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LETTERS

A New Method for the Preparation of Olefins from Vicinal Diols

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Abstract: A novel method is reported for the transformation of vicinal diols to olefins. This methodology consists in the conversion of iodothiocarbonates such as **16** to olefin **17** with phenyl lithium in excellent yield. Compounds **7** and **12** were prepared by this methodology in order to determine if they would be recognized by the enzymes, 5-lipoxygenase and 15-lipoxygenase, respectively. © 1999 Elsevier Science Ltd. All rights reserved.

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A number of useful methods have appeared for the conversion of 1,2-diols to the corresponding olefins.[1] These methods include deoxygenation of vicinal diols by free-radical fragmentation of *bis*-xanthates with tributyltin hydride, by high-temperature heating of cyclic thionocarbonates in trimethylphosphite (111 °C) or triethylphosphate (156 °C) or at room temperature with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine and by chlorodiphenylphosphine/imidazole/iodine treatment.

We are reporting here on a high-yield conversion of thionocarbonates to olefins (Table 1). We were interested in the preparation of primary olefins as synthetic intermediates for the synthesis of natural products of interest to us namely leukotrienes, HETES, oxo-ETES, and isoprostanes.[2-5] All these natural products carry some of the double bonds present in parent polyunsaturated fatty acids such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). For example, we needed compound **6** for further synthetic transformation. In our first preparation of this derivative, we performed the cleavage of diol **1** with lead tetraacetate followed by low-yield one-carbon Wittig olefination in 34 percent overall yield. This was unacceptable considering that we were several steps away from our natural product. We also used the literature thionocarbonate conversion to olefins and found them not particularly suited to our substrates.

We have recently reported a method for the conversion of vicinal diols to the corresponding primary iodohydrins.[6] This reaction is highly regioselective and the primary iodide is the only observed product in most cases.[6] Very conveniently we have utilized this method for the preparation of key synthons used in the total syntheses $iPF_{2\alpha}$-IV and $iPF_{2\alpha}$ -V.[5,7]

In our initial attempt to prepare the iodohydrin **5** from iodothiocarbonate **2**, we used butyl lithium in THF (Scheme 1). We thought that by treating the iodothiocarbonate **2** with BuLi, we would generate a tight ion pair **4** which would hydrolyze upon aqueous workup to the iodohydrin **5**. We obtained instead the terminal olefinic compound **6** as the only product of the reaction under these conditions. Although this was not entirely unexpected, we were impressed with the high yield and ease of the reaction.

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Scheme 1

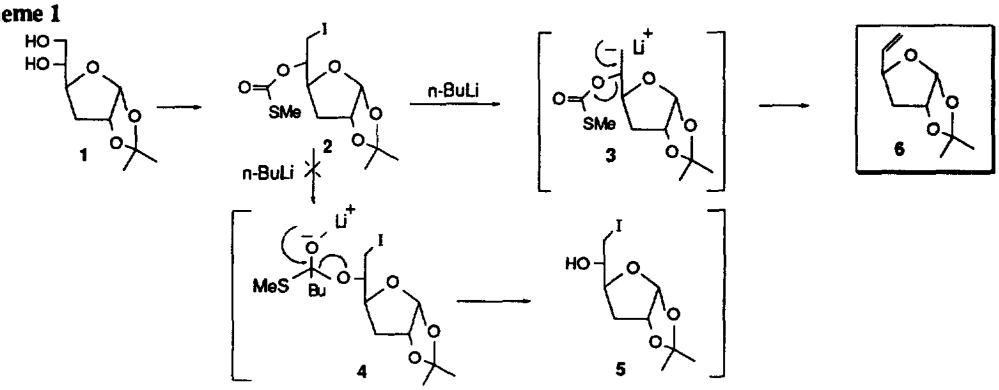


Table 1 shows the different examples we used to illustrate this conversion. In all the entries we used phenyl lithium instead of BuLi as in some cases it performed better.

A typical procedure is as follows. To a solution of the iodothiocarbonate **19** (165 mg, 0.42 mmol) in anhydrous THF (2.1 mL) was added PhLi (1.1 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, quenched with saturated NH_4Cl (5 mL) and extracted with diethyl ether. The solvent was removed and the residue can be also chromatographed [ether/pentane (1:9)] to give an analytically pure sample **20** (95%).

Because of the high yields, it is not necessary to isolate the iodo derivative, and we routinely carried the two steps in an one-pot reaction. Typically, the thionocarbonate is refluxed with excess methyl iodide in dichloroethane for 18 hr.[6] The reaction mixture is evaporated to dryness and dry THF added followed by the PhLi as described above. We have also isolated iodobenzene and biphenyl as by-products of the reaction.

In entry 7 no more than two equivalent of PhLi are used in order to avoid interference with the carbonyl group. As can be seen from the examples selected, the reaction is compatible with a carboxylic acid group as in entry 7; with other halogens, entry 9; silyl ethers (entries 1, 3, 5); olefins (entries 1, 7, 8); and ethers (entries 3, 4, 6). We have attempted the reaction with the methyl ester of **32**. In this case, the ester function is reactive and interferes with the trans metallation reaction.

Entries 7 and 8 are of special interest as the products **7**[8] and **12**[9] were designed to include the minimum structural features necessary for enzyme recognition (Scheme 2). Acid **7** was designed as a substrate for 5-lipoxygenase (5-LO) and the product **12** in entry 8 incorporates the minimal structural elements necessary for 15-

Scheme 2

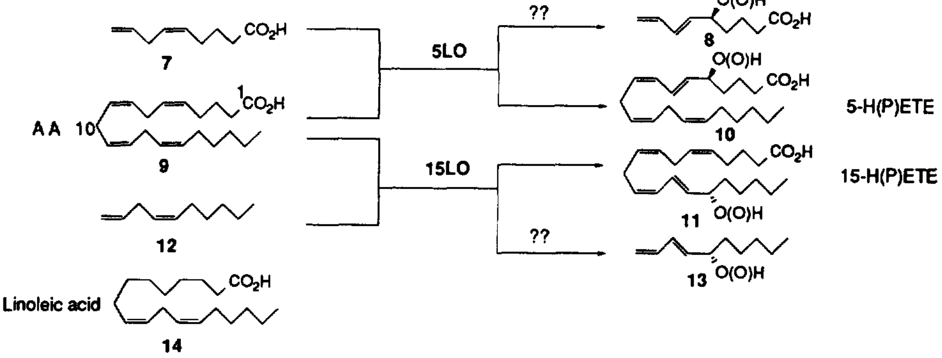
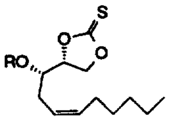
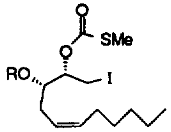
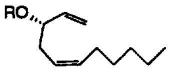
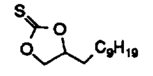
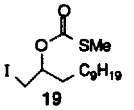
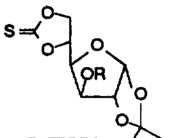
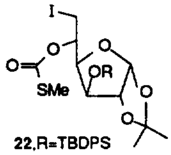
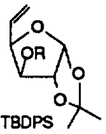
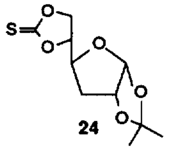
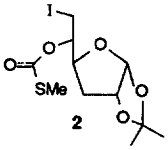
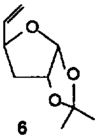
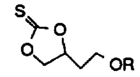
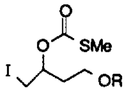
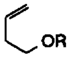
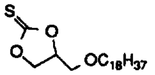
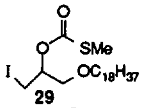
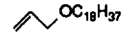
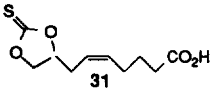
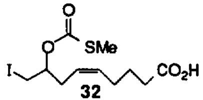
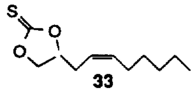
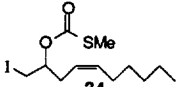
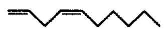
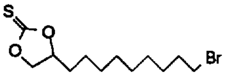
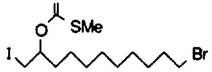


Table 1

Entry	Thionocarbonate[a]	Primary iodo deriv.	% Yield	Olefin	% Yield
1	 15,R=TBDPS	 16,R=TBDPS	95	 17,R=TBDPS	99
2	 18	 19	99	 20	95
3	 21,R=TBDPS	 22,R=TBDPS	97	 23,R=TBDPS	99
4	 24	 2	95	 6	76[b]
5	 25,R=TBDPS	 26,R=TBDPS	96	 27,R=TBDPS	97
6	 28	 29	quant.	 30	94
7	 31	 32	92	 7	91
8	 33	 34	98	 12	97[b]
9	 35	 36	82	 37	95[c]

[a] The thionocarbonates in entries 4 and 6 were prepared by us previously.[6] The thionocarbonates in entries 1,2,3,5,7 and 8 were prepared similarly from the vicinal diols.

[b] The reactions are quantitative as judged by TLC. The products are volatile, hence reducing the isolated yield.

[c] Product contaminated with the by-product, iodobenzene (close on TLC).

lipoxygenase (15-LO) recognition.

The free carboxylic acid group is essential in substrates for 5-LO activity. Conversely, a free COOH is not required for 15-LO activity and an ω6 and ω9 double bonds are necessary with that enzyme.

AA **9** is the preferred substrate for 5-LO and is an excellent substrate for 15-LO. The best substrate for 15-LO is linoleic acid (LA) **14**, which happens also to be the predominant fatty acid in low density lipoprotein (LDL).[10]

The question we are asking is how essential are carbon C10 to 20 in AA for 5-LO enzyme recognition and the rate of enzymatic oxygenation? Equally, how important is carbon 1 to 10 in AA for the 15-LO enzymatic reaction? The stereochemistry of oxygen incorporation in the enzymatic products **8** and **13** will have to be confirmed.

Preliminary experiments indicate that **12** reacts with 15-LO from soybean as judged by UV chromophore 235 of the conjugated diene in product **13**. Work is in progress to ascertain the identity of the products and the comparative kinetics with AA.

In summary, we have developed an efficient method to convert vicinal diols to corresponding olefins. This method has the following advantages: 1) the high-yield of the two steps, the conversion from diol to olefin can be carried as an one-pot reaction; 2) the reaction time is short; and 3) the reaction can be performed at low temperatures, which might improve selectivity when needed.

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8. The NMR data of compound **7**: ^{1}H NMR (CDCl$_3$) δ 5.81 (m, 1H), 5.45 (m, 2H), 5.02 (br dd, J = 10.1 and 5.1 Hz, 2H), 2.79 (br t, J = 5.8 Hz, 2H), 2.37 (t, J = 7.44 Hz, 2H), 2.12 (q, 2H), 1.72 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 180.2, 137, 129.7, 128.2, 114.9, 33.6, 31.7, 26.5, 24.7.
9. The chemical shifts and the splitting pattern of the olefinic protons of **12** are identical to those of **7**.
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