

## Recent advances in the synthesis of carbohydrate analogs\*

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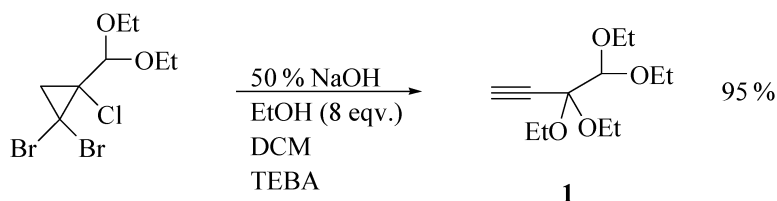
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*Abstract:* With 3,3,4,4-tetraethoxy-1-butyne as starting material, we are investigating the preparation of a range of alkylated, partially deoxygenated carbohydrate derivatives. In the lecture, an overview of recent results was given, with particular emphasis on progress in the synthesis of perfluoroalkyl-substituted deoxygenated analogs. Since many of the results discussed in the lecture have recently been or are in the process of being published, this paper focuses on our recent advances in preparing fluorinated analogs.

*Keywords:* perfluoroalkylation; propargylic alcohols; tetraethoxybutyne; sodium dithionite; pyranoses; furanoses.

### INTRODUCTION

The basis for the results reported here is the easy access to 3,3,4,4-tetraethoxybut-1-yne (**1**), denoted TEB, and some of the compound's fundamental chemical properties, which make it an excellent starting material in organic synthesis. As for its preparation, the compound, a protected ketoaldehyde, is formed and isolated in almost quantitative yield when 1,1-dibromo-2-chloro-2-diethoxymethylcyclopropane, dissolved in a mixture of dichloromethane, ethanol (8 equiv relative to the cyclopropane), and a catalytic amount of triethylbenzylammonium chloride (TEBA), is treated with an excess of 50 % aqueous sodium hydroxide at room temperature [1–6] (Scheme 1).



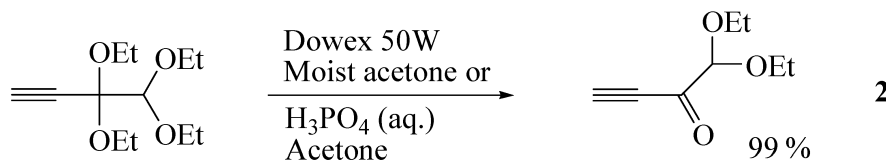
Scheme 1

Regarding basic chemical properties, **1** appears to be thermally stable in the temperature range investigated, viz. at temperatures up to around 150 °C. When kept neat at 100 °C and below for five days, no changes were detected, and the same observation was made when solutions of the compound in chlorobenzene and bromobenzene were refluxed at 132 and 155 °C, respectively [6]. Thus, TEB appears to be thermally stable in the temperature range prevailing during most reactions used to carry out transformations in organic chemistry. The compound is also essentially unreactive when exposed to

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both water and slightly basic aqueous solutions, but in the presence of strong acids it decomposes, and under slightly acidic conditions, e.g., in moist acetone in the presence of some Dowex 50W or phosphoric acid, the ketal function was deprotected regioselectively and furnished another interesting compound, 1,1-diethoxybut-3-yn-2-one (**2**), essentially in quantitative yield [5,6] (Scheme 2). Thus, TEB has the properties it takes to be a valuable starting material in organic synthesis and a vehicle for incorporation of functional in organic molecules.



Scheme 2

### FOCUS ON PERFLUOROALKYLATED CARBOHYDRATE DERIVATIVES

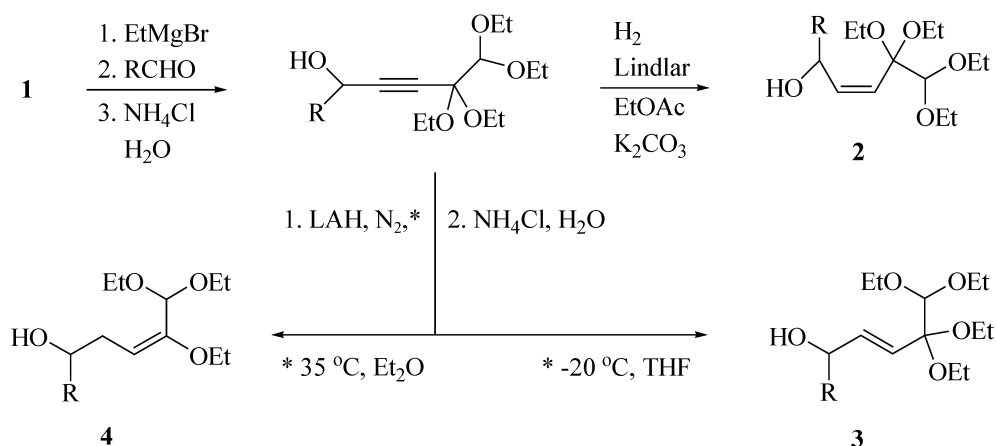
We have previously reported on the synthesis of alkylated, partly deoxygenated carbohydrate derivatives with both furanose and pyranose structures using TEB as starting material [5]. Such carbohydrate analogs play important roles in medicine and biology, for instance, quite notably as active chemical entities in the immune system, and as structural motifs of important drugs with the capability to interact with active sites *in vivo* and thus contribute to changing the activity and targeting of drugs [7–17]. During our studies, we became aware of the increasing focus on perfluoroalkylated carbohydrate derivatives in recent years, which, due to their hydrophobic alkyl group and a polar, biocompatible moiety, seem to have the potential of being useful surfactants and emulsifiers for biomedical application, of having special liquid-crystalline properties, and, if being attached to drug core structures, of becoming important drug-targeting modifiers [18]. We therefore decided to explore the possibility of synthesizing perfluoroalkyl-substituted, partly deoxygenated carbohydrate derivatives using TEB as starting material.

An arsenal of methods has become available in recent years for the preparation of fluorinated organic compounds [19–22]. Most of the methods involve organometallic species, with a negative charge on the fluorinated moiety, which are allowed to react with ketones or aldehydes with the carbonyl group at the carbon atom to which the perfluoroalkyl group ( $R_f$ ) is going to be attached. This approach has the disadvantage that introduction of protecting groups, and therefore additional, undesirable steps, is required. On this basis, we started to look for alternative methods to achieve our goal, and this turned our attention to an alternative perfluoroalkylation method, *viz.* sodium dithionite-mediated radical addition of  $R_fI$  to carbon–carbon double bond (called the sulfinate dehalogenation reaction) [23]. Screening of the literature showed that this transformation has been used successfully to prepare carbohydrate derivatives with an  $R_f$  group attached to C-2 as well as C-6 [18, 23]. We therefore decided to apply this method on selected alkenes, which we were able to obtain in good yields using TEB as starting material (*vide infra*).

In order to become familiar with the behavior of sodium dithionite as a radical initiator and characteristic features of the sulfinate dehalogenation reaction, addition of some 1-iodoperfluoroalkanes to cyclohexene and allylbenzene was carried out as described by Zhu and Li [18]. To our satisfaction, reproducible results and good yields of addition products were experienced, and this encouraged us to proceed following our strategy.

### MAKING SUITABLE SUBSTRATES FOR RADICAL PERFLUOROALKYLATION

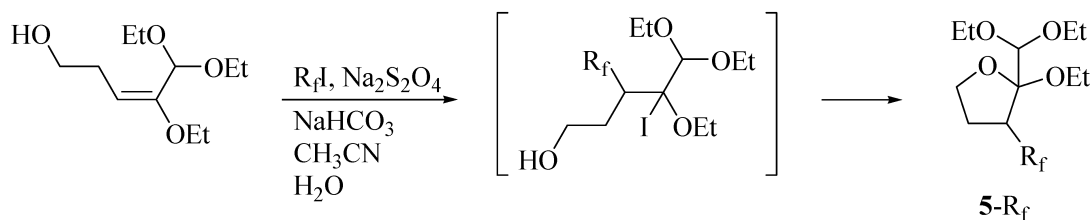
The aim is to synthesize carbohydrate analogs, the adopted strategy requires access to 1,1,2,2-tetraethoxypentene and/or 1,1,2,2-tetraethoxyhexene derivatives, and such compounds were obtained from TEB following the reaction sequences depicted in Scheme 3 [5]. The propargylic alcohols were isolated in good to excellent yields, and hydrogenation over Lindlar's catalyst afforded the corresponding *Z*-allylic alcohol (**2**) in good yields under optimum conditions. Likewise, the corresponding *E* alcohols (**3**) were obtained by using the standard reagent for such conversions, lithium aluminium hydride (LAH), but the outcome of the reaction was sensitive to both the solvent and the reaction temperature: In diethyl ether at room temperature, two products were obtained, the corresponding and expected *E*-allylic alcohol (**3**), and the corresponding 1-substituted 4,5,5-triethoxypent-3*E*-en-1-ol (**4**), which is both a homoallylic alcohol and a vinyl ether. By variation of the reaction conditions, we succeeded in controlling the **3/4** ratio so that both sets of compounds were obtained under different conditions in high yields; in refluxing diethyl ether alcohol, **3** was formed almost exclusively, whereas enol ether **4** was by far the predominant product when tetrahydrofuran (THF) was used as solvent and the reaction was carried out at  $-20\text{ }^{\circ}\text{C}$  [5].



Scheme 3

### PREPARATION OF PERFLUOROALKYL-SUBSTITUTED DEOXYGENATED CARBOHYDRATES

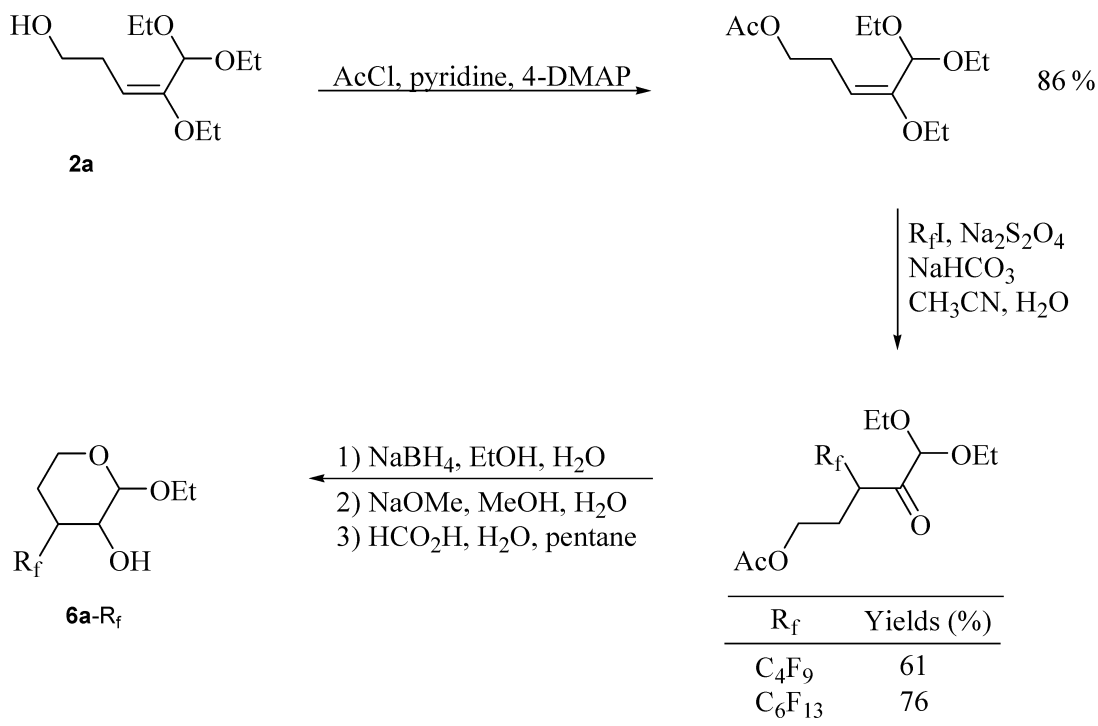
With alkenes **2–4** at hand (for instance, with R = hydrogen, methyl, hexyl, phenyl) screening experiments with R = H (**2a**, **3a**, and **4a**, respectively) were performed to get an impression of their relative reactivity toward perfluoroalkyl 1-iodides in the presence of sodium dithionite under the conditions described by Zhu and Li [18]. When using 1-iodoperfluorobutane, which had successfully been added to cyclohexene and allylbenzene (vide supra), neither **2a** nor **3a** gave detectable quantities of the corresponding perfluoroalkylated alcohols. Vinyl ether **4a**, on the other hand, with a carbon–carbon double bond that is more electron-rich, more polarized, and sterically significantly less congested, did react and appeared to give one addition product. However, this product turned out to be unstable under the reaction conditions due to cyclization and formation of the corresponding furanose derivative **5-R<sub>f</sub>** (Scheme 4; with R<sub>f</sub> = C<sub>4</sub>F<sub>9</sub> the compound is denoted **5-C<sub>4</sub>F<sub>9</sub>**). When reactions were carried out quite carefully with perfluorinated butyl, hexyl, and octyl 1-iodides, the corresponding furans **5-C<sub>4</sub>F<sub>9</sub>**, **5-C<sub>6</sub>F<sub>13</sub>**, and **5-C<sub>8</sub>F<sub>17</sub>** were isolated in 75, 59, and 51 %, respectively. The fact that only one addition product was formed in each case is interesting, because that means that the intermediate R<sub>f</sub> radical at-



Scheme 4

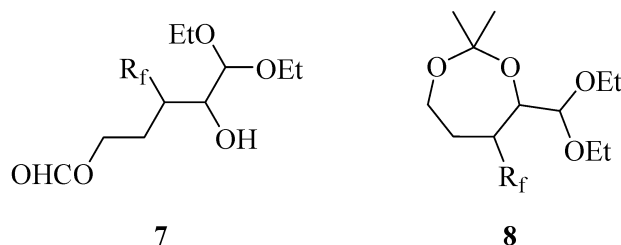
tacks the carbon–carbon double bond regioselectively at the most electron-rich and sterically less hindered end, which of course makes sense.

In order to be able to isolate of the product that existed before **5-R<sub>f</sub>** was formed and then perform cyclization in a controlled fashion to either furanose or pyranose derivatives in a separate step, protection of the hydroxyl group was an obvious measure to take. Exploratory experiments proved that esterification of the hydroxyl group was sufficient to achieve this, and when the acetates of **4** were used, perfluoroalkylation of the C=C bond without subsequent cyclization was experienced, in the case of the acetate of **4a** in 60–75 % yield (Scheme 5). In order to avoid furanose formation in the cyclization step, the carbonyl group was reduced. Subsequent deacetalization afforded the corresponding diol, which cyclized to the corresponding 3-R<sub>f</sub>-substituted pyranose (**6a-R<sub>f</sub>**) under acidic conditions (Scheme 5). Thus, we have managed to achieve controlled synthesis of both perfluoroalkylated furanoses and perfluoroalkylated pyranoses. The drawbacks of the approach outlined in Scheme 4 have therefore been overcome, and the reaction sequence depicted in Scheme 5 therefore represents a viable and attractive strategy for controlled synthesis of perfluoroalkylated deoxygenated carbohydrate analogs with a pyranose configuration.

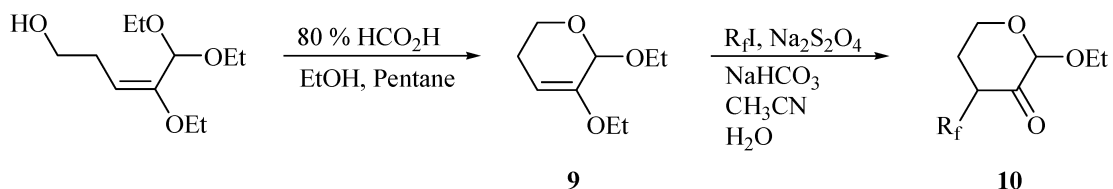


Scheme 5

So far, the pyranoses synthesized as outlined in Scheme 5 have not been isolated in yields above 50 %, the reason being that significant by-product formation intercepts cyclization and prevents it from occurring. When a mixture of pentane and aqueous formic acid is used in the last step, 52 % of formate **7** is formed, and when moist acetone with a little sulfuric acid is applied instead, a fair amount of acetone **8** is obtained. Investigations into this problem are about to be started.



From enol ethers **4**, an alternative synthesis of pyranoses **6-R<sub>f</sub>** can be envisaged: Instead of starting with perfluoroalkylation and then carrying out cyclization, the two steps could be interchanged, the result of which is the stepwise synthesis shown in Scheme 6 (when compound **2a** is used as an example). (The cyclization to dihydropyran **9** is in essence an alternative protection of the hydroxyl group, which means that two objectives are achieved in one step.) When **4a** was reacted as indicated in Scheme 6, **9** was formed in approximately 70 % yield, and when 5-substituted analogs of **4a** were reacted under the same conditions, the yields increased to almost quantitative yield.



**Scheme 6**

With **9** at hand in significant quantities, sodium dithionite-catalyzed addition of perfluorinated butyl, hexyl, and octyl 1-iodides was carried out, again following the procedure of Zhu and Li. Work-up furnished the corresponding ketones **10-C<sub>4</sub>F<sub>9</sub>**, **10-C<sub>6</sub>F<sub>13</sub>**, and **10-C<sub>8</sub>F<sub>17</sub>** in 70, 70, and 68 %, respectively. When 5-substituted analogs of **9** were reacted in the same manner, the perfluoroalkyl-substituted ketones corresponding to **10** were obtained in even better yields.

We are currently applying the methodologies described here to synthesize a range of perfluoroalkylated deoxygenated alkyl-substituted monosaccharides.

## CONCLUSION

The studies reported here have revealed that 3,3,4,4-tetraethoxybutyne is a good starting material for the preparation of deoxygenated carbohydrate analogs, including a range of partly 4-deoxygenated furanoses and pyranoses with a perfluoroalkyl group attached to C-3. By using the right protective groups, the methodology developed permits selective synthesis of both groups of compounds. The scope of the reactions and the success of new transformations are currently under investigation.

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