MASTER THESIS

DEPARTMENT OF CHEMISTRY

Towards the Synthesis of β-Hydroxy 1,3-Dithiane Derivatives

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Thank you dearly

Abstract

The β-hydroxy dithiane, 3-(1,3-dithiane-2-yl)-1,1-diethoxypropan-2-ol, was synthesized from the versatile synthon 3,3,4,4-tetraethoxybut-1-yne (TEB). 1,1-Diethoxy-3-(2-methyl-1,3-dithian-2-yl)propan-2-ol was successfully formed in low yield (13%) by an alkylation reaction involving the dithiane and MeI in the presence of *n*-BuLi.

An attempt at a silylation reaction using the dithiane failed to produce the trimethylsilyl protected hydroxy derivative. Hydrolysis of the benzyl protected β-hydroxy dithiane was successful (35%) but attempted chain elongation of the corresponding aldehyde using Wittig olefination failed.

Alternative procedures for synthesizing 1,1-diethoxybut-3-yn-2-one (TEB-ketone), needed in the formation of the β-hydroxy dithiane, were explored. As a result, a new a three-step method for generating the TEB-ketone was developed. A novel four-step synthesis of the β-hydroxy dithiane from easily available and inexpensive ethyl 2,2-diethoxyacetate is also described.

Selected Abbreviation

^{13}C	Carbon-13 nucleus
^{1}H	Hydrogen-1 nucleus
aq	Aqueous
Bn	Benzyl
DCM	Dichloromethane
eq	Equivalent(s)
hr	Hour(s)
IR	Infrared
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
rt	Room temperature
TBAHS	Tetrabutylammonium hydrogensulfate
TBAI	Tetrabutylammonium iodide
TEB	3,3,4,4-Tetraethoxybut-1-yne
TEB-ketone	1,1-Diethoxybut-3-yn-2-one
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl

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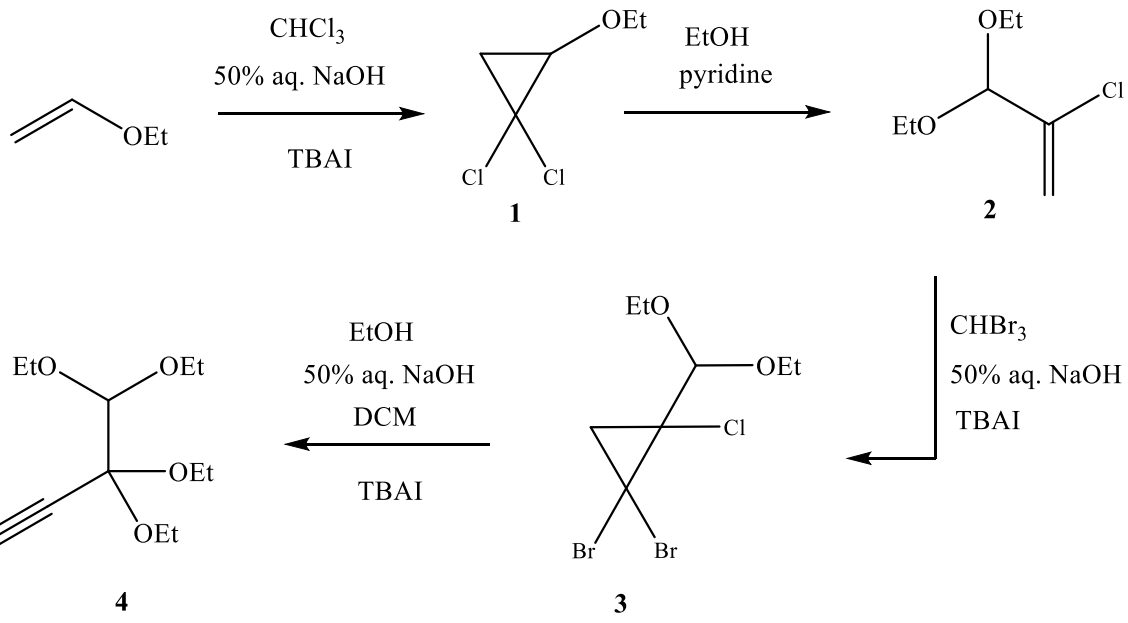
Scientific background

1 Synthesis of TEB

For years 3,3,4,4-tetraethoxybut-1-yne, referred to as TEB, has served as the key molecule of the Sydnes research group. This is due to it being densely functionalized and an excellent starting material for many valuable reactions. The compound is synthesized in four steps using ethyl vinyl ether as starting material. The first and third steps involve a Makosza-Wawrzyniewicz cyclopropanation, while the second and fourth steps involve thermal and base-induced ring-opening reactions, respectively, with subsequent attack of ethanol (Scheme 1).[1]



Scheme 1: The four-step synthesis of TEB from ethyl vinyl ether

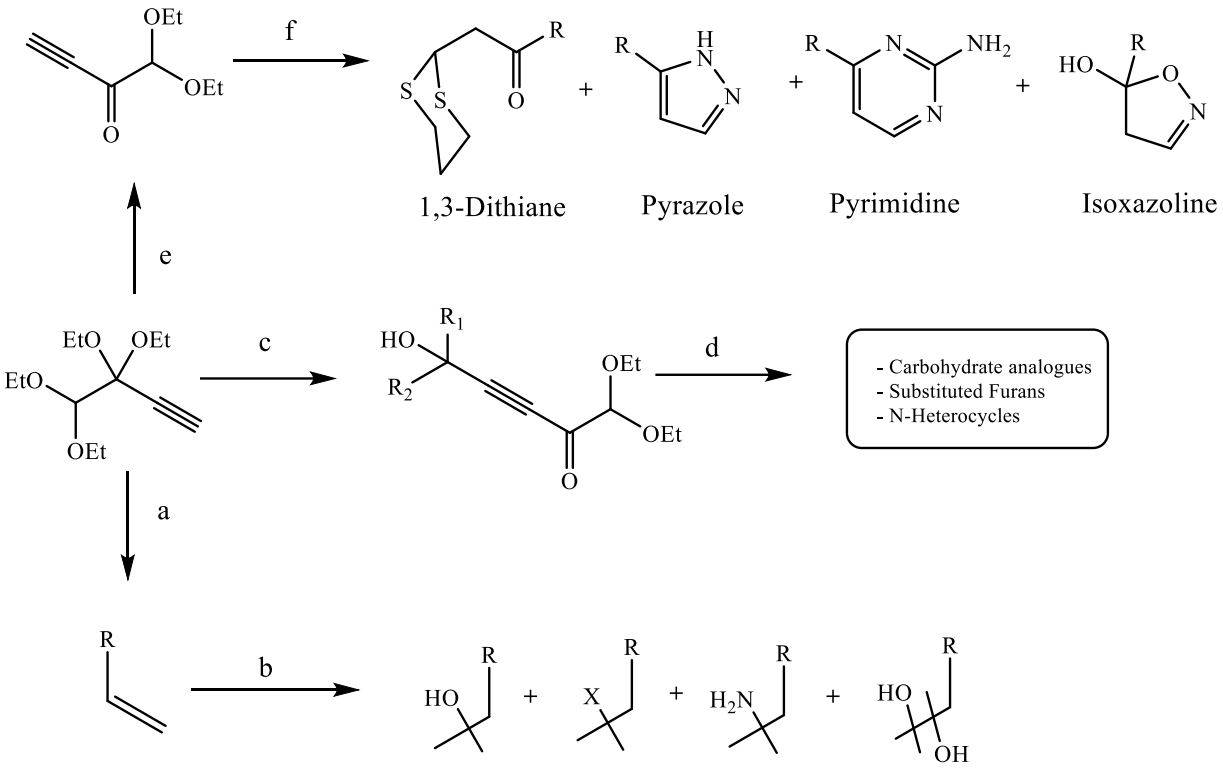
TEB is thermally quite stable and survives both neutral and basic conditions. Under acidic conditions on the other hand, it undergoes valuable transformations, such as deketalization.[2] These properties, combined with its high density of functional groups, are what makes TEB such a brilliant starting material in organic synthesis.

1.1 Synthetic transformations with TEB

Some of the wide range of reactions that TEB undergoes are summarised in scheme 2 below. The terminal acetylene could selectively be reduced either by hydrogenation or hydride reduction to the corresponding alkene (route a).[3] The alkene can subsequently undergo a variety of common olefin transformations like hydration, hydrogenation, hydroamination and dihydroxylation (route b).

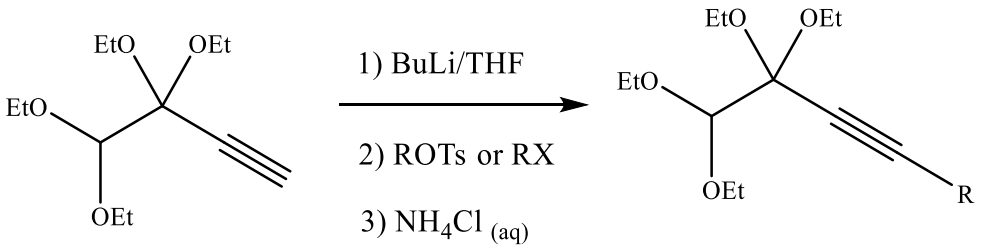
Due to the acidic nature of terminal alkynes, the acetylenic proton of TEB can be abstracted by a strong base, such as BuLi. The acetylide that is formed can then undergo a broad spectrum of different chain-elongation reactions with electrophiles, for instance, aldehydes or ketones to form propargylic alcohols (route c). After chain elongation, numerous different compounds can be made, inluding carbohydrate analogues, substituted furans and *N*-heterocycles (route d).[4, 5]

As TEB contains both an acetal and a ketal moiety, one could expect deprotection under acidic conditions to result in the formation of the corresponding ketoaldehyde. However, this does not happen when TEB is reacted, instead only a deketalization reaction occurs and the acetal is left unaffected, as shown in route **e**. The corresponding alkynone, TEB-ketone, is of great interest to this project as it undergoes Michael reactions with different bisnucleophiles to yield various heterocycles (route f).[4, 6, 7] In the case of hydrazine, guanidine, hydroxylamine and 1,3-propane dithiol a secondary reaction happens in which cyclisation occurs. The reaction with hydrazine and guanidine forms the aromatic systems pyrazole and pyrimidine, respectively, through loss of water. On the other hand, hydroxylamine does not give aromatic heterocycles when reacted under similar conditions.[7] In every case, isoxazoline is the only product formed which can ultimately be turned into an aromatic compound.



Scheme 2: A selection of possible TEB transformations

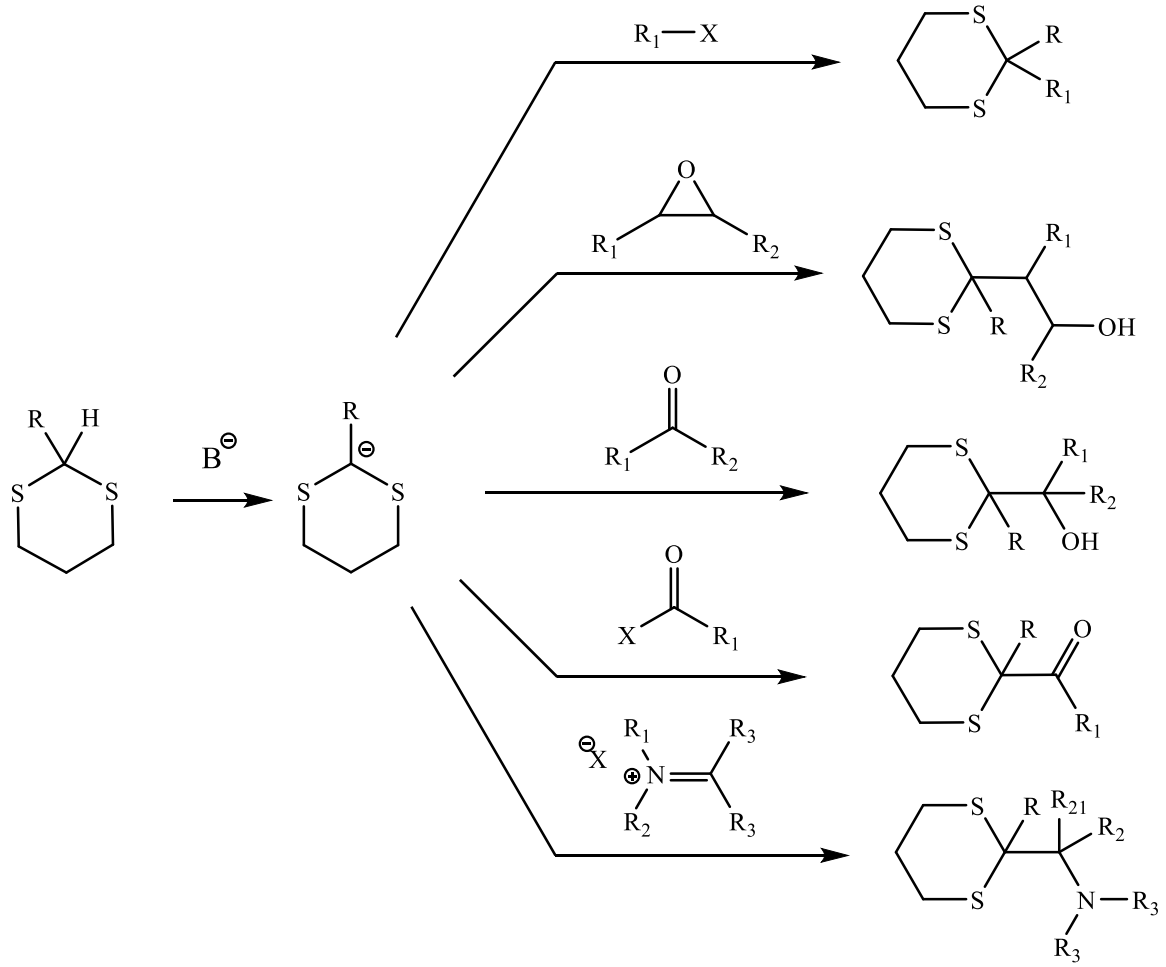
Most recently chain elongation reactions by alkylation of the acetylide using alkyl halides and alkyl tosylates have been researched (Scheme 3). Unfortunately, reacting alkyl tosylates with the TEB acetylide yielded poor results and using alkyl halides gave at best moderate yields. Further study and optimization of these reactions could be of interest in the future. [8, 9]



Scheme 3: Reaction of TEB with alkyl halides or tosylates

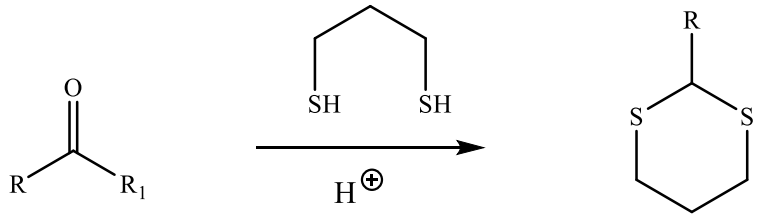
2 Dithianes

One of the many compounds that can be formed from TEB are 1,3-dithianes which have been found to be versatile compounds of great applicability, and have proven to be valuable in the total synthesis of complex natural products. These achievements are due to the anion-stabilizing property of the sulphur, caused by the electron back-donation into vacant sulphur d orbitals.[10, 11] Generally, there are three approaches to forming dithiane derivatives. One method involves using the anion of 1,3-dithiane, with or without substitution around the ring, and reacting it with any of a wide range of different functional groups (Scheme 4).[12]

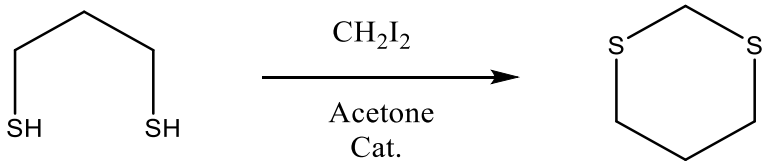


Scheme 4: Selected formations of 1,3-dithiane derivatives using the dithiane anion

Alternatively, the 1,3-dithiane moiety may also be introduced by thioacetalisation of a carbonyl group, either using acid or Lewis acid catalysis (Scheme 5),[12] or of a 1,1-dihalide (using transition metal catalysis) (Scheme 6).[13]

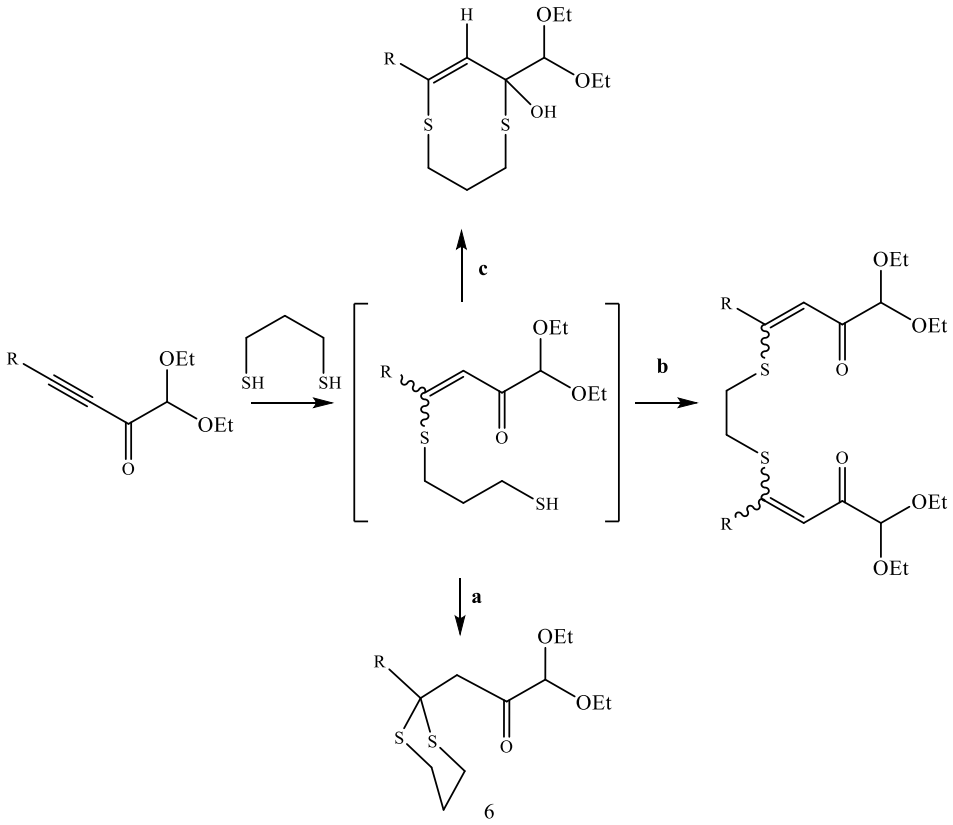


Scheme 5: Formation of 1,3-dithiane by thioacetalisation



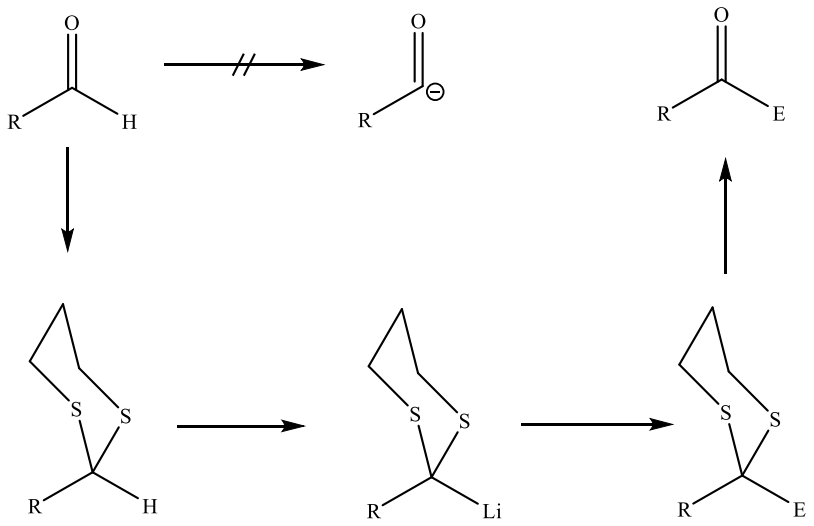
Scheme 6: Thioacetalisation of a dihalide to form 1,3 dithiane

Finally, conjugate addition to a Michael system, such as a propargylic ketone (like TEB-ketone), using 1,3-propane dithiol will furnish a dithiane functional group (Scheme 7, route a).[14] The dithioacetal is also suitable for use as protection of carbonyl groups, because it is stable towards acidic conditions,



Scheme 7: Formation of compound **6**, its dimer derivative and the thiohemiacetal

The dithiane moiety is similarly chemically interesting as it displays a reactivity pattern called "umpolung". In 1965 Corey and Seebach proposed the idea that certain sulphur stabilised anions could be suitable for use as masked nucleophilic acylating agents.[15] Scheme 8 illustrates the sulphur stabilised anion directly reversing the conventional reactivity pattern of the carbonyl group making it equivalent to an acyl anion.[12, 14] The corresponding ketone could then be formed by hydrolysing the dithioacetal moiety with an electrophile. This temporary reversal of the characteristic of a functional group was termed "umpolung" by Corey and Seebach.[15]

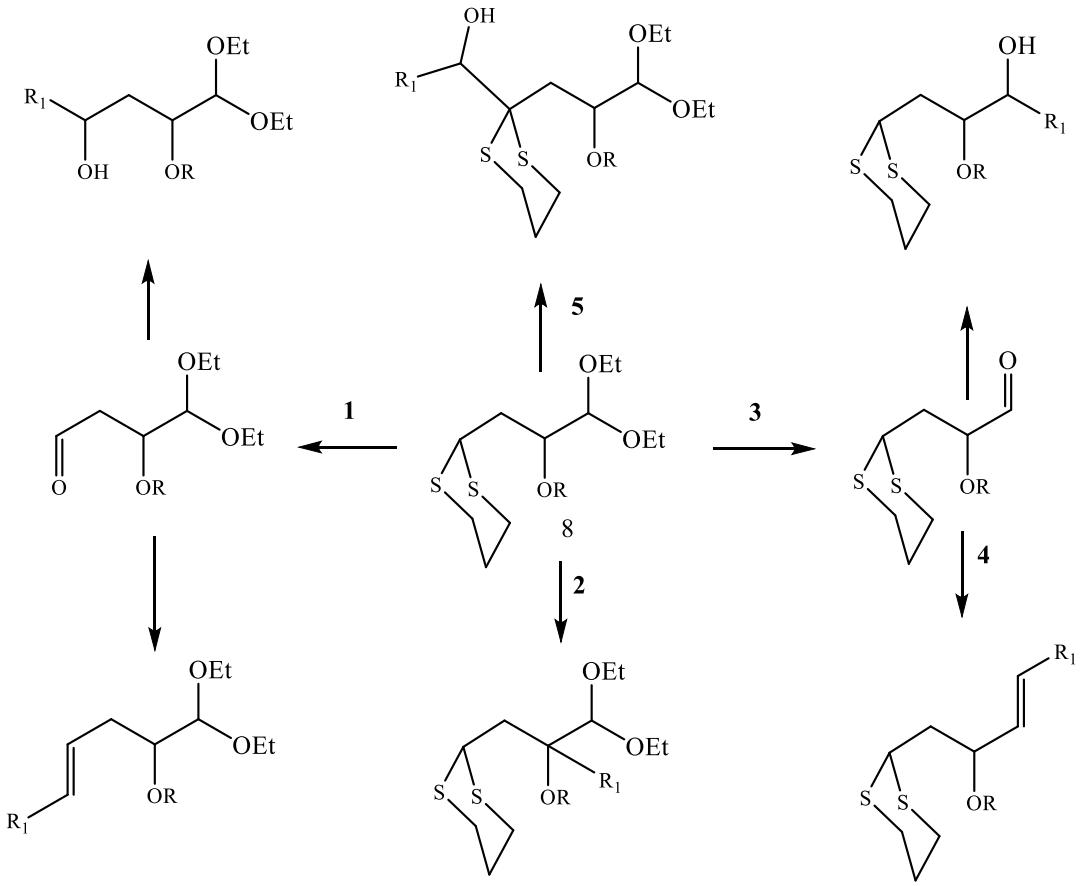


Scheme 8: Umpolung of an aldehyde, producing an acyl anion equivalent

In this thesis the double conjugate Michael addition of 1,3-propane dithiol to the propargylic TEB-ketone was chosen as the primary method of forming the dithiane moiety. In the reaction between the thiol and the β-carbon in the Michael system, a β-thio alkenone is formed as an intermediate (Scheme 7).[14] The unreacted thiol in the intermediate can react by three conceivable reaction routes. Pathway **a** shows how sulphur could attack the β-carbon to form the desired β, β-dithiane, compound **6**. The attack could also happen intermolecularly to form the dimer in pathway **b**. Valdersnes has reported that if the group attached to the β-carbon of the triple bond is large and bulky enough, the second addition of the sulphur may occur at the carbonyl group, giving the thiohemiacetal (pathway c).[14]

2.1 Synthetic transformations with β-hydroxy dithiane

Once the dithiane ring is formed, the ketone can easily be reduced to form the β-hydroxy dithiane which, packed with many different functional groups, presents many possible strategies to furnish carbohydrate derivatives. Selected synthetic possibilities some of which have been explored by former students in our research group are illustrated in Scheme **9** below.



Scheme 9: Some possible synthesis routes from β-hydroxy dithiane

While pathways **1, 2** and **5** have been researched by Flemmen, Leiren and Valdersnes, pathway **4** remains relatively unexplored.[14, 16, 17] In pathway **1** the dethioacetalization provides the expected aldehyde that can undergo different addition and Wittig reactions. Leiren performed chain elongations on the β carbon (pathway **2**) and Flemmen had success with coupling reactions using aldehydes and ketones added to β-hydroxy dithiane as shown in pathway **5**. Pathway **4** presents an opportunity for potentially interesting reactions; this includes different chain elongation reactions like Wittig olefination for instance. Various addition reactions to the alkene group are also conceivable as a reaction pathway.

3 Aim of the study

Previous studies by Leiren and Valdersnes show that the highly functionalized β-hydroxy dithiane is quite versatile and undergoes many different reactions.[14, 18] This encouraged us to further explore the reactivity of the substrate and synthesize β-hydroxy 1,3-dithiane derivatives. Wittig olefination reactions on the aldehyde, after removal of the acetal group, are of special interest is to perform.

The synthesis of TEB does not always go smoothly, as experienced, and many steps are required to synthesize the starting material, TEB-ketone, via TEB. The scope of the project would thus later be expanded to include exploration of alternative ways of synthesizing the TEB-ketone in order to optimize the generation of the β-hydroxy 1,3-dithiane.

Results & Discussion

4 Preparation of TEB- ketone from TEB

In order to synthesize the desired starting material for this project, the β-hydroxy dithiane, the formation of TEB-ketone was first needed.

4.1 Synthesis of TEB

At the outset, TEB was synthesized from ethyl vinyl ether following the established four-step synthesis outlined in Scheme 1. The first two steps appeared to be good reactions that gave the expected products in high yields. The products obtained were pure, and in accordance with the literature[2], without the need for any further purification.

Step 3 of the TEB synthesis, on the contrary, proved problematic and so different approaches were made to improve results. When this step was performed in a 0.1 mol scale for the first time, distillation of the crude product provided too little product to continue with step 4, especially given that the final step is known to be a low yielding step. Some students had previously skipped distillation of the crude from the third step and still managed to isolate a good amount of TEB from the final step. An attempt of this was made with the same 0.1 mol scale, and TEB was successfully formed but the yield was very low at 7%.

When step 3 was attempted on a larger scale (0.55 mol) the reaction overheated and boiled over before it could be quenched the next day. This is believed to have been caused by a combination of insufficient cooling of the reaction and either excessive addition of base, or the base being added too rapidly. The reaction was therefore tried again, but this time the ice-bath was refilled with ice 2 hr after all the base was added, before it was left in the bath to slowly reach rt overnight. Disappointingly, the reaction mixture boiled over again. The larger scale reaction could still be insufficiently cooled but at this point the main suspect in the reaction failure was the base. Despite the last reaction boiling over, enough product was isolated after distillation of the crude to continue with step 4. This step proceeded without any problems, but the yield was quite low after distillation at 20% pure product. The low yields of these reactions could also

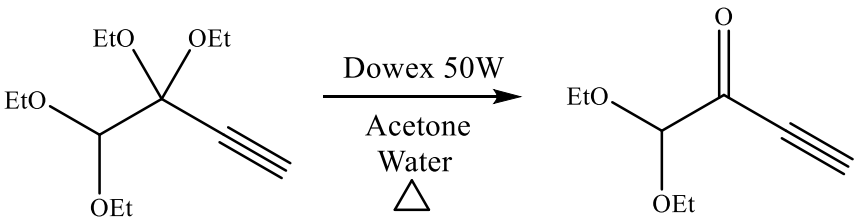
partially be affected by the use of old and perhaps decomposed solvents and reagents, especially the bromoform that has notably caused problems for other students previously.

The work-up involved in step 3 is known to be difficult due to the formation of a dark coloured side product, which tends to coagulate, making the organic phase arduous to extract. Nevertheless, acidifying the reaction mixture with 6 M HCl made the process easier.

From the final attempt, TEB was synthesised with an overall yield of 4% essentially pure product, purified by distillation. Reluctant to go through the four-step synthesis of TEB again alternative methods to proceed would be explored.

4.2 Synthesis of 1,1-diethoxybut-3-yn-2-one (TEB-ketone) (5a)

The next step from TEB was deprotection of the ketal moiety to afford the TEB-ketone. This was done by treating TEB with Dowex 50W in moist acetone under reflux (Scheme 10).[3, 14] After purification, the reaction produced ketone in excellent yield of 91%.



4 **5a**

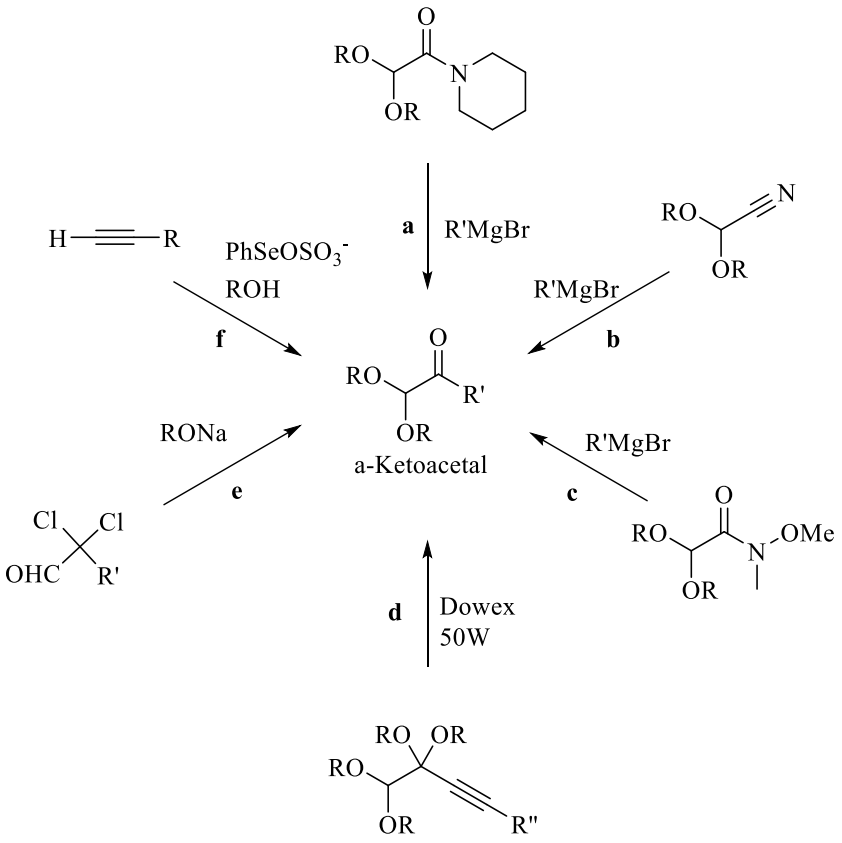
Scheme 10: Deketalization of TEB to form TEB-ketone

As reported, no reaction of the acetal group was observed. This is owed to the stability of the TEB-ketone that is resistant to deacetalization.[3]

5 Synthesis of TEB-ketone from ethyl diethoxyacetate

Complications with the TEB synthesis, resulting in low yields and failed reactions, was discouraging, especially as it was apparent that more TEB or at least more starting material for the dithiane synthesis would be optimal. Obtaining large amounts of TEB from the classic synthetic route is a challenge to begin with as the final two steps in the synthesis both generally yield lower than 50% product. Reluctant to start the TEB synthesis for the third time and potentially having to increase the scale even further, a search for alternative ways to proceed began.

TEB-ketone being an α-ketoacetal meant good news in this regard, as various convenient methods for synthesizing α-ketoacetals have been published. Traditionally, they have been made following the method outlined by Wohl and Lang in 1908.[19] This method involved reacting various bromomagnesium Grignard reagents with 1-(diethoxyacetyl)piperidine to produce the corresponding α-ketoacetals in good yields (Scheme 11, reaction a). Later, in 1966 Dulou took a similar approach, reacting Grignard reagents with diethoxyacetonitrile which would form the corresponding ketoacetals upon hydrolysis (reaction b).[20] In these reports, both α-ketoacetal precursors were prepared from readily available and inexpensive ethyl diethoxyacetate. Weinreb amides are also popular to use to synthesize different α-ketoacetals. Zepeda *et al.* for example, have had success making them, again utilising ethyl diethoxyacetate as starting material. They formed the α-ketoacetals through the addition of nucleophiles, such as Grignard reagents or alkyllithiums to the Weinreb amide (reaction c).[21] Apparently, direct treatment of α,α-dialkoxyacetates with Grignard reagents produces the desired α-ketoacetals but is always accompanied by the corresponding tertiary alcohols.[21] And this is the reason for the substitution of a better leaving group like pipridine, nitrile or *N,O*-Dimethylhydroxylamine on to diethoxyacetate before performing the Grignard reaction. Deketalization of TEB, or one of its chain elongated derivatives also affords α-ketoacetals (reaction d). Other methods for preparing variously modified α-ketoacetals include treatment of α,α-dichloroketones with MeONa (reaction e),[22] or selenium-catalyzed conversion of terminal alkynes, [23] in the presence of MeOH (reaction f).



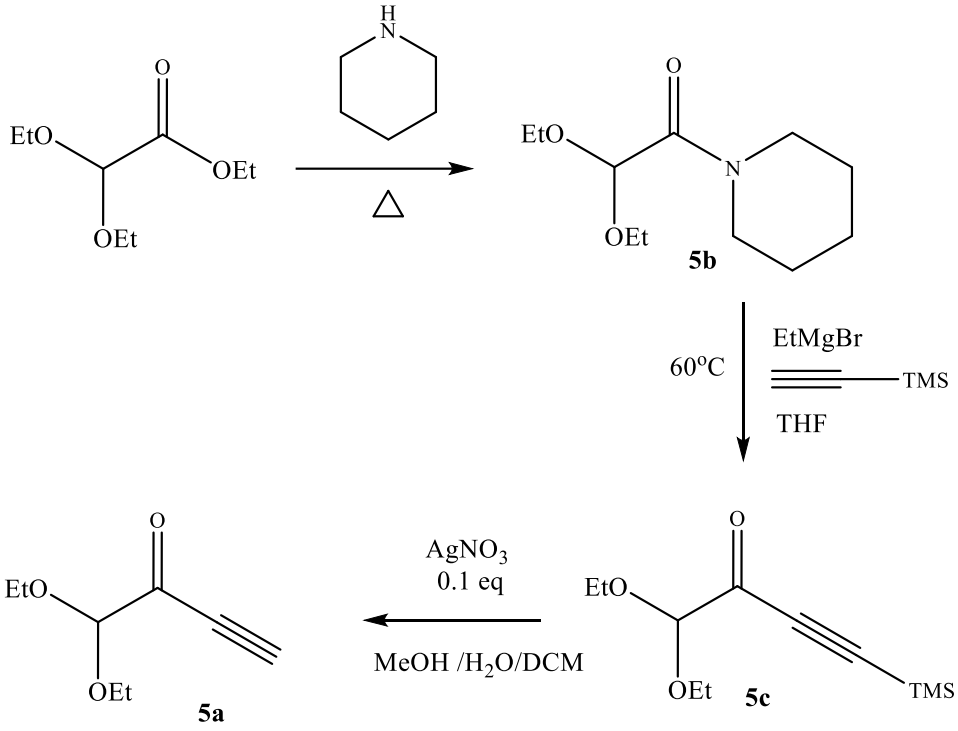
Scheme 11: Different ways of synthesizing α-ketoacetals

These methods provide several ways to make α-ketoacetals in just a few easy steps and often in reliably good yields. They essentially offer opportunities to shorten the 5 synthesis steps required to make TEB-ketone via TEB to just 2-3 steps.

5.1 Synthesis of TEB-ketone using Wohl and Lang methodology

While pondering over a convenient and more efficient way to move forward, a fellow student recommended a synthesis route similar to one he had performed with TEB. This method would lead to the formation of 1,1-diethoxy-4-(trimethylsilyl)but-3-yn-2-one (**5c)** using a method originally published by Wohl and Lang.[8, 19] Compound **5c** could then be deprotected to afford the TEB-ketone (5a). This method would produce TEB-ketone from ethyl diethoxyacetate in three steps, instead of the five steps required from ethyl vinyl ether, and the overall yield was anticipated to be higher than that of the TEB route. This substitute three-step synthesis involves

a substitution reaction, displacement of the piperidine, and finally a desilylation reaction (Scheme 12).

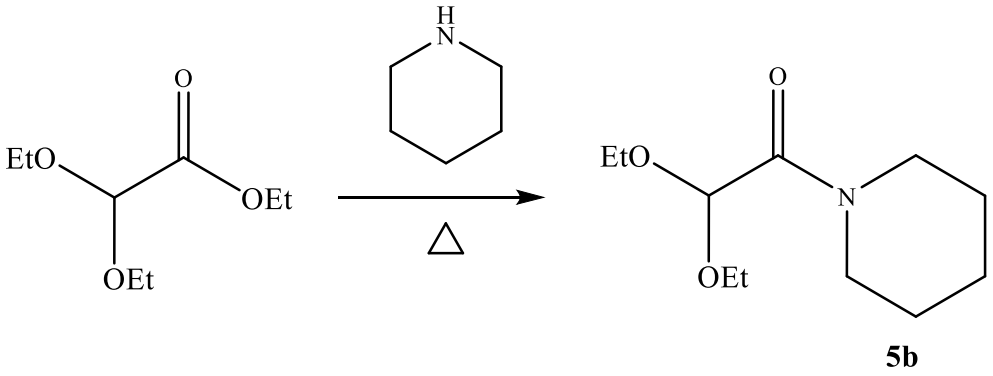


Scheme 12: Synthesis of TEB-ketone from commercially available ethyl 2,2-diethoxyacetate

5.1.1 Synthesis of 1-(Diethoxyacetyl) piperidine (5b)

To obtain compound **5a** through this new method, first 1-(diethoxyacetyl) piperidine (5b) was synthesized by a substitution reaction including piperidine and the commercially available ester, ethyl 2,2-diethoxyacetate (Scheme 13). The procedure is somewhat altered from what was first published by Wohl and Lang.[19] The reaction was performed by heating ester and an excess amounts of piperidine at reflux allowing the substitution reaction to take place, simultaneously as the alcohol generated from the reaction was slowly distilled off. The reaction was heated for 48 hr until no more ethanol was being distilled from the reaction flask. The excess amount of piperidine was transformed into piperidinium salt by addition of acid and washed out with water to yield pure amount of the titled compound (91%) as a viscous faintly orange/yellow liquid. No further purification of the product was needed as the product was pure

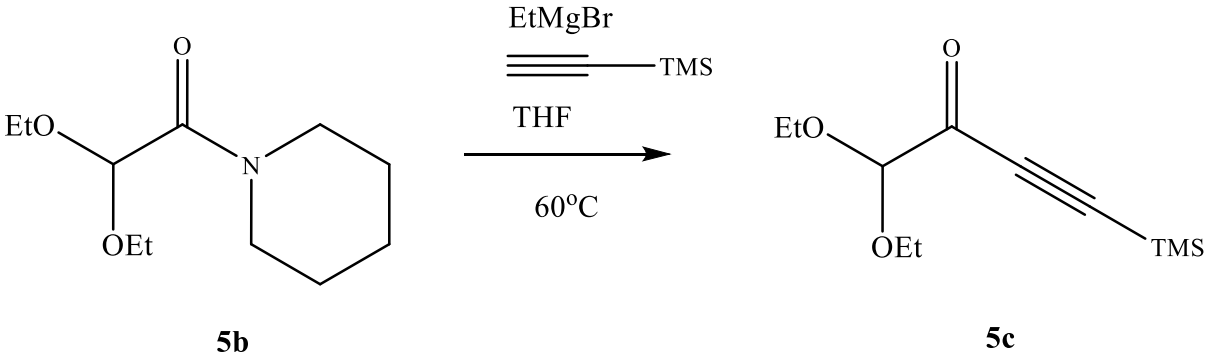
according to NMR analysis. In the original procedure, the reaction was performed at a larger scale and the reaction ran for 15 hr, distillation was also required to obtain pure product.[19]



Scheme 13: Formation of 1-(diethoxyacetyl) piperidine from ethyl 2,2-diethoxyacetate

5.1.2 1,1-Diethoxy-4-(trimethylsilyl)-but-3-yn-2-one (5c)

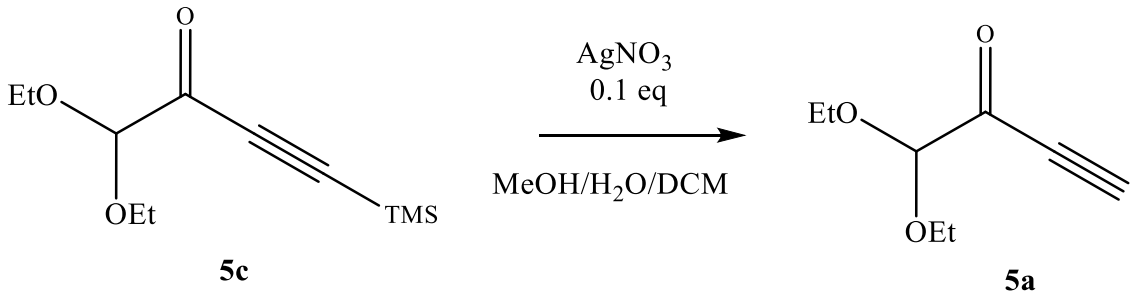
After acquiring compound **5b,** the next step involved reacting ethylmagnesium bromide and a TMS protected alkyne to furnish the corresponding TMS protected TEB-ketone 1,1-diethoxy-4-(trimethylsilyl)-but-3-yn-2-one (5c) (Scheme 14). In the initial part of the reaction, ethylmagnesium bromide is allowed to react with TMS-ethyne to create the appropriate nucleophile ((TMS)ethynyl) magnesium bromide that will attack the electrophilic compound **5b**. The subsequent displacement of the piperidine, leads to the expected title compound **5c**, which was isolated as a yellow liquid by flash chromatography in a good yield (72%).



Scheme 14: Synthesis of TMS protected TEB-ketone

5.1.3 Silver catalysed TMS deprotection

In order to finally obtain TEB-ketone, a silver catalysed deprotection of the trimethylsilane was performed and pure TEB-ketone was easily isolated after flash column chromatography in 70% yield (Scheme 15). TLC of the crude product showed signs of some unreacted starting material, which implied that not all of it was converted. Longer reaction time, or perhaps higher amount of methanol and/or silver cation could be needed to make the reaction go to completion. Less complex acetylenes where used in the literature,[24] so it is plausible that optimization for TEB-ketone is needed here.



5c **5a**

Scheme 15: TMS deprotection to obtain TEB-ketone

Orsini *et al.*[24], the publishers of the deprotection method used here, suggest that in order to achieve silver catalysed deprotection of TMS, the silver counter-ion of the introduced silver salt must be nucleophilic enough to attack the silicon atom upon silver activation. This would lead to cleavage of the C–Si bond and to the *in-situ* formation of an alkynyl silver and a silyl-X species. In protic solvents, the latter would be hydrolysed leading to a better proton source, strong enough to hydrolyse the alkynyl silver species. Silver ion would then be released, allowing for a catalytic cycle to take place.[24]

5.1.4 TMS deprotection using K_2CO_3/MeOH

Hoping to obtain even more TEB-ketone from the removal of TMS, a trimethylsilane deprotection method using saturated K_2CO_3 in methanol described by Vasella *et al.* was

attempted.[25, 26] Regrettably, adding K_2CO_3 dissolved in methanol to compound **5c**, as described in the literature, led to an immediate darkening of the reaction mixture. Work up and rotatory evaporation only yielded a dark crude. Comparison between the ^{1}H-NMR spectrum (Figure 1) of the crude and the spectrum of TEB-ketone suggests that a different product had been synthesized.

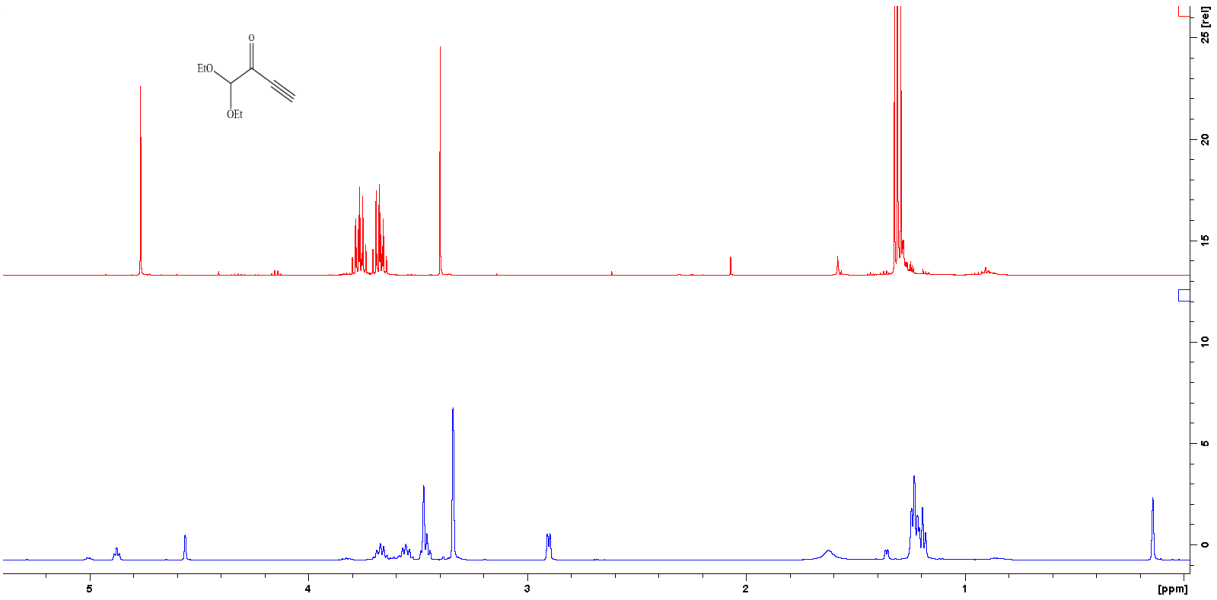


Figure 1: NMR spectra of the dark crude obtained from (bottom) and the expected product TEB-ketone

To examine the composition of the crude product, a TLC analysis was performed, using samples from the crude of the K_2CO_3/MeOH deprotection reaction (**a**), compound **5a** (**b**), and the TMS protected TEB-ketone (**c**). The result suggests that neither compound **5a,** nor the TMS protected compound **5c** were present after the attempted deprotection, further implying that a different product to the TEB-ketone was obtained (Figure 2).

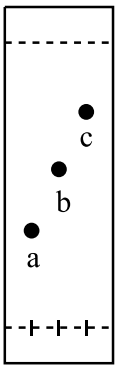
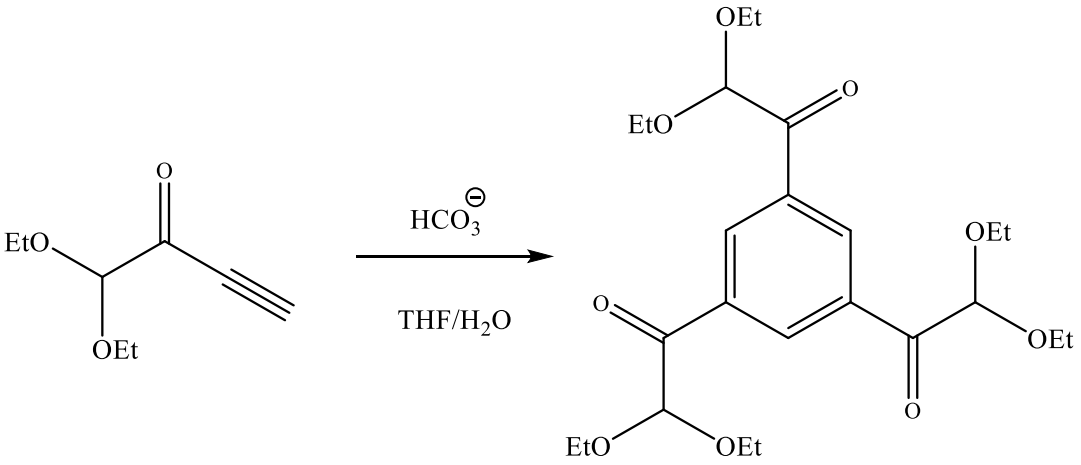


Figure 2: TLC plate of the crude products of **a** as well as the isolated products **b** and **c**.

Sengee experienced that TEB-ketone in the presence of bicarbonate would undergo cyclotrimerization as a result of bicarbonate attack on the triple bond and form 1,3,4-tris(2,2-diethoxyacetyl(benzene) (Scheme 16).[27] In our case, this product could not be isolated but hints of it was noticed. At 8.11 ppm for example, a singlet peak can be observed, and this peak could possibly be the expected benzylic protons from the cyclotrimerized product (Figure 3).



Scheme 16: Cyclotrimerization of TEB-ketone after reaction with bicarbonate

Determining the identity of the crude product, proved difficult without MS analysis. Based on the NMR data alone it is quite challenging to determine the identity of the crude, or even if the crude contains one or multiple products. Efforts were instead put into redoing the reaction and optimizing it.

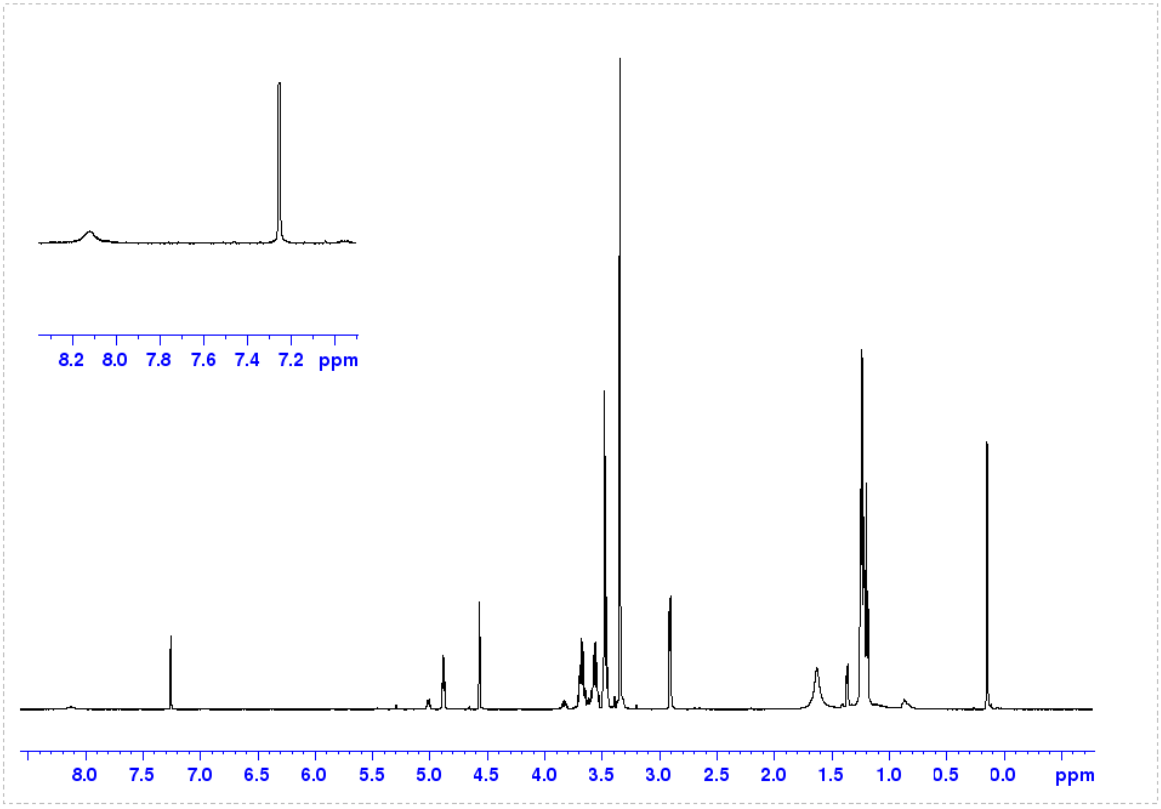


Figure 3: ^{1}H NMR spectrum of the crude obtained from the deprotection of compound **5c** using K_2CO_3/MeOH

In order to further investigate the potential effect K_2CO_3 in methanol had on compound **5c**, three new experiments were carried out in parallel. Since TMS was successfully removed in the synthesis of compound **6,** from compound **5c** (see section 6.1), the three reactions were modelled after it. Meaning that the reagents were added in the same ratio used for the synthesis of compound **6** (method c). In flask A, compound **5c** was dissolved in DCM, before NaOMe and some methanol was added. The reaction mixture was stirred at ambient temperature for 2 hr. In flask B, compound **5c** was dissolved in some DCM before K_2CO_3 and methanol was added. And in flask C, compound **5c** was dissolved in some DCM before saturated K_2CO_3 in methanol was added. In all three flasks, the amount of compound **5c**, DCM and methanol were kept the same, the only varied factor being the base. Interestingly, all three reactions successfully removed the TMS group according to NMR data of the crude samples. All three NMR spectra clearly showed the expected acetylenic proton of TEB-ketone, which is not

present in the spectrum of the starting material, compound **5c** (Figure 4). The only noticeable difference between the three reactions was that flask C turned darker, almost orange, compared to the other two pale yellow solutions. This colour change is believed to indicate the generation of unwanted products or possibly polymerization, because dark colour changes seems to be a trend with failed TEB reactions. The investigation led to the conclusion that the desilylation method reported by Vasella *et al.*[25, 26] was simply too concentrated for compound **5c**, and that the addition of DCM as solvent to dilute the reaction mixture made the intended reaction work. The need for the dilution of the solution is likely due to the fact that TEB-ketone is more reactive than the substrates used in the literature.

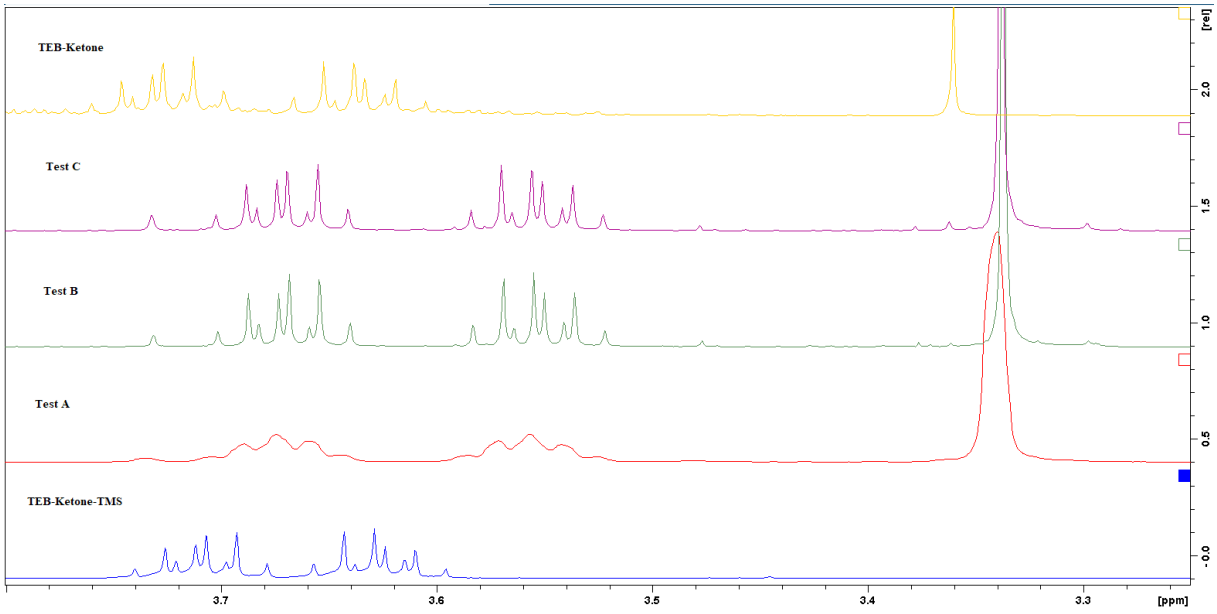
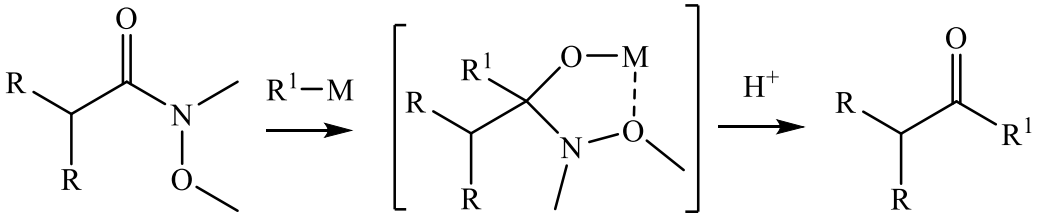


Figure 4: Comparison of the acetylenic proton of TEB-ketone and the crude products obtained from tests A, B and C, with the TEB-ketone-TMS as reference

^{1}H-NMR spectra of the TEB-ketone shows the signal of the acetylenic proton in the region from 3.3 to 3.5 ppm. When comparing the spectra of TEB-ketone (topmost spectrum, Figure 4) and the crude products obtained from tests A, B and C, the expected acetylenic proton at 3.3-3.4 ppm is present in each of the tests, confirming a successful desilylation.

5.2 Synthesis of TEB-ketone using Weinreb amide

N-Methoxy-*N*-methyl amides have been widely recognized as an effective tool in organic synthesis.[27] This is because of its general ease of preparation, the selective formation of ketones by nucleophilic addition of organometallic reagents, and the easy reduction to form aldehydes without accompanied formation of alcohols. The high selectivity can be credited to the stable five-membered chelate, which is formed upon nucleophilic addition of an organometallic species (Scheme 17). This cyclic intermediate prevents the attack of a second nucleophile and therefore, after acidic work-up, results in the selective generation of the corresponding carbonyl compound.[28] This reaction seemed promising, hence there was great interest in trying it.

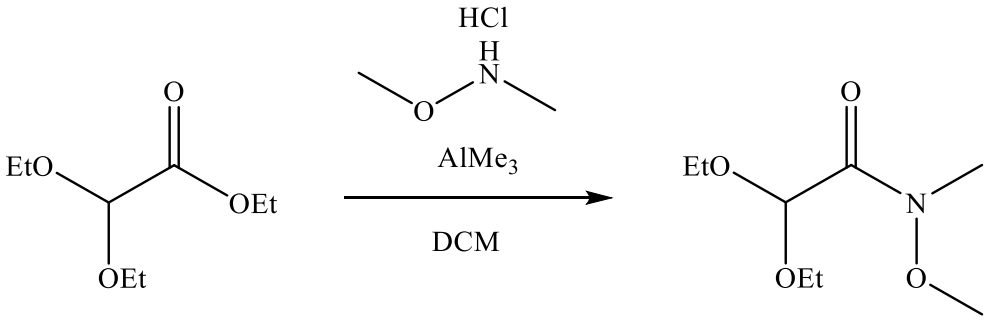


Scheme 17: Formation of carbonyl compounds from N-methoxy-N-methyl amides via the intermediate chelate

5.2.1 Synthesis of 2,2-diethoxy-N-methoxy-N-methylacetamide

The synthesis of the Weinreb amide was carried out according to the procedure published by Meester where ethyl 2,2-diethoxyacetate was reacted with *N,O*- dimethylhydroxylamine-HCl to furnish the Weinreb amide (Scheme 18).[28] In the original procedure, trimethylaluminum solution in hexanes was used as a coupling agent to promote the amide synthesis from the ester. In our attempt, the same amount of trimethylaluminum in toluene was used instead, as the hexane solution was not available. The resulting clear crude product was very interesting. Its NMR spectrum showed clear signs of toluene presence, even though toluene should have been removed by the rotary evaporation, where the pressure was reduced as low as 10 mmHg and with the solution heated to 40 ^{o}C. Normally, toluene is expected to evaporate at 77 mmHg with a water bath temperature of 40 ^{o}C.[29] Increasing the bath temperature to 60 ^{o}C did not help remove it either, and this led us to believe that perhaps it had reacted with something in the

solution. The NMR spectrum did also show signs of the desired amide having been made however, and with purification the Weinreb amide would likely have been isolated (Figure 5). However, due to time constraints and the need to wait for reagents, for the subsequent reaction, this was not pursued any further as our attention was focused elsewhere. Nevertheless, using Weinreb amides to synthesize TEB-ketone remains an interesting subject for future investigation.



Scheme 18: Synthesis of Weinreb amide

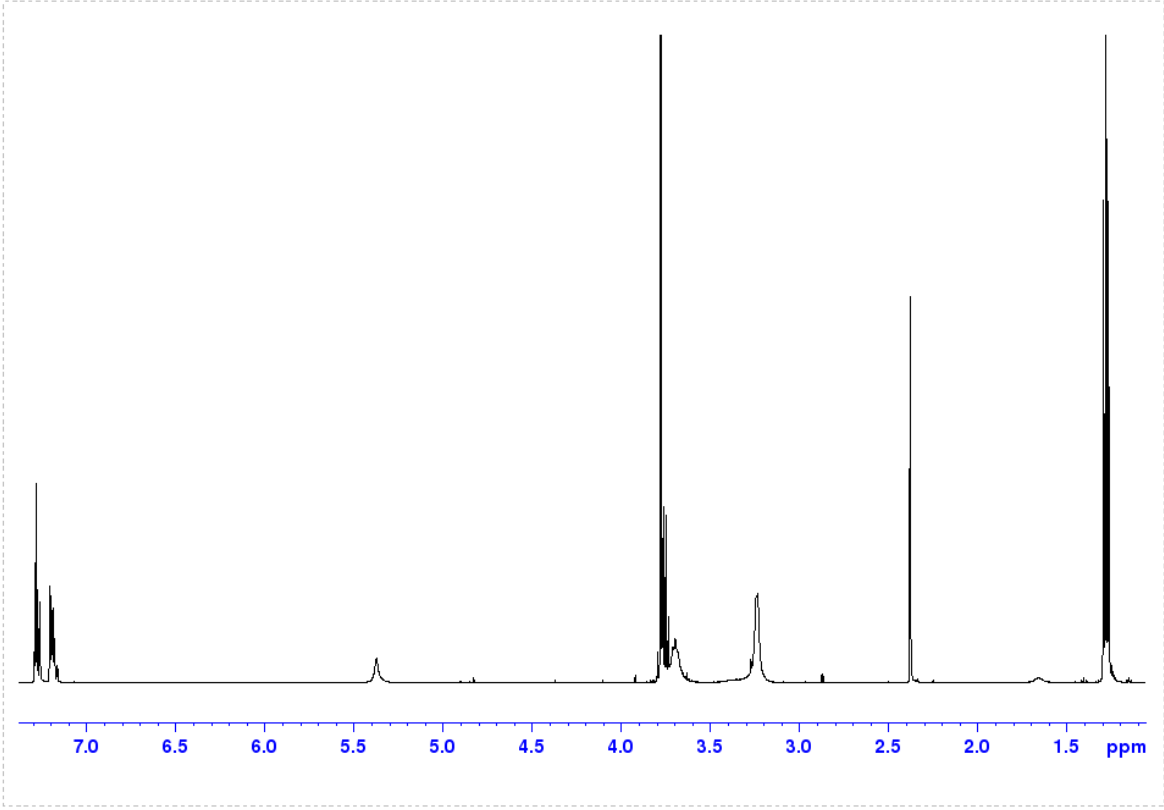
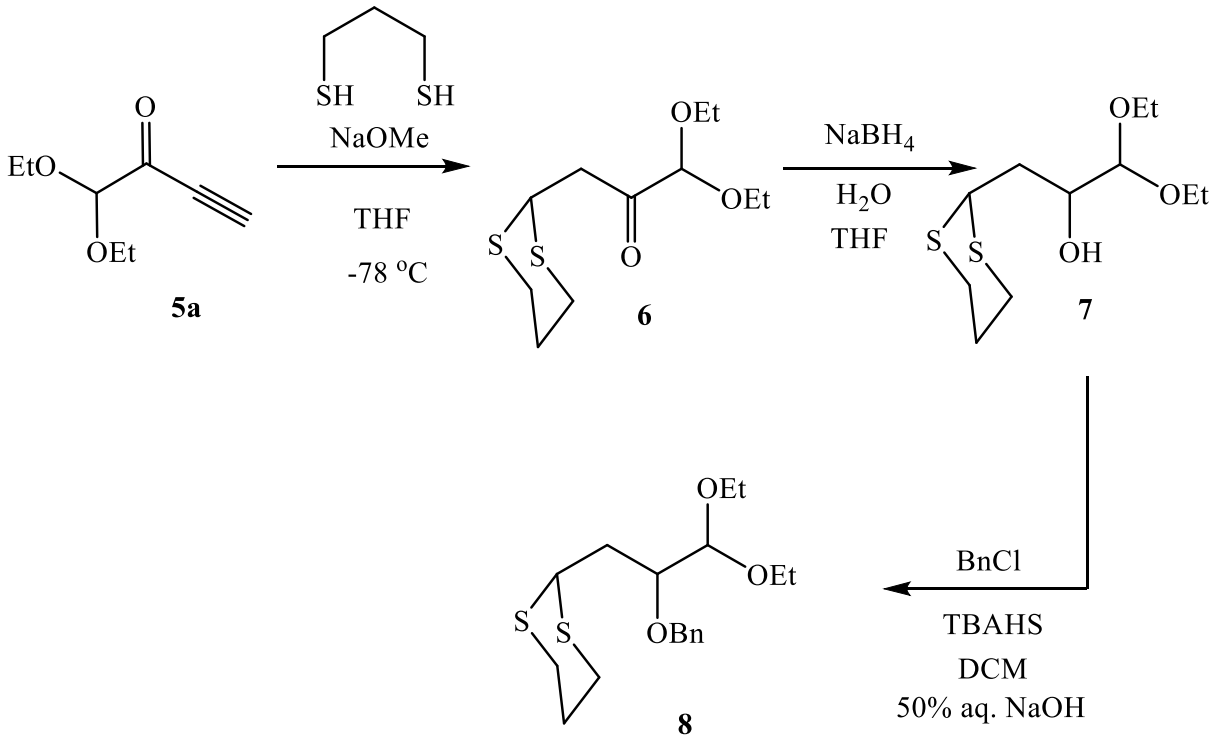


Figure 5: ^{1}H NMR spectrum of the crude product from the Weinreb amide synthesis

6 Preparation of the β-hydroxy dithiane from TEB- Ketone

With TEB-ketone at hand, the synthesis of the β-hydroxy dithiane could start. The synthesis was carried out using a strategy to produce the terminal dithiane 2-(2-(benzyloxy)-3,3-diethoxypropyl)-1,3-dithiane (**8**) from TEB-ketone in a few steps (Scheme 19), inspired by a methodology developed by Valdersnes.[14] This substrate would provide opportunity to perform different coupling reactions and in this thesis coupling reactions performed on the acetal side of the molecule were of primary interest.



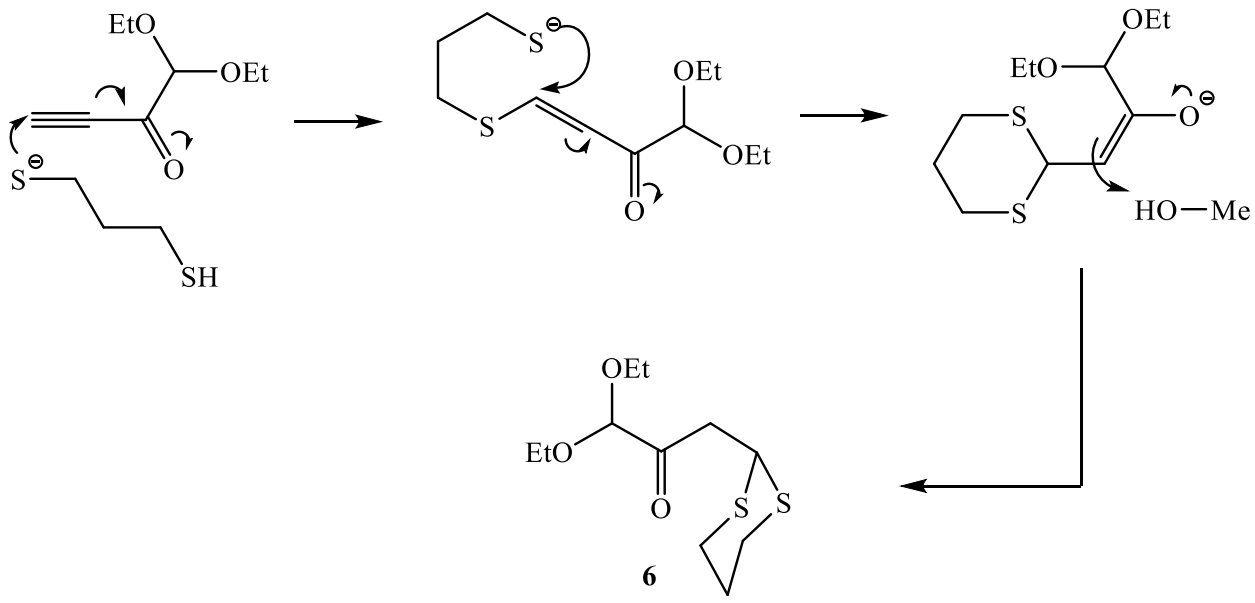
Scheme 19: Synthesis of the β-hydroxy dithiane from TEB- Ketone

The synthesis of the dithiane moiety was first attempted using the procedure described by Valdersnes where 91% of the pure product was isolated after the reaction. The reaction involved stirring TEB-ketone in methanol in the presence of sodium methylate and 1,3-propane dithiol under nitrogen atmosphere and kept at -10 °C for 16.5 hr before work up.[14] Equal success was not experienced in our attempt, with the reaction only producing the product in 25% yield. A different method was consequently tried.

Difficulty keeping this reaction stable at -10 ^{o}C for 16 hr was first believed to be the main cause of the low yield. It was believed that the reaction was sensitive to the temperature and that unwanted reactions would occur as the temperature would rise above -10 ^{o}C. It could be of note that the nitrogen used to keep the reaction in an N_2 atmosphere has previously been suspected to be poor and causing reactions to fail, [9] this could also have been a factor. After some research, the key factor, leading to the low yield of compound **6**, was assumed of being that the slow intramolecular reaction, that happens in the ring formation, was not going to completion. Ley *et al.*[30] experienced that in their reactions, maintaining the reaction temperature at -10 °C, or lower throughout, resulted in the reaction failing to go to completion within 24 hr. They concluded that the reaction needs up to 18 hours at ambient temperature to fully be completed. This depended on the degree of steric hindrance of the ynone and is presumably caused by the increased electron density imparted by the first sulphur substituent on the enone acceptor. They combated this by removing the cooling after the initial reaction and letting it further react in rt.[30]

6.1 Synthesis of 3-(1,3-dithiane-2-yl)-1,1-diethoxypropan-2-one (6)

The second attempt to prepare the dithiane using a different method was more successful. This base-induced double conjugate Michael-type addition of 1,3-propane dithiol to the propargylic ketone, TEB-ketone, (Scheme 20) afforded pure product which was isolated by flash chromatography in acceptable yields (52%).



Scheme 20: Double conjugate Michael addition of 1,3-propane dithiol to the terminal alkyne

The original procedure involved 1,3-propane-dithiol, sodium methoxide, DCM, and methanol at -10 °C in order to get the best yield and minimize dimerization.[30, 31] In our instance using THF as solvent, instead of DCM and methanol, and reducing the temperature to -78 ^{o}C before allowing the reaction to react in rt overnight, as noted by Flemmen was the best option.[14, 16, 17] This could be attributed to the difference in propargylic ketone used as starting material. With the modified Michael addition procedure used in this project, NMR analysis of the crude product showed no signs of vinylic protons in the region 4.5-6.7 ppm to indicate the products from pathways b and c in Scheme **7**.

Interested to try a new reaction, the TMS-protected 1,1-diethoxy-4-(trimethylsilyl)-but-3-yn-2-one (5c) was reacted with 1,3-propane dithiol under the same conditions as the synthesis of compound **6**. This was done hoping to isolate 1,1-diethoxy-3-(2-(trimethylsilyl)-1,3-dithian-2-yl)propan-2-one (Figure 7) which could either be used in further reactions or deprotected to gain compound **6**. Interestingly however, this reaction yielded compound **6** in excellent yields instead (Scheme 21). It is well documented that methanol under basic conditions, for example using K_2CO_3 dissolved in methanol, will cleave TMS to give the corresponding alkyne.[25] In the formation of the dithiane ring, methanol is generated and since the solution is already basic,

this provides ideal conditions for the desilylation to take place. By flash chromatography compound **6** was isolated in an excellent yield (82%) using this methodology. This discovery meant that the β-hydroxy dithiane, compound **7**, can be synthesized in just four steps from ethyl diethoxyacetate.

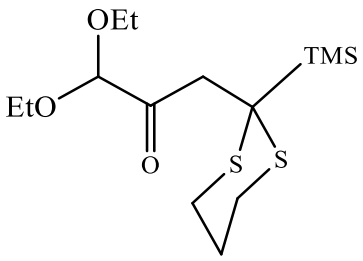
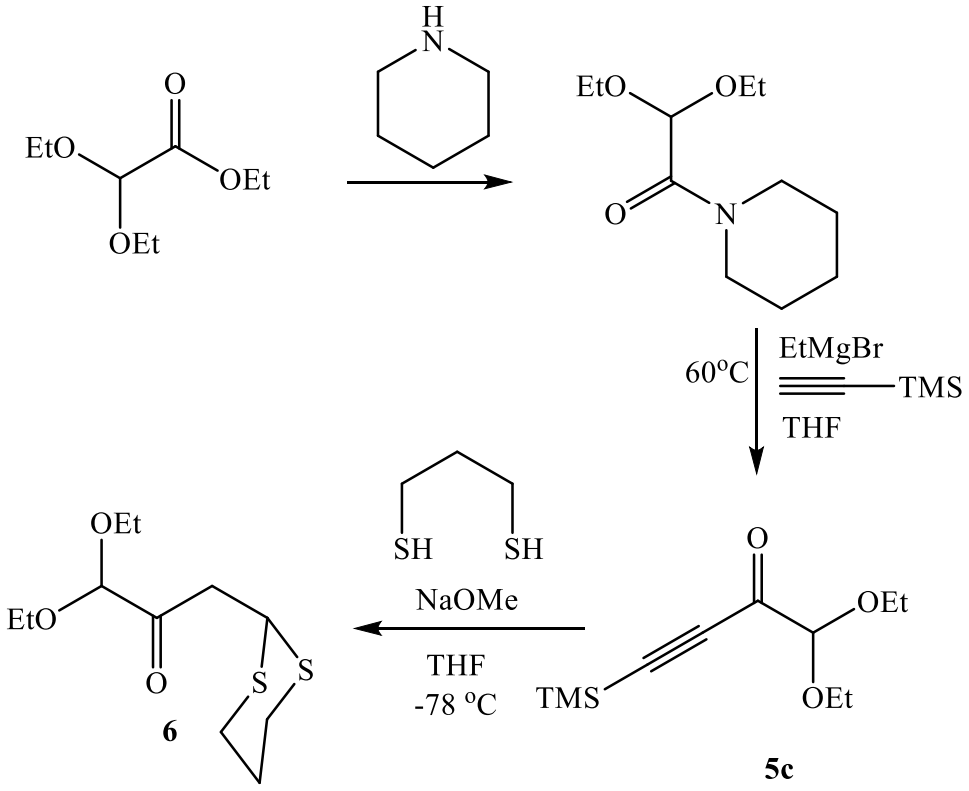


Figure 7: Structure of 1,1-diethoxy-3-(2-(trimethylsilyl)-1,3-dithian-2-yl) propan-2-one

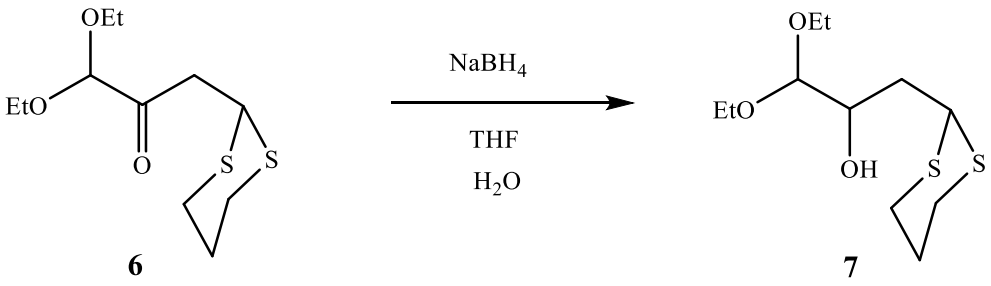
Moving forward this new procedure would be the favoured method of synthesizing compound **6** in this thesis (Scheme 21).



Scheme 21: Synthesis of compound **6** from 1,1-diethoxy-4-(trimethylsilyl)-but-3-yn-2-one

6.2 Synthesis of 3-(1,3-dithiane-2-yl)-1,1-diethoxypropan-2-ol (7)

With the dithiane moiety formed, turning the ketone into an alcohol was required next. The reduction of the carbonyl group in compound **6** to give the corresponding alcohol, was achieved utilising sodium borohydride in wet THF (Scheme 22), following a slightly modified literature procedure published by Zeynizadeh and Behyar.[32] 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. These modified conditions proved to be enough to reduce this ketone. The title compound was isolated in 56% yield after purification by flash chromatography. As a quick test, this reaction was repeated using newer sodium borohydride and this resulted in a quantitative yield (95%) of the alcohol. The results from the test raises an interesting question as to how many of the yields reported in this project could be improved, by the use of fresher solvents or reagents.



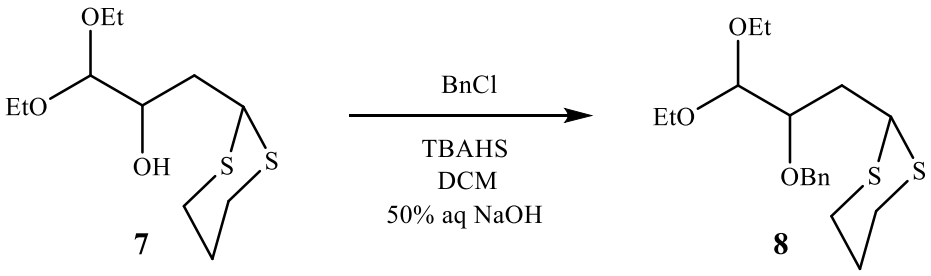
Scheme 22: Reduction of 3-(1,3-dithiane-2-yl)-1,1-diethoxypropan-2-one

Enantioselective reduction of the ketone could also feasibly be performed using chiral solvents or reagents, for example using the CBS (Corey-Bakshi-Shibata catalyst) protocol, to avoid getting a racemic solution of the product[14]. Leiren *et al.*[18] however, noted that in their attempt using (*S*)-oxazaborolidine that the ee value was as low as 20% determined by NMR spectroscopy of the benzyl-ether derivative of compound **7**, employing (-)-(R)-2-acetoxy-2-phenylacetic acid as solvating agent (*vide infra*).[16] Why the ee value is so low is not clear, but they theorised that the chiral reducing-agent complex is not sufficiently stable when exposed to compound **6**, and forms in part one or several achiral complexes through complexation with chalcogen atoms present in **6**, which is achiral.

6.3 Synthesis of 2-(2-(benzyloxy)-3,3-diethoxypropyl)-1,3-dithiane (8a)

Leiren *et al.*[18] have reported that deacetalization of compound **7** leads to polymerization. Their isolated product from the attempted deacetalization was a white solid containing mainly ether and thioether moieties, as well as OH groups, but no aldehyde group. They concluded that a hemiacetal formation is the key to the destructive reaction leading to the polymerization. Therefore, it is important to protect the OH group before attempting to remove the acetal.[18]

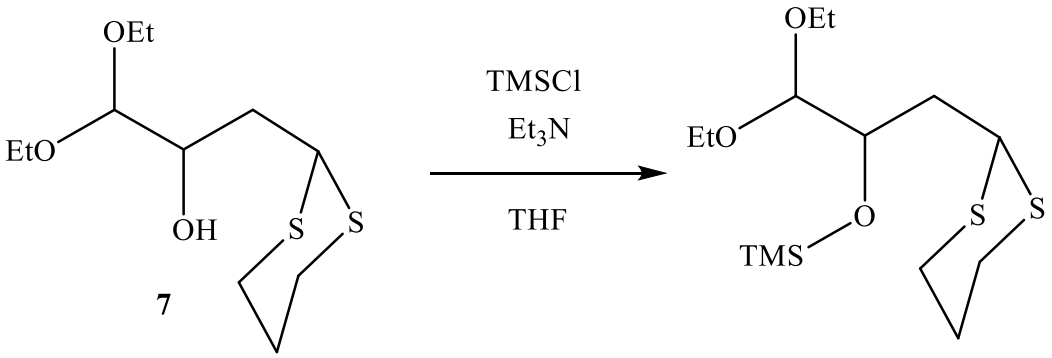
With this in mind, the OH group in compound **7** was protected by a benzylation reaction under phase-transfer conditions to furnish the desired β-hydroxy dithiane 2-(2-(benzyloxy)-3,3-diethoxypropyl)-1,3-dithiane (**8**) (Scheme 23). This method was originally published by Vogel *et al.*[33] and slightly modified by Valdersnes to work with compound **7**.[14, 33] The reaction involves compound **8** reacting with benzyl chloride under basic conditions and using the catalyst TBAHS as swell as stirring vigorously. The titled compound was isolated in 86% yield after purification by flash chromatography.



Scheme 23: Benzylation of the alcohol

6.4 Synthesis of 2-(2-(trimethylsiloxy)-3,3-diethoxypropyl)-1,3-dithiane (8b)

In the literature published by Valdersnes,[14] hydrolysis of the benzyl protected β-hydroxy dithiane required 6 days go through to completion. The very long reaction made it of interest to see if the reaction time could be shortened. Subsequently the curiosity arose to invetigate the potential effect a protective group would have on the reaction, and whether it was the cause of the slow reaction. Thus, the plan was to use the commonly employed hydroxyl protection, TMS, instead of benzyl and see if it had any effect on the reaction time of the hydrolysis.



Scheme 24: Silylation of the alcohol

For the silylation two different procedures were found and both were expected to produce the corresponding TMS protected alcohol in very good yields. Sadly, the reagents needed for one of the procedures[34] were not available, and the other procedure[35] did not mention the amounts of the different reagents used. However, since both procedures involved the alcohol, base, TMS-Cl and a solvent, it was decided to use the values reported in the first procedure for the second. Following the modified literature procedure, the alcohol **7**, TMS-Cl and triethylamine were combined in a molar ratio of 2:5:2 and stirred overnight at room temperature (Scheme 24). An oily liquid was isolated apart from the starting material by flash column chromatography.

The ^{1}H NMR spectrum of the product was very interesting, as it showed a few unexpected signals, in addition to lack of anticipated signals of the TMS protected β-hydroxy dithiane (Figure 8). One thing was reasonably certain however, and that was that the expected product had not been formed.

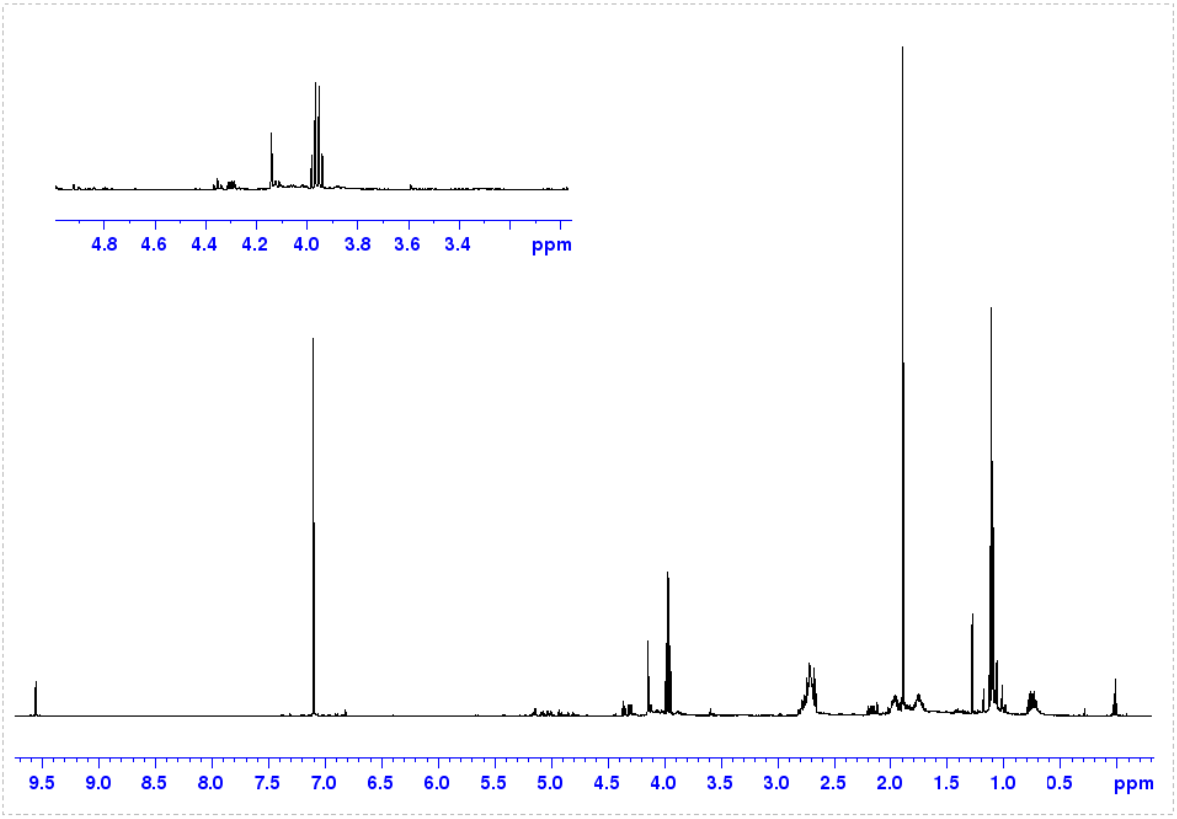


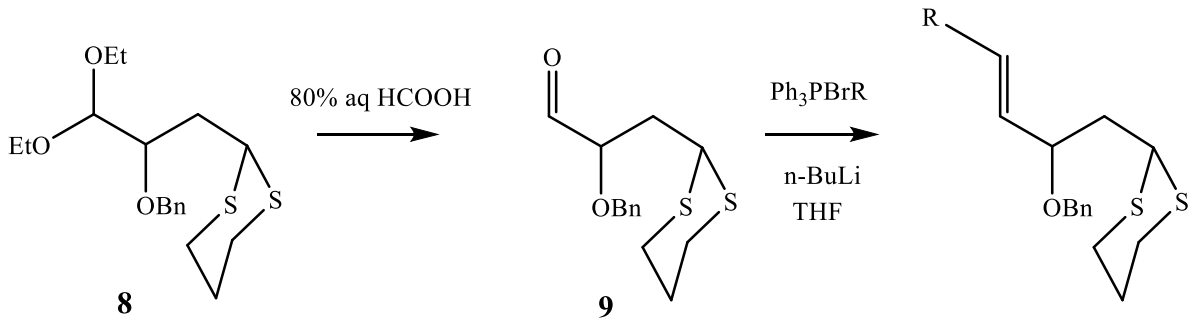
Figure 8: NMR of the isolated product from the silylation of compound **7**

The dithiane ring seems intact, with all its expected signals present in the spectrum (the signals in the region 1.5-3.0 ppm). The expected signals for TMS can also be seen furthest upfield, possibly implying that the protection of the hydroxyl group was successful. The inconsistencies with what was expected, happen further downfield.

Absence of the characteristic multiplet signals indicating the methylene of the diethoxy group (expected between 3.2-3.8 ppm), of the compound **7,** and appearance of a signal at 9.5 ppm could imply deprotection of the acetal. Leiren *et al.*[18] have examples of the dithiane forming an aldoxime in the presence of an amine under slightly acidic conditions. Although the generation of a hydroxylamine, required for the formation of aldoxime, is unlikely in our case, the reaction shows that deprotection of the acetal is possible under similar conditions used. Unfortunately, there was not enough of the isolated product to perform further analysis, and MS analysis would not have been available in time. Instead of attempting the reaction again, our attention was focused elsewhere.

7 Chain elongation of the β-hydroxy dithiane using Wittig reactions

With the β-hydroxy dithiane at hand, it was time for chain elongations using Wittig olefination. The strategy involved a two-step approach, first performing a deacetalization to furnish the appropriate Wittig reagent; the aldehyde **9**. Then with the aldehyde, subsequent chain elongations could be performed (Scheme 25).



8 **9**

Scheme 25: Hydrolysis of the acetal and Wittig coupling

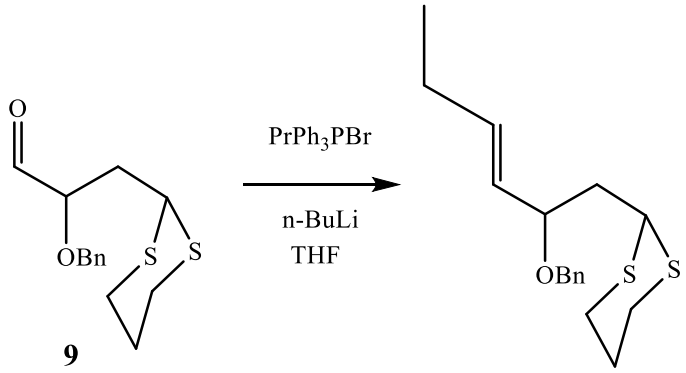
7.1 Synthesis of 2-(benzyloxy)-3-(1,3-dithian-2-yl) propanal (9)

The acid catalysed hydrolysis of compound **8** was carried out using 80% aq formic acid to yield the titled compound 2-(benzyloxy)-3-(1,3-dithian-2-yl) propanal (**9**) as described by Valdersnes[14]. From the literature the hydrolysis was reportedly finished after 6 days and yielded 94% of the titled compound.[14] After 6 days of stirring compound **8** in the presence of formic acid, the reaction only yielded a very low amount of the aldehyde **9** (10%). TLC of the crude product showed a strong signal of the starting material suggesting poor conversion to the aldehyde. With this in mind the reaction was therefore repeated using a more concentrated amount of formic acid (undiluted) with subsequent addition of 80 % aq formic acid on the second and third day. Increasing the concentration of the acid proved more successful and mostly compound **9** was present in the crude product, which was purified to yield 35% of the titled compound. Even though the yield after the modified reaction was low, almost no starting material could be seen when TLC analysis of the crude product was performed.

Instead the signal of the product had a long tail which might indicate decomposition during analysis or the presence of polymeric material.

7.2 Synthesis of 2-(2-(benzyloxy) hex-3-en-1-yl)-1,3-dithiane

Valdersnes performed a Wittig reaction on the benzyl protected β-hydroxy dithiane and succeeded in synthesizing the expected alkene 2-(2-(benzyloxy)-but-3-enyl)-1,3-dithiane in a moderate yield (58%).[14] The reaction involved methylenetriphenylphosphorane (2.1 equiv), which was generated by reacting methyltriphenylphosphonium bromide with *n*-BuLi, and then allowing it to react with aldehyde in THF. These results encouraged us to try a Wittig reaction using a longer alkyl chain under the same conditions. The Wittig reaction was performed by slowly adding compound **9** to the cooled reaction mixture (-78 ^{o}C) of propylene triphenylphosphorane in THF generated by the reaction of propyltriphenylphosphonium bromide and *n*-BuLi. The mixture was then stirred for 4 hr before quenching and general work up (Scheme 26).



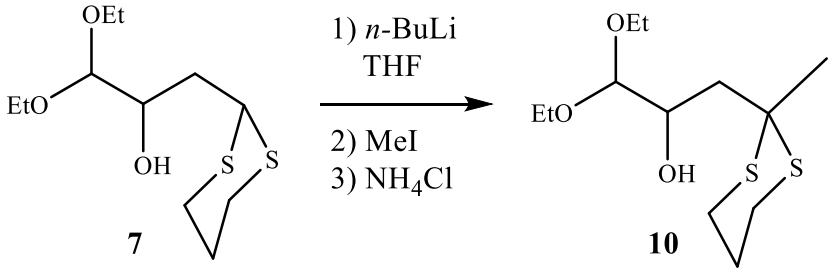
Scheme 26: Wittig coupling on compound **9**

The reaction yielded an orange crude product surrounded by what looked like a milky liquid. Thinking nothing of what is now believed to be the start of precipitation and/or further reaction of the product, the crude product was stored in the fridge overnight. The next day what was found instead of an orange liquid was a paler solid. This product was insoluble in several organic solvents (chloroform, hexane, ethyl acetate), so purification was impossible.

Before being stored overnight however, a quick TLC experiment was performed using the crude, and two distinct signals could be seen likely indicating the desired product **10** and the starting material. This could mean that the desired product was obtained but it reacted further because of instability.

8 Alkylation of the β-hydroxy dithiane

Flemmen succeeded in adding both aldehydes and ketones to the sulphur stabilized anion of the β-hydroxy dithiane, achieved by abstraction of the proton by use of BuLi, to produce chain elongated diols.[17] Reactions that are reminiscent of the TEB reactions in pathway **c** which generate the propargylic alcohols by reacting the TEB acetylide anion to ketones and aldehydes (Scheme 2). Since the TEB acetylide anion also successfully undergoes alkylation, especially with methyl iodide,[9] it is very interesting to see if the anion of the β-hydroxy dithiane could undergo the same reaction. Therefore, the β-hydroxy dithiane was subjected to a classic alkylation using *n*-BuLi as base for deprotonation and methyl iodide as an electrophile (Scheme 27).



Scheme 27: Alkylation of the β-hydroxy dithiane

8.1 synthesis of 1,1-diethoxy-3-(2-methyl-1,3-dithian-2-yl) propan-2-ol (10)

Alkylation of compound **7** was carried out using the same conditions as the alkylation of TEB, [9] which means using a surplus amount of both *n*-BuLi and the electrophile. The purified product was isolated in poor yield (13%). The product gave the expected mass of the sodium adduct at *m/z* = 303.10645 (Figure 9) when HRMS was taken and NMR data correspond to what was expected of the product. Optimization of the reaction could be interesting for future work, for example using 2 equivalents of n-buthyllithium (*n*-BuLi) which was used in the previously mentioned coupling reactions performed by Flemmen.[17]

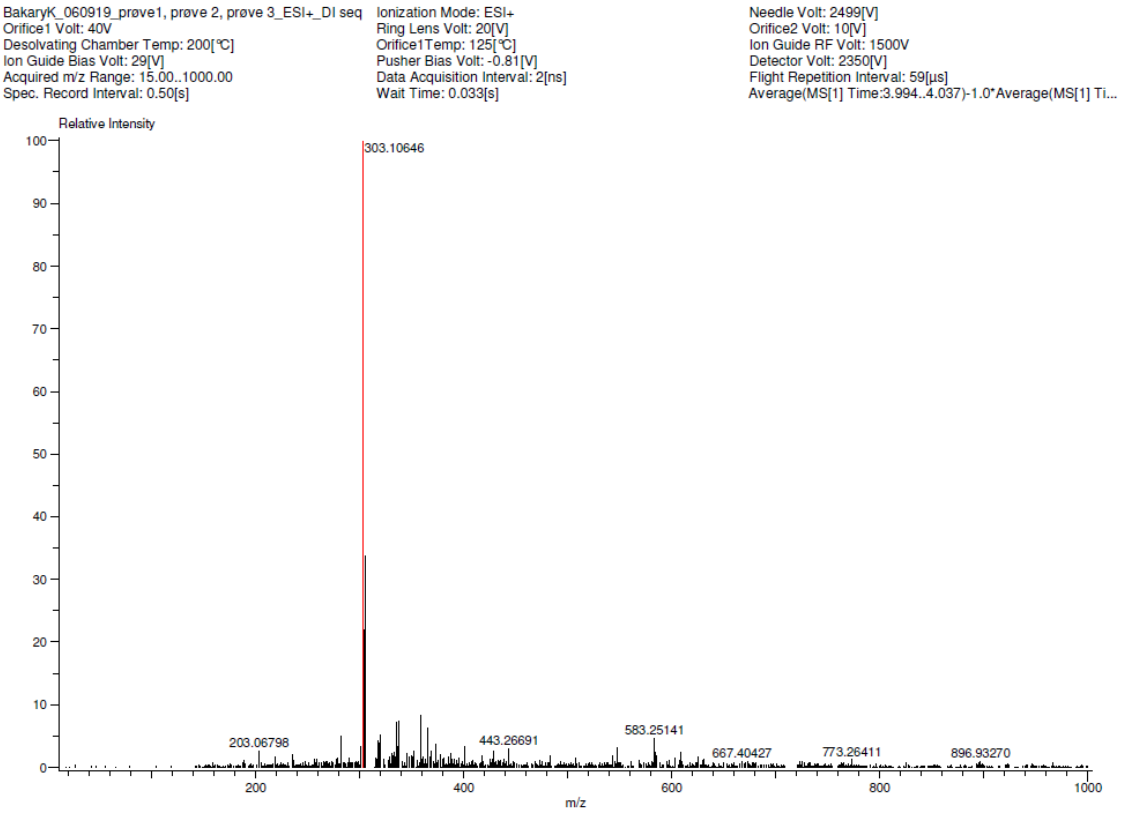


Figure 9: HRMS (ESI+/TOF) of the product *m/z* = 303.10645

9 Summary

Synthesis of β-hydroxy dithiane derivatives

The β-hydroxy dithiane 2-(2-(benzyloxy)-3,3-diethoxypropyl)-1,3-dithiane (**8**) was successfully synthesized from 3,3,4,4-tetraethoxybut-1-yne (TEB). When treated with Dowex 50W in wet acetone, TEB was transformed into TEB-ketone in excellent yield (91%). Michael addition using 1,3-propane dithiol then introduced the dithiane moiety to form compound **6** in acceptable yields (52%) and subsequent reduction of the ketone produced the β-hydroxy dithiane (**7**) in a reaction that yields 56-95% of the product. Alkylation of the product was successful to produce compound **11** in 13% yield.

To avoid polymerization of compound **7** in the following hydrolysis, the alcohol was protected by benzylation in a reaction that yielded 86% of the product, **8a**. An attempt to protect the alcohol by silylation was made, but this reaction ultimately failed and was not pursued further.

Compound **8a** was successfully hydrolysed using formic acid to produce the aldehyde **9** (35%). Unfortunately, an attempt to couple a propyl group to the aldehyde using Wittig reaction was unsuccessful.

It was revealed that the compound **6** could be synthesized from 1,1-diethoxy-4-(trimethylsilyl)-but-3-yn-2-one directly. This could be done in one pot under the same conditions described for the synthesis of compound **6** from TEB-ketone. This discovery means that the β-hydroxy dithiane can be synthesized in four steps from ethyl diethoxyacetate, with each step yielding high amounts of product.

Alternative ways of synthesizing the TEB-ketone

TEB-ketone was successfully synthesized from readily available and inexpensive ethyl diethoxyacetate in three steps. First 1-(diethoxyacetyl) piperidine **5b** was synthesized in excellent yields (91%), then the acetylene was introduced by a displacement reaction to generate compound **5c** in very good yields (72%). Deprotection of the TMS using either a silver catalysed reaction produces the TEB-ketone in moderate yield (70%). Optionally, TMS can be removed using K_2CO_3/MeOH as well. An attempt to synthesize TEB-ketone using Weinreb amide was made but this method was, in the end, not pursued any further.

10 Further research

Since the β-hydroxy dithiane can be synthesized from 1,1-diethoxy-4-(trimethylsilyl)-but-3-yn-2-one, optimization of its synthesis could be of interest for further work. Using the Weinreb amide[21] or perhaps the Dulou methodology,[20] the substrate could potentially be synthesized in overall higher yields.

Alkylation of the β-hydroxy dithiane was successful but produced very low amounts of product (13%). Further optimization of the reaction and exploration into various alkylation reactions the dithiane can undergo, would be interesting.

As the formation of aldehyde **9** from the β-hydroxy dithiane requires **6** days to be completed, investigation into the cause of the slow reaction would be very interesting for study. A comprehensive study of the relationship between the hydroxy protection group and reaction time would also be exciting.

Chain elongation by Wittig olefination performed on the aldehyde **9** in this project failed. However, Valdersnes has documented that Wittig reactions on compound **9** is possible,[14] therefore exploration of the reactivity of compound **9** in the presence of various Wittig reagents could further expand the coupling potential of the substrate. Further study into different coupling reactions the aldehyde could undergo, could be attempted, for instance to see whether it can undergo pinacol coupling reactions.

The two deprotection methods used for 1,1-diethoxy-4-(trimethylsilyl)-but-3-yn-2-one to furnish the TEB-ketone were not the most optimal, with the highest yield obtained being 70%. Therefore, optimization of the silver catalysed method or exploration of a different deprotection reaction could increase yields. This would allow for an even more efficient way of synthesizing the dithiane.

Isolating 1,1-diethoxy-3-(2-(trimethylsilyl)-1,3-dithian-2-yl)propan-2-one (Figure 7) from the Michael reaction between 1,1-diethoxy-4-(trimethylsilyl)-but-3-yn-2-one and 1,3-propane dithiol could still be valuable in use for further synthesis. The substrate could potentially provide access to a 4-carbon synthon with unique functionality.

Experimental

11 General

Chemicals

Except for ethanol, all commodity chemicals were acquired from Merck, formerly Sigma Aldrich Chemical Company, and used without further purification. Ethanol was obtained from Arcus (Oslo, Norway) and stored over molecular sieves (4 Å). Anhydrous THF was obtained from the solvent purification system SPS-800 by MBRAUN and stored over the same sieves.

IR spectroscopy

FT-IR spectra were recorded on a Nicolet Protégé 460 FT-IR spectrometer equipped with an attenuated total reflectance (ATR) attachment. Samples were analysed neat on a ZnSe crystal and the absorption frequencies are given in wave numbers (cm^{-1}). Intensities are not reported as the ATR technique renders them inaccurate.

NMR spectroscopy

NMR spectra were recorded on a Bruker BioSpin AV500 (500 MHz for ^{1}H, 125 MHz for ^{13}C). Coupling constants (*J*) are given in Hz and the multiplicity is reported as a singlet (s), doublet (d), triplet (t), quintet (q), sextet (sxt), nonet (non), double doublet (dd), doublet of triplet (dt) and multiplet (m). The chemical shifts are reported in ppm using the residual $CHCl_3$ peak (7.25 ppm) as the internal reference for 1H spectra and the central peak of the $CDCl_3$ triplet (77.17 ppm) for ^{13}C spectra.

Chromatography

Thin-layer chromatography (TLC) analysis were performed with aluminium sheets covered with silica gel (60 F_{254}), the solvent system consisting of various mixtures of hexane isomers and ethyl acetate. Staining was achieved with either exposure to UV light (254 nm) or a 20 %

solution of phosphomolybdic acid (PMA) in ethanol. Flash chromatography was performed with silica gel (230-400 mesh) and the same mobile phase as for the TLC analyses. The eluent composition is given in each case.

12 Experimental procedures

12.1 Synthesis of TEB-ketone

1,1 Dichloro-2-ethoxycyclopropane (1)

Ethyl vinyl ether (53 mL, 0.55 mol), chloroform (175 mL, 2.20 mol) and TBAI (0.91 g, 2,40 mol) were transferred to a 500 mL three-Necked round-bottom flask fitted with a mechanical stirrer, a dropping funnel and a condenser. The mixture was cooled (ice/ water bath) before 50% aq NaOH solution (132 g, 1.65 mol) was added dropwise to the solution under vigorous stirring. NaOH was added over a period of 1 hr, after which the solution was left vigorously stirring, slowly reaching rt. After 23 hr the mixture was cooled (ice/water bath) and quenched using 6 M HCl (165 mL). The organic phases were separated and the aq layer was extracted with DCM (3 x 75 mL). The combined organic extracts were combined, dried over MgSO4, filtered and concentrated *in vacuo* on a rotary evaporator to give a pale-yellow residue (78.18 g, 92%). The spectroscopic data are in accordance with the literature.[36]

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

A 1000 mL round- bottom flask equipped with a magnetic stirrer and a condenser, was charged with **1** (77 g, 0.5 mol), absolute ethanol (350 mL), and pyridine (53 mL). The reaction mixture was heated to reflux (95 ^{o}C) for 48 hr, then cooled to rt and concentrated *in vacuo* on a rotary evaporator to remove the ethanol. Water (200 mL) and DCM (100mL) were added, the phases separated and the aq phase washed with DCM (3x 100 mL). To remove unwanted pyridine from the reaction the organic phase was washed with 0.7 M solution of $CuSO_4$ (3 x 100 mL), dried over ($MgSO_4$) and filtered through a plug of Al_2O_3. The crude product was concentrated *in vacuo* on a rotary evaporator to yield a yellow residue (54.8 g, 66%) as an essentially pure product based on NMR data which are in accordance with previously reported literature.[36]

1,1-Dibromo-2-chloro-2-(diethoxymethyl)-cyclopropane (3)

In a 250 mL three-necked round bottom flask fitted with a condenser, dropping funnel and a mechanical stirrer was charged **2** (54.8, 0.33 mol), bromoform (117 mL), and TBAI (0.8 g, 2.2 mmol). Over a period of 1 hr 50% aq NaOH solution (160 mL, 2 mol) was added dropwise to the cooled mixture (ice/ water bath) under vigorous stirring. The mixture was left stirring in the ice bath and could slowly rise to rt over 24 hr. A 6 M aqueous solution of HCl was slowly added followed by separation of the phases and extraction of the aq phase with DCM (3x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and was concentrated *in vacuo* on a rotary evaporator. The crude product was distilled (80-85 ^oC. 0.1 mmHg, lit. 80-82 ^oC, 0.15 mmHg) to yield 3 as a brown liquid (36.58 g, 30%). The spectroscopic data are in accordance with the literature.[2]

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

A 250 mL three-necked round-bottom flask equipped with a condenser with a drying tube, a dropping funnel and a mechanical stirrer, was charged with **3** (46.88 g, 0.14 mol), absolute ethanol (50 mL), TBAI (0.31 g,) and DCM (110 mL). The mixture was cooled (ice/ water bath) before 50% aq NaOH solution (50 g, 1.3 mol) was added dropwise to the solution under vigorous stirring over a period of 1 hr. The mixture was left stirring at bath temperature slowly reaching rt over 24 hr. An aq solution of 3 M HCl (100 mL) was added, the phases separated and the aq layer was extracted with DCM (3 x 100 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* on a rotary evaporator. The crude product was distilled (60 ^oC, 0.2 mmHg, lit. 53-58 ^oC, 0.2 mmHg) to yield TEB (6.35 g, 20%) as a yellow liquid. The spectroscopic data are in accordance with the literature.[2]

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

TEB (2.30 g, 10 mmol) was refluxed in a mixture of acetone (10 mL) and water (0.25 mL), with Dowex 50W (0.50 g) as acid. After 4.5 hr the heating was terminated to allow the reaction mixture to cool down to room temperature before being filtered to remove Dowex 50W. Evaporation of the acetone gave a crude product which was purified by flash-chromatography to yield 1.43 g (91%) of the title compound as a yellow liquid. The spectroscopic data were in agreement with literature. [14]

12. 2 Alternative preparation of TEB-ketone (5)

1-(Diethoxyacetyl) piperidine (5b)

A round bottom flask equipped with a thermometer, a condenser and an outlet with another round bottom flask attached was charged with piperidine (17 mL, 235 mmol) and ethyl 2,2-diethoxyacetate (18.06 g, 102.30 mmol) and heated to reflux (150 ^{o}C) for 48hr. The reaction was quenched with HCl (50 mL, 3M) then the organic phase was extracted with DCM (3 x 50 mL) and washed with brine (3 x 50 mL). Organic extract was then dried over $MgSO_4$ and concentrated *in vacuo* on a rotary evaporator to give a light-yellow product (20.14 g, 91%) that was essentially pure according to NMR.

1,1-Diethoxy-4-(trimethylsilyl)-but-3-yn-2-one (5c)

Dried THF (80 mL) and ethynyl-TMS (5.60 g, 57.01 mmol) were added to a two necked round bottom flask equipped with a magnetic stirrer, septum, a condenser and a drying tube; that were oven dried and flushed with N_2 prior. Ethyl magnesium bromide (solution in diethyl ether) (18 mL, 55.00 mmol) was added dropwise to the mixture which was then refluxed at 60 ^{o}C for 2 hr. Then compound **5b** (11.88 g, 55.00 mmol) was added to the reaction mixture. After 20 hr the mixture was quenched with 1 N H_2SO_4, extracted with diethyl ether, dried over $MgSO_4$ and concentrated *in vacuo* on a rotary evaporator to give the crude product as a pale brown liquid (14.27 g). Due to lack of a flash column large enough to purify all the crude product at once.

At the time, 1.60 g of the crude was purified at a time to yield approximately 1 g of the title compound. This resulted in 9 g (72%) total of pure product.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.75 (s, 1H), 3.75-3.60 (m, 4H), 1.26 (t, 6H), 0.25 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 183.5, 103.4, 102.2, 101.1, 63.8, 15.9, 0.004.

IR (neat) νmax: 2977, 2932, 2900, 2153, 1691, 1480, 1445, 1393, 1371, 1319, 1252, 1222, 1162, 1067, 928, 842, 761, 704, 668, 625.

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

A 50 mL round-bottomed flask was charged with **5c** (0.23 g, 1.0 mmol), AgNO3 (0.017 g, 0.1 mmol) and a mixture of DCM:H_2O:MeOH in a 7:1:4 ratio (20 mL). The solution was stirred for 16 h and the reaction was then quenched by the addition of a saturated aq solution of NH_4Cl (5 mL). The organic phase was separated in a separatory funnel and the aq phase was extracted with DCM (3 x 20 mL). The combined organic extracts were concentrated in vacuo and the resulting crude product purified by flash column chromatography (hexanes:ethyl acetate, 9:1) to yield the title compound (0.12 g, 70%) essentially pure according to NMR and in accordance with literature.[14] Traces of the starting material were also isolated as a separate fraction.

2,2-Diethoxy-N-methoxy-methylacetamide

In a 100 mL round-bottomed flask *N,O*-dimethylhydroxylamine x HCl (4.11 g, 42.0 mmol) was dissolved in DCM (50 mL) and cooled to 0 ^{o}C. $AlMe_3$ (21 mL, 42.0 mmol, 2M in toluene) was then added to the solution before the mixture was allowed to warm up to rt and was stirred for 1 hr. The reaction mixture was cooled again to 0 ^{o}C before ethyl 2,2-diethoxyacetate (3.65 g, 21 mmol) in 20 mL DCM was slowly added over 2 hr, after which the mixture was left to stir at rt for an additional 2 hr. Then the reaction mixture was slowly poured into ice-cold HCL (50 mL, 0.5 M) and stirred at 0 ^{o}C for 30 min and the layers separated. The aq phase was extracted with diethyl ether (2 x 20 mL), and the combined organic phases were washed with brine (50 mL), dried over dried over $MgSO_4$ and concentrated *in vacuo* on a rotary evaporator to give the crude product.

12.3 Preparation of a β-hydroxy dithiane from TEB-ketone

3-(1,3-Dithiane-2-yl)-1,1-diethoxypropan-2-one (6)

Method A

TEB-ketone (0.28 g, 2 mmol) was stirred in an ice/acetone bath (-10 ^{o}C) with DCM (30 mL), methanol (7 mL), sodium methylate (1.28 g, 2.4 mmol) and 1,3-propane dithiol (0.23 g, 2.1 mmol) under inert atmosphere. The reaction mixture was evaporated to remove most of the solvent 16.5 hours later. The resulting slush was diluted was diluted with water and extracted with DCM, after which the combined extracts were dried ($MgSO_4$) and filtered. Concentration of the solution gave the crude product which was isolated by flash chromatography to yield 0.152 g (25 %) of an orange liquid. Spectroscopic data agreed with the literature[14].

Method B

In an oven dried two-necked round bottom flask equipped with a magnet stirrer and septa 1,3-propane dithiol (1.44 g, 13 mmol), sodium methylate (0.74 g) and THF (110 mL) were stirred (-78 ^{o}C) while N_2 was flushed through for 5 min. Compound **5a** (1.43 g, 9 mmol) in dry THF (25 mL) was added dropwise to the solution which was stirred for 2hr in a -78^{o}C bath then left to slowly reach rt overnight. A saturated aq solution of NH_4Cl (75 mL) as well as water (50 mL) and DCM (100 mL) were added and the organic phase extracted. The aq phase was extracted with DCM (2 x 100 mL) before the organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* on a rotary evaporator. Flash chromatography of the crude product afforded 1,23 g (52 %) of the title compound **6**. Spectroscopic data agreed with the literature[14].

Method C

In method c compound **5c** is used instead of the TEB-ketone but the procedure is otherwise identical to method b. This method yielded 2.32 g (82%) of the titled compound of which the spectroscopic data were in agreement with literature.[14]

3-(1,3-Dithiane-2-yl)-1,1-diethoxypropan-2-ol (7)

Compund **6** (1.42 g, 5.4 mmol), $NaBH_4$ (0.12 g, 3 mmol), THF (22 mL) and water (1 mL) were added to a round-bottom flask equipped with a magnetic stirring bar. The reaction mixture was placed in an ice/water bath (0^oC) and stirred for 45 min. Additional water (10 mL) was added to the mixture before THF was evaporated on a rotary evaporator, and the remaining solution transferred to a separatory funnel. DCM (3 x 20 mL) was later added and the phases separated. The organic phases were then extracted from the aq phase using DCM and combined to be dried over $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator. Flash chromatography of the crude product (8:2) afforded the title compound as a pale-yellow liquid (0.80 g, 56%). The reaction was repeated with fresher $NaBH_4$ and from 2.32 g of compound **6**, 2.2 g (95%) of essentially pure product was yielded. The spectroscopic data were in agreement with literature.[14]

2-(2-(Benzyloxy)-3,3-diethoxypropyl)-1,3-dithiane (8)

Compound **7** (1.1 g, 4 mmol) was dissolved in DCM (5 mL), then benzyl chloride (1.0 g, 8 mmol), TBAHS (0.10 g, 0.3 mmol) and 50% (w/w) sodium hydroxide (3 g) were added and the mixture was refluxed (50 ^oC) while stirring vigorously. Additional benzyl chloride (0.5 g, 4 mmol) was added after 4 hours. After a total of 23 hr the reaction mixture was allowed to cool down to room temperature and water was added, followed by extraction with DCM (3x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator to give the crude product a yellow liquid. Flash chromatography of the crude product (9:1) afforded the title compound as a pale-yellow liquid (1.22 g, 86%). The spectroscopic data were in agreement with literature.[14]

2-(Benzyloxy)-3-(1,3-dithian-2-yl) propanal (9)

A 25ml round-bottom equipped with a magnetic stirrer was charged with compound **8** (1.22 g, 3.40 mmol), pentane (15 mL) and formic acid (5 drops) and stirred. After 24 hr 1 mL of 80% aq formic acid was added and the reaction mixture was left stirring for another 5 days. After a

total of 6 days water was added and the mixture extracted three times with DCM. The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* on a rotary evaporator giving the give the crude product. This was purified by flash chromatography to yield the titled compound as a pale-yellow liquid (0.33 g, 35%) that was pure according to literature values.[14]

2-(2-(Benzyloxy) hex-3-en-1-yl)-1,3-dithiane

In a round bottom flask equipped with a magnetic stirrer and a septum $PrPh_3PBr$ (0.7 g, 2.0 mmol) was dissolved in THF (20 mL) and cooled to -10 ^oC (ice/acetone bath) for 15 min. BuLi (1.6 M in hexane) was then slowly added (1.1 mL, 1.8 mmol) before further cooling the solution to -78 ^oC (acetone/dry ice) for 15 min. Compound **9** (0.15 g, 0.5 mmol) dissolved in THF (3 mL) was added dropwise followed by removal of the cooling. After 4 hr saturated aq ammonium chloride (20 mL) was added to quench the reaction. The mixture was extracted three times with DCM (15 mL) and the organic extracts combined to be dried over $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator to give the crude as an orange liquid.

2-(2-(Trimethylsiloxy)-3,3-diethoxypropyl)-1,3-dithiane

A two necked round bottom flask equipped with a magnetic stirrer was charged with compound **7** (1 g, 3.8 mmol) dissolved in THF (10 mL). Later Et_3N (0.4 g, 3.8 mmol) was added followed by slow addition of TMSCl (1 g, 9.5 mml). The reaction mixture was stirred in rt overnight before it was quenched with 1 N H_2SO_4, extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo* on a rotary evaporator to give the crude product as pale yellow liquid. Flash chromatography of the crude product (9:1) afforded the title compound as a pale-yellow liquid.

12.4 Alkylation of β-hydroxy dithiane

1,1-Diethoxy-3-(2-methyl-1,3-dithian-2-yl) propan-2-ol (10)

A two-necked round-bottomed flask, equipped with a condenser, drying tube, magnetic stirrer and septum, was charged with anhydrous THF (15 mL) and compound **7** (0.7 g, 2.6 mmol) and flushed with N_2. The reaction mixture was cooled to -78 °C (acetone/dry ice) followed by dropwise addition of *n*-BuLi (1.3 mL, 3.3 mmol, in 2.5 M hexane) over 15 min. It was then stirred at -78 °C for 45 min before warming to 0 °C (ice/water) followed by addition of the electrophile, methyl iodide (0.6 g, 4.23 mmol) over 10 min. The reaction was left stirring for 24 hr and reached rt as ice the bath melted. The reaction was then quenched with the addition of saturated aq solution of NH_4Cl (20 mL), the phases separated, and the aq phase extracted with DCM (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product which was purified by flash chromatography to yield the product as a clear liquid (0.13 g, 13%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.54 (s, 1H), 4.36-4.35 (d, 1H), 3.76-3.47 (m, 4H), 2.79-2.92 (m, 4H), 2.12-1.80 (m, 5H), 1.23 (m, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz): δ 104.3, 63.8, 63.3, 60.4, 59.3, 43.7, 41.6, 36.3, 30.2, 29.4, 26.1, 15.9

IR (neat) νmax: 3426, 2973, 2897, 1423, 1374, 1275, 1242, 1162, 1060, 908, 776, 739, 698, 663, 571.

HRMS (ESI+/TOF) calcd for $C_{12}H_{24}O_3S_2Na$ [M+Na^+] 303.10645

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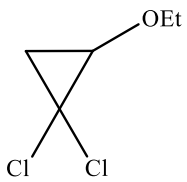
Appendix

Isolated Compounds



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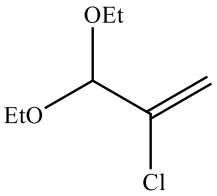

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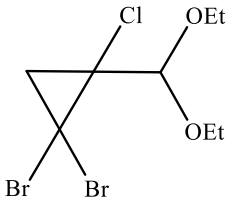

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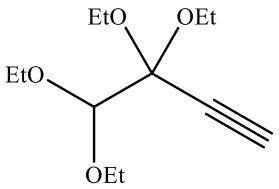
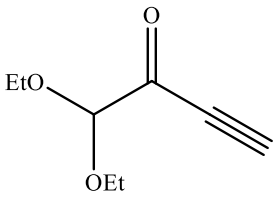
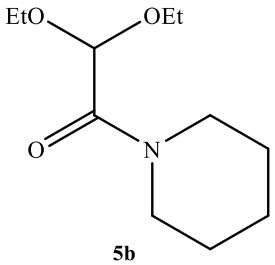


4



5a



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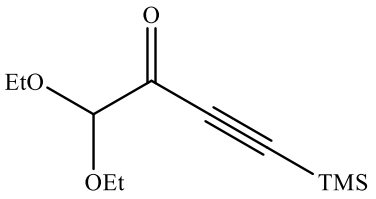

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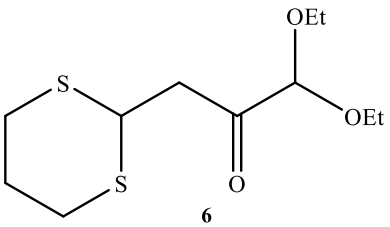

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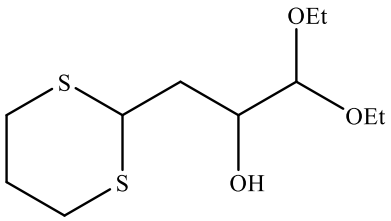

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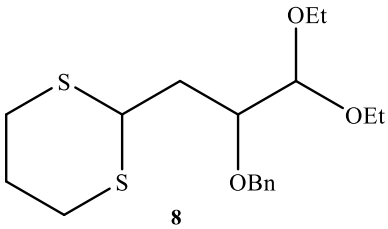

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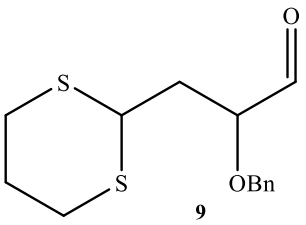

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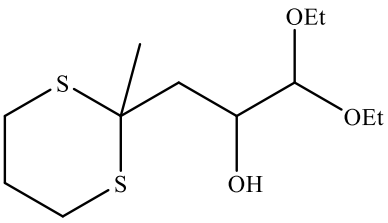
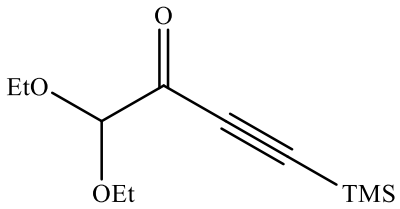
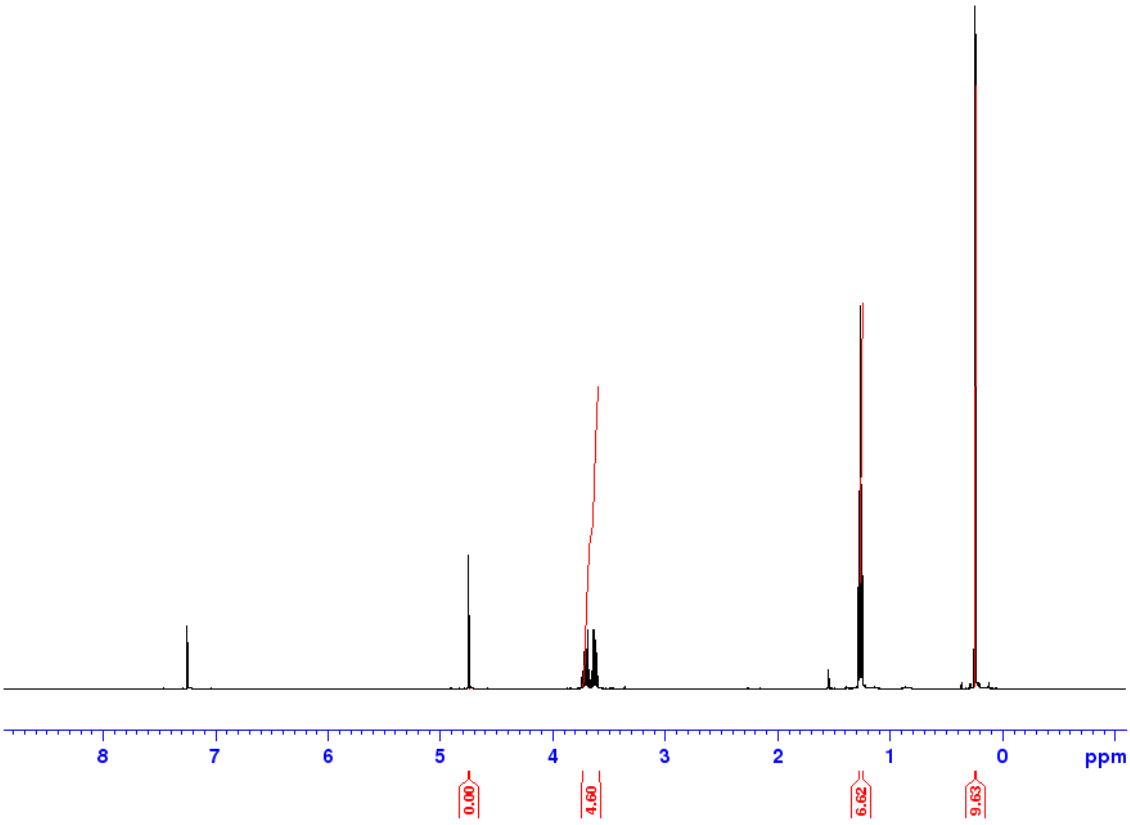


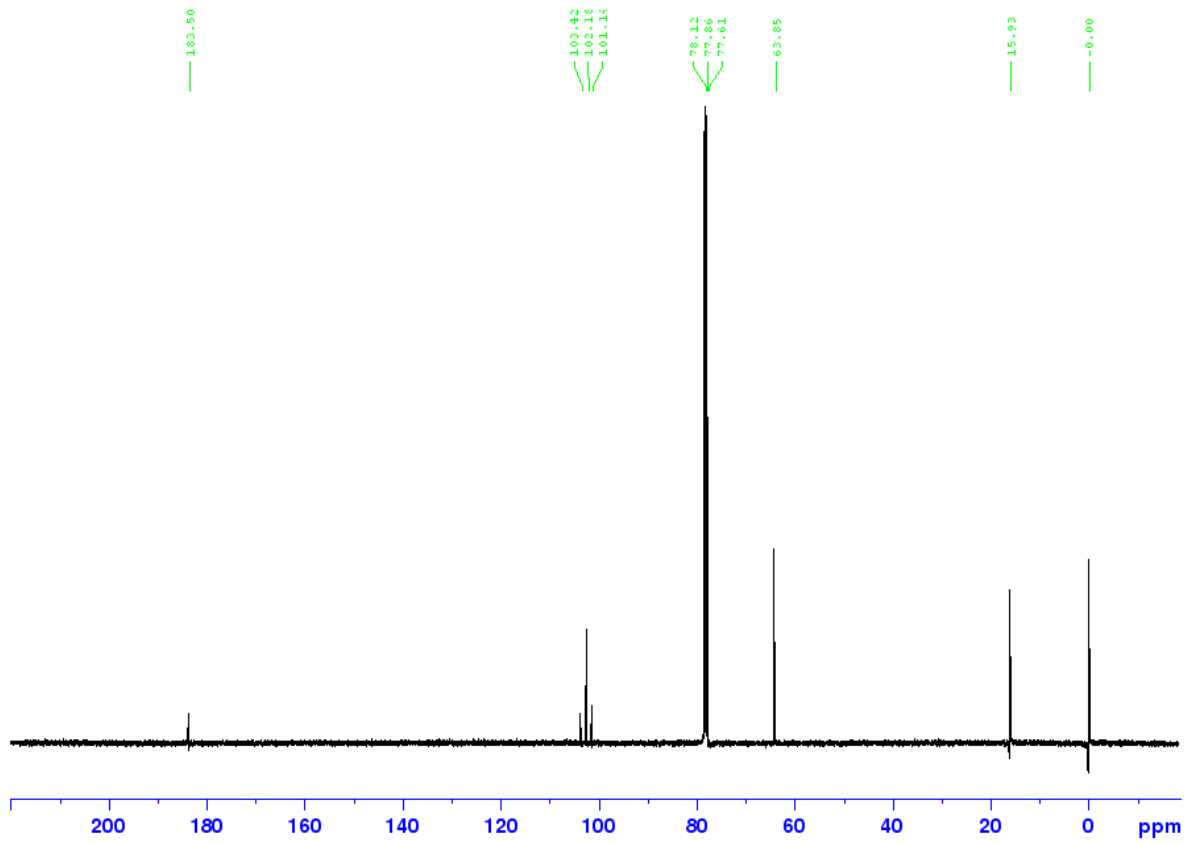
10

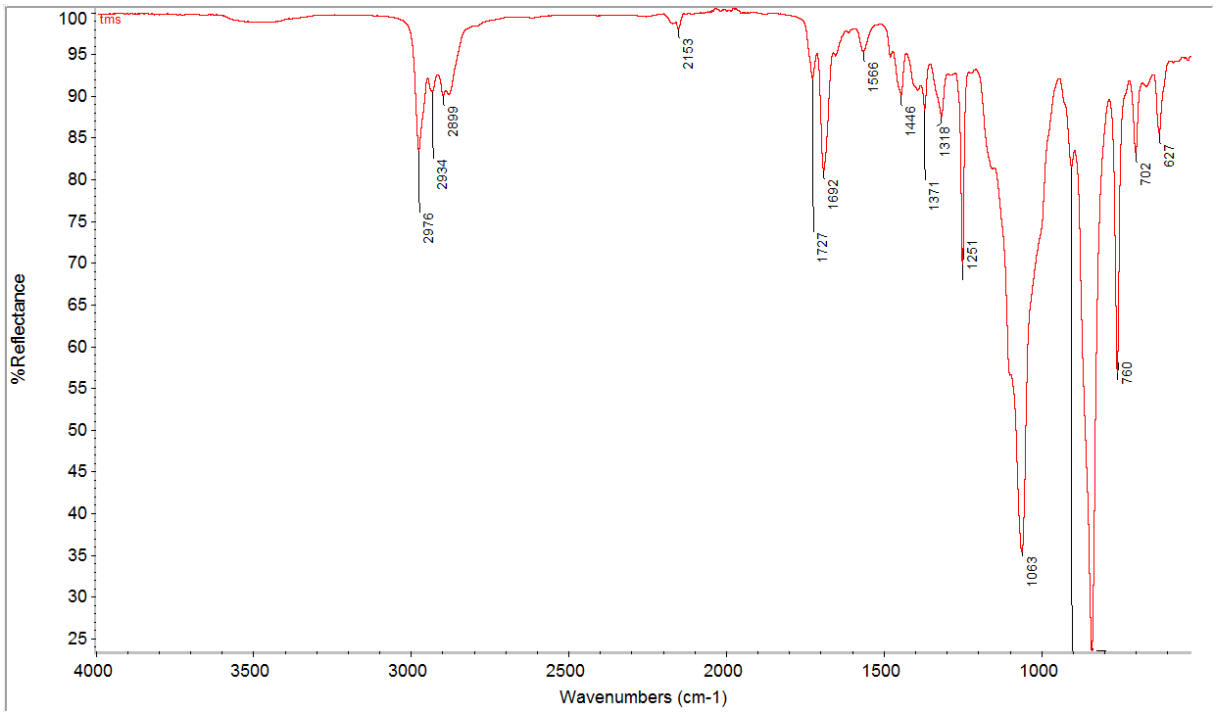
Spectra of new compounds

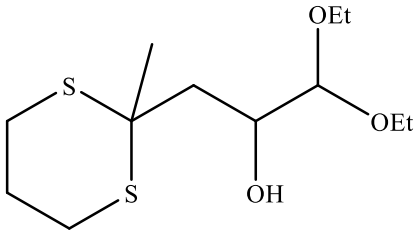


1,1-Diethoxy-4-(trimethylsilyl)but-3-yn-2-one **(5c)**

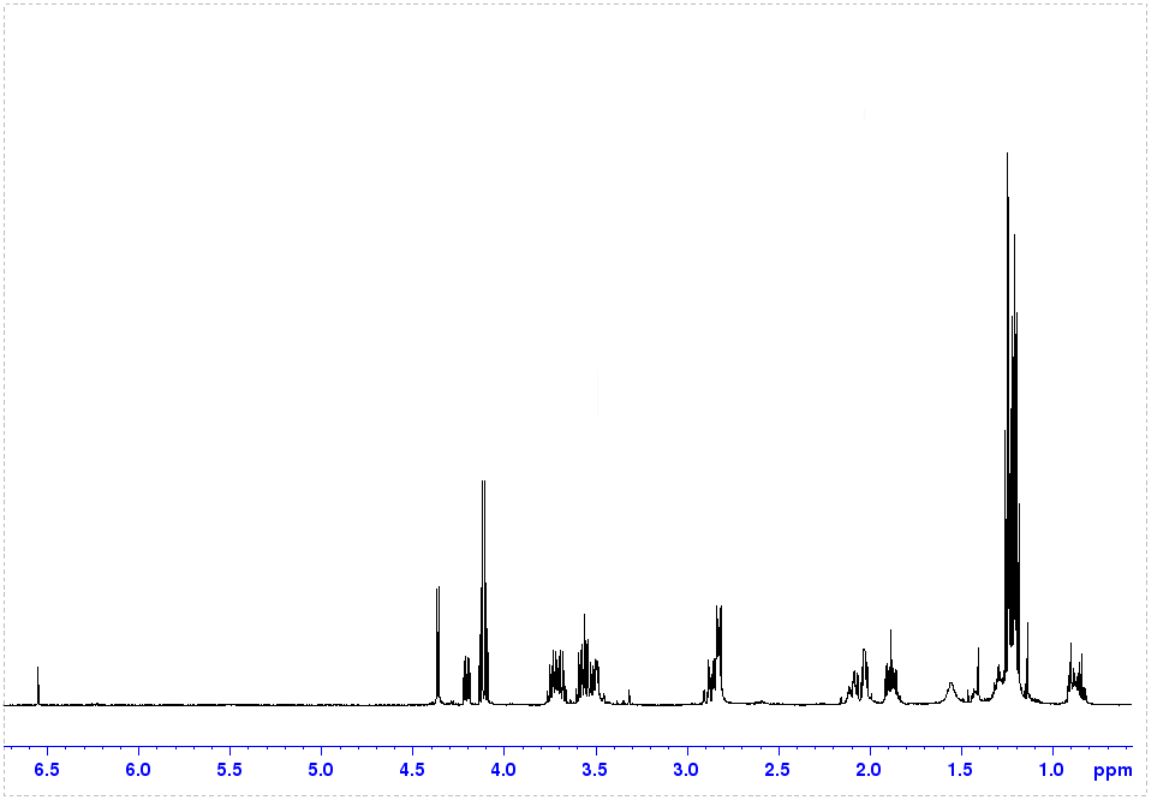


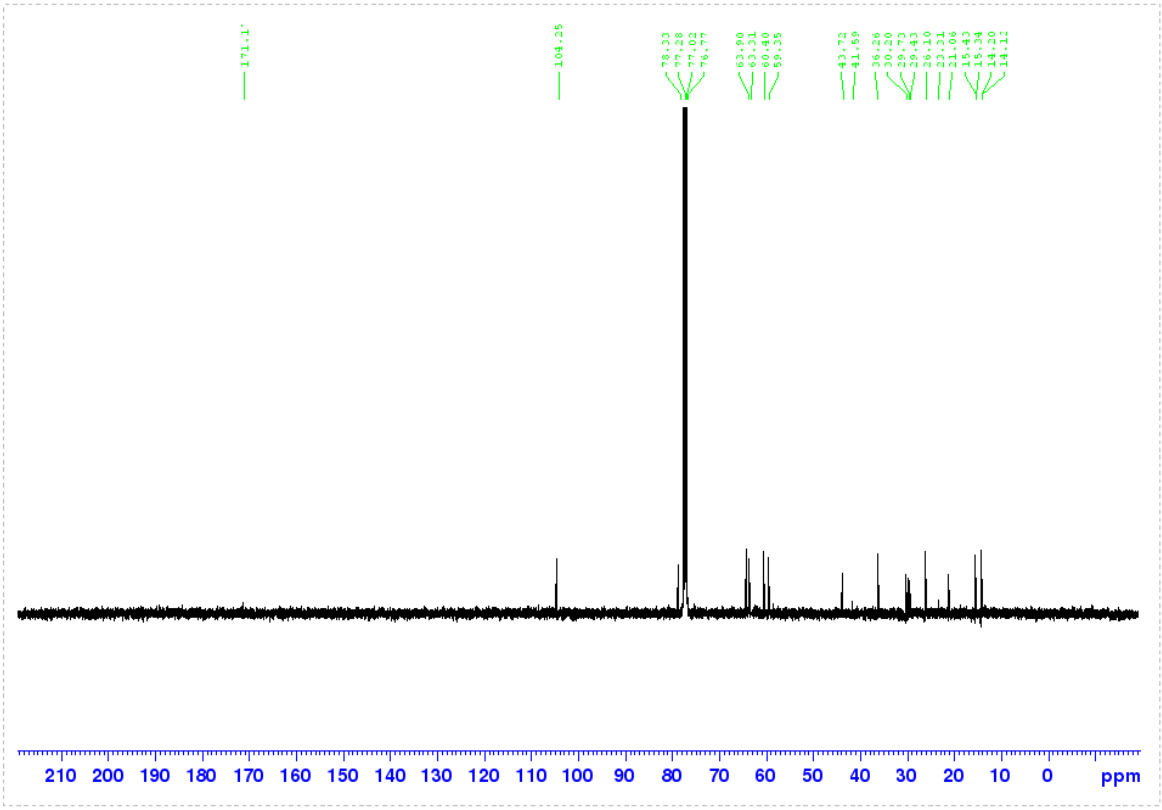

183.50
103.42
102.18
101.14
78.12
77.86
77.61
63.85
15.93
-0.00
200
180
160
140
120
100
80
60
40
20
0
ppm

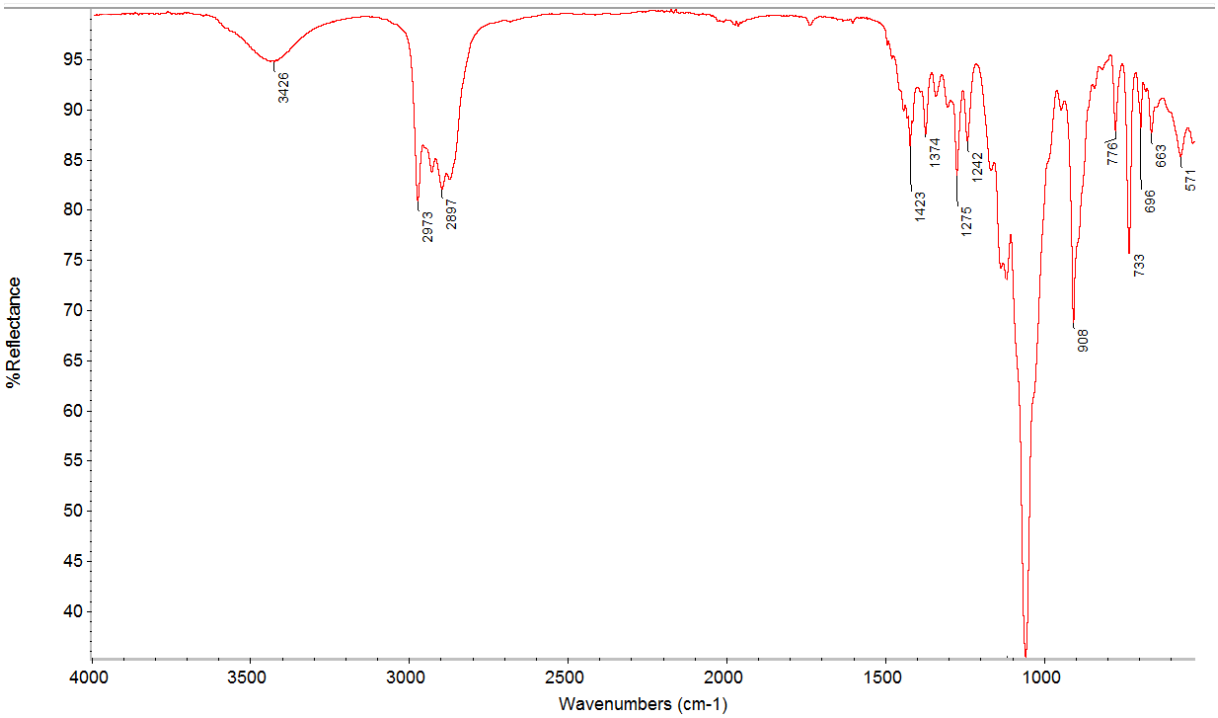

tms
%Reflectance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
2976
2934
2899
2153
1727
1692
1566
1446
1371
1318
1251
1063
760
702
627



1,1-Diethoxy-3-(2-methyl-1,3-dithian-2-yl)propan-2-ol **(10)**




171.17
104.25
78.33
77.28
77.02
76.77
63.90
63.31
60.40
59.35
43.72
41.59
36.26
30.20
29.73
29.43
26.10
23.31
21.06
15.43
15.34
14.20
14.12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


%Reflectance
95
90
85
80
75
70
65
60
55
50
45
40
3426
2973
2897
1423
1374
1275
1242
908
776
733
696
663
571
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

BakaryK_060919_prøve1, prøve 2, prøve 3_ESI+_DI seq
Orifice1 Volt: 40V
Desolvating Chamber Temp: 200[℃]
Ion Guide Bias Volt: 29[V]
Acquired m/z Range: 15.00..1000.00
Spec. Record Interval: 0.50[s]

Ionization Mode: ESI+
Ring Lens Volt: 20[V]
Orifice1Temp: 125[℃]
Pusher Bias Volt: -0.81[V]
Data Acquisition Interval: 2[ns]
Wait Time: 0.033[s]

Needle Volt: 2499[V]
Orifice2 Volt: 10[V]
Ion Guide RF Volt: 1500V
Detector Volt: 2350[V]
Flight Repetition Interval: 59[µs]
Average(MS[1] Time:3.994..4.037)-1.0*Average(MS[1] Ti...