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Intramolecular sulfur-assisted $NaBH_4$ reduction of esters synthesis of 5-oxo-ETE and 5-oxo-12-HETE

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Abstract

Ester groups are reduced very efficiently in sulfur-containing molecules situated at close proximity to the ester group. We have used this procedure to regioselectively, efficiently and in high yield reduce an ester group in the presence of another ester group further removed from the sulfur atom.

Keywords: $NaBH_4$; MeOH; 5-oxo-ETE.

5-Oxo-ETE **1** is a product of the 5-lipoxygenase pathway and a new mediator of inflammation. It is a potent chemotactic agent for neutrophils, but the major target for 5-oxo-ETE is the human eosinophil. It induces pulmonary infiltration of eosinophils in vivo,[1,2] raising the possibility that it may play an important role in the recruitment of these cells to the lungs of asthmatics.

We have reported a synthesis of 5-oxo-ETE **1**,[3] tetradeutero derivative **2**[4] for the development of a GC and LC/MS assay, and ^{3}H-5-oxo-ETE **3**[4] for the study of its metabolism and for the generation of a binding assay. In addition, we have performed the total synthesis of 6,7-dihydro-5-oxo-ETE **4**[3] and 5-oxo-12-HETE **5**[5] (Scheme 1) and have used the synthetic products to identify their formation in neutrophils and platelets, respectively. All these syntheses are convergent and have in common a dithiolane derivative **9** as the key intermediate synthon (Scheme 2). It was prepared in moderate yields from dithiolane ester **6** via aldehyde **7**. The low yield is the result of *o*-alkylation of dithiolane carboxaldehyde **7**.[4] 5-Oxo-ETE **1**, its derivatives **2** and **3**, as well as **5**

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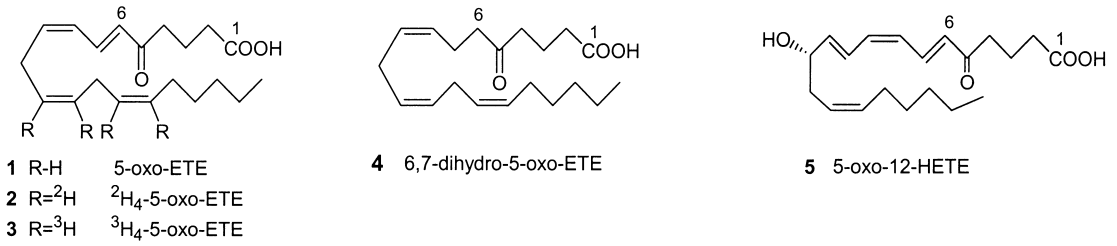
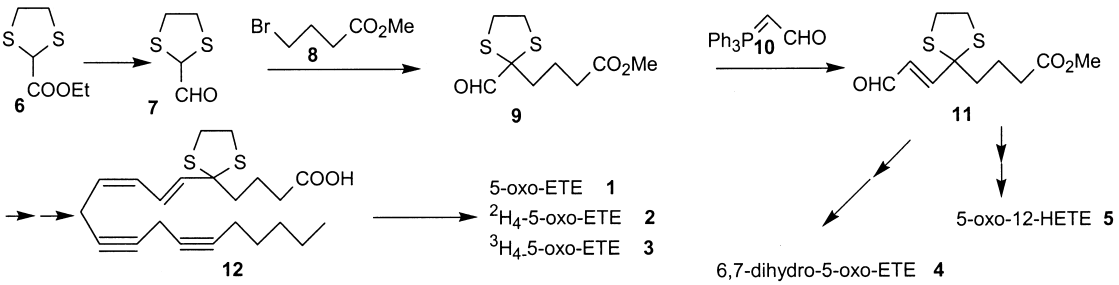
are unstable compounds and repeated preparation and purification are necessary. For that reason, we decided to look into improving the synthesis of **9** (Scheme 2).

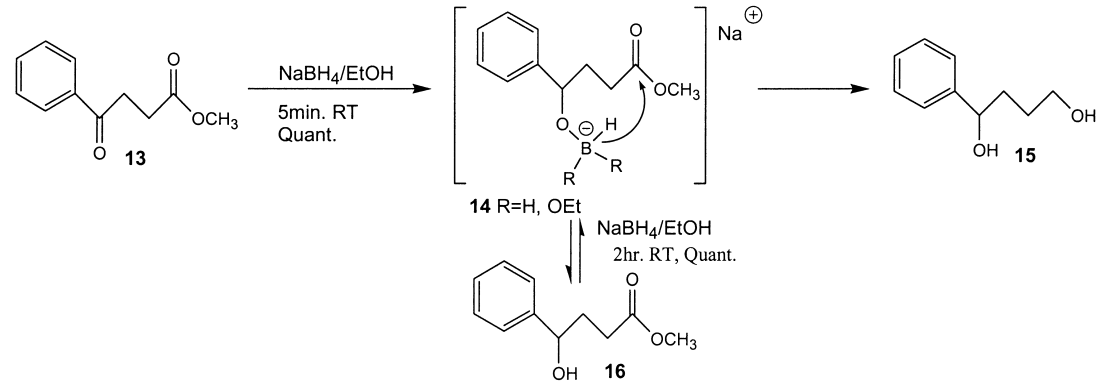


Scheme 1.

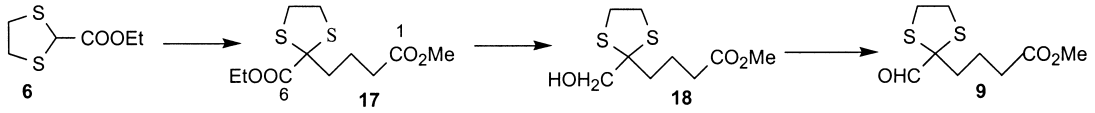


Scheme 2.

We performed the synthesis of the diester **17** as shown in Scheme 4 from commercial **6** and attempted the reduction with $NaBH_4$. We wanted to find out if the C-6 carboxylic ester of **17** could be selectively reduced in the presence of the one at C-1. The carbon numbering used corresponds to the position of the synthon in 5-oxo-ETE **1**. The rationale behind the attempt is based on our previous experience (Scheme 3) in which an ester was reduced with $NaBH_4$ with the assistance of a proximal alcohol group.[6,7] Since then, several such cases have been reported.[8] In the specific case we were interested in, we were hoping that the sulfur in **17** would assist in the reduction of the nearest ester group.



Scheme 3.

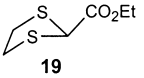
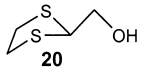
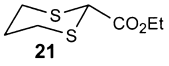
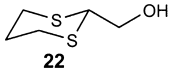
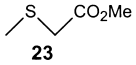
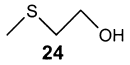
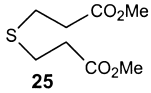
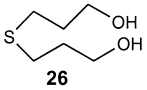
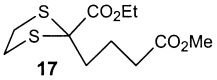
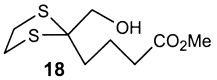
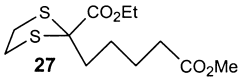
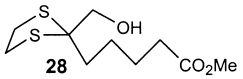
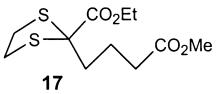
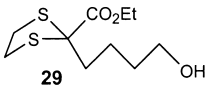
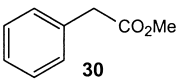
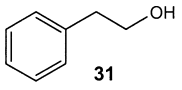


Scheme 4.

The reduction of the ester at C-6 proceeded better than anticipated and **18** was obtained in high yield by treatment of **17** with 4 equivalents of $NaBH_4$ in ethanol or ether/MeOH. The syntheses of 5-oxo-ETE and its tetradeutero and its tetratritiated derivatives were completed as described by us previously and summarized in Scheme 2.

We were impressed with the regioselectivity and efficiency of this reduction and decided to explore its scope and selectivity. Table 1 shows the cases studied. The esters **19** and **21** in entries 1 and 2 are easily reduced as anticipated, the esters bearing the same relationships to the sulfur as the one in **17** (Scheme 4). Entry 3 is an example of an open chain sulfide. In entry 4, the ester is

Table 1

Entry	Ester	Alcohol	Reaction Time	% Yield[a]
1	 **19**	 **20**	15min	100
2	 **21**	 **22**	15min	100
3	 **23**	 **24**	10min	92[b]
4	 **25**	 **26**	15min	100
5	 **17**	 **18**	15min	86
6	 **27**	 **28**	15min	88
7[c]	 **17**	 **29**	15min	92
8	 **30**	 **31**	38hr	96

[a]Isolated yield.

[b]The reaction is quantitative as judged by TLC. The product is volatile, hence reducing the isolated yield.

[c]Reduction by DIBAL-H

further removed from the sulfur as compared to 1 and 2. In this case, too, the reduction is rapid and efficient and, as in all the preceding cases, only a single product is observed on TLC and by NMR.[9] In fact, a chromatographic purification is not necessary as the product can be used as such for further chemical elaboration. Entry 5 shows the first selective reduction of the carboxylate ester close to the sulfur in the dithiolane ring. As mentioned previously, **9** is the synthon that we used for the synthesis of several oxo-eicosanoid mediators as shown in Scheme 2. The reduction in this case was done under the same conditions as the other cases. Only the carboxylate ester near the sulfur atom is reduced. This means that the ester at position 1 in **17** is out of reach of the sulfur $NaBH_4$ complex, which we assume is necessary in order to reduce the nearby ester. Entry 7 shows the reduction of **17** using this time DIBAL-H. As expected, and in contrast to entry 5, the less hindered carboxylate ester group at position 1 is reduced selectively, and a high yield of **29** is obtained. Entry 6 is another example showing the selective reduction of the proximal ester. This synthon **28** can be used to construct such metabolites as 20-hydroxy 15-oxo-ETE, a potential 15-HETE metabolite in neutrophils. Entry 8 is an example of an ester without sulfur in the molecule. Under the usual reaction conditions, ether/MeOH/$NaBH_4$, ester **30** has been reduced in 38 h in high yield. The reduction in this case most probably occurs due to the formation of a methoxy borohydride species. Reduction of ester groups, using $NaBH_4$/alcohols/other solvents under reflux conditions has been reported.[10–16] In one report the reductive species implicated appears to be trimethoxy sodium borohydride.[17]

The following is a typical procedure we used in the reductions in Table 1 (entries 1–6 and 8). To a solution of 2-carboethoxy-1,3-dithiane **21** (1 mmol) in anhydrous ether (3 ml) was added $NaBH_4$ (4 mmol) with stirring under argon. To this reaction mixture was added dry MeOH (1 ml) dropwise at room temperature and stirred for 15 min. Solvent was concentrated under reduced pressure. The residue was neutralized with 1N HCl and extracted with EtOAc. The organic layer was washed with brine, dried, and concentrated to afford the alcohol. Filtration through SiO_2 gave the analytically pure alcohol **22** in quantitative yield.

There is little doubt that in the reduction described in entries 1 to 6, a complex between the $NaBH_4$ and sulfur is formed and is assisting in the reduction of a close-by ester. It is likely that species such as mono, di and trimethoxy borohydrides participate in this complexation to perform the reduction. In fact, it seems unlikely that distance alone without activation of $NaBH_4$ can be the factor in such an efficient 'intramolecular' $NaBH_4$ reduction. Most likely a more reactive hydride species is being formed between the sulfur and $NaBH_4$ and/or mono, di and trimethoxy borohydride. The fact that it took 38 h to reduce an ester (entry 8), compared to 10 to 15 min in entries 1 to 6, is an indication that extra activation of the methoxy borohydrides by complexation with the sulfur is necessary to perform a reduction approximately 150 times faster (15 min versus 38 h). Further support for the involvement of methoxy or alkoxy borohydride species in the complexation with sulfur is provided by the fact that **30**, on attempted reduction with $NaBH_4$ in dioxane, is recovered unchanged as expected after 38 h. Under the same conditions **19** afforded a 17% yield of **20**, perhaps indicating that $NaBH_4$ itself can complex with sulfur in **19** providing slightly augmented nucleophilicity of the hydrides. However, since our reductions in entries 1–6 are completed within 15 min, it is perhaps safe to assume that under these conditions mostly methoxy borohydride species are implicated in the intramolecular sulfur-assisted $NaBH_4$ reductions.

It is noteworthy that the reduction in entry 8 proceeds cleanly in high yield albeit with long reaction time. This can provide an interesting option for a mild selective and efficient reduction of non-activated esters in complex molecules.

Acknowledgements

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9. The NMR data of compound **17**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.1 (q, $J=7.1$ Hz, 2H), 3.56 (s, 3H), 3.29 (m, 4H), 2.25 (t, $J=7.4$ Hz, 2H), 2.1 (m, 2H), 1.68 (m, 2H), 1.19 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 173.15, 171.81, 69.15, 62.07, 51.44, 39.81, 39.20, 33.70, 23.06, 13.90. Compound **18**: ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H), 3.64 (s, 2H), 3.27 (m, 4H), 2.30 (t, $J=7$ Hz, 2H), 1.82 (m, 2H), 1.78 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 173.93, 72.46, 69.44, 51.68, 39.83, 39.23, 37.66, 33.92, 21.93.
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