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 in pharmacy –

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My parents let me freely choose education based on interest, for which I am very grateful.

Rock on!

Guro Flemmen

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ABSTRACT

The starting material for this investigation was 3,3,4,4-tetraethoxybut-1-yne (TEB). This compound is highly functionalized as it contains a triple bond, a protected ketone, and a protected aldehyde, and can undergo a variety of different reactions.

The aim of this project was to synthesize 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. These compounds are valuable as they can undergo further reactions to form modified carbohydrate analogues, a class of compounds of great interest for the development of new drugs.

The target compounds were synthesized in moderate to excellent yields using *n*-butyllithium and aldehyde or ketone as reactants. Two of the compounds were also synthesized by first using sodium hydride instead of one of the two equivalents of *n*-butyllithium. This method gave low to moderate yields.

The target compounds have previously been synthesized, but by a different route, and these compounds have further been reacted to form carbohydrate analogues by deprotection of the dithiane moiety and subsequent cyclization. The conversion of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol into 1-substituted 5,5-diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diols makes it possible to synthesize the same carbohydrate analogues by a new route involving fewer steps and introducing the different substituents at a later stage in the synthetic route.

Based on the results obtained in this thesis, further work has been suggested.

ABBREVIATIONS

^1H	hydrogen-1 nucleus
^{13}C	carbon-13 nucleus
Ac	acetyl
Bn	benzyl
CBS	Corey-Bakashi-Shibata
DEM	diethoxymethyl
DEPT	distortionless enhancement by polarization transfer
ee	enantiomeric excess
HMPA	hexamethylphosphoramide
HSQC	heteronuclear single quantum coherence
IR	infrared
Mp	melting point
MRSA	methicillin-resistant *Staphylococcus aureus*
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
ppm	parts per million
PTC	phase-transfer catalysis/conditions
PTSA	*para*-toluenesulfonic acid
R_f	retention factor
rt	room temperature

t-BuLi   *tert*-butyllithium

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   TEB: A valuable starting material

The starting marterial for this investigation, 3,3,4,4-tetraethoxybut-1-yne (TEB, **4**), is highly functionalized as it contains a triple bond, a protected ketone, and a protected aldehyde. TEB is easily synthesized from ethyl vinyl ether over four steps as described by Sydnes *et al.*[1] The synthesis of TEB is depicted in Scheme 1.1.
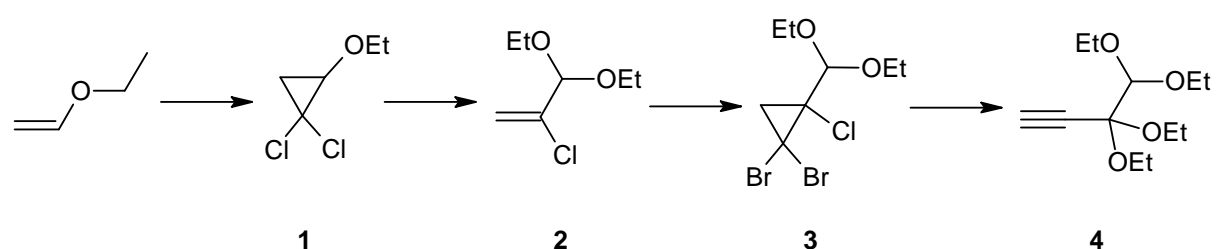
Scheme 1.1: *Synthesis of TEB.*

Several reactions can be undertaken selectively by utilizing the different functional groups.[1] Some reactions are depicted in Scheme 1.2.
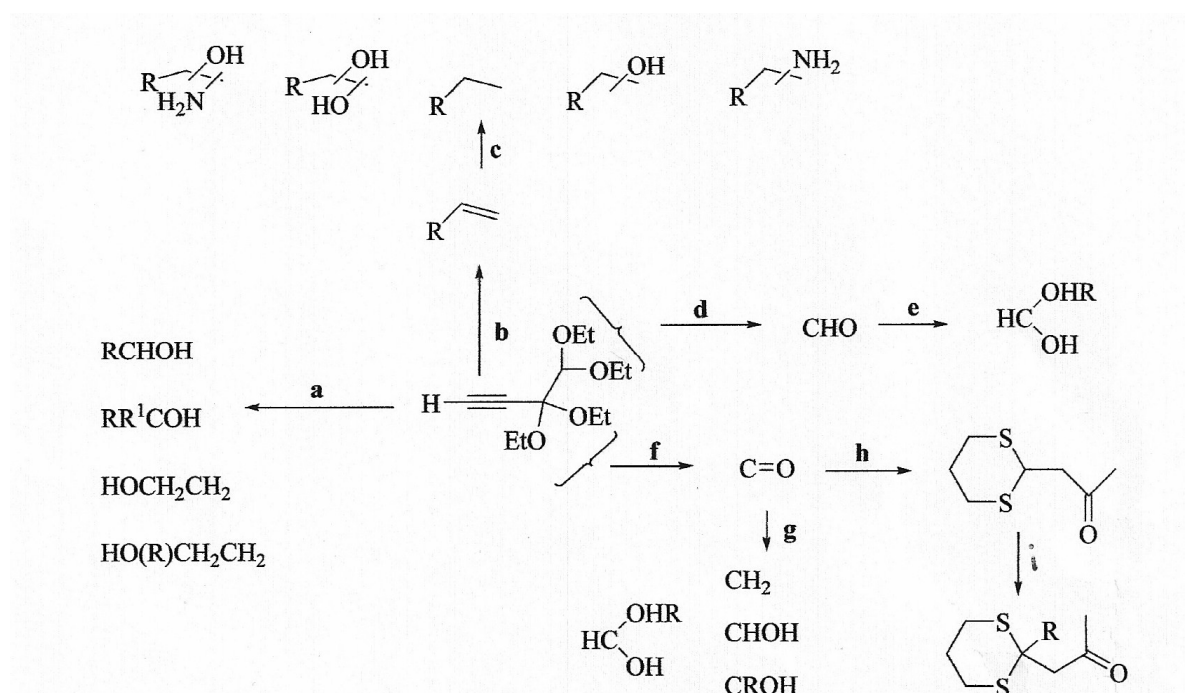
Scheme 1.2: *Possible transformations of TEB.*[1]

Route **a**: Abstraction of the acetylenic proton and reaction with aldehydes, ketones, and oxiranes to give the corresponding alcohols. Route **b**: Tranformation from alkynols to alkenols via reduction of the triple bond. Route **c**: Alkene reactions including hydrogenation, hydration, amination, dihydroxylation, and hydroxyamination. Route **d**: Deprotection of the acetal moiety. Route **e**: Aldehyde reactions, including formation of hemiacetals. Route **f**: Deprotection of the ketal moiety producing the conjugated acetylenic ketone. Route **g**: Ketone reactions, including reduction and formation of hemiketlas. Route **h**: Double Michael addition of propane-1,3-dithiol to give the 2-substituted 1,3-dithiane. Route **i**: Addition to an electrophilic agent.

Route **d** has proved to be difficult. The aldehyde function has not been obtained yet.[1] Route **i** has not been thoroughly studied so far,[2] and is the main focus in this project, but after reduction of the ketone moiety.

The large number of functional groups and possible transformations make TEB a valuable starting material for the synthesis of a range of compounds, including carbohydrate mimics.[1] Carbohydrate mimics are of interest to bind to existing drug molecules, either to non-glycosylated drugs to make the glycosylated analogoues, or for substitution of the carbohydrate moiety already a part of glycosylated drugs, to see if the biological activity and/or specificity of the drug changes, or preferably enhances.

1.2   Carbohydrates

Carbohydrates are one of the four major classes of biomolecules along with proteins, nucleic acids, and lipids. They are abundant in nature, and serve four main purposes:[3]

1. As energy stores, fuels, and metabolic intermediates.

2. As part of the structural framework of RNA and DNA (ribose and deoxyribose sugars).

3. As structural elements in the cell walls of bacteria and plants (polysaccharides).

4. Linked to many proteins and lipids, where they play a key role in mediating interactions among and between cells and other structures in the cellular environment.

Carbohydrates are built from monosaccharides. These molecules contain a small number of carbon atoms (typically three to nine), and one or more of the carbon atoms can be chiral centres.

Monosaccharides can be linked in various ways to form different oligosaccharides and polysaccharides. This means that carbohydrates have the possibility of an enormous structural diversity, and this diversity is the key property to their role as mediators of cellular interactions.[3]

1.2.1 Monosaccharides

Monosaccharides are aldehydes or ketones that have two or more hydroxyl groups attatched to the carbon chain.[3] If the monosaccharide is an aldehyde, it is called an aldose, and if it is a ketone, it is called a ketose. The simplest monosaccharides contain three carbon atoms and are called trioses; four carbon atoms give a tetrose, five carbon atoms give a pentose, and so on. Aldoses with four or more carbon atoms, and ketoses with five or more carbon atoms, exist as diastereomers.

| Dihydroxyacetone | D-Glyceraldehyde | L-Glyceraldehyde |
| (a ketose) | (an aldose) | (an aldose) |
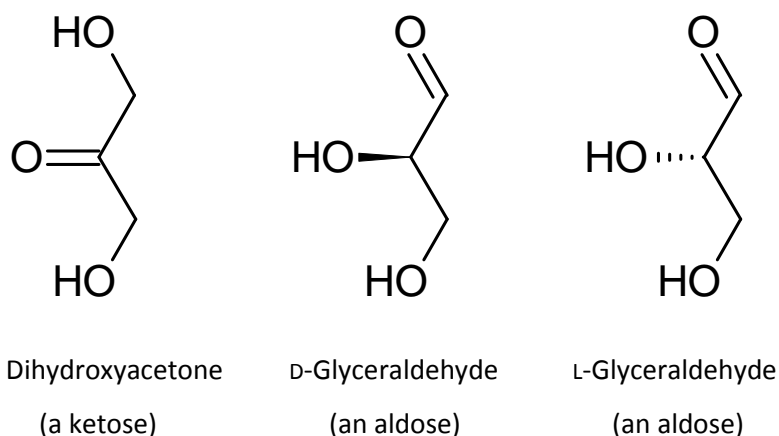
Scheme 1.3: *The three trioses.*

In solution, the predominant form of most monosaccharides is not an open chain, but a cyclic structure.[3] The carbonyl group reacts intramolecularly with one of the hydroxyl groups to form a cyclic hemiacetal or hemiketal. A six-membered ring is called a pyranose because of its similarities to pyran, and a five-membered ring is called a furanose because of its similarities to furan. The ring formation gives two structures as the carbonyl carbon atom becomes an additional chiral centre. The two forms are called anomers.
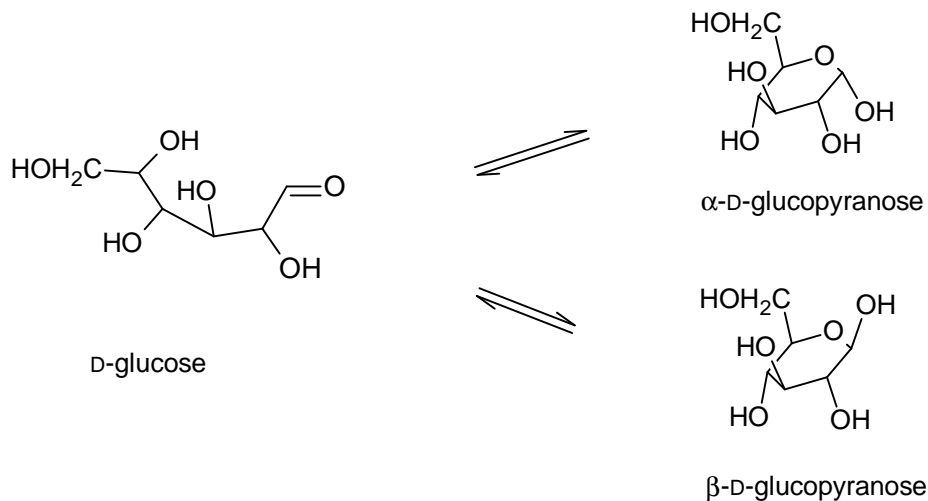
Scheme 1.4: *The two anomeric forms of D-glucopyranose.*

In equilibrium, a mixture of glucose contains approximately ⅓ α anomer, ⅔ β anomer, and << 1% of the open-chain form.[3]

1.2.2 Carbohydrates linked to peptides

Carbohydrate groups can be covalently attached to many different proteins to form glycoproteins or proteoglycans.[3] Many glycoproteins are components of cell membranes, where they play a variety of roles in processes such as cell adhesion. The protein structure and the cell type in which the protein is expressed determine which of the potential sites on the amino-acid sequence that is glycosylated.

Proteins termed lectins are located on the cell surface and bind to specific carbohydrate structures, and the main function in animals is to facilitate cell-cell contact.[3] A lectin usually contains two or more binding sites for carbohydrate units. Lectins on the surface of one cell interact with carbohydrates on the cell surface on another cell or free in solution. The interaction consists of relatively weak intermolecular bonds that ensure specificity yet permit unlinking as needed. Lectins have been shown to be involved in specific adhesion of symbiotic and pathogenic microorganisms to host tissue, in specific adhesion of tumour cells to organ cells in metastatic spread, and in certain interactions within the cellular immune system.[4]

1.3   Modified carbohydrates

Several drugs contain carbohydrate moieties. Some are depicted in Scheme 1.5.
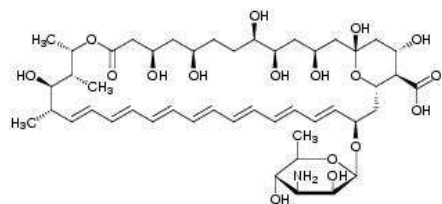
Amphotericin B (antifungal)
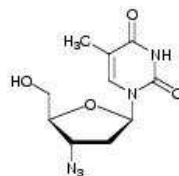
Zidovudine (nucleoside reverse transciptase inhibitor, antiviral, HIV)

Vancomycin (antibacterial)

Tobramycin (antibacterial)

Digitoxin (cardiac glycoside)

Erythromycin (antibacterial)

Auranofin (antirheumaticum)

Scheme 1.5: *Examples of drugs containing carbohydrate moieties.*[5]
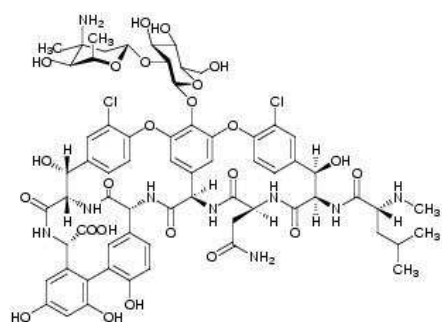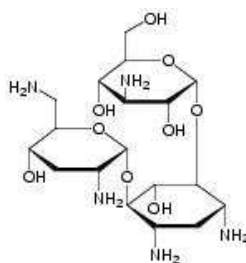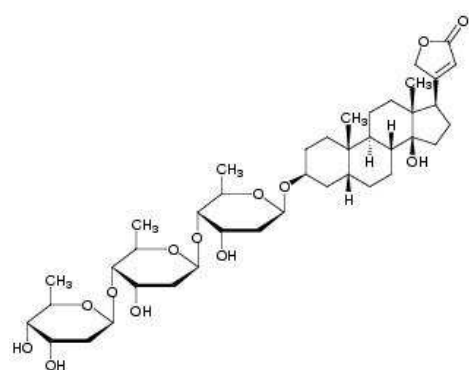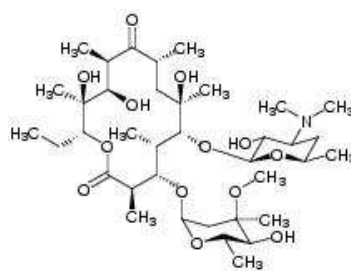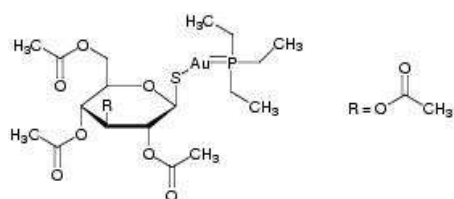
1.3.1 Vancomycin and altered antibacterial activity due to changing the carbohydrate moiety

Vancomycin is a glycopeptide antibiotic which is used to treat life-threatening infections caused by gram-positive bacteria otherwise resistant to first-line antibiotics. These infections include those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and enterococci such as *Enterococcus faecium* and *E. faecalis.*[6,7] These bacteria have become an increasing problem in USA and Europe where they cause infections that are difficult to treat, in hospitalised patients. Development of resistance towards Vancomycin has further diminished the options for treatment of these infections.[6,7]

Vancomycin works by inhibition of the formation of the cell wall in gram-positive bacteria. *S. aureus* synthesizes building blocks of the cell wall, which are then linked together.[8]
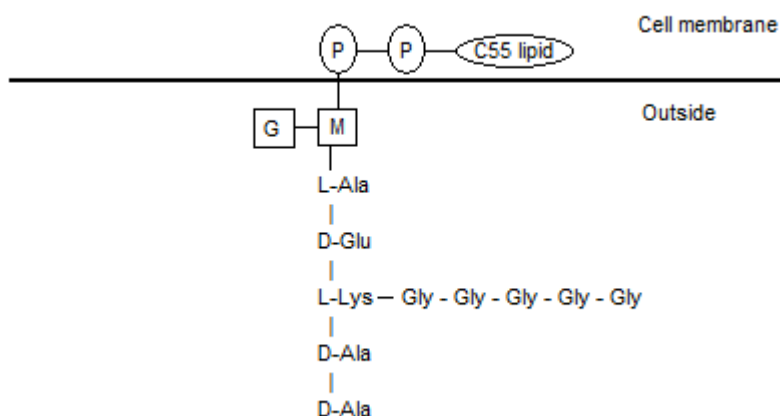
Scheme 1.6: The building block of the cell wall in S. aureus. (G: N-acetylglucosamine; M: N-acetylmuramic acid)

The building block is transferred to an acceptor (the growing peptidoglycan layer), where the disaccharides are linked together, and the pentapeptides are cross-linked via the Gly_5-chain. During this cross-linking, the terminal D-Ala is cleaved off.[8] Vancomycin binds to the D-Ala-D-Ala residue of the pentapeptide,[9] thereby inhibiting the cleaving necessary for the cross-linking.

Several attempts have been made to modify Vancomycin to avoid problems of resistance, including modification of the carbohydrate moieties.[6,10] For example, Thayer and Wong has managed to synthesize Vancomycin analogues which exhibit enhanced activity against a Vancomycin-resistant strain of *Enterococcus.*[10]

1.3.2 Glycoconjugates as possible drugs

The synthesis of specific carbohydrates that have an affinity for amino-acid sequences in proteins attached to specific cell types might be a way to deliver drugs, attached to the carbohydrate, to specific cell types and organs. For example, multivalent carbohydrate clusters have been synthesized and found to act as ligands to different lectins (carbohydrate-binding proteins). These oligosaccharides can potentially be used as drug carriers, anti-inflammatory compounds, and microbial antiadhesins. [11]

A study undertaken by Steuer *et.al.*[12] (original article not available, see mini-review by Beuth *et al.*[4]) compared the efficacy and tolerability of a defined carbohydrate solution, meant to inhibit lectins on bacteria taking part in adhesion of bacteria to host tissue, with standard aminoglycoside therapy (gentamicin, bactericidal effect) for the treatment of *otitis externa diffusa acuta* (infection in the external auditory canal) caused by *Pseudomonas aeruginosa*. The results were comparable, suggesting that lectin-binding might be an alternative treatment of infections as this inhibits the bacteria from binding to the host cells.

1.4   Previous work

Valdersnes has synthesized carbohydrate analogues from TEB by the route depicted in Scheme 1.7.[2] The route consists first of chain elongation, producing different analogues, then protection of the hydroxyl group, deprotection of the ketal moiety, addition of dithiol to the triple bond giving a masked carbonyl moiety, reduction of the ketone, deprotection of the masked carbonyl moiety giving a carbonyl group, deprotection of the protected hydroxyl group, and cyclization giving a carbohydrate analogue.
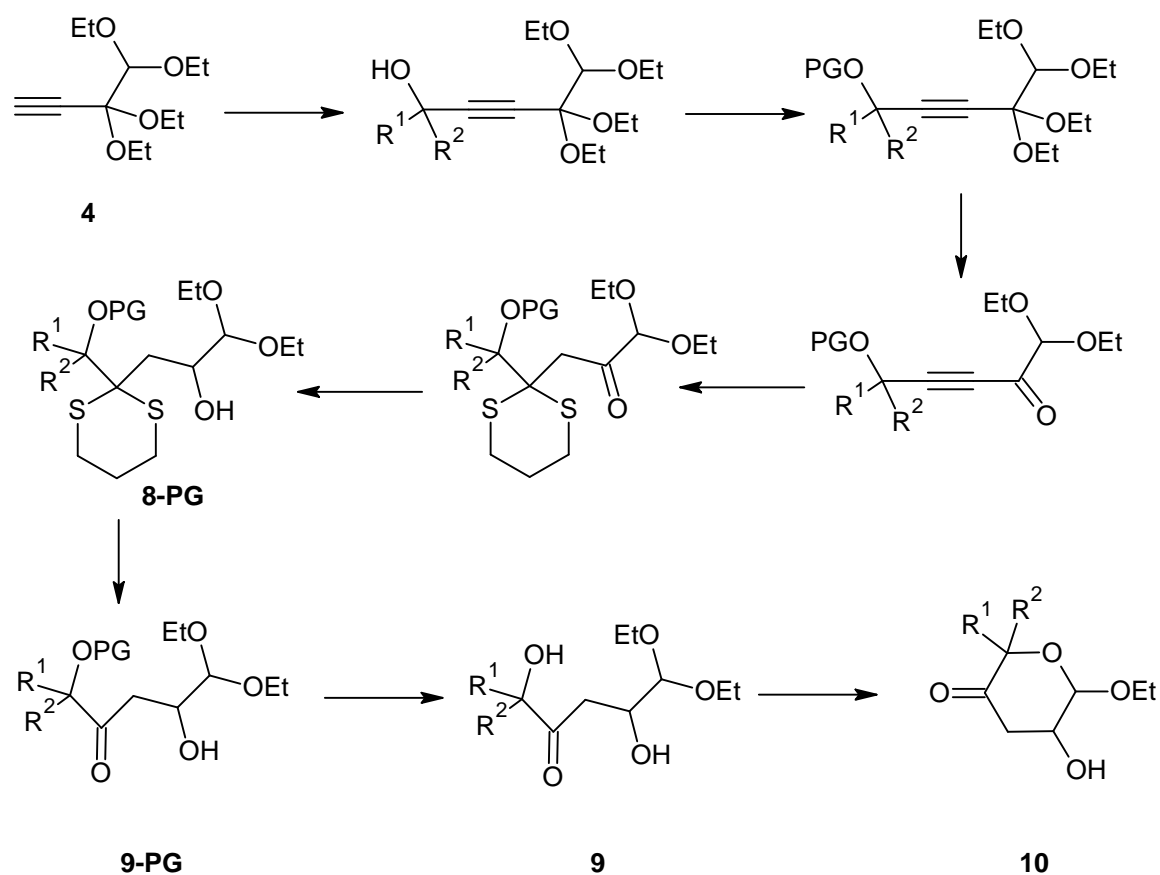
Scheme 1.7: *Synthetic route of carbohydrate analogues from TEB. (PG = protecting group)*

Valdersnes also tried to synthesize compounds **8-Bn** (Bn = benzyl) by the reaction sequence in Scheme 1.8, but that approach was unsuccessful.[2]
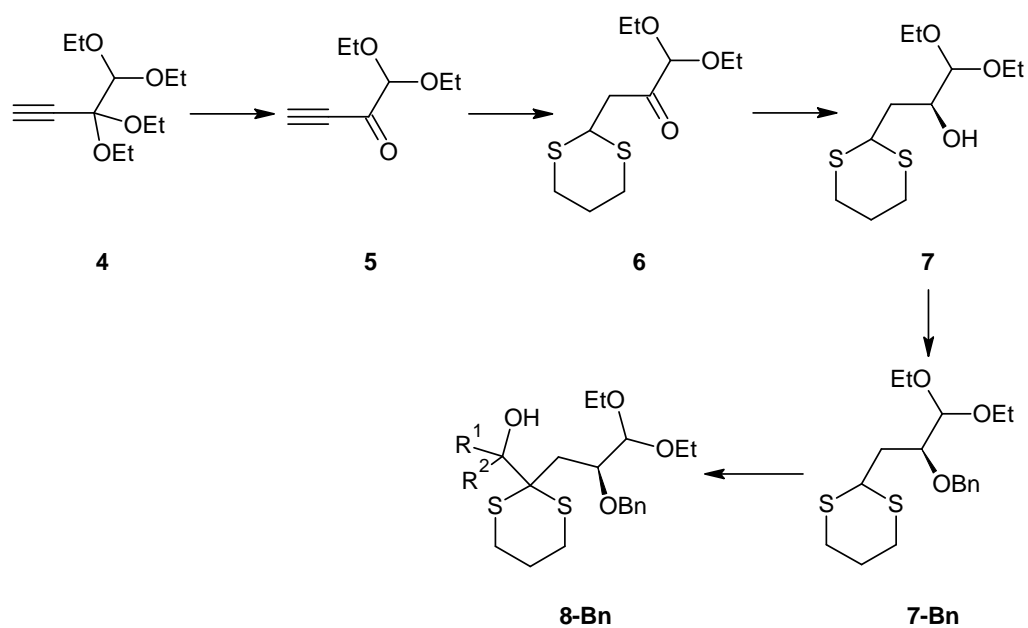
Scheme 1.8: *Attempted alternative reaction route producing compound **8-Bn** from TEB.*

When benzyl-protected **7** was treated with 1 mol equivalent of *tert*-butyllithium (*t*-BuLi) and a ketone in tetrahydrofuran (THF) at -78 °C, only unreacted starting material was obtained from the reaction mixture. Addition of hexamethylphosphoramide (HMPA, 10% v/v) as a co-solvent gave a product, but not the desired one, **8-Bn**; instead alcohol **8-Bn'** was obtained in 19 and 24% yield using acetone and cyclohexanone, respectively.[2]

7-Bn   **8-Bn'**

Scheme 1.9: *Addition of **7-Bn** to $R_1R_2C=O$.*

One attempt was made to add unprotected **7** to cyclohexanone using the same conditions except that 2 mol equivalents of *t*-BuLi was applied due to the presence of a hydroxyl group. This produced the desired product in 14% yield.[2]

On the basis of the work done by Valdersnes, it was desirable to further investigate the addition of alcohol **7** to different aldehydes and ketones.
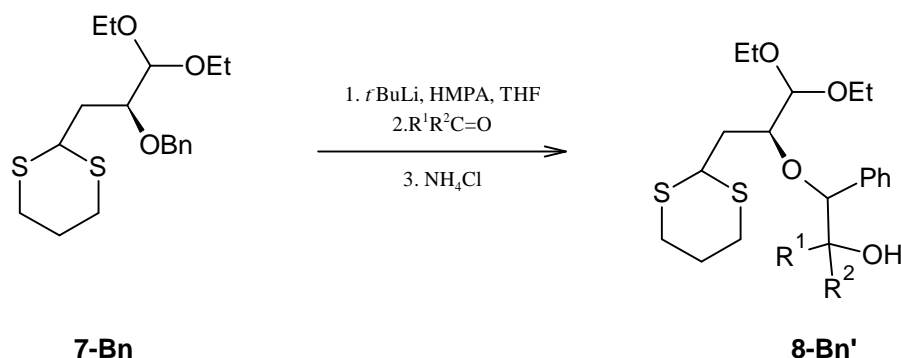
1.5 Aim

The aim of this project is to synthesize the diols **8** from TEB as depicted in Scheme 1.10. First, TEB will be deprotected to form ketone **5**, which will be converted to the corresponding 1,3-dithiane **6** by reaction with propane-1,3-dithiol using a literature procedure. Subsequent reduction of the carbonyl group as described in the literature, will give alcohol **7**, which is the starting material for this investigation. The main part of the project will be the addition of the sulphur-stabilized anion of **7** to various aldehydes and ketones to produce the chain-elongated diols **8**.
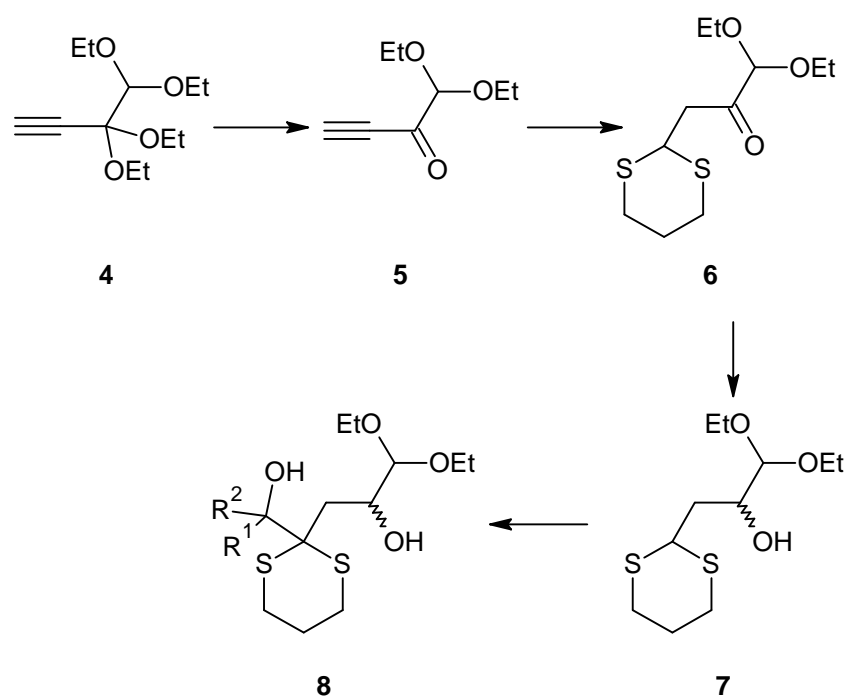
Scheme 1.10: *Aim of the project.*

A successful reaction sequences will provide an alternative route to the previously investigated route depicted in Scheme 1.7. The new route will be less time consuming as one avoids the protection and deprotection of an alcohol. Furthermore, the deprotection of the ketal to ketone, addition of dithiol, and reduction of the ketone will only have to be carried out once as these reactions precede the introduction of the different analogues.

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2   RESULTS AND DISCUSSION

2.1   Preparation of starting materials

2.1.1   Preparation of TEB

TEB was synthesized in a four-step synthesis from ethyl vinyl ether as described by Sydnes *et al.,*[1] and details with respect to reagents and conditions are depicted in Scheme 2.1. The overall yield was 20%.
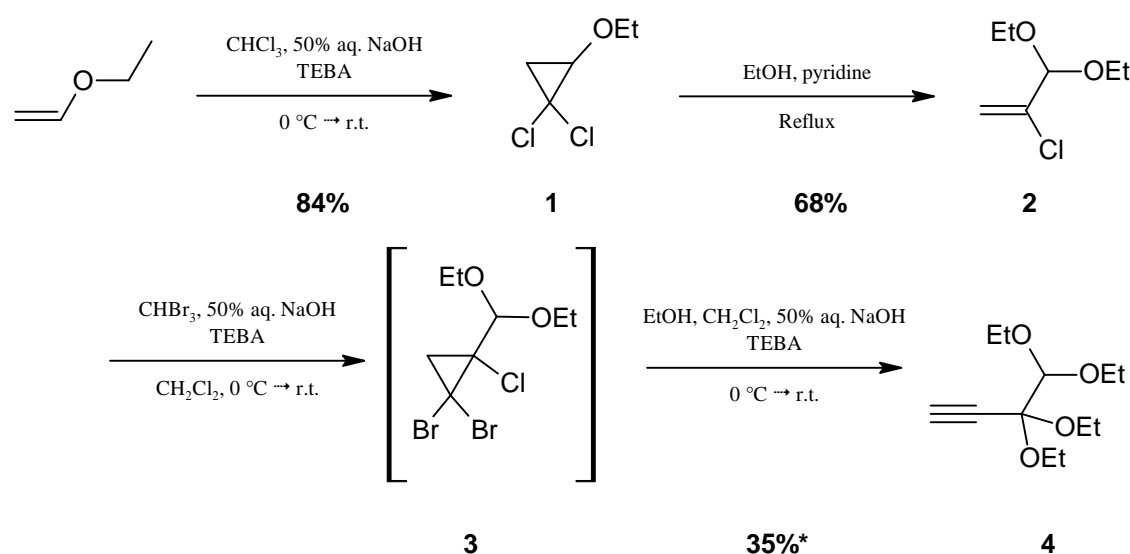
*Scheme 2.1: Synthesis of TEB from ethyl vinyl ether.*The yield is calculated over two steps as compound **3** was not isolated.*

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

The title compound was prepared by cyclopropanation of ethyl vinyl ether using Makosza's method,[2] giving an 84% yield on a 0.5 mol scale.

The synthesis of *gem*-dichlorocyclopropanes by addition of dichlorocarbene to olefins has been thoroughly investigated by Doering and co-workers.[3,4] Makosza and Wawrzyniewicz modified the reaction conditions to the PCT-condition depicted in Scheme 2.1,[2] which includes reaction of the olefin with chloroform in the presence of a concentrated aqueous solution of sodium hydroxide and catalytic amounts of triethylbenzylammonium chloride (TEBA). In our case, four equivalents of

chloroform and six equivalents of sodium hydroxide were used. As the proton abstraction from chloroform and formation of the carbanion quaternary ammonium cation ion-pair are thought to occur at the boundary between the two phases,[5,6] the reaction requires vigorous stirring to achieve proper mixing. Because the reaction is highly exothermic, an ice-water bath is needed during the addition of aqueous sodium hydroxide. The bath can be removed after one hour of stirring at small scale reactions (~0.1 mol), but must be kept for a longer period of time when the reaction is run on a larger scale (up to 2 mol) to avoid boiling.[7]

The synthesis was first reported by Doering and Henderson,[4] and later by Skattebøl.[8] By using the PCT method, the reaction has been scaled up to a 2-mol reaction by Kvernenes.[7] The yield after distillation has been reported as high as 97%,[1] but is lower on a small scale due to the relatively larger amount left behind in the distillation apparatus.

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

The title compound was prepared by ring opening of **1** using the procedure published by Skattebøl,[8] giving a 68% yield. Pyridine was of puriss grade, and was not purified further before use.

The synthesis of **2** from **1** was first described by Skattebøl,[8] using either sodium ethoxide or pyridine as base. The reaction is thought to take place via an allylic-cation intermediate caused by a thermally-induced, concerted ring opening with loss of one of the chlorine atoms. Ethanol then performs a nucleophilic attack on the positively charged carbon atom. The base is present to neutralize the acid formed. If the acid is not neutralized, it will react with **2** and form the corresponding aldehyde.[8]

Kvernenes simplified the reaction conditions using commercial absolute ethanol and commercial pyridine without any purification.[7] Following this procedure, the yield has been reported as high as 73%, the higher scale (up to 2 mol) giving a better yield than the smaller scale.[7] If pyridine is thoroughly purified, an 89% yield can be obtained.[1]

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

The title compound was prepared by cyclopropanation of **2** using Makosza's method.[2] Unreacted bromoform was distilled off from the crude product, and this left **3** as a brown but otherwise quite pure product, which was used without further purification in the final step. ^{1}H NMR showed that the sample still contained some bromoform.

The synthesis of **3** from **2** consists of a cyclopropanation by Makosza's method similar to the synthesis of **1**.[2] In this case, bromoform, rather than chloroform, is used as the source of the halocarbene. Bromoform is required in large excess (10 eq.), but unreacted bromoform can be recycled as it can be removed by distillation.[7] Kvernenes reports a yield of 60% when run on a 1-mol scale using fresh bromoform.[7] The use of recovered distilled bromoform increases the yield of the reaction, probably because some starting material and/or product distilled with the bromoform.[9] Valdersnes reports a 89% yield when using recycled bromoform.[9]

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

The title compound was prepared by ring opening of **3** (not pure) using the procedure published by Sydnes and Bakstad.[10-13] The yield of **4** was 35% from **2**. During the distillation of the crude product, a mixture of bromoform and **2** (4.61 g in total) was obtained before the product distilled off. After the distillation, approximately 7 g of black, tarry residue was left in the distillation flask.

The reaction mechanism of **4** from **3** has been thoroughly investigated.[10-12] The reactions of 1,1,2-trihalocyclpropanes under this phase-transfer condition (PTC) usually gives a mixture of the acetylenic ketal and acetylenic acetal depending on the R groups,[10] but the reaction conditions can be modified to give regiospecific ringopening of the cyclopropane, and hence only one of the isomers.[11]

1,1-Dibromo-2-chloro-2-diethoxymethylcyclopropane (**3**) contains diethoxymethyl (DEM) as the R group. This substituent is bulky, but polar enough to form hydrogen bonds that redirect the ethanol attack from C-3 to C-2 (the same carbon atom as the substituent), and therefore gives only the ketal product.[1,12,14]

2.1.2   Preparation of *β*-hydroxydithiane from TEB

Alcohol 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**) was synthesized from TEB in three steps as outlined in Scheme 2.2. The overall yield was 52%.
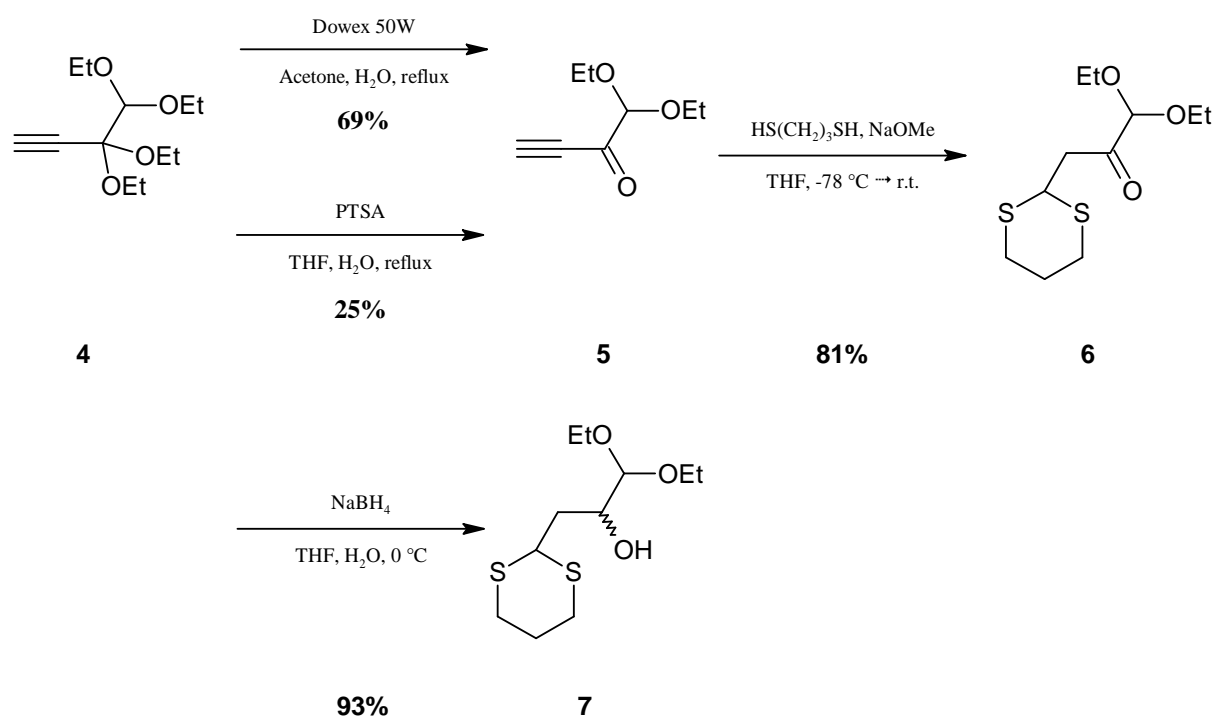
Scheme 2.2: *Preparation of β-hydroxydithiane from TEB.*

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

The deprotection of the ketal moiety is done by treating TEB with an excess of aqueous acid. Dowex 50W (method A, as described by Kvernenes[7]) gave a higher yield than *para*-toluenesulfonic acid (PTSA, method B[15]). In each case the reaction was slow for TEB, requiring quite a long reaction time.

Method A required 24 h to give a full conversion of ketal to ketone. An 8-hour reaction time gave a mixture of ketal and ketone, which could not be separated by simple distillation. Separation by flash chromatography was not attempted as the two compounds have very similar R_f values on the TLC plate.

Method B was at first attempted with a reaction time of 11 h. This yielded a mixture of ketal and ketone. The crude product was an orange liquid, but after distillation, a black, tarry residue was left in the distillation flask, which indicates that decomposition had taken place. A reaction time of 16.5 h gave the ketone as the only product, but the yield was quite low after flash chromatography. The crude product was an orange liquid with a black, tarry material at the bottom. Thus, long reaction times with PTSA seemed to give this decomposition.

Method A was deemed to be the best alternative as it gave the ketone as the single product in relatively good yield when a sufficiently long reaction time was used.

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

The title compound was prepared in 81% yield by a double Michael addition under basic conditions as described in the literature.[16,17] The use of a mixture of TEB and ketone **5** did not complicate the reaction, since the ketal does not reacts with the dithiol.

The introduction of a dithiane moiety is quite useful as it is a masked carbonyl moiety, yet can act as a nucleophile. This gives the opportunity to form C-C bonds by reactions with various aldehydes and ketones in a chain-elongating step producing a hydroxyl group under basic conditions.[18] The reversal of the reactivity pattern has been termed "umpolung".
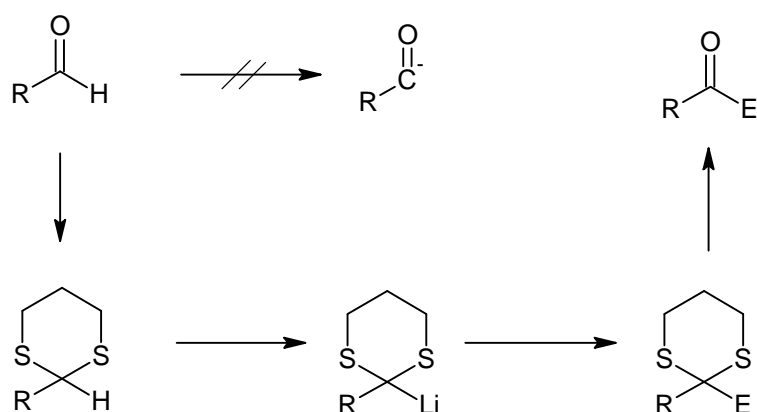
Scheme 2.3: *Umpolung of an aldehyde, producing an acyl anion equivalent.*[9]

The reactions originally published by Ley *et al*. involved propane-1,3-dithiol, sodium methoxide, CH$_2$Cl$_2$, and methanol at -10 °C, but the solvent was later altered to THF and the temperature lowered to -78 °C to minimize dimer formation.[16,17] In our case, the reaction was run in THF at -78 °C, as this method was expected to produce the highest yields.[9] No dimer formation was observed in the reaction of ketone **5** to **6**.

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

Reduction of 1,1-diethoxy-3-(1,3-dithian-2-yl)propane-2-one (**6**) was achieved with sodium borohydride in aqueous THF following a modified literature procedure published by Zeynizadeh and Behyar.[19] The reaction was carried out with 0.5 mol equivalents of NaBH$_4$ instead of 2 mol

equivalents, and at 0 °C (ice-water bath) instead of at reflux temperature (66 °C).[15] These modified conditions proved to be sufficient to reduce this ketone. The reaction was very fast; TLC showed that most of the starting material had been consumed within 5 minutes, and the title compound was isolated in 93% yield.

Alcohol **7** was stored for several weeks and used as starting material in reactions with aldehydes and ketones. After about five weeks a progressive degradation of the compound was suspected. ^{1}H NMR was run and showed the appearance of impurities as reflective in the spectra shown in Scheme 2.4.
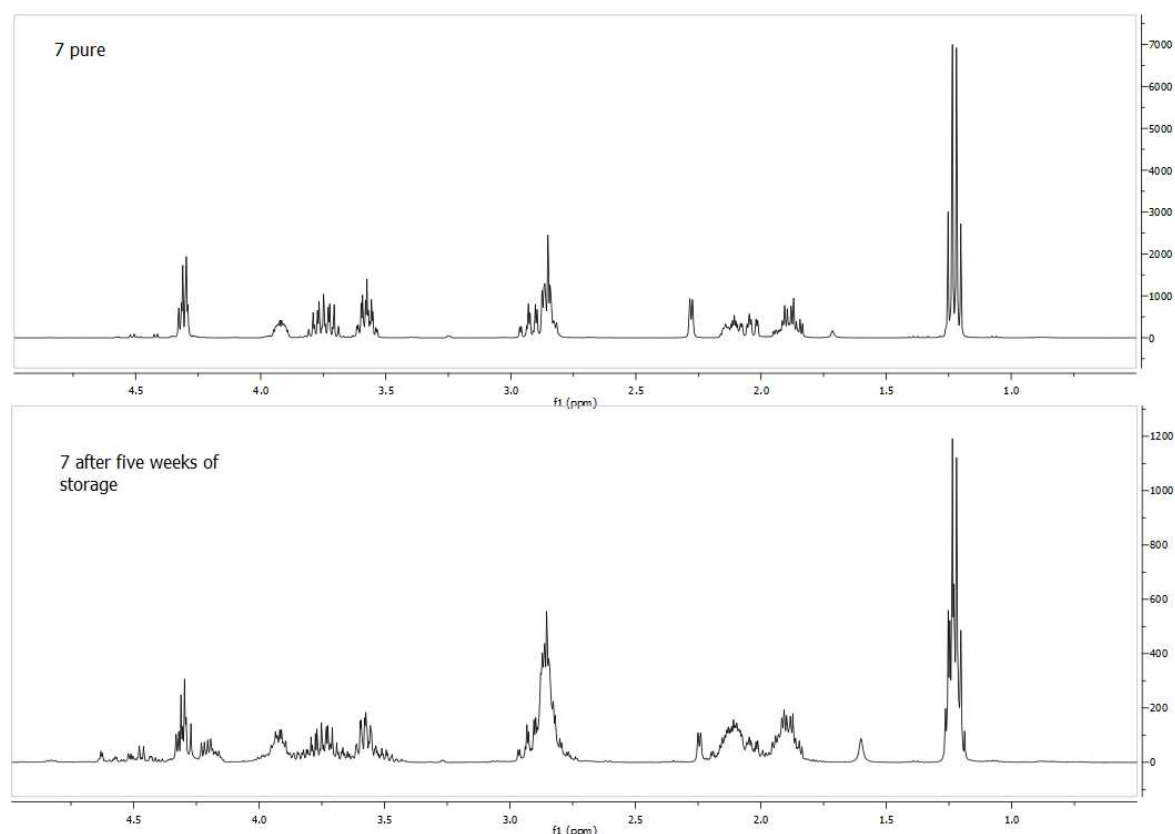
Scheme 2.4: Comparison of the ^{1}H-NMR spectra of compound **7** after zero and five weeks.

The synthesis of alcohol **7** was repeated, and some of the compound was stored in the refrigerator in a closed flask, whereas some was kept at room temperature in an open flask. The sample stored in the refrigerator was tested for appearance of new spots on TLC after 9, 12, 15, 21, and 24 days, and the sample stored at room temperature was tested after 0, 3, 9, and 12 days.

In the

refrigerator:

At room

temperature:

Rf = 0.55 and 0.58

Rf = 0.37

Rf = 0.14 and 0.20
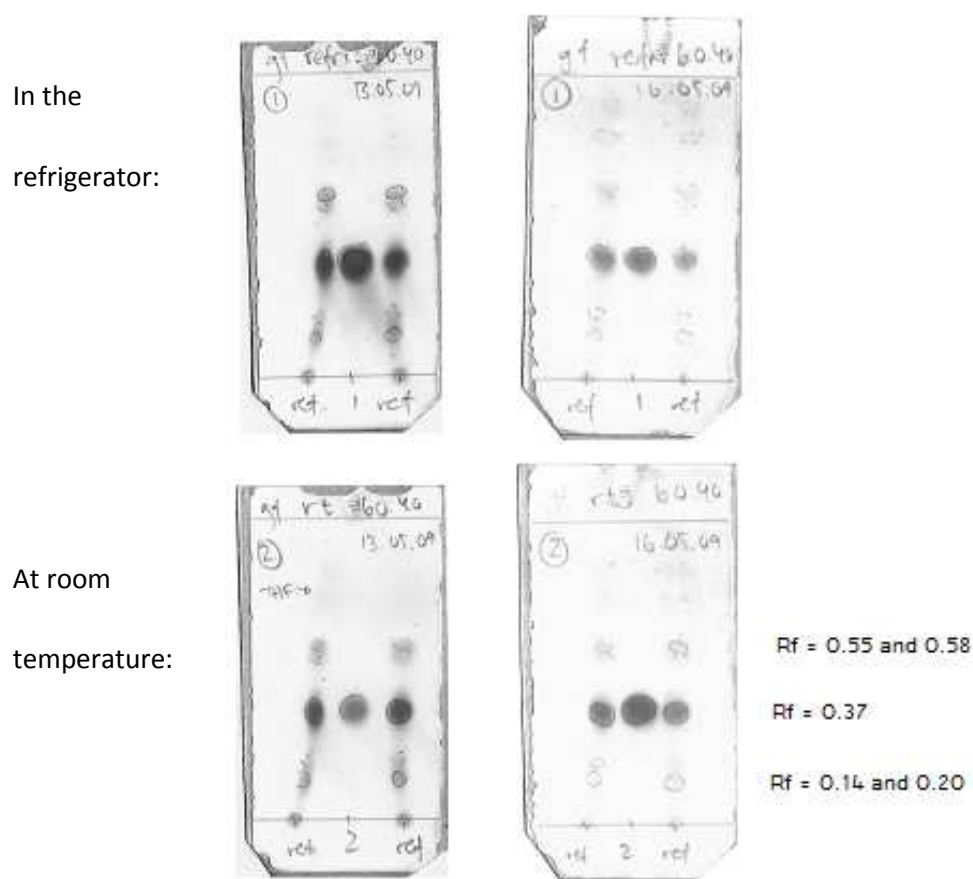
Scheme 2.5: TLC plates of compound 7. Ref: after approximately 10 weeks, most of the time in room temperature, 1: refrigerator, 2: room temperature.

The TLC plates show only one spot for the samples, but several for the reference.

^{1}H NMR was obtained from the two samples after 26 days for the one in the refrigerator, and 14 days for the one in room temperature.
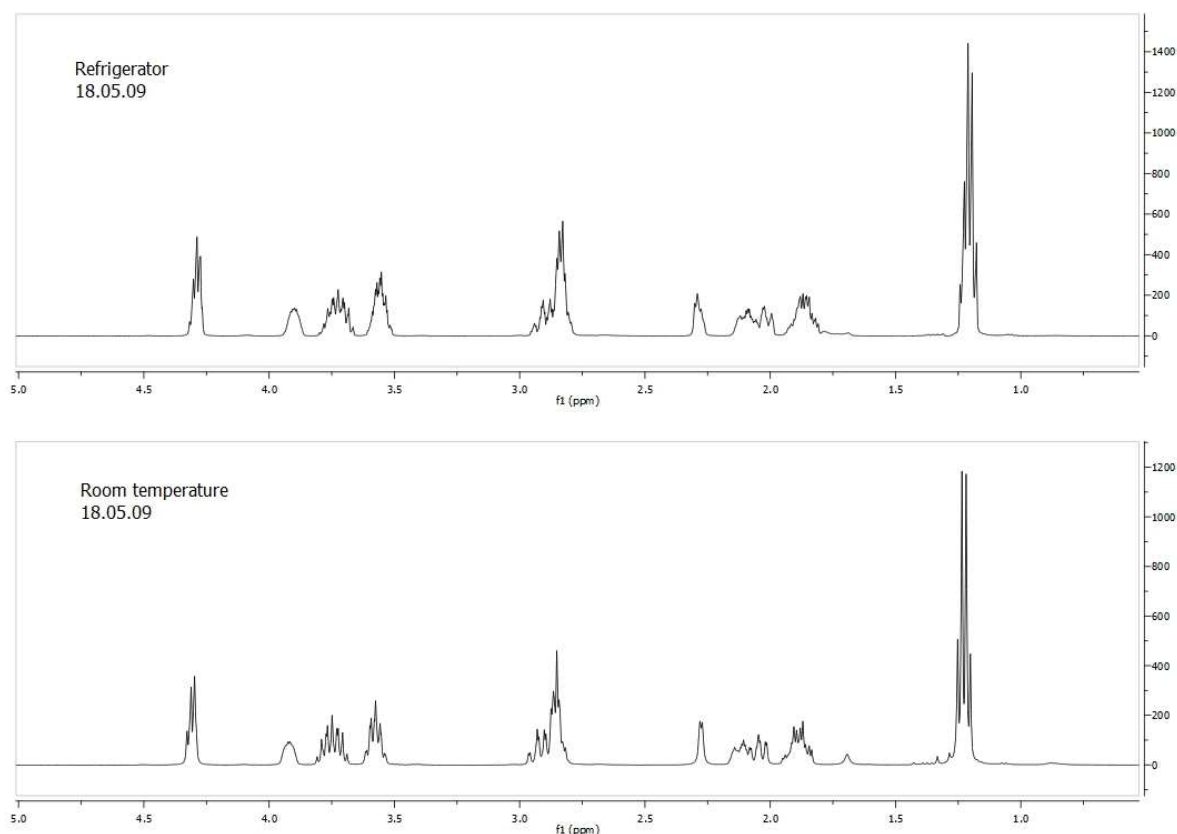
Scheme 2.6: ^{1}H-NMR spectra of samples of compound **7**.

As seen from the ^{1}H-NMR spectra in Scheme 2.6, alcohol **7** appears to be stable at room temperature for at least 2 weeks and in the refrigerator for at least 4 weeks.

Before discovering the appearance of impurities in the sample of compound **7**, it had been kept at room temperature for about a week before being placed in the refrigerator. The flask had also been heated several times at 40 °C in connection with sample preparation.

When placed in the refrigerator, the appearance of the sample changed from a clear, light-yellow liquid, to an opaque, less yellow, and very viscous liquid. In contrast, a pure sample of the compound **7** is clear, light yellow liquid with low viscosity, and it does not change appearance when placed in the refrigerator. When a sample of the viscous liquid was dissolved in a little hexane:ethyl acetate (80:20) to prepare for flash chromatography, a white precipitate appeared.

When running flash chromatography to purify the sample containing impurities, the first two samples eluted from the column (R_f = 0.55 and 0.58, see Scheme 2.5) gave the white solid. An ^{1}H-NMR spectrum was obtained from the sample with the larger R_f value and from a mixture of the compounds with R_f 0.14 and 0.20 (see Scheme 2.5, not separated, liquid). The compound with R_f = 0.55 was not isolated from the compound with R_f = 0.58.
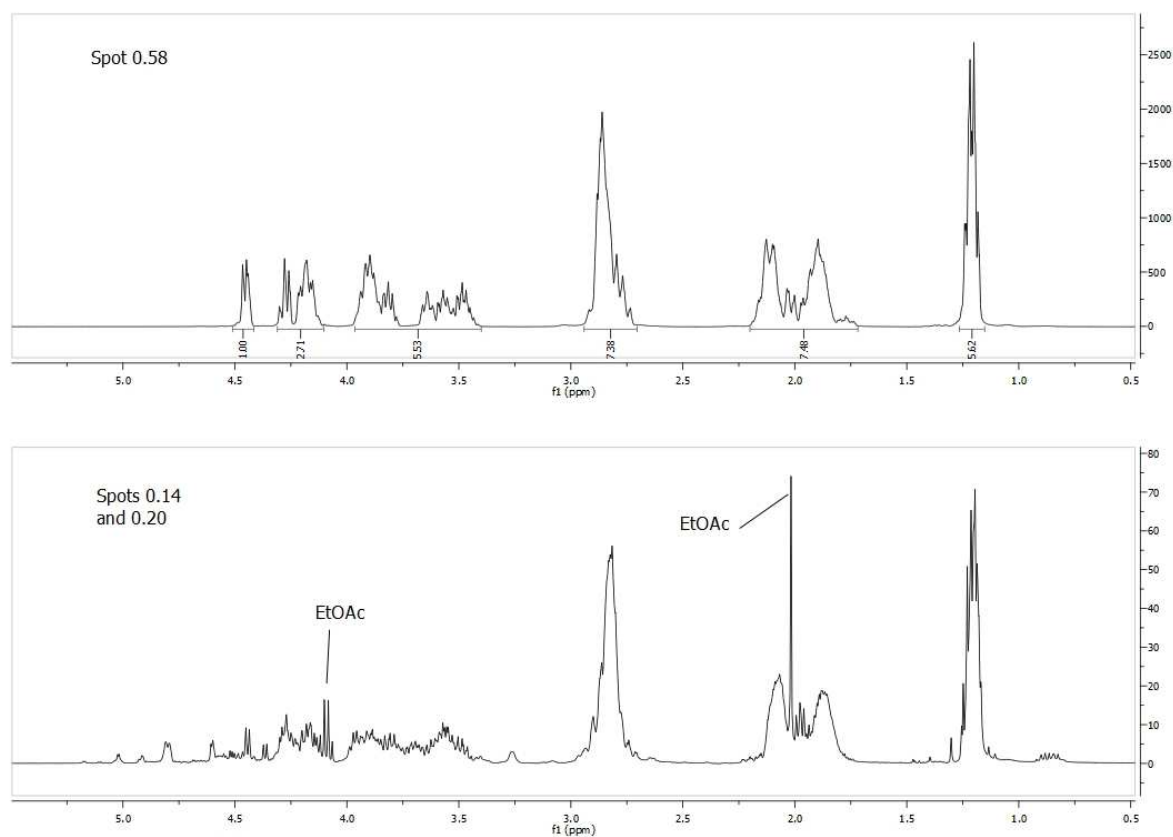
Scheme 2.7: *¹H-NMR spectra of two of the fractions obtained from flash chromatography of compound 7 containing impurities.*

Both spectra in Scheme 2.7 contain many overlapping signals, and the signals appear in all the areas where there are signals from compound **7**. No structures of the compounds have been suggested.

2.2   ADDITION TO ALDEHYDES AND KETONES

With 1,1-diethoxy-3-(1,3-dithian-2-yl)propane-2-ol (**7**) at hand, coupling with several aldehydes and ketones were carried out to make the corresponding diols **8**, as summarized in Scheme 2.8. Three methods were applied.
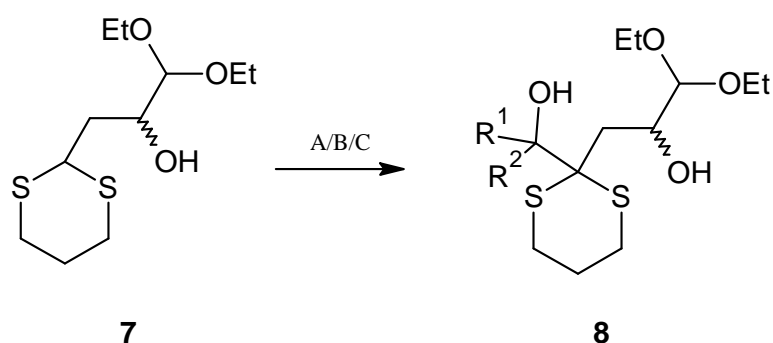
Scheme 2.8: Addition of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**) to aldehyde or ketone. Method A: 1. n-BuLi (2 eq.), 2. R_1R_2CO (1.2 eq.), 3. NH_4Cl (sat., aq.). THF, -78 °C; method B: 1. n-BuLi (2 eq.), 2. R_1R_2CO (1.2 eq.), 3. NH_4Cl (sat., aq.). THF, 0 °C; method C: 1. NaH (1 eq.), 2. n-BuLi (1 eq.), 3. R_1R_2CO (1.2 eq.), 4. NH_4Cl (sat., aq.). THF, 0 °C.

2.2.1   Comparison of the different methods

As seen from Table 2.1, method B gives the best yields of **8**. This method includes the use of 2 equivalents of *n*-buthyllithium (*n*-BuLi), one to abstract the unprotected hydroxyl proton, and the other to abstract the proton at the 2-position of dithiane. As *n*-BuLi is a more expensive and less stable reagent than NaH, it was of interest to use NaH as base to abstract the hydroxyl proton ($pK_a \approx$ 20),[20] and then add 1 eq. of *n*-BuLi to abstract the other, less acidic proton ($pK_a \approx$ 38 in THF).[21]

Table 2.1: Yields of the addition product **8**.

	R_1	R_2	Method A (%)	Method B (%)	Method C (%)
8a	CH_3	H	6	52	20
8b	Phenyl	H		95	55
8c	*n*-Hexyl	H		78[i]	
8d	H	H		31	
8e	CH_3	CH_3		61[ii]	
8f	-(CH_2)_5-			62 [i]	

i: estimated value, not obtained as pure compound. ii: contains small amounts of starting material.

Method B gave moderate to excellent yields of all the products except when paraformaldehyde was used. Even though paraformaldehyde was allowed to react longer (1 h as opposed to 30 min for all the other carbonyl compounds), the reaction mixture still contained white particles of the aldehyde, suggesting that paraformaldehyde dissolves slowly in THF and the rate of solubility might be a

limiting factor. In the first attempt with paraformaldehyde, the reaction time was 3 h, but this did not improve the yield (31% and 13%, respectively).

Compounds **8c** and **8f** were not isolated as pure compounds, but as mixtures with the starting material due to similar R_f values on the TLC plates. An estimation of the relative integration values in the ^{1}H-NMR spectra were made to give an approximate yield. In the spectrum in Scheme 2.15, the only signal from the starting material not overlapping with signals from the product, is the signal around 2.25 thought to be from the hydroxyl proton (see ^{1}H-NMR spectrum of **7** in appendix). It is generally not preferred to use hydroxyl protons for calculations based on integral values, but as the signal integrates to nearly 1 in the ^{1}H-NMR spectrum, and the estimation of the yield of **8c** is only an approximate value, it is deemed to be sufficient. The signal *b* has been compared to the signal at 2.25, and the yield of **8c** is estimated to 78%. Similarly for compound **8f**, the spectrum in Scheme 2.29 shows as signal from **7** at approximately 3.93 which is the signal from the hydrogen attached to the hydroxyl-bearing carbon atom (see ^{1}H-NMR spectrum of **7** in appendix). The signal *a* in Scheme 2.29 has been compared to the signal at 3.93, and the yield of **8f** is estimated to 62%.

Methode C gave poor to moderate yields of **8**. The sodium hydride was a 60% dispersion in mineral oil. The reaction was first attempted without removing the oil, and even though the colour of the reaction mixture changed to yellow after addition of NaH, only recovered starting material was obtained. This suggests that none of the NaH reacted with the alcohol, and that the subsequent addition of *n*-BuLi only abstracted the hydroxyl proton. When the oil was removed repeated hexane washings, the colour of the reaction mixture changed to yellow 10 minutes after the addition of NaH, and to a yellowish pink after 20 minutes. This colour lasted under the addition of aldehyde or ketone and until the reaction mixture was quenched with saturated aqueous NH_4Cl, when the organic phase became strongly yellow. NaH was allowed a reaction time of 1.5 h as this was the reaction time used by Brimble *et al*. for abstraction of hydroxyl proton under very similar conditions.[22]

Method A was the first to be attempted, and was carried out with ethanol only. The reaction was run twice, and in both cases only a small amount of product was formed (6% in the second attempt and <13% in the first (contains some impurities)) and a considerable amount of starting material was obtained (66-67%). Ide and Nakata[23] found that HMPA was needed as a co-solvent for anion generation in the reaction of *n*-BuLi in THF with 2-substituted dithiane at -78 °C. At 0 °C however, the use of *n*-BuLi without co-solvent gave a 79% exchange of H with D after quenching with D_2O.[23] It has been suggested that in polyfunctionalized molecules, encapsulation of the lithiated dithiane is responsible for the lack of reaction when HMPA is not present.[1]

2.2.2   Assignment of ^{1}H-NMR spectra

The assignment of the different NMR signals was a challenge, but the proton signals were possible to assign based on observation of the multiplicities and COSY-H,H spectra. For the carbon spectra the signals are only reported as being from primary, secondary, tertiary, or quaternary carbon atoms as two-dimensional HSQC (heteronuclear single quantum coherence) was not run.

All the compounds (**8a**-**f**) contain a carbon chain with at least two bulky substituents (the diethoxy group and the sulphur-containing ring). Consequently, each compound is therefore a mixture of interconverting rotamers,[24] as depicted in Scheme 2.9.
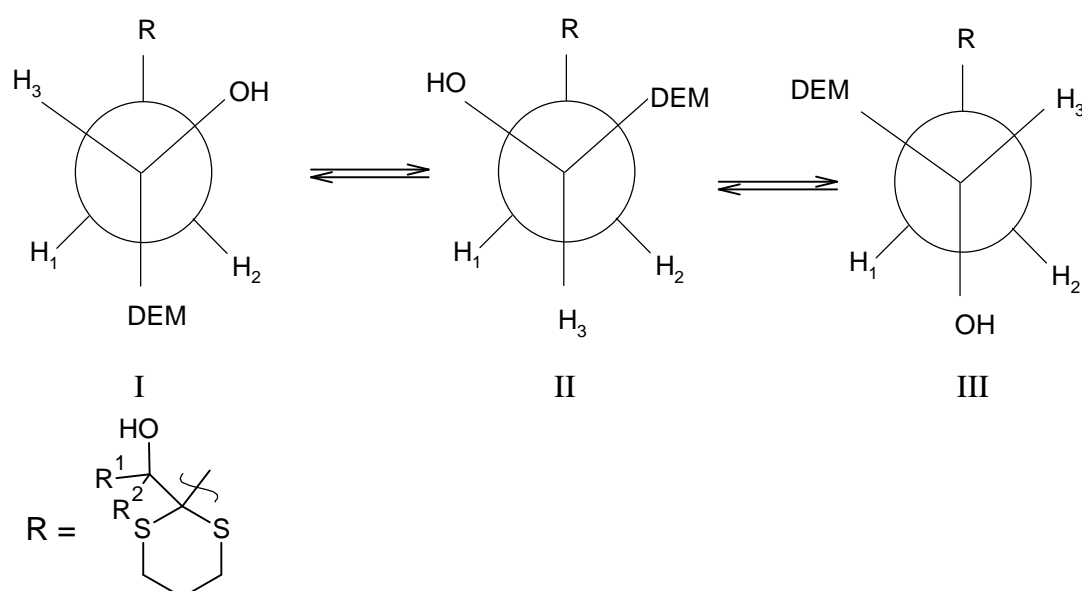
Scheme 2.9: *Newman projection of one C-C bond in compounds* **8**. *One of the enantiomers is depicted.*

In order to show that hydrogens 1 and 2 are non-equivalent, the chemical shifts appearing from the shielding of the nearest and second nearest neighbours of hydrogens 1 and 2 in the different rotational isomers are listed.

H_1:   DEM,H/H,R (δ_1)   H,H/OH,R (δ_2)   OH,H/DEM,R (δ_3)

H_2:   DEM,H/OH,R (δ_4)   H,H/DEM,R (δ_5)   OH,H/H,R (δ_6)

All six environments are different. The chemical shifts of each of the hydrogens will be averaged out due to fast rotation around the C-C bond. The average chemical shifts will be:

$$\bar{\delta}_{H_1} = x_I \delta_1 + x_{II} \delta_2 + x_{III} \delta_3$$

(Eq. 2.1)

$$\bar{\delta}_{H_2} = x_I \delta_4 + x_{II} \delta_5 + x_{III} \delta_6$$

(Eq. 2.2)

x_I, x_{II}, and x_{III} are the mole fractions appearing in each rotational isomer at any time taking into account the relative probabilities of the three rotational isomers I-III. The chemical shift of the two hydrogens will not be equal unless they coincide accidentally.[24] The other enantiomer (swap OH and H_3) will transform δ_1 to δ_4, δ_2 to δ_6, and δ_3 to δ_5, which just means that the chemical shifts of H_1 and H_2 will swap places. This also holds true for compound **7**.

As three of the compounds, i.e. **8a**, **b**, and, **c**, are diastereomers, the spectra will appear more complex for those.

As the compound **8** contain at least two large, bulky groups, the opportunity to rotate freely around the C-C bond in the centre of the Newman projection, as seen in Scheme 2.10, must be very limited. This will also contribute to the complexity of the spectra.
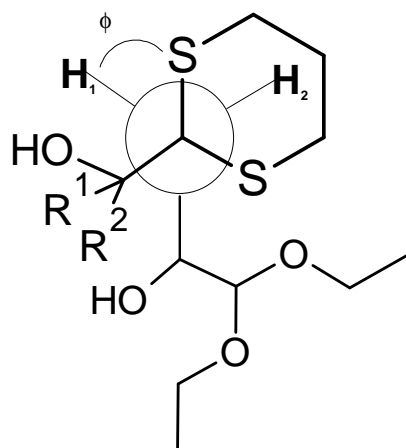
Scheme 2.10: Newman projection of another C-C bond in compounds **8**. (φ = dihedral angle between two substituents on different carbon atoms)

The carbon atom bonded to the two ethoxy groups is a pro-chiral centre, meaning that if the two ethoxy groups rotate differently, the carbon atom will be chiral for a short time, making the two ethoxy groups temporarily non-equivalent. This is seen from the rather complex double multiplets the methylene protons of the ethoxy groups give rise to (see ^{1}H-NMR spectra of compounds **5-7** in the appendix).

In the ¹H-NMR spectrum of compound **8a** in Scheme 2.11, the proton signals have been assigned.
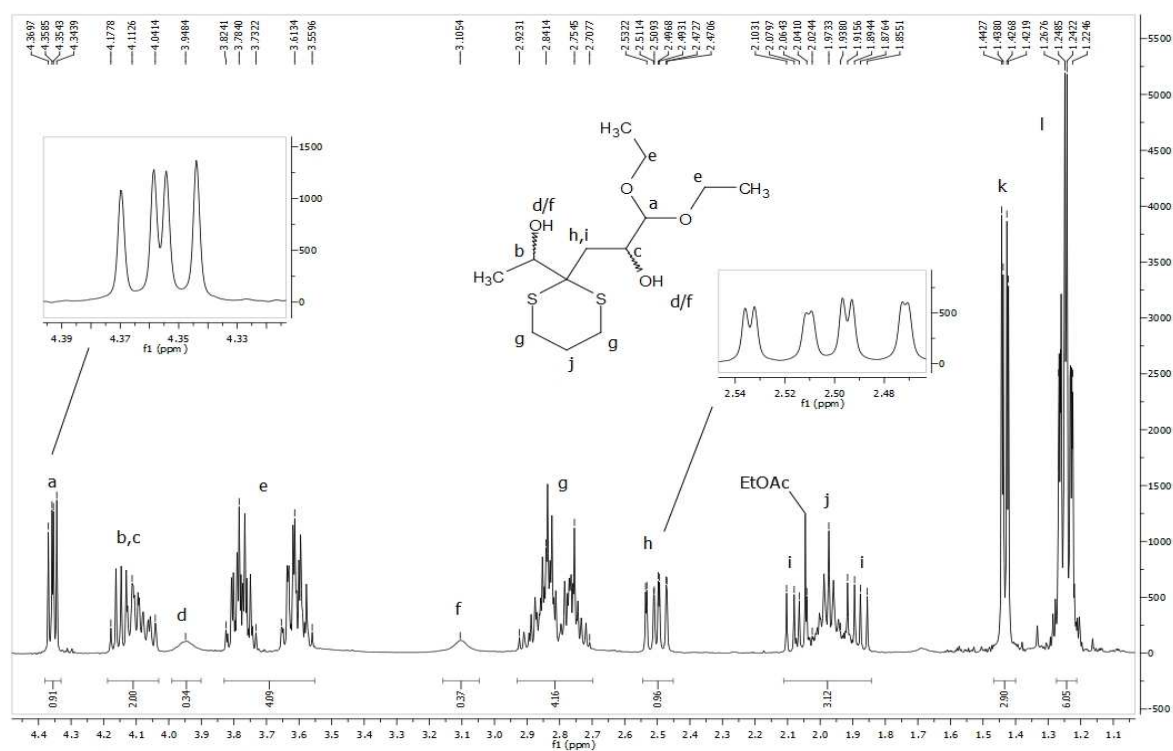
Scheme 2.11: *¹H-NMR spectrum of compound **8a**.*

The basis of this assignment was the COSY-H,H spectrum in Scheme 2.12.
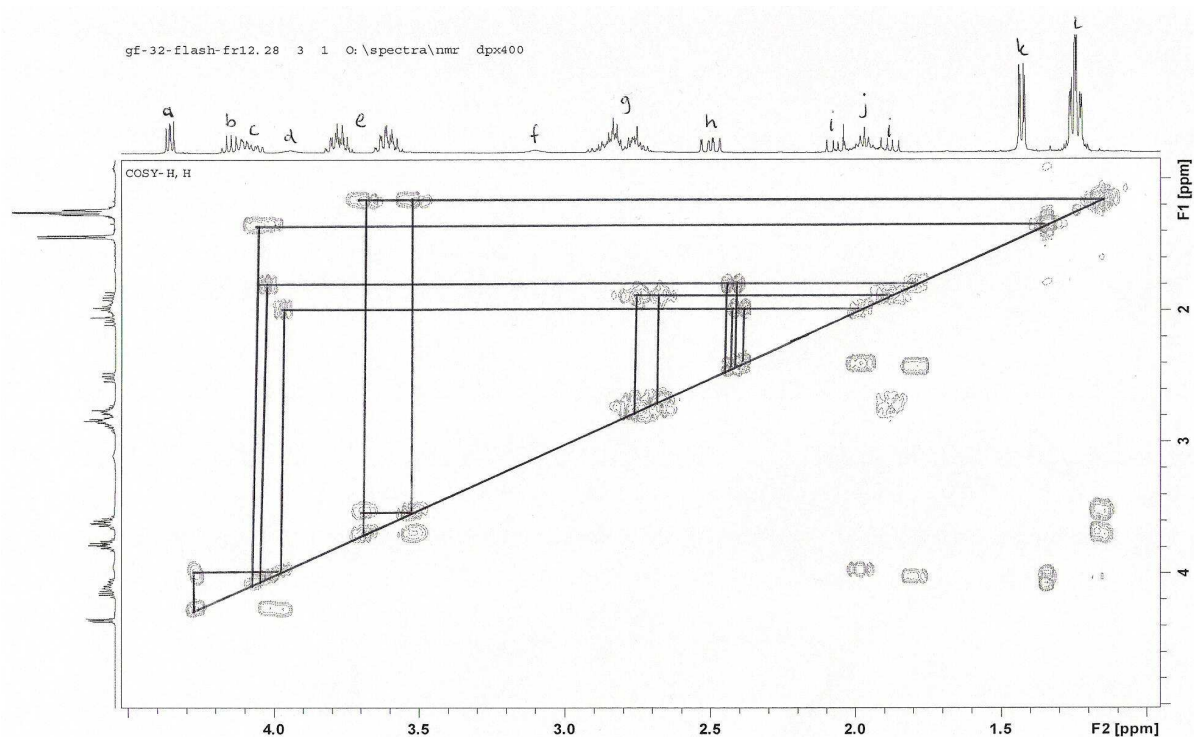
Scheme 2.12: *COSY-H,H spectrum of compound **8a**.*

It is quite clear which hydrogen atoms are giving which signals as signals *e*, *g*, *j*, and *l* are known from the spectra from compounds **5**-**7** (see appendix), the two broad signals which do not couple with any other hydrogen must be the hydroxyl hydrogens, and positive assignment of hydrogens *k* give hydrogen *b*. This leaves hydrogens *a*, *c*, *h*, and *i*. The assumption that the hydrogen atom bonded to the carbon atom with the two ethoxy groups appears at the highest chemical shift leads to a plausible assignment of the rest of the hydrogens. The same pattern of signals and coupling is seen for all the compounds **8**, aiding the assignment of the hydrogens for the other compounds.

As expected, the hydrogens *h* and *i* exhibit quite different chemical shifts. The correlation signals between the two hydrogens show that they pair up: The signal from *i* furthest upfield couples with the signals 1 and 3 from *h* (signal 1 being the one furthest downfield, *J* = 15.7 Hz), and the signal from *i* furthest downfield couples with the signals 2 and 4 from *h* (*J* = 15.5 Hz). Each of the signals from hydrogen *i* also show correlation to different parts of the signal from hydrogen *c*. It appears that each of these groupings of signals come from different diastereomers. Hydrogen *h* couples to *c* with *J* = 1.5 and 0.8 Hz, and hydrogen *i* couples to *c* with *J* = 9.4 and 8.5 Hz, depending on the diastereomer (see experimental section for values). The trend is seen even more clearly in the COSY-H,H spectrum from compound **8b** (see appendix).

As seen from the COSY-H,H spectrum in Scheme 2.12, the correlation signal between hydrogens *c* and *h* is missing. This might be explained by assuming that the preferred conformation of the compounds is such that the dihedral angle between the two hydrogens is close to 90°, and that the coupling constant therefore is very small, as seen above. ^3J = 0 means that there will be no polarization transfer between the two hydrogens during the COSY pulse sequence, and hence no correlation signal.[24] Scaling up the intensities in the correlation spectrum gave a hint of signal.

Scheme 2.13 shows the assignment of the hydrogens belonging to compound **8b.**
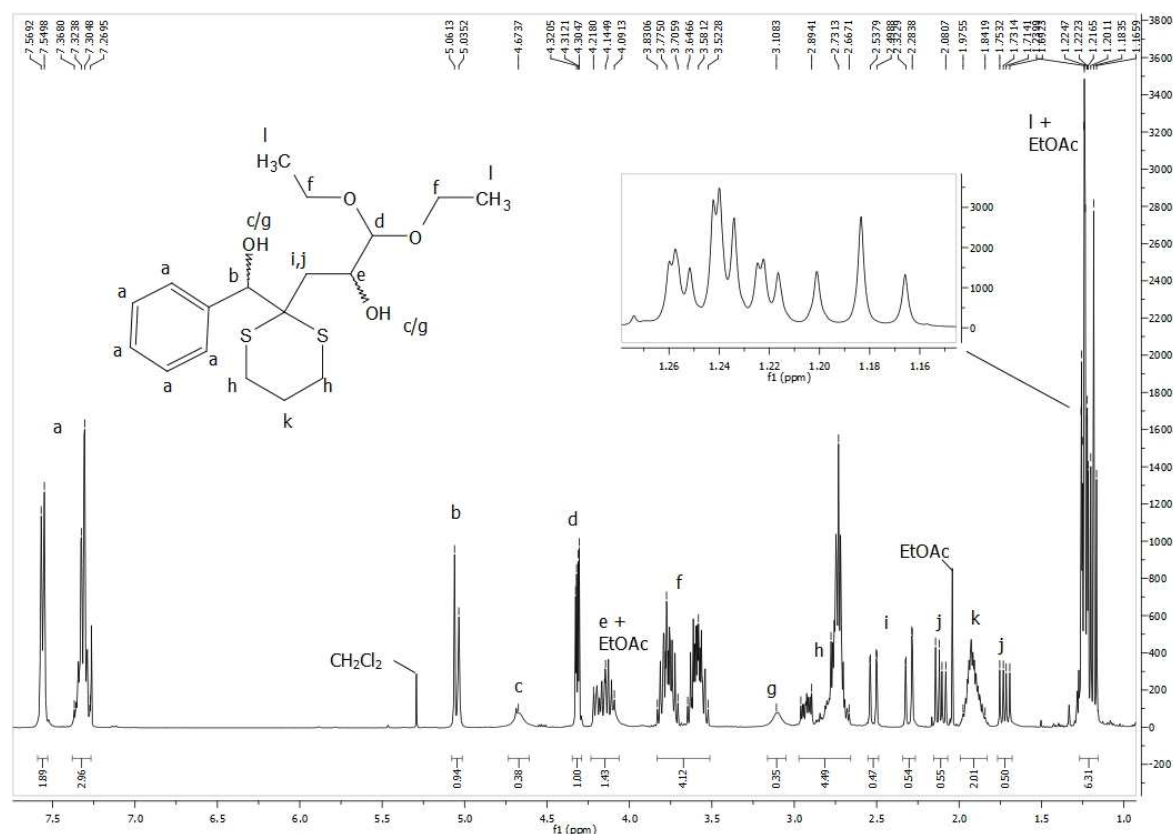
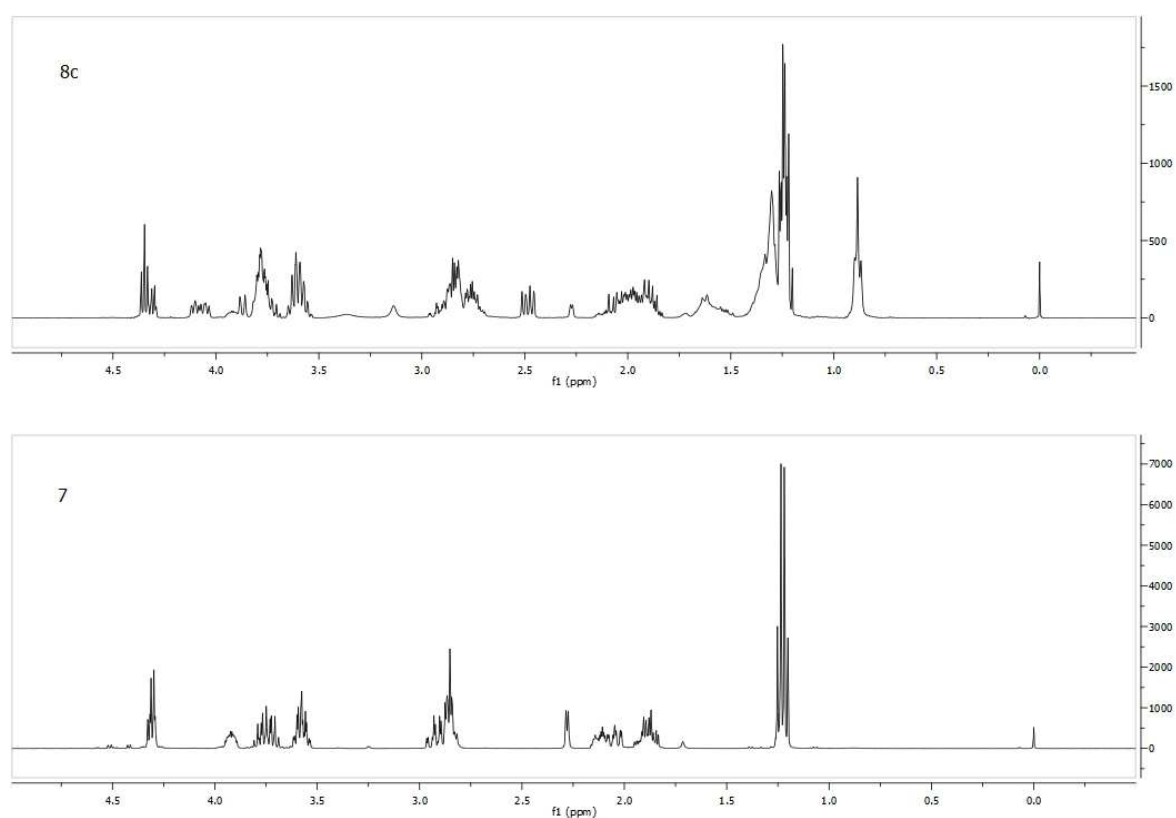

Scheme 2.13: *^{1}H-NMR spectrum of compound 8b.*

All the five aromatic hydrogens are assigned to the same letter, but as there are two rather separate regions integrating to two and three hydrogens, and since alkyl substituents on the ring tend to shift the hydrogens in the *ortho* and *para* positions further upfield than the hydrogens in the *meta* position,[24] it can be assumed that the two hydrogens giving the signals furthest downfield are the two in the *meta* position to the alkyl substituent, and that the three remaining hydrogens give the signal upfield.

Hydrogens *d, e, f, h, i, j, k,* and *l* are assigned as for compound **8a**. The broad signals *c* and *g* are assumed to be the hydroxyl protons. The hydrogen in the benzylic position does not couple with any other hydrogen, and the proximity to the aromatic ring gives the signal furthest downfield of the non-aromatic signals as two overlapping singlets (*b*). The methyl protons (*l*) appear as four overlapping triplets.

The COSY-H,H-spectrum (see appendix) indicate, as was seen for compound **8a**, that the signals from hydrogens *e, i,* and *j* appear in two groups. For compound **8b**, the coupling between hydrogens *e* and *i* is clearer than for compound **8a**, though the signal is still weak. Of the signals from hydrogens *i* and

j, the two signals in the middle (2.30 and 2.11), each integrate to approximately 0.54 (0.54 and 0.55), and the two on the sides (2.52 and 1.72) integrate to approximately 0.48 (0.47 and 0.50). This gives a 1.1:1.0 ratio of diastereomers. However, the doublet from hydrogen *b* gives a 1.0:1.0 ratio, so it is likely that the diastereomers exist in an approximately 1:1 ratio.

The hydrogen signals from compound **8c** were especially difficult to interpret, especially since the compound was not obtained as a pure product, but as a mixture of the product and starting material **7**. A comparison between the hydrogen spectrum of the product mixture and the starting material is shown in Scheme 2.14.

Scheme 2.14: *Comparison of the ^{1}H-NMR spectra of compounds **7** and product mixture after addition to heptaldehyde.*

Some of the signals from the starting material stand out, while others partly overlap with the signals from compound **8c**. Assignment of the hydrogen signals from compound **8c** is depicted in Scheme 2.15.

Int.:   1   1   5   1   1   4   1   3   2   14   3
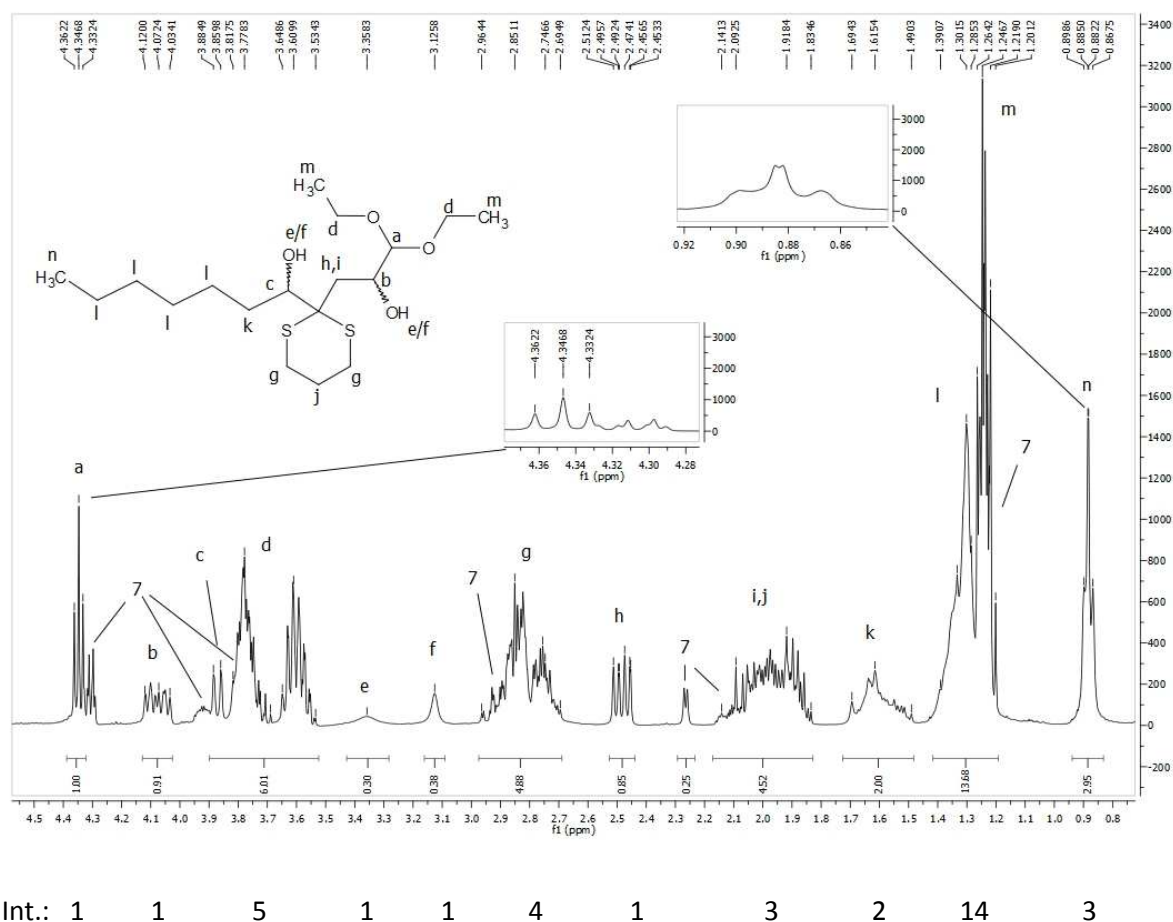
**Scheme 2.15:** [1]*H-NMR spectrum of a mixture of compounds* **7** *and* **8c**.

Several of the integrals show higher values than the assignment of the protons would indicate. The expected integrals based on the assignment are shown under the spectrum in Scheme 2.15.

Signals *a*, *b*, *h*, and *i*, *d* and *m*, and *g* and *j* are assigned as for the compounds **8a** and **8b**. Signals *n* were easy to distinguish, and the coupling to signals *l* is clear from the COSY-H,H spectrum (see appendix). The ^{1}H-NMR spectrum of heptanal was obtained from the Spectral Database of Organic Compounds[25] (^{1}H-NMR spectrum of 1-heptanol was not available), and was used to assign the signals *k*, and to ascertain the number of hydrogens making up signal *l*. From the COSY-H,H spectrum there is a weak signal of *k* coupling to *c*, so even though signals *c + d* integrates to approximately 6 hydrogen atoms, it is assumed that the signals are due to 5 hydrogen atoms in the compound **8c**, and that the higher value is due to overlapping signal from the starting material. There is a weak signal in the COSY-H,H spectrum that can only be seen when increasing the signal intensities, and that is assumed to arise from the coupling of the last two of the hydrogens *l* with hydrogen *k*. .

The signal from hydrogens *n* is highlighted in Scheme 2.15. It appears that the signal might consist of two overlapping triplets, but this is difficult to ascertain. The three protons in the methyl group

should appear as a triplet due to the two neighbouring hydrogens, and two overlapping triplets could be a result of the fact that the compound exists as diastereomers. The uncertainty gives rise to assigning the signal as a multiplet. Also, the methyl carbon gives only one signal in the ^{13}C-NMR spectrum, see below.

The carbon spectrum of the product mixture consists of a multitude of signals. Scheme 2.16 shows a comparison between the carbon spectrum of the starting material and the product mixture.
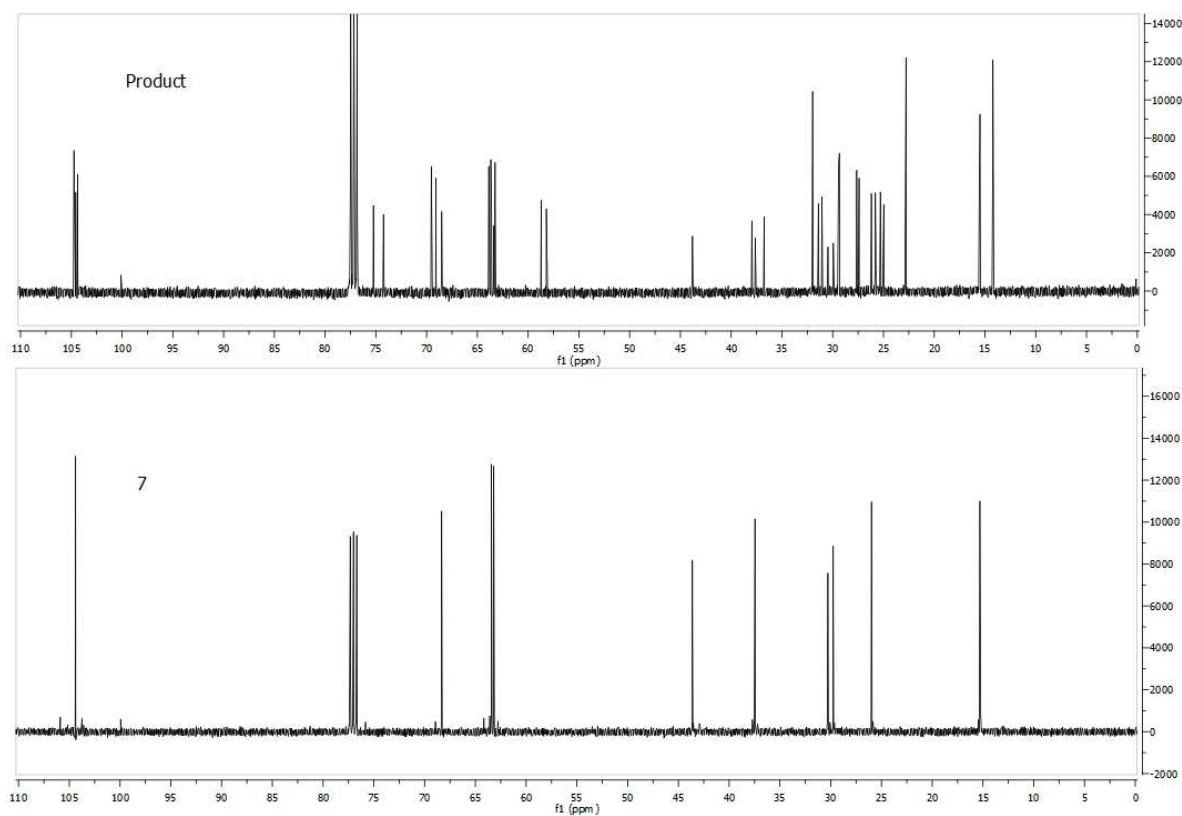

*Scheme 2.16: Comparison of the ^{13}C-NMR spectra of compound **7** and the product after addition to heptaldehyde.*

When the signals from the starting material are subtracted from the product spectrum, the signals arising from compound **8c** are obtained.
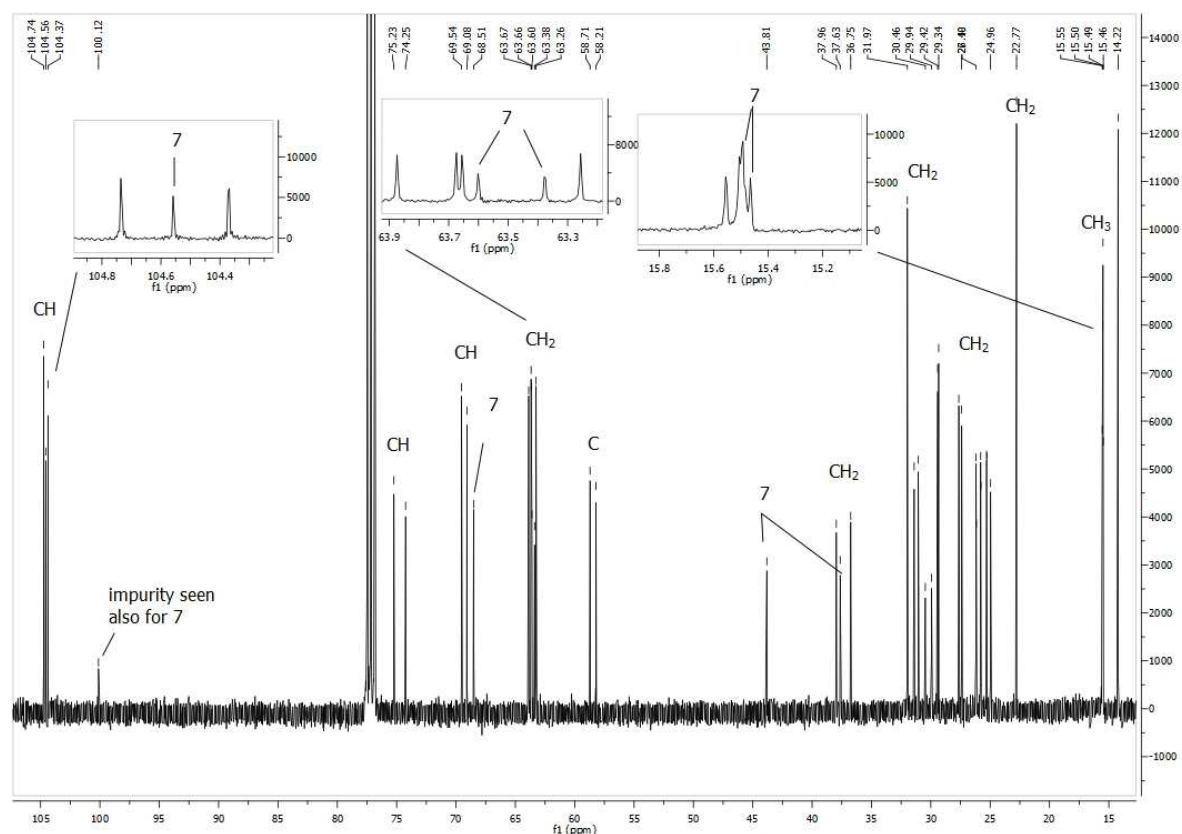
Scheme 2.17: ^{13}C-NMR spectrum of a mixture of compounds **7** and **8c**.

The area 20-35 ppm is shown separately in Scheme 2.18, as it contains a large number of peaks.
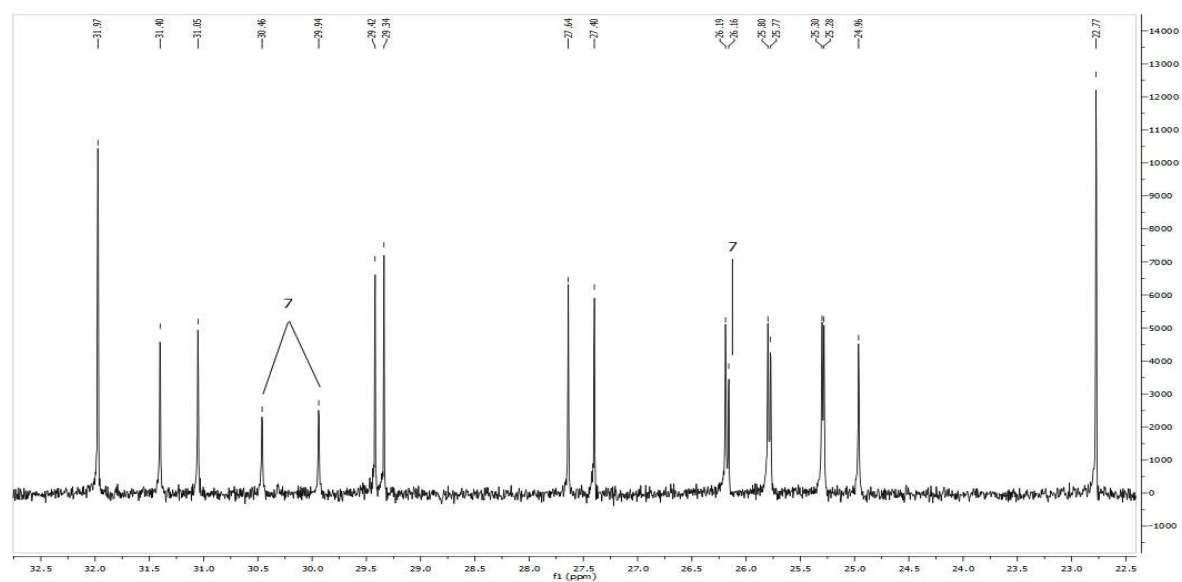
Scheme 2.18: ^{13}C-NMR spectrum of a mixture of compounds **7** and **8c** showing the area 20-35 ppm.

The compound **8c** gives rise to 30 carbon signals, and most of them seem to pair up. As there are 18 carbons in the compound, the numbers will add up if six of them give one signal, and twelve give two signals. All the three methyl groups give rise to only one signal each.


Hexane:ethyl acetate 60:40:

R_f = 0.48, compound **8c**

R_f = 0.42, starting material
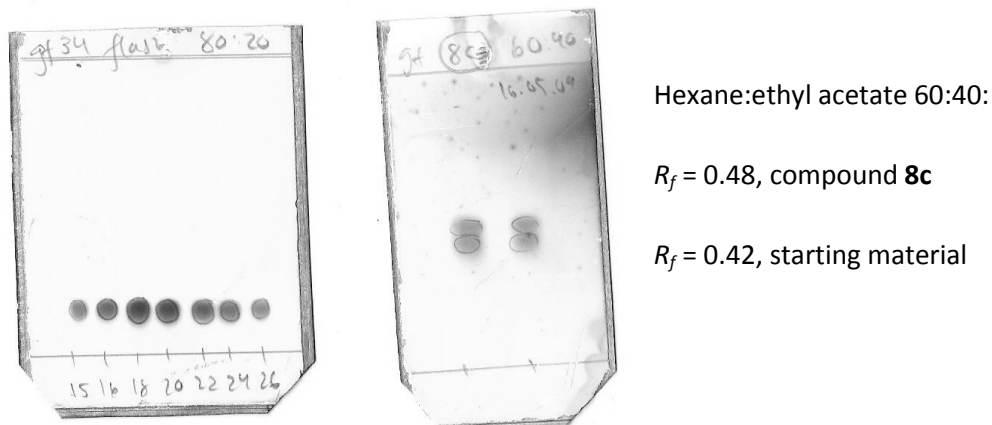
Scheme 2.19: *TLC plate from flash chromatography (to the left) and of the product mixture after addition to heptaldehyde (to the right).*

Scheme 2.19 shows two TLC plates, the first one is from monitoring the course of the flash chromatography using hexane:ethyl acetate (80:20), the second is of the product using a 60:40 mixture. The R_f values are so similar that the two compounds could not be separated on the column. The TLC on the left shows the shift from eluting the product to eluting the starting material. As the difference in R_f values is even smaller for the 80:20 mixture than for the 60:40 mixture, it is difficult to say when the starting material actually starts being eluted from the column.

One interesting point here is that the product, the diol, has a lower retention on the TLC plate than the starting material, an alcohol. For the other compounds **8**, the product has a higher retention than the starting material and was eluted last from the column. In the case of compound **8c**, the large, hydrophobic *n*-hexyl group might lead to a lower retention and higher R_f value.
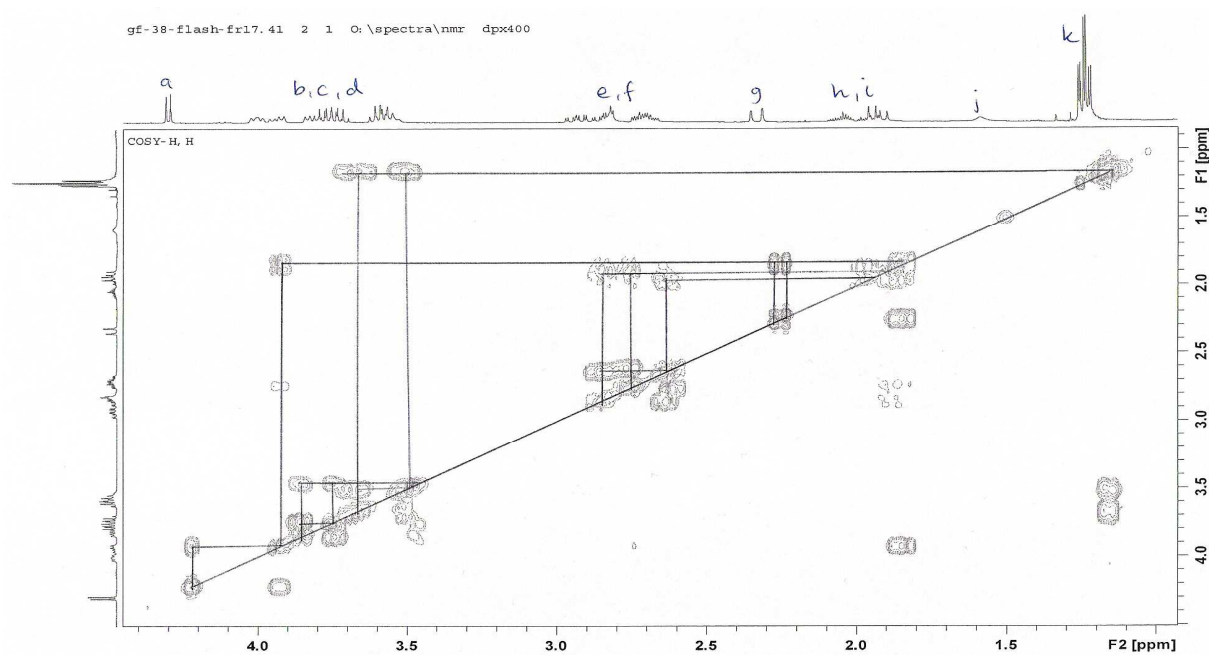
Compounds **8d**, **8e**, and **8f** are not diastereomers as the R^1 and R^2 groups are equivalent.

The assignment of the hydrogen signals in compound **8d** is shown in Scheme 2.20.
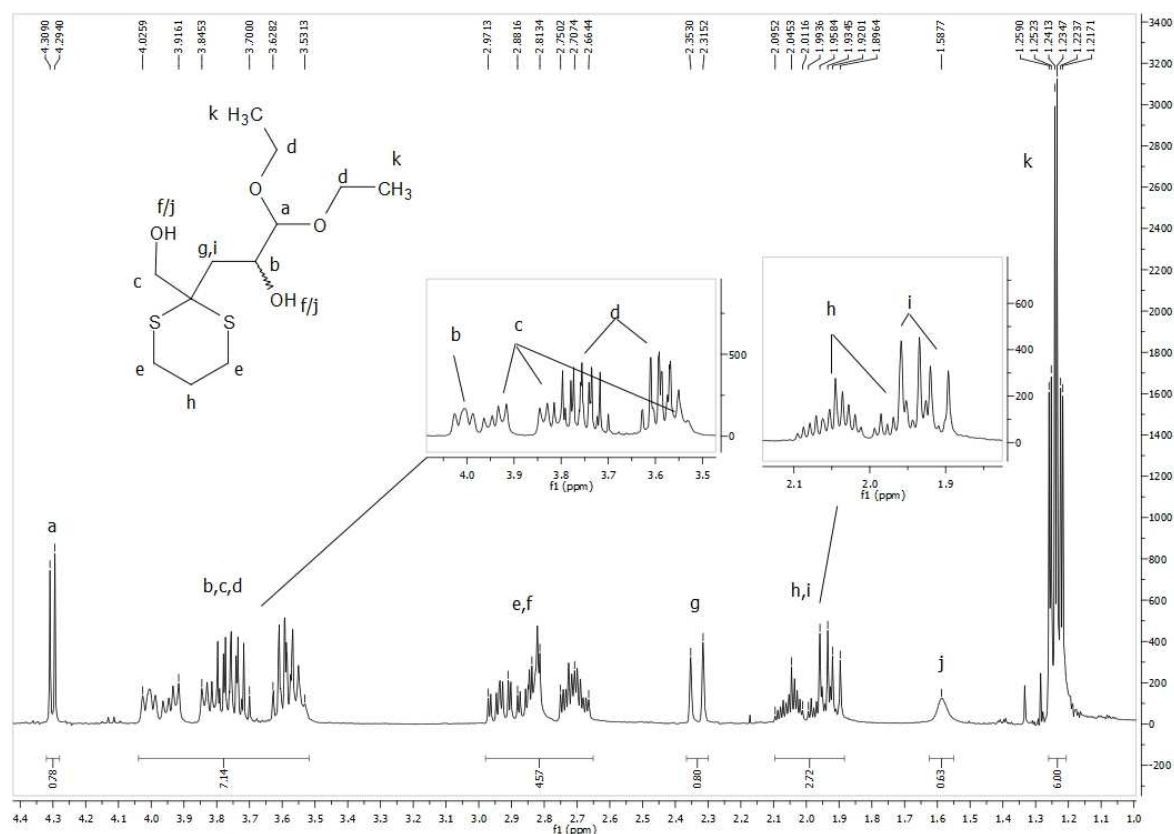
Scheme 2.20: *¹H-NMR spectrum of compound **8d** containing starting material.*

The basis of the assignment is the COSY-H,H spectrum in Scheme 2.21.

Scheme 2.21: *COSY-H,H spectrum of compound **8d** containing starting material.*

Schemes 2.20 and 2.21 show that even though **8d** has only one chiral centre, the signals from hydrogens *g* and *i* are quite far apart, as expected based on the different environments around the two hydrogens, and that hydrogens *c* are present as two, or possibly more, multiplets.

For the carbon atoms, however, there is only one signal from each carbon in the ^{13}C-NMR spectrum, as seen in Scheme 2.22. This is consistent with the fact that the compound does not exist as diastereomers. The signal at 100.1 is marked with a question mark and is thought to arise from some small impurity in the starting material.
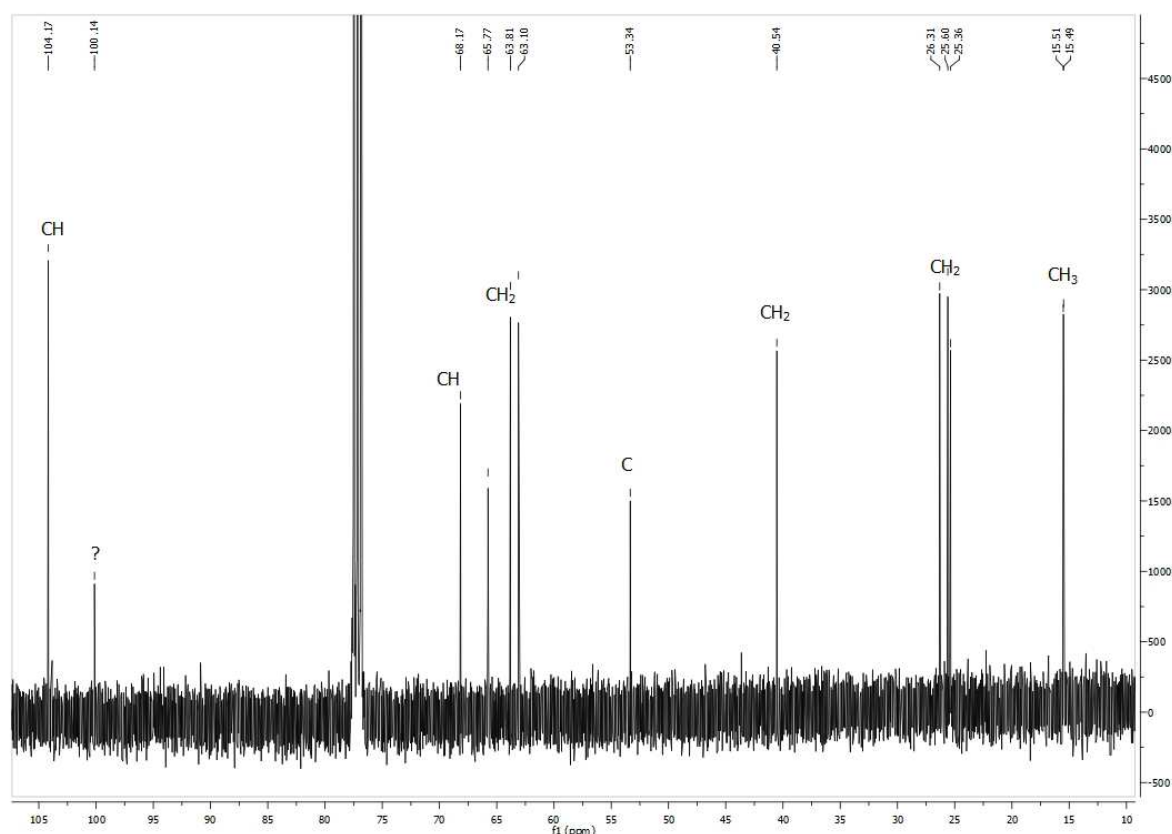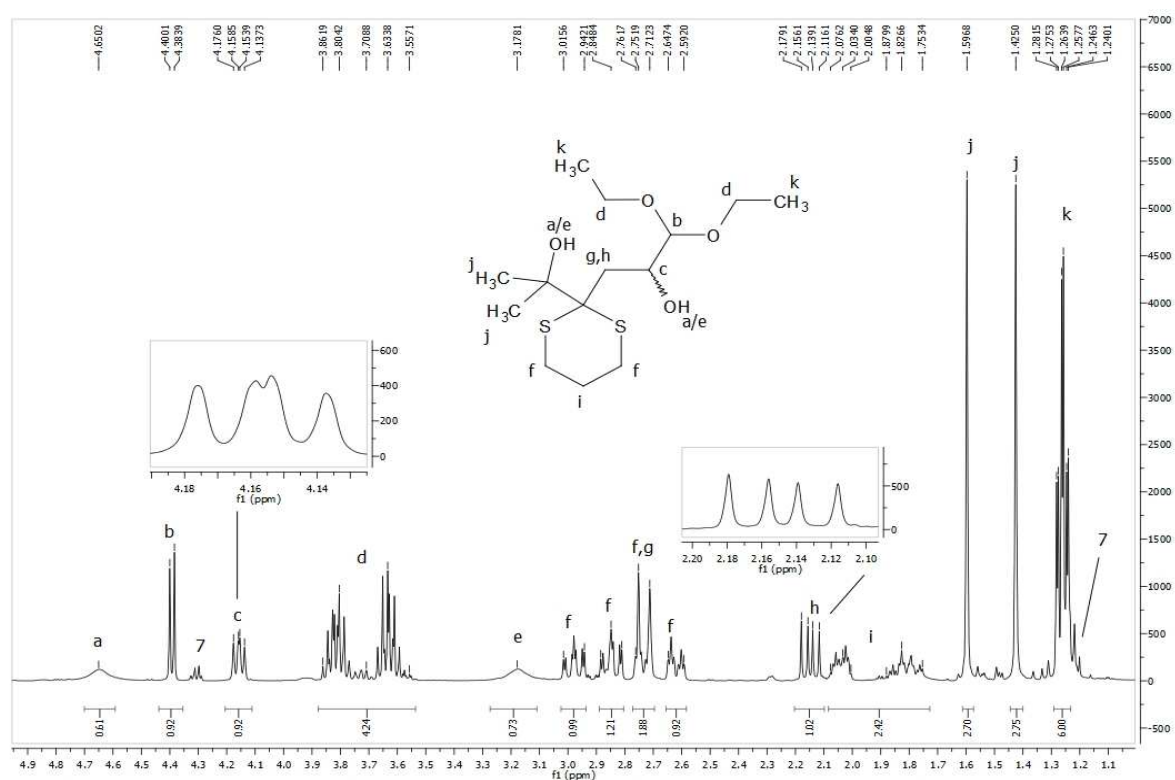

Scheme 2.22: *^{13}C-NMR spectrum of compound **8d**.*

The ^{1}H-NMR spectrum of compound **8e** shows small impurities from the starting material. Monitoring the flash chromatography by TLC showed that the separation was not perfect, and the fractions containing both compounds could probably have been purified by running a second flash. This was not done, as the impurities in the spectra of the compound were not identified until all laboratory work had been completed.
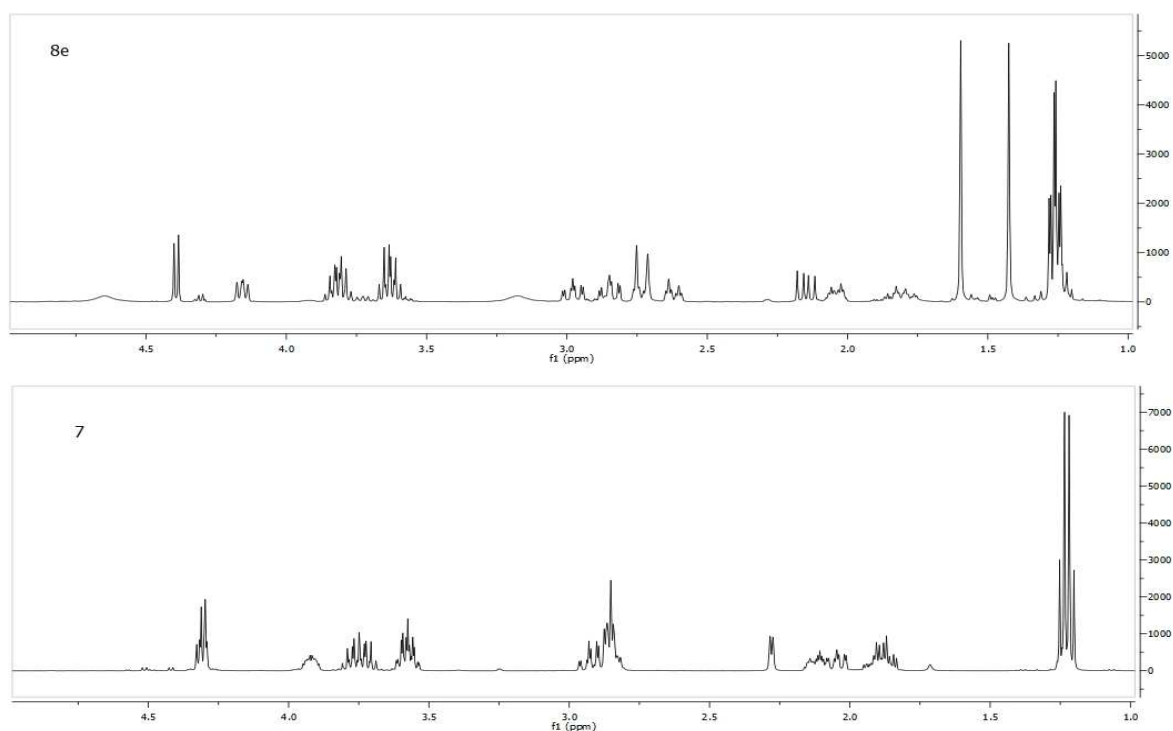
Scheme 2.23: *Comparison of the ^{1}H-NMR spectra of compound **7** and the product after addition to acetone.*

The assignment of the hydrogen signals for compound **8e** is shown in Scheme 2.24.
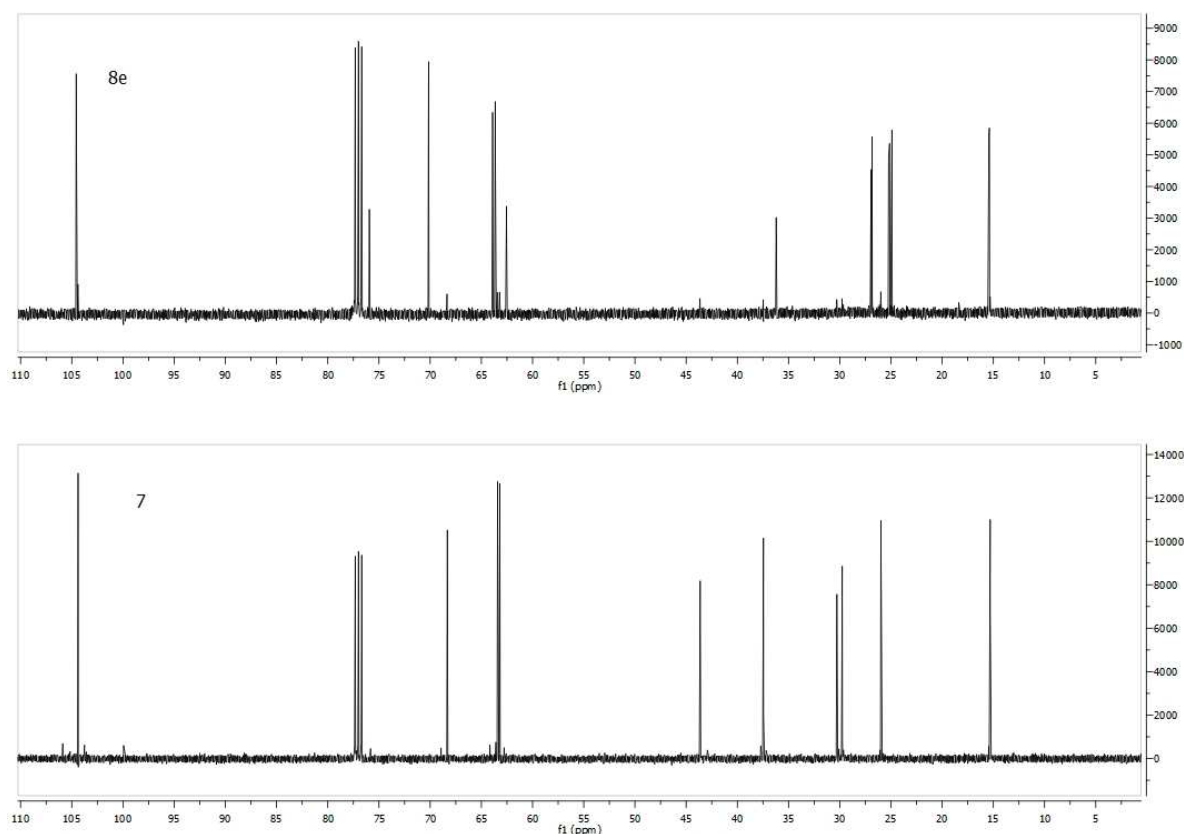

Scheme 2.24: *^{1}H-NMR spectrum of compound **8e**.*

One noteworthy feature about this hydrogen spectrum is the appearance of the signals from the hydrogens on the dithiane ring. The two hydrogens in the 5-position (*i*) give rise to two large multiplets at around 1.9. The four hydrogens in the 4- and 6-position (*f*) all give separate signals in the spectrum, one overlapping with the signal from hydrogen *g*. In the hydrogen spectra for compounds **8a-d**, the four hydrogens in the 4- and 6-position have given rise to complex multiplets. The COSY-H,H spectrum (see appendix) shows that of the four signals, signals 1 and 3 are from hydrogens bonded to the same carbon, and signals 2 and 4 are from the hydrogens bonded to the other carbon atom.

Another interesting point is that the two methyl groups bonded to the quarternary carbon atom appear at quite different chemical shifts (1.60 and 1.43). The non-equivalence of the two methyl groups should be possible to explain by limited rotation around the C-C bond between the C-2 of the dithiane and the carbon bearing hydrogens *g* and *h*, as is seen from the Newman projection in Scheme 2.10.

The signal from hydrogen *c* appears to be a doublet of doublets. Hydrogen *c* has hydrogens *g* and *h*, and *b* on neighbouring carbon atoms and would be expected to give a doublet of triplets (dt) if hydrogens *g* and *h* were equivalent, or a doublet of doublets of doublets (ddd) when *g* and *h* were non-equivalent. The fact that the signal looks like a doublet of doublets might be explained by the dihedral angle, φ, between the two hydrogens being close to 90°, as mentioned above. One problem with the assignment as doublet of doublets, is that the coupling constants for the doublets do not match. The two signals on the left give J = 7.0 Hz, and the two signals on the right give J = 6.6 Hz. The coupling constant for hydrogen *b* is 6.5 Hz, so the doublet of doublets should arise from a doublet with the same coupling constant as *b* being split apart by one of the hydrogens *g* and *h* (J = 8.8 Hz). It is uncertain why the two doublets are different from each other.

A comparison of the carbon spectra of the starting material and the product also shows that the product contains small amounts of starting material.

Scheme 2.25: *Comparison of the ^{13}C-NMR spectra of compounds **7** and the product after addition to acetone.*

As can be seen in the experimental section and from the carbon spectrum (see appendix), only the fourteen signals with the largest intensities have been assigned to the carbon atoms in the molecule. The signals with smaller intensities come from the starting material, as can be seen in Scheme 2.25. As the signal intensities from compound **7** are quite small compared to the signals from compound **8e**, the amount of starting material in the product is reckoned to be small.

Compound **8f** has previously been synthesized by Valdersnes,[9] and the spectroscopic data agree to a large extent with those published. The product is however not pure, as there were three spots on the TLC plate that were not separated by flash chromatography. The melting point interval of the compound was very large, and the sample melted at a lower temperature than given in the literature,[9] clearly indicating that the product was not pure.
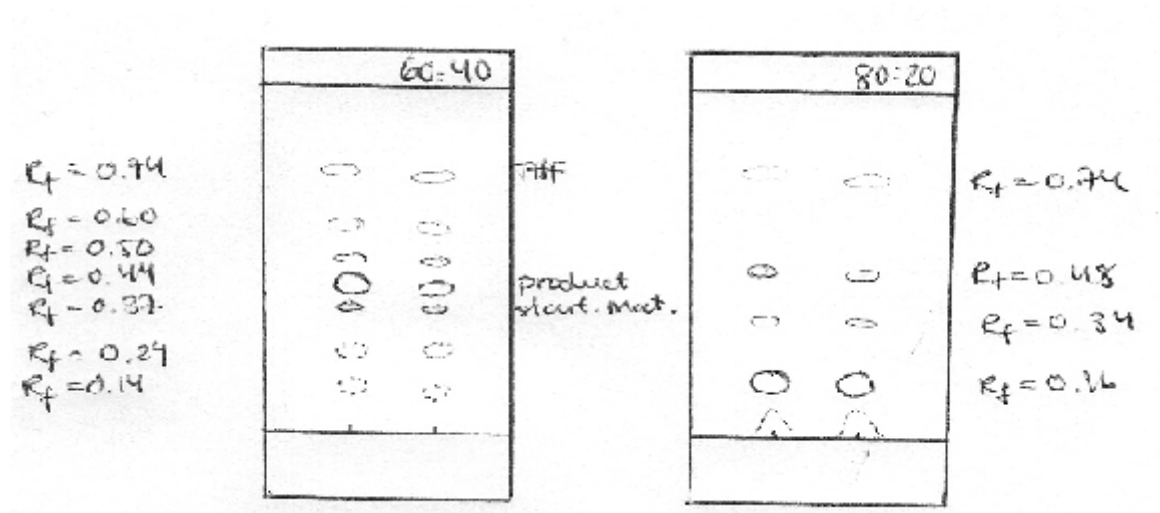
Scheme 2.26: TLC plates of the crude product of **8f**.

It is a bit uncertain which of the product or the starting material give the spots with R_f = 0.37 and 0.44, as the starting material obtains an R_f value of 0.37 in Scheme 2.5, and 0.42 in Scheme 2.19 using the same solvent system. The flash chromatography had to be run with hexane:ethyl acetate as a 80:20 mixture as eluent to be able to separate the product from the traces of compounds with higher R_f values, but unfortunately it was impossible to separate the product from the starting material and the unindentified compound with an R_f value of 0.50 in the 60:40-mixture. The three spots in the 60:40 mixture made one big spot in the 80:20 mixture, and the three compounds were eluted together from the column. A second flash could possibly have separated the compounds, but even for the 60:40 mixture the difference in R_f values between the compounds is not big enough to give a good separation, and the R_f values are so large that the compounds would most likely be eluted from the column together and early in the course. ^{1}H NMR was obtained for all the different fractions coming out of the column except for THF, but there were so many overlapping signals of low intensity compared to signals from the solvents that no useful information could be obtained from the spectra. The hydrogen spectrum of the fraction with R_f value 0.48 is shown in Scheme 2.27.
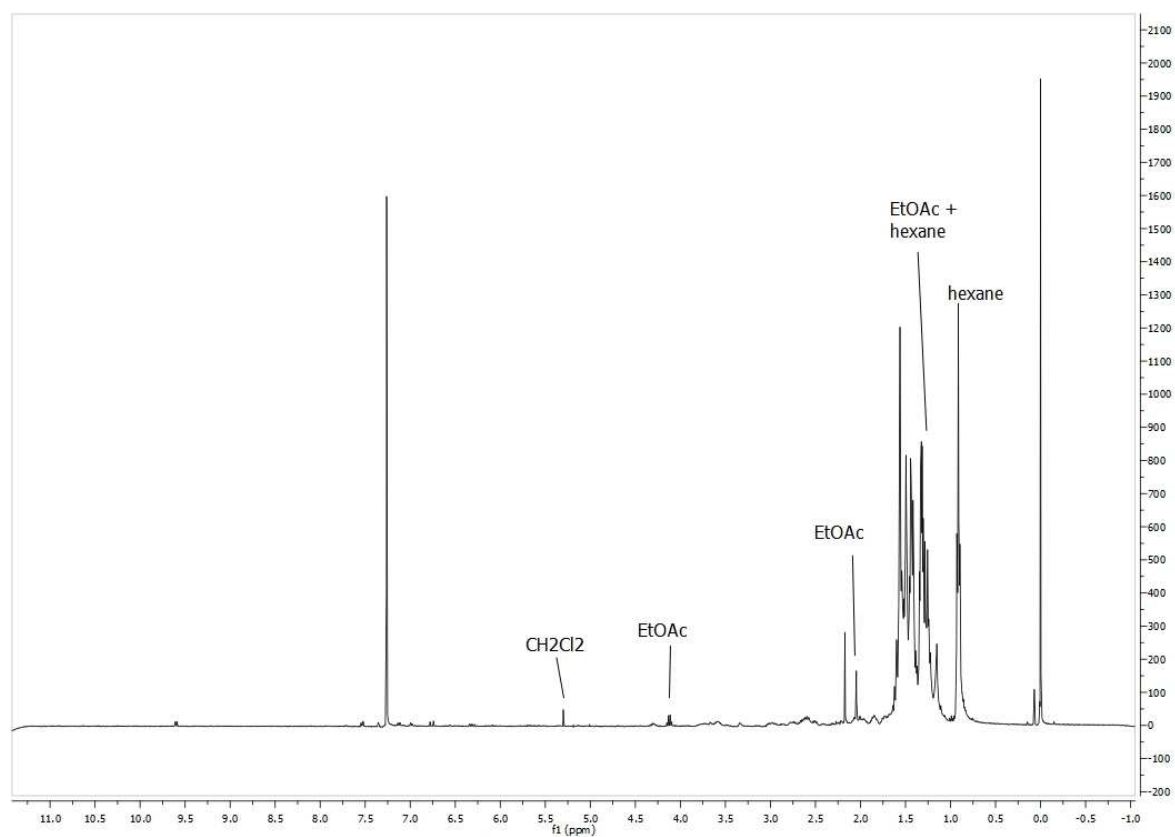
Scheme 2.27: ^{1}H-NMR spectrum of the first fraction to be eluted from the column when flashing the crude product of **8f**.

As can be seen in Scheme 2.28, the comparison of the hydrogen spectrum of the starting material with the one obtained from the product mixture clearly shows that the starting material is present in the sample.
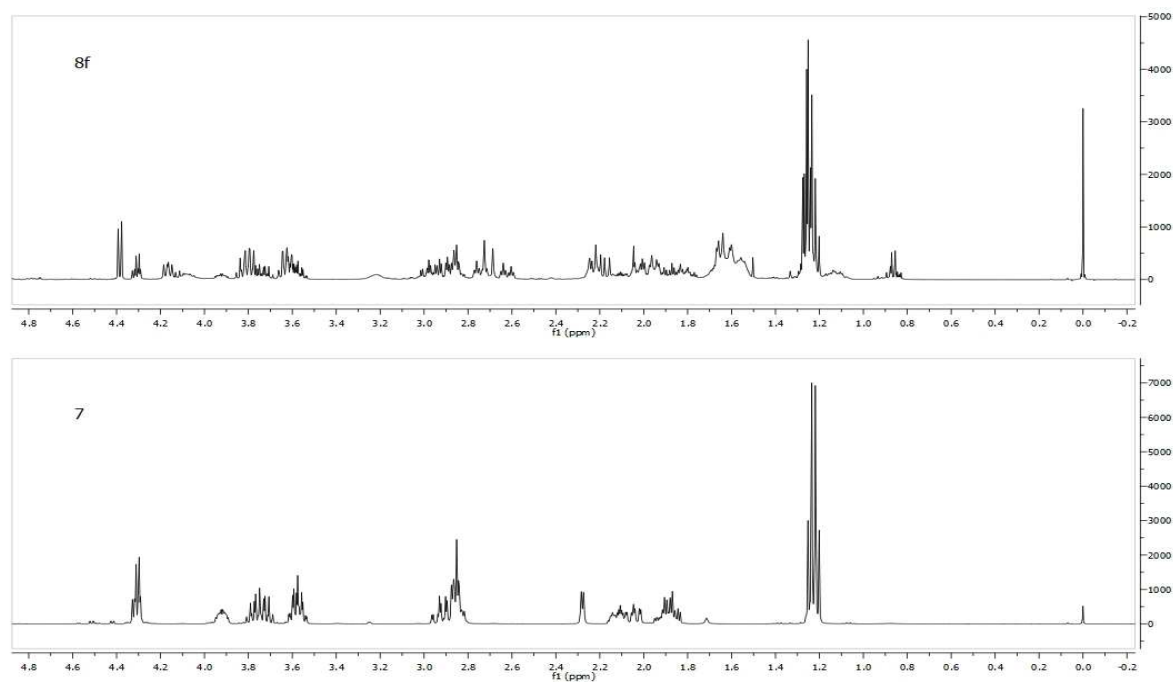
Scheme 2.28: *Comparison of* ^{1}*H-NMR spectra of compound* **7** *and after addition to cyclohexanone.*

Assignment of the hydrogens are shown in Scheme 2.29.
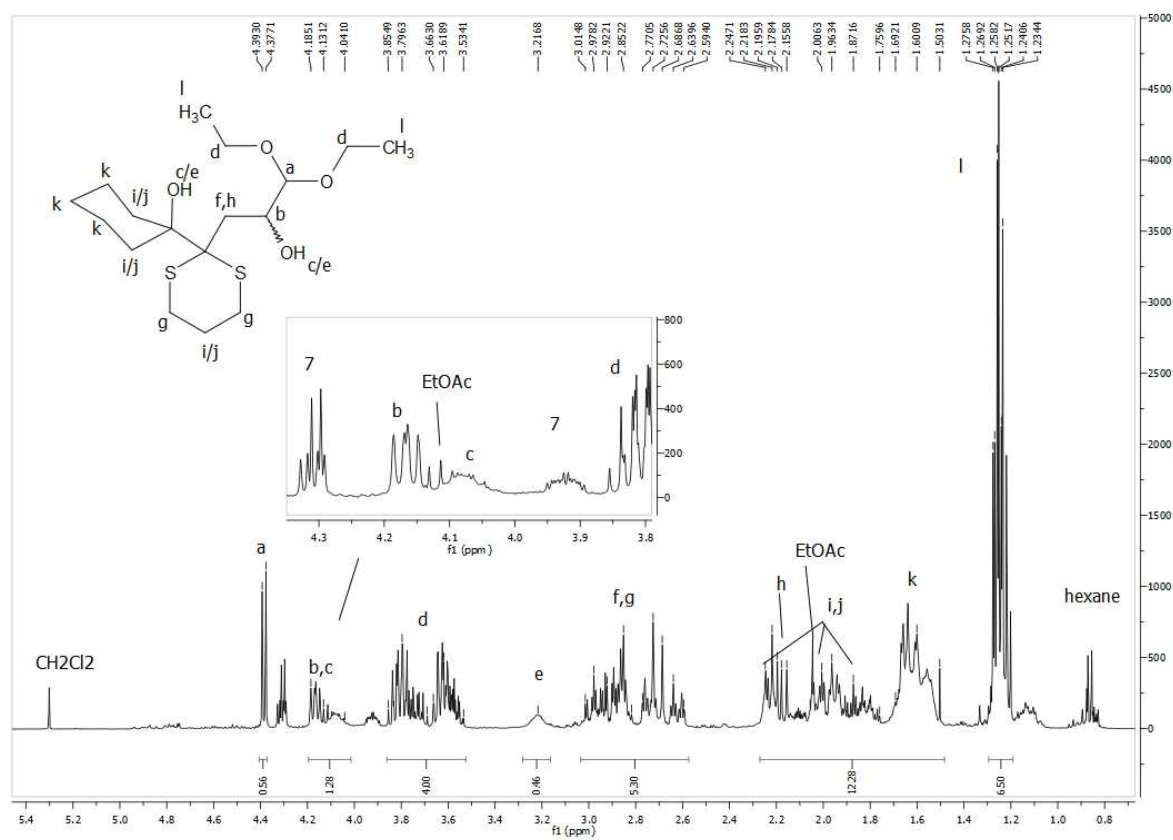
Scheme 2.29: ^{1}*H-NMR spectrum of product after addition to cyclohexanone.*

There is one difference in the assignment of the protons in Scheme 2.29 compared to the literature.[9] The signal *c* is not included in the literature, but is in Scheme 2.29 assigned to be one of the hydroxyl protons, and the interval 2.25-1.50 is assigned to 14 hydrogens in the literature, but only 13 in Scheme 2.29 as only hydrogen *h* appears in this interval, while hydrogen *f* appears in the interval 3.01-2.59. The signals were assigned based on the COSY-H,H spectrum (see appendix).

As for the carbon spectrum, the comparison between the spectra in Scheme 2.30 also shows that the starting material is present in the product.
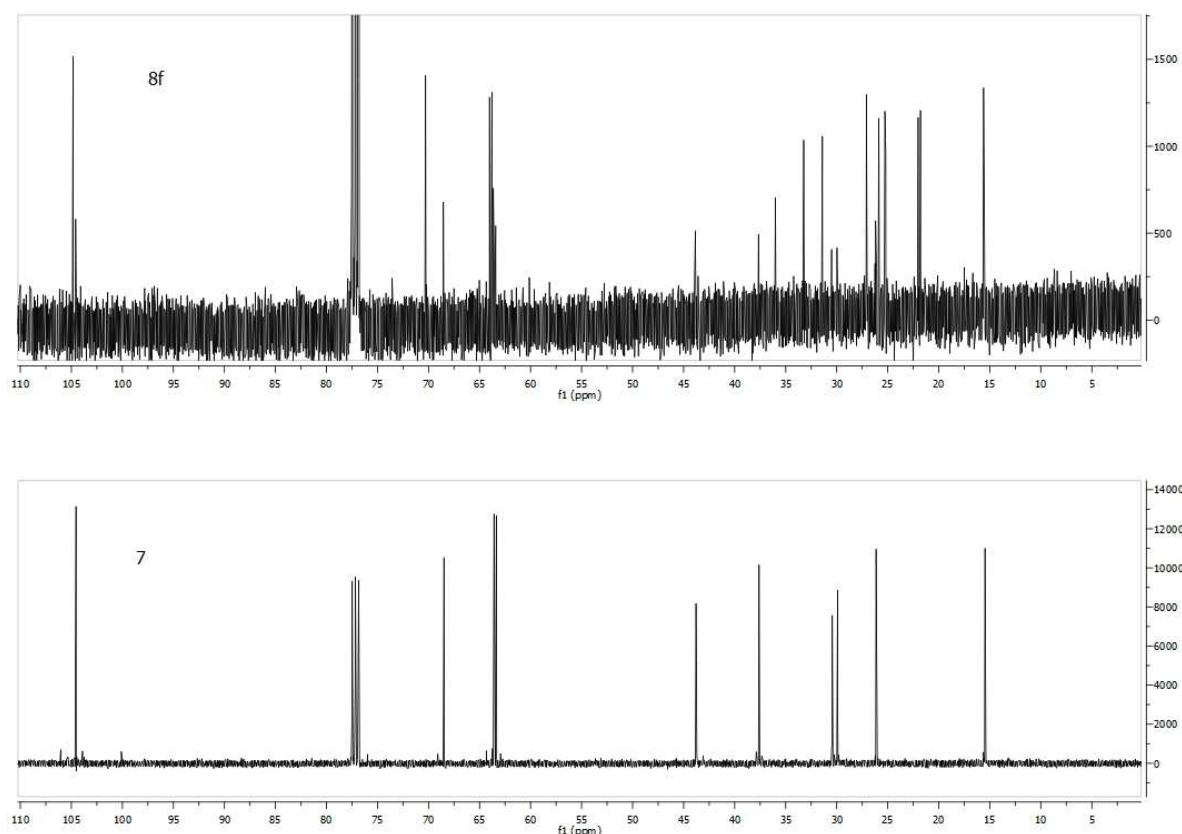
Scheme 2.30: *Comparison of the* ^{13}*C-NMR spectra of compound* ***7*** *and the product after addition to cyclohexanone.*

The other impurity in the product mixture does not seem to give any signals in the ^{1}H- and ^{13}C-NMR spectra, unless some of the signals coincide, and the compound is therefore thought to be present in only a small amount.

2.3   Further work

2.3.1   Reaction scale-up and purification

The reactions have only been run at a 0.8 mmol scale. Reaction scale-up should be performed both to ascertain whether the outcomes would be similar on a larger scale, and to be able to perform further reactions on the compounds **8a-f**. It would also be interesting to see if the use of NaH instead of one equivalent of *n*-BuLi could give comparable results to the use of two equivalents of *n*-BuLi on the larger scale.

Several of the compounds **8** were not obtained as pure samples by flash chromatography as the R_f values of product and starting material were too close on TLC using the same solvent system. There is a need to find solvent systems giving a better separation.

2.3.2   Deprotection of thioacetal to form dihydroxyketoacetals

The diols **8** can undergo a deprotection of the thioacteal moiety to form the corresponding dihydroxyketoacetals **9**.[9]
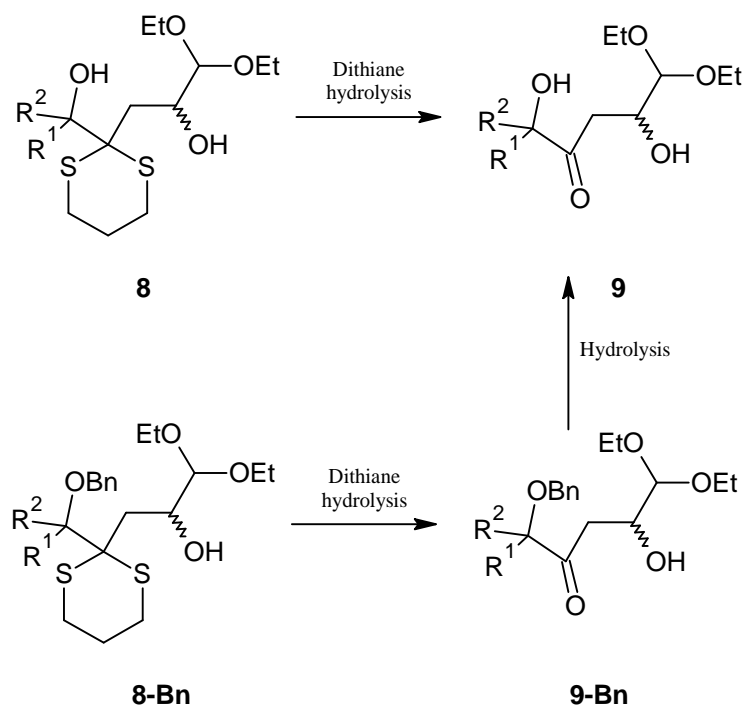
Scheme 2.31: *Hydrolysis of the thioacetal.*

Several procedures can be undertaken to hydrolyse the thioacetal. Valdersnes hydrolysed the benzyl-protected diols (**8-Bn**) to the corresponding benzyl-protected dihydroxyketoacetals (**9-Bn**) in moderate to excellent yields using different methods.[9]

Method A: $NaNO_2$, AcCl, CH_2Cl_2.

Method B: MeI, $CaCO_3$, acetonitrile, H_2O, THF.

Method C: MeI, $CaCO_3$, acetonitrile, H_2O (a modification of method B).

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

The two more successful methods were C and D. Method A did not give any product, and mainly recovered starting material was obtained from the crude product.

The dihydroxyketoacetals **9** have been prepared by Valdersnes by hydrolysis of the benzyl protection.[9]

2.3.3   Stereochemistry of the hydroxyl groups

As the stereochemistry of the hydroxyl groups of carbohydrates is important to their biological properties, it is desirable to be able to obtain the hydroxyl groups enantioselectively.

Several possibilities exist for enantioselective reduction of ketones. One possibility is the Corey-Bakashi-Shibata (CBS) reduction involving $BH_3 \cdot THF$ and (*S*)-oxazaborolidine in THF at 25 °C.[26]

Valdersnes managed to enantioselectively reduce the ketone **6** to the alcohol **7** using the CBS method giving an enantiomeric eccess (*ee*) of 20% of the benzyl-protected dithiane (**7-Bn**).[9] It was not possible to measure the *ee* of alcohol **7** by integration using ^{1}H-NMR analysis with added chiral solvating reagent, due to overlapping signals.
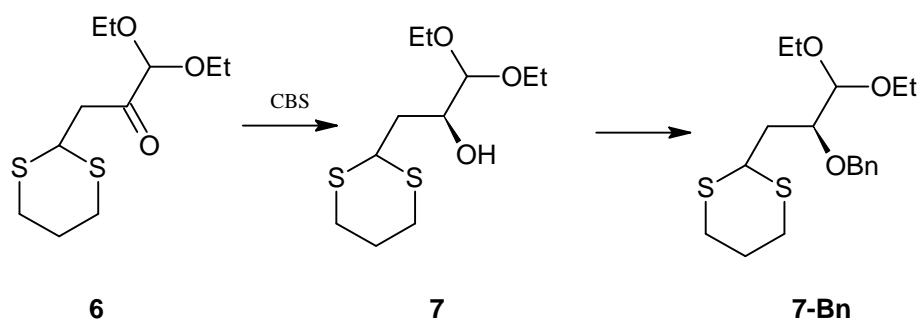
Scheme 2.37: *Enantioselective reduction of ketone 6 followed by benzyl protection.*

An *ee* of 20% is not noteworthy nowadays, and further investigations into more highly selective means of reduction are necessary. Ways to enantioselectively add compound **8** to aldehydes and ketones should also be investigated.

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3   EXPERIMENTAL

3.1   General

Dry THF was obtained by distillation from sodium/benzophenone or from the Department of Chemistry anhydrous solvent delivery system. Dichloromethane and diethyl ether were of technical grade. A mixture of hexane isomers of puriss grade was used for chromatographic purposes. All other solvents were of puriss grade and used as received. All reagents were used as received. 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 the 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. 15-20 mmHg. Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected.

IR spectra were obtained on a Nicolet impact 410 spectrometer with the samples as a film between two sodium-chloride plates. Absorptions are given in wavenumbers (cm^{-1}), and intensities are characterized as (s) for strong, (m) for medium, (w) for weak, (br) for broad, and (sh) for shoulder. Some of the spectra are contaminated with a C=O absorption around 1740 cm^{-1} due to ethyl acetate used under flash-chromatographic purification.

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, δ_H = 0.00 ppm) as the internal reference. Chemical shifts are reported downfield from the reference standard, and 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 (multiplicity, coupling constant *J*/Hz, number of protons). ^{13}C-NMR spectra were recorded at ambient temperatures on the same spectrometer at 100 MHz with the central peak of the CHCl$_3$ triplet (δ_C = 77.16 ppm) as the internal reference. COSY-H,H, and DEPT-90 (distortionless enhancement by polarization transfer) and DEPT-

135 were used when appropriate, to aid the assignment of signals in the ^{1}H- and ^{13}C-NMR spectra, respectively.

3.2   Preparation of starting materials

3.2.1   Preparation of TEB

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

A 1 L three-necked, round-bottom flask equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with ethyl vinyl ether (37.27 g, 0.52 mol), chloroform (249.18 g, 2.09 mol) and TEBA (0.27 g). The flask was immersed in an ice-water bath, and 50% aqueous NaOH (61.38 g (1.53 mol) in 61.40 g H_2O) was added dropwise (45 min) to the solution. The reaction mixture was left stirring for 24 h while the ice melted and the temperature gradually reached rt, and was subsequently neutralized by adding 3 M HCl. The solution was transferred to a separatory funnel, and the reaction flask was washed with CH_2Cl_2 (2 x 30 mL) and H_2O (1 x 30 mL), which were also transferred to the funnel. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 250 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated on a rotary evaporator. The residue was distilled to give 67.57 g (84%) of the title compound as a clear, colourless liquid, b.p. 33-37 °C/15 mmHg (lit.[1] 53.5-53.6 °C/28 mmHg). The IR, ^{1}H-NMR, and ^{13}C-NMR data are in agreement with those published in the literature.[2]

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

A 1 L round-bottom flask equipped with a condenser and a magnetic stirring bar was charged with **1** (67.57 g, 0.44 mol), pyridine (51.72 g, 0.65 mol) and ethanol (300 mL), and the solution was refluxed for 48 h. Ethanol was evaporated on a rotary evaporator, and the remaining liquid was transferred to a separatory funnel. The flask was washed with EtO_2 (2 x 50 mL) and H_2O (1 x 50 mL), which were also transferred to the funnel. The phases were separated, and the aqueous phase was extracted with EtO_2 (3 x 100 mL). The combined extracts were washed with 0.7 M $CuSO_4$ solution (2 x 450 mL), dried ($MgSO_4$), filtered under vacuum through an Al_2O_3 plug, and concentrated on a rotary evaporator. The residue was distilled to give 48.76 g (68%) of the title compound as a clear, colourless liquid, b.p. 56-

66 °C/15 mmHg (lit.[3] 70-78 °C/25 mmHg). The IR, ^{1}H-NMR, and ^{13}C-NMR data are in agreement with those published in the literature.[3]

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

A 1 L three-necked, round-bottom flask equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with **2** (48.76 g, 0.296 mol), bromoform (748.69 g, 2.96 mol) and TEBA (0.33 g). The flask was placed in an ice-water bath, and 50% aqueous NaOH (63.07 g (1.58 mol) in 63.30 g H_2O) was added dropwise (70 min) to the solution. The reaction mixture was left stirring for 24 h while the ice melted and the temperature gradually reached rt, and 300 mL saturated aqueous NaCl was added. The solution was transferred to a separatory funnel, and the flask was washed with CH_2Cl_2 (2 x 30 mL) and saturated aqueous NaCl (2 x 30 mL), which were also transferred to the funnel. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The extracts were washed with H_2O (4 x 200 mL), combined and dried ($MgSO_4$), filtered and concentrated on a rotary evaporator. Bromoform (613.12 g) was removed by distillation, b.p. 31-36 °C/15 mmHg (lit.[4] 149.5 °C/760 mmHg). The residue was a brownish, viscous liquid (74.32 g), which was essentially pure and gave IR, ^{1}H-NMR, and ^{13}C-NMR data in agreement with those published in the literature.[2] The compound was not purified, but used in the next reaction as obtained.

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

A 1 L three-necked, round-bottom flask equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with the crude product of **3** (74.32 g), ethanol (41.68 g, 0.90 mol), CH_2Cl_2 (150 mL) and TEBA (0.2 g). The flask was placed in an ice-water bath, and 50% aqueous NaOH (73.63 g (1.84 mol) in 70.35 g H_2O) was added dropwise (40 min) to the solution. The reaction mixture was left stirring for 24 h while the ice melted and the temperature gradually reached rt, and H_2O was added (200 mL). The solution was stirred for 20 min and then transferred to a separatory funnel, and the flask was washed with CH_2Cl_2 (2 x 30 mL) and H_2O (2 x 30 mL) , which were also transferred to the funnel. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The extracts were washed with H_2O (3 x 150 mL), combined and dried ($MgSO_4$), filtered and concentrated on a rotary evaporator. The residue was distilled to give 23.85 g (35% over two steps) of the title compound as a clear, colourless liquid, b.p. 92-97 °C/15 mmHg (lit.[5] 53-58 °C/0.2 mmHg). The IR, ^{1}H-NMR, and ^{13}C-NMR data are in agreement with those published in the literature.[5]

3.2.2   Preparation of β-hydroxydithiane from TEB

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

Method A:

A 100 mL round-bottom flask equipped with a condenser and a magnetic stirring bar was charged with **4** (2.104 g, 9.14 mmol), Dowex 50W (2.494 g), acetone (40 mL), and H_2O (2.0 mL), and refluxed for 24 h. The Dowex 50W was filtered off before acetone was removed on the rotary evaporator. CH_2Cl_2 (ca 100 mL) was added, and the solution was dried ($MgSO_4$), filtered and concentrated on a rotary evaporator. The title compound (0.989 g, 69%) was obtained as a clear, yellow liquid by flash chromatography using hexane-ethyl acetate (90:10).

Method B:

A 250 mL round-bottom flask equipped with a condenser and a magnetic stirring bar was first charged with **4** (2.019 g, 8.77 mmol), H_2O (25 mL) and ethyl acetate (60 mL) by mistake. Ethyl acetate was evaporated on a rotary evaporator, before THF (60 mL) and PTSA·$1H_2O$ (0.497 g, 2.61 mmol) was added, and the reaction mixture was refluxed for 16.5 h. 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 (1 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 30 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated on a rotary evaporator. The title compound (0.347 g, 25%) was obtained as a clear, light yellow liquid by flash chromatography using hexane-ethyl acetate (90:10).

The IR, ^{1}H-NMR, and ^{13}C-NMR data are in agreement with those published in the literature.[6]

1,1-Diethoxy-3-(1,3-dithian-2-yl)propan-2-one (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 (1.655 g, 30.6 mmol), propane-1,3-dithiol (3.0 mL, 3.2 g, 30 mmol), and dry THF (200 mL). Nitrogen gas was flushed through. **5** (3.157 g, 20.2 mmol) was dissolved in dry THF (50 mL), and the solution was added dropwise (30 min) to the reaction flask at -78 °C under nitrogen atmosphere. The reaction mixture was left stirring for 15 h while the temperature gradually reached rt. Saturated NH_4Cl (200 mL) was added to the reaction

mixture, and a white precipitate form. 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 (1 x 50 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, and H_2O (100 mL) was added to the aqueous phase to dissolve the percipitate. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator. The title compound (4.224 g, 81%) was obtained as a clear, yellow liquid by flash chromatography using hexane-ethyl acetate (90:10). The IR, ^{1}H-NMR, and ^{13}C-NMR data are in agreement with those published in the literature.[6]

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

A 250 mL round-bottom flask equipped with a condenser and a magnetic stirring bar was charged with **6** (5.07 g, 19.2 mmol), $NaBH_4$ (0.37 g, 9.8 mmol), THF (75 mL), and H_2O (2.5 mL). The reaction flask was placed in an ice-water bath, and the reaction mixture was stirred for 45 min before H_2O (25 mL) was added. THF was evaporated on a rotary evaporator, and the remaining liquid was transferred to a separatory funnel. The flask was washed with CH_2Cl_2 (2 x 20 mL) and H_2O (1 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 50 mL). The combined extracts dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator. The title compound (4.77 g, 93%) was obtained as a clear, slightly yellow liquid by flash chromatography using hexane-ethyl acetate (80:20). The IR, ^{1}H-NMR, and ^{13}C-NMR data are in agreement with those published in the literature.[6]

3.3   ADDITION TO ALDEHYDES AND KETONES

General procedures:

The amounts used in each case are given for each synthesis.

Method A:

A 25 mL two-necked, pear-shaped flask equipped with a condenser with a nitrogen inlet, a septum, and a magnetic stirring bar was charged with **7** in dry THF (6 mL). *n*-BuLi (2 eq.) was added dropwise

(3 min) to the flask at -78 °C under nitrogen atmosphere. After 30 min, aldehyde dissolved in dry THF (3 mL), was added dropwise (3 min). The reaction mixture was kept at -78 °C and under nitrogen atmosphere, and was allowed to react for 1 h. Saturated NH_4Cl (15 mL) was added to the reaction mixture before it was allowed to reach rt. THF was evaporated on a rotary evaporator, and the residue was transferred to a separatory funnel. The flask was washed with CH_2Cl_2 (2 x 5 mL) and H_2O (1 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 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator.

Method B:

A 25 or 50 mL two-necked, round-bottom or pear-shaped flask equipped with a condenser with a nitrogen inlet, a septum, and a magnetic stirring bar was charged with **7** in dry THF (6 mL). The flask was placed in an ice-water bath, and *n*-BuLi (2 eq.) was added dropwise (3 min) to the flask under nitrogen atmosphere. After 30 min, aldehyde/ketone dissolved in dry THF (3 mL), was added dropwise (3 min). The reaction mixture was kept at 0 °C and under nitrogen atmosphere, and was allowed to react for 30 min. Saturated NH_4Cl (15 mL) was added to the reaction mixture before it was allowed to reach rt. THF was evaporated on a rotary evaporator, and the residue was transferred to separatory funnel. The flask was washed with CH_2Cl_2 (3 x 10 mL) and H_2O (1 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 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator.

In the case of paraformaldehyde, 9 mL of dry THF was added to the flask instead of 6 mL, and paraformaldehyde was added directly to the reaction mixture in one pot 30 min after addition of *n*-BuLi.

Method C:

A 25 or 50 mL two-necked, round-bottom or pear-shaped flask equipped with a condenser with a nitrogen inlet, a septum, and a magnetic stirring bar was charged with **7** in dry THF (4 mL). The flask was placed in an ice-water bath, and placed under nitrogen atmosphere. NaH (1 eq) was washed with hexane several times, and was added to the reaction flask with a pipette as a suspension in THF (2 mL). After 1.5 h, *n*-BuLi (1 eq.) dissolved in dry THF (3 mL) was added dropwise (2 min) to the flask. After further 30 min, aldehyde dissolved in dry THF (3 mL), was added dropwise (2 min). The reaction mixture was kept at 0 °C and under nitrogen atmosphere, and was allowed to react for 30 min. Saturated NH_4Cl (15 mL) was added to the reaction mixture before it was allowed to reach rt. THF

was evaporated on a rotary evaporator, and the residue was transferred to a separatory funnel. The flask was washed with CH_2Cl_2 (3 x 10 mL) and H_2O (1 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 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator.

1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol (8a)

Method A:

Compound **7** (0.211 g, 0.79 mmol) was reacted with *n*-BuLi (1.1 mL, 1.6 M, 1.8 mmol) and ethanal (0.057 g, 1.29 mmol). The title compound (0.014 g, 6%), a mixture of diastereomers, was obtained as a clear, yellow liquid by flash chromatography using hexane-ethyl acetate (70:30).

Method B:

Compound **7** (0.216 g, 0.81 mmol) was reacted with *n*-BuLi (1.1 mL, 1.6 M, 1.8 mmol) and ethanal (0.053 g, 1.20 mmol). The title compound (0.132 g, 52%), a mixture of diastereomers, was obtained as a clear, yellow liquid by flash chromatography using hexane-ethyl acetate (60:40).

Method C:

Compound **7** (0.234 g, 0.88 mmol) was reacted with NaH (0.032 g, 1.33 mmol), *n*-BuLi (0.6 mL, 1.6 M, 1.0 mmol) and ethanal (0.047 g, 1.07 mmol). The title compound (0.055 g, 20%), a mixture of diastereomers, was obtained as a clear, yellow liquid by flash chromatography using hexane-ethyl acetate (70:30).

IR (NaCl), $\bar{v}$ (cm^{-1}): 3600-3100 (s), 3582 (sh), 2975 (s), 2935 (s), 2907 (s), 2832 sh), 1482 (w), 1444 (m), 1422 (m), 1392 (sh), 1373 (m), 1343 (m), 1297 (m), 1245 (m), 1245 (w), 1142 (s), 1122 (s), 1064 (s), 939 (m), 910 (m), 868 (w), 843 (w), 810 (w), 734 (w), 665 (m).

^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 4.36 and 4.35 (two overlapping d, *J* = 6.2 Hz and *J* = 5.8 Hz, resepctively, 1H), 4.18-4.04 (m, 2H), 3.95 (bs, 1H), 3.82-3.56 (m, 4H), 3.11 (bs, 1H), 2.92-2.71 (m, 4H), 2.51 and 2.49 (two overlapping dd, J_1 = 1.5 Hz and J_2 = 15.7 Hz, and J_1 = 0.8 Hz and J_2 = 15.5 Hz, respectively, 1H), 2.07 and 1.89 (two sets of dd, J_1 = 9.4 Hz and J_2 = 15.5 Hz, and J_1 = 8.5 Hz and J_2 = 15.7 Hz, 1H), 2.02-1.94 (m, 2H), 1.43 and 1.44 (two overlapping d, *J* = 6.4 Hz for both, 3H), 1.27-1.22 (m, 6H).

^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 104.7 (CH), 104.3 (CH), 71.0 (CH), 70.6 (CH), 69.6 (CH), 69.0 (CH), 63.9 (CH$_2$), 63.7 (2 x CH$_2$), 63.3 (CH$_2$), 58.7 (C), 58.2 (C), 38.0 (CH$_2$), 36.4 (CH$_2$), 26.2 (CH$_2$), 25.8 (CH$_2$), 25.6 (CH$_2$), 25.3 (CH$_2$), 25.2 (CH$_2$), 25.0 (CH$_2$), 17.4 (CH$_3$), 17.1 (CH$_3$), 15.5 (3 x CH$_3$).

MS: The spectrum of the sample of the compound handed in had not been run when the thesis had to be submitted.

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

Method B:

Compound **7** (0.193 g, 0.72 mmol) was reacted with *n*-BuLi (1.0 mL, 1.6 mmol) and benzaldehyde (0.092 g, 0.87 mmol). The title compound (0.256 g, 95%), a mixture of diastereomers, was obtained as a clear, yellow liquid by flash chromatography using hexane-ethyl acetate (70:30).

Method C:

Compound **7** (0.210 g, 0.79 mmol) was reacted with NaH (0.029 g, 1.21 mmol), *n*-BuLi (0.5 mL, 0.8 mmol) and benzaldehyde (0.117 g, 1.10 mmol). The title compound (0.162 g, 55%), a mixture of diastereomers, was obtained as a clear, yellow liquid by flash chromatography using hexane-ethyl acetate (70:30). IR was run on a sample of **7** obtained by evaporating an NMR sample. That explains the presence of a C-D absorption at 2246 cm^{-1}.

IR (NaCl), ṽ (cm^{-1}): 3600-3100 (s), 3583 (sh), 3087 (w), 3062 (m), 3030 (m), 2794 (s), 2929 (s), 2903 (s), 2831 (sh), 2246 (w), 1954 (w), 1888 (w), 1811 (w), 1634 (w), 1603 (w), 1494 (m), 1480 (w), 1453 (m), 1444 (m), 1424 (m), 1418 (m), 1374 (m), 1335 (m), 1299 (m), 1276 (m), 1242 (m), 1192 (sh), 1174 (sh), 1141 (s), 1118 (s), 1059 (s), 1027 (s), 910 (s), 848 (w), 800 (w), 757 (m), 732 (s), 701 (s), 665 (m), 647 (s).

^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 7.57-2.27 (m, 5H), 5.06 and 5.04 (two overlapping s, 1H), 4.67 (bs, 1H), 4.32 and 4.31 (two overlapping d, *J* = 5.8 Hz and *J* = 36.3 Hz, respectively, 1H), 4.22-4.09 (m, 1H), 3.83-3.52 (m, 4H), 3.11 (bs, 1H), 2.96-2.67 (m, 4H), 2.52 and 2.30 (two sets of dd, J_1 = 1.4 Hz and J_2 = 15.6 Hz, and J_1 = 1.0 Hz and J_2 = 15.6 Hz, respectively, 1H), 2.11 and 1.72 (two sets of dd, J_1 = 9.2 Hz abd J_2 = 15.6 Hz and J_1 = 8.7 Hz and J_2 = 15.6 Hz, respectively, 1H), 1.98-1.84 (m, 2H), 1.24, 1.24, 1.23, and 1.18 (four overlapping 7, *J* = 7.2 Hz, 6H).

^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 138.7 (C), 138.3 (C), 129.0 (2 x CH), 128.1 (CH), 128.0 (CH), 127.4 (2 x CH), 104.6 (CH), 104.4 (CH), 77.6 (CH), 76.8 (CH), 69.7 (CH), 69.5 (CH), 63.8 (CH$_2$), 63.7 (CH$_2$), 63.6

(CH$_2$), 58.7 (C), 57.9 (C), 38.8 (CH$_2$), 36.8 (CH$_2$), 26.5 (CH$_2$), 26.1 (CH$_2$), 26.0 (CH$_2$), 25.7 (CH$_2$), 24.7 (CH$_2$), 24.5 (CH$_2$), 15.5 (CH$_3$).

MS: The spectrum of the sample of the compound handed in had not been run when the thesis had to be submitted.

1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)undecane-2,5-diol (8c)

Compound **7** (0.235 g, 0.88 mmol) was reacted with *n*-BuLi (1.2 mL, 1.9 mmol) and heptanal (0.134 g, 1.17 mmol). The title compound (0.310 g, estimated to 78%), a mixture of diastereomers, was obtained as a clear, yellow liquid containing starting material by flash chromatography using hexane-ethyl acetate (80:20).

IR (NaCl), $\tilde{\nu}$ (cm^{-1}): 3600-3100 (m), 3583 (sh), 2973 (s), 2954 (s), 2927 (s), 2872 (s), 2858 (s), 1480 (sh), 1455 (m), 1444 (m), 1424 (m), 1393 (m), 1375 (m), 1340 (m), 1299 (m), 1276 (m), 1242 (m), 1216 (w), 1119 (s), 1065 (s), 966 (w), 909 (m), 884 (w), 841 (w), 816 (w), 800 (w), 776 (w), 725 (w), 666 (m). The spectral data are of the mixture of starting material and product.

^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 4.35 and 4.34 (two overlapping d, *J* = 6.0 Hz, 1H), 4.12-4.03 (m, 1H), 3.95-3.53 (m, 5H), 3.13 (bs, 1H), 2.96-2.69 (m, 4H), 2.50 and 2.47 (two overlapping signals, the first a d, and the second a dd, *J* = 6.7 Hz, and *J*$_1$ = 1.6 Hz and *J*$_2$ = 7.0 Hz, respectively, 1H), 2.27 and 2.26 (two overlapping s, 1H), 2.14-1.83 (m, 3H), 1.69-1.49 (m, 2H), 1.39-1.20 (m, 14H), 0.90-0.87 (m, 3H).

^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 104.7 (CH), 104.4 (CH), 75.2 (CH), 74.2 (CH), 69.5 (CH), 69.1 (CH), 63.9 (CH$_2$), 63.7 (2 x CH$_2$), 63.3 (CH$_2$), 58.7 (C), 58.2 (C), 38.0 (CH$_2$), 36.8 (CH$_2$), 32.0 (CH$_2$), 31.4 (CH$_2$), 31.1 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 27.6 (CH$_2$), 27.4 (CH$_2$), 26.2 (CH$_2$), 25.8 (2 x CH$_2$), 25.3 (2 x CH$_2$), 25.0 (CH$_2$), 22.8 (CH$_2$), 15.6 (CH$_3$), 15.5 (CH$_3$), 14.2 (CH$_3$).

MS: The spectrum of the sample of the compound handed in had not been run when the thesis had to be submitted.

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

Compound **7** (0.194 g, 0.73 mmol) was reacted with *n*-BuLi (1.0 mL, 1.6 mmol) and paraformaldehyde (0.050 g, 1.67 mmol). The aldehyde was allowed to react for 1 h before quenching with saturated NH_4Cl. The title compound (0.067 g, 31%) was obtained as a clear, yellow liquid by flash chromatography using hexane-ethyl acetate (60:40).

IR (NaCl), $\bar{v}$ (cm^{-1}): 3700-3050 (s), 3667 (sh), 2975 (s), 2953 (s), 2932 (s), 2913 (s), 1643 (m), 1633 (m), 1479 (sh), 1453 (sh), 1444 (s), 1423 (s), 1392 (s), 1375 (s), 1342 (m), 1298 (s), 1278 (s), 1240 (m), 1142 (sh), 1119 (s), 1060 (s), 946 (m), 909 (m), 889 (m), 873 (m), 840 (w), 819 (m), 799 (m).

^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 4.30 (d, *J* = 6.0 Hz, 1H), 4.03-3.53 (m, 7H), 2.97-2.66 (m, 5H), 2.33 (d, *J* = 15.1 Hz, 1H), 2.10-1.90 (m, 3H), 1.59 (bs, 1H), 1.24 (two overlapping t, *J* = 7.0 Hz for both, 6H).

^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 104.2 (CH), 68.2 (CH), 65.8 (CH$_2$), 63.8 (CH$_2$), 63.1 (CH$_2$), 53.3 (C), 40.5 (CH$_2$), 26.3 (CH$_2$), 25.6 (CH$_2$), 25.4 (CH$_2$), 15.5 (2 x CH$_3$).

MS: The spectrum of the sample of the compound handed in had not been run when the thesis had to be submitted.

1,1-Diethoxy-5-methyl-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol (8e)

Compound **7** (0.203 g, 0.76 mmol) was reacted with *n*-BuLi (1.1 mL, 1.8 mmol) and acetone (0.057 g, 0.98 mmol). The title compound (0.151 g, 61%) was obtained as a clear, slightly yellow liquid containing small amounts of starting material by flash chromatography using hexane-ethyl acetate (70:30).

IR (NaCl), $\bar{v}$ (cm^{-1}): 3600-3050 (s), 3624 (sh), 3582 (sh), 2975 (s), 2930 (s), 2906 (s), 2830 (m), 1444 (s), 1418 (s), 1380 (s), 1341 (m), 1301 (m), 1278 (s), 1242 (m), 1228 (m), 1173 (s), 1140 (s), 1119 (sh), 1061 (s), 1028 (s), 983 (m), 949 (w), 929 (w), 908 (m), 885 (m), 869 (m), 840 (w), 798 (w), 777 (w), 681 (m), 660 (m).

^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 4.65 (bs, 1H), 4.40 (d, *J* = 6.5 Hz, 1H), 4.16 (dd, *J$_1$* = 6.6/7.0 Hz and *J$_2$* = 8.8 Hz, 1H), 3.86-3.56 (m, 4H), 3.18 (bs, 1H), 3.02-2.94 (m, 1H), 2.88-2.81 (m, 1H), 2.76-2.71 (m, 2H), 2.65-2.59 (m, 1H), 2.17 og 2.13 (two overlapping d, *J* = 9.2 Hz for both, 1H), 2.08 (m, 2H), 1.60 (s, 3H), 1.43 (s, 3H), 1.26 and 1.26 (two overlapping t, *J* = 7.0 Hz for both, 6H).

^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 104.7 (CH), 76.1 (C), 70.3 (CH), 64.1 (CH$_2$), 63.8 (CH$_2$), 62.7 (C), 36.4 (CH$_2$), 27.1 (CH$_3$), 27.0 (CH$_2$), 25.4 (CH$_3$), 25.3 (CH$_2$), 25.1 (CH$_2$), 15.6 (CH$_3$), 15.5 (CH$_3$).

MS: The spectrum of the sample of the compound handed in had not been run when the thesis had to be submitted.

1,1-Diethoxy-4-(1-hydroxycyclohexyl)-4,4-(propyl-1,3-disulfanyl)butan-2-ol (8f)

Compound **7** (0.204 g, 0.77 mmol) was reacted with *n*-BuLi (1.05 mL, 1.7 mmol) and cyclohexanone (0.114 g, 1.16 mmol). The title compound (0.218 g, estimated to 62%) was obtained as white crystals surrounded by a liquid film thought to be starting material, by flash chromatography using hexane-ethyl acetate (80:20). Mp: 66-93 °C (lit.[6] 100-104 °C). The ^{1}H-NMR and ^{13}C-NMR data are in agreement with those published in the literature.[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.   Skattebøl, L. *Journal of Organic Chemistry* **1966,** *31*, 1554-1559.
4.   Weast, R. C., Ed. *Handbook of Chemistry and Physics*, 45th ed.; The Chemical Rubber CO: Cleveland, Ohio, 1964.
5.   Sydnes, L. K.; Holmelid, B.; Kvernenes, O. H.; Sandberg, M.; Hodne, M.; Bakstad, E. *Tetrahedron* **2007,** *63*, 4144-4148.
6.   Valdersnes, S., *Modified carbohydrates from 3,3,4,4-tetraethoxybut-1-yne*, PhD thesis, University of Bergen, **2006**.

4   CONCLUSION

In this project, 1-substituted 5,5-diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diols were synthesized from 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-ol in moderate to excellent yields (31-95%) on a 0.8 mmol scale. The reactions were done by reacting the starting material with two equivalents of *n*-butyllithium before addition of aldehydes and ketones, and the highest yields were obtained at 0 °C. Carrying out the reaction at -78 °C was only attempted with addition of ethanal and gave a poor yield.

Exchanging one of the two equivalents of *n*-butyllithium with one equivalent of sodium hydride reduced the yields from 95% to 55% for benzaldehyde, and from 52% to 20% for ethanal.

Three of the products were not obtained as pure compounds, but as a mixture of product and starting material, due to similar retentions on the TLC plates.

On the basis of the results obtained, it seems as if the new route from TEB to 1-substituted 5,5-diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diols is promising.

APPENDIX
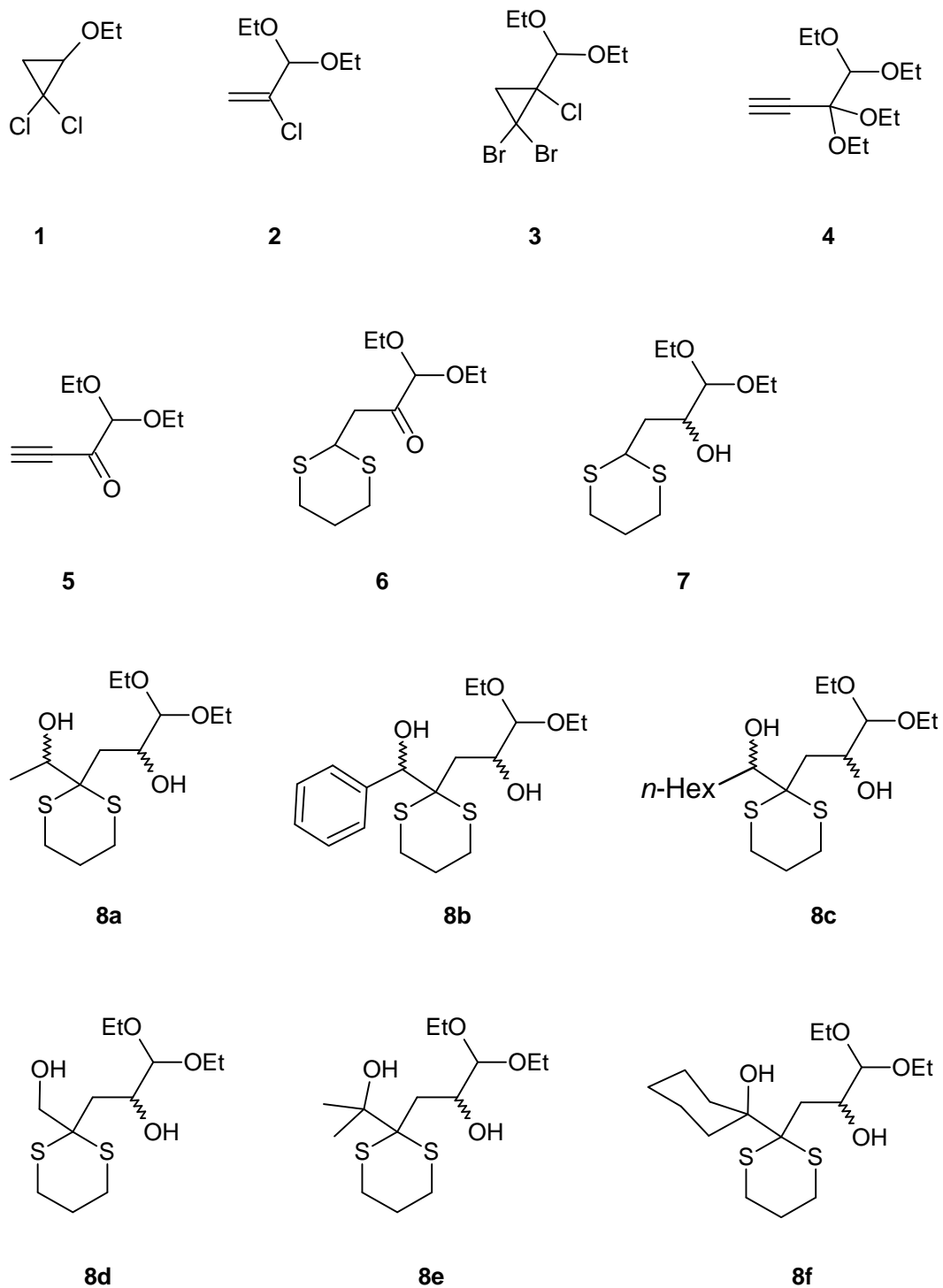
Scheme A.1: *The compounds relevant to this investigation.*
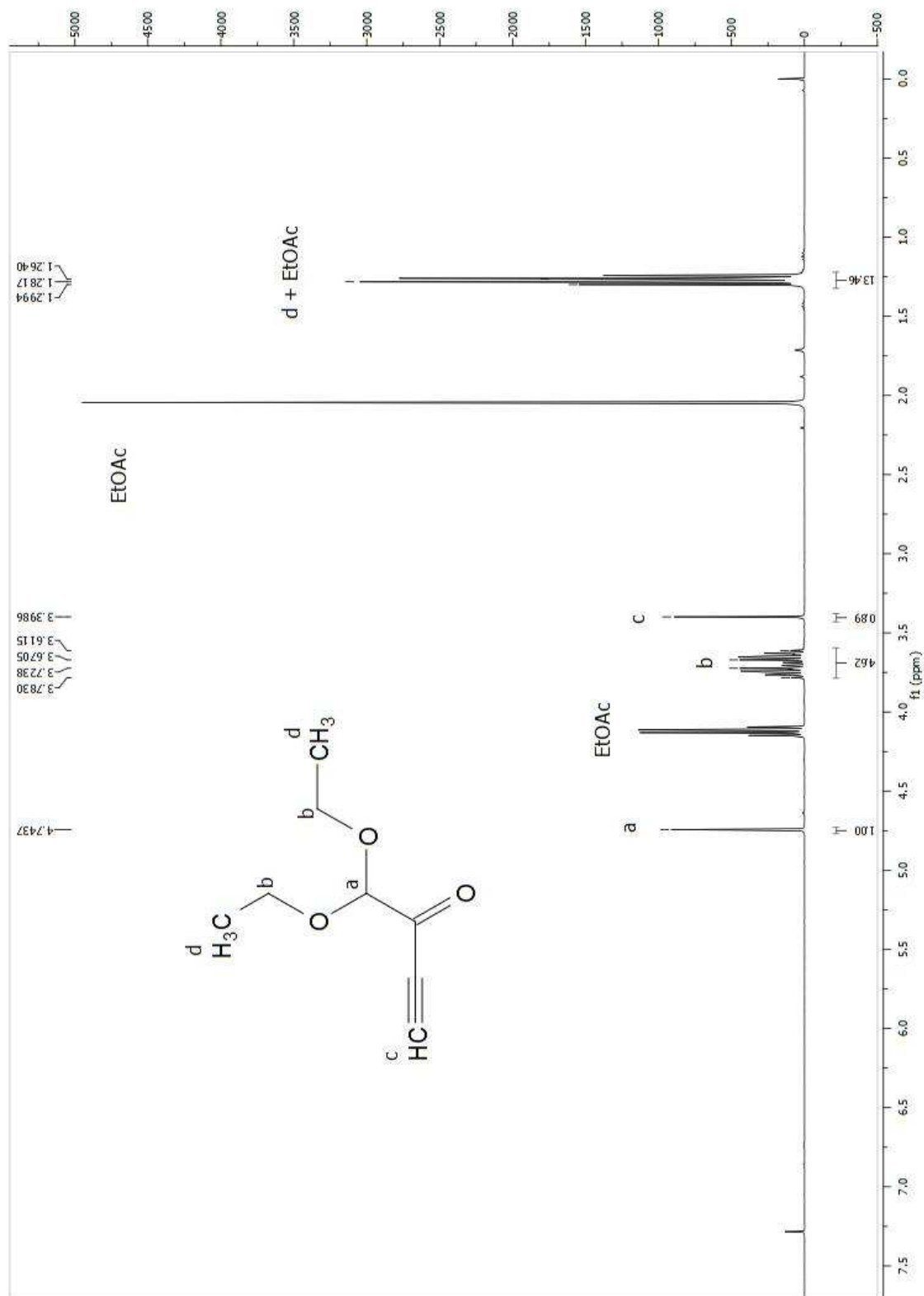
Scheme A.2: ^{1}H-NMR spectrum of 1,1-diethoxybut-3-en-2-one (**5**).
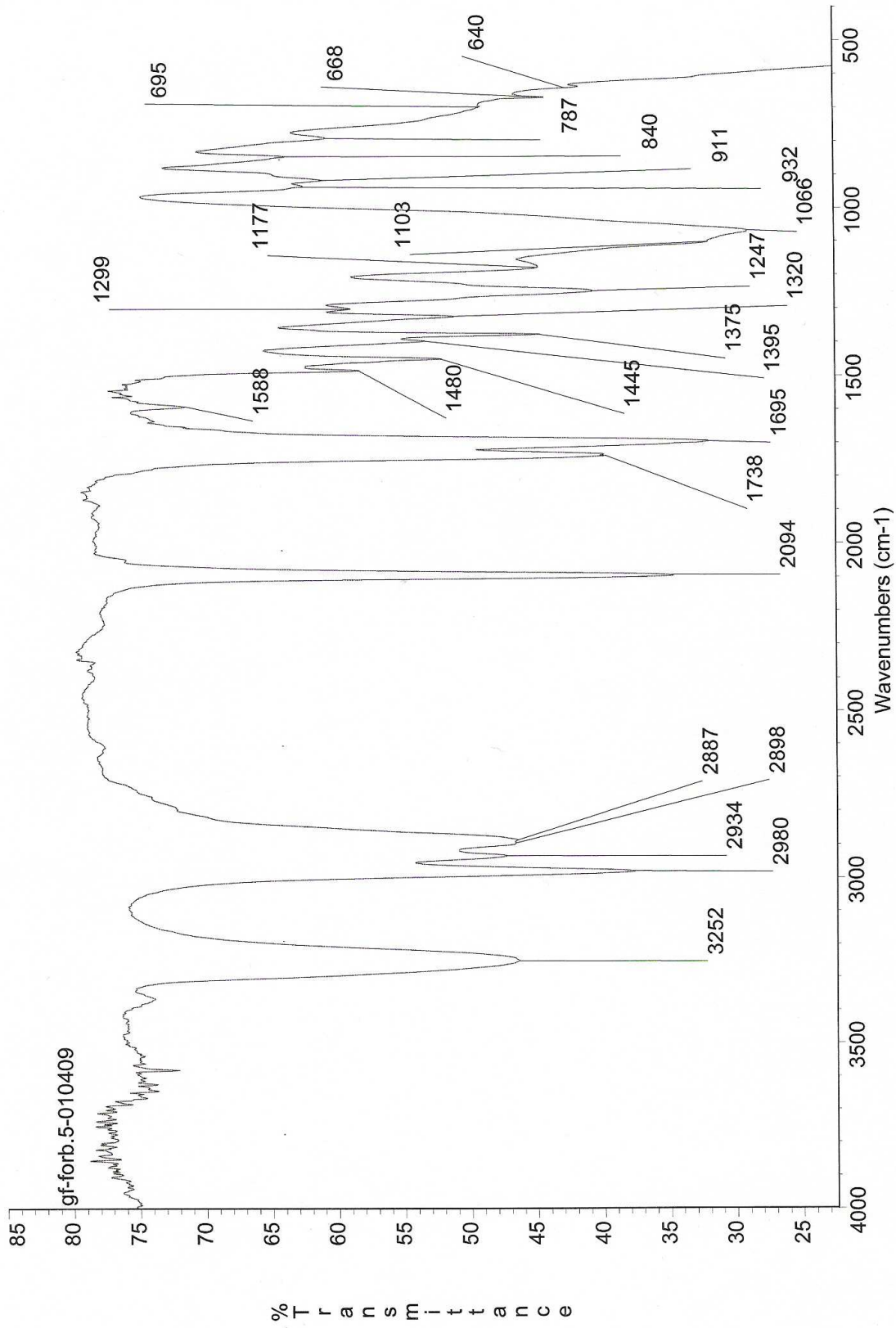
Scheme A.3: IR spectrum of 1,1-diethoxybut-3-en-2-one (**5**).
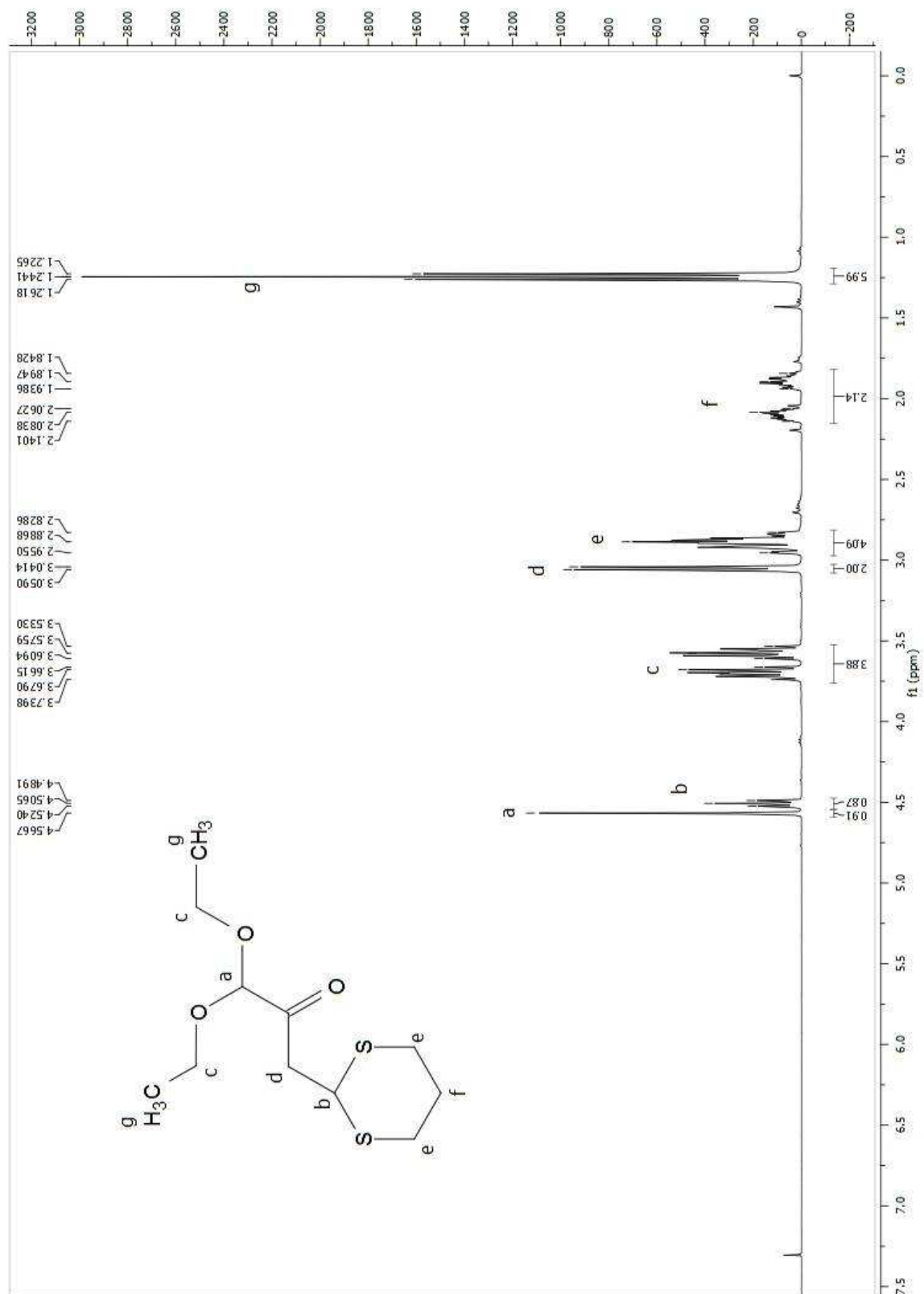
Scheme A.4: *¹H-NMR spectrum of 1,1-Diethoxy-3-(1,3-dithian-2-yl)propan-2-one (6).*
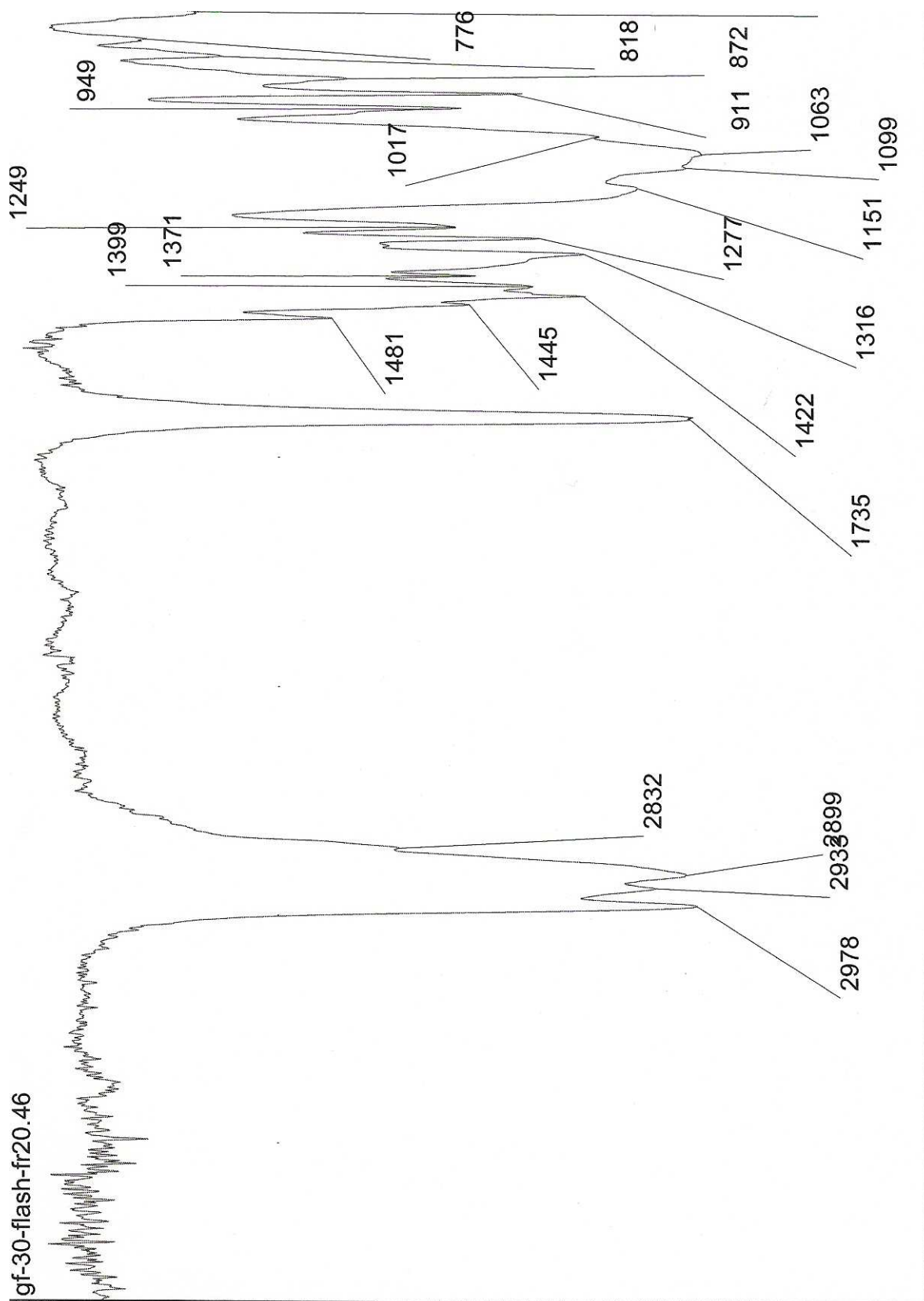
Scheme A.5: *IR spectrum of 1,1-Diethoxy-3-(1,3-dithian-2-yl)propan-2-one (**6**).*
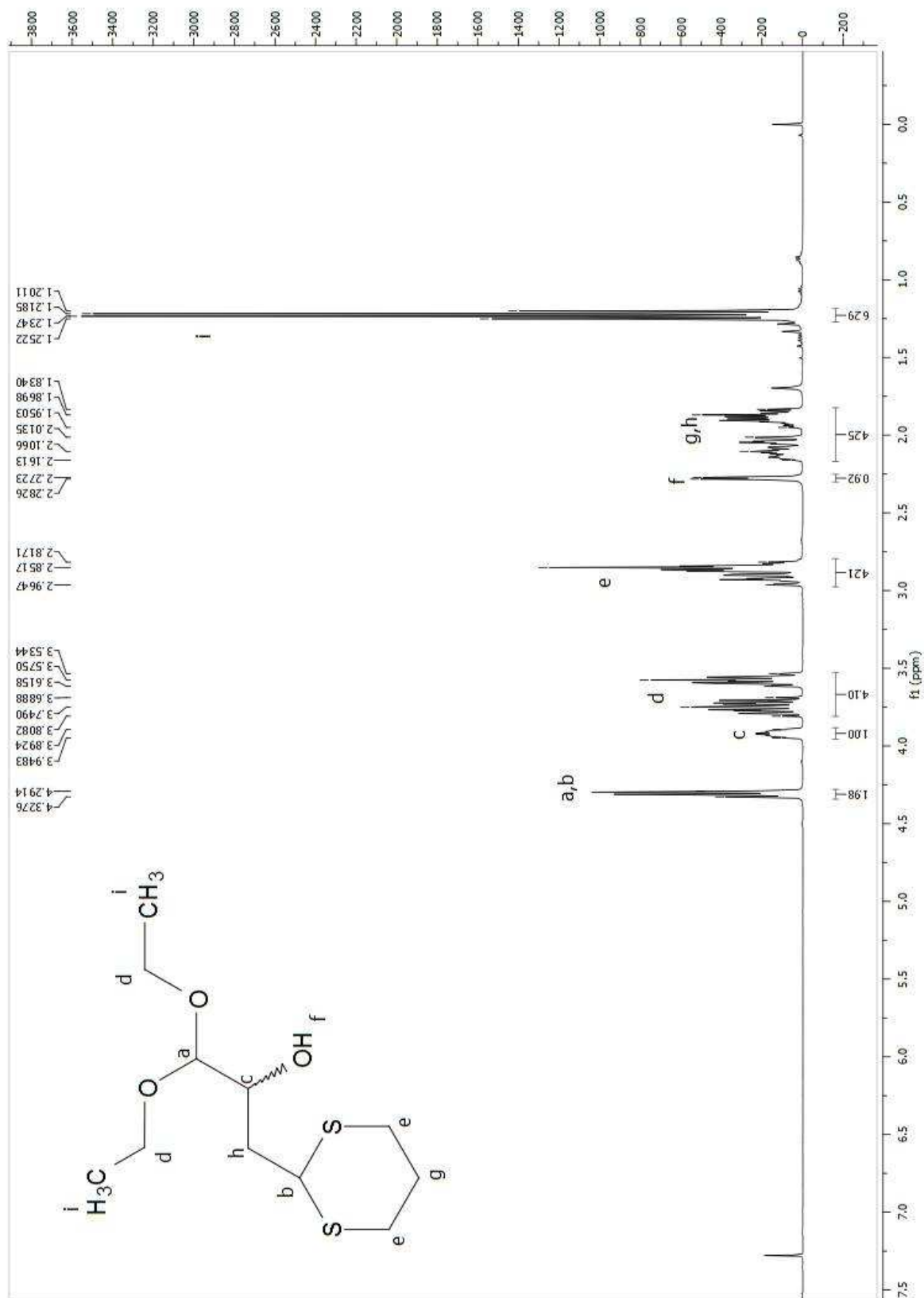
Scheme A.6: ^{1}H-NMR spectrum of 1,1-Diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**).
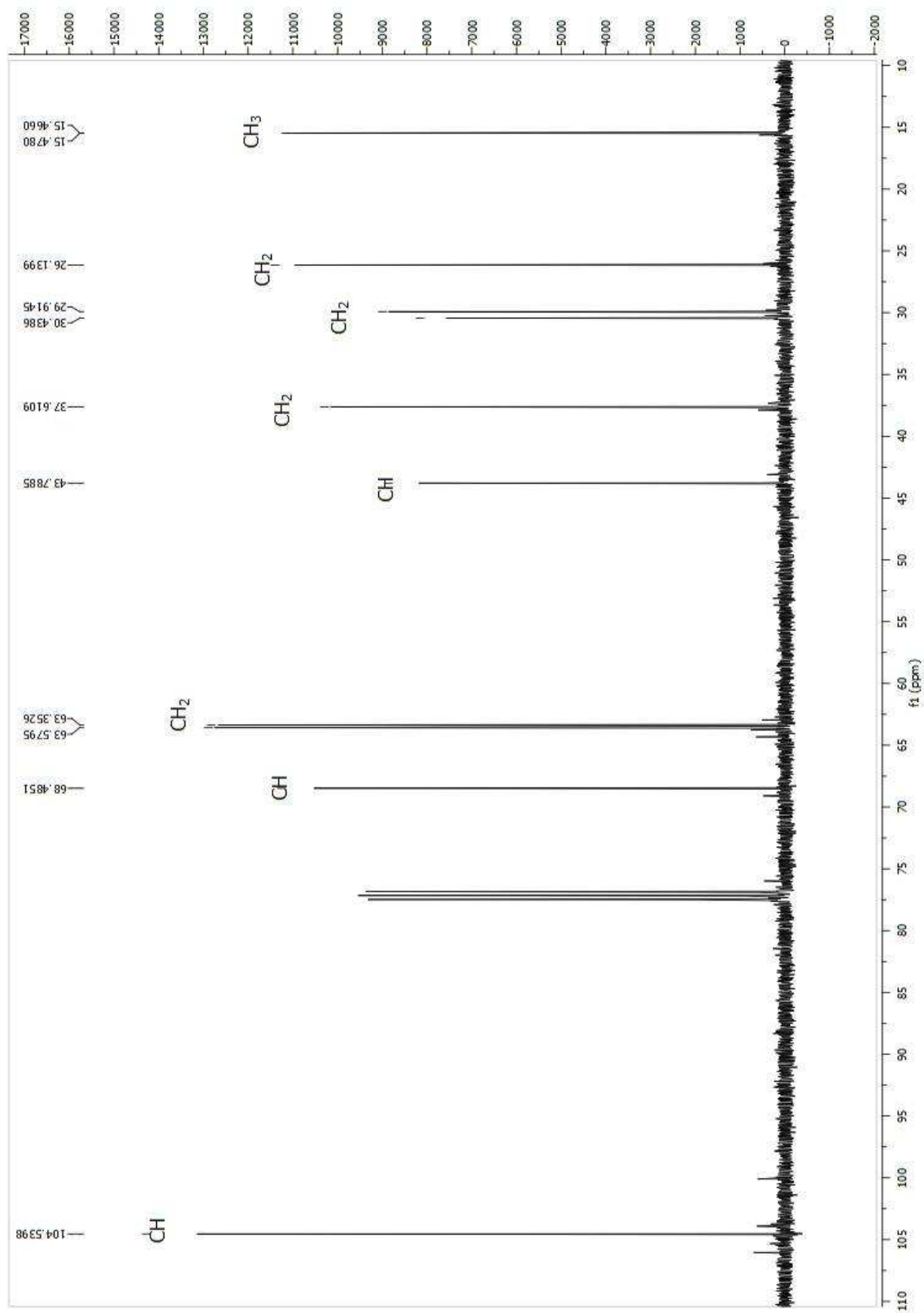
Scheme A.7: ^{13}C-NMR spectrum of 1,1-Diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**).
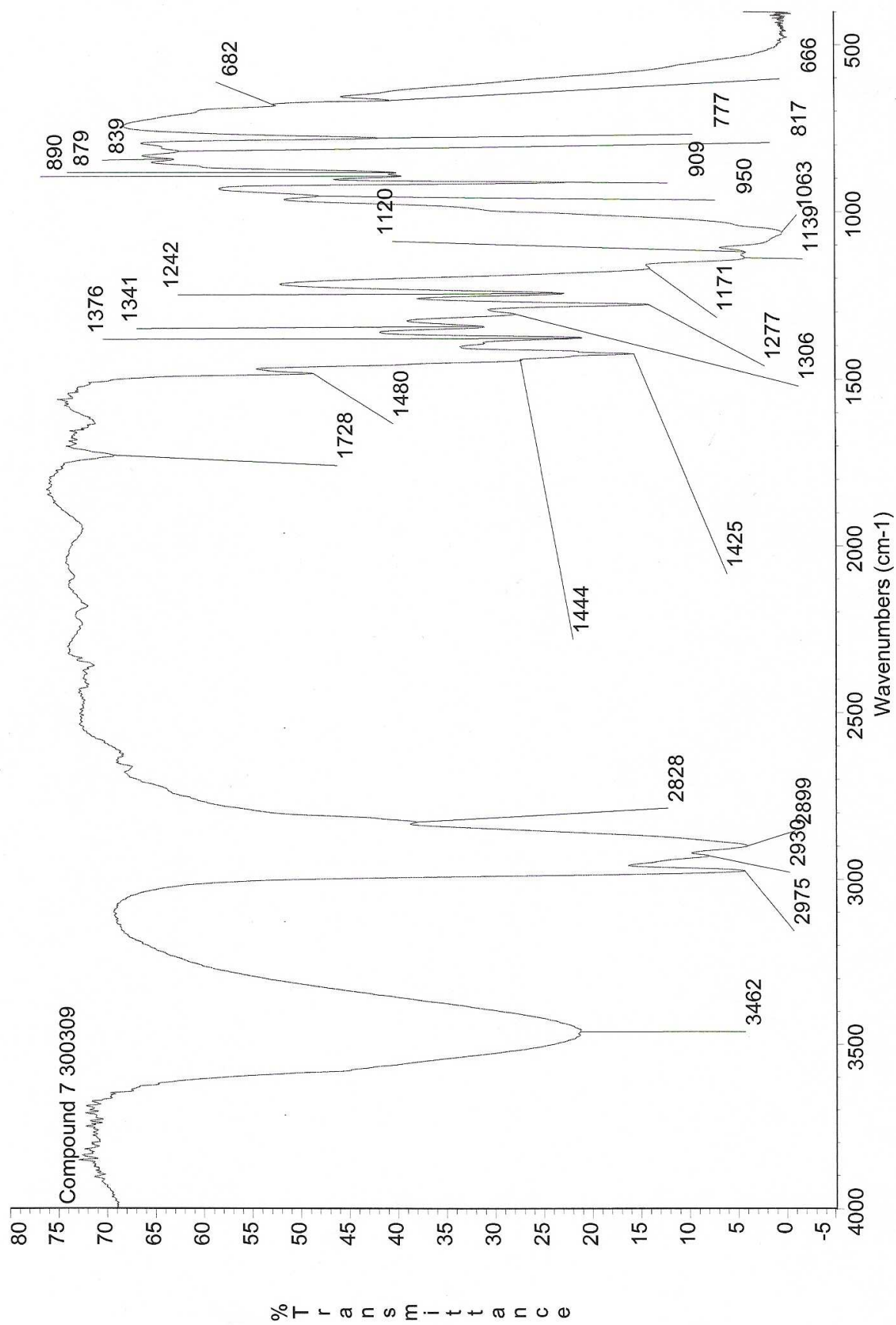
Scheme A.8: *IR spectrum of 1,1-Diethoxy-3-(1,3-dithian-2-yl)propan-2-ol (**7**).*
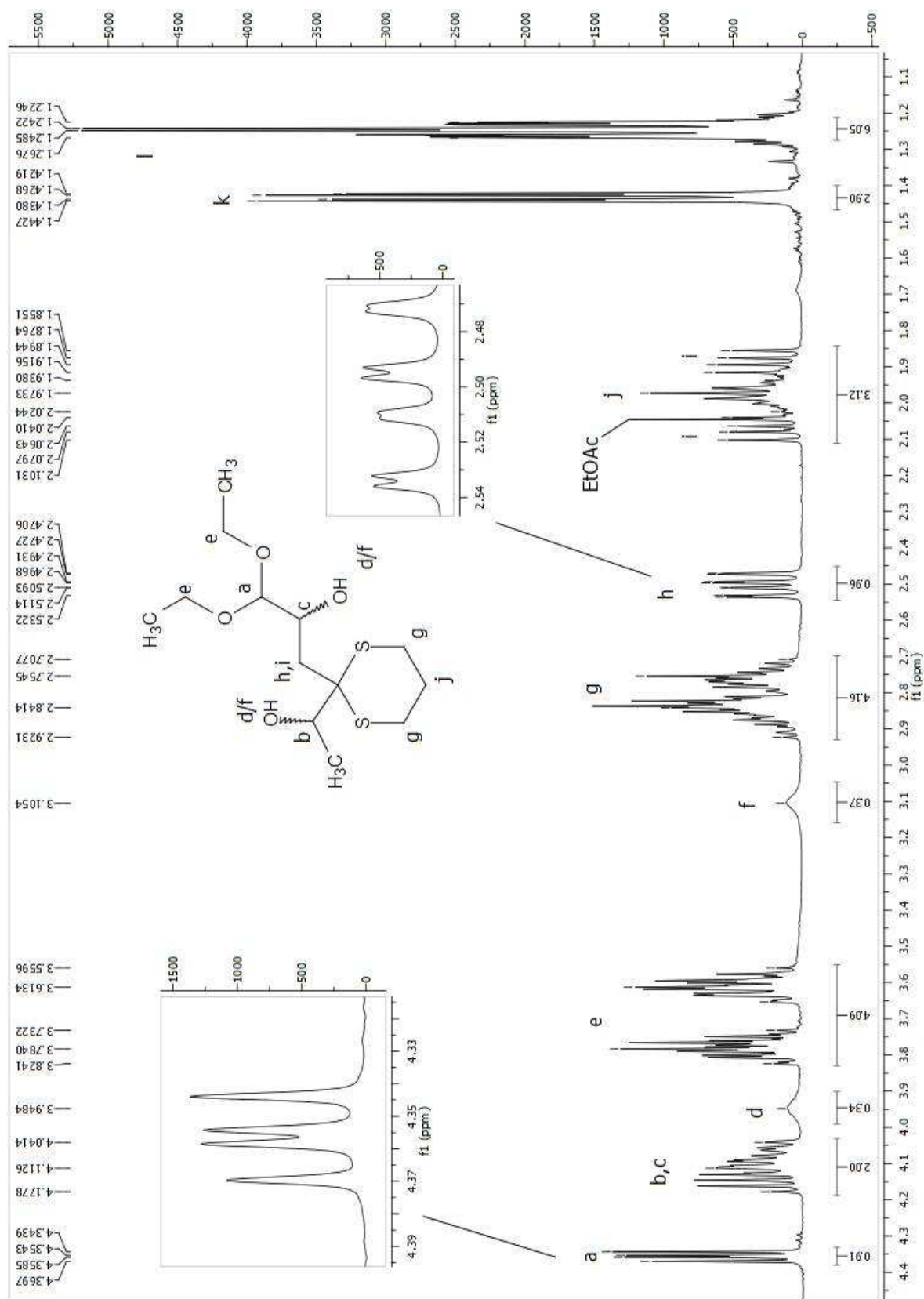
Scheme A.9: ^{1}H-NMR spectrum of 1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol (**8a**).
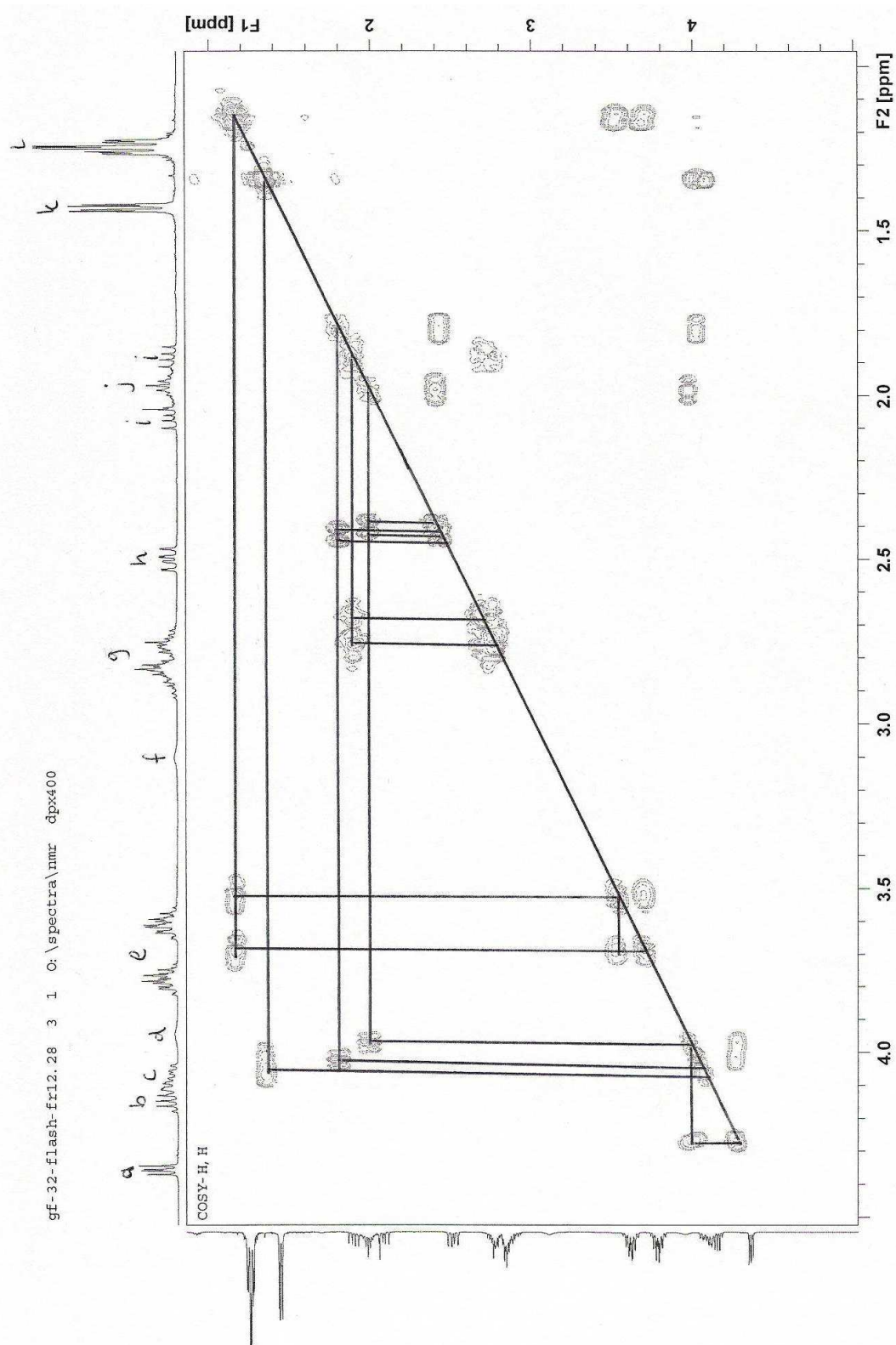
Scheme A.10: *COSY-H,H spectrum of 1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol (**8a**).*
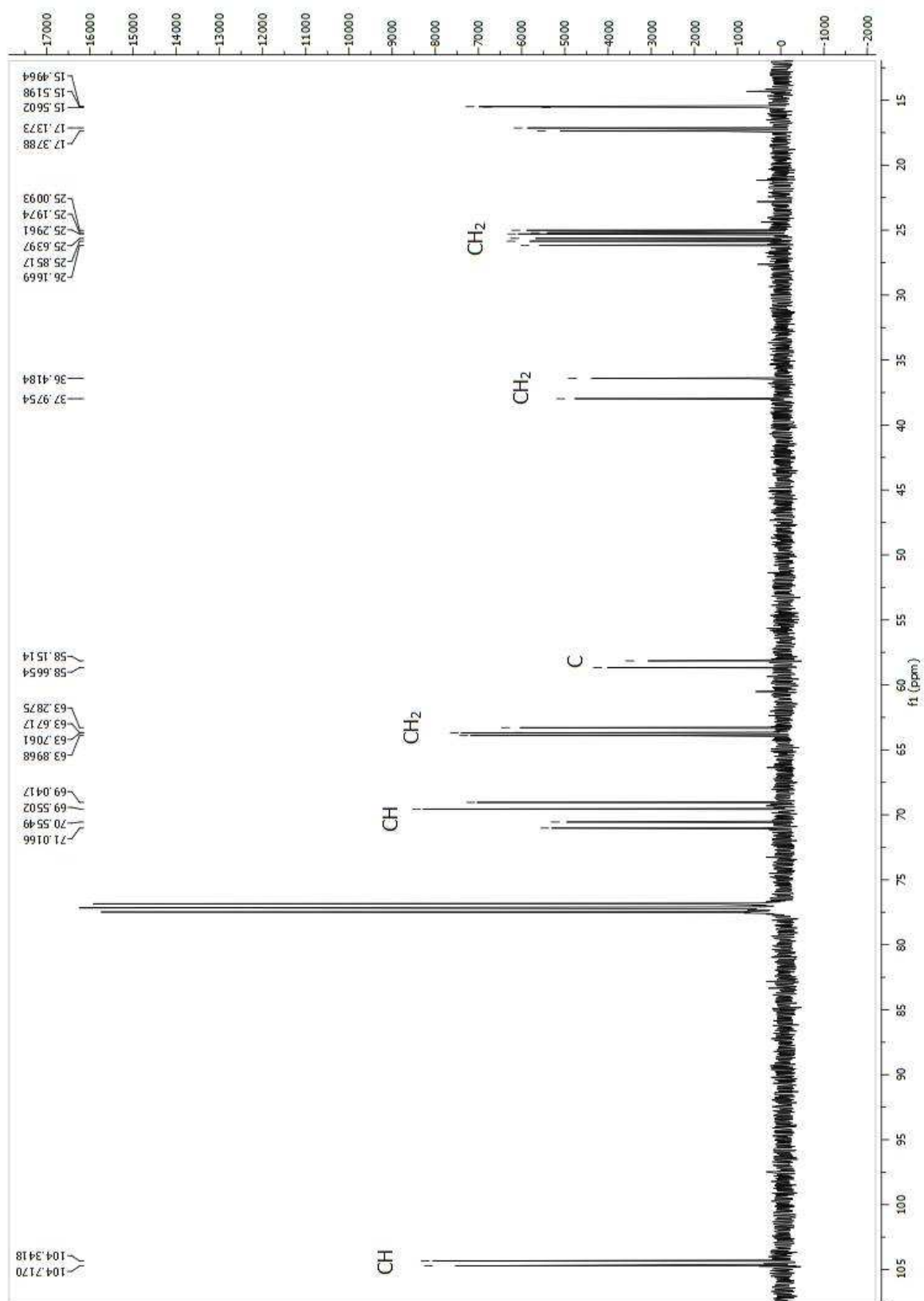
Scheme A.11: ^{13}C-NMR spectrum of 1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol (**8a**).
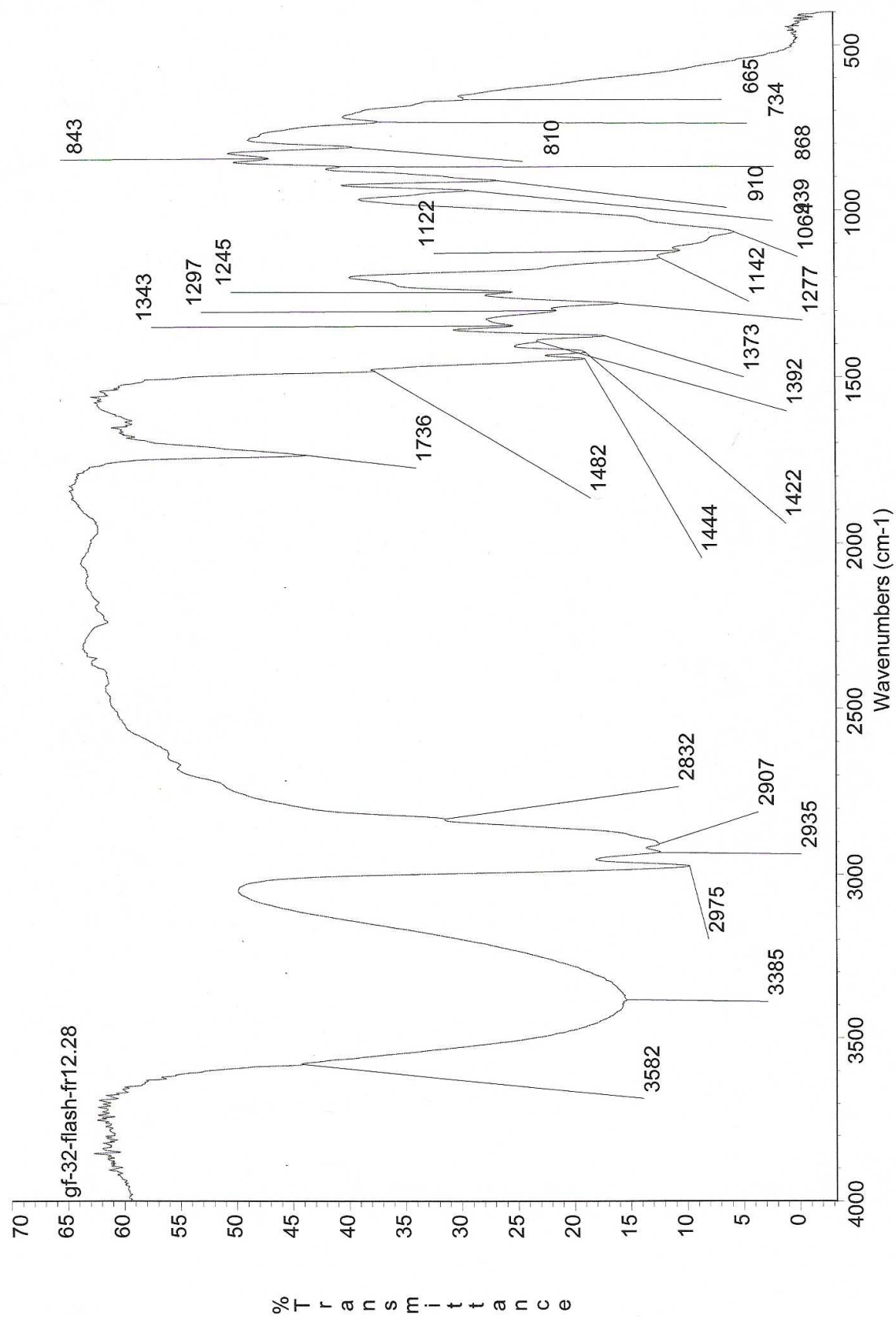
Scheme A.12: *IR spectrum of 1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol (**8a**).*
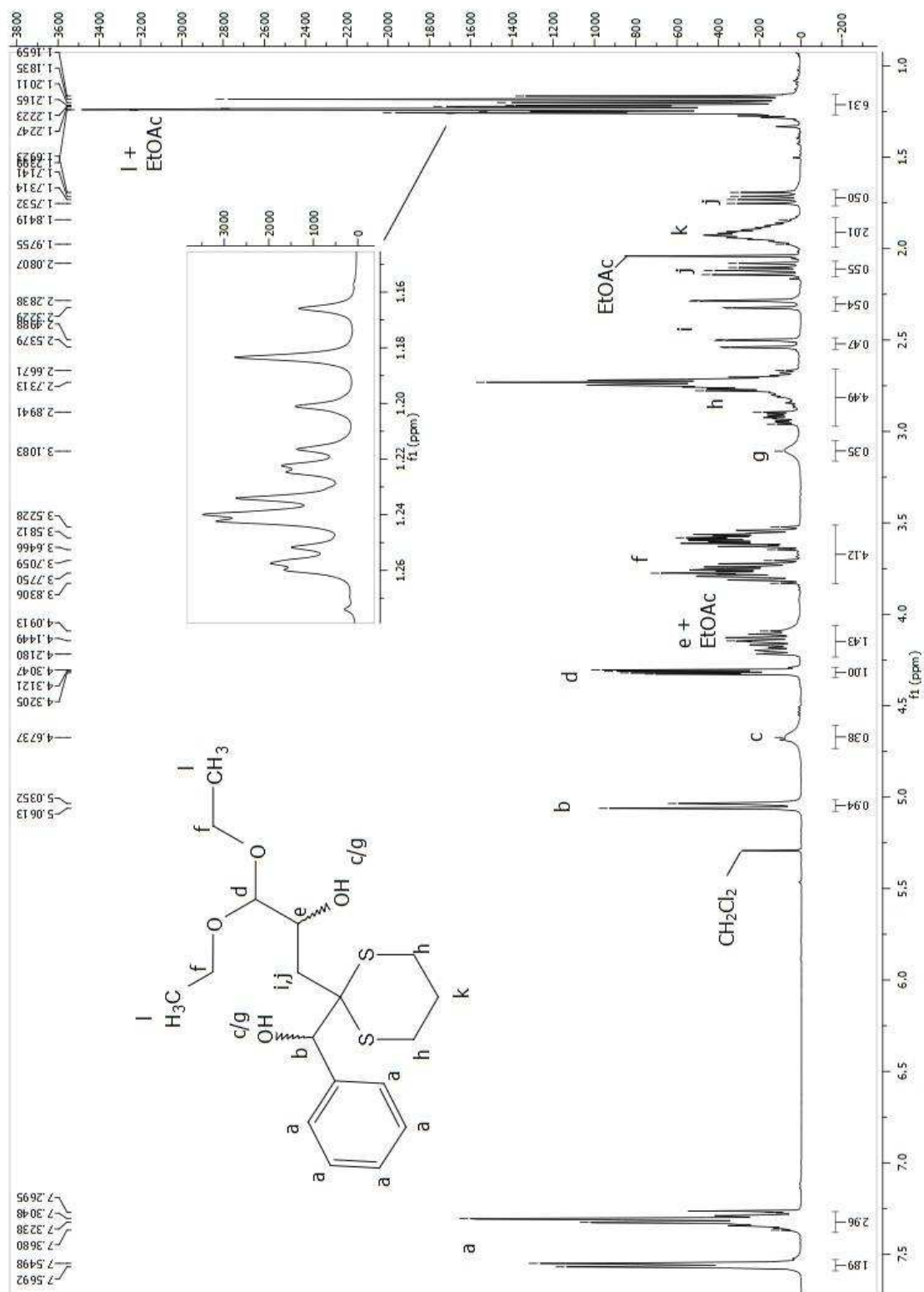
Scheme A.13: ^{1}H-NMR spectrum of 5,5-Diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol **(8b)**.
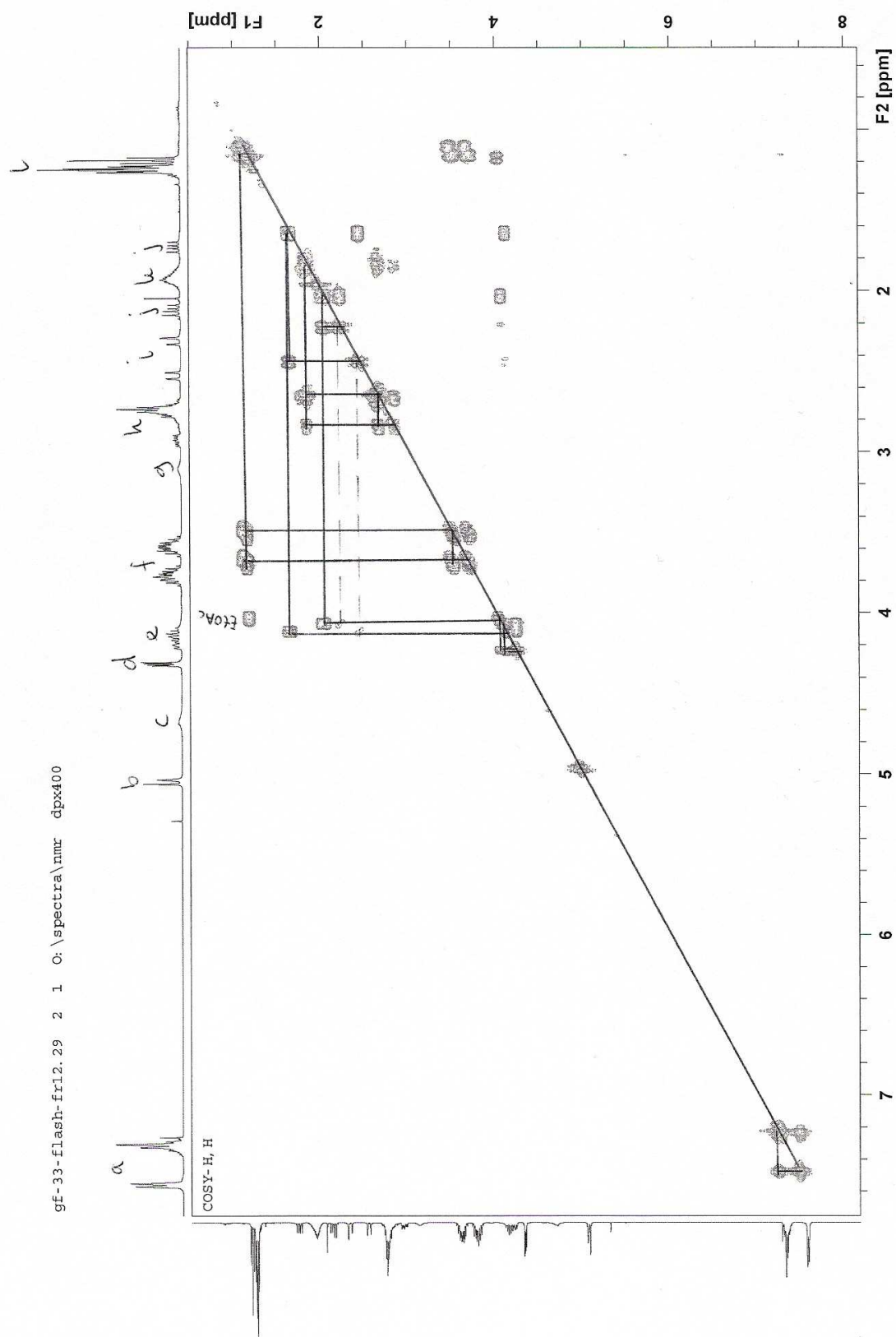
Scheme A.14: COSY-H,H spectrum of 5,5-Diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8b**).
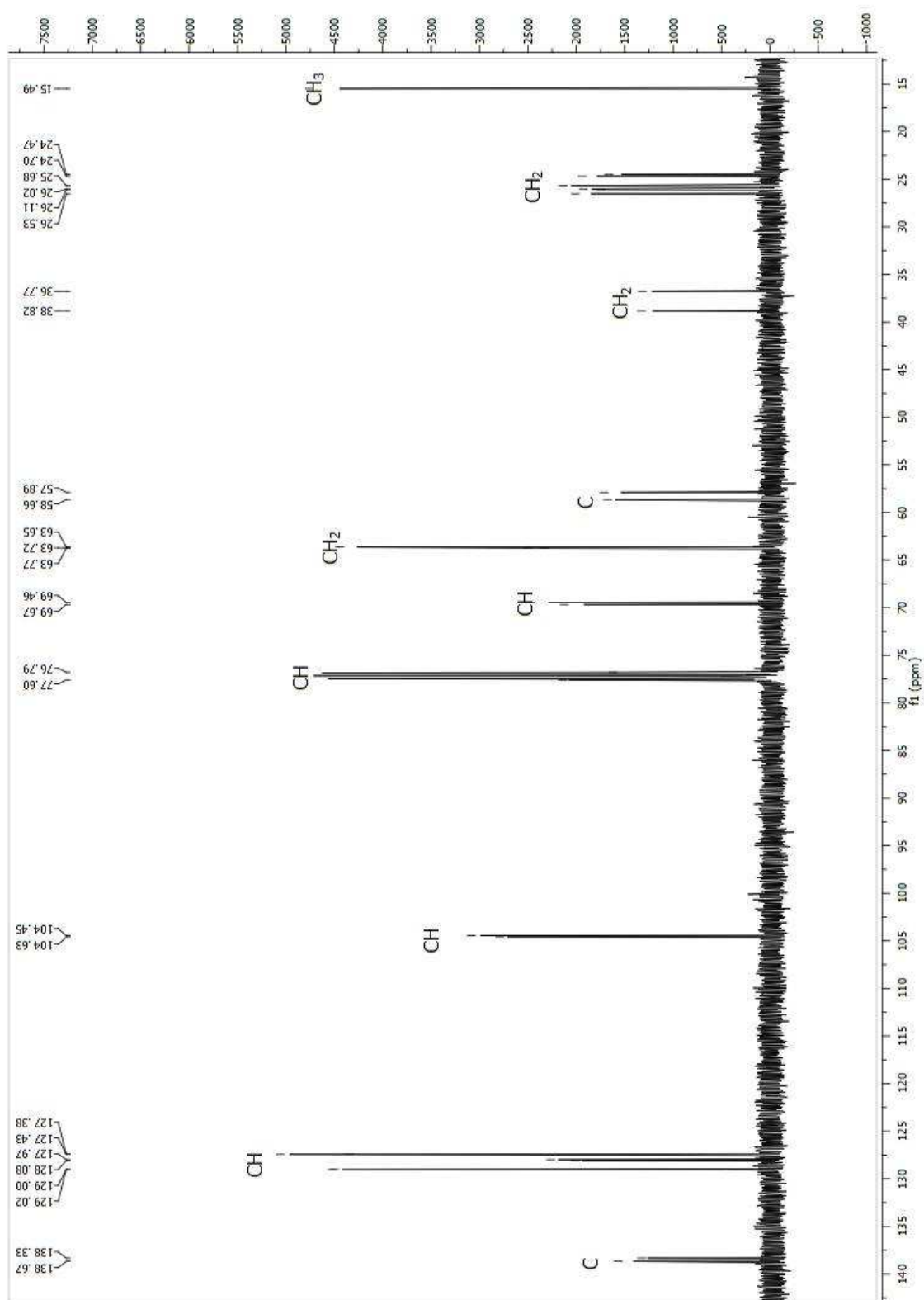
Scheme A.15: ^{13}C-NMR spectrum of 5,5-Diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8b**).
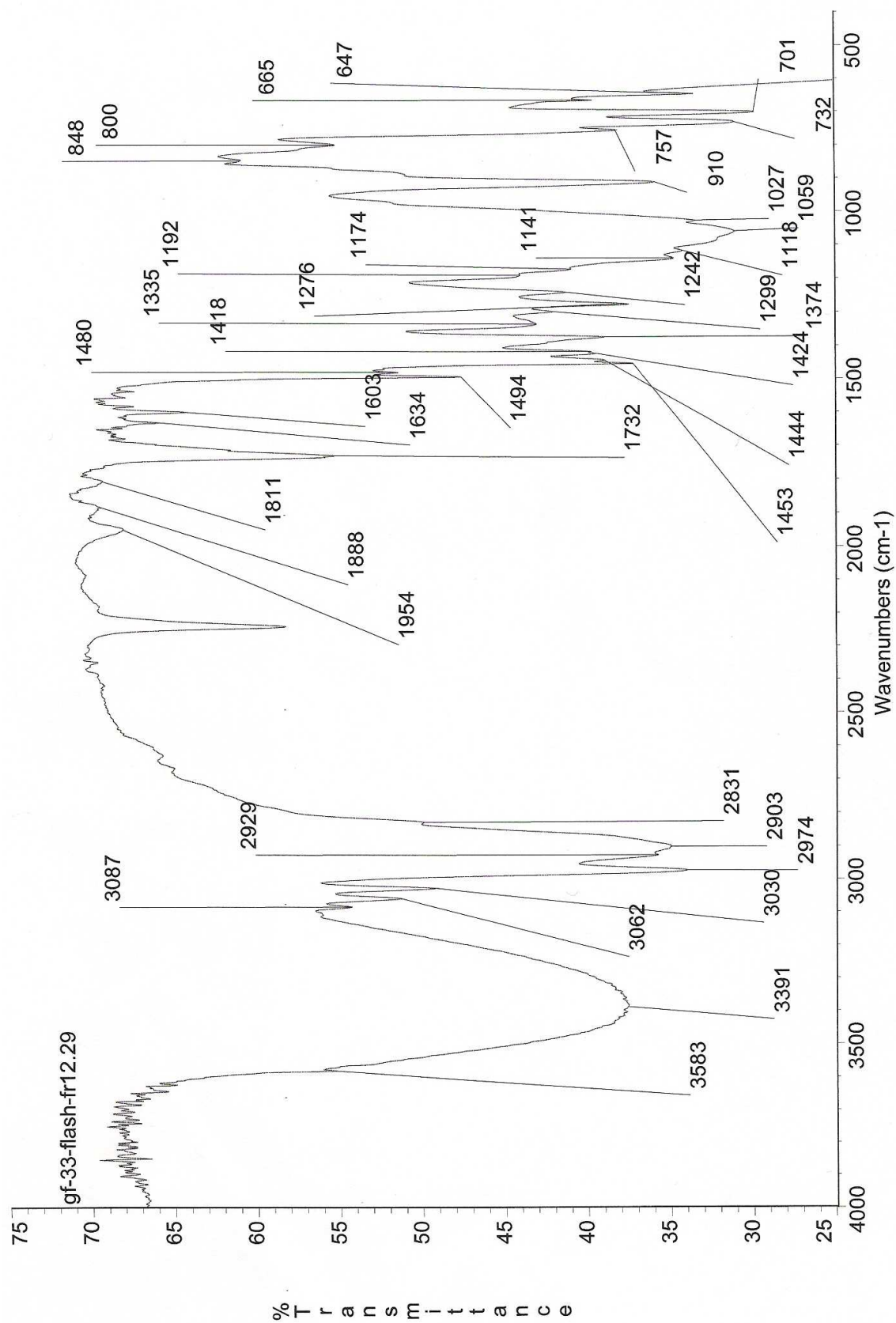
**Scheme A.16:** *IR spectrum of 5,5-Diethoxy-1-phenyl-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8b**).*
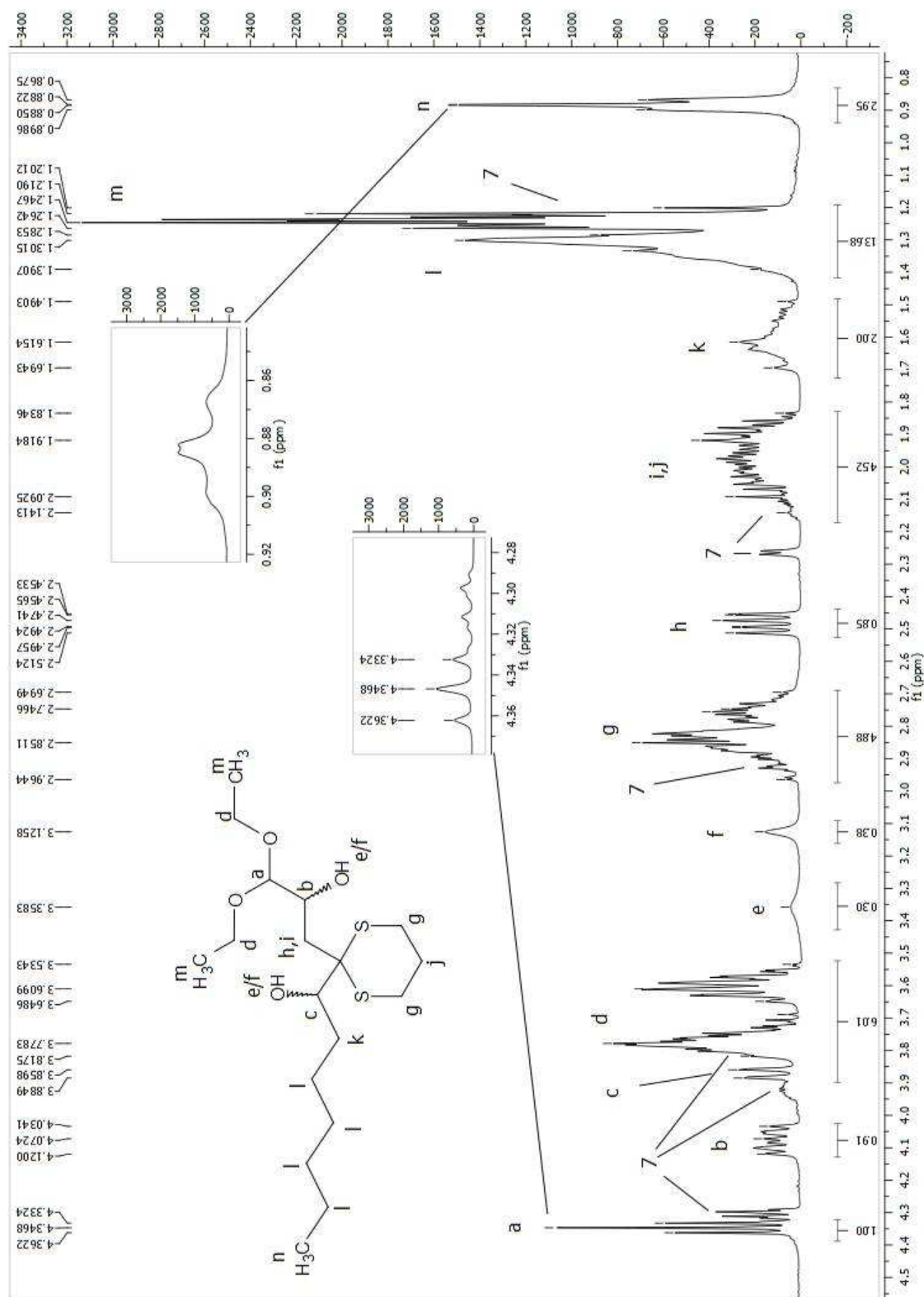
Scheme A.17: ^{1}H-NMR spectrum of the mixture of alcohol **7** and 1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)undecane-2,5-diol (**8c**).
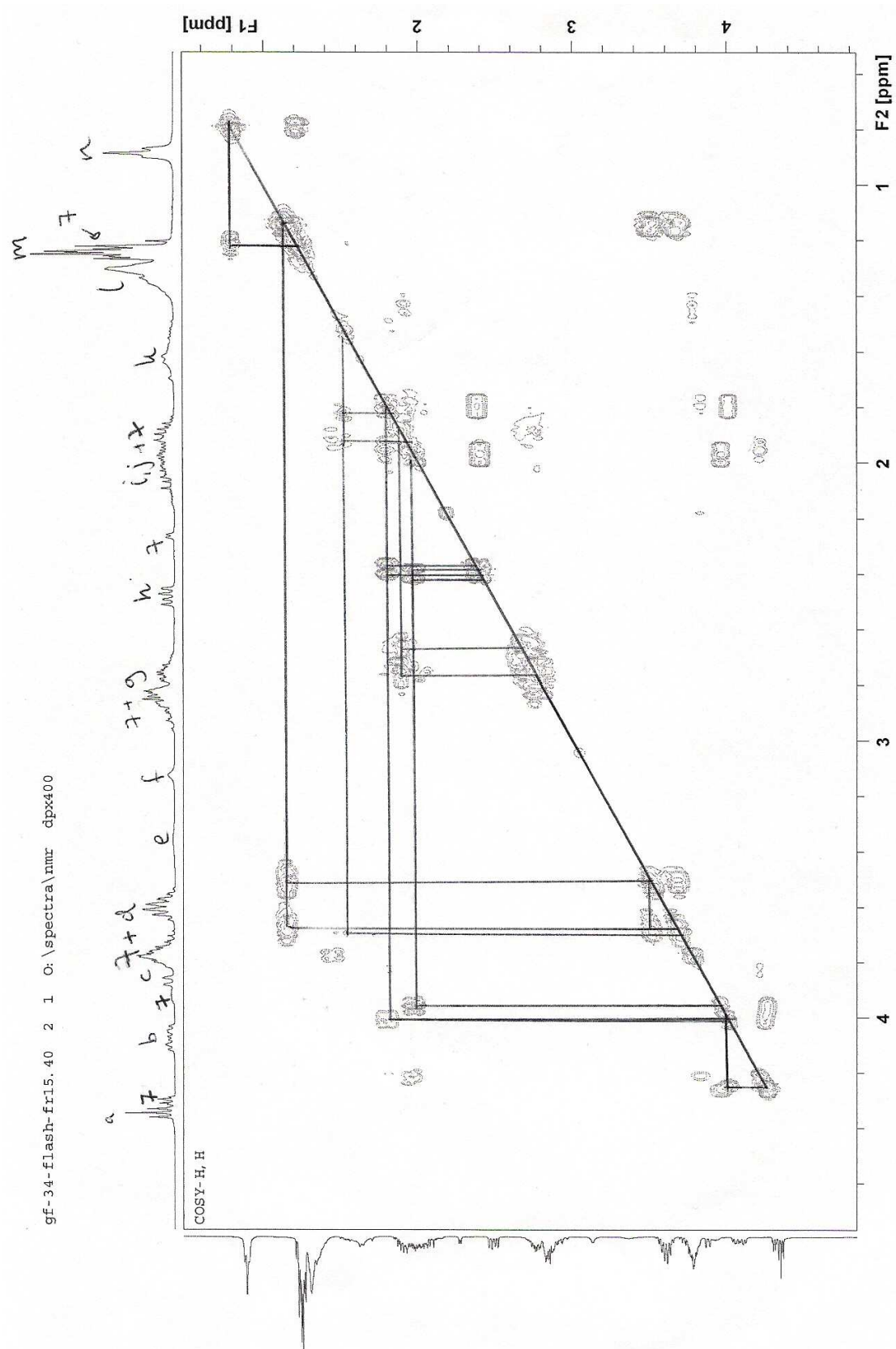
Scheme A.18: COSY-H,H spectrum of the mixture of alcohol **7** and 1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)undecane-2,5-diol (**8c**).
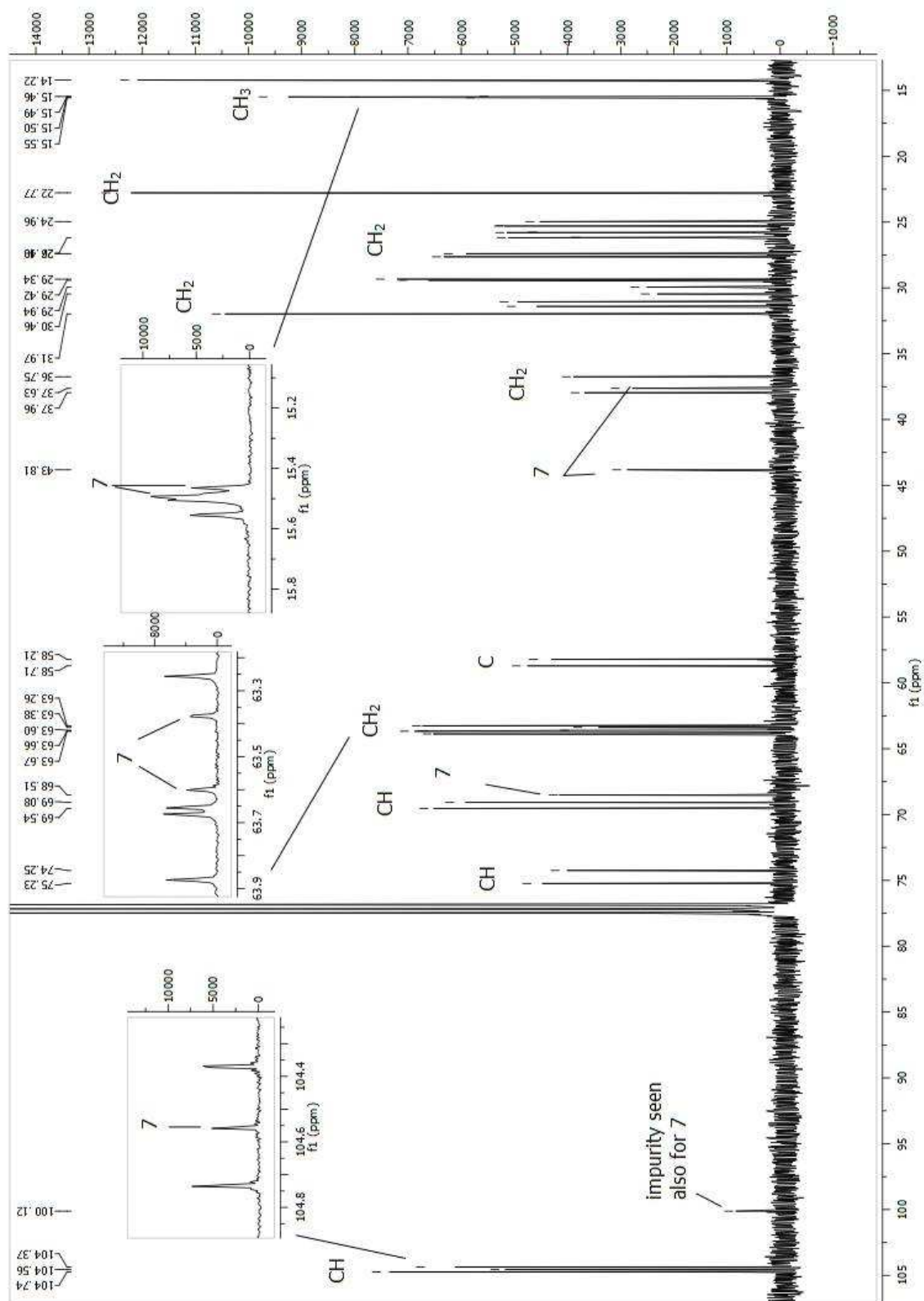
Scheme A.19: ^{13}C-NMR spectrum of the mixture of alcohol **7** and 1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)undecane-2,5-diol (**8c**).
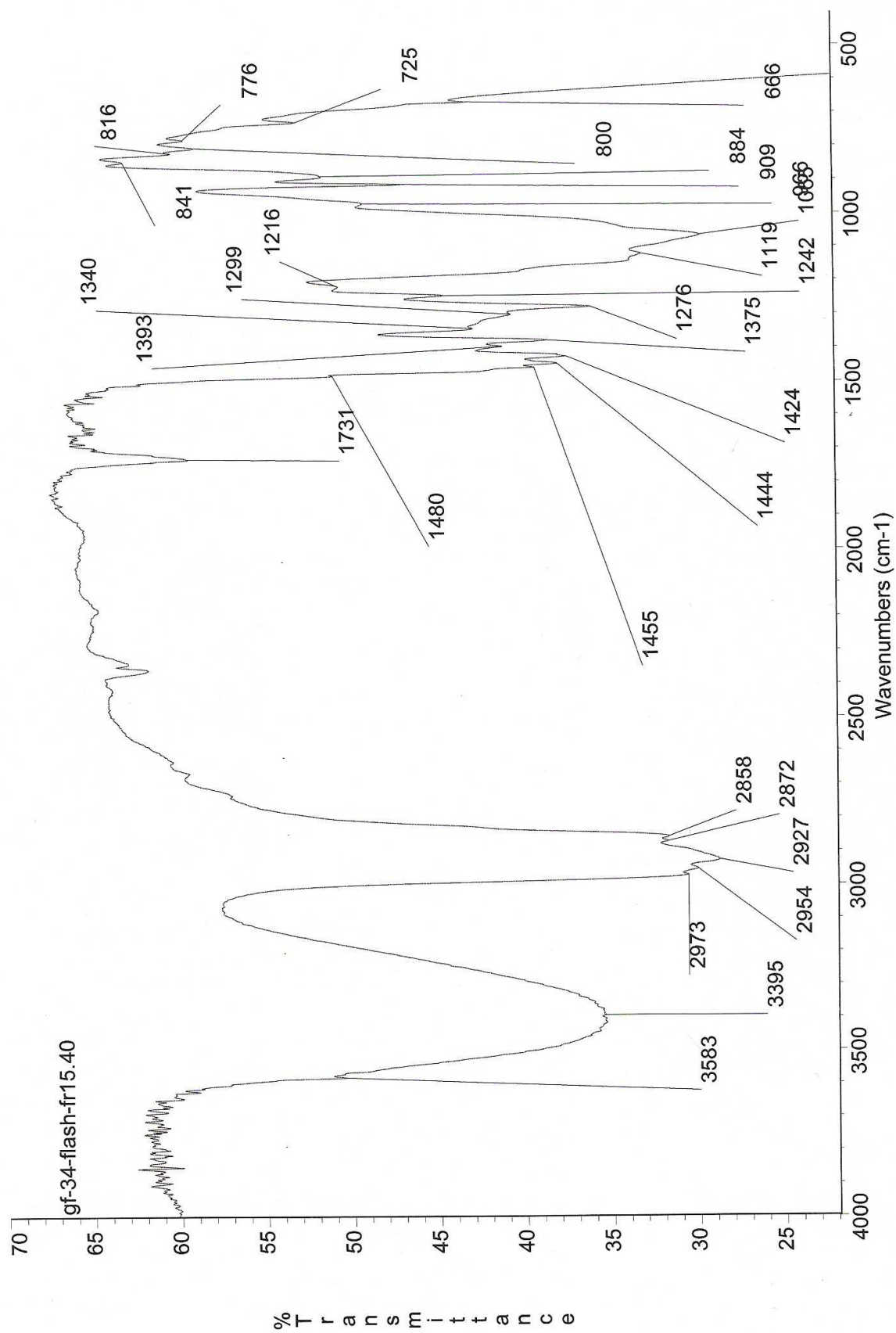
Scheme A.20: *IR spectrum of the mixture of alcohol **7** and 1,1-Diethoxy-4,4-(propyl-1,3-disulfanyl)undecane-2,5-diol (**8c**).*
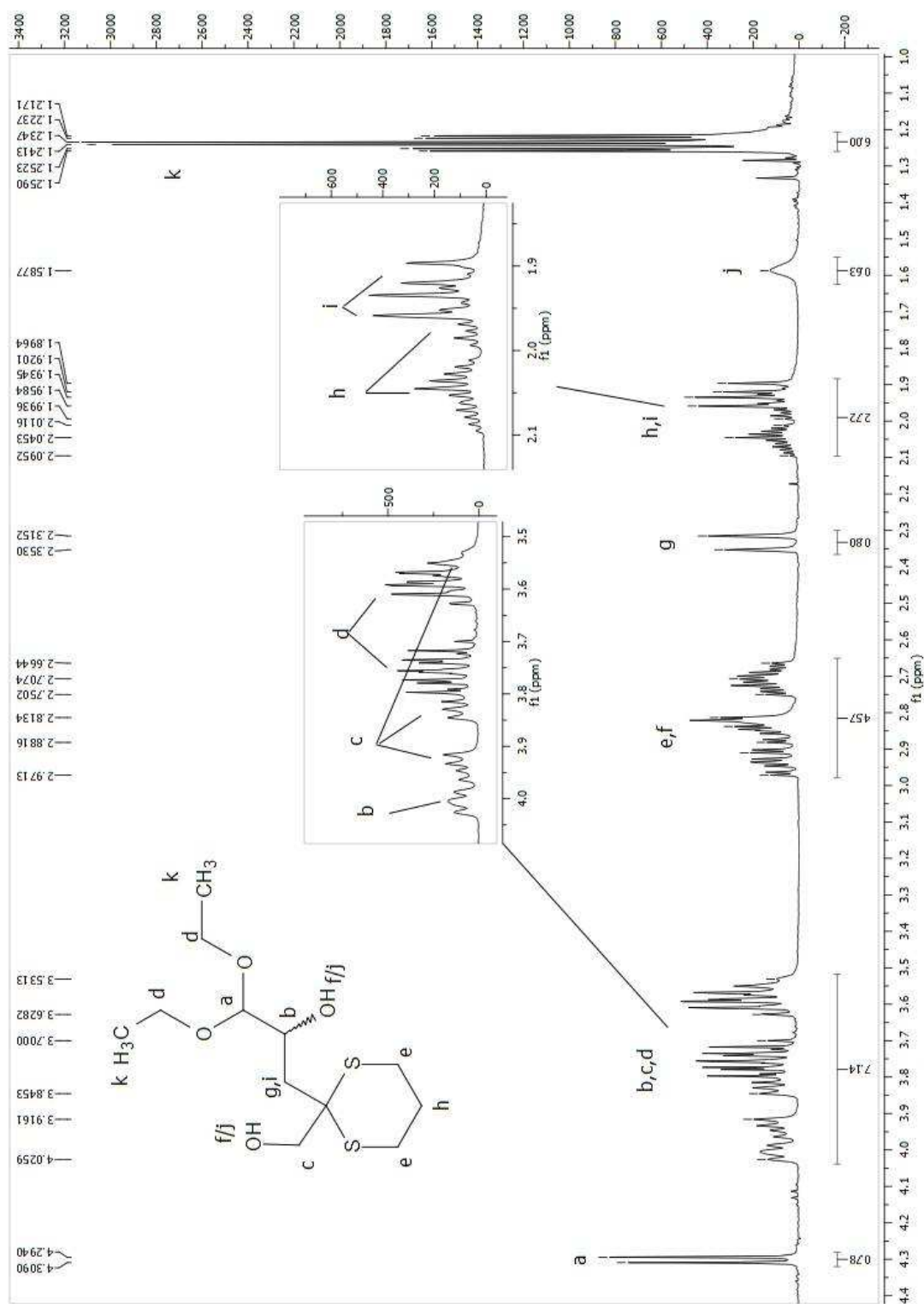
Scheme A.21: *^{1}H-NMR spectrum of 5,5-Diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8d**).*
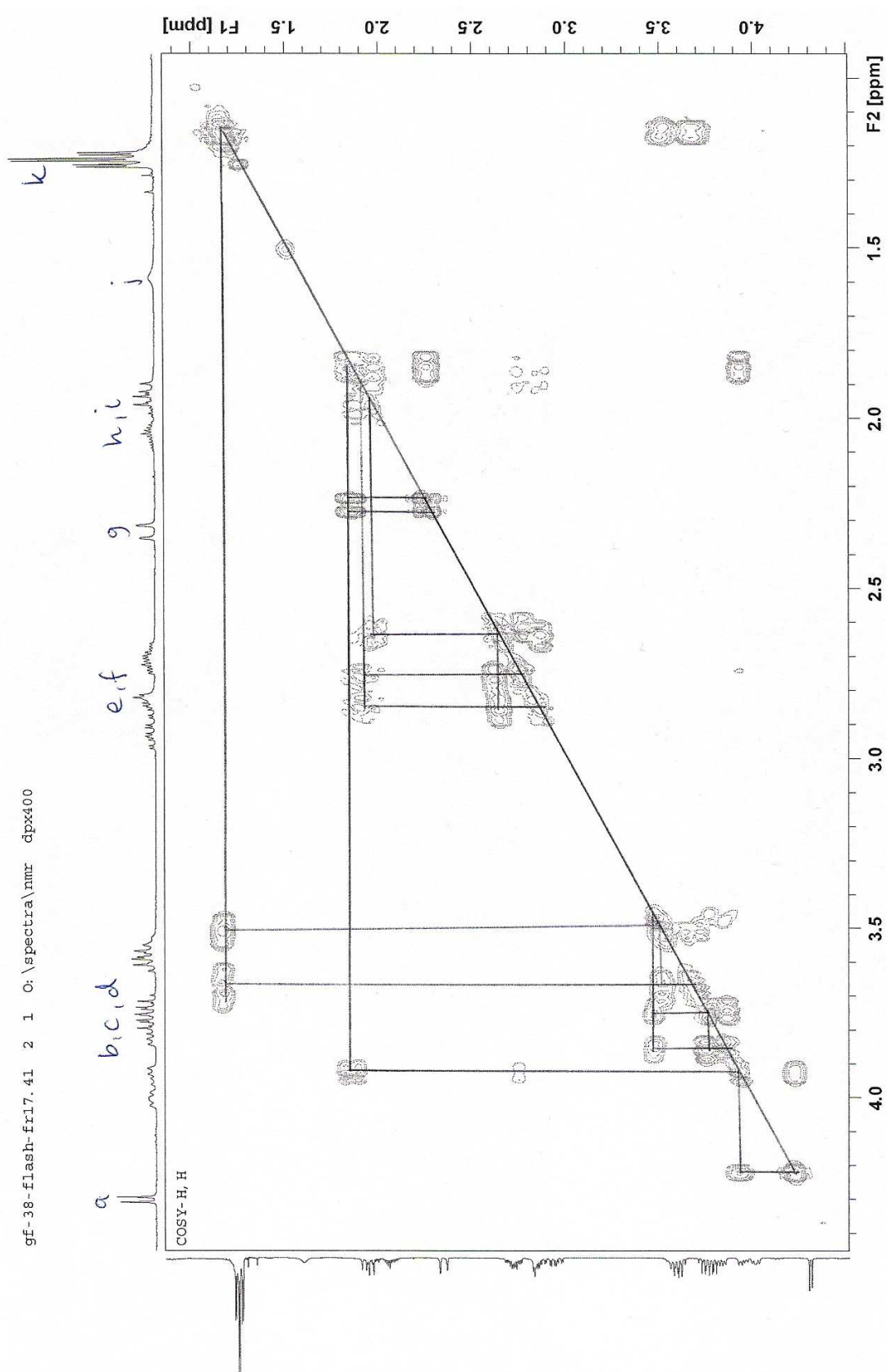
**Scheme A.22:** *DEPT-H,H spectrum of5,5-Diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8d**).*
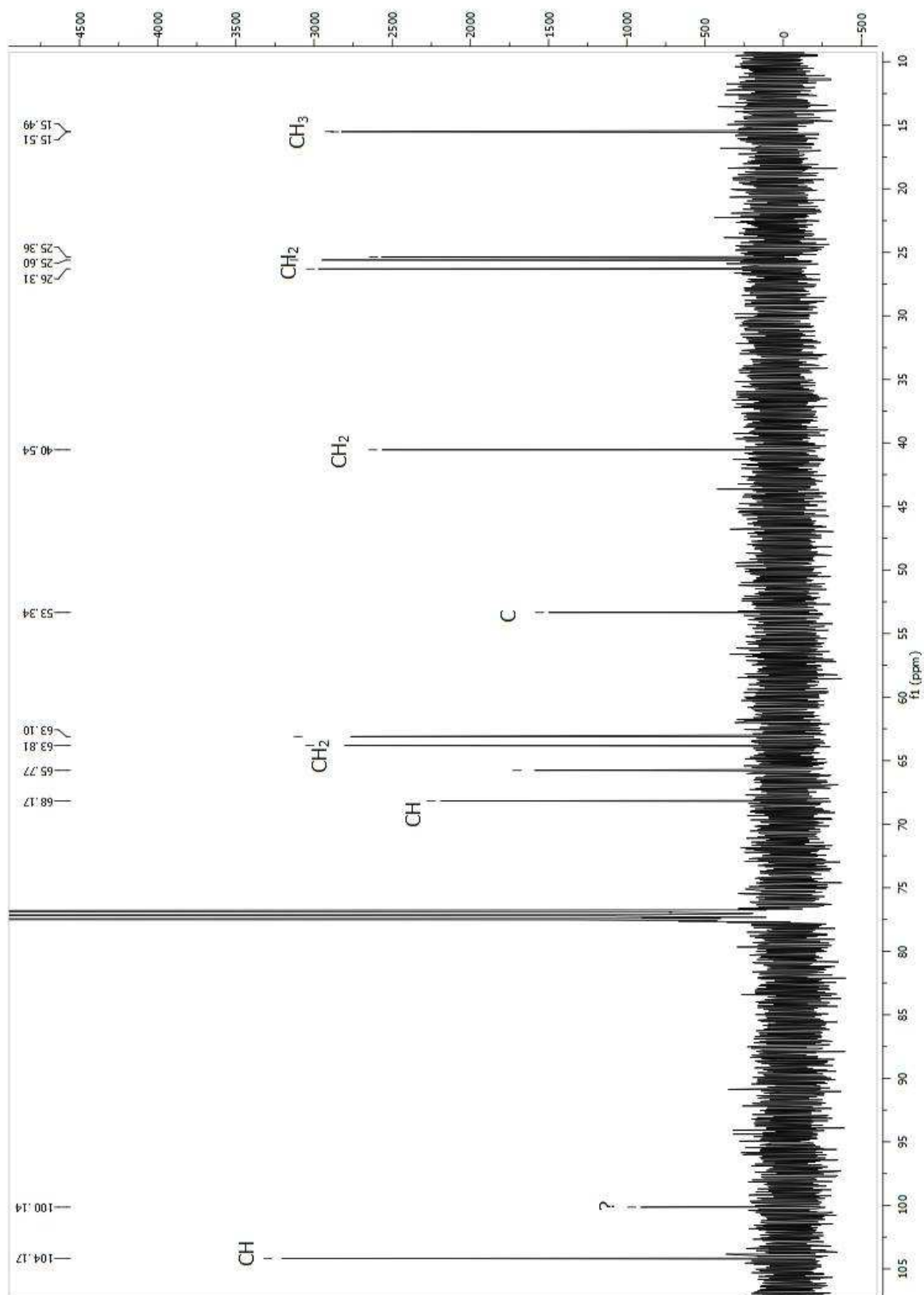
Scheme A.23: ^{13}C-NMR spectrum of 5,5-Diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8d**).
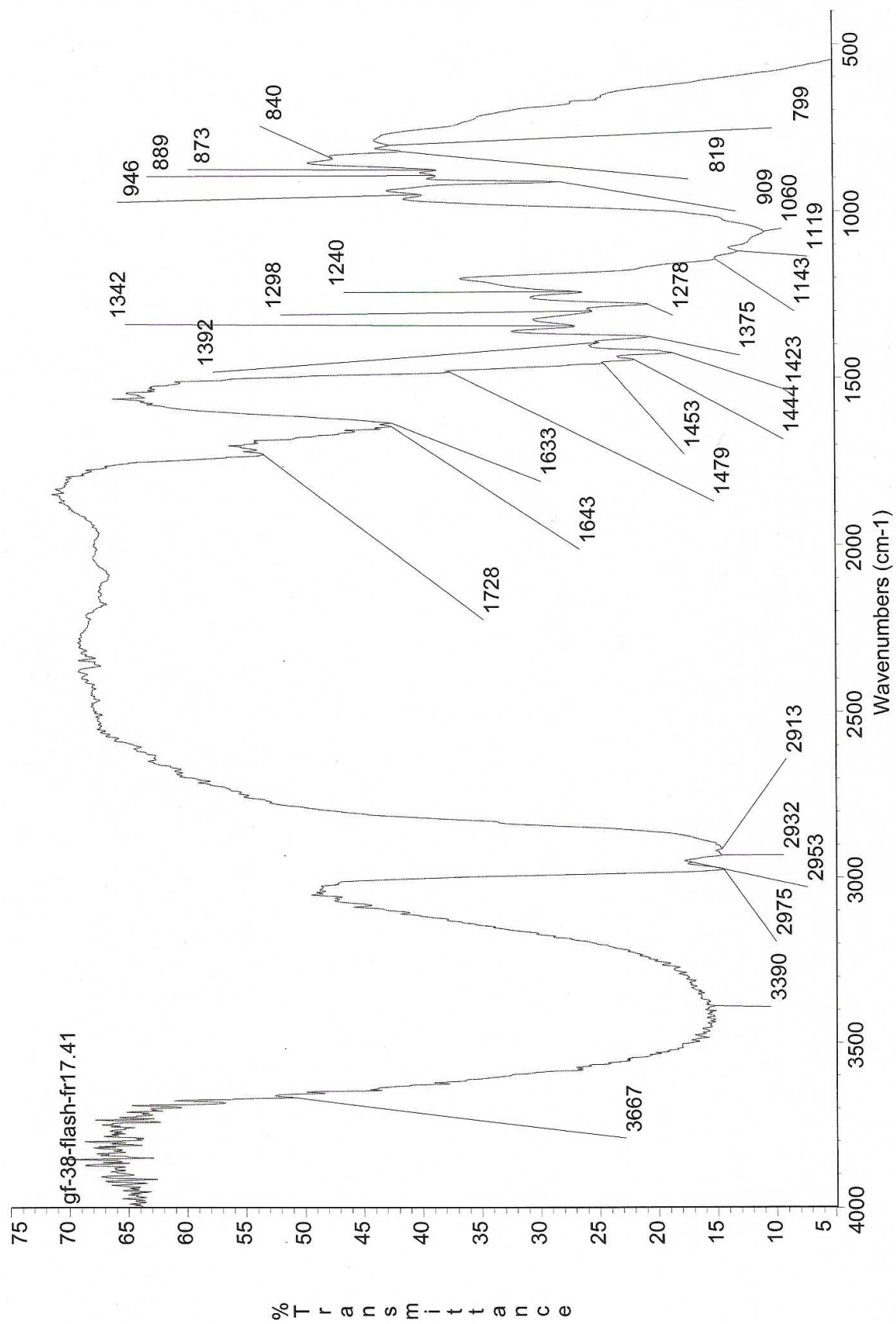
Scheme A.24: *IR spectrum of 5,5-Diethoxy-2,2-(propyl-1,3-disulfanyl)pentane-1,4-diol (**8d**).*
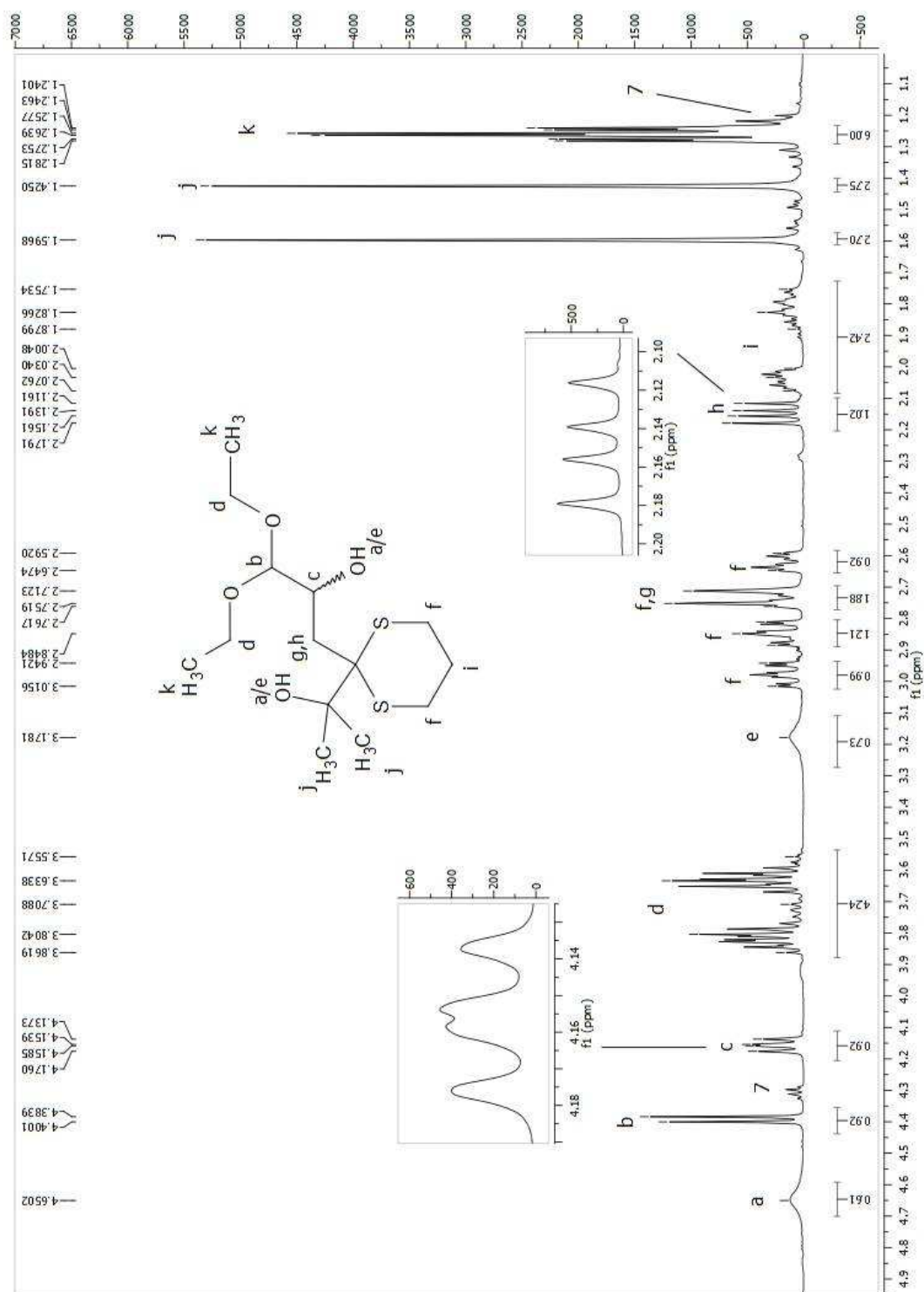
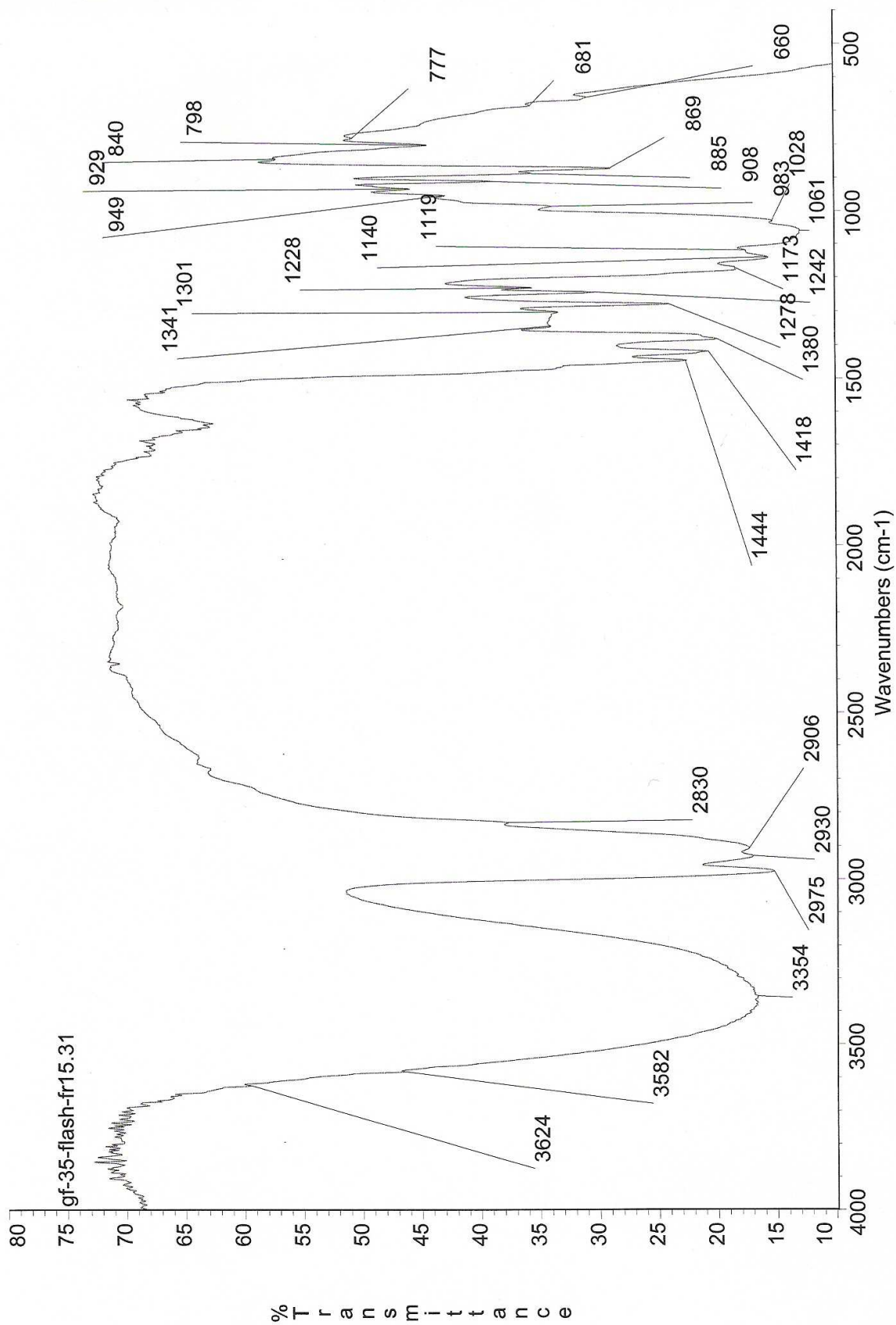**Scheme A.25:** *^{1}H-NMR spectrum of 1,1-Diethoxy-5-methyl-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol (8e).*
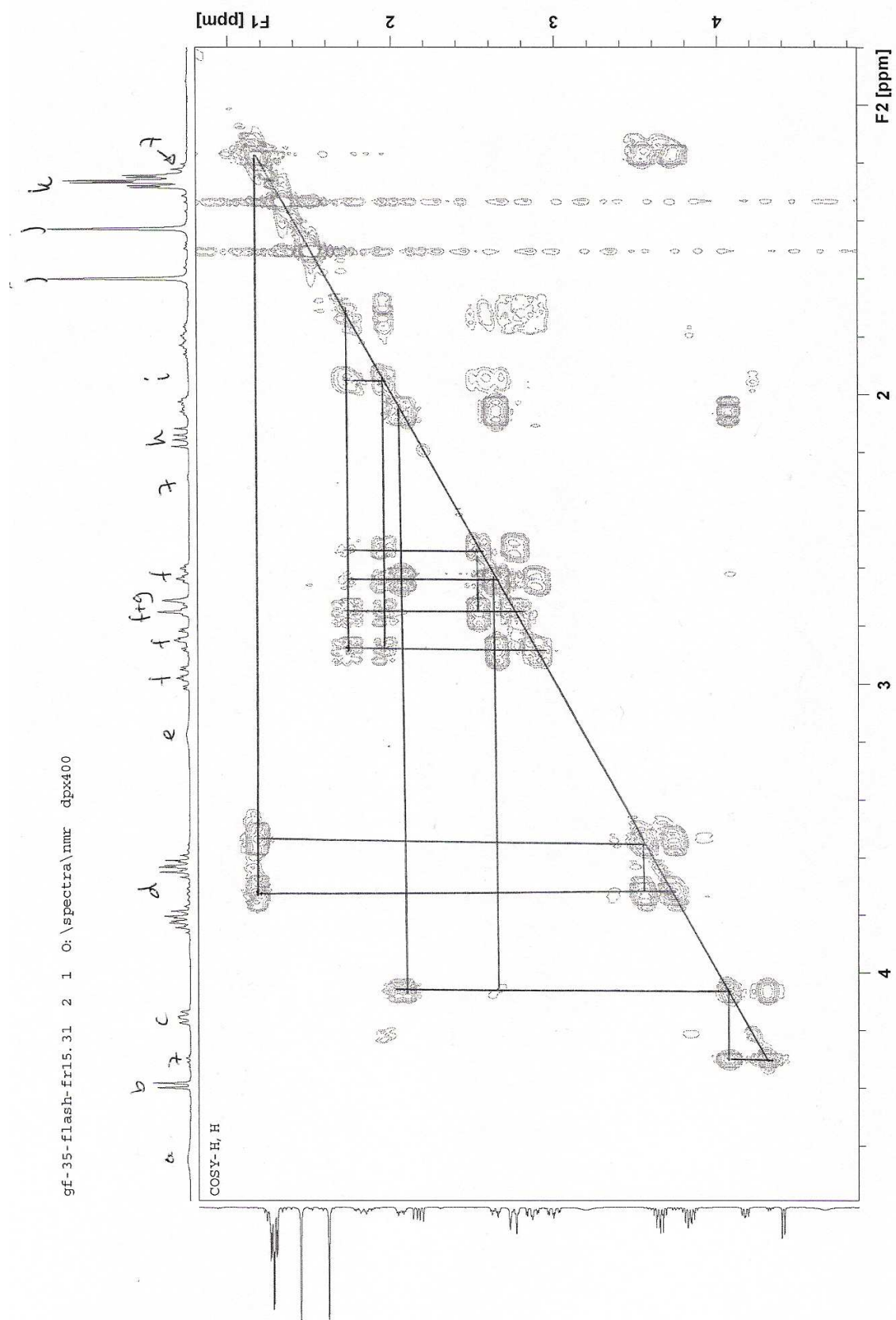
Scheme A.26: COSY-H,H spectrum of 1,1-Diethoxy-5-methyl-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol (8e).
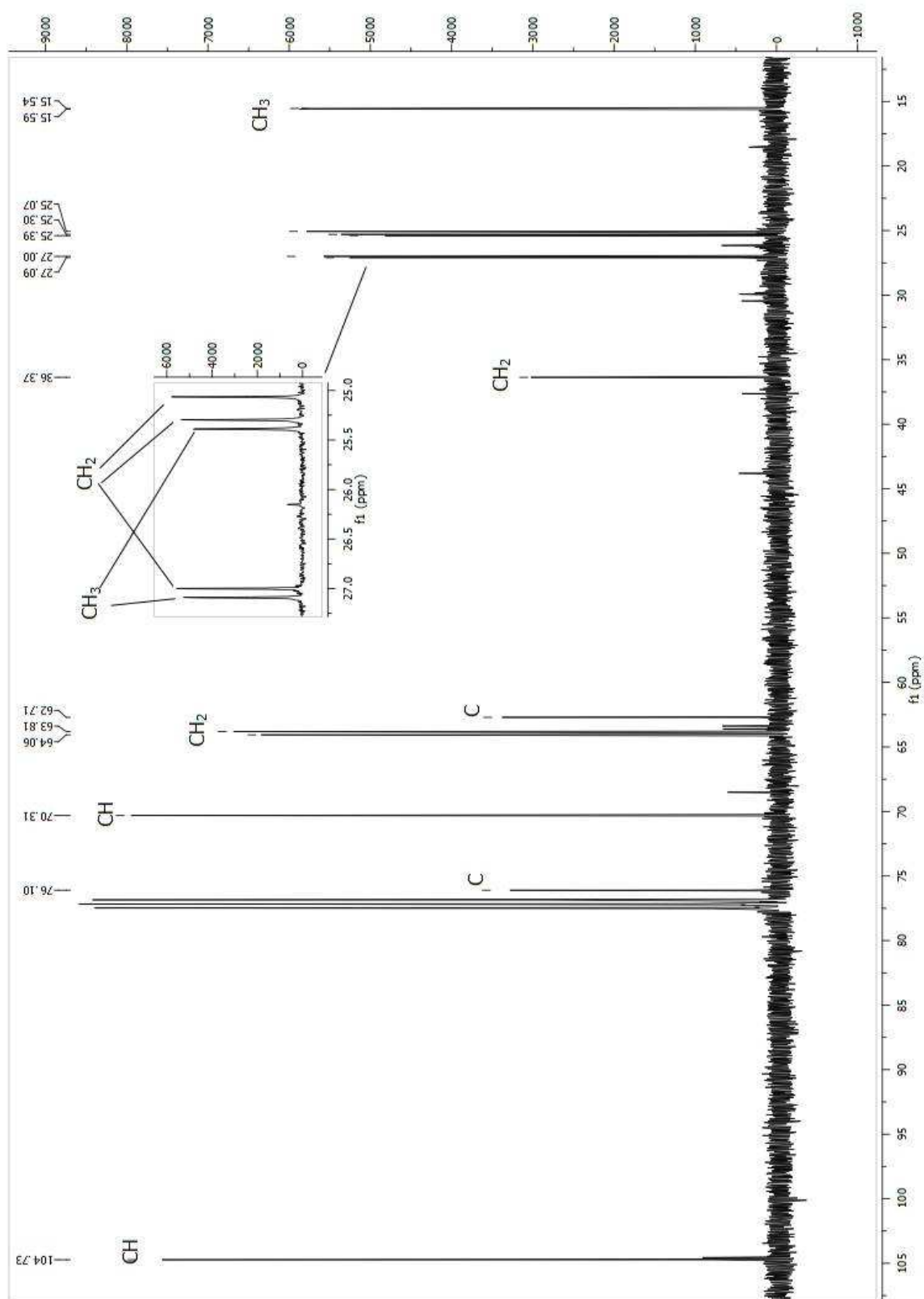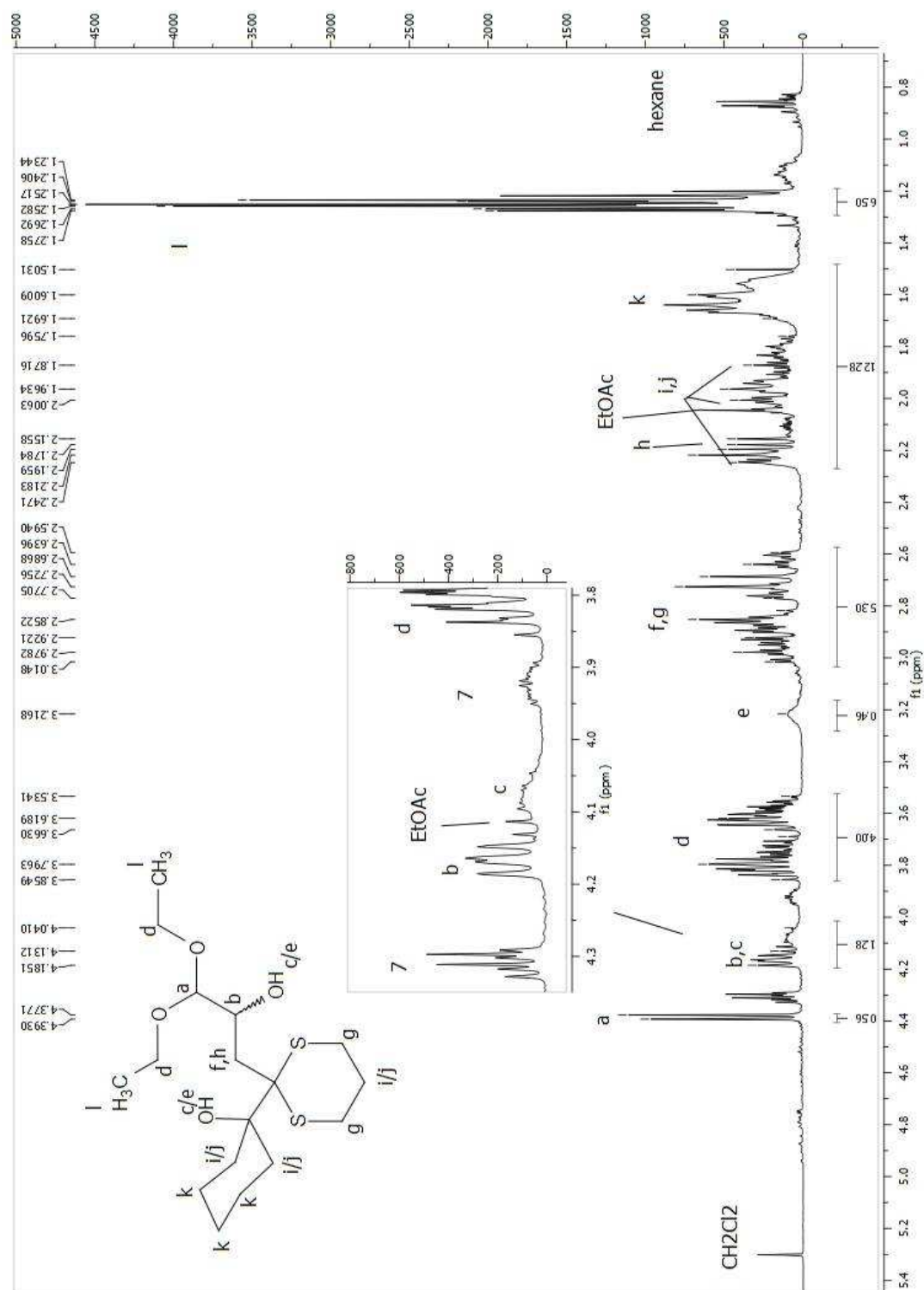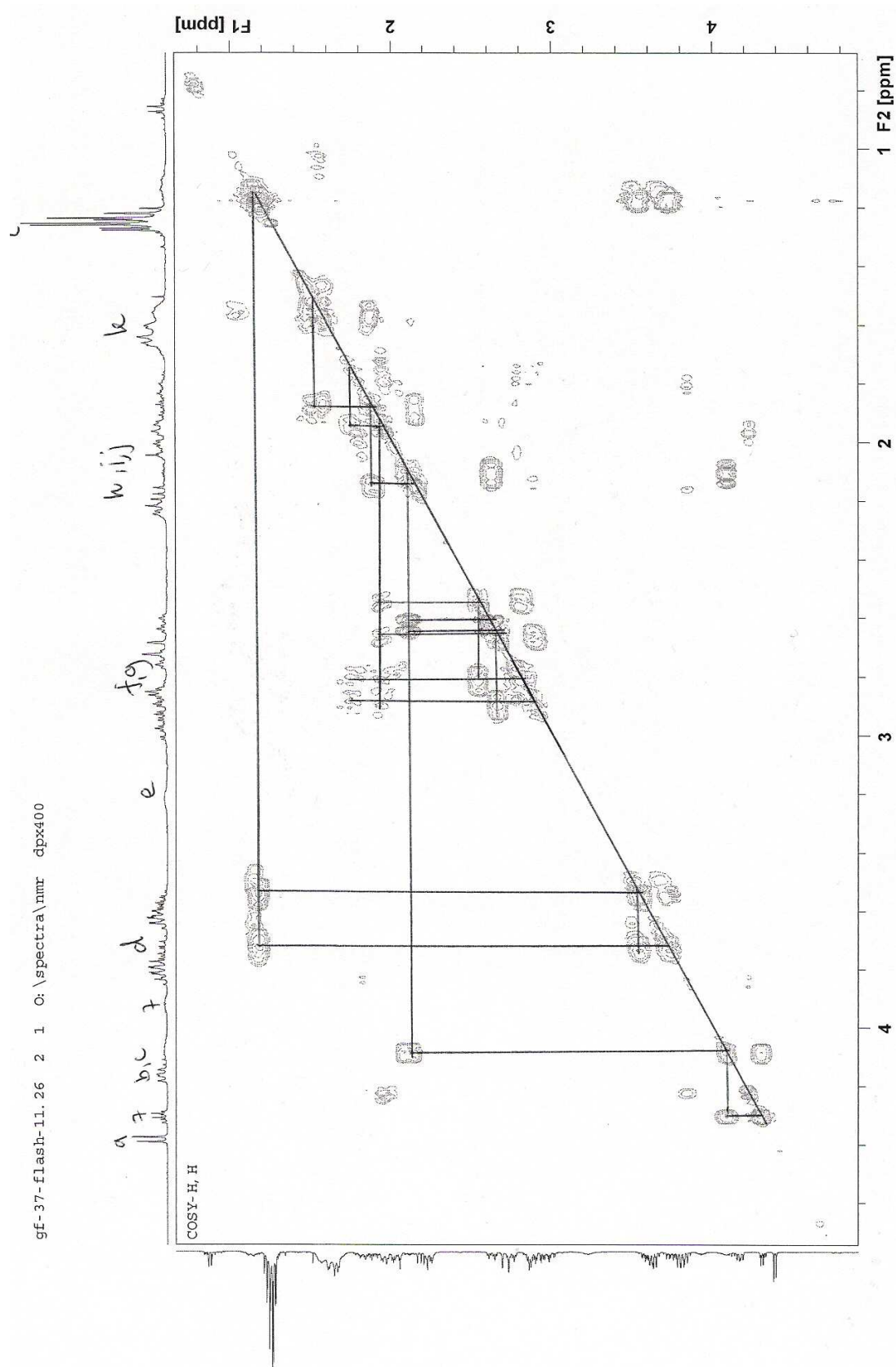
Scheme A.27: ^{13}C-NMR spectrum of 1,1-Diethoxy-5-methyl-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol **(8e)**.
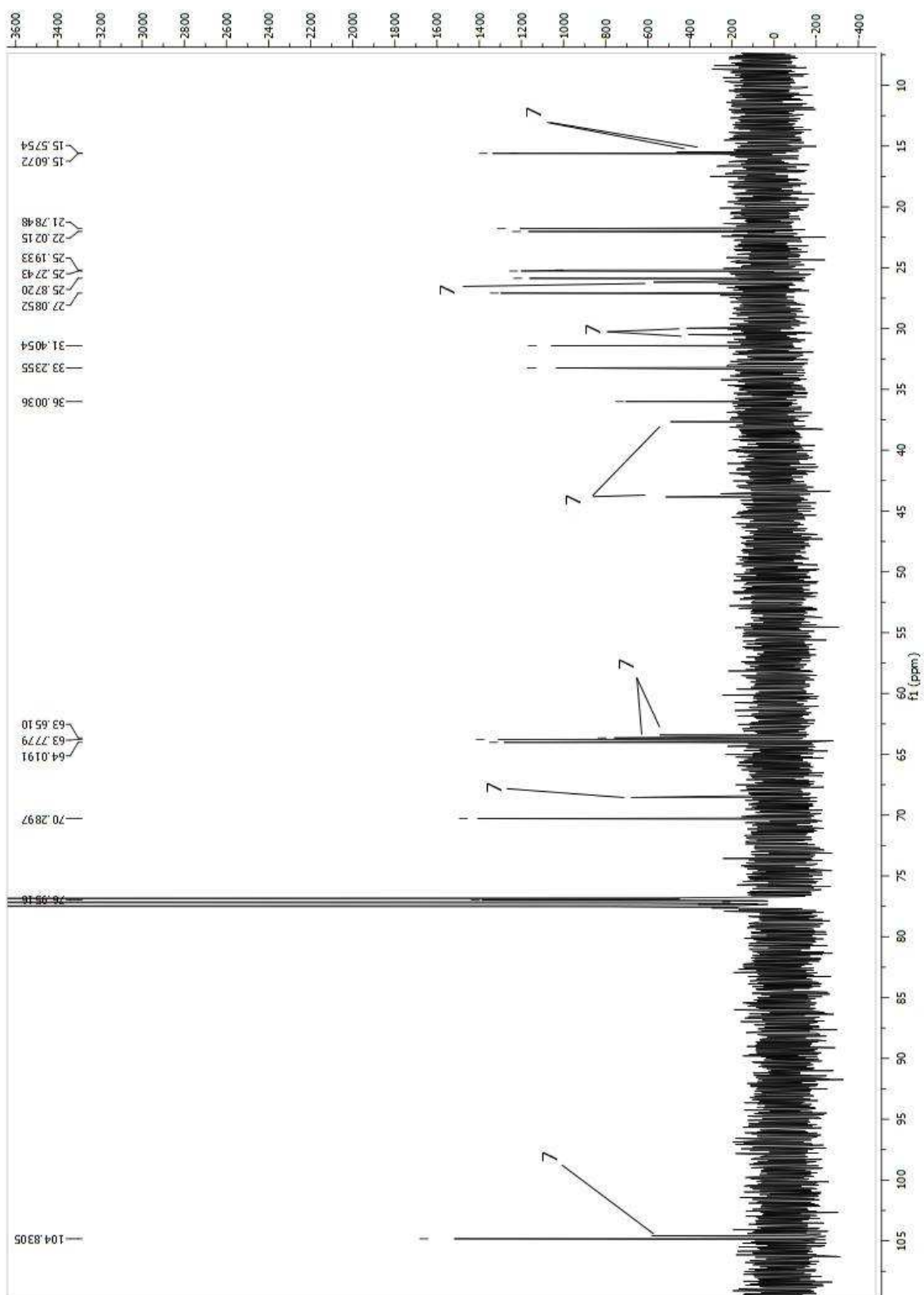
Scheme A.28: *IR spectrum of 1,1-Diethoxy-5-methyl-4,4-(propyl-1,3-disulfanyl)hexane-2,5-diol (**8e**).*

Scheme A.29: *^{1}H-NMR spectrum of the mixture of alcohol **7** and 1,1-Diethoxy-4-(1-hydroxycyclohexyl)-4,4-(propyl-1,3-disulfanyl)butan-2-ol (**8f**).*

Scheme A.30: COSY-H,H spectrum of the mixture of alcohol **7** and 1,1-Diethoxy-4-(1-hydroxycyclohexyl)-4,4-(propyl-1,3-disulfanyl)butan-2-ol (**8f**).

Scheme A.31: ^{13}C-NMR spectrum of the mixture of alcohol **7** and 1,1-Diethoxy-4-(1-hydroxycyclohexyl)-4,4-(propyl-1,3-disulfanyl)butan-2-ol (**8f**) showing signals from the starting material (**7**).