithian-2-yl)-prpan-2-ol



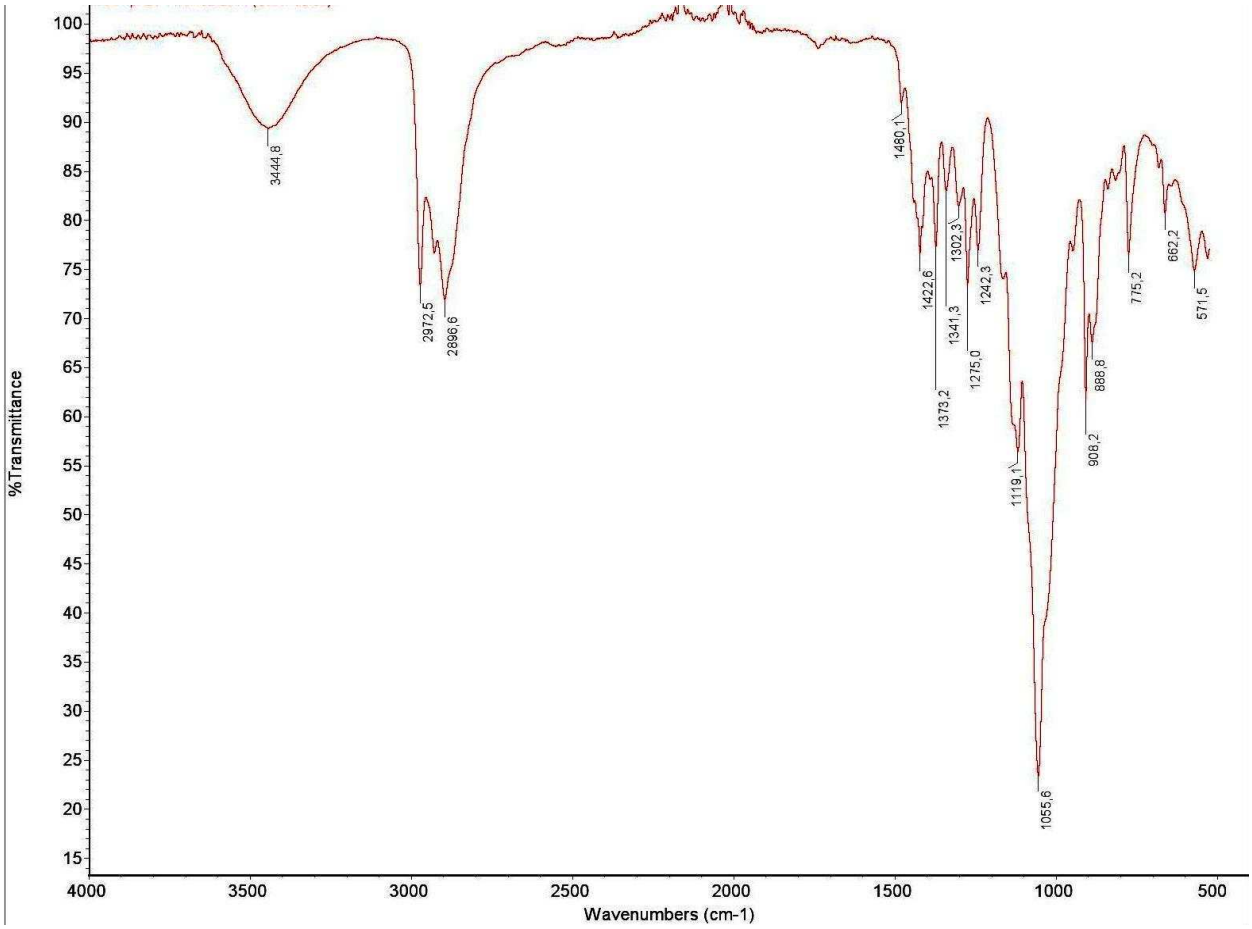


Figure A8 IR spectrum of 1,1-diethoxy-3-(1,3-dithian-2-yl)-propan-2-ol (**7**).

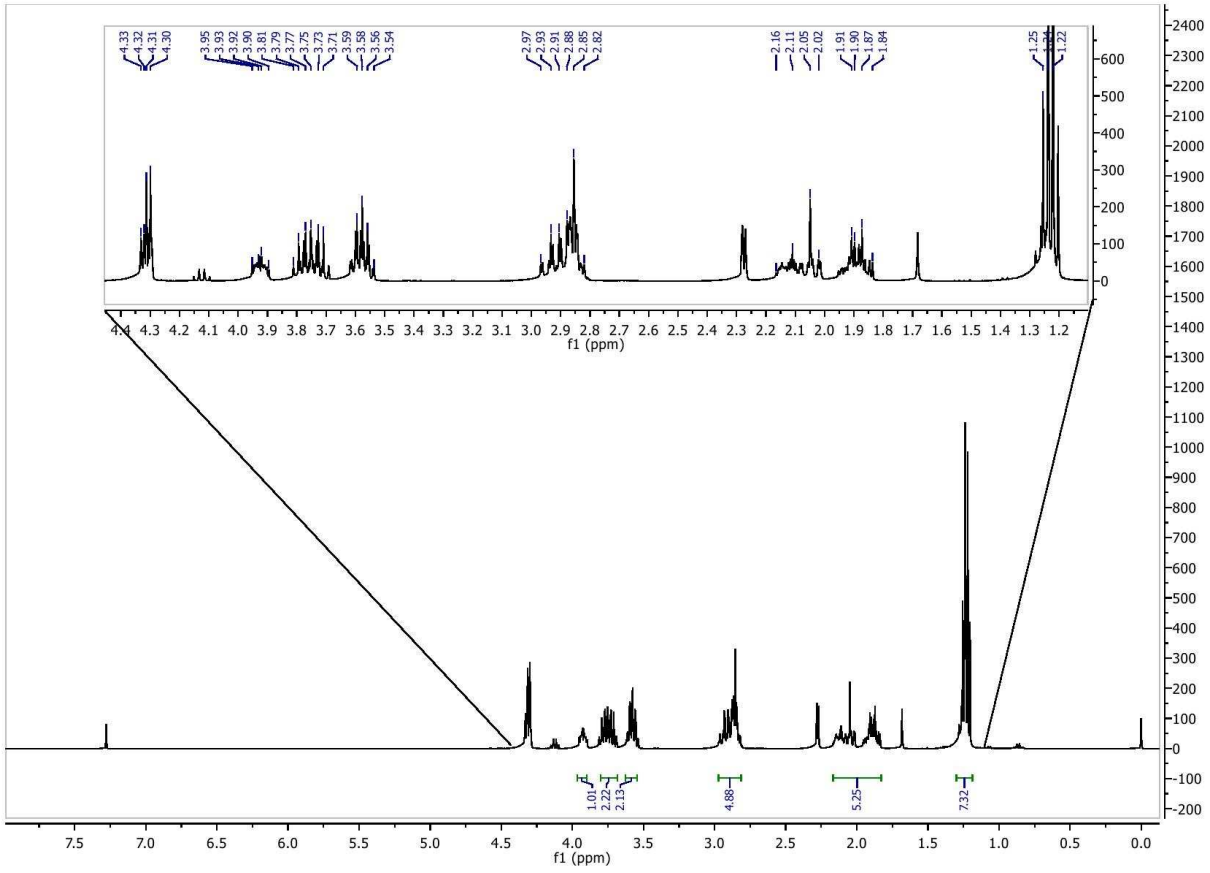


Figure A9 ^{1}H-NMR spectrum of 1,1-diethoxy-3-(1,3-dithian-2-yl)-propan-2-ol (**7**).

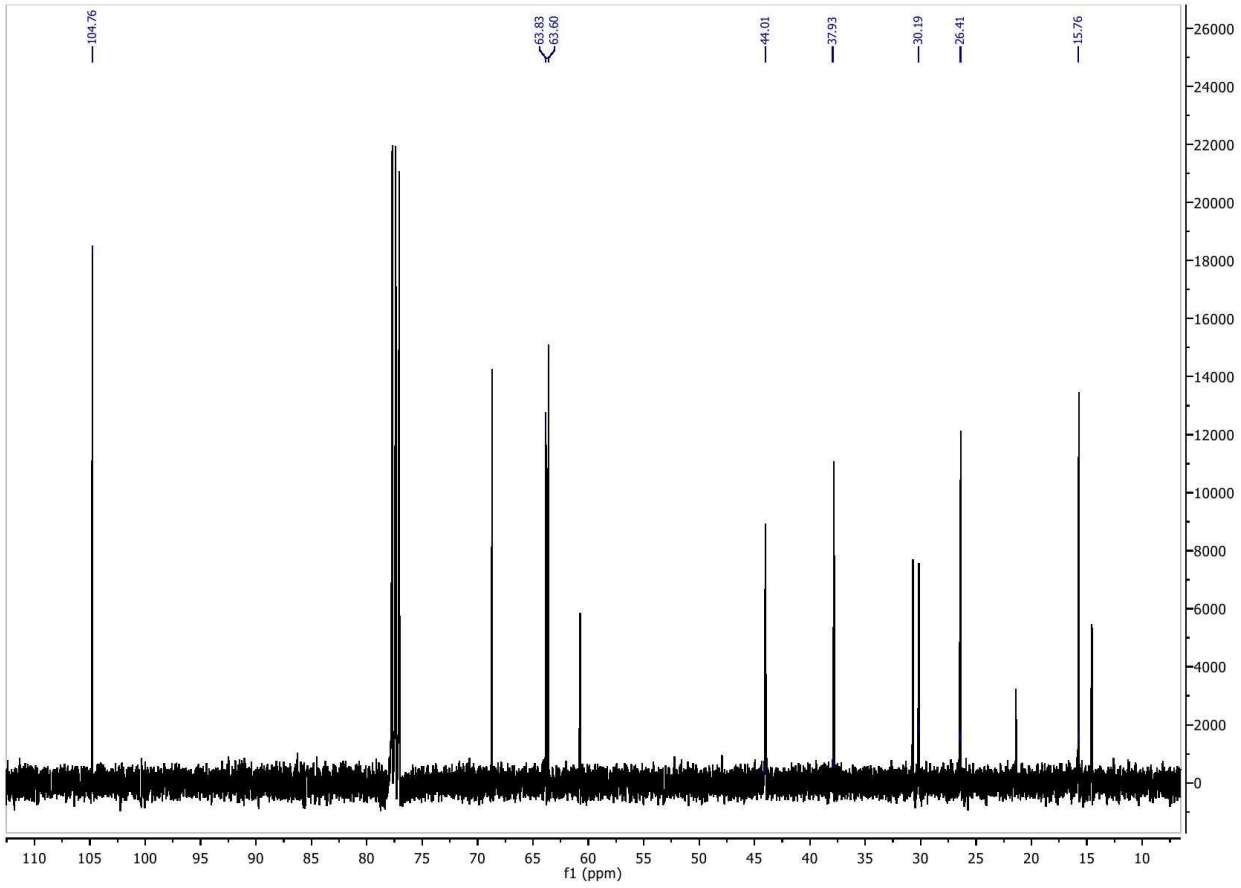
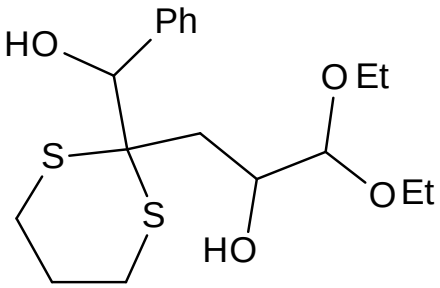


Figure A10 ^{13}C-NMR spectrum of 1,1-diethoxy-3-(1,3-dithian-2-yl)-propan-2-ol (**7**).

5,5-Diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol



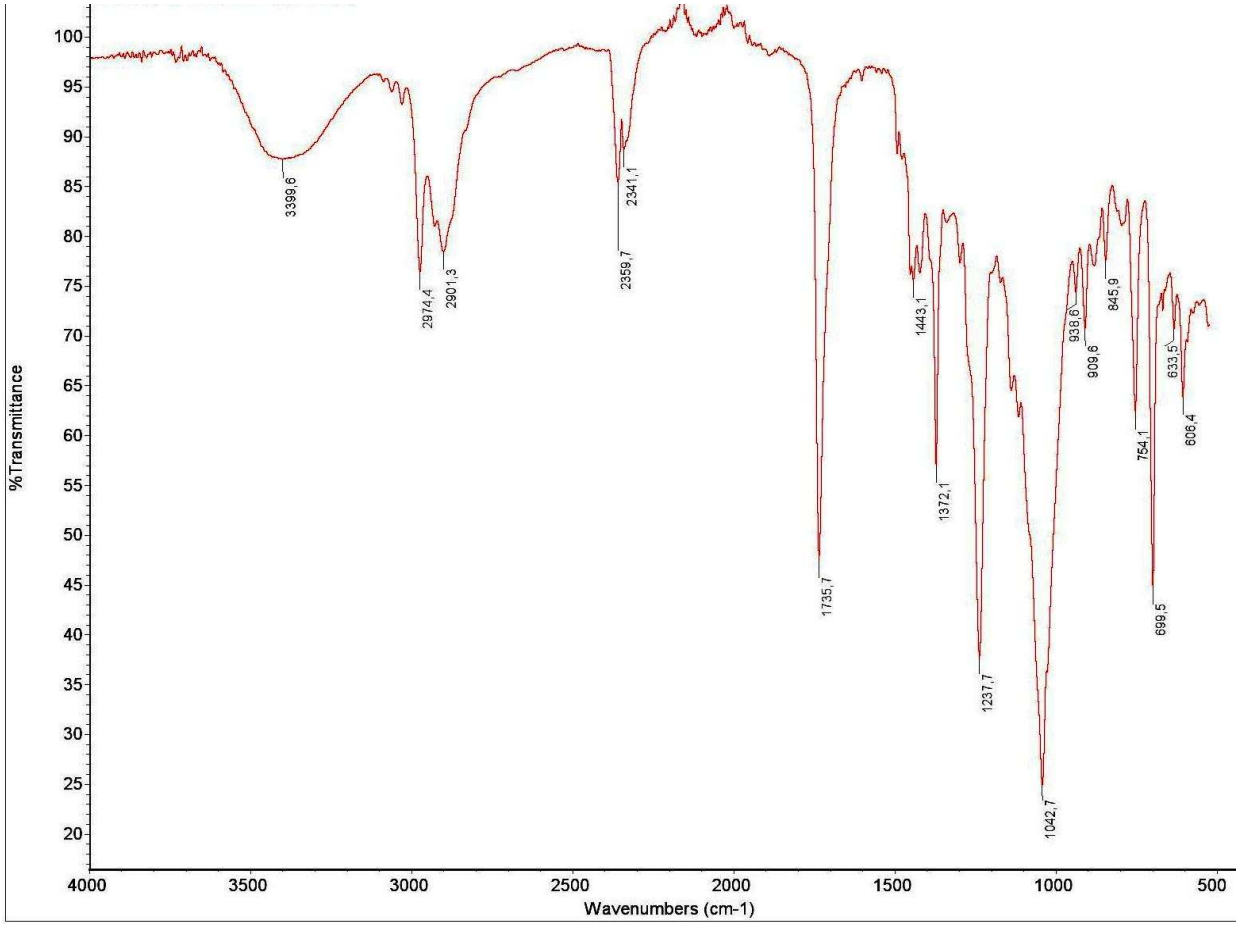


Figure A11 IR spectrum of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**).

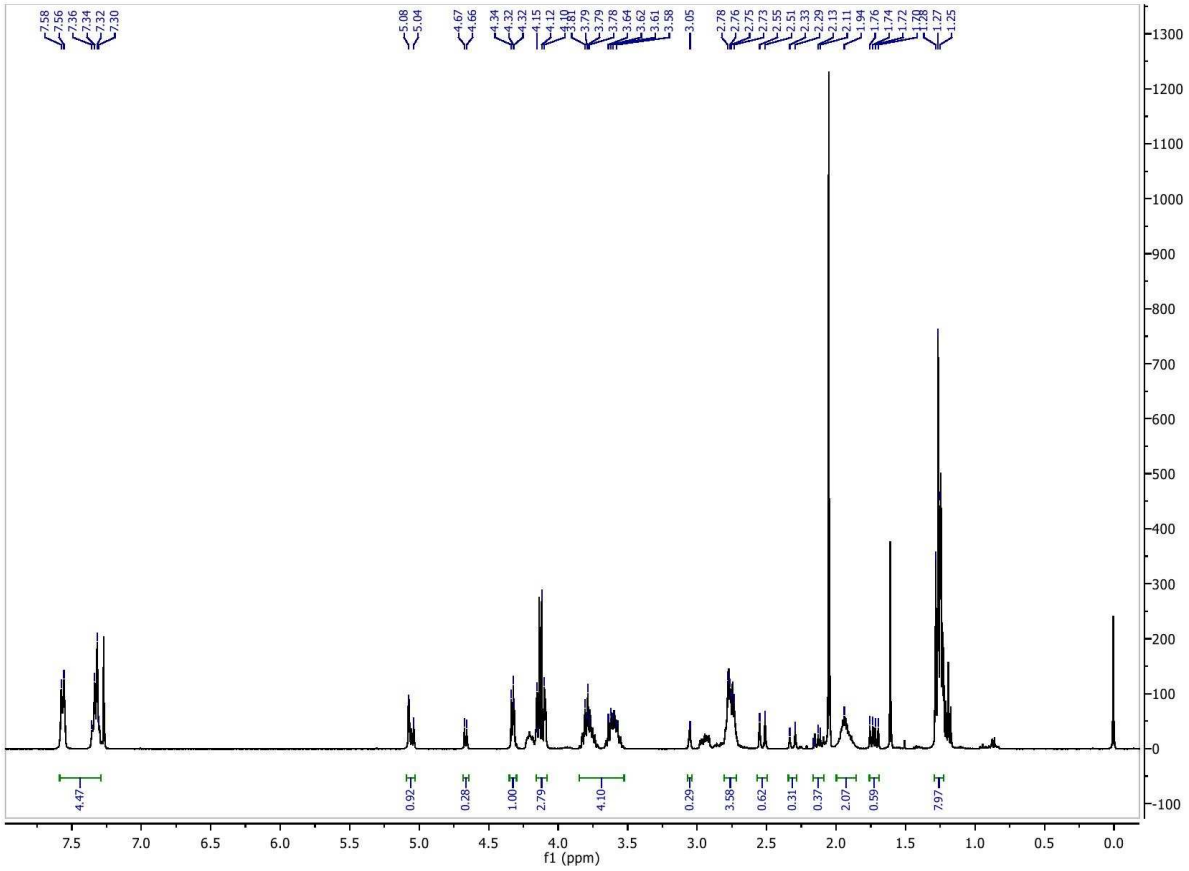


Figure A12 ^{1}H-NMR spectrum of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**).

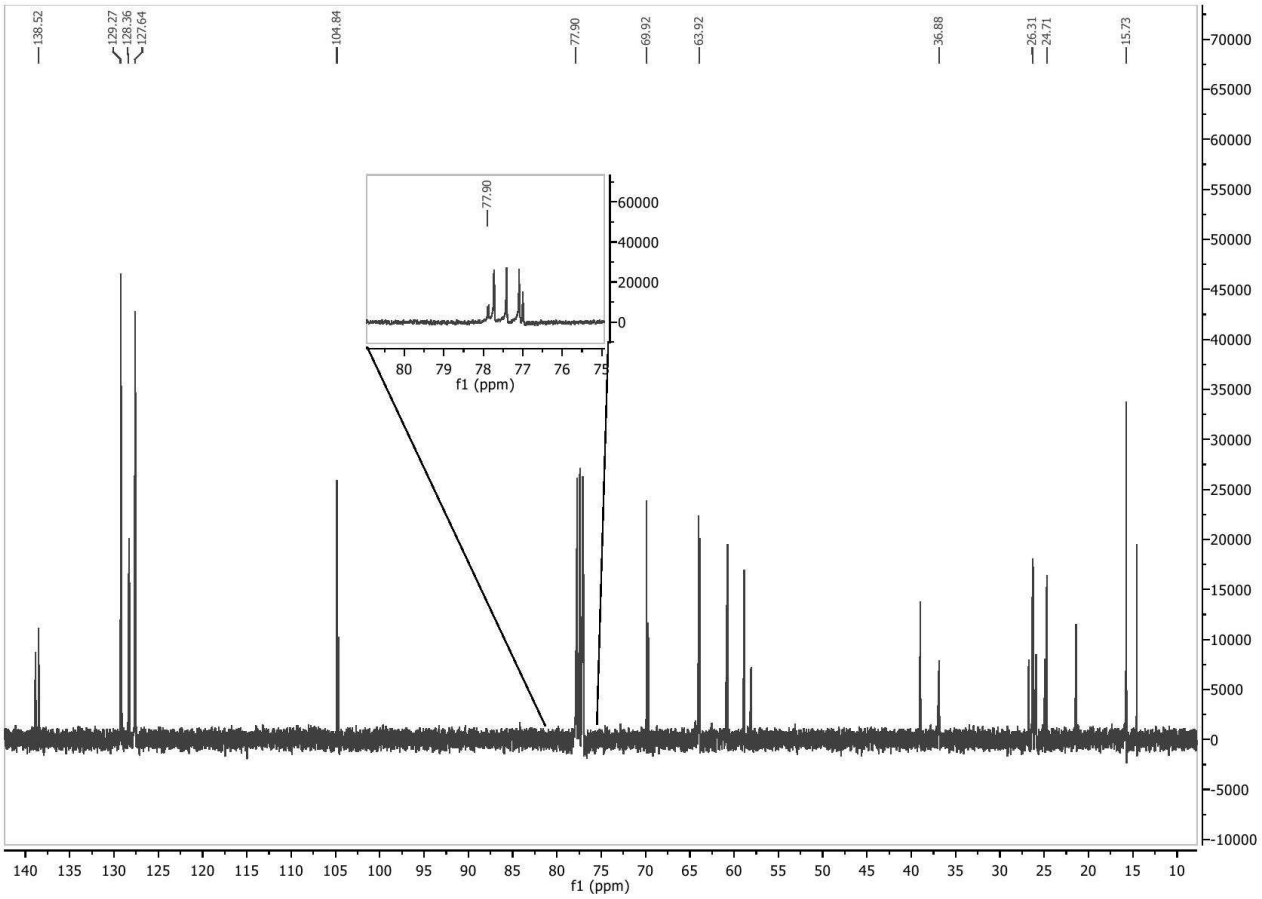
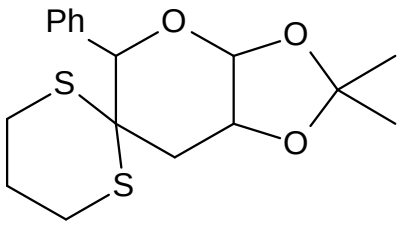


Figure A13 ^{13}C-NMR spectrum of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**).

8-Oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide



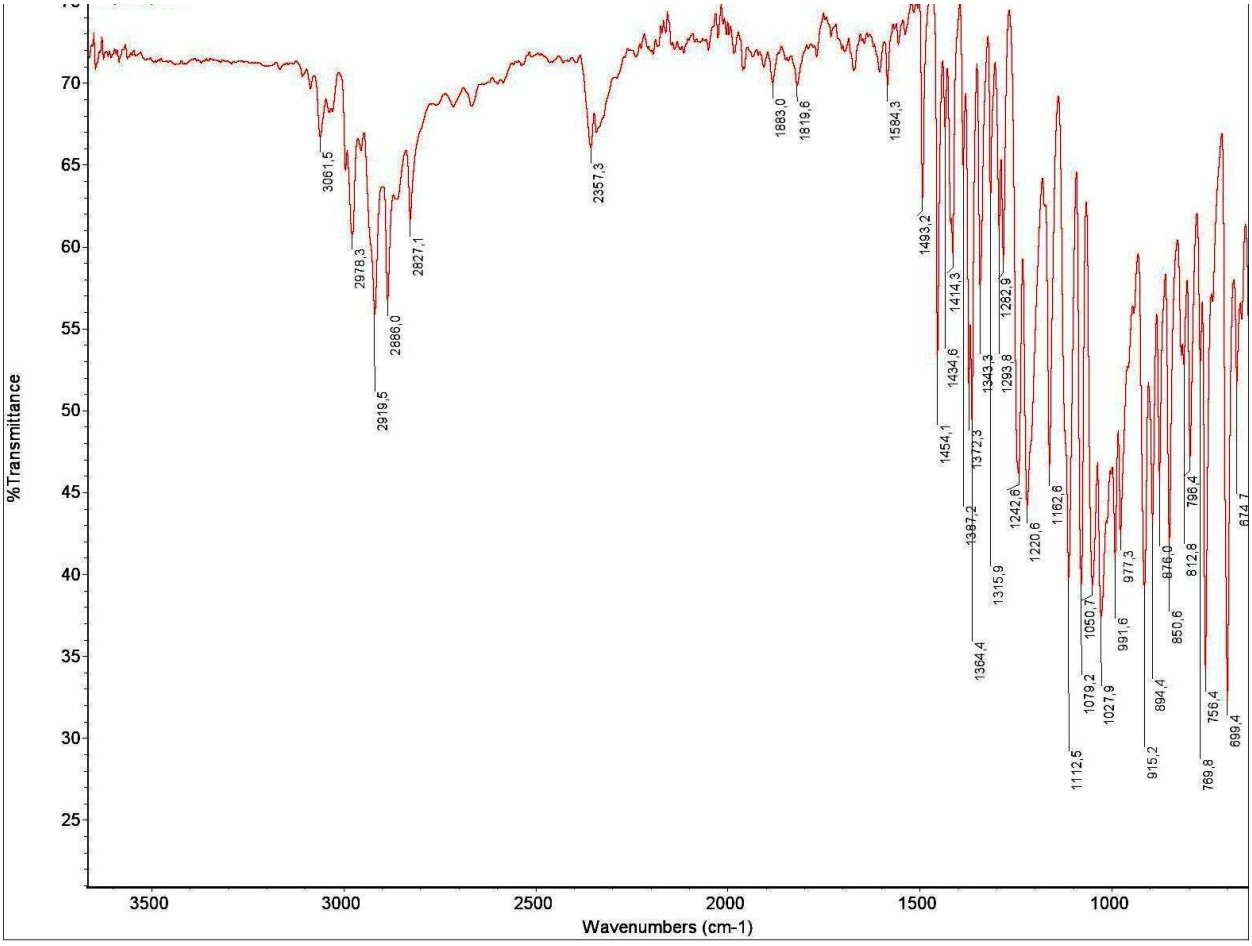


Figure A14 IR spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**9**).

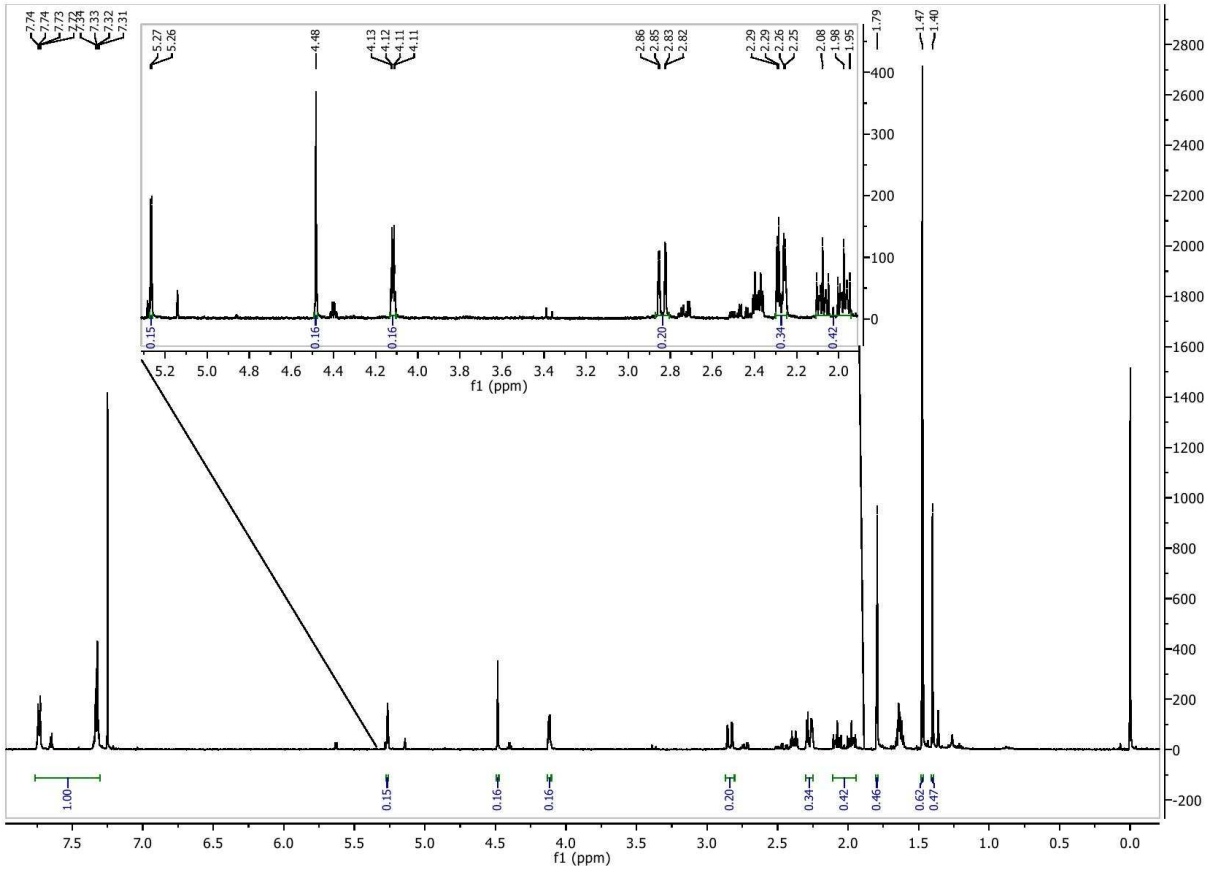


Figure A15 ^{1}H-NMR spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**9**).

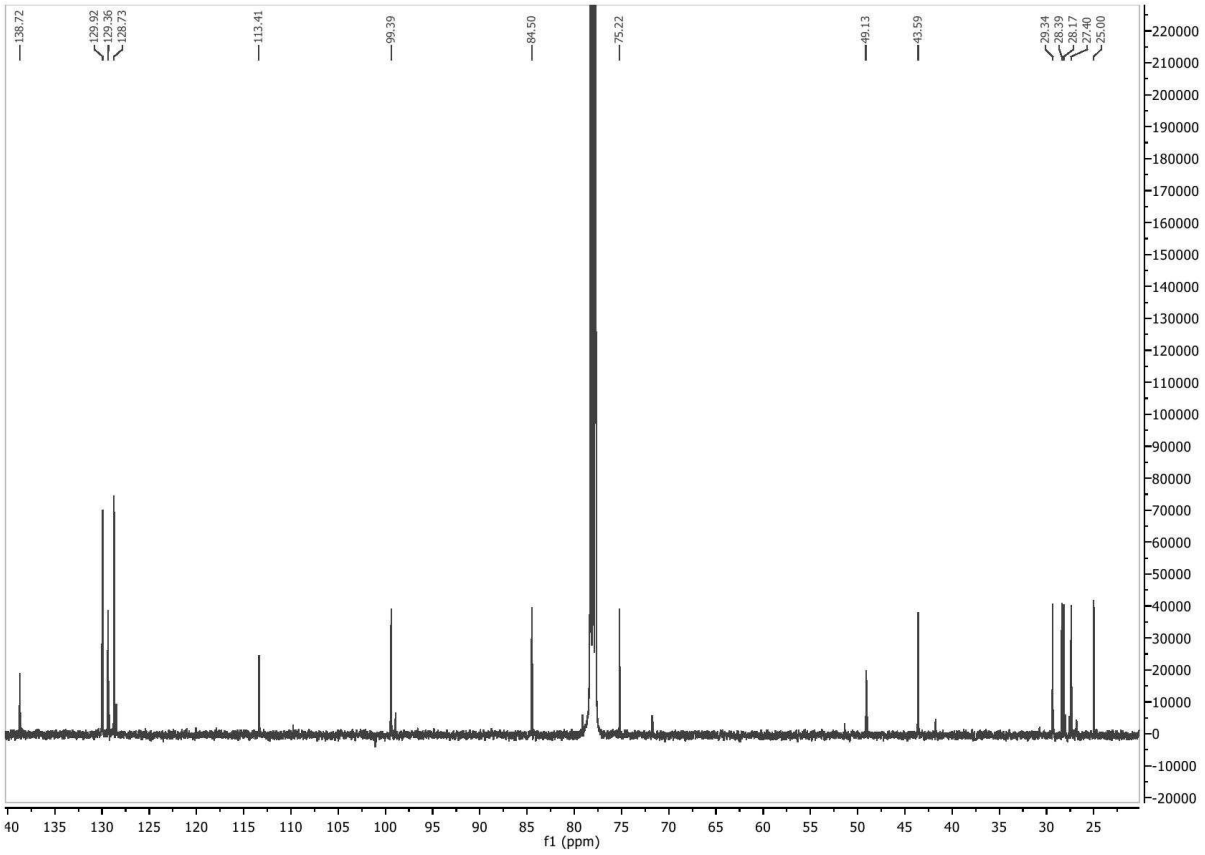


Figure A16 ^{13}C-NMR spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**9**).

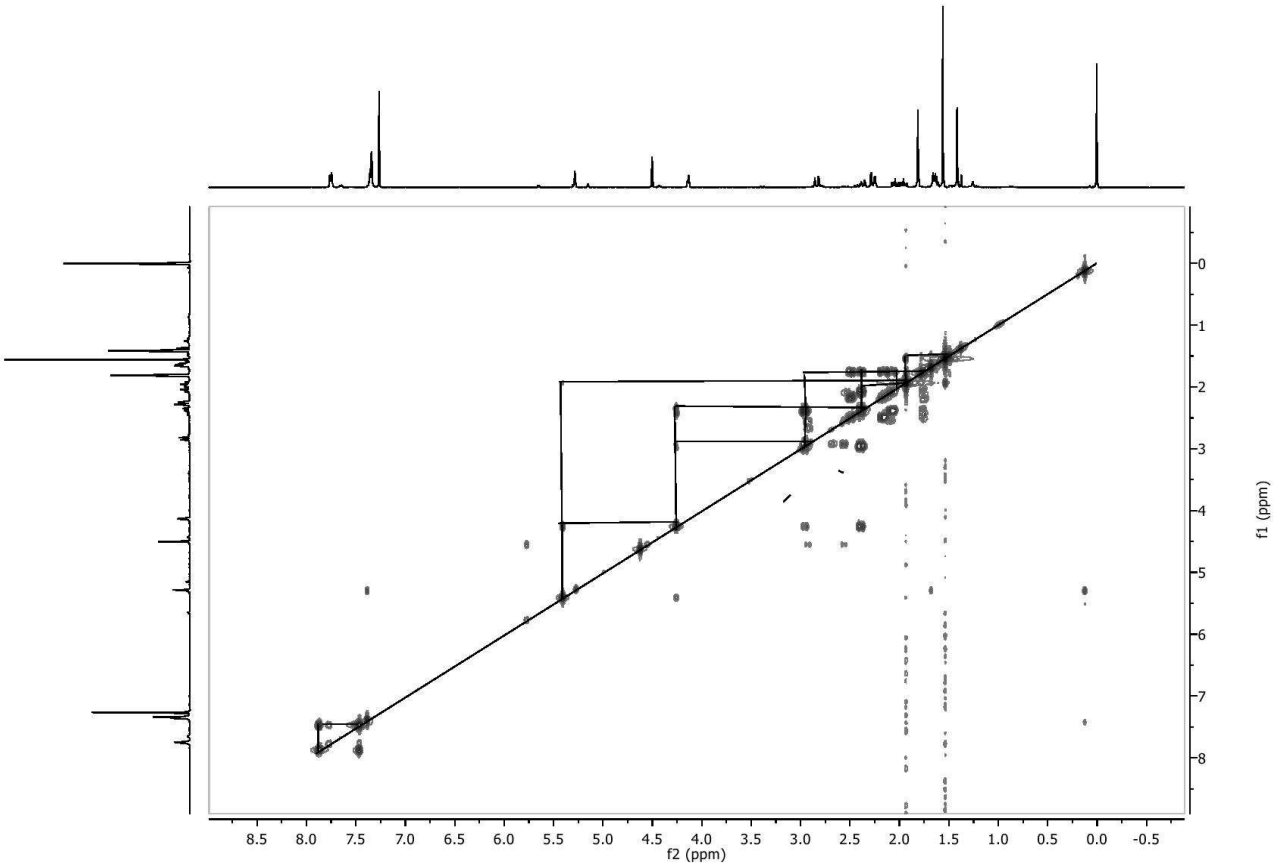


Figure A17 ^{1}H-^{1}H COSY spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**9**).

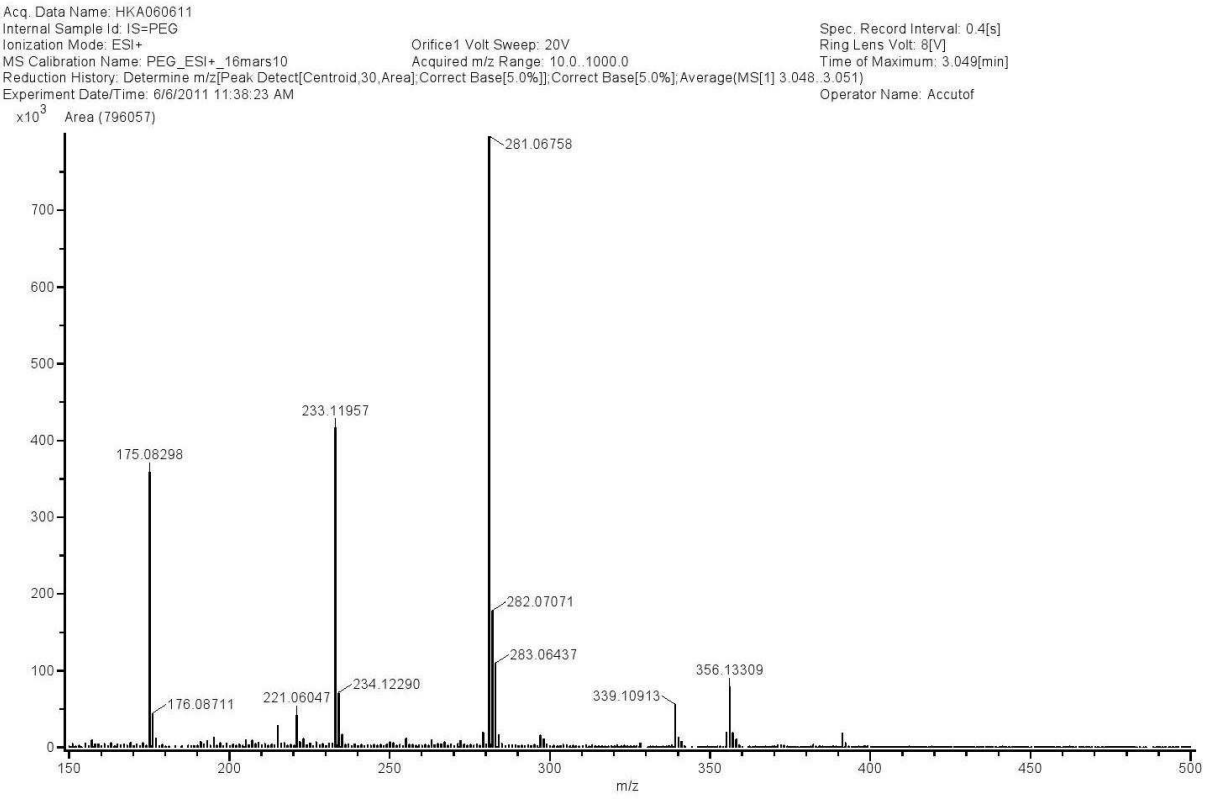
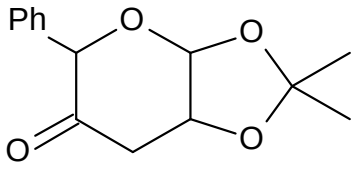


Figure A18 MS spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**9**).

2,3,6-trisubstituted-5-pyranone



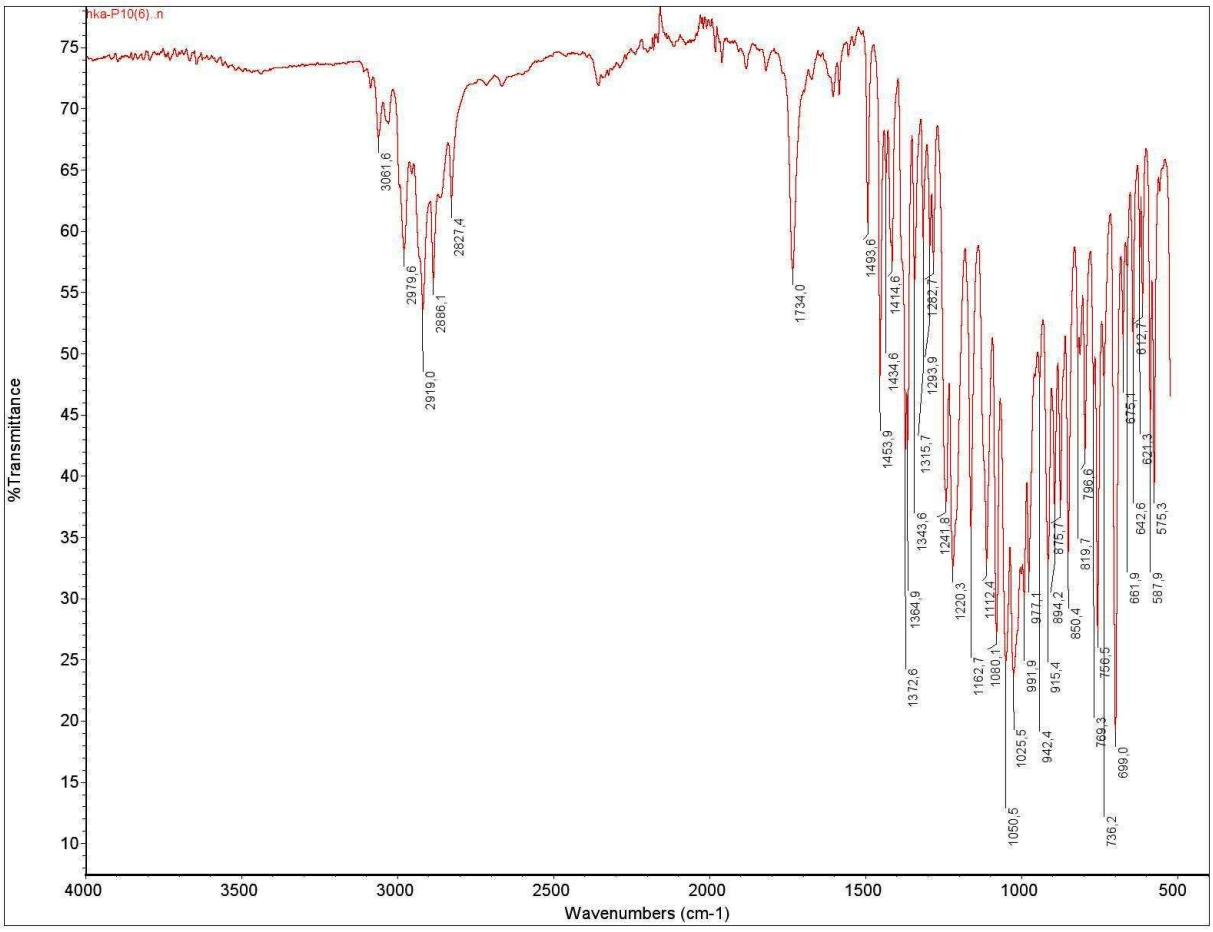


Figure A19 IR spectrum of 2,3,6-trisubstituted-5-pyranone (**10**).

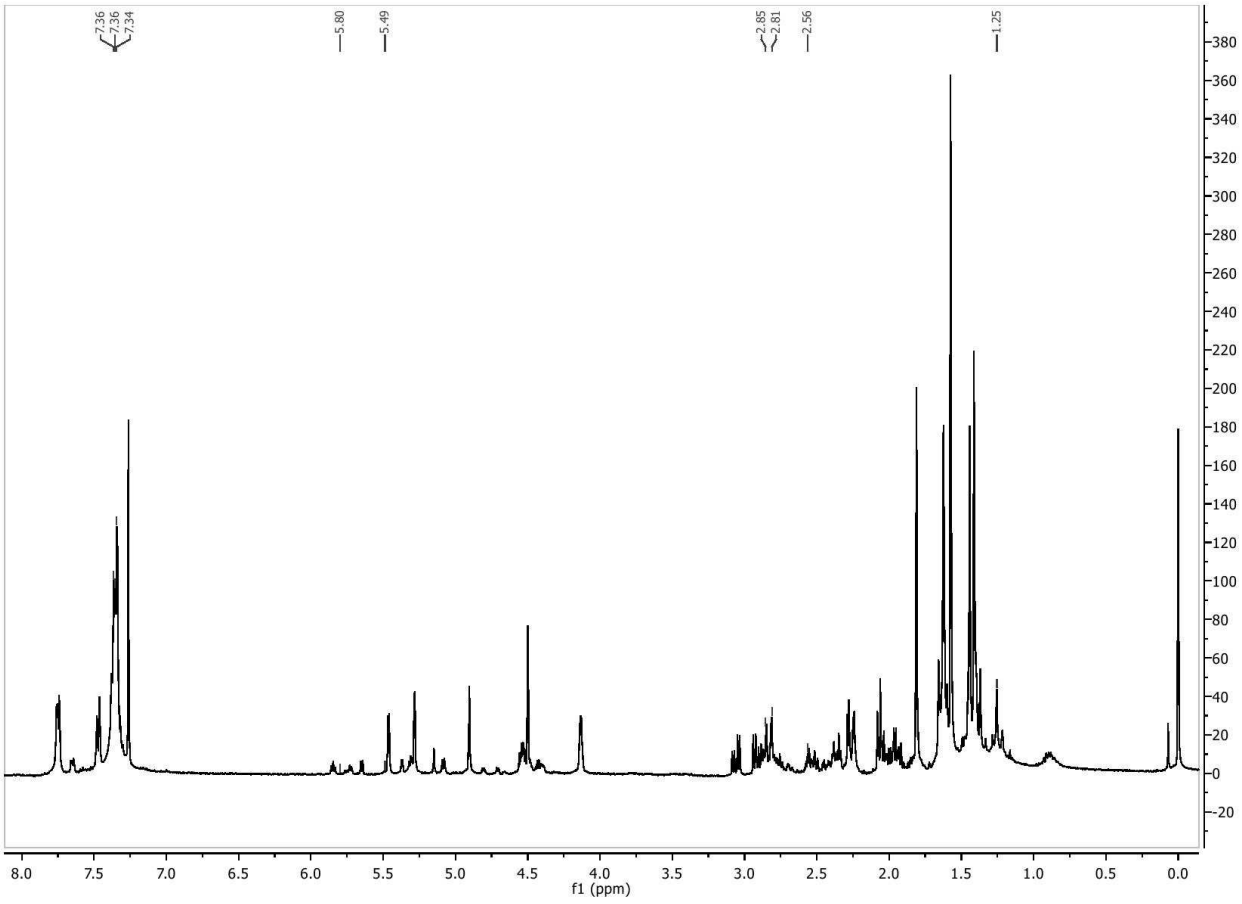


Figure A20 ^{1}H-NMR spectrum of 2,3,6-trisubstituted-5-pyranone (**10**).

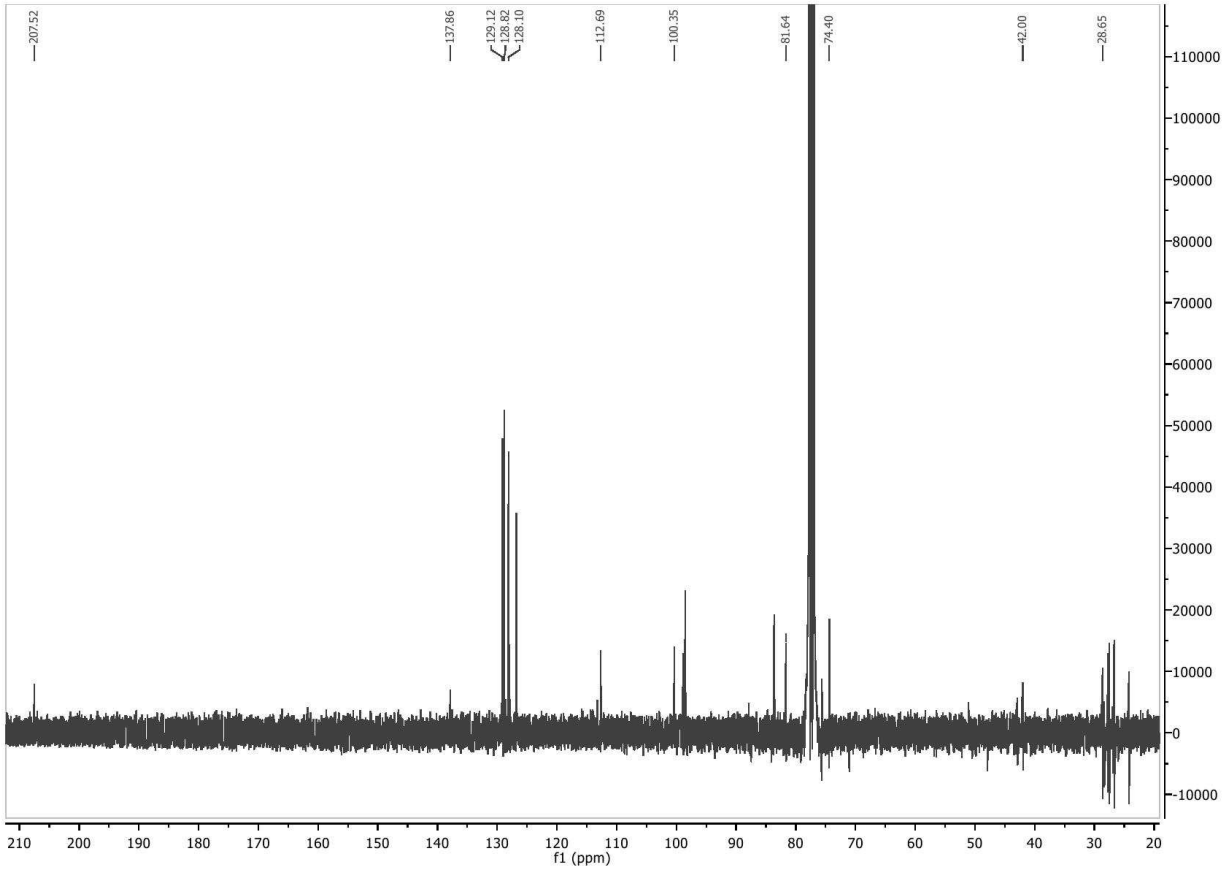


Figure A21 ^{13}C-NMR spectrum of 2,3,6-trisubstituted-5-pyranone (**10**).