ATTEMPTED SYNTHESIS OF A 3-PYRANONE FROM 3,3,4,4-TETRAETHOXYBUT-1-YNE

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-Master thesis in pharmacy-

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Elisabeth Nikoline Nilsen

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ABSTRACT

The starting material for this project was the highly functionalised compound 3,3,4,4-tetratethoxybut-1-yne (TEB). One of the compounds that can be synthesised from TEB is 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (β-hydroxydithiane), which is used as the starting material in this investigation. TEB and β-hydroxydithiane have previously been synthesised in good yields using various reaction routes.

The addition of benzaldehyde to β-hydroxydithiane furnished the corresponding 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol in a very good yield, using reaction conditions that previously has only been attempted on a smaller scale.

The subsequent deprotection of the dithiane moiety in 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol gave only a poor yield of 5,5-diethoxy-1,4-dihydroxy-1-phenylpent-2-one. The cyclization attempt of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol was however more successful, and furnished 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide as the major product.

ABBREVIATIONS

^{1}H	Hydrogen-1 nucleus
^{13}C	Carbon-13 nucleus
Ac	Acetyl
ATR	Attenuated total reflection
COSY	Correlation Spectroscopy
DNA	Deoxyribonucleic Acid
HIV	Human Immunodeficiency Virus
HMPA	Hexamethylphosporamide
IR	Infrared Spectroscopy
FT-IR/ATR	Fourier Transform Infrared Spectroscopy in the Attenuated Total Reflection Mode
Mp	Melting point
MS	Mass Spectrometry
n-BuLi	*n*-Butyllitium
NMR	Nuclear Magnetic Resonance
ppm	parts per million
PTC	Phase-transfer catalysis/conditions
PTSA	*para*-Toluensulfonic acid
R_f	Retention factor
r.t.	Room temperature
t-BuLi	*tert*-Butyllitium
TEB	3,3,4,4,-Tetraethoxybut-1-yne
TEBA	Triethylbenzylammonium chloride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Tetramethylsilan

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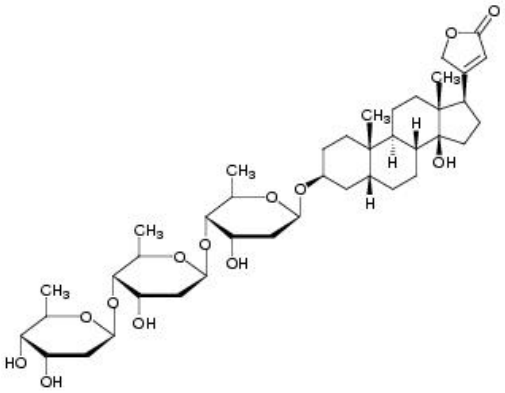
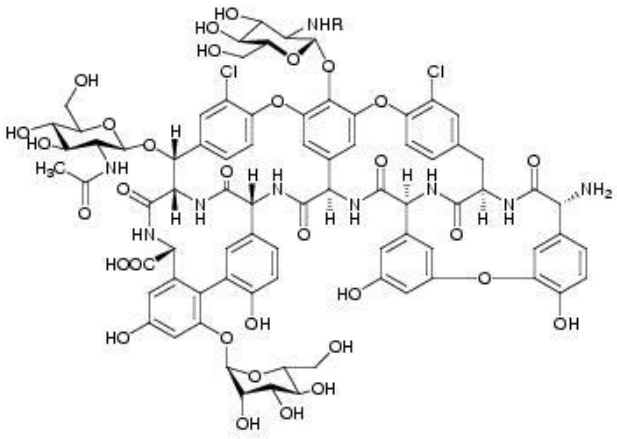
1 INTRODUCTION

1.1 Carbohydrates in medicine

Several drugs in use today are carbohydrates, or contain carbohydrates as part of their structure. Examples include the antiviral drugs zidovudine used against HIV infection, and the antiherpes drug aciclovir which contain an incomplete sugar unit. Heparin itself is a polysaccharide and is used as an anticoagulant to prevent blood clots, while the glycosides digoxin and digitoxin are drugs used in cardiovascular medicine. Some important antibiotics also contain carbohydrate units within their structures, such as streptomycin, erythromycin, and vancomycin.[1]



Digitoxin



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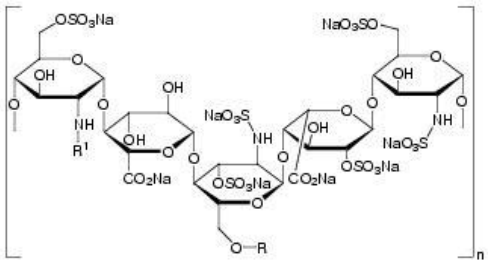
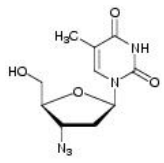
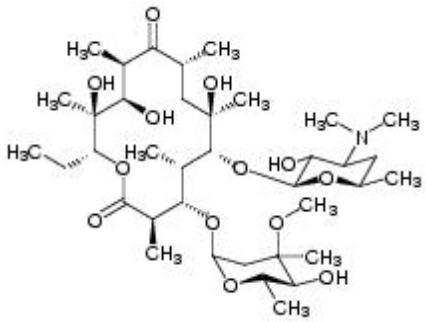


Heparin



Zidovudine

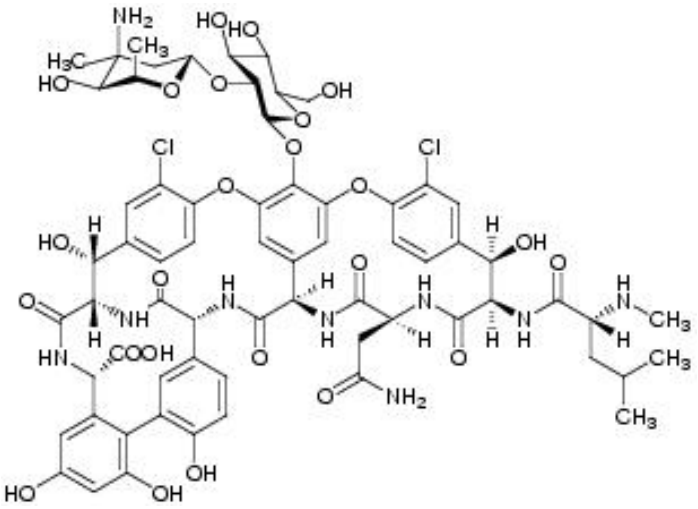


Erythromycin

Scheme 1.1: *Examples of some drugs that contain carbohydrates as part of their structure.*[2]

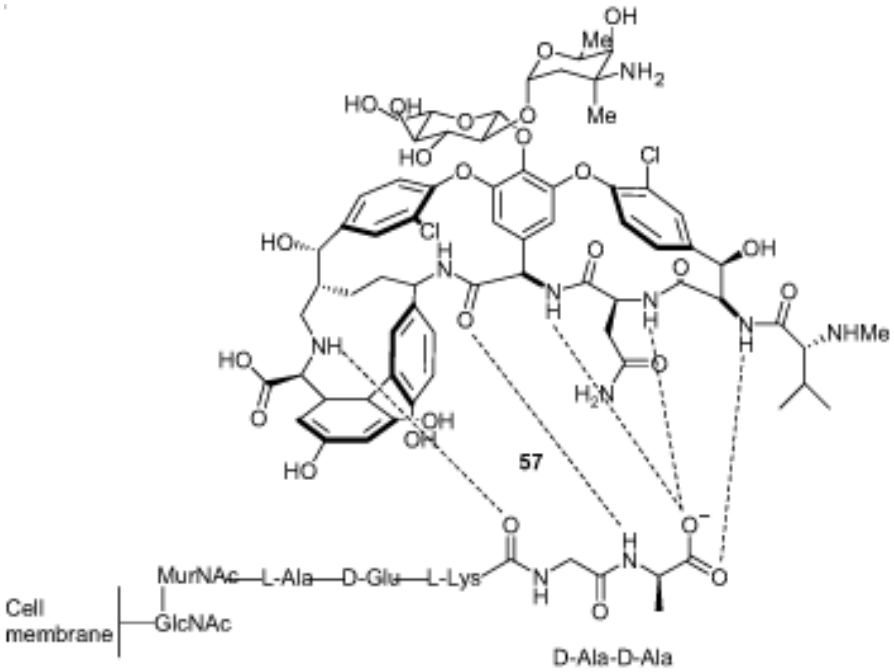
1.2 Vancomycin

Bacteria have been able to develop resistance against many of the antibiotics in use today, due to their ability to pass genetic information between the different species very rapidly. This requires a continuous development of new antibiotics. One way of tackling this problem is to modify already existing drugs, such as the glycopeptide antibiotic vancomycin, which is clinically used worldwide as one of the last-resort drugs against antibiotic resistant infections. Strains of bacteria that cause life threatening diseases (such as *Enterococcus faecalis, Mycobacterium tuberculosis,* and *Pseudomonas aeruginosa*) have already developed resistance to many of the antibiotics.[3, 4] The first signs of resistance towards vancomycin by *Staphylococcus aureus* has also been identified.[5]



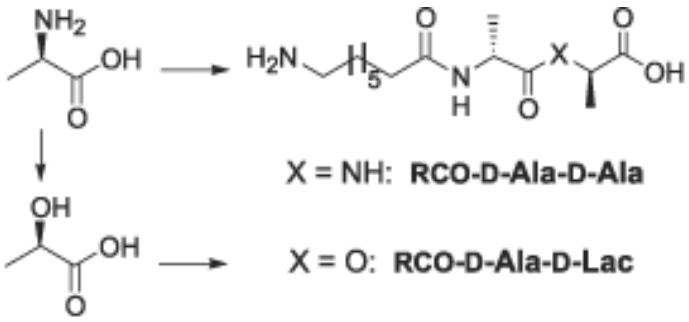
Scheme 1.2: *The structure of vancomycin.*[2]

Structurally vancomycin belongs to a family of glycopeptide antibiotics which all share similar, extended heptapeptide backbones with extensively cross-linked side chains and a variety of carbohydrate substituents.[6] The substance inhibits the synthesis of the peptide-precursors that forms peptidoglycan in the bacterial cell-wall, a structure that is important for the survival of the bacteria. The inhibition takes place by non-covalent binding between vancomycin and the D-Ala-D-Ala peptide sequence that is present in the building block, and involves a set of complementary hydrogen bonds as depicted in Scheme 1.3.[1, 7]



Scheme 1.3: *Vancomycin function by binding to the peptide-precursors that forms peptidoglycan via five hydrogen bonds.*[8]

Resistance against vancomycin occurs when the bacteria change the composition of the peptide portion of the peptidoglycan, and involve the acquisition of a set of genes which encodes proteins that direct the peptidoglycan precursors to incorporate D-Ala-D-Lac instead of D-Ala-D-Ala.[9, 10] This modified peptide sequence enables the bacteria to be resistant, as the result is a loss of a hydrogen bond between the peptide portion of vancomycin and the peptide precursors, as can be seen in Scheme 1.4 where an oxygen replaces the nitrogen in the structure.[11] The binding affinity of vancomycin for the D-Ala-D-Lac substrate decreases 1000-fold compared to the D-Ala-D-Ala substrate, thus leading to a great loss of biological activity for vancomycin.[12]



Scheme 1.4: *Bacteria develop resistance against vancomycin by changing the peptide sequence from D-Ala-D-Ala to D-Ala-D-Lac.*[13]

Although the main function of vancomycin is by binding of the peptide portion of the drug, it has also been established that the carbohydrate portion in vancomycin plays a vital part for its activity too. A set of carbohydrate derivatives of vancomycin that were active against resistant bacterial strains was discovered by Nagarajan in 1993, and experimental data from this study indicated that the in vivo activity of aglyco-vancomycin was five times less than that of vancomycin.[14] Later Ge et *al.*[15] proposed that these carbohydrate derivatives operate by a different mechanism than vancomycin, and that peptide binding is not required for the activity of the drug. Ge et *al*. suggest that mimics of the vancomycin glycan may exert antibacterial activity by inhibition of the transglycolsylase rather than the transpeptidase. The results support the theory that vancomycin analogues containing modified carbohydrates are very active against resistant microorganisms, and there was a marked difference in the inhibition patterns for the various analogues tested in the study. The hypothesis that peptide binding is not required for activity against resistant bacterial strains suggest new strategies for designing better glycopeptides antibiotics.[15] The findings by Chen et *al.*[16] also support this hypothesis, as the results from their study are consistent with the findings by Ge et *al*.

Another study reports the results of a structural comparison of vancomycin and its aglycon analogue, to see if the carbohydrate substituents on vancomycin greatly enhance the dimerization of the antibiotic, which is important for its therapeutic activity. Their results indicate that the disaccharide substituent leads to significant conformational changes of the antibiotic aglycon. The carbohydrates affect the orientation of the aromatic rings with respect to the antibiotic backbone, and influence the alignment of the amide protons important for dimerization and cell-wall binding. The carbohydrate susbtituents are believed to be

responsible for a number of favourable interactions in the formation of the dimer. This influence of the carbohydrate substituents on the dimerization has led to a prediction that the antibiotic aglycons are less active.[6]

All these studies show that the carbohydrate moiety of vancomycin is of great importance, and this has created a large interest in the field of synthesising new carbohydrate analogues in the hope of finding a new, improved and better antibiotic for the resistant bacteria. There has now been developed chemistry to attach both carbohydrates sequentially to the vancomycin aglycon and it is therefore possible to explore the effects of replacing either or both of the carbohydrates.[17] This requires new research into the field of synthesising various carbohydrate analogues.[3, 18-19] The glycopeptides antibiotics have been intensively investigated, and several reviews on this class of molecules have been published.[3-4, 20-22]

1.3 Carbohydrates

Carbohydrates are a large class of compounds that exist widely in nature as part of natural products, as sources of metabolic energy, as building blocks of the structural frameworks of cells, and as key components for various intercellular recognition processes, such as infection, inflammation and regulation of signalling.[23] Carbohydrates also plays an important part for the mechanism of some drugs, but although the development of carbohydrate-based therapeutics appears to have great potential, such as for vancomycin discussed above, it has not been easy to find a good way for the synthesis of such compounds as there are many obstacles that needs to be defeated in this field of chemistry.

A relatively small amount of research has been carried out on carbohydrate-based drugs compared to peptide-based drugs. This is partly due to the greater complexity involved in synthesising and modifying carbohydrates. Carbohydrates are densely functionalised molecules with hydroxyl groups of similar reactivity, leading to many challenges associated with their synthesis, including laborious protecting group manipulations and the need for regioselective and stereoselective reactions.[1] One way to overcome some of the problems are to design mimics of carbohydrates that have improved properties with regard to stability, specificity, affinity and synthetic availability.[25] These carbohydrate mimics potentially allow the targeting of the numerous natural processes in which carbohydrates are involved, without causing the problems that arise from the undesirable properties of carbohydrates.

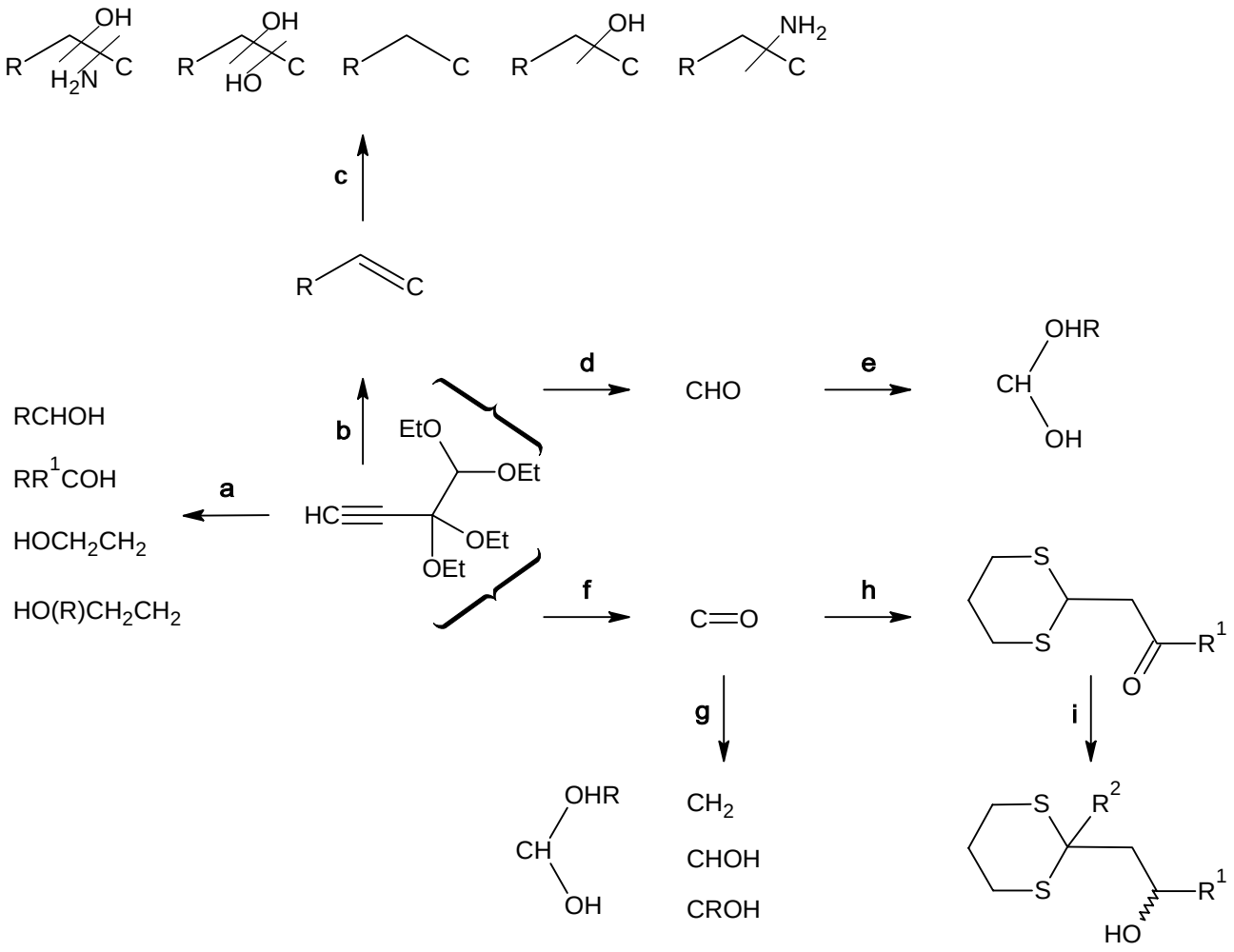
Deoxy sugars are some of the carbohydrate derivatives that are of interest for medicinal chemistry. Deoxy sugars are derived from common sugars by the replacement of at least one hydroxyl group with a hydrogen or a non-*O*-linked functional group and this substitution induces various changes in the properties of the carbohydrate that can be of advantage when designing new drugs.[26] There are various important deoxy sugars found in nature, such as deoxyribose for example, which serves as an important part of the nucleic acid DNA. However, in addition to have various roles in human physiology, these sugars also serve as important constituents of secondary metabolites in bacteria, including cardiac glycosides and macrolide antibiotics. Removal of the deoxy sugars often reduces the efficacy and specificity in these compounds, and many such natural products are found to loose their biological activity if their carbohydrate moiety is changed or removed.[27, 28]

In order to find a short and reliable synthetic route to various carbohydrate analogues, a good starting synthon is needed. Starting the synthesis with a functionalised compound that can be manipulated in many various ways eases the work in making different carbohydrate derivatives from the same starting material. One such starting synthon can be 3,3,4,4-tetraethoxybut-1-yne (TEB) developed in my group.[29] This compound is densely functionalised, and can be converted into many various compounds by only few steps. Earlier attempts has, among other, proved that TEB is a good starting synthon for developing various deoxy sugars.[30]

1.4 TEB as a starting material for modified carbohydrate analogues

3,3,4,4-Tetraethoxybut-1-yne (TEB), is found to be a good starting synthon for the purpose of synthesising a variety of different carbohydrate analogues.[31] This is due to the fact that TEB is a highly functional molecule, as it contains a triple bond, a ketal group, and an acetal group that can all be further reacted to form various compounds.

As depicted in Scheme 1.5, there are a variety of different possibilities for the further reactions of the compound TEB.[29, 31] The triple bond is a good starting point for a chain elongation since the acetylenic proton is acidic, and when this is abstracted the resulting acetylide will make TEB reactive towards aldehydes, ketones and oxiranes to give the corresponding alcohols, as shown in route **a**. The triple bond can also be reduced to give an alkene, as shown in route **b**, where upon the alkene can react as shown in route **c** via reactions such as hydrogenation, hydration, amination, dihydroxylation and hydroxyamination. The acetal group can be deprotected as shown in route **d** to give an aldehyde. This aldehyde can further react through route **e** to furnish hemiacetals under the right conditions. The ketal group can also be deprotected as shown in route **f,** to give a ketone that can go through various ketone reactions including reduction and formation of hemiketals as shown in route **g**. Route **h** also shows how the double Michael addition of propane-1,3-dithiol under basic conditions give a 2-substituted 1,3-dithiane, a reaction that has successfully been tried based on the publication of Ley and co-workers.[32, 33] Route **i** shows the possibility of addition of the 2-substituted 1,3-dithiane to an electrophilic agent, after reduction of the carbonyl group, which also has been investigated successfully before.[30, 34] After this, it is possible to make carbohydrates based on these structures.

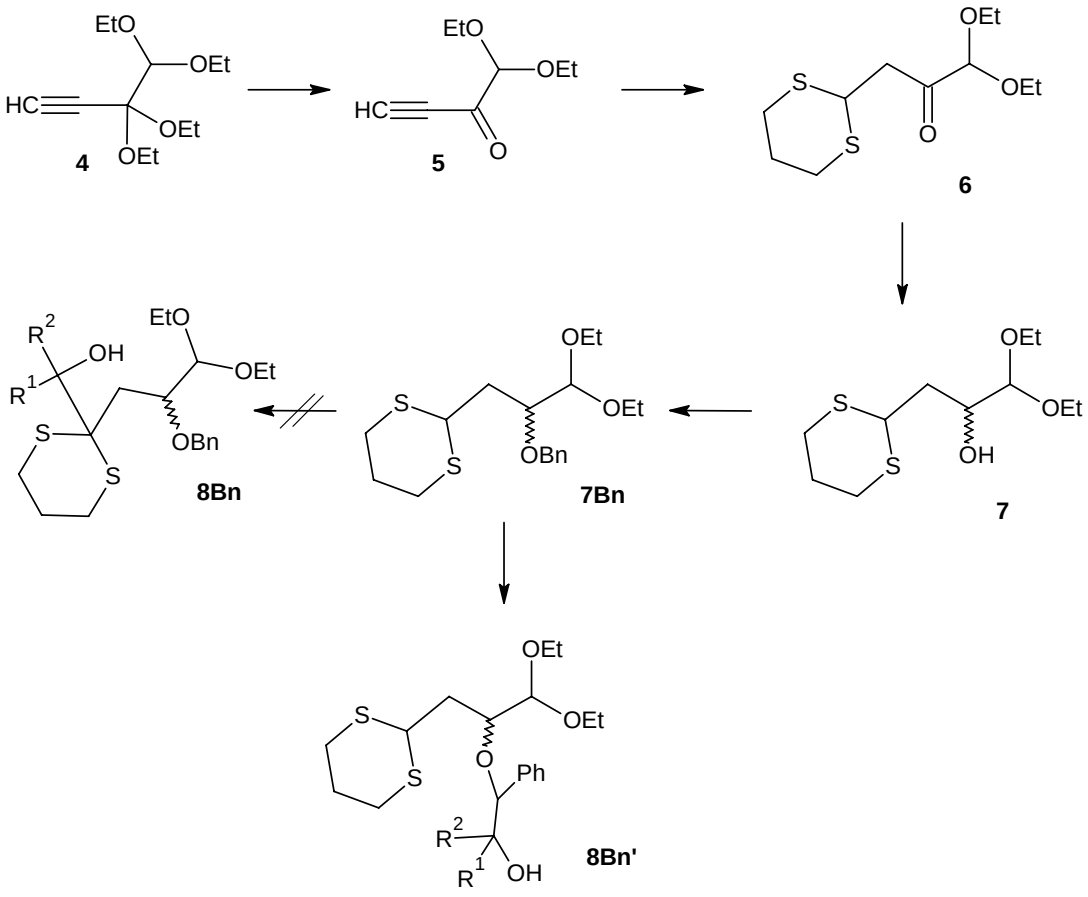


Scheme 1.5: *Possible reactions for TEB.* [29, 31]

1.5 Previous work

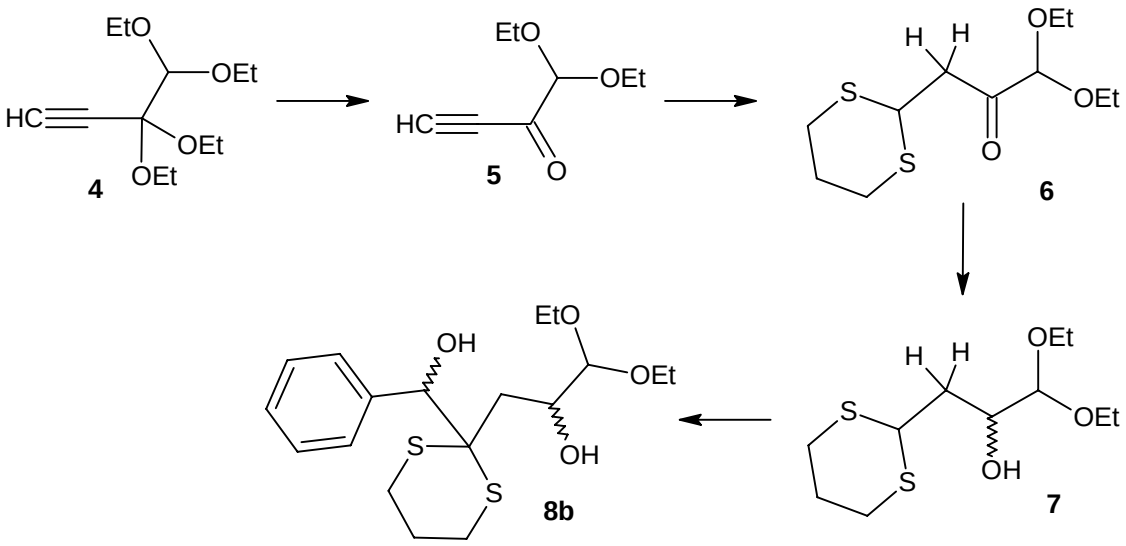
As depicted in Scheme 1.5, routes **h** and **i** are the most interesting ones in this study. These reactions have successfully been tried before by Valdersnes, in the attempt of synthesising various carbohydrate analogues from TEB.[30] Valdersnes first tried a reaction sequence where he produced chain-elongated analogues by coupling TEB with aldehydes and ketones, before conjugate addition of propane-1,3-dithiol. Later, he tried an alternative shorter reaction route for the synthesis, where the idea was to add the aldehydes and ketones late in the reaction sequence instead, after making the benzylprotected β-hydroxydithiane **7-Bn** first. This attempt was unsuccessful, as the product obtained was not the wanted **8-Bn**, but **8-**Bn', as can be seen in Scheme 1.6.

The addition reaction was first tried by treating **7-Bn** with *tert*-butyllithium (1 mol eq.) and a carbonyl compound in THF under dry ice conditions (- 78 ºC). Only unreacted starting material was obtained from this reaction; but the addition of hexamethylphosphoramide (HMPA) as a co-solvent gave a product for the reaction, although not the desired one. The product **8-Bn'** was obtained instead, as the benzylic position was more labile to deprotonate than the dithiane. When unprotected **7**, however, was tried as the starting material for the addition reaction, the desired product was made in a 14% yield. The reaction conditions were the same, except that 2 mol equivalents of *t*-BuLi was used in stead as there was an extra hydroxyl group present.[30]



Scheme 1.6: *Valdersnes' attempt at synthesising various carbohydrate analogues from TEB.*[30]

Valdersnes successful attempt at adding carbonyl compounds directly to the unprotected compound **7** made the basis for Flemmen's master thesis.[34] Her project aimed at synthesising the β –hydroxydithiane **7** from TEB first, and then adding different aldehydes and ketones to this compound. She worked on a small scale (0.8 mmol), using three different methods to add aldehydes and ketones to **7**, giving various yields. The results from Flemmen's work show that the best method for the additions is method B, as it gave the most satisfactory yields, especially for the compound **8b** that was made from the addition reaction with benzaldehyde (95%) as can be seen in Scheme 1.7.

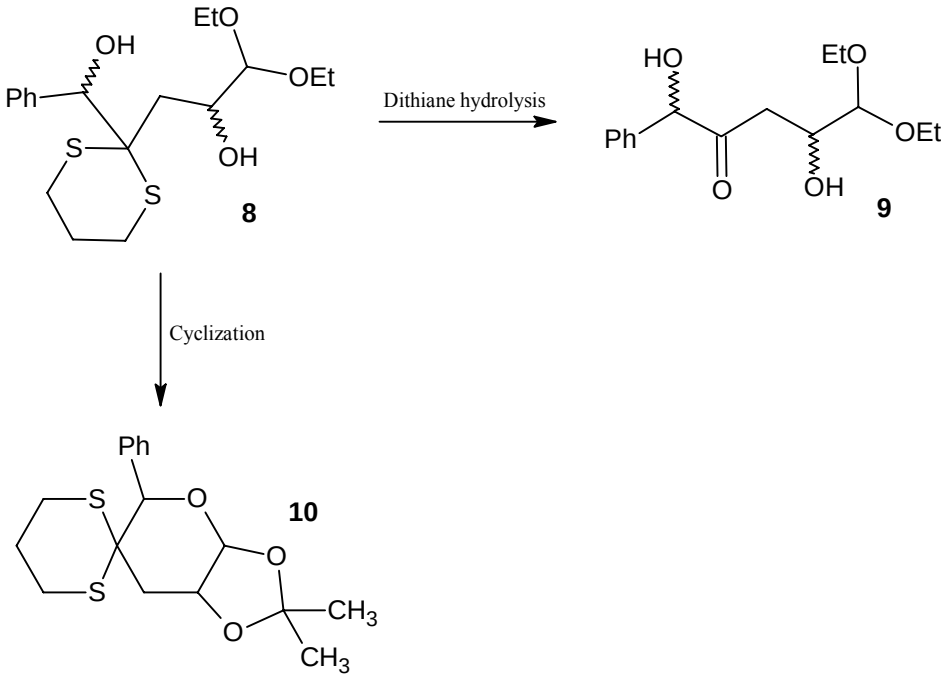


Scheme 1.7: *The transformations studied in Flemmen's master thesis. Compound* ***8b*** *gave the most satisfactory yield of all the addition reactions she tried*.[34]

On the basis of Flemmen's work, it was desirable to further investigate the more successful addition of benzaldehyde to **7** on a larger scale. This will also make it possible to see if the reactions could be carried on further so as to synthesise a carbohydrate analogue from compound **8**, by removing the dithiol group, and attempting to cyclizise the compound to furnish a 3-pyranone.

1.6 Aim

The aim for this project is to continue the work started by Flemmen and to synthesise the diol **8** from TEB as depicted in Scheme 1.8, by using the best method Flemmen tried, method B, and add benzaldehyde to compound **7**.[34] Another aim is to see if this synthesis also works equally well on a larger scale, giving the same satisfactory yield. It is also desirable to get a good yield so as to have enough material to continue the synthesis and remove the dithiane moiety from compound **8**, making compound **9**, and to cyclizise compound **8** and make compound **10**, based on the work done by Valdersnes.[30] Compound **9** can also be further cyclizised via an intramolecular transacetalisation reaction as described under further work later.



Scheme 1.8: *The possible reaction route from TEB to a carbohydrate analogue.*

In the reaction route for this project, TEB will first be deprotected to form ketone **5,** followed by a conversion of the product into to the 1,3-dithiane **6** by a reaction with propane-1,3-dithiol according to literature procedures. A reduction of the carbonyl group as described in the literature will then give alcohol **7**, which is the starting material for the first part of this investigation. Compound **7** is a substrate packed with differentiated functional groups, and many strategies would be possible to explore in order to furnish carbohydrate derivatives.[30] One possibility is the addition of various aldehydes and ketones to **7**, which will produce the

chain-elongated diols **8**, where in this case the addition of benzaldehyde will be tried. Unmasking the carbonyl group in compound **8** by reducing the dithiane moiety will yield compound **9**, while cyclizisation of compound **8** will furnish compound **10**.

A successful reaction sequence will be a confirmation upon the work previously done by Flemmen and Valdersnes, synthesising β –hydroxydithiane from TEB, and the following addition of aldehydes to the β –hydroxydithiane as done by Flemmen.[30, 34] It will also be possible to see whether the small scale synthesis by Flemmen when making the diol **8** still works on a larger scale with the same method giving a satisfactory yield. This will also make it possible to continue with the reactions as previously done by Valdersnes and make a carbohydrate analogue that can further be analysed as possible carbohydrate substituent for antibiotics such as vancomycin.[30]

References:

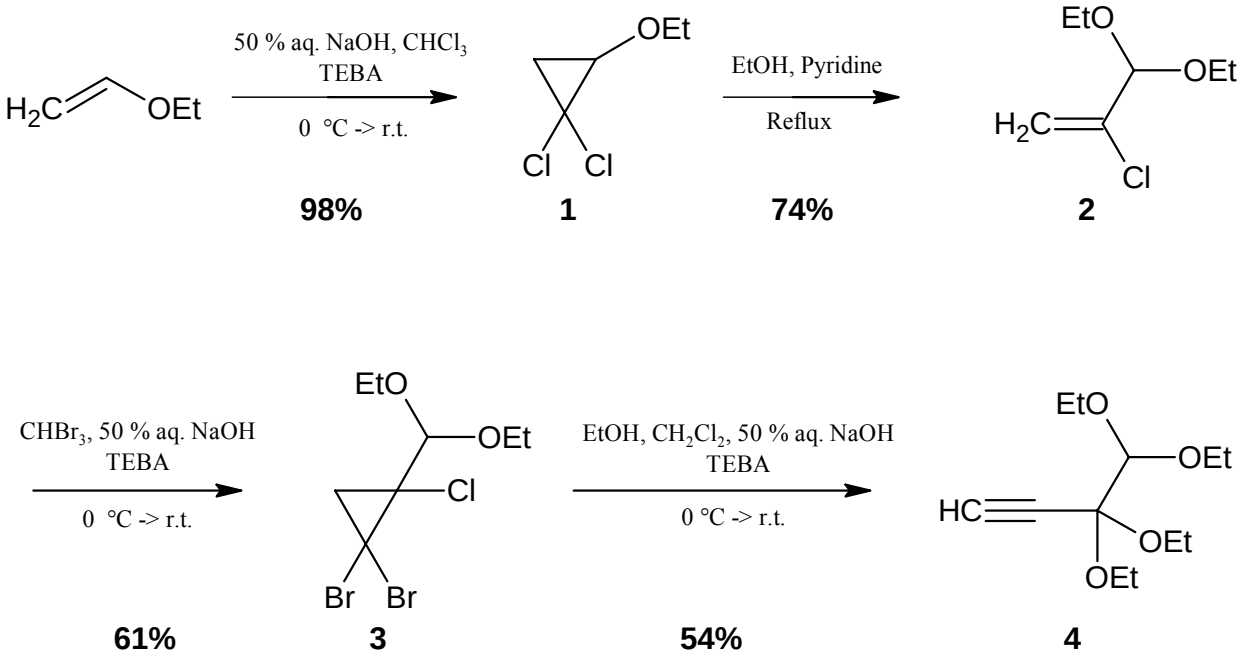
1. Patrick, G. J. *An introduction to medicinal chemistry*, 3rd ed. Oxford University press, New York, **2005**
2. http://felleskatalogen.no/felleskatalogen/show.do?filename=/content/static/pdf/FormelRegister.pdf. Accessed: May 3rd 2010.
3. Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angewandte Chemie International Edition***, 1999**, 38, 2096-2152
4. Wong, C. H.; Ritter, T. K. *Angewandte Chemie International Edition*, **2001**, 40, 3508-3533
5. Hiramatsu, K. *Drug Resistance Updates*, **1998**, 1, 135-150
6. Grdadolnik, S.; Pristovsek, P.; Mierke, D. F. *Journal of Medicinal Chemistry*, **1998**, 41, 2090-2099
7. Anderson, J. S.; Matsuhashi, M.; Haskin, M. A.; Strominger, J. L. *Biochemistry*, **1965**, 53, 881-889
8. Abreu, P. M.; Branco, P. S. *Journal of the Brazilian Chemical Society* **2003**, 14, 675-712
9. Bugg, T. D.; Dutka-Malen, S.; Arthur, M.; Courvalin, P.; Walsh, C. T. *Biochemistry*, **1991**, 30, 2017-2021
10. Walsh, C. T.; Fisher, S. L.; Park, I. S.; Prahalad, M.; Wu, Z. *Chemistry & Biology*, **1996**, 3, 21-28
11. Arthur, M.; Courvalin, P. *Antimicrobial Agents and Chemotherapy*, **1993**, 37, 1563-1571
12. Bugg, T. D.; Wright, G. D.; Dutka-Malen, S.; Arthur, M.; Courvalin, P.; Walsh, C. T. *Biochemistry*, **1991**, 30, 10408-10415
13. Silveira, G. P.; Nome, F.; Gesser, J. C.; Mandolesi, M.; Terenzi, H. *Química Nova* **2006**, 29, 844-855
14. Nagarajan, R.; *The Journal of Antibiotics*, **1993**, 46, 1181-1195
15. Ge, M.; Chen, Z.; Onishi, H. R.; Kohler, J.; Silver, L. L.; Kerns, R.; Fukuzawa.; Thompson, C.; Kahne, D. *Science*, **1999**, 284, 507-511
16. Chen, L.; Walker, D.; Sun, B.; Hu, W.; Walker, S,; Kahne, D. *Proceedings of the National Academy of Sciences of the United States of America,* **2003**, 100, 5658-5663
17. Ge, M.; Thompson, C.; Kahne, D. *Journal of American Chemical Society*, **1999**, 121, 1237-1244
18. Ge, M.; Thompson, C.; Kahne, D. *Journal of American Chemical Society*, **1998**, 120, 11014-11015
19. Nicolaou, K. C.; Mithcell H. J.; Jain, N. F.; Winssinger, N.; Hughes, R.; Bando, T. *Angewandte Chemie***, 1999**, 111, 249-253
20. Malabarba, A.; Nicas, T. I.; Thompson, R. C. *Medicinal Research Reviews*, **1997**, 17, 69-137
21. Williams, D. H.; Bardsley, B. *Angewandte Chemie International Edition*, **1999**, 38, 1172-1193
22. Gao, Y. *Natural Product Reports*, **2002**, 19, 100-107
23. Berg, J. M.; Tymoczko, J. L.; Stryer, L. *Biochemistry*, 5th rf.; W. H. Freeman and Company, New York, 2002.
24. Anderson, J. S.; Matsuhashi, M.; Haskin, M. A.; Strominger, J. L. *Biochemistry*, **1965**, 53, 881-889
25. Sears, P.; Wong, C. H. *Angewandte Chemie International Edition*, **1999**, 38, 2300-2324
26. Hallis, T. M.; Liu, H. W. *Accounts of Chemical Research*, **1999**, 32, 579-588
27. Nicolaou, K. C.; Mithcell H. J. *Angewandte Chemie International Edition*, **2001**, 40, 1576-1624
28. Weymouth-Wilson, A. C. *Natural Product Reports*, **1997**, 14, 99-110
29. Kvernenes, O.H. *3,3,4,4-Tetraethoxybut-1-yne and analogues as synthons in organic synthesis: an approach to the synthesis of deoxygenated sugars,* Dr.Scient thesis, University of Bergen, **2005**
30. Valdersnes, S. *Modified carbohydrates from 3,3,4,4-tetraethoxybut-1-yne,* PhD thesis, University of Bergen, **2006**
31. Sydnes, L.K.; Kvernenes, O.H.; Valdersnes, S. *Pure and Applied chemistry* **2005**, 77, 119-130
32. Gaunt, M.J.; Sneddon, H.F.; Hewitt, P.R.; Orsini, P.; Hook, D.F.; Ley, S.V. *Organic & Biomolecular Chemistry,* **2003**, 1, 15-16
33. Sneddon, H.F.; van den Heuvel, A.; Hirsch, A.K.H.; Booth, R.A.; Shaw, D.M.; Gaunt, M.J.; Ley, S.V. *Journal of Organic Chemistry,* **2006**, 71, 2715-2725
34. Flemmen, G. *Synthesis of some 1-substituted 5,5-diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diols from 1,1-diethoxy-3-(1,3-dithian-2-yl)-propan-2-ol*, Master thesis, University of Bergen, **2009**

2 RESULTS AND DISCUSSION

2.1 Preparation of starting materials

2.1.1 Preparation of TEB

The synthesis of TEB is depicted in Scheme 2.1, and consists of four steps as described by Sydnes et *al*.[1] The overall yield for my synthesis of TEB was 26% on a 0.3 mol scale. Compound **1** and **2** was not purified before the following steps, as the crude products appeared to be pure enough based on their ^{1}H-NMR spectra.



Scheme 2.1: *The synthesis of TEB from ethyl vinyl ether.* [1]

Synthesis of 1,1-dichloro-2-ethoxycyclopropane (1)

The synthesis of TEB starts with cyclopropanation of ethyl vinyl ether by Makosza's method[2], as described by Kvernenes.[3] This gave 98% of the crude product of 1,1-dichloro-2-ethoxycyclopropane (**1**) on a 0.3 mole scale. The title compound can be purified by distillation, but this was not attempted since the ^{1}H-NMR spectrum showed that the crude product was essentially pure, and could be used in the next step of the reaction as it were

Doering and co-workers[4, 5] were the first to report the synthesis of dihalocyclopropanes by the addition of dihalocarbene to alkenes. Makosza[2] then modified the reaction conditions to the Phase Transfer Conditions (PTC) used in our synthesis of **1**, where the reaction has been scaled up to 2 mol by Kvernenes.[3, 6] In this reaction the alkene ethyl vinyl ether is reacting with an excess of chloroform, four equivalents, in the presence of six equivalents of a 50% aqueous solution of sodium hydroxide, and a phase transfer catalyst (triethylbenzylammonium chloride, TEBA).

As the reaction is highly exothermic, an ice-water bath is required for the reaction mixture during the addition of NaOH. This bath can be removed after one hour for small scale reactions, but for larger scales the bath should be kept throughout the reaction to avoid that the reaction boils dry, although there is no need to refill the ice during this period.[3]

Synthesis of 2-chloro-3,3-diethoxyprop-1-ene (2)

The second step in the synthesis of TEB is a thermally induced ring opening of cyclopropane **1** using a procedure by Skattebøl[7], which gave 74% of the crude product of 2-chloro-3,3-diethoxyprop-1-ene (**2**). The title compound can be purified by distillation, but that was not attempted since the ^{1}H-NMR spectrum showed that the crude product was essentially pure, and could be used in the next step of the reaction as it were.

The mechanism for the reaction is believed to be a concerted ring opening of **1**, with loss of chloride to give an allylic-cation intermediate. Heat induces this ring opening[8]; ethanol then attacks the intermediate, the positively charged carbonyl moiety, to give the final product.[7]

Skattebøls reaction conditions have been simplified by Kvernenes, by using commercial absolute ethanol and commercial pyridine without any further purification in the reaction.[3] Pyridine is only present in the reaction to neutralise the HCl formed in the reaction. The removal of pyridine from the reaction is solved by washing the organic extracts with an aqueous copper-sulphate solution that seems to complex well with the pyridine. This complex is further removed by the filtering of the extracts through a small plug of alumina.[3]

Synthesis of 1,1-dibromo-2-chloro-2-diethoxymethylcyclopropane (3)

The third step in the TEB synthesis is a cyclopropanation by Makosza's method similar to the first step in the reaction[2], but here bromoform is used as the haloform instead of chloroform. This reaction gave a yield of 61% for the product of 1,1-dibromo-2-chloro-2-diethoxymethylcyclopropane (**3**) after distillation. A lot of polymeric residue was left in the distillation flask at the end of the distillation.

The excess bromoform is recycled after the reaction by distilling it off before the product. The yield is reported to be higher when recycled bromoform is used in the reaction, compared to fresh bromoform, as some unreacted starting material and some product probably follows the bromoform during the distillation.[8] Since this reaction also is highly exothermic, an ice-bath is required throughout the reaction to prevent the reaction mixture from overheating.

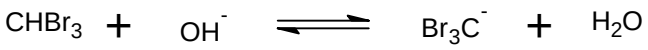
As reported by Kvernenes, a large excess, 10 equivalents, of bromoform is required in this reaction to give a good yield for the cyclopropane.[3] However, there is then a potential risk that tetrabromomethane, CBr_4, will form as a by-product during the reaction. In my case, the reaction was run with 13 equivalents of bromoform due to some error in calculating the real amount of **2** added in the reaction at first. As a result the presence of tetrabromomethane can be seen in the ^{13}C-NMR spectrum of a sample obtained during distillation, between the collection of the excess bromoform and the product **3**. The by-product CBr_4 does not contain any protons, and is expected to give a peak at -28.5 ppm on a ^{13}C-NMR spectrum.[9] My spectrum clearly show a large peak at -28.7 ppm which indicates that CBr_4 has been made in the reaction. The ^{1}H-NMR spectrum of the by-product obtained in the reaction shows the presence of product **3**, among other unidentified peaks.

The large amount of bromoform used in the reaction may explain why this happened, although this has not been reported as a problem when 10 equivalents have been used before by other members of my group. Future reactions of this step in the synthesis, where less bromoform is used, may not give the same problem with tetrabromomethane as by-product, but the overall yield for the reaction should be taken into consideration here as previous reports states that a satisfactory yield only is achieved with the large amount of bromoform used.[3]

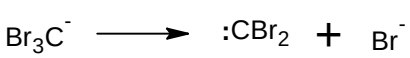
It is believed that too much of bromoform in the reaction facilitates the formation of tetrabromomethane. This can happen because the anion that is formed after the proton has been extracted, can further react as both a base, and as a nucleophile. As a base it will react with another bromoform molecule, as seen in Scheme 2.2, and create another anion while regenerating itself as a bromoform molecule again. As a nucleophile, however, the anion will react with a bromoform molecule, abstracting a bromide atom instead of a proton, and thereby create the by-product tetrabromomethane , as seen in Scheme 2.2

<u>The normal reaction where bromoform is turned into dibromocarbene:</u>

1: Quick reaction:



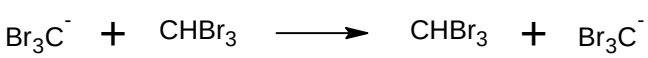
2: Slow reaction:



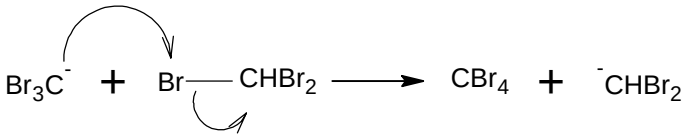
(Then: addition of the ***:****CBr_2 to alkene)*

<u>A lot of bromoform, however, will give an anion, $^{-}CBr_3$, that acts:</u>

Either as a base:



Or as a nucleophile:



Scheme 2.2: *The possible formation of a by-product in the third step of the TEB-synthesis.*

Synthesis of 3,3,4,4,-tetraethoxybut-1-yne (TEB) (4)

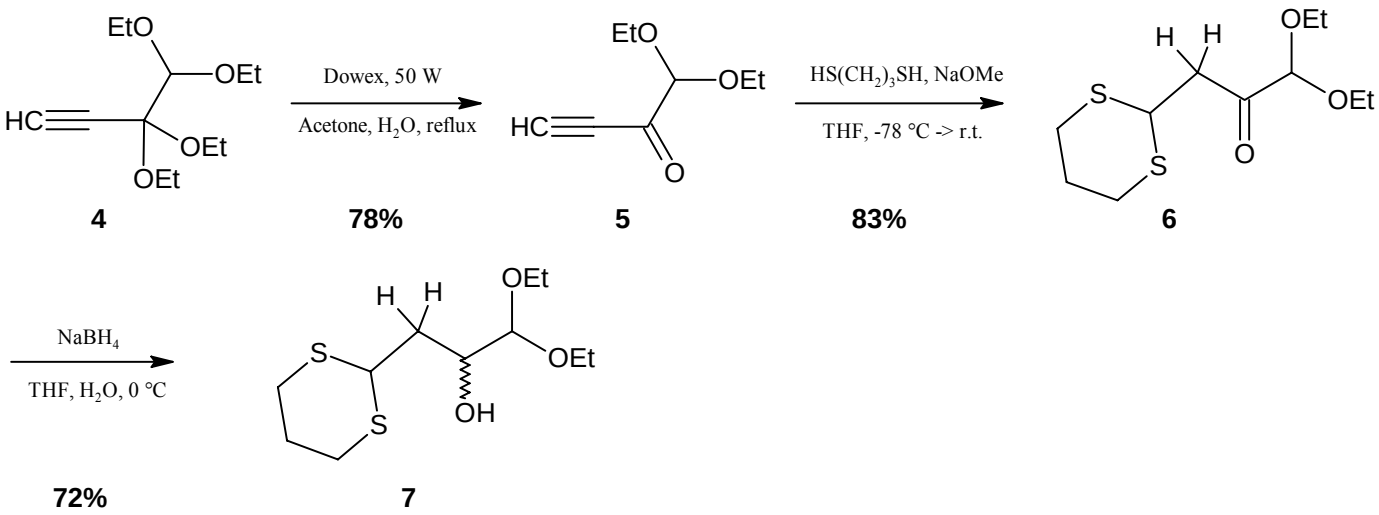
The last step in the TEB synthesis is a regioselective ring opening of trihalocyclopropane **3** following a procedure published by Sydnes and Bakstad.[10-13] This reaction gave a yield of 54% for the product of 3,3,4,4,-tetraethoxybut-1-yne (TEB) (**4**) after distillation. The overall yield of TEB is, however, not solely based on the product **3** from the previous step alone, but also from a small amount (4.182 g, 0.0126 mol) of **3** that was synthesised in an earlier attempt as well. An ice-bath is required throughout this reaction to prevent it from overheating.

During the distillation of the product, a mixture of bromoform and CBr_4 was obtained before the product distilled off. The distillation apparatus had to be changed before the product was distilled, due to the fact that CBr_4 is solid at 91 ºC[14] and contaminated the entire apparatus. The starting compound **3** seemed to be pure from the ^{1}H-NMR and ^{13}C-NMR spectra, but as observed here it is obvious that some by-product still has been present in the sample. After the distillation of the product **4** a black, tarry residue was left in the distillation flask. After the product **4** had distilled, unreacted starting material **3** distilled at almost the same temperature, which did unfortunately contaminate the product. TEB now has some traces of **3** in it, as can be seen from the ^{1}H-NMR spectrum.

The last step in the TEB synthesis is the regioselective ring opening of **3**, a reaction that has been studied thoroughly before.[10-12, 15-16] Ring opening of trihalocyclopropanes under PTC usually gives a mixture of acetylenic acetals and acetylenic ketals depending on the R-groups present[10], but the reaction conditions can be modified so as to give a more regiospecific ring opening.[11] The R-group present in **3** is diethoxymethyl which is a bulky substituent, but it is believed to possess sufficient polarity to form hydrogen bonds that redirect the ethanol attack and therefore gives only the ketal product.[1,12-13, 17]

2.1.2 Preparation of β-hydroxydithiane from TEB

The synthesis of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**) from TEB is depicted in Scheme 2.3 and consists of 3 steps as described by Valdersnes and later Flemmen.[8, 18] The overall yield for my reaction was 43.5% on a 43.7 mmol scale.



Scheme 2.3: *The synthesis of β-hydroxydithiane from TEB.* [8, 18]

Synthesis of 1,1-diethoxybut-3-yn-2-one (5)

The hydrolysis of the ketal moiety in TEB to give ketone **5** is done according to the procedure described by Kvernenes.[3] This reaction gave a yield of 78% for the pure product of 1,1-diethoxybut-3-yn-2-one (**5**) after flash chromatography.

Dowex 50 W is a strongly acidic resin, and when it is added to **5,** dissolved in a solution of a mixture of acetone and water, the reaction results in selective deprotection of the ketal, leaving the acetal untouched.[3] The reason for this regioselectivity is believed to be due to the electronic 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.[3]

Flemmen originally compared the use of Dowex 50 W as the acid catalyst (a 24 h reaction) against the use of PTSA as the acid catalyst (a 15 h reaction), whereupon she found that the yield with Dowex 50 W was better (69% yield) than for the reaction with PTSA (25% yield).[18] Flemmen therefore concluded that the Dowex 50 W method was the best to use when making ketone **5** from TEB. A fellow student tried to repeat this Dowex 50 W procedure several times, but she was unsuccessful, and got a fair amount of by-product during the reaction. Then the use of only a 12 h reaction time instead with the same procedure, was suggested, which had been successful for some.[19] Kvernenes originally tried a reaction time of only 8 h.[3] It therefore seems that a shorter reaction time than the original 24 h described by Flemmen is sufficient to convert most of the TEB into ketone **5**, and that a long reaction time only gives the opportunity for more by-product to be formed.

In addition, the use of another batch of Dowex 50 W that seemed to be of better quality than the one previously used in the more unsuccessful attempts, could also be of importance. My reaction was therefore tried with a new batch of Dowex 50 W, and for a 12 h reaction, and this time a satisfactory yield was gained, with an outcome of 78% product at a 43.7 mmol scale.

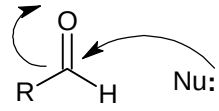
Synthesis of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-one (6)

The addition of dithiol to ketone **5** is a double conjugate Michael addition under basic conditions as described in the literature.[20, 21] This reaction gave a yield of 83% for the product 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-one (**6**) after flash chromatography. The use of a mixture of TEB and ketone **5** will not complicate the reaction, since the ketal does not react with the dithiol.

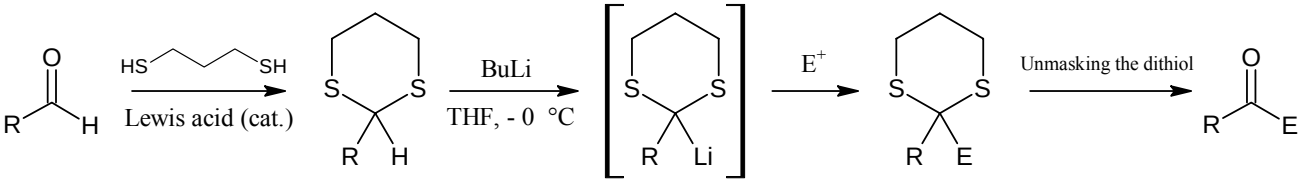
The reaction conditions described in the literature by Ley and co-workers[20, 21] has been modified by Valdersnes[8] to the use of THF as a solvent rather than methanol, and the reaction has been run at –78 ºC instead of – 10 ºC so as to minimize the possible dimer formation. [20, 21]

The reaction uses lithiated 1,3-dithianes as nucleophilic acylating agents, and allows a reversal of the normal reactivity of carbonyl group. The German term "Umpolung" is used for this inversion of reactivity. The lithiated 1,3-dithiane can be viewed as a masked acyl anion that is able to react with various electrophiles, as seen in Scheme 2.4.[22]

The normal reactivity for carbonyl compounds is addition of a nucleophile:



The dithiane acts, however, as a masked carbonyl anion, where the addition reaction of electrophiles now is possible:



Scheme 2.4: *Umpoloung of an aldehyde, producing an acyl anion equivalent.*[22]

Synthesis of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (7)

The β-hydroxydithiane **7** is synthesised by reducing the carbonyl group on the dithiane **6** by the use of sodium borohydride in aqueous THF. The reaction gave a total yield of 72% for two fractions of the product 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**) after flash chromatography. Fraction 1 (34% yield) was not as pure as fraction 2 (38% yield) as could be seen from TLC, although there are only minor impurities observed in the ^{1}H- NMR spectrum for fraction two, that most likely will not affect any further uses of the compound.

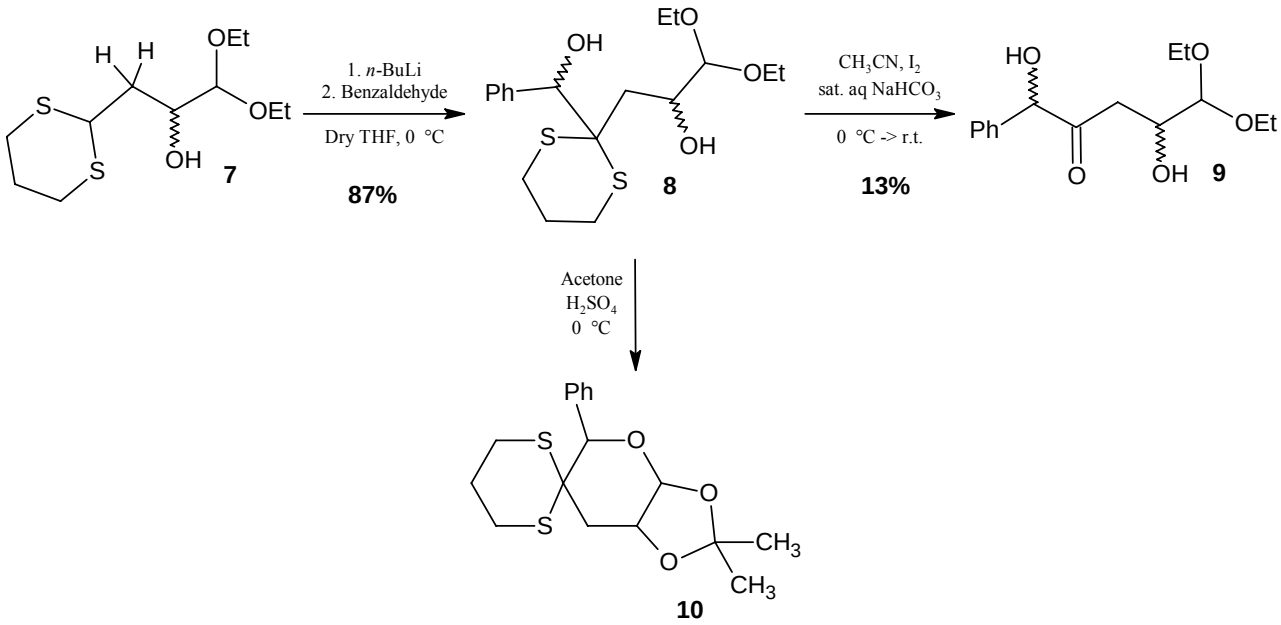
The original procedure was published by Zeynizadeh and Behyar[23], but the reaction conditions has been modified in my group by using 0.5 mol equivalents of $NaBH_4$, instead of 2 mol equivalents, and running the reaction at 0 ºC (ice water bath) instead of at reflux temperature (66 ºC).[18]

According to the work previously done by Flemmen, compound **7** is stable for at least 2 weeks in r.t. and for at least 4 weeks in the refrigerator.[18] She reported that for the decomposed sample of **7** that was stored in r.t. for several weeks, both the colour and the viscosity had changed. After my compound had been stored for 4 weeks in the refrigerator, it was still clear and colourless, and it had the same viscosity as it had when it was freshly made. A new ^{1}H-

NMR spectrum taken of compound **7** after the 4 weeks storage in the refrigerator confirms that no decomposition has taken place.

2.2 Chain elongation using β-hydroxydithiane 7

The synthesis of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**), 5,5-diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (**9**) and 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**10**) from β-hydroxydithiane (**7**), as described by Flemmen and Valdersnes, is depicted in Scheme 2.5.[8, 18]



Scheme 2.5: *The synthesis of compounds **8**, **9** and **10** from β-hydroxydithiane.*[8, 18]

Synthesis of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (8)

The addition of benzaldehyde to **7** is done according to the procedure described by Flemmen,[18] and gave a yield of 87% for the pure product of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**) after flash chromatography.

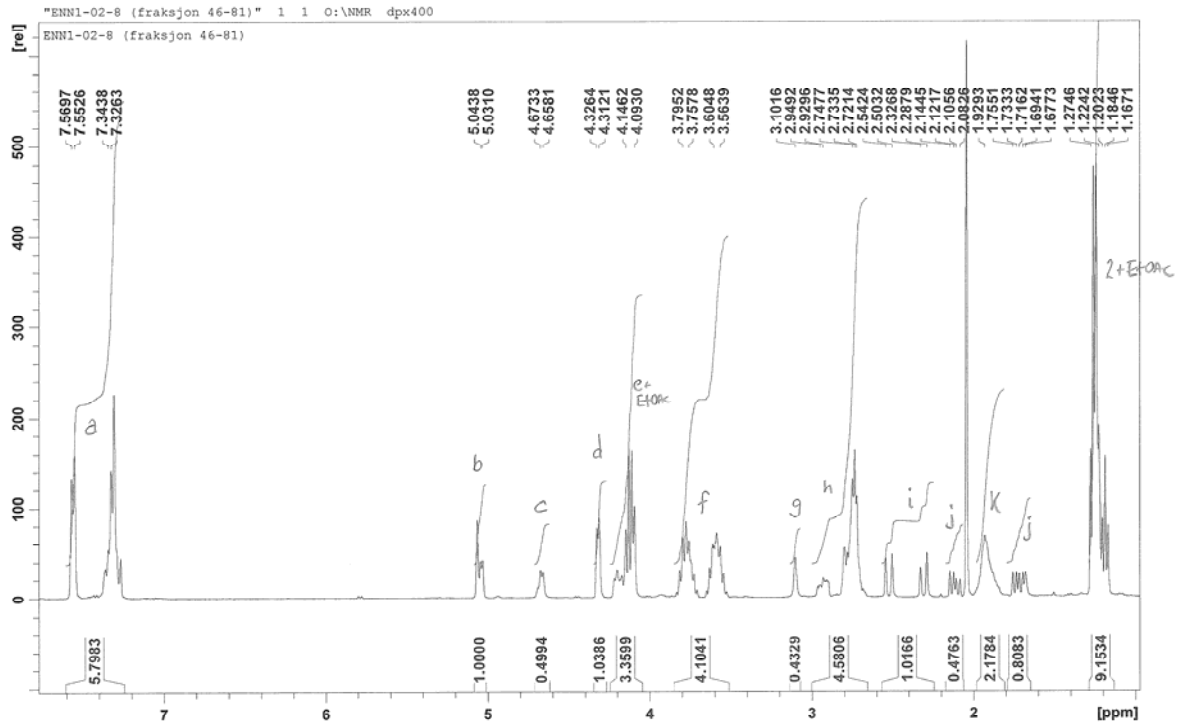
The dithiane moiety introduced in compound **6** is a masked carbonyl moiety, which makes it possible for the compound to react with electrophiles in addition reactions (see Scheme 2.4).[22]

In most cases treatment of dithianes with *n*-BuLi at temperatures of -30 °C is sufficient for the preparation of the lithio derivatives.[22] In my case the reaction is run at 0 °C.[18]

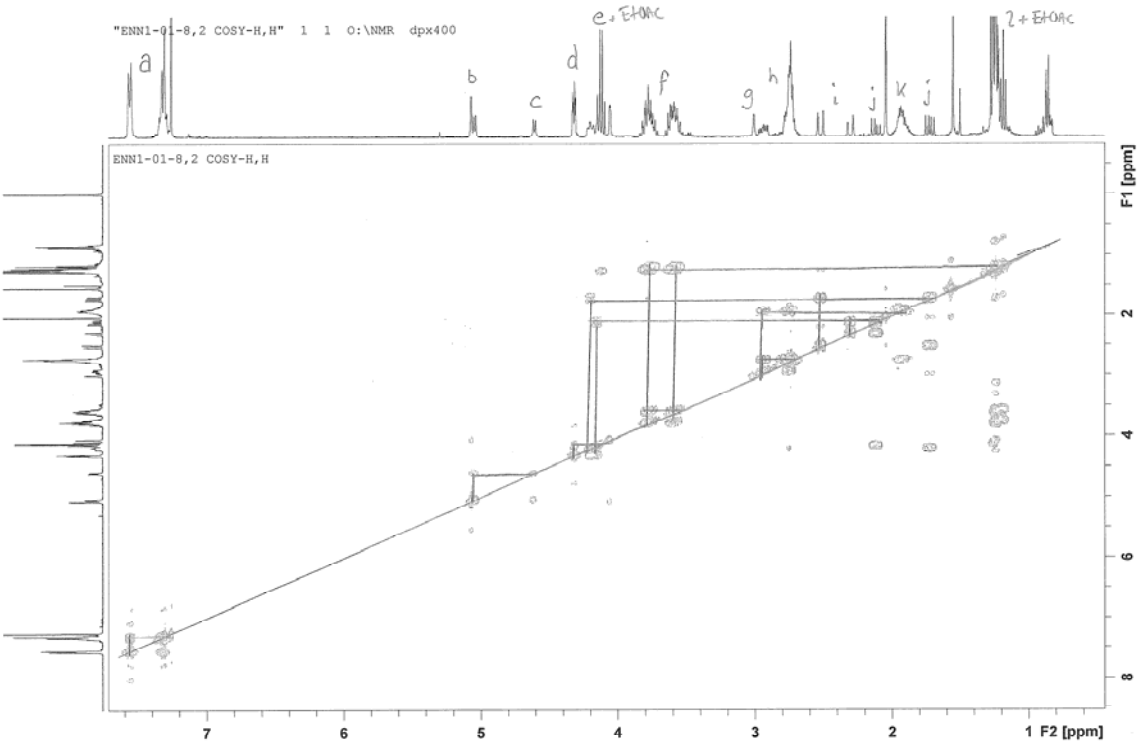
Valdersnes[8] originally treated compound **7** with *t*-BuLi in THF at - 78°C, and added HMPA as a co-solvent in the reaction since the lithiated dithiane exists as a contact ion pair in THF.[24] HMPA separates the ion pair, which helps increase the yield in the reaction. Ide and Nakata found that HMPA was needed as a co-solvent for anion generation in the reaction with *n*-BuLi at -78 °C, but not at 0 °C which is the temperature used in this reaction.[25]

This reaction requires two equivalents of *n*-BuLi, one to abstract the unprotected hydroxyl proton, and the other to abstract the proton at the 2-position of the dithiane.

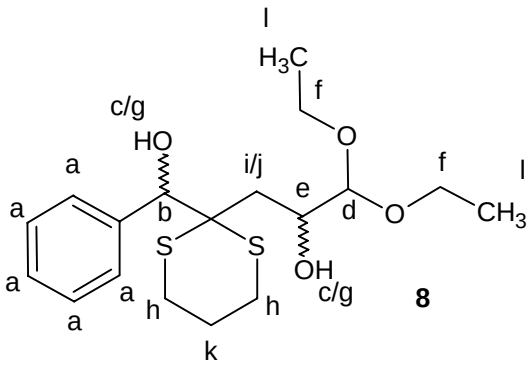
Assignment of ^{1}H-NMR spectra for compound 8



Scheme 2.6: *^{1}H-NMR spectrum of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**).*



Scheme 2.7: *COSY-H,H spectrum of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**).*



8

Scheme 2.8: *Compound **8** and the letters assigned to the different hydrogens.*

All spectra for compound **8** are in agreement with the spectroscopical data interpretated by Flemmen in her thesis.[18] The signals from hydrogens *d*, *e*, *f*, *h*, *k* and *l* (see Scheme 2.8) are previously known from the spectra for compounds **5-7** (see appendix), and are assigned in a similar fashion. As seen from scheme 2.6, the hydrogens *i* and *j* exhibits different chemical shifts as expected, and appears as two sets of doublets upfield, and two sets of double doublets further downfield. The COSY-H,H spectrum, as seen in Scheme 2.7, show that *i* and *j* are coupled to each other (J = 15.6 Hz) through geminal coupling. The broad signals that do not couple with any other hydrogen are assumed to be the hydroxyl hydrogens *c* and *g*.[18]

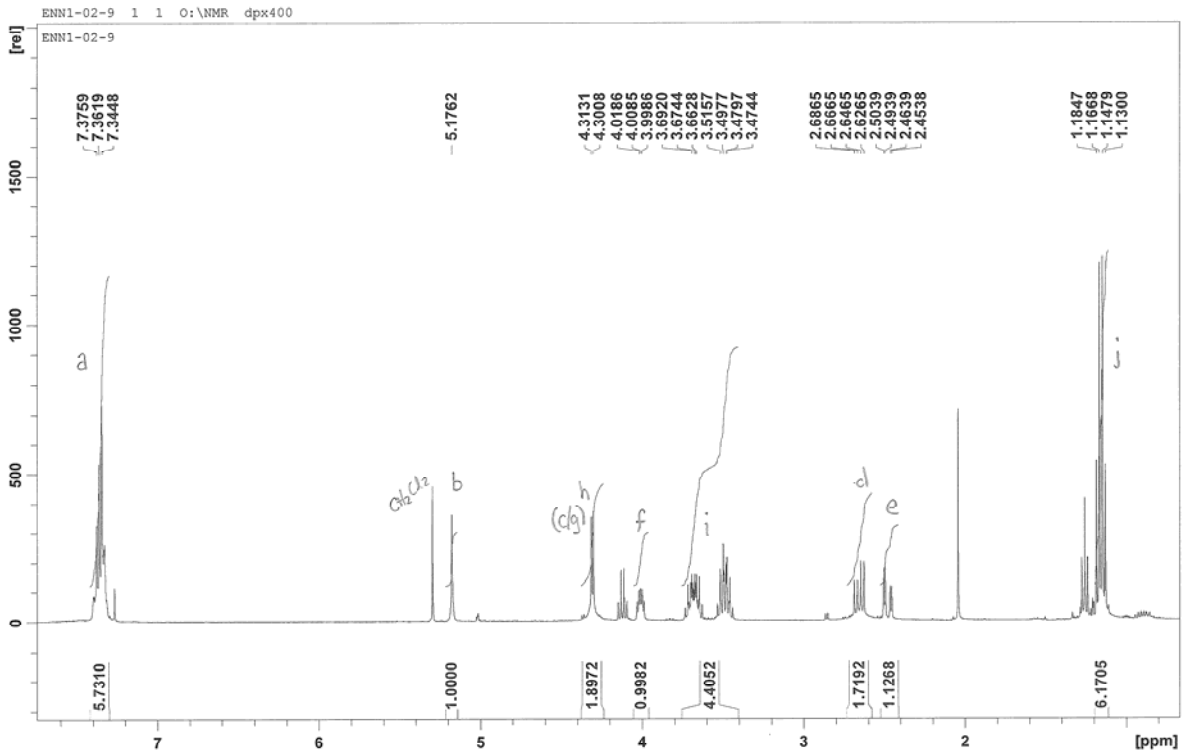
The five aromatic hydrogens are all assigned to the same letter, although there are two separate regions where the signals for the hydrogens appear on the spectra. This was also noted by Flemmen due to the different positions of the hydrogens on the phenyl-group. Hydrogen *b* in the benzylic position does not couple to any other proton, and because it is close to a phenyl group, it is further downfield.[18]

Synthesis of 5,5-diethoxy-1,4-dihydroxy-1-phenylpent-2-one (9)

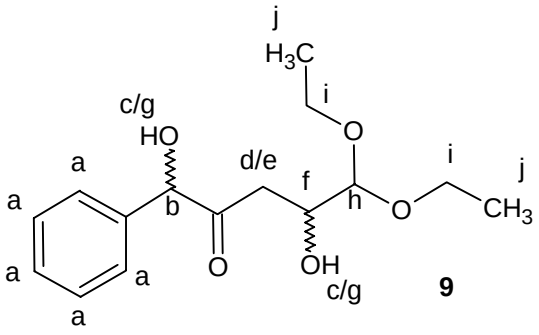
The removal of the dithiane in compound **8** gave a yield of 13% for the pure product 5,5-diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one **(9)** after flash chromatography. The reduction was carried out by treating compound **8** with iodine in a solution of acetonitrile and saturated aqueous sodium bicarbonate, following a procedure described by Valdersnes.[8, 26] Valdersnes tried several different methods reducing compounds similar to **8**, and found that the best yields for the more substituted compounds came from the method used in this reaction.[8]

The yield of ketone **9** is much lower than expected.[8] TLC analysis of the crude product show that it consists of at least four different compounds, where only the main product has been characterised. A fellow student attempting the same reaction with a lesser substituted compound has noted the same problem.

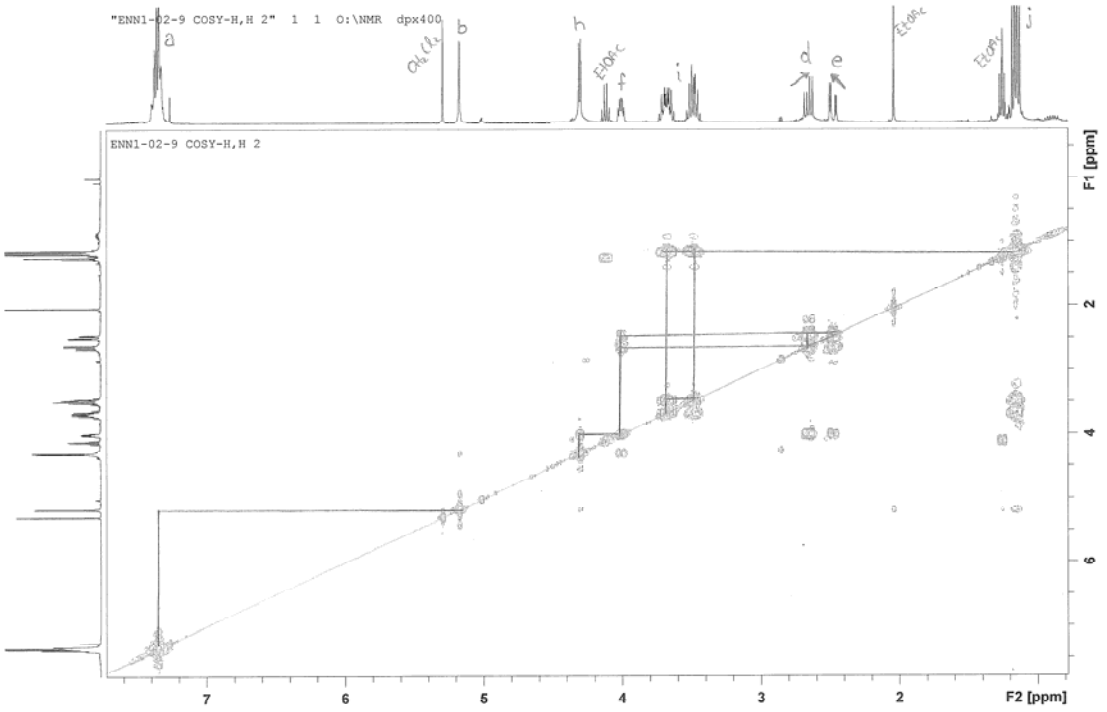
Assignment of ^{1}H-NMR spectra for compound 9



Scheme 2.9: *^{1}H-NMR spectrum of 5,5-diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (**9**).*



Scheme 2.10: *Compound **9** and the letters assigned to the different hydrogens.*



Scheme 2.11: *COSY-H,H spectrum of 5,5-diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (**9**).*

The signals from the aromatic hydrogens *a* as seen in Scheme 2.9, are assigned to the same chemical shift as for compound **8**, although for compound **9** there is only one region where the signals appear as compared to the two separate regions of signals as seen for compound **8** (Scheme 2.6). The COSY-H,H spectrum for compound **9** does not show any strong coupling of the aromatic hydrogens to other hydrogens (Scheme 2.11), but there is however a weak coupling observed between the hydrogens at *a* and the benzylic proton *b*.

Hydrogen *b* is assigned to having a similar chemical shift as for the hydrogen in the benzylic position for compound **8**. This signal has however shifted a bit more downfield due to the removal of the dithiane moiety as the carbonyl group is more electronegative than sulphur. The signal is a strong singlet because the hydrogen does not couple to any other hydrogens in the compound, but as mentioned above, there has been observed a very weak coupling between *b* and the aromatic hydrogens *a*.

Hydrogen *h* appears as a doublet as expected, and couples to hydrogen *f*. The signal for *h* is however very broad at the base of its peak, and is not as sharp as compared to the rest of the spectrum. There might be some overlap with the hydroxyl signals for *c* and *g* as they can have the same chemical shift as hydrogen *h*. The signals for *c* and *g* can not be clearly seen in the spectrum. The signal for *h* integrates for two hydrogens, although *h* is assigned for only one hydrogen, which is conclusive with the theory that the signals from *c* and *g* might be overlapping with *h*.

As observed in the ^{1}H-NMR spectrum for compound **8**, the signals from hydrogens *d* and *e* in compound **9** give rise to quite different peaks. The hydrogens for *d* appears as a double doublet at 2.68-2.62 ppm with a coupling constant J = 8.0 Hz; while the hydrogens for *e* appears as a double doublet at 2.50-2.45 ppm with a coupling constant J = 4.0 Hz. The correlation signal also shows that *d* and *e* do couple to each other through geminal coupling (J = 16.0 Hz), which is confirmed by the signals that are skewing towards each other too. The chemical shift where the signals appear is expected for α-hydrogens to a carbonyl group that also are close to a hydroxyl group. The sharp peaks indicate that the compound has a stable conformation with little mobility in the compound.

Hydrogen *f* appears as a multiplet at 4.02-3.98 ppm, which is typical for hydrogens α to a hydroxyl group. As expected, the pattern is a multiplet because *f* couples to at least *d*, *e* and *h* in the compound, as can be seen from the COSY-H,H spectrum. The coupling constant for *f* is J = 4.0 Hz, which is the same as the coupling constant for *e*.

The hydrogens *i* and *j* are assigned in a similar fashion as for earlier compounds in this investigation. The signals appear at the same chemical shifts with a similar multiplicity pattern as seen before for the diethoxy group in all the previous compounds (see appendix).

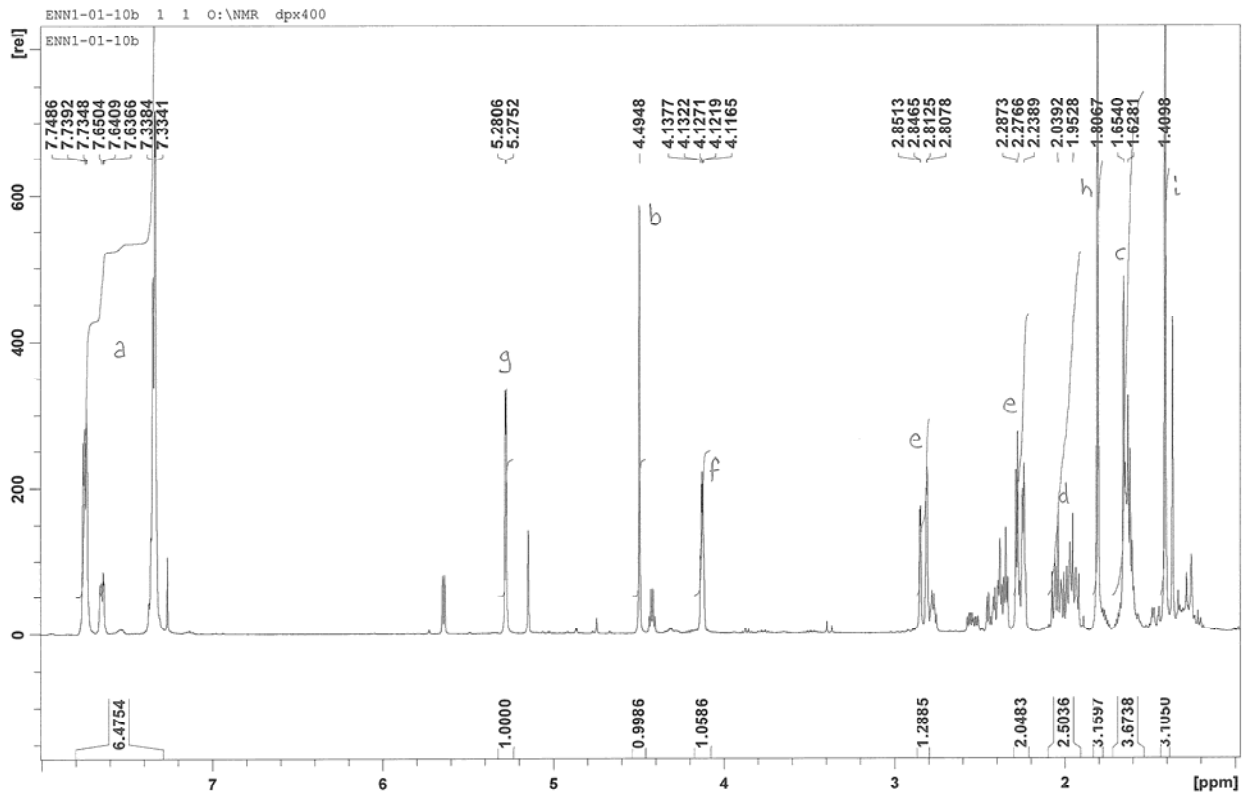
Synthesis of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (10)

Cyclization of the compound **8** was also attempted before the removal of the dithiane group. This was done as an exploratory experiment, following a method described by Valdersnes using wet acetone at 0 °C, with concentrated sulphuric acid as a catalyst.[8] Valdersnes noted that this reaction did not work very well for the more substituted substrates, and the only

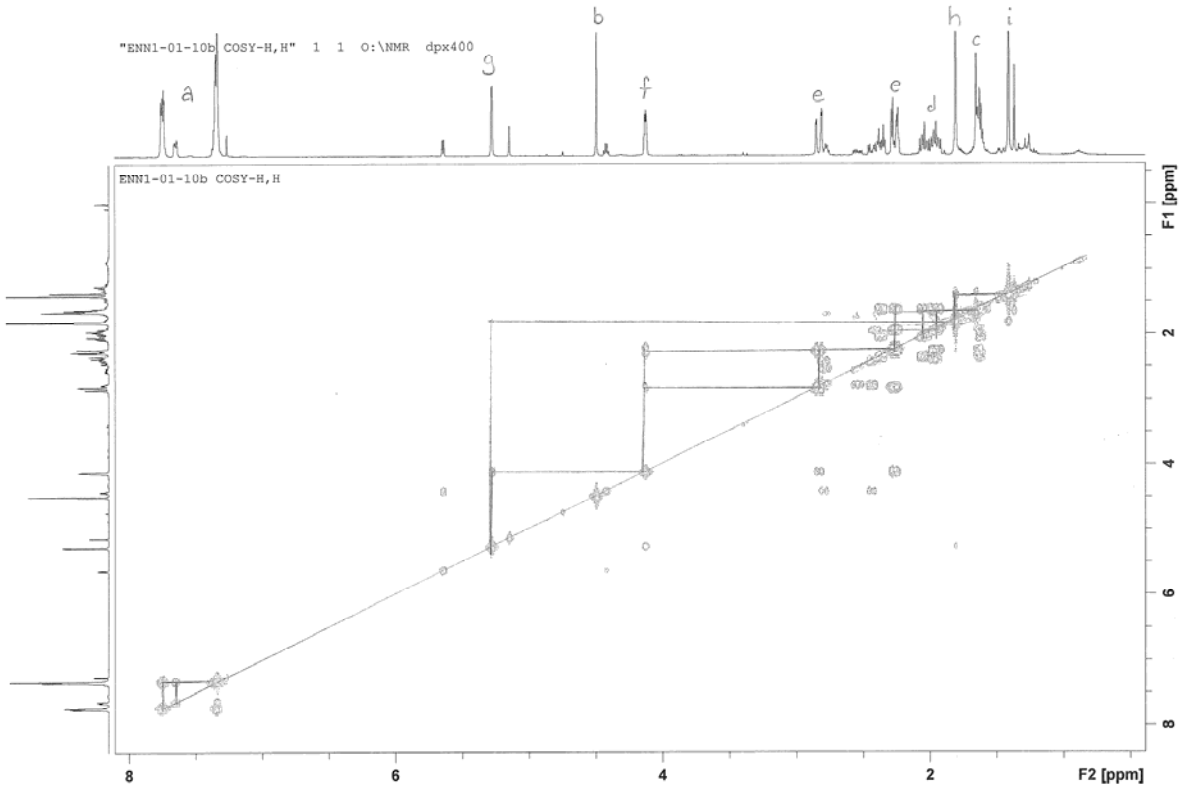
successful cyclization was when the two R groups in the compound were both hydrogens. Compound **8** in this investigation has a phenyl group and a hydrogen as the R substituents.

The title compound was obtained as 0.045 g of a white, slightly yellow, solid from flash chromatography; but as seen from the ^{1}H-NMR spectrum of the compound it is not entirely pure. In addition to the title compound this reaction gave two other fractions of liquid compounds, which have not been analysed any further.

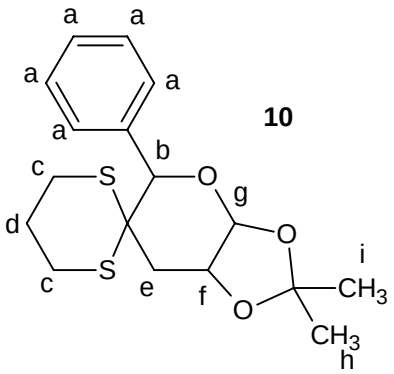
Assignment of ^{1}H-NMR spectra for compound 10



Scheme 2.12: *^{1}H-NMR spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**10**).*



Scheme 2.13: *COSY-H,H spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**10**).*



10

Scheme 2.14: *Compound **10** and the letters assigned to the different hydrogens.*

As seen in Scheme 2.12, the aromatic hydrogens *a* appears at the same chemical shift as for compounds **8** and **9**, but in three regions, all of which couple to each other as seen in the COSY-H,H spectrum in Scheme 2.13. Hydrogen *b* in the benzylic position appears as a strong

singlet, and do not couple to any other hydrogen. The chemical shift for *b* is, however, more upfield than as seen for compound **8** and **9** because of the ring current effect in the system.

The hydrogens *d* appears as a double multiplet at 2.07-1.91 ppm with a coupling constant J = 7.0 Hz. This signal is previously known from earlier compounds, and the correlation signal show that *d* couple to *c*. The hydrogens *c* appears as a multiplet at 1.65 ppm, which is much more upfield than observed in previous compounds having the same structure. This is due to the effect of the ring current from the phenyl group.

The signals for hydrogens *e* appears in two sets of double doublets, similar to what is observed for earlier compounds. The first region of *e* appears at 2.85 and 2.81 ppm with a coupling constant J = 1.9 Hz; while the other region appears at 2.28 and 2.24 ppm with a coupling constant J = 4.0 Hz. The correlation signal shows that both regions for *e* couples to each other through geminal coupling (J = 15.5 Hz). The COSY-H,H spectrum also shows coupling between both regions of *e* to *f*. The hydrogens *e* for the region most upfield in the spectrum also couples weakly to the hydrogens *c* and *d* in the ring structure of the dithiane moiety, but this is not caused by through-bond coupling, and is most likely due to through-space coupling.

As expected, hydrogen *f* appears as a triplet, with a coupling constant J = 2.1 Hz. The correlation signal shows that *f* couple to both regions of *e*, and also to hydrogen *g*. The signal for hydrogen *g* is very similar to what is observed from Valdersnes' ^{1}H-NMR spectrum for a similar compound.[8] The signal appears as a doublet at 5.28-5.27 ppm, with a coupling constant J = 2.1 Hz. In addition to the coupling to *f*, *g* also couples weakly to hydrogen *h* as seen from the COSY-H,H spectrum.

The two signals for *h* and *i* also show a great similarity to Valdersnes' ^{1}H-NMR spectrum[8], as they appear as two very strong singlets at 1.80 and 1.40 ppm. Both signals integrate for three hydrogens each, and they also couple to each other as seen in the COSY-H,H spectrum.

The ^{1}H-NMR spectrum also revealed minor impurities in the sample, but as seen from the COSY-H,H spectrum these impurities do not couple to any of the hydrogens in the major product.

2.3 Further Work

2.3.1 Reducing the amount of bromoform

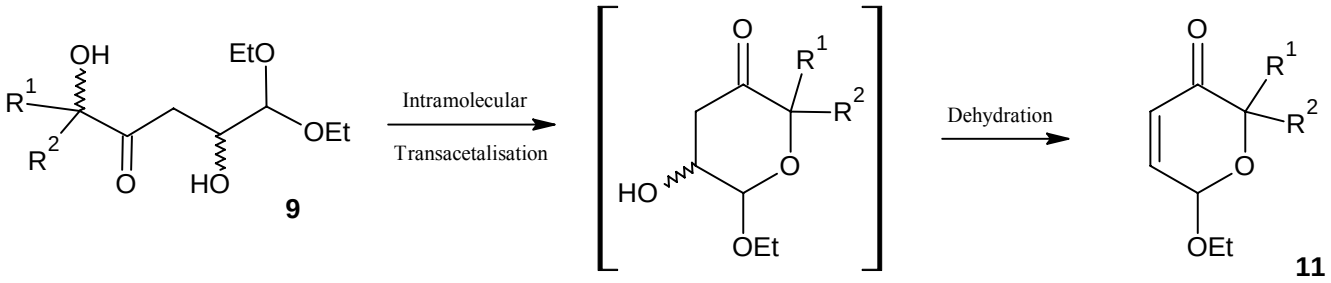
As observed in this investigation, a large excess of bromoform may give the by-product tetrabromomethane when synthesising 1,1-dibromo-2-chloro-2-diethoxymethylcyclopropane in the third step of the TEB synthesis. Although there has been previously reported a need for 10 equivalents of bromoform to get a good yield for this reaction[3], it would be interesting to observe if a lesser amount of bromoform could be used successfully and giving a satisfactory yield, but without obtaining any by-products.

2.3.2 Reaction scale up

Only one of the previous reactions performed by Flemmen[18], adding aldehydes and ketones to β-hydroxydithiane **7**, was scaled up from the original 0.8 mmol scale. Further additions with various aldehydes and ketones should therefore be performed on compound **7,** producing the corresponding diols **8** to see if the reaction conditions still apply for a larger scale. If successful, these compounds can undergo subsequent reduction of the dithiane moiety, followed by a cyclization, which will in turn furnish various 3-pyranones.

2.3.3 Cyclization of 5,5-diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (9) to form a 3-pyranone

5,5-Diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (**9**) can be cyclizised via an intramolecular transacetalisation followed by a subsequent dehydration to furnish the 3-pyranone **11** as depicted in Scheme 2.15. Valdersnes successfully cyclizised a compound similar to **9** by treating it with HBF_4 in acetonitrile at 0 °C. However, the starting material used by Valdersnes was not as substituted as compound **9** in this investigation, which can affect the yield of the reaction.



Scheme 2.15: *The cyclisation of compound* ***9*** *to furnish the 3-pyranone* ***11***.[8]

Valdersnes' compound: R^1, R^2 = H, H [8]

Compound **9** in this investigation: R^1, R^2 = H, Ph

Due to the many functionalised groups in compound **9**, attempting a ring formation can be very difficult as depicted in Scheme 2.16.[8] Depending on where the protonation will occur, various compounds can be made in the reaction. Protonation at **b** can yield two carbonyl compounds via a retro-aldol reaction, while protonation at the secondary alcohol **c** can produce an α,β-unsaturated ketone by loss of water via an E1 mechanism. Protonation at either of the acetal ethoxy groups could lead to an intramolecular transacetalisation with the hydroxyl group at **a**, giving the desired product. This product is however also labile for further protonation as to complicate matter further.[8]

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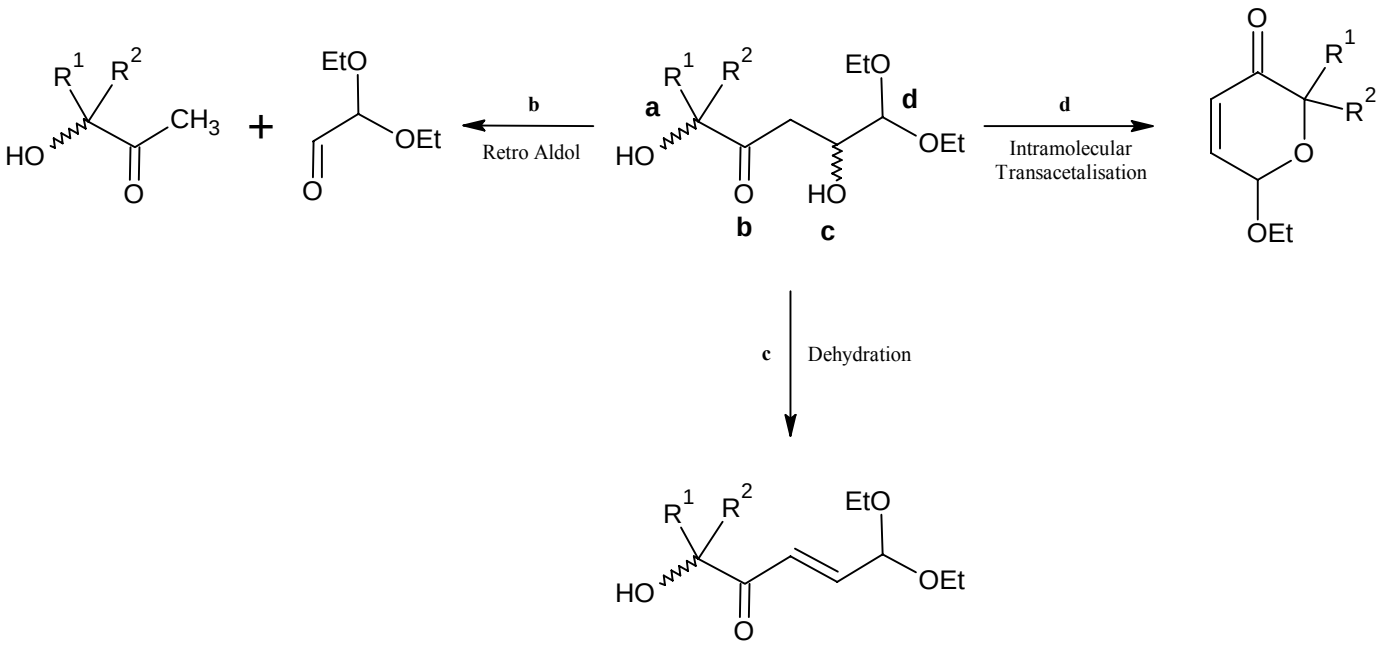


Scheme 2.16: *Possible reaction outcomes when treating* ***9*** *with acid.*[8]

References:

1. Sydnes, L.K.; Kvernenes, O.H.; Valdersnes, S. *Pure and applied chemistry* **2005**, 77, 119-130
2. Makosza, M.; Wawrzyniewicz, M. *Tetrahedron Letters* **1969**, 4659-4662
3. Kvernenes, O.H. *3,3,4,4-Tetraethoxybut-1-yne and analogues as synthons in organic synthesis: an approach to the synthesis of deoxygenated sugars,* Dr.Scient thesis, University of Bergen, **2005**
4. Doering, W.V.E.; Hoffmann, A.K. *Journal of the American Chemical Society* **1954**, 76, 6162-6165
5. Doering, W.V.E.; Henderson, W.A. *Journal of the American Chemical Society* **1958**, 80, 5274-5277
6. Sydnes, L. K.; Kvernenes, O. H. *Organic Syntheses* **2006**, 83, 184-191
7. Skattebøl, L. *Journal of Organic Chemistry* **1966**, 31, 1554-1559
8. Valdersnes, S. *Modified carbohydrates from 3,3,4,4-tetraethoxybut-1-yne,* PhD thesis, University of Bergen, **2006**
9. Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; VCH Verlagsgesellschaft, Weinheim, 1987
10. Sydnes, L.K.; Bakstad, E. *Acta Chemica Scandinavica* **1996**, 50, 446-453
11. Bakstad, E.; Sydnes, L.K. *Acta Chemica Scandinavica* **1998**, 52, 1029-1033
12. Sydnes, L.K. *European Journal of Organic Chemistry* **2000**, 3511-3518
13. Sydnes, L.K.; Holmelid, B.; Kvernenes, O.H.; Sandberg, M; Hodne, M; Bakstad, E. *Tetrahedron* **2007**, 63, 4144-4148
14. Weast, R. C., Ed. *Handbook of Chemistry and Physics,* 45th ed.; The Chemical Rubber CO: Cleveland, Ohio, 1964
15. Bakstad, E.; Olsen, A.S.; Sandberg, M.; Sydnes, L.K. *Acta Chemica Scandinavica* **1999**, 53, 465-473
16. Sydnes, L.K.; Alnes, K.F.S.; Erdogan, N. *Monatshefte für Chemie* **2005**, 136, 1737-1749
17. Holmelid, B.; Kvernenes, O.H.; Hodne, M; Sydnes, L.K. *ARKIVOC* **2008**, 26-41
18. Flemmen, G. *Synthesis of some 1-substituted 5,5-diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diols from 1,1-diethoxy-3-(1,3-dithian-2-yl)-propan-2-ol*, Master thesis, University of Bergen, **2009**
19. Farooq, T., *Personal communication*
20. Gaunt, M.J.; Sneddon, H.F.; Hewitt, P.R.; Orsini, P.; Hook, D.F.; Ley, S.V. *Organic & Biomolecular Chemistry,* **2003**, 1, 15-16
21. Sneddon, H.F.; van den Heuvel, A.; Hirsch, A.K.H.; Booth, R.A.; Shaw, D.M.; Gaunt, M.J.; Ley, S.V. *Journal of Organic Chemistry,* **2006**, 71, 2715-2725
22. Corey, E.J.; Seebach, D. *Angewandte Chemie-International Edition* **1965**, 4, 1075-1077
23. Zeynizadeh, B.; Behyar, T. *Bulletin of the Chemical Society of Japan* **2005**, 78, 307-315
24. Reich, H.J.; Borst, J.P.; Dykstra, R.R. *Tetrahedron* **1994**, 50, 5869-5880
25. Ide, M.; Nakata, M.. *Bulletin of the Chemical Society of Japan*, **1999**, 72, 2491-2499
26. Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R., Hook, D. F.; Ley, S. V. *Org. Lett*. **2003**, 5, 4819-4822

3 EXPERIMENTAL

3.1 General

Dry THF was obtained by distillation from sodium/benzophenone. All other solvents and reagents were of puriss grade, and used as received from Sigma-Aldrich Norway. Dichloromethane was of technical grade. A mixture of hexane isomers of puriss grade was used for chromatographic purposes. Reactions carried out under inert atmosphere were done using nitrogen gas passed through a container with sodium hydroxide pellets.

Flash column chromatography was carried out using J.T. Baker Silica Gel for Flash Chromatography as stationary phase, and mixtures of hexane/ethyl acetate as the mobile phase. Analytical TLC was performed on Macherney-Nagel pre-coated TLC-sheets with silica gel 60 with fluorescent indicator UV_{254} and visualised by staining using ethanolic acidic phosphomolymdic acid solution.

Boiling points are uncorrected. The pressure from the water aspirator pump was estimated to ca. 10-20 mmHg.

IR spectra were obtained on a Nicolet impact 410 spectrometer with the samples as a film between to sodium-chloride plates, except for the IR spectrum for compound **10** that was obtained on a Nicolet Protege 460 FTIR spectrometer. Absorptions are given in wavenumbers (cm^{-1}), and intensities are characterised as (s) for strong, (m) for medium, (w) for weak, (br) for broad, and (sh) for shoulder.

The MS spectra reported were obtained on a JEOL AccuTOF MS JMS-T100LC.

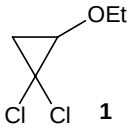
^{1}H-NMR spectra were recorded at ambient temperatures on a Bruker Avance DMX 400 spectrometer at 400 MHz with tetramethylsilane (TMS, $\delta_H = 0.00$ ppm) as the internal reference. Chemical shifts are reported downfield from the reference standard, and the coupling constants are given in Hertz. Multiplicity is given as (s) for singlet, (d) for doublet, (t) for triplet, (dd) for doublet of doublets, and (m) for multiplet. The proton spectra are reported

as follows δ/ppm (number of protons, multiplicity, coupling constant *J*/Hz). ^{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 (δ_c = 77.36 ppm) as the internal reference.

3.2 Preparation of starting materials

3.2.1 Preparation of TEB

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

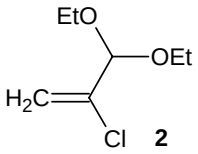


1

A 500 mL, three-necked, round-bottomed flask, equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with ethyl vinyl ether (22.99 g, 0.32 mol), chloroform (145.38 g, 1.22 mol) and TEBA (0.3 g). The reaction flask was placed in an ice bath, and after it had been cooled for approximately 15 min, a 50% aqueous solution of sodium hydroxide (36.23 g (0.91 mol) in 36.75 g H_2O) was added dropwise to the solution over 15 min, upon where the reaction mixture turned white. The reaction mixture was then left stirring vigorously for 24 h to ensure proper mixing between the two phases, while the bath temperature gradually reached r.t. The reaction was quenched by adding 90 mL of 6 M hydrochloric acid, and the hydrolysate was transferred to a 1 L separatory funnel. The reaction flask was washed with CH_2Cl_2 (3 x 20 mL) and H_2O (3 x 30 mL), which were also added to the funnel. After addition of more H_2O (200 mL) to the funnel, the mixture was shaken and the organic layer separated from the aqueous layer. The aqueous phase was then extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were dried overnight with magnesium sulphate ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator to give the title compound (48.37 g, 0.31 mol, 98% yield) as an almost colourless (slightly yellow), clear liquid. The ^{1}H-NMR spectrum of the crude product showed that it was essentially pure, so it was used directly in the next step of the synthesis without further purification. (The crude product can however be distilled under reduced pressure to give the purified title compound at b.p. 53.5-53.6 ºC/28 mmHg[1] although this might reduce the yield.)

The IR, ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[2, 3]

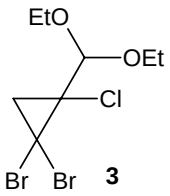
2-Chloro-3,3-diethoxyprop-1-ene (2)



2

A 500 mL, single-necked, round-bottomed flask, equipped with a magnetic stirrer and a condenser, was charged with absolute ethanol (260 mL, 205.24 g), pyridine (39.890 g, 0.5 mol) and **1** (48.37 g, 0.31 mol). The mixture was stirred at a moderate speed (600 turn/min) at reflux for 66 h (oil bath at 100 ºC). The reaction mixture was then allowed to cool to room temperature before being concentrated under reduced pressure on a rotary evaporator (40 ºC at 175 mbar). The residue was transferred to a 1 L separatory funnel, and the reaction flask washed with H_2O (2 x 50 mL) and CH_2Cl_2 (3 x 50 mL), which were also added to the separatory funnel, in addition to some more H_2O (100 mL). The organic layer was separated from the aqueous layer, and the aqueous phase extracted with CH_2Cl_2 (first 1 x 100 mL, then 2 x 50 mL). The combined organic phases were washed with 0.7 M aqueous solution (first 3 x 70 mL, then 2 x 50 mL) of copper sulphate ($CuSO_4$), then dried with magnesium sulphate ($MgSO_4$) overnight, and filtered through a 2 cm tall plug of aluminium oxide. The resulting mixture was concentrated under reduced pressure on a rotary evaporator to give the title compound (38.02 g, 0.23 mol, 74% yield) as a clear yellow liquid, which was essentially pure according to ^{1}H-NMR spectrum. (The product can however be obtained even purer by distillation under reduced pressure, b.p. 70-78 ºC/25 mmHg[4]. This is not done due to the high volatility of the product.) The IR, ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature. [2, 3]

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

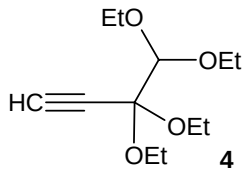


3

A 1 L three-necked, round-bottom flask, equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with **2** (38.02 g, 0,23 mol), recycled bromoform (751 g, 2.97 mol) and TEBA (0.6 g). Then, a 50% aqueous solution of sodium hydroxide (98.35 g (2.46 mol) in 99.03 g H_2O) was added dropwise over a period of 25 min, while the reaction mixture, kept at 0 ºC (ice-water bath), and was stirred vigorously for 24 h. During the reaction, the mixture gradually changed colour from yellow to orange to dark brown/blackish tar. Due to the high volume of the resulting mixture, approximately only half of the reaction mixture was transferred to a 1 L separatory funnel, that was filled with a saturated sodium chloride solution (250 mL), and the organic phase were separated from the water phase. The separatory funnel was only carefully shaken before the separation, due to the extreme risk of emulsion between the two phases. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL, and 1 x 50 mL), and the procedure was then repeated for the rest of the reaction mixture. The combined organic phases were dried overnight with magnesium sulphate ($MgSO_4$), filtered over 5 days (because of some difficulties regarding the mixture of the product and drying agent that combined into a mush that was not easy to separate), dried again, filtered, and concentrated under reduced pressure on a rotary evaporator.

The crude product was then distilled several times. First to recycle the bromoform, at ca. b.p. 35 ºC/ 15 mmHg (lit.[5] b.p. 149.5 ºC, 760 mmHg). Then, upon more heating, tetrabromomethane, a by-product of the reaction, came at ca. b.p. 75 ºC/ ca. 15 mmHg (lit.[5] b.p. 189.5 ºC/ 760 mmHg). CBr_4 has a very characteristic appearance, as it has a melting point at 91 ºC[5], which could be seen during distillation because of the solid material that materialised in the condenser. The tarry residue left in the distillation flask was then distilled at b.p. 75-85 ºC/0.25 mmHg (lit.[6] b.p. 80-82 ºC/0.15 mmHg) to give the title compound (46.343 g, 0.14 mol, 61% yield) as a clear liquid. The IR, ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[2, 6]

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

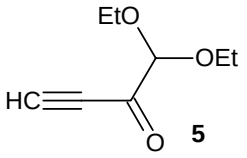


4

A 1 L three-necked, round-bottomed flask, equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with **3** from the previous step (46.343 g, 0.14 mol), but also **3** from an earlier synthesis (4.182 g, 12,6 mmol) (in total of **3**: 50.525 g, 0.15 mol), ethanol (43.43 g, 0.94 mol), TEBA (0.3 g) and CH_2Cl_2 (215 mL). The reaction flask was placed in an ice bath, and the mixture was stirred vigorously. Then, a 50% aqueous solution of sodium hydroxide (48.69 g (1.22 mol) in 49.98 g H_2O) was added dropwise to the reaction mixture over 25 min. (Due to the fact that the dropping funnel was not completely fitted, a few drops of NaOH was lost during the addition, the amount is unknown.) The reaction mixture was stirred at a moderate speed (the apparatus became too hot to stir it vigorously as required) at bath temperature for 6 h, before a new system was set up, and the mixture continued to stir (more vigorously) for another 22 h (this after the reaction mixture had been standing still for 15 h between the two periods), in total 28 h of reaction time with stirring. During this time, the colour changed to orange. Then H_2O (200 mL) was added, and the reaction mixture transferred to a separatory funnel. The reaction flask was washed with CH_2Cl_2 (2 x 20 mL) and H_2O (2 x 20 mL) that was also added to the funnel, the phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3 x 100 mL, then 1 x 50 mL). The combined organic phases were then washed with H_2O (3 x 150 mL) and dried overnight ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator. Distillation of the crude residue (red colour) gave the title compound (19.077 g, 0.0828 mol, 54%) as a clear, slightly yellow, liquid, at b.p. 54-62 ºC/0.1 mmHg (lit.[6] b.p. 53-58 ºC/0.2 mmHg). The IR, ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[2, 6]

3.2.2 Preparation of β-hydroxydithiane from TEB

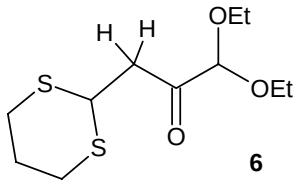
1,1-Diethoxybut-3-yn-2-one (5)



5

A 500 mL round bottom flask equipped with a condenser and a magnetic stirring bar was charged with **4** (10.07 g, 43.72 mmol), Dowex 50W (12.535 g), pure acetone (200 mL) and H_2O (10.0 mL). The mixture was refluxed for 12 h (oil bath 90 ºC) and after it had cooled down to r.t., drying agent ($MgSO_4$) was added and the mixture dried overnight. The Dowex 50 W and $MgSO_4$ were then filtered off before acetone was removed on the rotary evaporator under reduced pressure. The title compound (5.35 g, 34.24 mmol, 78%) was obtained as a clear, yellow liquid by flash chromatography (separated into two portions for flash because of high weight of the crude product) using hexane-ethyl acetate (90:10). The IR, ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[7]

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

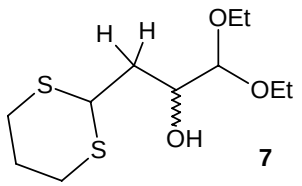


6

A 500 mL three-necked, round-bottom flask equipped with a condenser with a nitrogen inlet, a septum and a magnetic stirring bar, was charged with NaOMe (2.6918 g, 49.83 mmol), propane-1,3-dithiol (5.0 mL, 5.39 g, 49.8 mmol) and dry THF (200 mL). Nitrogen gas was flushed through. **5** (4.92 g, 31.5 mmol) was dissolved in dry THF (50 mL), and the solution was added dropwise (30 min) to the reaction flask at -78 ºC (ice bath with dry ice in acetone) under nitrogenic atmosphere. The reaction mixture was left stirring for 16 h while the temperature gradually reached r.t. Saturated NH_4Cl (200 mL) was added to the reaction mixture, and a white precipitate formed. The mixture was transferred to a separatory funnel,

and the reaction flask was washed with CH_2Cl_2 (2 x 20 mL) and H_2O (2 x 20 mL), which were also transferred to the funnel. CH_2Cl_2 (300 mL) was added to the funnel to get the organic phase below the aqueous phase. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator. The title compound (6.95 g, 26.3 mmol 83%) was obtained as a clear, yellow liquid by flash chromatography (separated into two portions for flash because of high weight of the crude product) using hexane-ethyl acetate (90:10). The IR, ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[7]

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

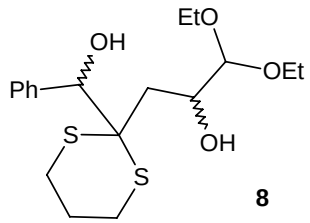


7

A 500 mL round-bottom flask equipped with a condenser and a magnetic stirring bar was charged with **6** (6.95 g, 26.3 mmol), $NaBH_4$ (0.512 g, 4.29 mmol), THF (100 mL) and H_2O (3.5 mL). The reaction flask was placed in an ice-water bath, and the reaction mixture was stirred for 45 min before H_2O (40 mL) was added. THF was evaporated on a rotary evaporator, and the remaining liquid was transferred to a separatory funnel. The reaction flask was washed with CH_2Cl_2 (3 x 20 mL) and H_2O (2 x 20 mL), which were also transferred to the funnel. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator. The title compound (5.07 g, 19 mmol, 72%) was obtained as a clear liquid in two fractions (fraction 1: 2.38 g, 8.94 mmol, 34%; fraction 2: 2.68 g, 10.07 mmol, 38%) by flash chromatography using hexane-ethyl acetate (80:20). The IR, ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[7]

3.3 Chain elongation using β-hydroxydithiane 7

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



8

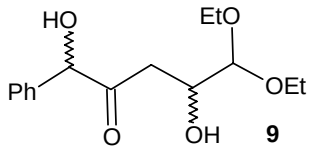
A 500 mL, three-necked, round-bottom flask equipped with a condenser with a nitrogen inlet, a septum, and a magnetic stirring bar was charged with **7** (2.11 g, 7.91 mmol) in dry THF (60 mL). The flask was placed in an ice-water bath, and 3 equivalents of *n*-BuLi (15 mL, 24 mmol) was added dropwise (15 min) to the flask under nitrogenic atmosphere. After 60 min benzaldehyde (0.308 g, 2.90 mmol) dissolved in dry THF (30 mL) was added dropwise (10 min) to the now deeply orange reaction mixture. The mixture was kept at 0 ºC under nitrogenic atmosphere, and allowed to react for 90 min. Saturated NH_4Cl (150 mL) was then added to the reaction, before it was allowed to reach r.t. THF was evaporated under reduced pressure on a rotary evaporator, and the residue was transferred to 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 to the funnel. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator. The title compound (2.58 g, 6.92 mmol, 87%) was obtained as a clear, yellow and very viscous liquid by flash chromatography using hexane-ethyl acetate (70:30). The IR, ^{1}H-NMR and ^{13}C-NMR spectra were in agreement of those published in the literature.[8]

IR (NaCl), ν_{max} (cm^{-1}): 3600-3100 (br, s), 3087 (w), 3059 (m), 3032 (m), 2976 (s), 2905 (s), 2362 (w), 2342 (w), 1962 (w), 1906 (w), 1814 (w), 1637 (w), 1605 (w), 1492 (m), 1450 (s), 1422 (s), 1374 (s), 1328 (m), 1297 (s), 1243 (s), 1069 (br, s), 945 (m), 911 (m), 884 (m), 848 (w), 812 (w), 736 (s), 703 (s), 606 (m).

^{1}H-NMR (400 MHz; $CDCl_3$), δ (ppm): 7.57-7.27 (5H, m), 5.06, 5.04 and 5.03 (1H, overlapping s and d), 4.66 (1H, broad s), 4.32 and 4.31 (1H, d, J = 5.7 Hz), 4.22-4.09 (1H, m), 3.83-3.52 (4H, m), 3.10 (1H, broad s), 2.94-2.72 (4H, m), 2.52 and 2.30 (1H, two sets of d, J= 15.6 Hz), 2.11 and 1.72 (1H, two sets of dd, J_1 = 9.2 Hz, and J_2 = 15.6 Hz, and J_1 = 8.7 Hz, and J_2= 15.7 Hz, respectively) 1.93 (2H, broad m), 1.27, 1.25, 1.24, 1.22 (6H, q, J = 6.6 Hz).

^{13}C-NMR (100 MHz; $CDCl_3$), δ (ppm): 138.8, 138.5, 129.2, 128.3, 128.2, 127.6, 127.6 , 104.8, 104.6, 77.8, 69.8, 69.7, 63.9, 63.9, 63.8, 58.9, 57.1, 39.0, 36.9, 26.7, 26.3, 26.2, 25.9, 24.9, 24.7, 15.7.

5,5-Diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (9)



9

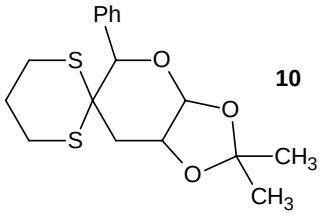
A 500 mL, three-necked, round-bottom flask equipped with a condenser and a magnetic stirring bar was charged with **8** (2.10 g, 5.64 mmol) dissolved in acetonitrile (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The mixture was cooled to 0 ºC on an ice-bath, and iodine (6.0 g, 23.7 mmol) was added portionwise to the mixture over 10 min. The reaction mixture was allowed to react for 14 h overnight, attaining r.t., before it was quenched with a 1:1 mixture of saturated aqueous sodium bicarbonate and saturated aqueous sodium dithionite (50 mL). The mixture was transferred to a separatory funnel, and the flask washed with CH_2Cl_2 (3 x 50 mL) and H_2O (2 x 20 mL), which were also transferred to the funnel. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator. The title compound (0.2024 g, 0.72 mmol, 13%) was obtained as a clear, yellow viscous liquid by flash chromatography using hexane-ethyl acetate (60:40).

IR (NaCl), ν_{max} (cm^{-1}): 3650-3100 (s), 3643 (sh), 3087 (w), 3063 (m), 3035 (m), 2796 (s), 2929 (s), 2898 (s), 2358 (w), 1954 (w), 1887 (w), 1717 (s), 1646 (w), 1601 (w), 1493 (m), 1453 (m), 1375 (m), 1343 (m), 1277 (m), 1119 (m), 1061 (s), 1030 (sh), 946 (w), 922 (w) 886 (w), 757 (m), 702 (s).

^{1}H-NMR (400 MHz; $CDCl_3$), δ (ppm): 7.39-7.31 (5H, m), 5.17 (1H, s), 4.31-4.30 (1H, d (broad), *J* 4.9 Hz), 4.02-3.98 (1H, m, *J* = 4.0 Hz), 3.71-3.43 (4H, m), 2.68-2.62 (1H, dd, J_1 = 8.0 Hz, and J_2 = 16.0 Hz respectively), 2.50-2.45 (1H, dd, J_1 = 4.0 Hz, and J_2 = 16 Hz respectively), 1.18, 1.16, 1.14, 1.13 (6H, q, J_1 = 7.2 Hz, and J_2 = 7.6 Hz).

^{13}C-NMR (100 MHz; $CDCl_3$), δ (ppm): 209.4, 137.9, 129.3, 129.0, 127.9, 104.1, 80.8, 69.5, 64.2, 64.1, 39.8, 15.6, 15.5.

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



10

A 100 mL, three-necked, round-bottom flask equipped with a condenser and a magnetic stirring bar was charged with **8** (0.138 g, 0.367 mmol) dissolved in acetone (25L) and water (4 drops). The mixture was cooled to 0 ºC on an ice-bath, H_2SO_4 (0.5 mL) was added, and the mixture was allowed to react for 1 h. Water (20 mL) was then added and the mixture was transferred to a separatory funnel, and the flask washed with CH_2Cl_2 (3 x 5 mL) and H_2O (1 x 5 mL), which were also transferred to the funnel. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure on a rotary evaporator. The title compound (0.045 g, not pure) was obtained as a white, slightly yellow solid by flash chromatography using hexane-ethyl acetate (60:40).

IR (ATR), ν_{max} (cm^{-1}): 3064 (w), 3036 (w), 2978 (m), 2918 (m), 2886 (m), 2827 (m), 1729 (w), 1645 (w), 1602 (w), 1493 (w), 1454 (w), 1420 (w), 1373 (m), 1364 (m), 1343 (m), 1315 (m), 1293 (m), 1284 (w), 1246 (m), 1222 (m), 1162 (m), 1113 (s), 1080 (s), 1028 (s), 1010 (s), 992 (s), 977 (s), 941 (s), 916 (s), 894 (m), 875 (s), 850 (s), 819 (m), 796 (m), 757 (s), 735 (s), 700 (s), 674 (m), 661 (m), 642 (m), 621 (m), 612 (w), 587 (m), 575 (m).

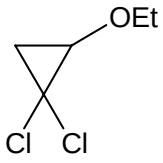
^{1}H-NMR (400 MHz; $CDCl_3$), δ (ppm): 7.74-7.33 (5H, m), 5.28 and 5.27 (1H, d, J = 2.2 Hz), 4.49 (1H, s), 4.13-4.12 (1H, t, J = 2.0 Hz), 2.85 and 2.81 (1H, two sets of dd, J_1 = 1.9 Hz, and J_2 = 15.5 Hz respectively), 2.28 and 2.24 (1H, two sets of dd, J_1 = 4.0 Hz, and J_2 = 15.4 Hz respectively), 2.07-1.92 (2H, m, J = 7.0 Hz), 1.80 (3H, s), 1.65-1.61 (4H, m), 1.40 (3H, s),

^{13}C-NMR (100 MHz; $CDCl_3$), δ (ppm): 137.9, 137.7, 129.2, 129.1, 128.7, 128.6, 128.0, 127.8, 112.6, 109.1, 98.5, 98.1, 83.6, 78.0, 74.3, 50.4, 47.9, 42.8, 40.6, 28.6, 27.7, 27.5, 27.2, 26.9, 26.7, 26.6.

References:

1. Doering, W.V.E.; Henderson, W.A. *Journal of the American Chemical Society* **1958**, 80, 5274-5277
2. Kvernenes, O.H. *3,3,4,4-Tetraethoxybut-1-yne and analogues as synthons in organic synthesis: an approach to the synthesis of deoxygenated sugars,* Dr.Scient thesis, University of Bergen, **2005**
3. Sydnes, L. K.; Kvernenes, O. H. *Organic Syntheses* **2006**, 83, 184-191
4. Skattebøl, L. *Journal of Organic Chemistry* **1966**, 31, 1554-1559
5. Weast, R. C., Ed. *Handbook of Chemistry and Physics,* 45th ed.; The Chemical Rubber CO: Cleveland, Ohio, 1964
6. Sydnes, L.K.; Holmelid, B.; Kvernenes, O.H.; Sandberg, M; Hodne, M; Bakstad, E. *Tetrahedron* **2007**, 63, 4144-4148
7. Valdersnes, S. *Modified carbohydrates from 3,3,4,4-tetraethoxybut-1-yne,* PhD thesis, University of Bergen, **2006**
8. Flemmen, G. *Synthesis of some 1-substituted 5,5-diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diols from 1,1-diethoxy-3-(1,3-dithian-2-yl)-propan-2-ol*, Master thesis, University of Bergen, **2009**

APPENDIX



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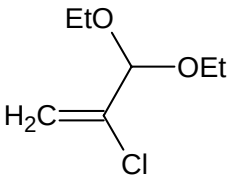

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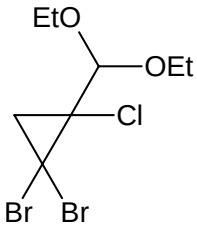

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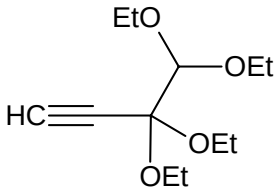

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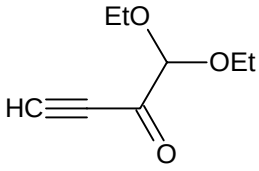

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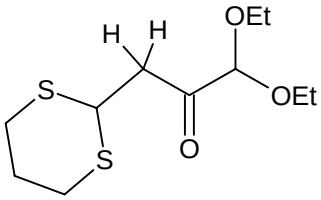

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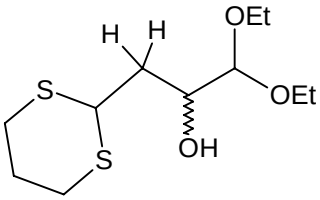

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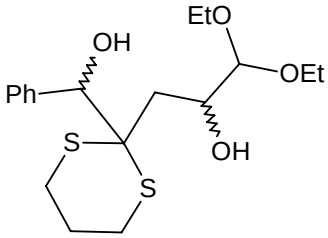

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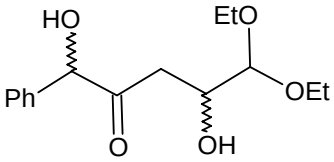

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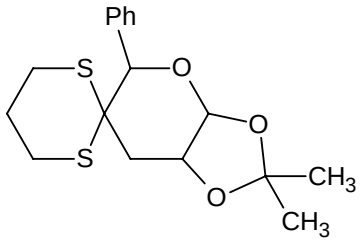
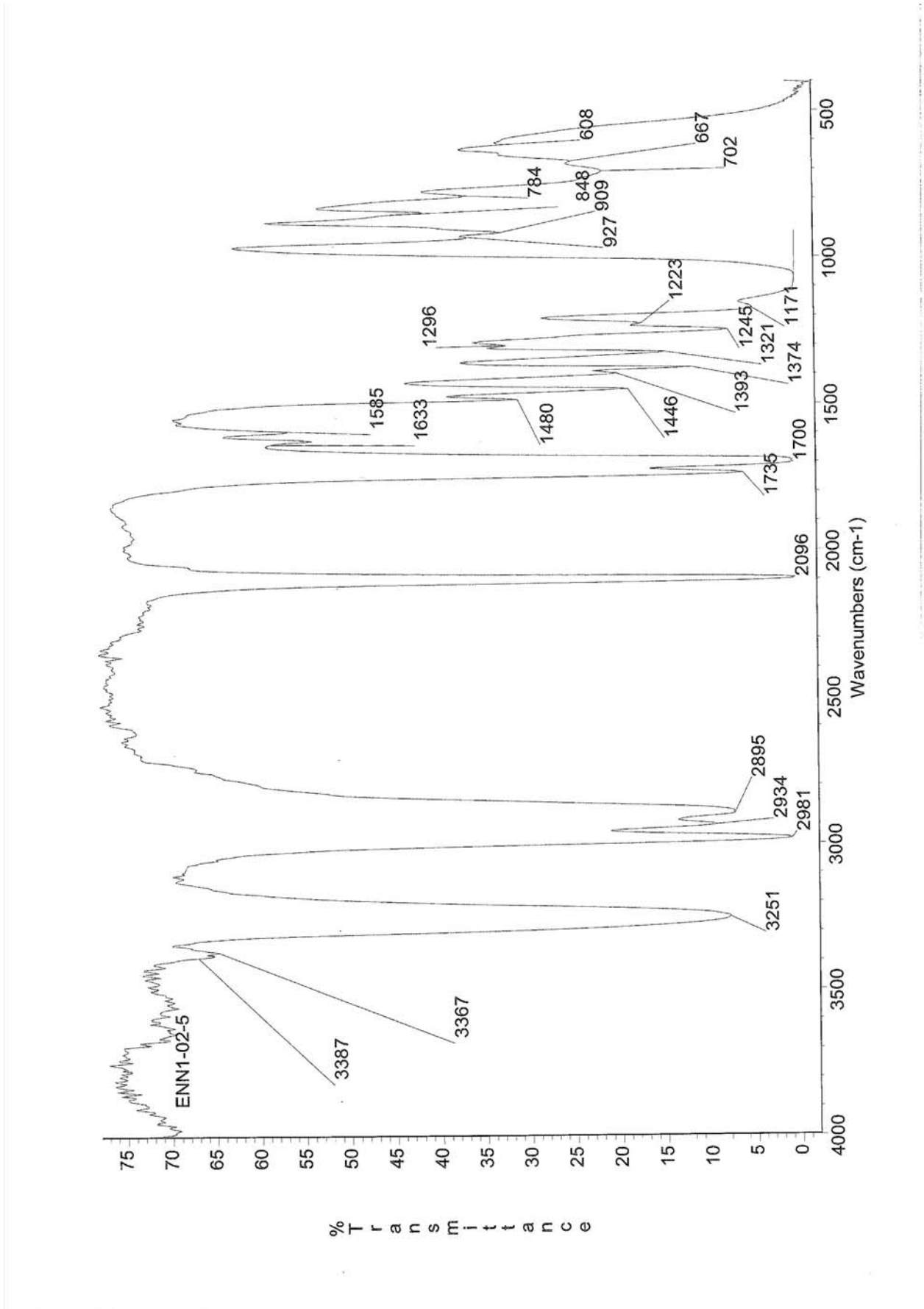
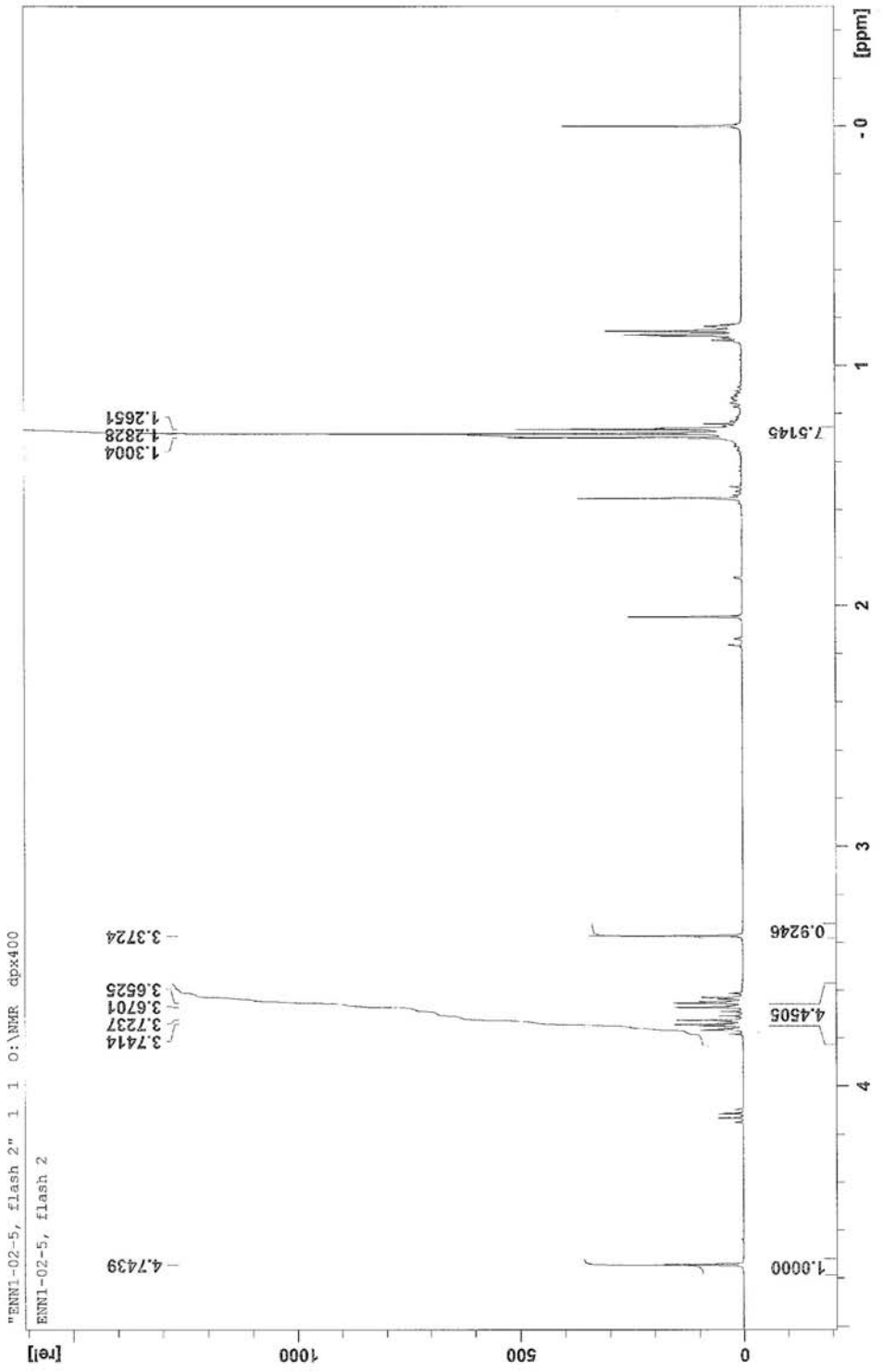


10

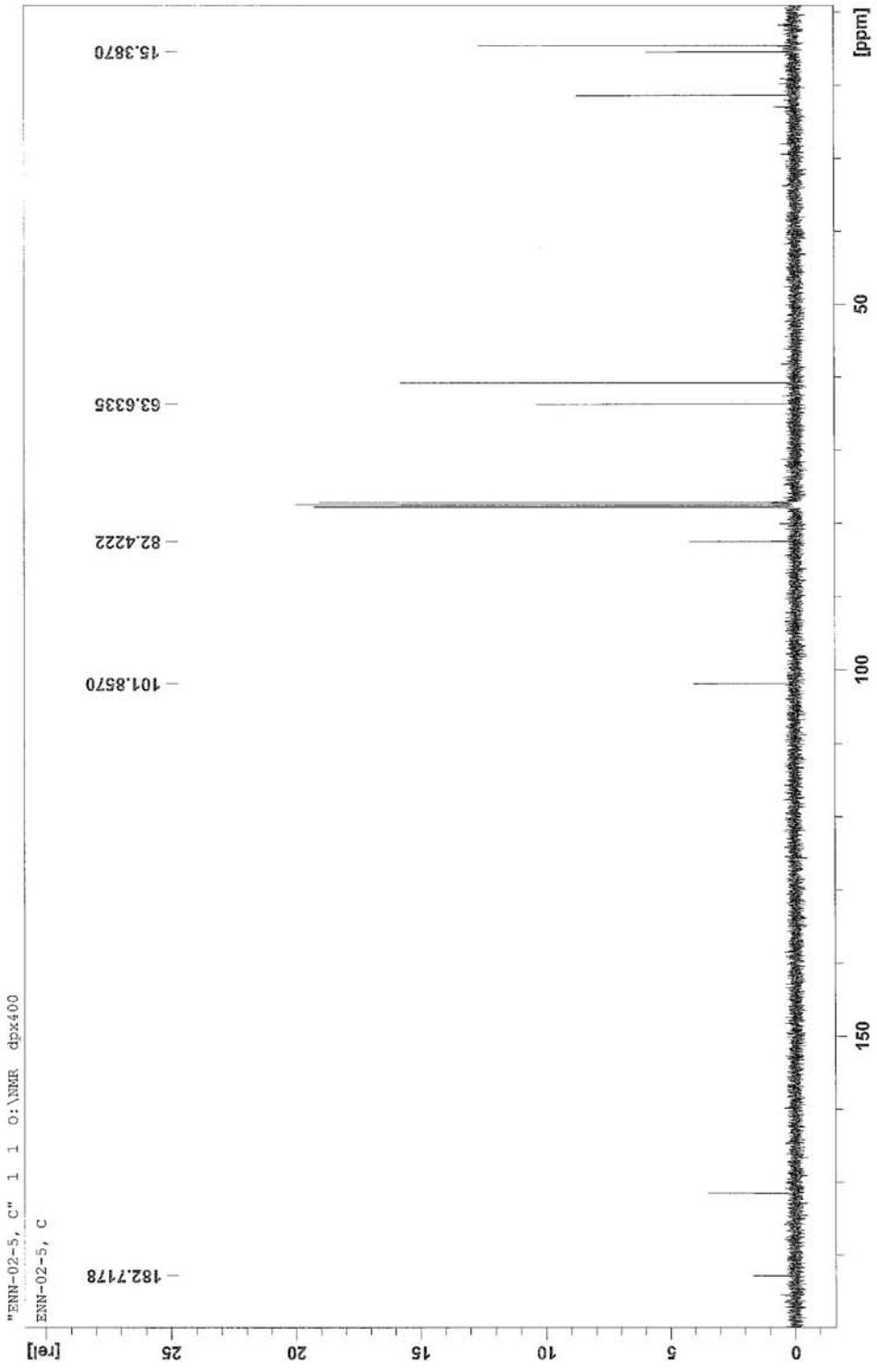
Scheme A.1: *The compounds relevant for this project.*



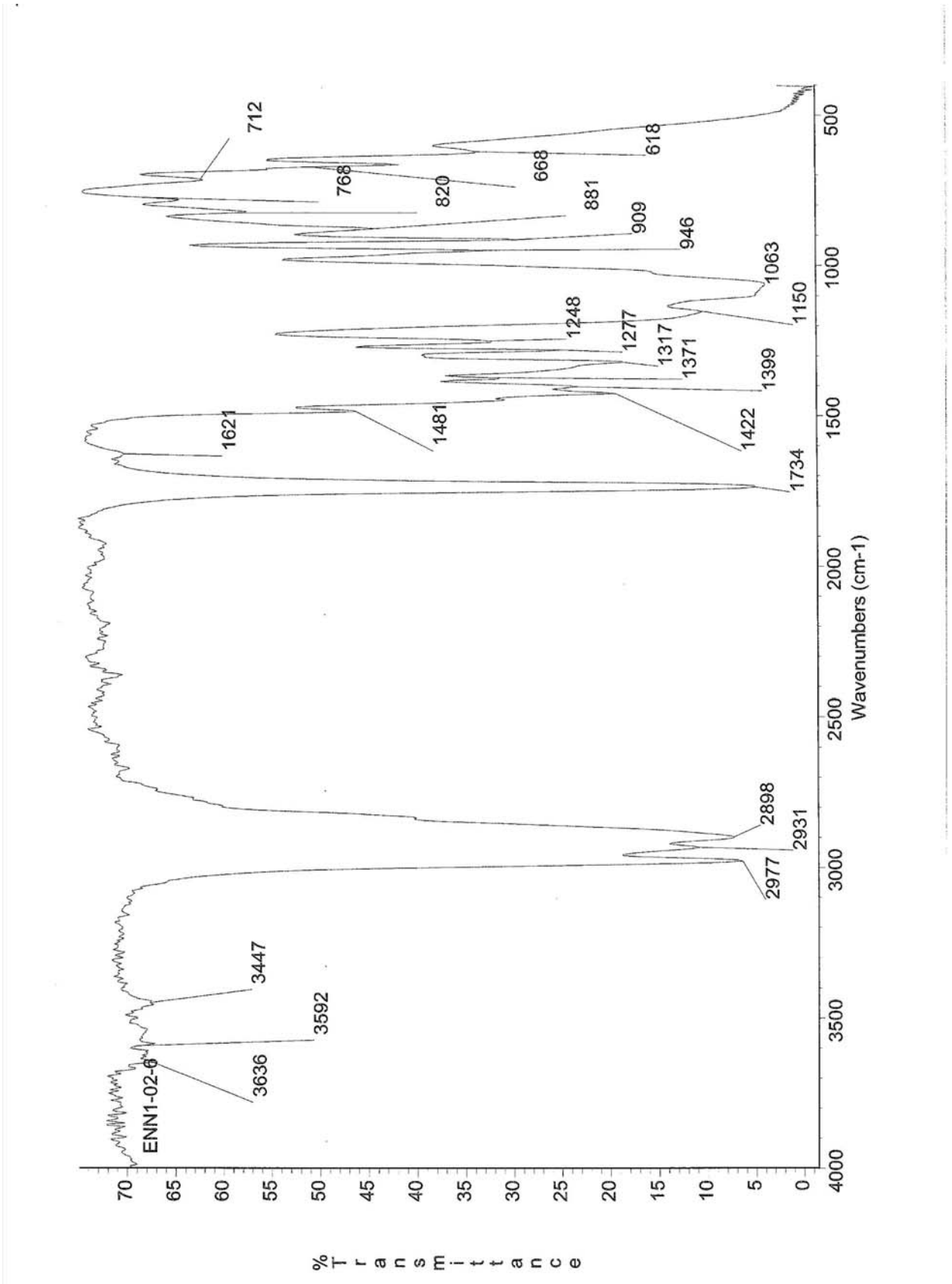
Scheme A.2: *IR spectrum of 1,1-diethoxybut-3-yn-2-one (**5**)*



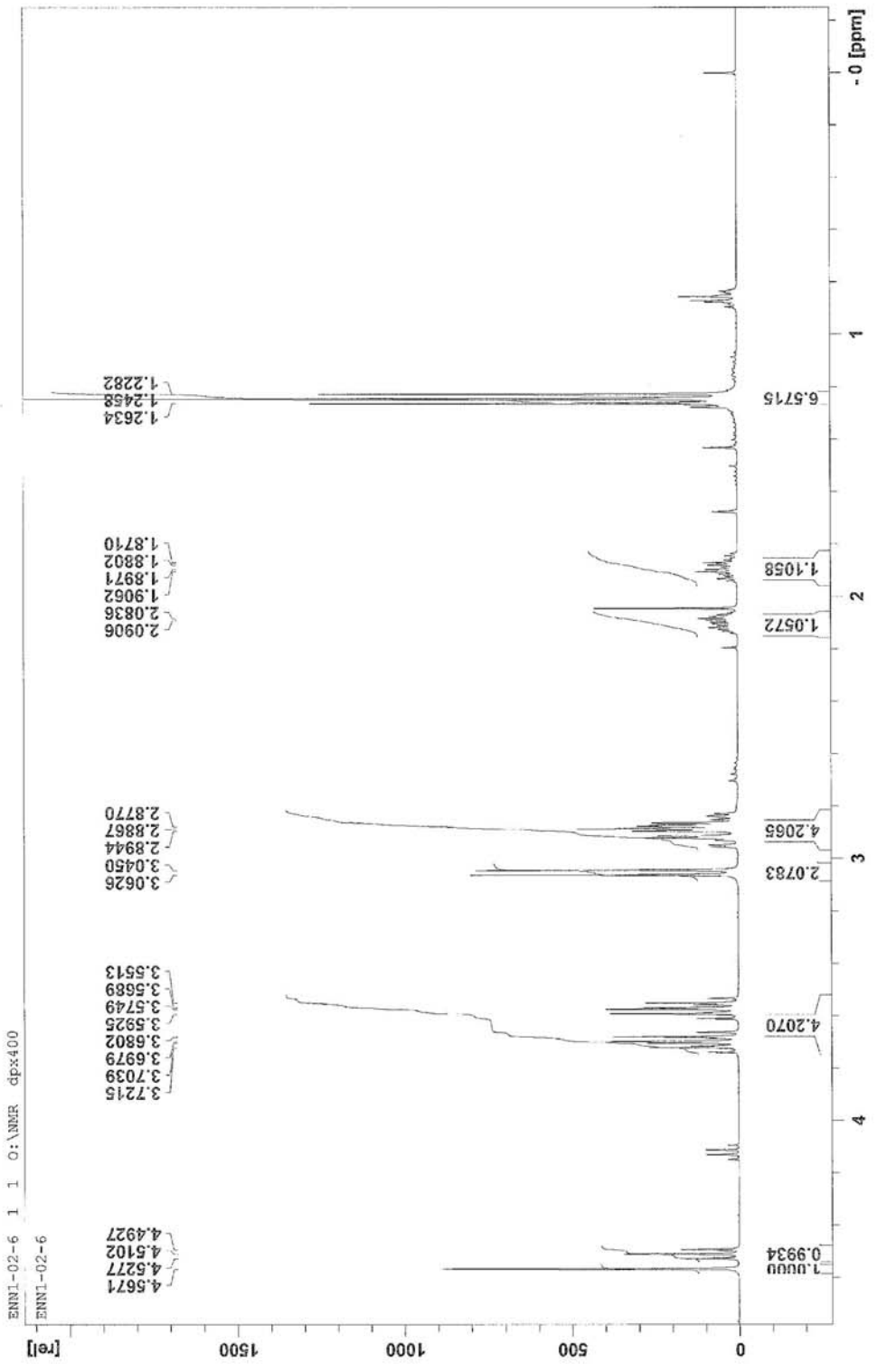
Scheme A.3: *^{1}H-NMR spectrum of 1,1-diethoxybut-3-yn-2-one (**5**).*



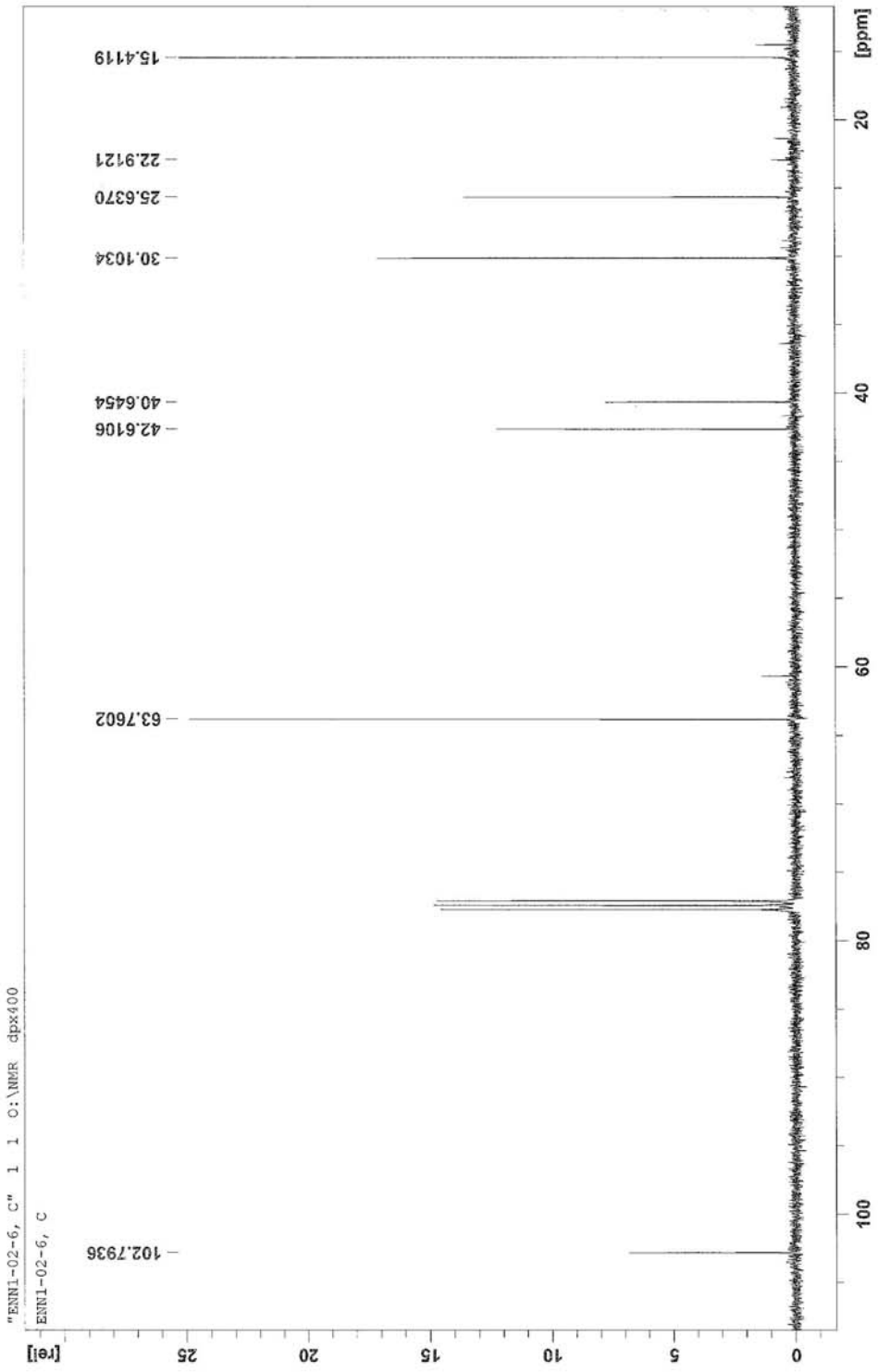
Scheme A.4: *^{13}C-NMR spectrum of 1,1-diethoxybut-3-yn-2-one (**5**).*



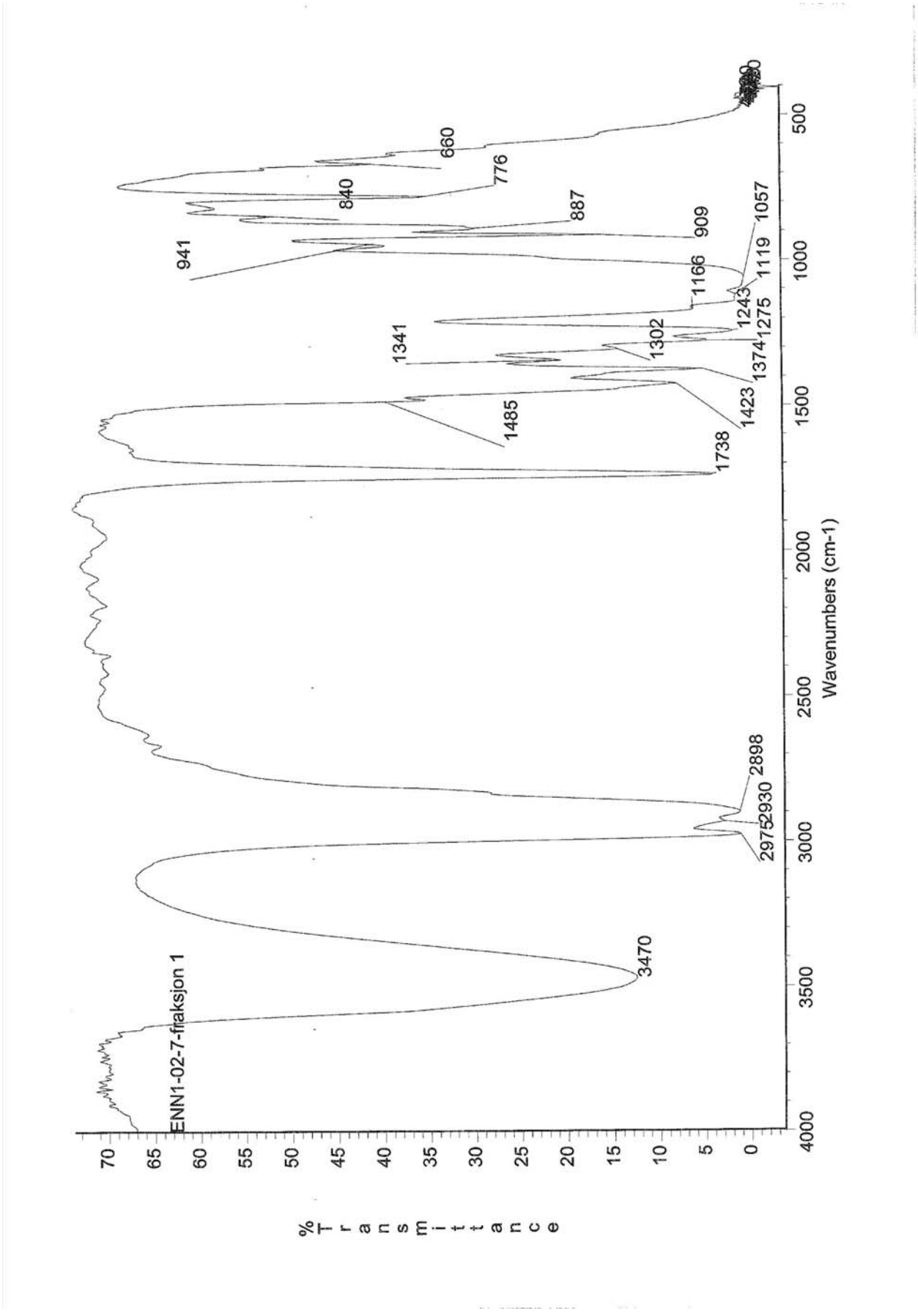
Scheme A.5: *IR spectrum of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-one (**6**).*



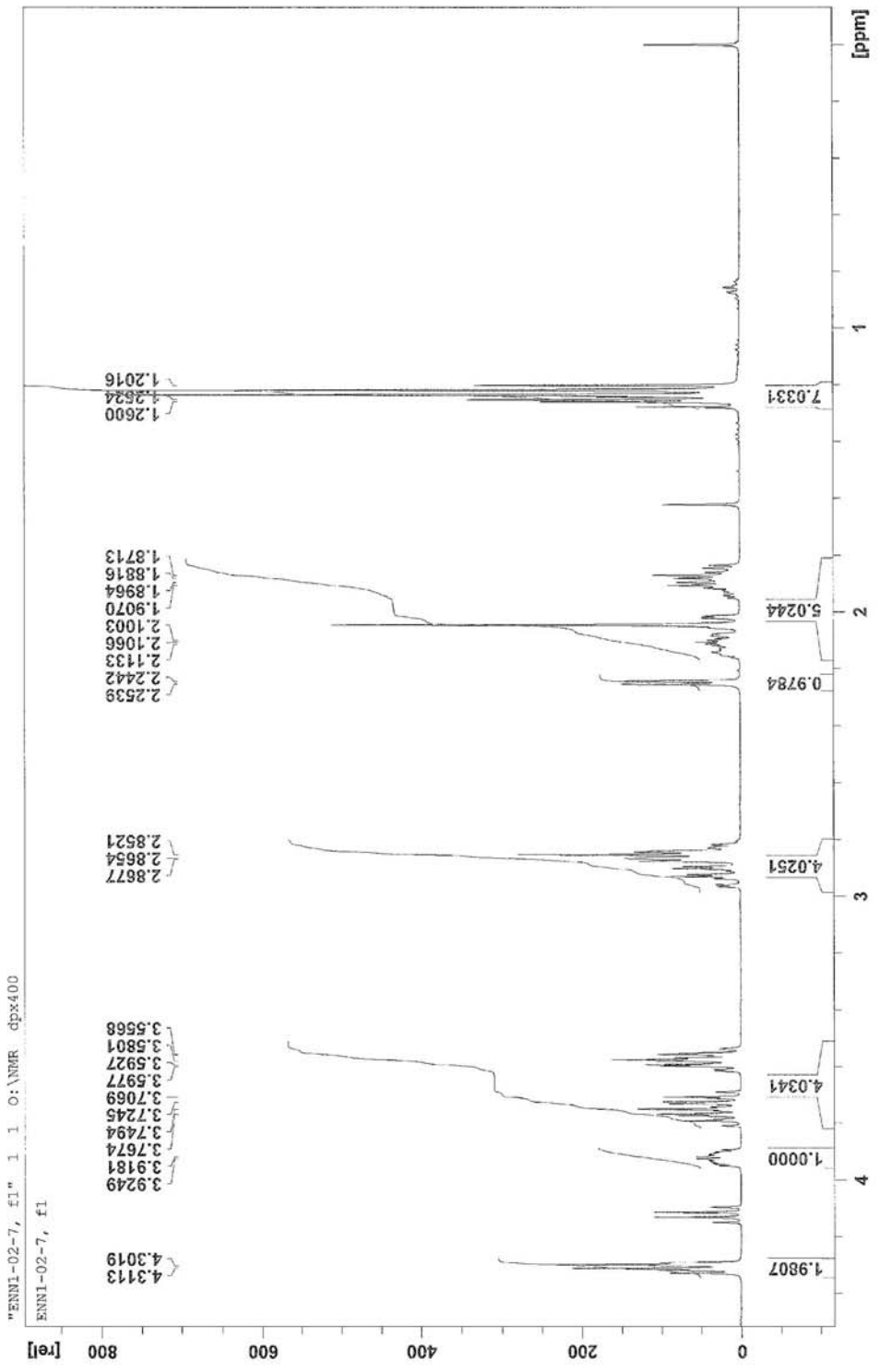
Scheme A.6: *[1]H-NMR spectrum of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-one (**6**).*



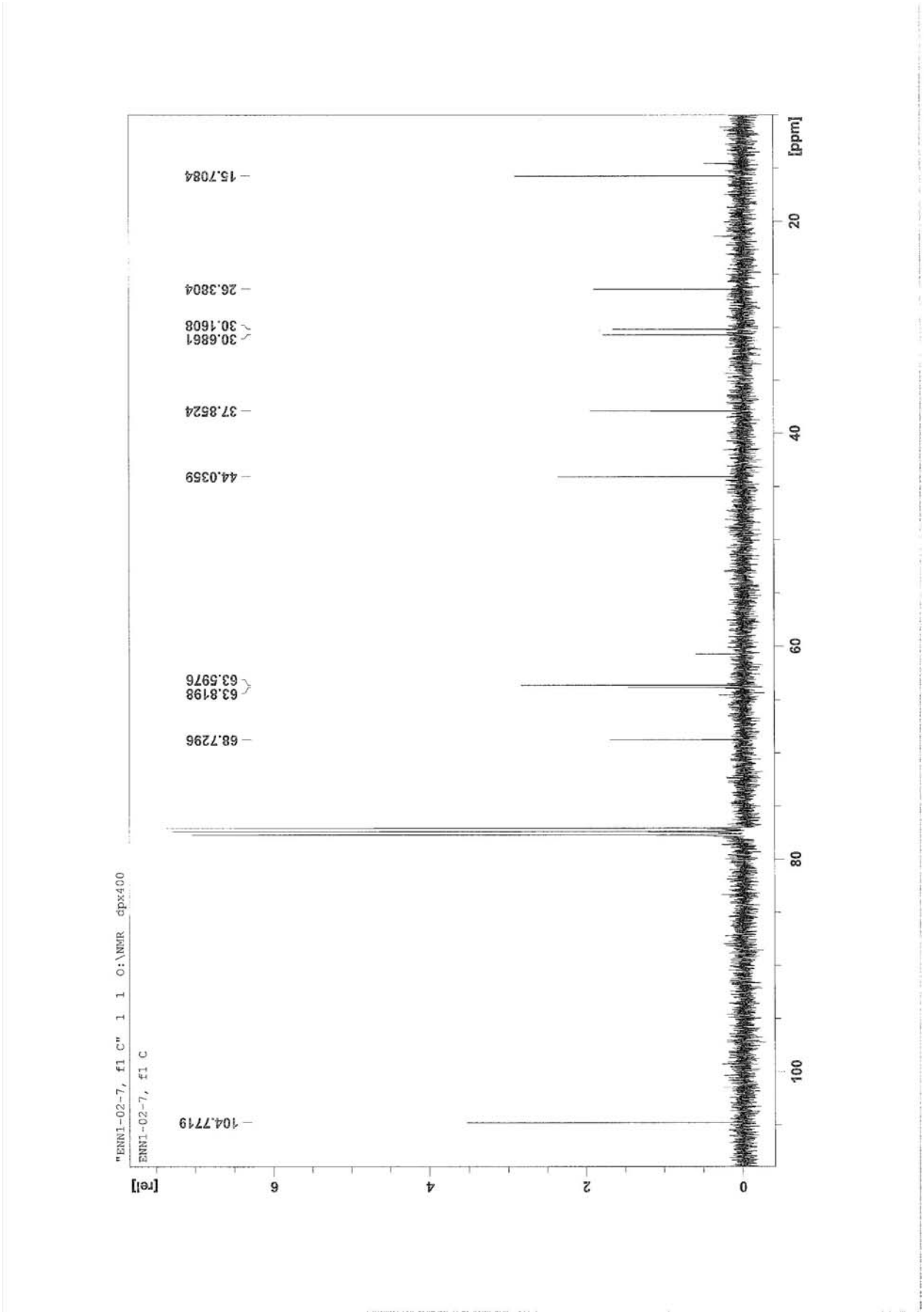
Scheme A.7: *^{13}C-NMR spectrum of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-one (**6**).*



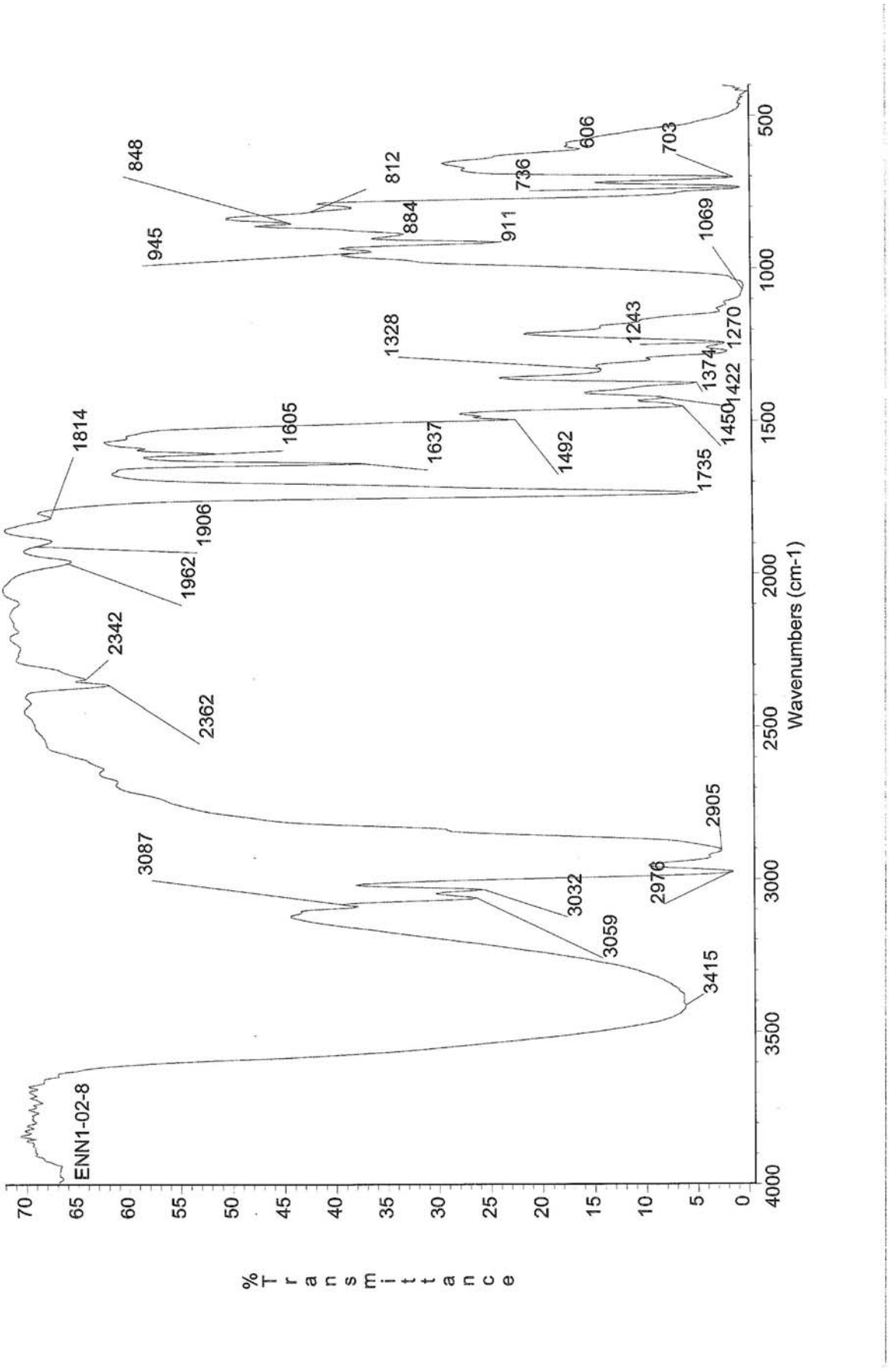
Scheme A.8: *IR spectrum of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**).*



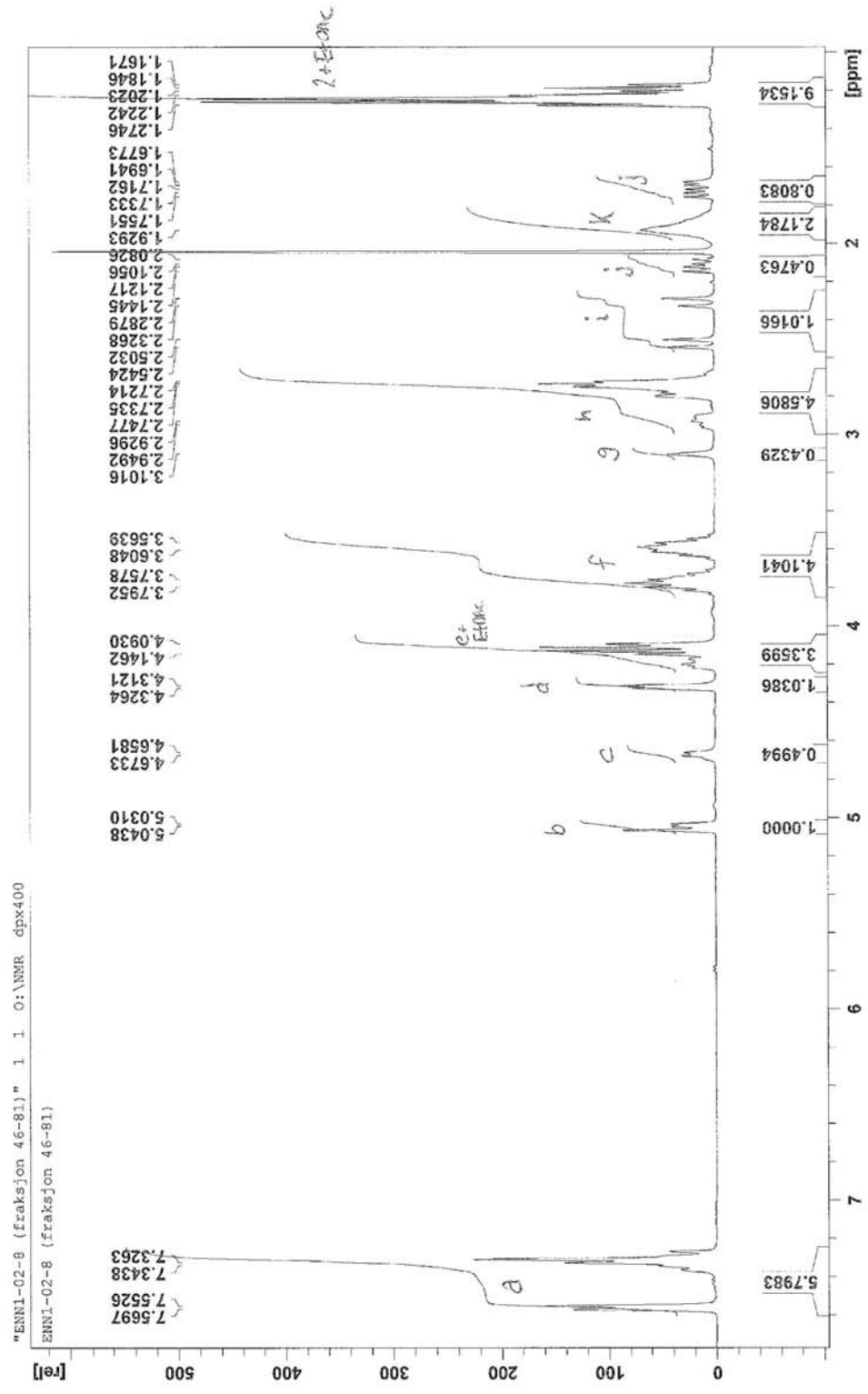
Scheme A.9: *^{1}H-NMR spectrum of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**).*



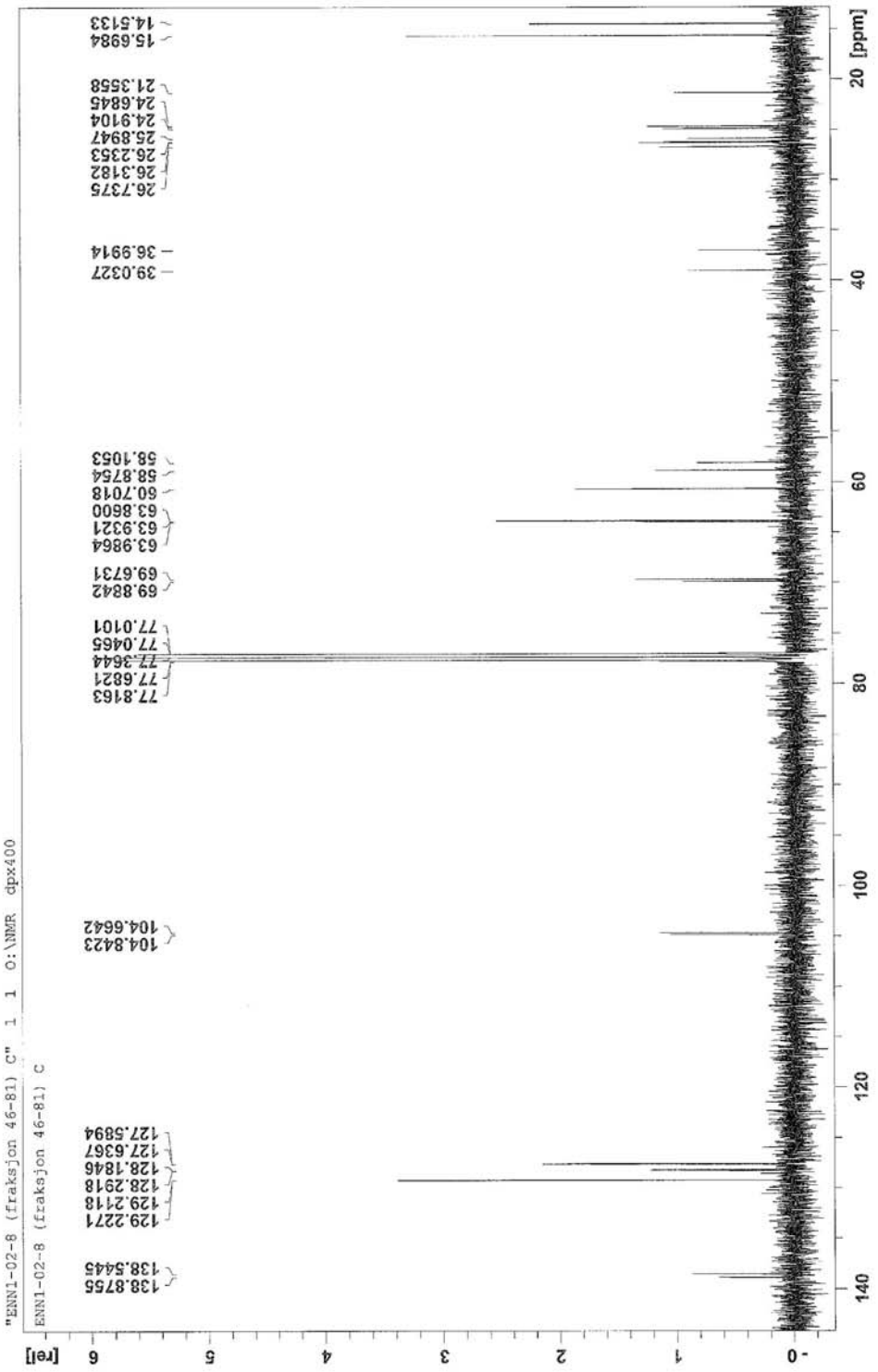
Scheme A.10: *^{13}C-NMR spectrum of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**).*



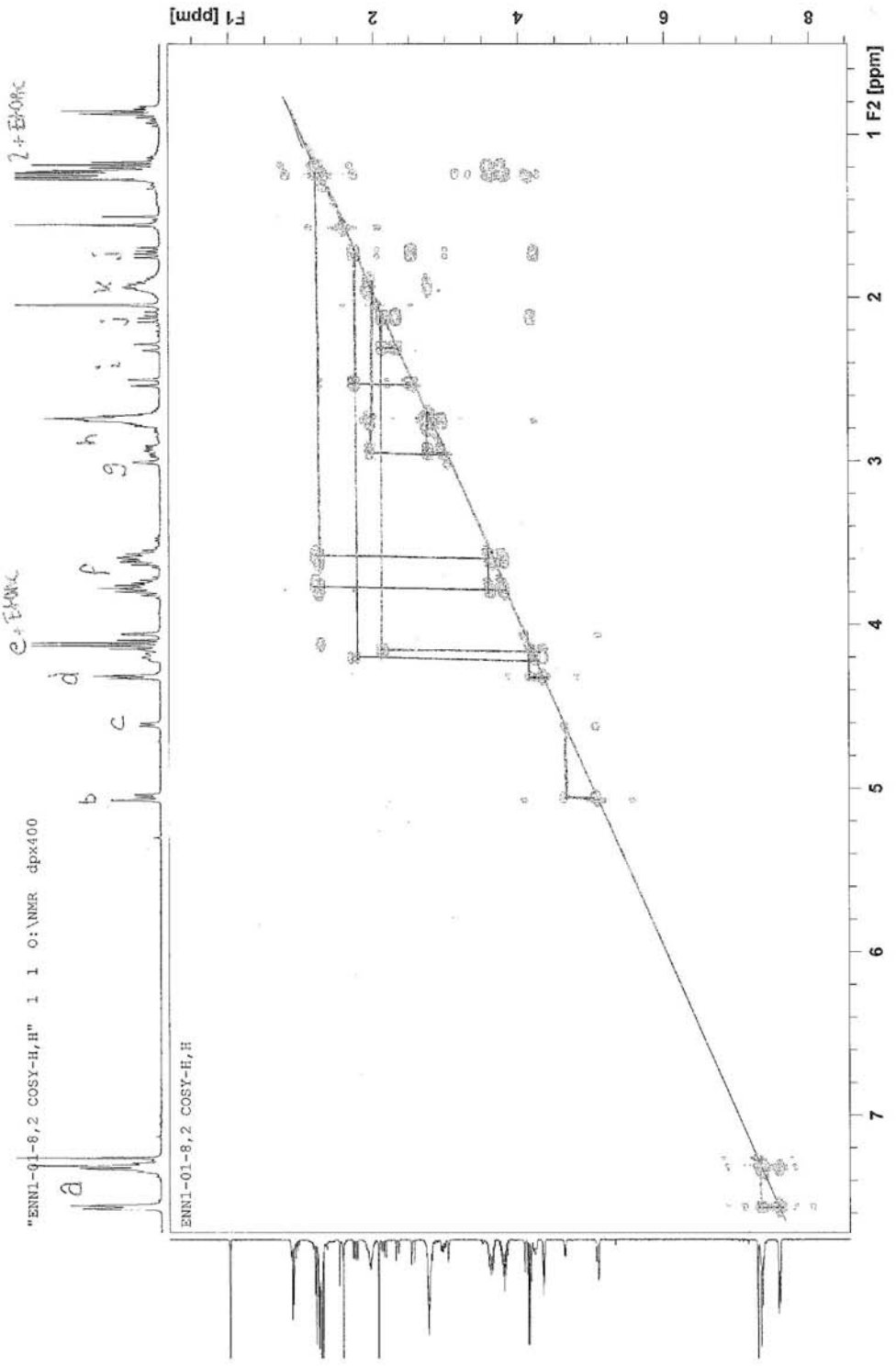
Scheme A.11: *IR spectrum of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**).*



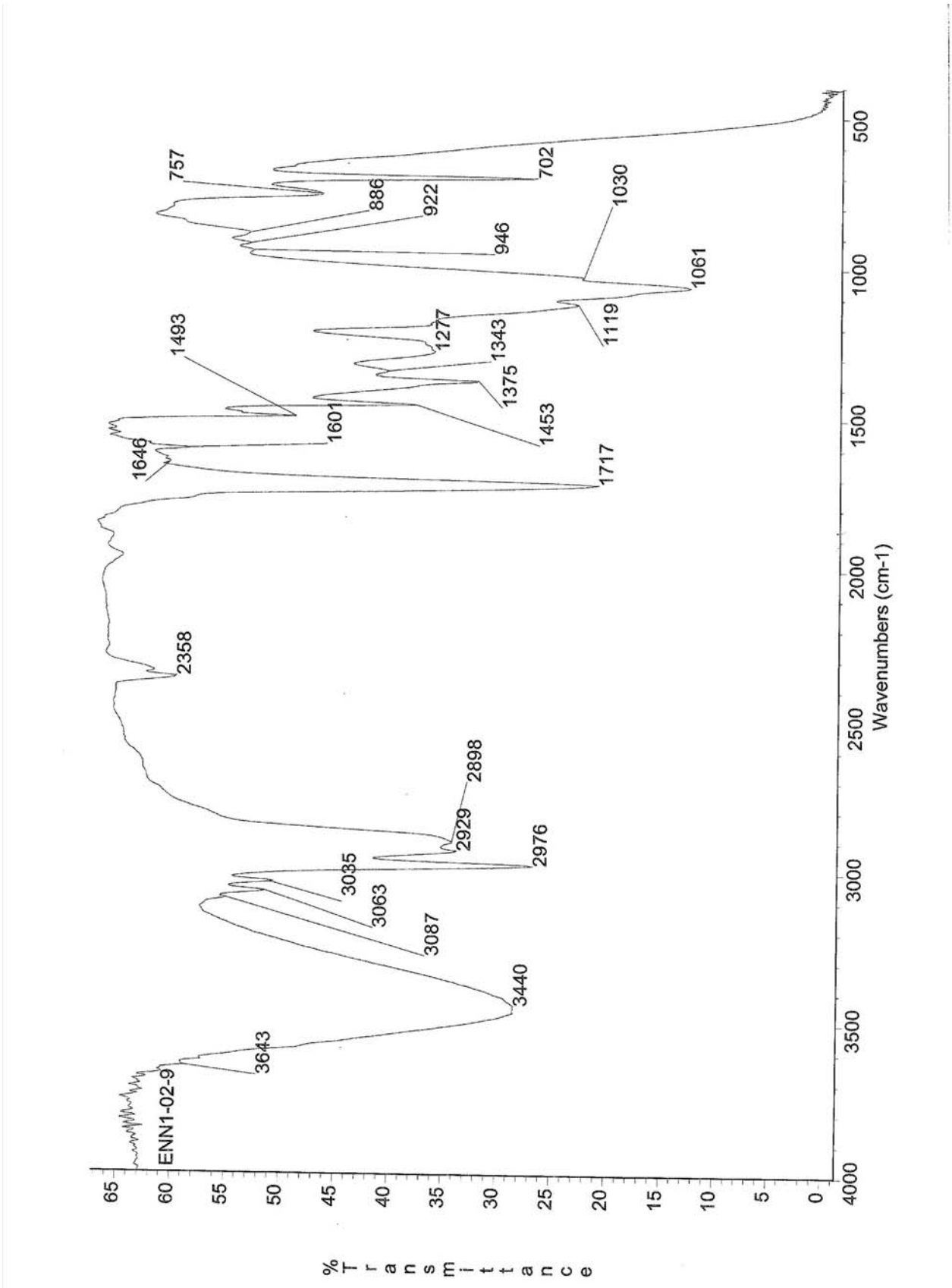
Scheme A.12: *[1]H-NMR spectrum of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**).*



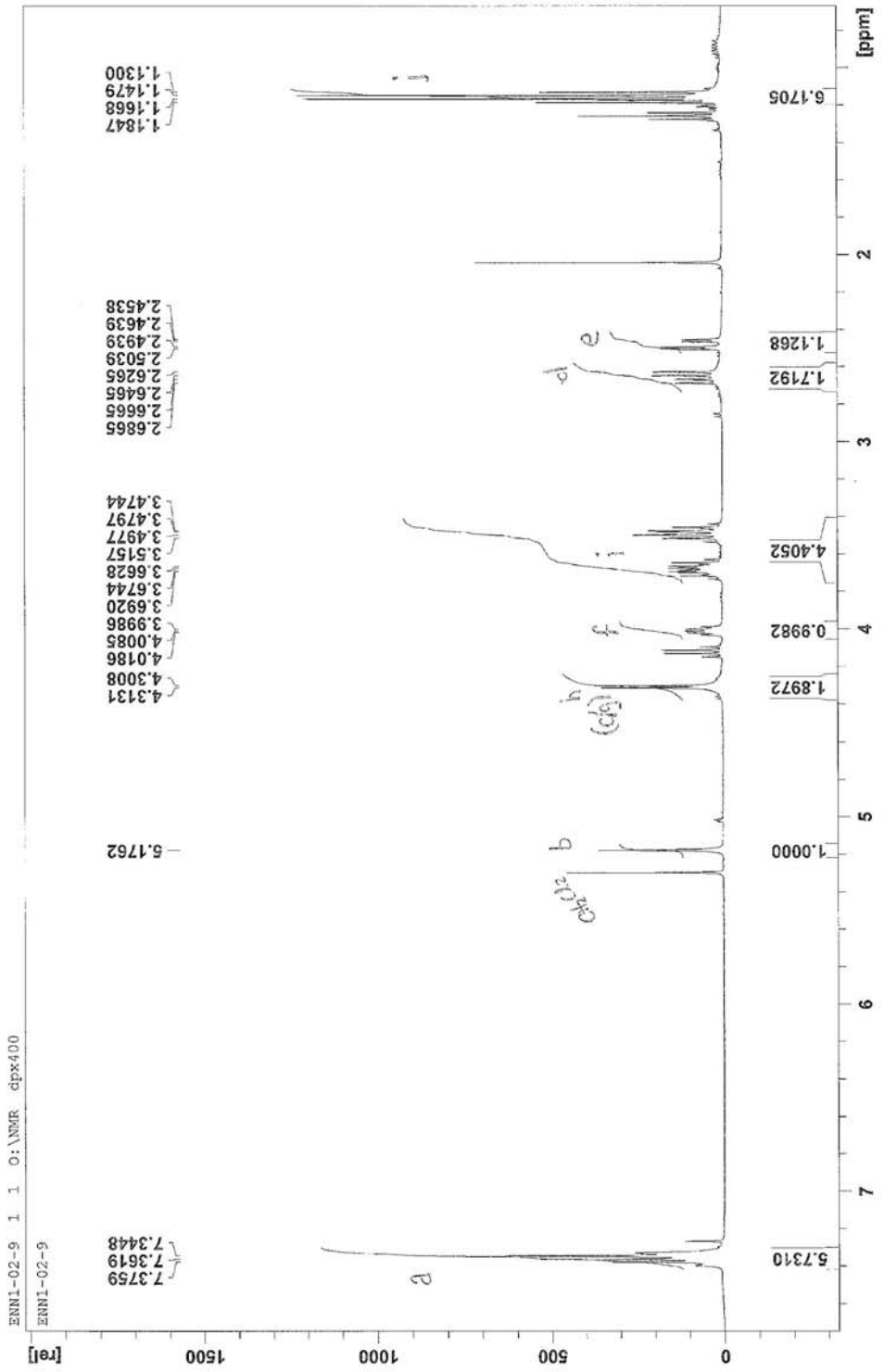
Scheme A.13: *^{13}C-NMR spectrum of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**).*



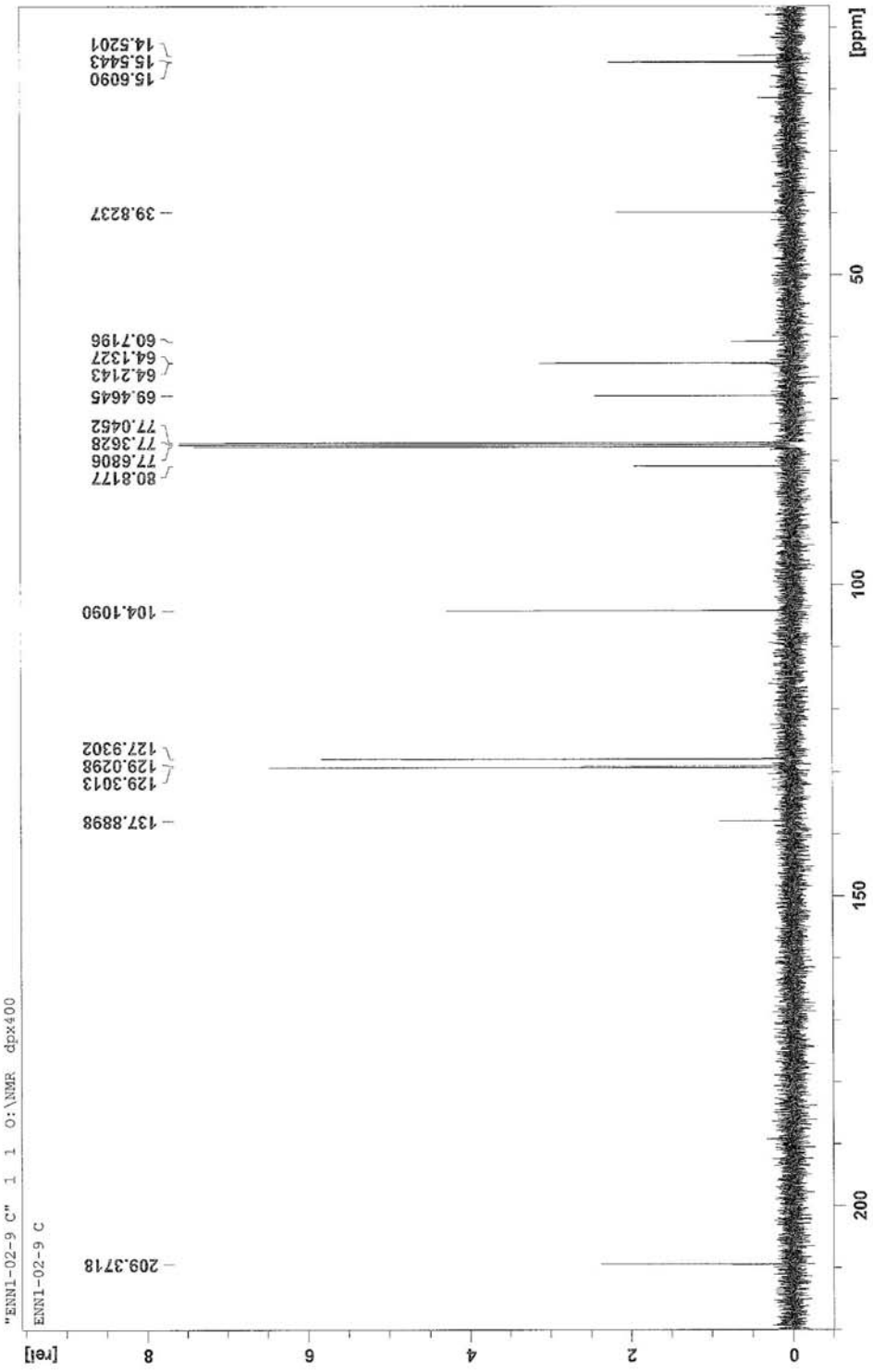
Scheme A.14: *COSY-H,H spectrum of 5,5-diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8**).*



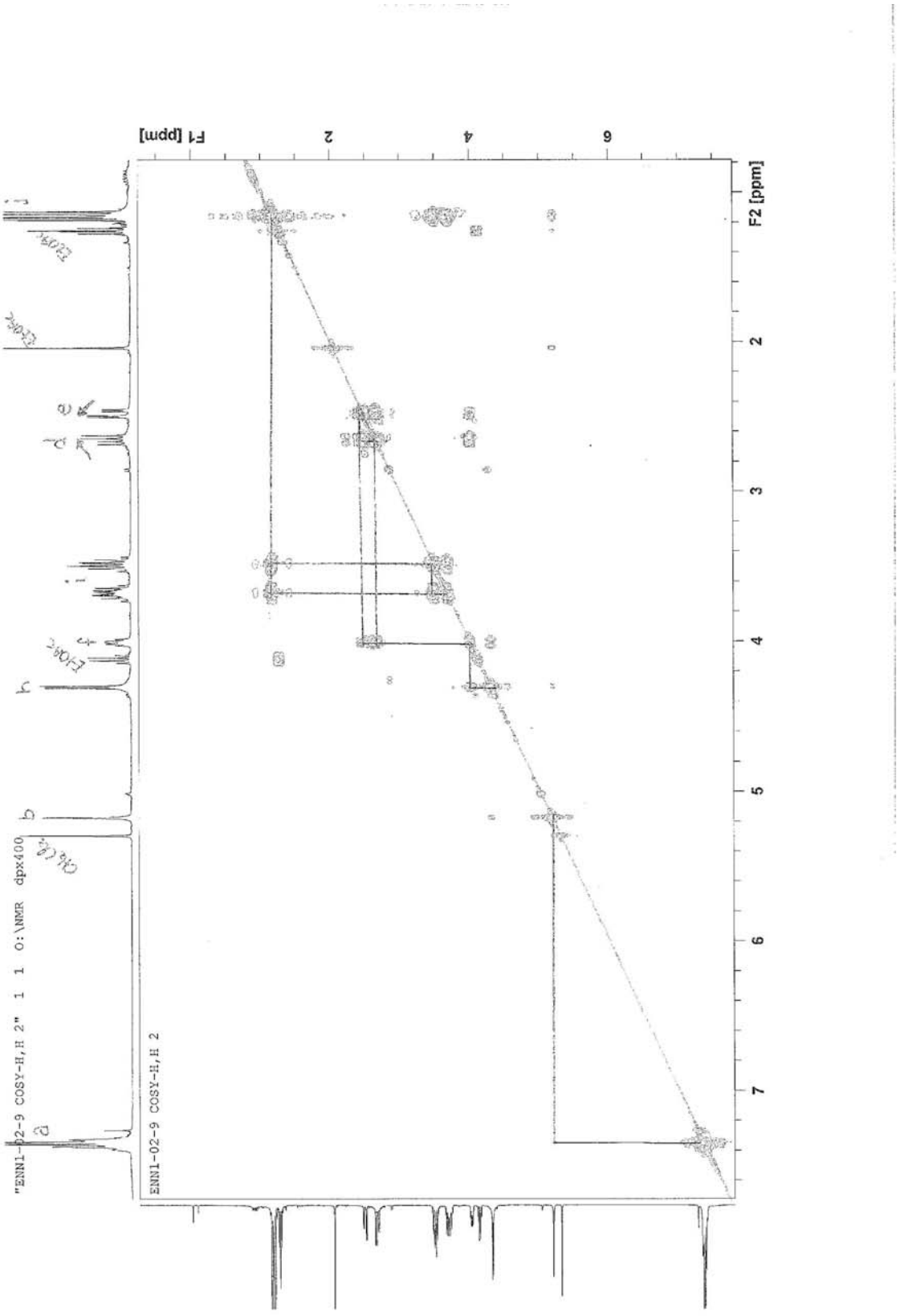
Scheme A.15: *IR spectrum of 5,5-diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (**9**).*



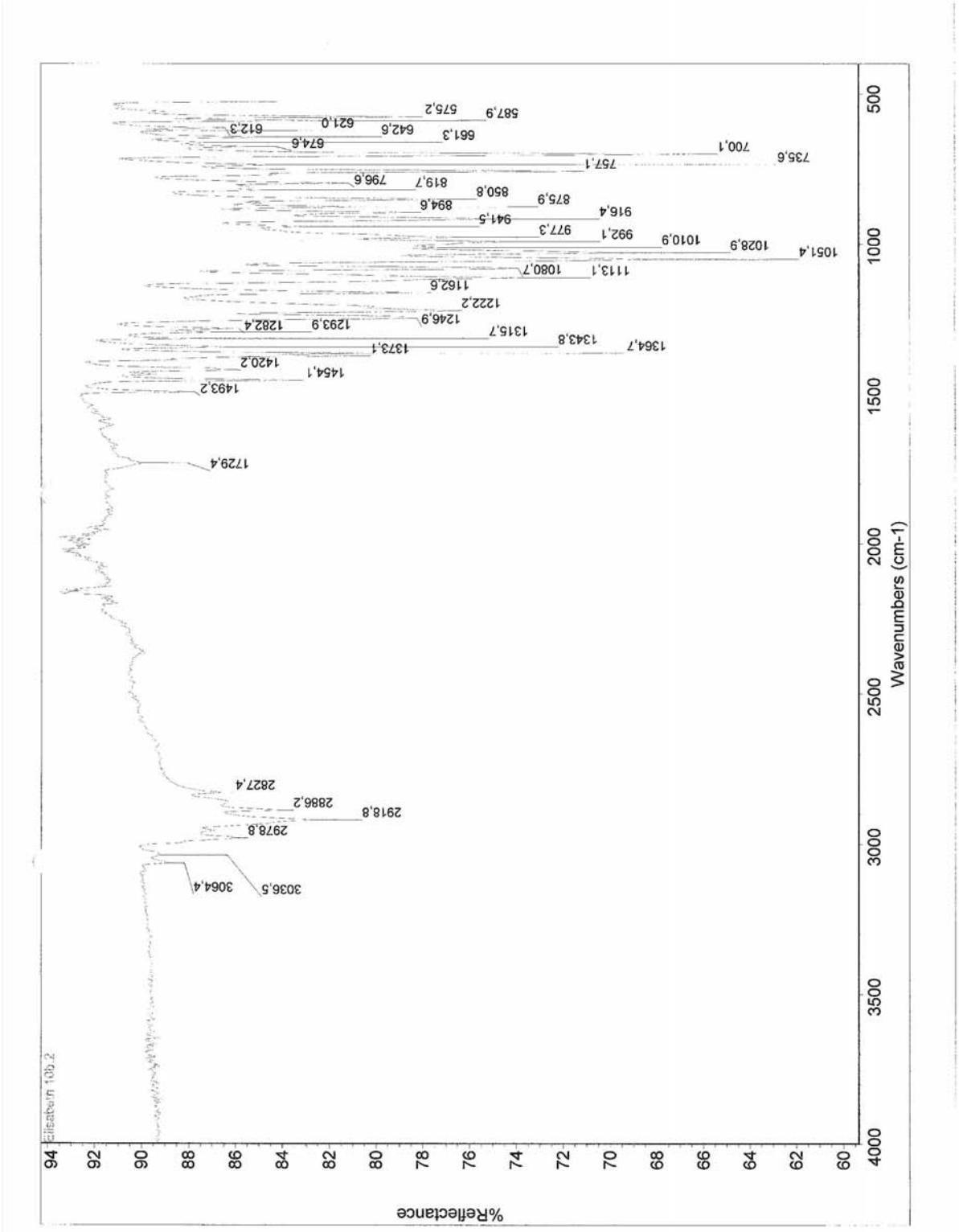
Scheme A.16: *^{1}H-NMR spectrum of 5,5-diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (**9**).*



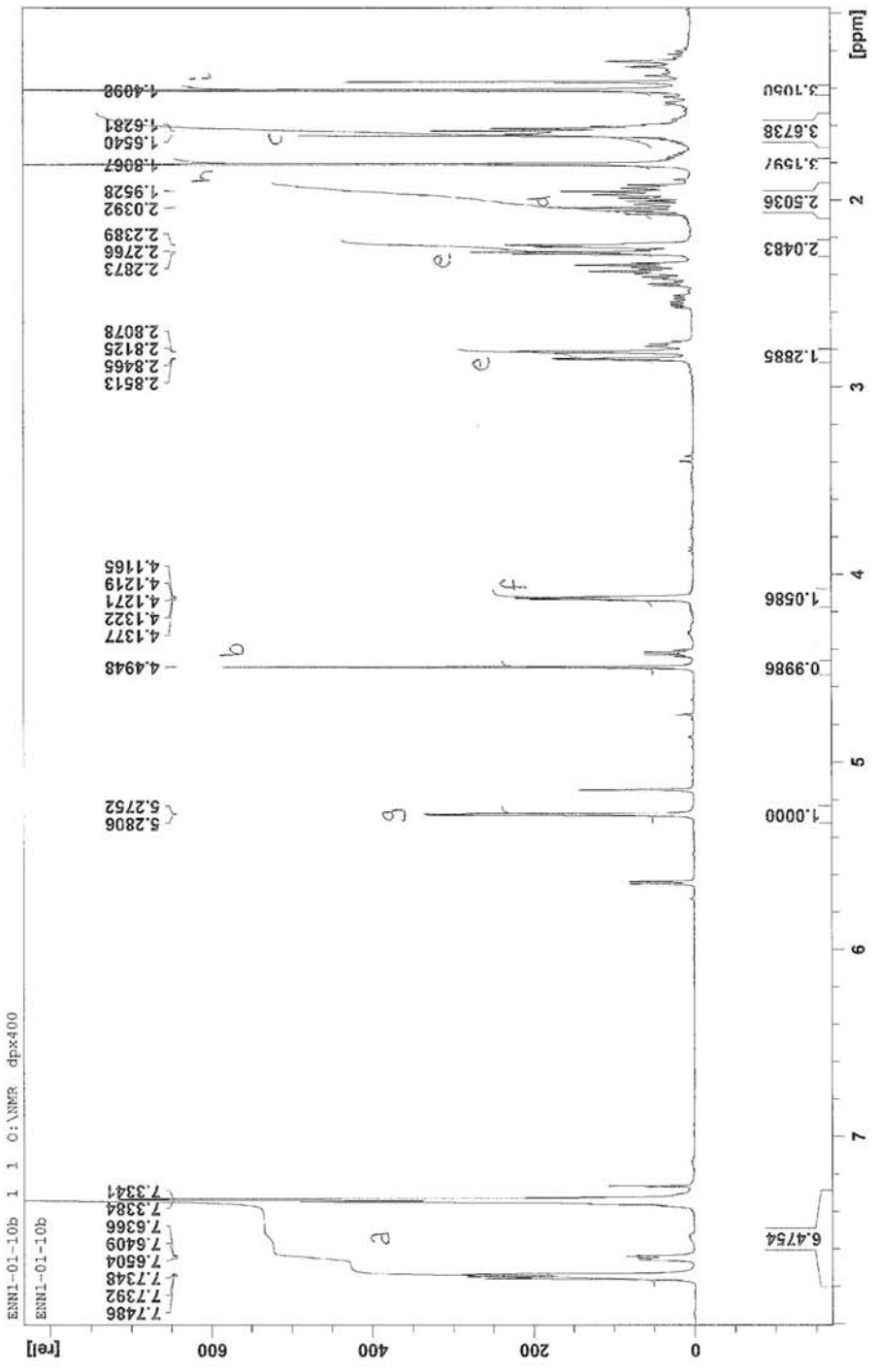
Scheme A.17: *^{13}C-NMR spectrum of 5,5-diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (**9**).*



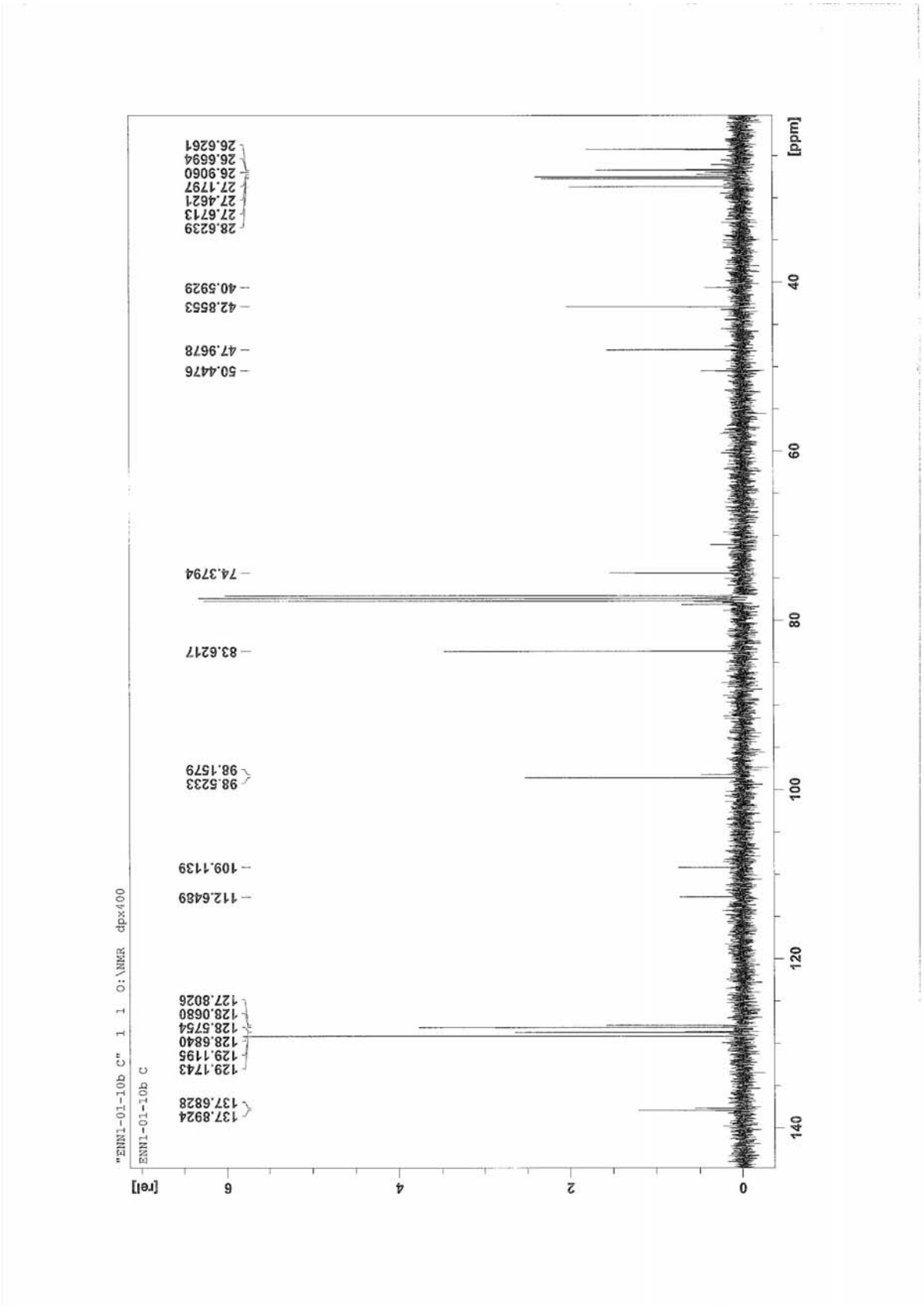
Scheme A.18: *COSY-H,H spectrum of 5,5-diethoxy-1,4-dihydroxy-1-phenyl-pent-2-one (**9**).*



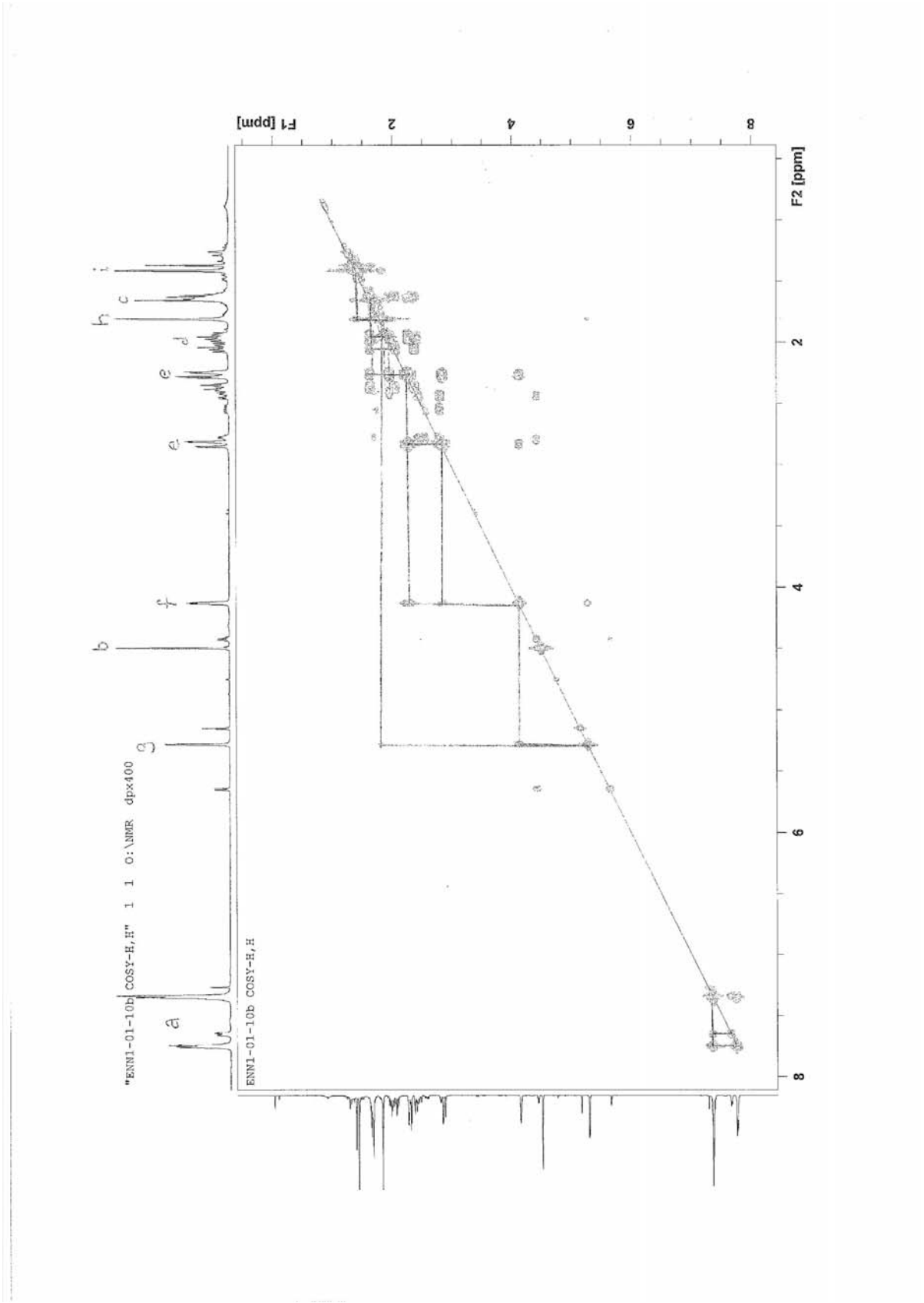
Scheme A.19: *IR spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**10**).*



Scheme A.20: *[1]H-NMR spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**10**).*



Scheme A.21: *^{13}C-NMR spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**10**).*



Scheme A.22: *COSY-H,H spectrum of 8-oxa-7-phenyl-1,5-dithiaspiro[5.5]undecane-9,10-diol acetonide (**10**).*