

From 3,3,4,4-tetraethoxybutyne to carbohydrate mimics*

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Abstract: 3,3,4,4-Tetraethoxy-1-butyne, available in high yield in four simple steps from ethyl vinyl ether, is a highly functionalized alkyne, which appears to be a versatile starting material for the synthesis of a range of alkylated, more-or-less deoxygenated carbohydrate mimics. However, many of the reactions used to achieve extension and subsequent structural modification of the carbon chain as well as removal of the protecting groups turn out to be rather sensitive to the substituents' steric and electronic influence. As a result, the reactivity pattern that emerges is somewhat complex.

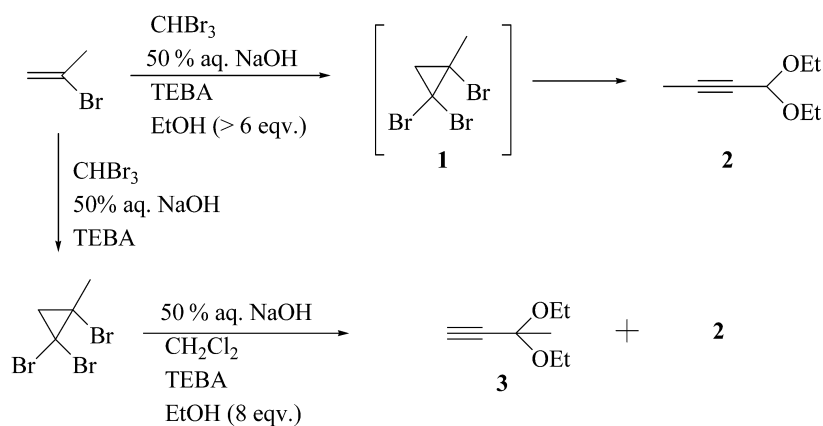
INTRODUCTION

The chemistry presented in this paper is not the result of work carried out in accordance with a structured research plan based on a good idea. Instead, it was made possible by a surprising discovery by one of my students who was going to prepare 1,1-dibromo-2-chloro-2-methyl-cyclopropane (**1**) by addition of dibromocarbene to 2-chloropropene. When this reaction is carried out properly under phase-transfer conditions using Makosza's procedure with triethylbenzylammonium chloride (TEBA) as catalyst [1], a small amount of ethanol is added to facilitate phase transfer. However, by mistake the student used a lot of ethanol, the result of which was that **1** was not observed at all; the only product obtained was 1,1-diethoxybut-2-yne (**2**), which was isolated in moderate yield [2]. This product contained one carbon atom more than the starting material, which clearly indicated that **1** had been formed, but had suffered ring-opening in a subsequent reaction. And sure enough, when the reaction was repeated with no ethanol present, cyclopropane **1** was the only product obtained, and furthermore, when **1** was treated with 50 % NaOH/TEBA/EtOH (8 equiv), ring-opening took place [3] (Scheme 1). However, it then appeared that **2** was not the only product formed; in addition, a ketal, viz. 3,3-diethoxybut-1-yne (**3**), was isolated, and **2** and **3** were obtained in approximately a 1:1 ratio [4–7].

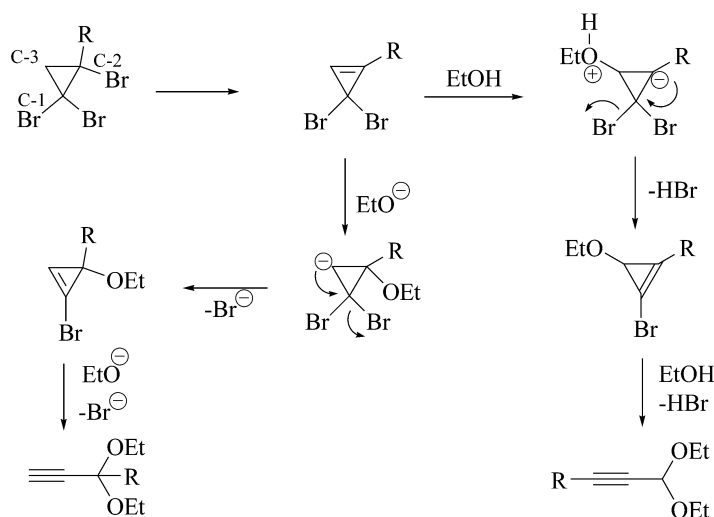
Through subsequent studies, the mechanism for the reaction was established to be as outlined in Scheme 2 [7,8]. A most noteworthy feature is the different regioselectivity exhibited by ethanol and ethoxide during the course of the transformation; whereas ethanol attacks the cyclopropene intermediate at C-3 only, ethoxide reacts with C-2 in a regioselective fashion.

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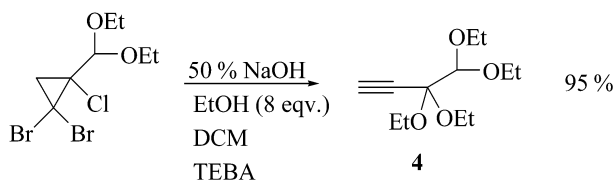


Scheme 1



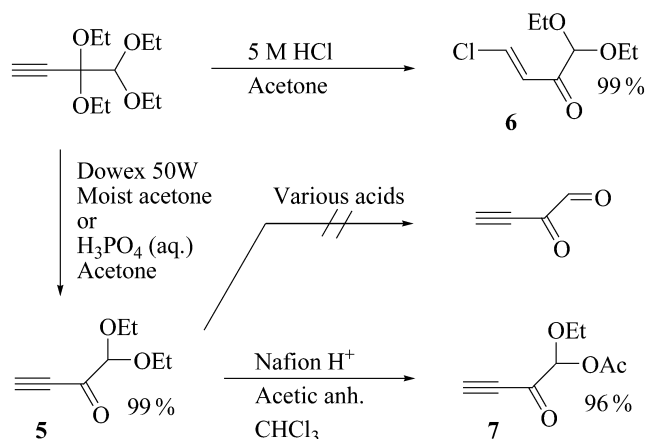
Scheme 2

On the basis of this mechanism, it was argued that if a substituent that could engage in hydrogen bonding was attached to C-2, it was reasonable to believe that one product only should be formed by performing ring-opening under our two-phase conditions; ethoxide would in any case attack C-2, whereas hydrogen bonding between ethanol and the substituent would redirect the ethanol attack from C-3 to C-2. A substituent judged to possess sufficient hydrogen-bonding ability was the diethoxymethyl group, and to our considerable satisfaction, when 1,1-dibromo-2-chloro-2-diethoxymethylcyclopropane was exposed to our phase-transfer conditions, the title compound, 3,3,4,4-tetraethoxybutyne (4), was obtained in 95 % yield as a pure product [8] (Scheme 3).



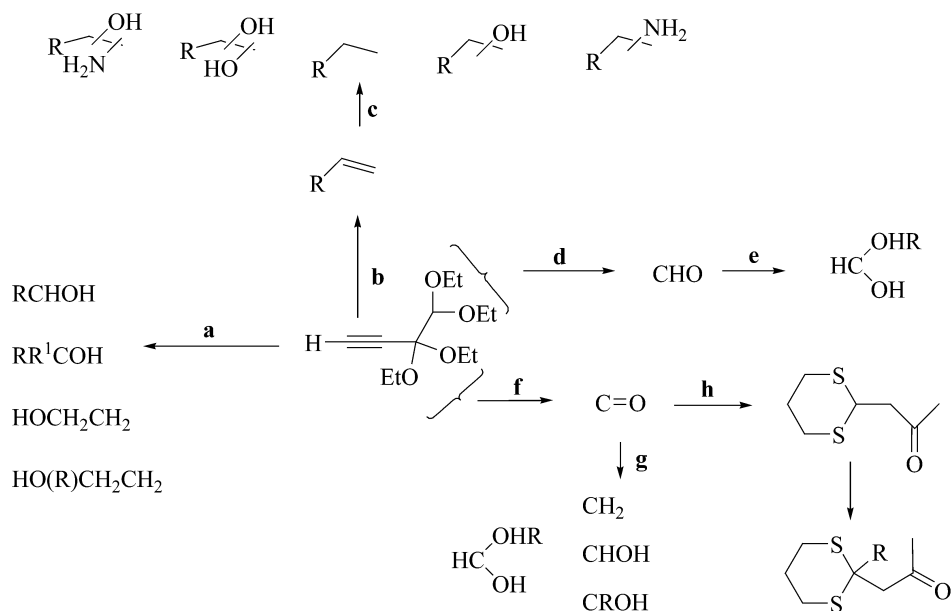
Scheme 3

Pure samples of the double-protected acetylenic ketoaldehyde **4** appeared to be stable at room temperature (rt) and below, both neat and when dissolved in common organic solvents. The compound was also compatible with water, but in moist acidic acetone, in the presence of Dowex 50W or phosphoric acid, the ketal function was deprotected and furnished 1,1-diethoxybut-3-yn-2-one (**5**) in excellent yield (Scheme 4). In diluted hydrochloric acid, however, deprotection was followed by addition of hydrogen chloride, and the final product was 4-chloro-1,1-diethoxybut-3-en-2-one (**6**), which was isolated in 90 % yield. A number of experiments aimed at regenerating the aldehyde function were unsuccessful; the only modification of the diethyl acetal function that gave a stable product, was the conversion to a (acetoxyl)(ethoxyl)methyl moiety (**5** $\rightarrow$ **7**). Ester **7** was isolated in 96 % yield and appeared to be rather stable at rt and below [9].



Scheme 4

Compound **4** contains functional groups with a range of properties that were judged to make this compound a useful starting material for the synthesis of a variety of functionalized molecules including carbohydrate mimics. Some basic transformations that are important to achieve this goal are depicted in Scheme 5. Firstly, the acetylenic proton is acidic and should be easy to abstract, and the resulting acetylide should react with aldehydes, ketones, and oxiranes and afford the corresponding unsaturated alcohols (route **a**). These alkynols should conceivably give the corresponding alkenols upon reduction (route **b**), and the double bond of these alkenols should be prone to undergo a variety of transformations including hydrogenation, hydration, amination, dihydroxylation, and hydroxyamination among (route **c**). After adequate modification of the ketal function we anticipated that the acetal moiety possibly would give the formyl group (route **d**), which should be able to furnish hemiacetals under the right conditions (route **e**). In a similar fashion, the ketal moiety was anticipated to give the keto function, which conceivably could be transformed to a methylene group or secondary and tertiary alcohols, or afford hemiketals under the proper conditions (routes **f** and **g**). Finally, on the basis of the work of Ley and coworkers [10], it was also envisaged that **4**, after having been converted to the corresponding conjugated acetylenic ketone, would undergo a double Michael addition when treated with propane-1,3-dithiol under basic conditions and give 2-substituted 1,3-dithiethanes (route **h**), which conceivably could be converted to 2,2-disubstituted 1,3-dithiethanes by treatment with butyllithium followed by an alkylating agent [11].



Scheme 5

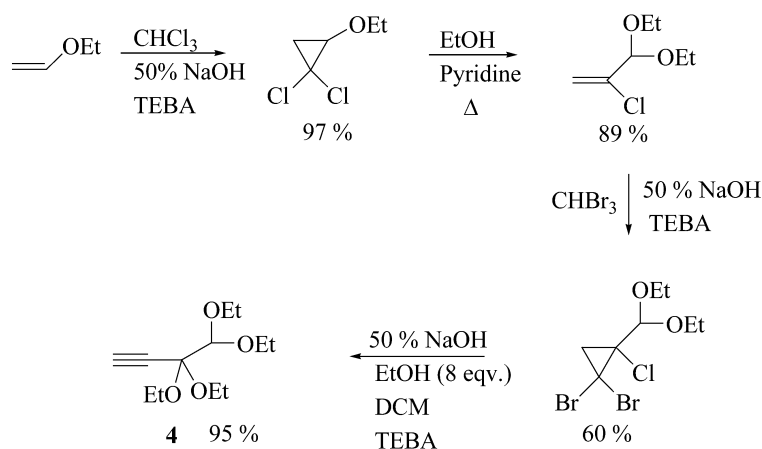
If the densely functionalized compound **4** is going to be an attractive starting material for the syntheses of carbohydrate mimics, at least four basic requirements have to be met.

- The compound has to be easily available in large quantities (reaction scale-up).
- The compound has to be able to undergo chain-elongation reactions in high yields, also in an enantioselective fashion.
- The triple bond must exhibit a certain range of reactivity.
- The ketal and acetal moieties must be so reactive that formation of furanose and/or pyranose can take place.

Considering the significant steric bulk of the tetraethoxyethyl group as well as the potential ability of this moiety to form complexes with organometallic species, it was not obvious that compound **4** would fulfil these requirements. These aspects have actively been studied for some time, and after a period with minor progress a number of interesting results have recently been obtained, some of which are presented here.

REACTION SCALE-UP

The title compound is prepared from ethyl vinyl ether in four steps as outlined in Scheme 6. In most steps the yield is not very sensitive to the purity of the chemicals as long as they are of reagent grade. The only exception is pyridine which had to be thoroughly purified as described in the literature [12] to obtain the reported yield [13]; if commercially available pyridine, even of the best quality, was used as received, the yield sometimes dropped significantly for unknown reasons. The reactions were easy to scale up, and the yields reported in Scheme 6 are isolated yields, obtained when the reactions were performed on a 1-mole scale. All products were isolated by distillation in better than 98 % purity, and the larger the scale, the easier the isolation. It is therefore concluded that the title compound appears to be an attractive starting material for the synthesis of highly functionalized molecules from a preparative point of view.



Scheme 6

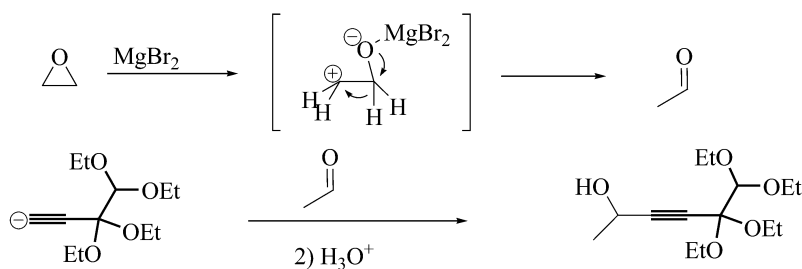
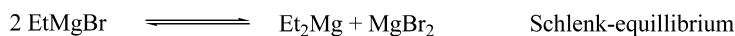
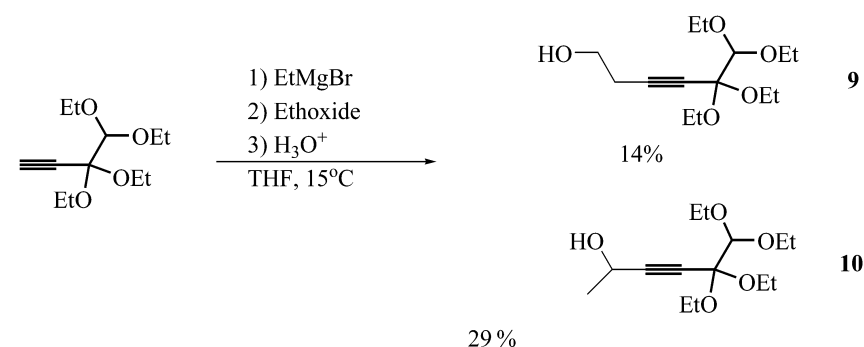
CHAIN ELONGATION

The basic strategy to increase the length of the carbon chain was to convert **4** to the corresponding acetylide and subsequently treat this anion with aldehydes, ketones, and oxiranes. Exploratory experiments revealed that better results were consistently obtained when the acetylide was prepared with ethylmagnesium bromide than with butyllithium; the former method [14] was therefore employed. Under these conditions, aldehydes and ketones with an electron-deficient carbonyl group gave the corresponding propargylic alcohols **8** in good to excellent yield (see Table 1, entries 1–7), but when the carbonyl group is relatively electron-rich, the yield drops considerably as expected (see Table 1, entry 8).

Table 1 Synthesis of propargylic alcohols from alkyne **4**.

Entry	R ¹ , R ²	Isolated yield (%)
1	R ¹ = R ² = H	92
2	R ¹ = R ² = Et	75
3	R ¹ = Me, R ² = H	75
4	R ¹ = Ph, R ² = H	70
5	R ¹ = <i>o</i> -Me-Ph, R ² = H	68
6	R ¹ = <i>m</i> -Cl-Ph, R ² = H	63
7	R ¹ = <i>p</i> -MeO-Ph, R ² = H	32
8	R ¹ = R ² = CH ₂ (CH ₂) ₃ CH ₂	78

The yields of the expected alcohols were also low when the acetylidemagnesium bromide from **4** was allowed to react with oxiranes. A typical example is shown in Scheme 7; the expected homo-propargylic alcohol (**9**) was obtained in insignificant yield due to formation of propargylic alcohol **10**, which conceivably is formed because an oxirane-to-aldehyde rearrangement has occurred to a considerable extent before acetylide attack takes place.



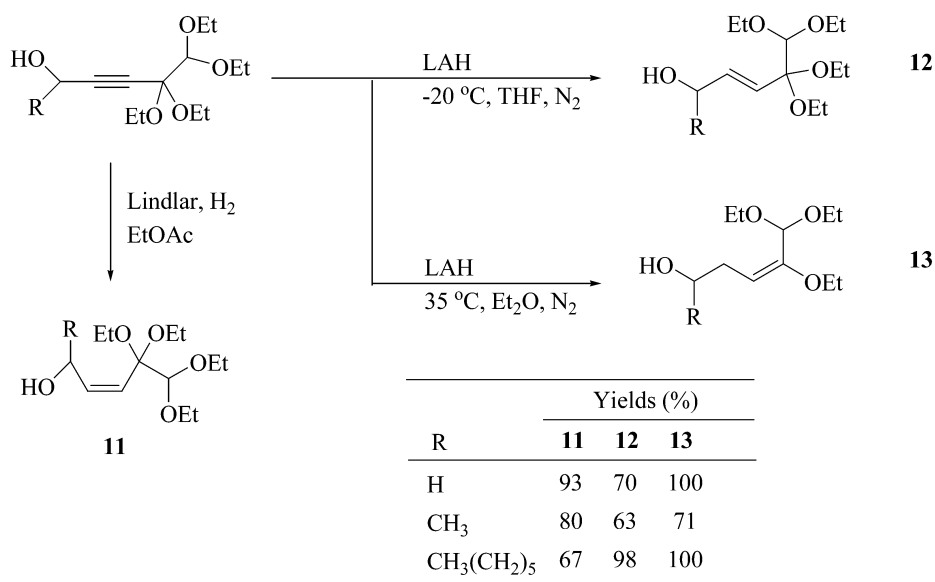
Scheme 7

Carreira and coworkers have recently developed a method for the preparation of optically active propargylic alcohols based on treatment of aldehydes with zinc acetylides in the presence of (+)-*N*-methylephedrine; one of the alcohols prepared in 90 % yield with an ee of 98 % was made from 3,3-diethoxyprop-1-yne [15]. We therefore expect that **4** will react and give the corresponding propargylic alcohols in excellent yield.

ELABORATION BASED ON CONVERSION OF ALKYNES TO ALKENES

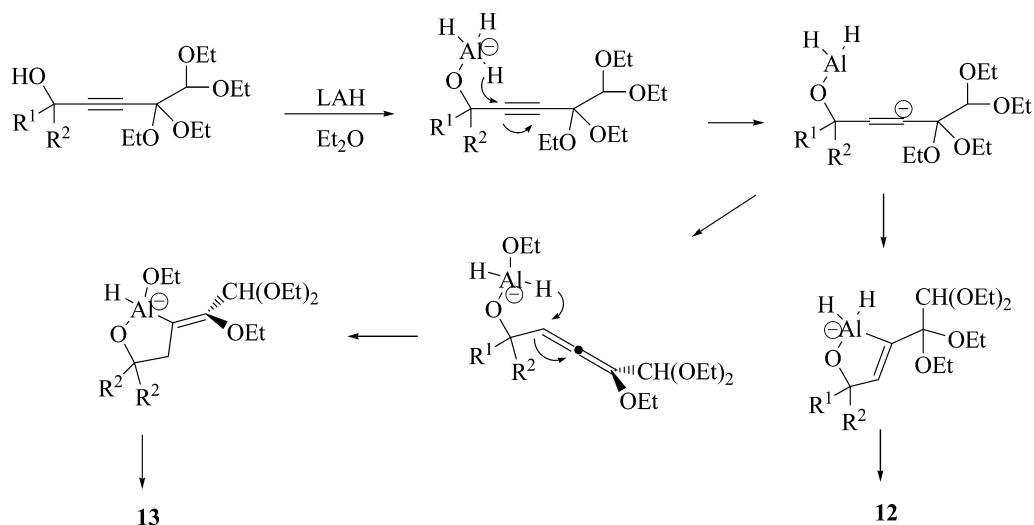
Triple-bond reactivity of **8**

For synthetic utilization of propargylic alcohols **8**, it is important that their triple bond can be reduced stereoselectively to the C=C bond and furnish the corresponding allylic alcohols in good yields. Two common methods to achieve this transformation are hydrogenation over Lindlar's catalyst and reduction using lithium aluminum hydride (LAH). The former method worked well and gave the *Z*-allylic alcohols (**11**) in good to excellent yield when thoroughly purified ethyl acetate was used as solvent (see the table in Scheme 8). However, application of LAH, using diethyl ether as solvent and performing the reaction at rt, gave generally a mixture of two products, the corresponding *E*-allylic alcohol (**12**) and the corresponding 1-substituted 4,5,5-triethoxypent-3*E*-en-1-ol (**13**). Experimentation with the reaction conditions revealed that either of the two products could be prepared under the right conditions. Thus, LAH reduction in diethyl ether at 35 °C gave only alcohol **12**, whereas enol ether **13** was the only product when THF was used as solvent and the reaction was carried out at −20 °C. For both reactions, the yields were good to excellent, as indicated by the examples compiled in Scheme 8.



Scheme 8

On the basis of literature precedence [16], the formation of compounds **12** and **13** can be rationalized as outlined in Scheme 9.

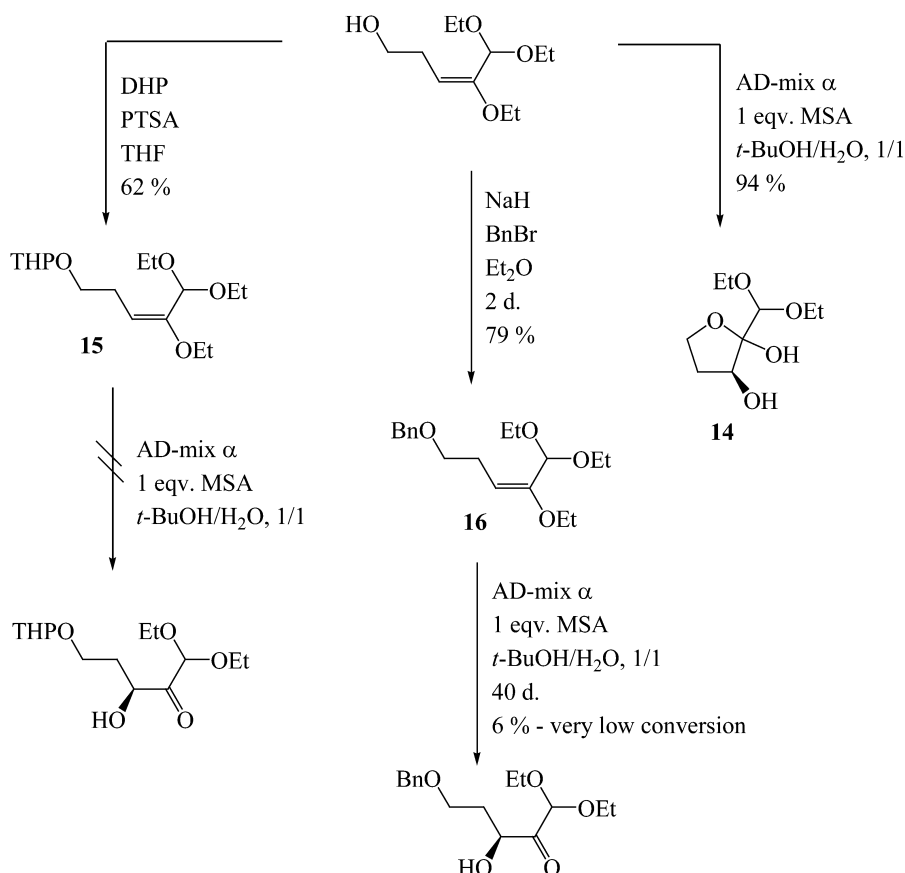


Scheme 9

Oxidation of **11**–**13**

Conversion of allylic alcohols **11** and **12** and enol ether **13** to carbohydrate analogs can conceivably be carried out in several ways, but among the most powerful methods are epoxidation and dihydroxylation of the $\text{C}=\text{C}$ bond, which can even occur in an enantioselective fashion if Sharpless' reagents are employed. It was therefore disappointing to observe that next to nothing happened when a selection of allylic alcohols **11** and **12** were treated as prescribed by Sharpless [17]. Since even 4,4,5,5-tetraethoxypent-3-en-1-ol appeared to be almost unreactive, it was reasonable to believe that steric hindrance prevented

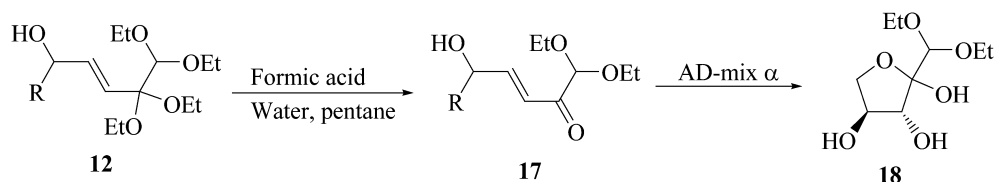
attack of the alkene moiety. Based on these observations, it was believed that homoallylic alcohols **13**, with less steric crowding next to a more polarized double bond, might be more reactive, and that turned indeed out to be the case. This is illustrated by a representative example, 4,5,5-triethoxypent-3*E*-en-1-ol, which is dihydroxylated with significant efficiency using Sharpless' AD-mix α [18] to give the partly protected and partly deoxygenated pentafuranose **14** in excellent yield (Scheme 10). The free hydroxyl group obviously plays a decisive role in the reaction, because when the protected analogs **15** and **16** were reacted under the same conditions, dihydroxylation barely occurs (Scheme 10).



Scheme 10

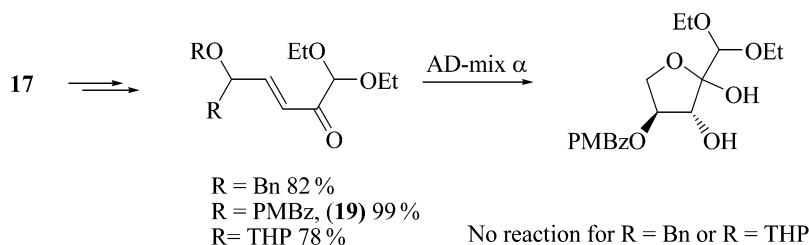
Dihydroxylation of derivatives of **12**

On the basis of the efficient dihydroxylation of homoallylic alcohols **13** and the ability of Sharpless' AD-mixes to attack α,β -unsaturated carbonyl compounds [17], we decided to convert hydroxyketals **12** to the corresponding hydroxyketones (**17**) (with formic acid in a mixture of pentane and water) and expose them to Sharpless' standard dihydroxylation conditions. When these reactions were carried out with selected ketals, dihydroxylation was indeed achieved, but the primary products were unstable under the reaction conditions and were transformed to the corresponding hemiketals (**18**), which were obtained in good yield as illustrated in Scheme 11 with 4,4,5,5-tetraethoxypent-2*E*-en-1-ol as starting material. Thus, allylic alcohols **12** appear to be valuable intermediates in the conversion of the title compound **4**, 3,3,4,4-tetraethoxybutyne, to partly protected and deoxygenated carbohydrate mimics. Studies of the scope of this synthesis are currently under way.



Scheme 11

In order to try to prevent cyclisation and formation of **18**, the hydroxyl group of **17** has to be protected before dihydroxylation is performed. The effect of such protection has so far been investigated for three protected analogues of one compound only, viz. the tetrahydropyranyl (THP) and benzyl (Bn) ethers as well as the *p*-methoxybenzoate (PMBz) of 1,1-diethoxy-5-hydroxypent-3*E*-en-2-one (**19**). When these derivatives of **19**, all prepared in excellent yield by standard methods (Scheme 12), were treated with Sharpless' AD-mix α under standard conditions, somewhat surprising results were obtained. Thus, when the ethers were reacted, nothing happened, perhaps for steric reasons, and the two compounds were recovered unchanged in quantitative yield. When the ester was reacted, however, dihydroxylation took place, but the PMBz protection was not stable enough to prevent cyclization and hemiketal formation. Spectroscopic studies reveal the presence of one PMBz-protected hemiacetal only, conceivably the isomer depicted in Scheme 12, which might indicate that acyl migration takes place during the oxidation process [19]. The mechanism for this transformation is currently under investigation.

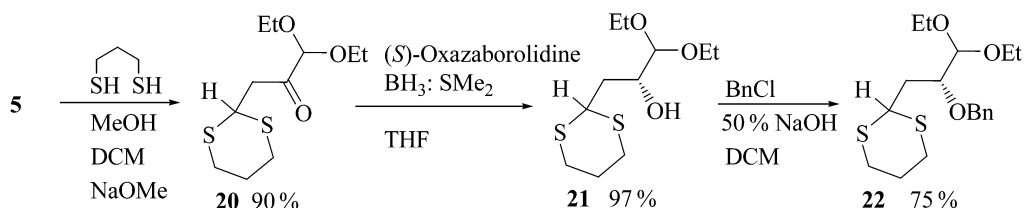


Scheme 12

ELABORATION BASED ON 1,3-DITHIANES

Chain elongation via a 2-substituted 1,3-dithiane

As mentioned previously, Ley and coworkers have found that α,β -unsaturated alkynones generally undergo a double Michael addition and form 1,3-dithianes when treated with propane-1,3-dithiol under basic conditions [10]. Ketone **5**, obtained in excellent yield by deketalization of 3,3,4,4-tetraethoxybutyne (Scheme 4), appears to be no exception to this rule and furnished 2-(3,3-diethoxy-2-oxopropyl)-1,3-dithiane (**20**) in excellent yield when reacted as outlined (Scheme 13). The ketone was reduced quantitatively to the corresponding alcohol (**21**) (using the (*S*)-oxazaborolidine chemistry developed by Corey et al. [20]), which was subsequently converted to the corresponding benzyl ether (**22**) in good yield.



Scheme 13

On the basis of extensive studies by Corey, Seebach, and others, the 2-substituted dithiane **22** was expected to be readily deprotonated by butyllithium in THF at low temperature and afford the corresponding 2-lithio-1,3-dithiane, which should react readily with both aldehydes and ketones and give masked α -hydroxycarbonyl compounds [11,21]. However, when this reaction sequence was applied to **22**, with benzaldehyde and formaldehyde as carbonyl compounds, unreacted starting material was obtained instead of the expected addition products. This was surprising since formation of a yellow-orange solution during the addition of BuLi was observed, strongly indicating that deprotonation occurred and formation of the 2-lithio intermediate of **22** took place. One explanation for this inability of the conceivable intermediate to react might be that the carbanion, which exists as a tight ion pair in THF solutions [22], is rendered inaccessible by complexation with the ether moieties as illustrated in Fig. 1. It is hoped that future ^6Li -NMR studies will give results that will help to clarify this question.

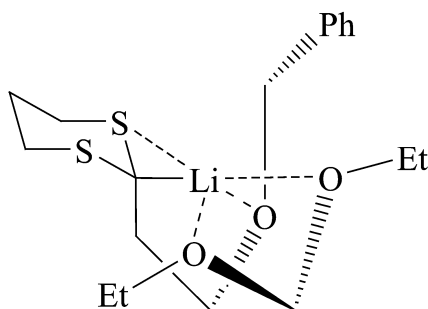
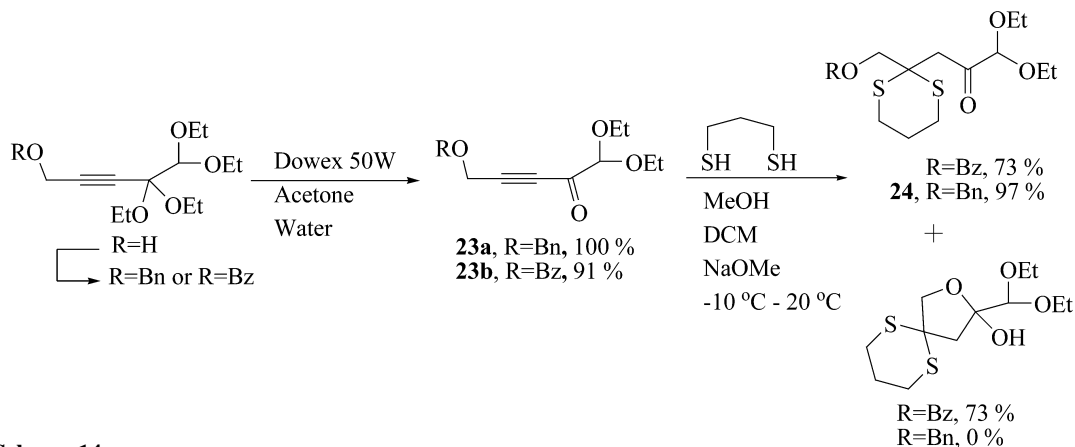


Fig. 1

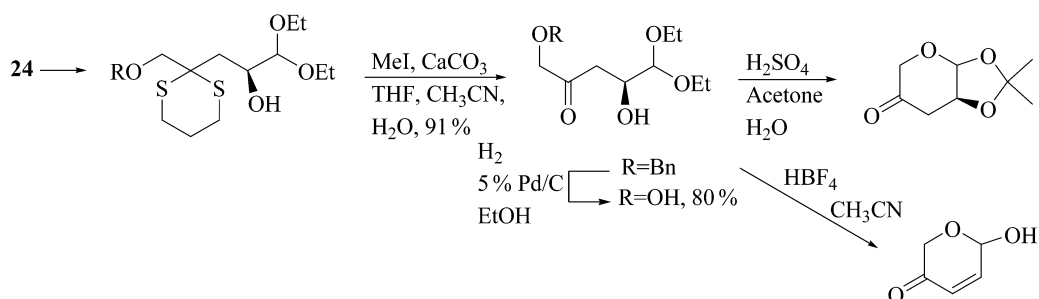
Modifications via 1,3-dithianes from substituted α,β -unsaturated alkynes

Due to the reluctance of dithiane **22** to react even with aldehydes, it was decided to change strategy and follow a route involving protection of propargylic alcohols **8**, deprotection of their ketal moiety to obtain the corresponding α,β -unsaturated alkynes, which were expected to undergo a double Michael addition and form 1,3-dithianes when treated with propane-1,3-dithiol under basic conditions [10]. As indicated by examples based on 4,4,5,5-tetraethoxypent-2-yn-1-ol (Scheme 14), this approach appeared to be successful provided the right protecting group was used. Thus, when the hydroxyl group of 1,1-diethoxy-5-hydroxypent-3-yn-2-one was protected as the benzyl ether (**23a**), the Michael addition gave one 1,3-dithiane (**24**) in 97 % yield whereas the corresponding benzoate-protected ketone (**23b**) afforded two 1,3-dithianes in a 1:3 ratio.



Scheme 14

Compound **24** was successfully converted to two carbohydrate mimics as outlined in Scheme 15; the yields are good and all the compounds are easy to isolate with high purity.



Scheme 15

The scope of this strategy is currently being investigated with respect to substituent tolerance. Furthermore, studies are also under way to prepare all chiral compounds in an enantiospecific fashion.

CONCLUSION

The studies reported here have revealed that 3,3,4,4-tetraethoxybutyne is an excellent starting material for the preparation of partly protected and deoxygenated pentafuranoses. The scope of the reactions employed and the success of new transformations are currently under investigation.

ACKNOWLEDGMENTS

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