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Regiocontrolled Formation of Iodohydrins and Epoxides from *Vic*-Diols

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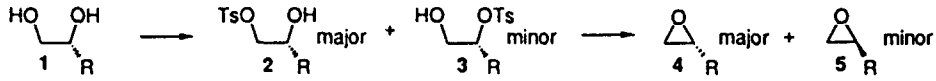
Abstract: A novel method for the stereoselective preparation of iodohydrins and epoxides from stereogenic vicinal diols is described. This new high-yield methodology consists of the conversion of thionocarbonates such as **12** to the primary iodo derivative **14** with complete regiocontrol. Deprotection of the secondary alcohol derivative in **14** gives the corresponding synthetically versatile iodohydrin **16**, which is converted to epoxide **17**. This methodology has been applied to complex tetraols **29** and **34**. In the case of diols the transformation is conveniently carried out in high yield as a one-pot reaction.

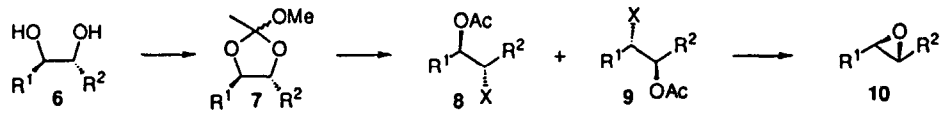
Chiral epoxides are useful intermediates in the synthesis of biologically and pharmaceutically important compounds. Several methods have been used for their preparation.[1] The most commonly used is the transformation of a vicinal diol **1** into an epoxide **4** *via* a tosylate intermediate **2** (Scheme 1).[2,3,4] The drawback of this procedure is that the primary tosylate **2** is invariably accompanied by a greater or lesser amount of the secondary tosylate **3**,[3] and purification results in substantial loss in yield.[3] If some of the minor secondary tosylate escapes purification, a partial racemization will occur in the formation of the epoxide **4**.

Scheme 1



Sharpless *et al* reported a solution to this problem.[5] Their method describes a stereoselective formation of epoxides from chiral diols that involves conversion of diol **6** to cyclic orthoacetate **7** and nucleophilic opening of the acetoxonium intermediate to give the acetate ester of halohydrins **8** and **9** with inversion at the halide receiving center. The saponification and cyclization with the second inversion at the halide center gives the epoxide **10** (Scheme 2).

Scheme 2

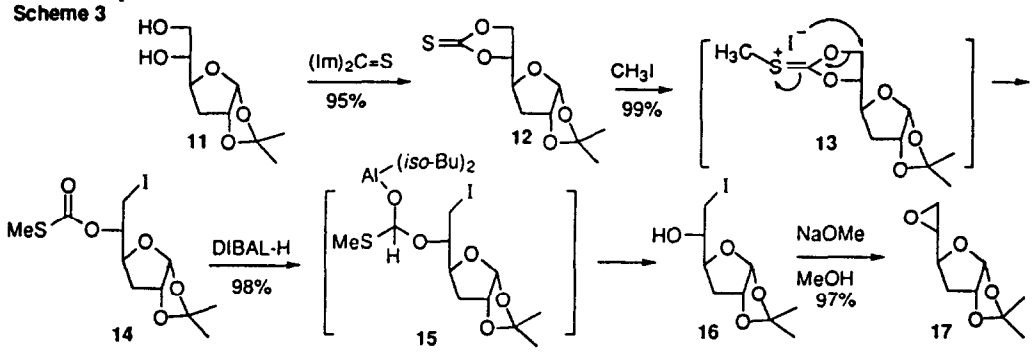


Since the transformation results in overall retention of configuration, the regioselectivity of the initially formed acetoxy halides **8** and **9** is inconsequent and epoxides are formed with the same ee as that of the diols used.

We wish to report another solution to the stereoselective formation of epoxides from chiral diols in which the focus is on complete regioselective formation of primary iodohydrins which are then converted to epoxides. Scheme 3 summarizes the approach used. This transformation can be carried out very conveniently in a one-pot reaction. In addition to their transformation to epoxides, the synthesis of the iodohydrins described here is of great value since iodo compounds are more reactive and versatile electrophiles and few direct methods for their preparation exist.[6] This method provides an approach to chiral primary iodohydrins inaccessible by

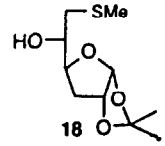
previous methods, such as the hydroxyiodination of olefins, introduction of iodomethyl group in to carbonyl derivatives, etc.[6] Recently, we used thionocarbonates as radical cyclization precursors in the synthesis of 8-*epi*-$PGF_{2\alpha}$.[7] It appeared to us that thionocarbonates could be useful intermediates for the preparation of chiral epoxides. More than two decades ago thionocarbonates were converted to olefins *via* iodo thiocarbonate intermediates.[8] We were interested to use a similar strategy with the purpose of preparing chirally pure hydroxy iodides and epoxides.

Scheme 3



The opening of the thionocarbonate ring system in **12** by iodide occurs exclusively at the primary carbon, presumably through an activated species **13**. No secondary iodo compound could be detected. This highly regioselective preference of iodide attack means that the stereochemistry of the secondary hydroxy group in the original diol **11** is completely retained in the iodohydrin **16** and epoxide **17**. The preparation of thionocarbonate **12** has been described by us previously.[7] The new thionocarbonates **20**, **25**, **30**, **35**, **40**, (table) as well as **44** (Scheme 4) have been prepared in a similar fashion at room temperature in very high yields[9] from batyl alcohol **19**, (R)-glycerol 1-benzyl ether **24**, 3,4-*O*-isopropylidene-D-mannitol **29**, (D)-threitol **34**, 1,2-*O*-isopropylidene-D-xylofuranose **39**, and (R)-phenyl-1,2-ethanediol **43**, respectively. The thionocarbonates are refluxed in dichloroethane or acetonitrile with excess methyl iodide for 24 hours, affording the primary iodo derivatives **14**, **21**, **26**, **31**, **36**, and **41** in nearly quantitative yield.

Our initial attempt to prepare the epoxide from iodo thiocarbonate **14** using NaOMe in methanol resulted in the formation of variable amounts of thio compound **18**. By-product **18** is probably formed by the reaction of the epoxide with the methanethiol generated during the reaction as evidenced by TLC.



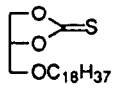
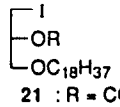
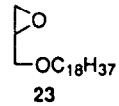
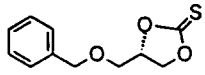
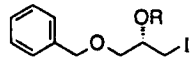
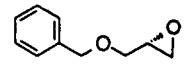
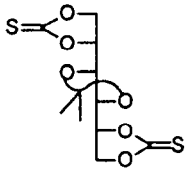
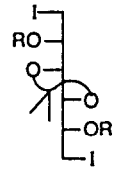
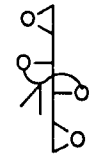
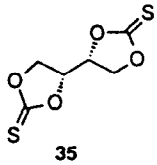
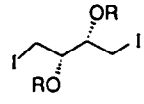
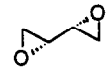
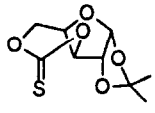
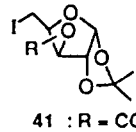
In order to solve this problem we needed a deprotecting reagent that would not liberate methanethiol under the reaction conditions. The selection of DIBAL-H for this purpose was motivated by the assumption that an intermediate complex such as **15**, Scheme 3, would be a tight one and only be hydrolyzed on work-up. As can be seen from the table, deprotection was smooth and afforded the iodohydrins **16**, **22**, **27**, **32**, **37**, and **42** in high to quantitative yield. Treatment of iodohydrins with sodium methoxide or potassium carbonate in methanol afforded the epoxides **17**, **23**, **28**, **33**, and **38** in very high yields.

One-pot procedure: A typical one-pot procedure is described for the preparation of epoxide **17**. A solution of the diol **11** (165 mg, 0.81 mmol) in 1,2-dichloroethane (4 mL) and 1,1'-thiocarbonyldiimidazole (173 mg, 0.97 mmol) was stirred at rt for 18 h. Methyl iodide (4 mL, 64 mmol) was added and the mixture refluxed for 18 h. The excess methyl iodide and solvent were removed *in vacuo*, the residue dissolved in

dichloromethane (2 mL) and DIBAL-H (2.4 mmol) added at -78 °C and stirred for 1 h. The reaction mixture was quenched with 5% aq. $KHSO_4$ and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried, evaporated, anhydrous methanol (2 mL) and NaOMe (1.6 mmol) (3.2 mL, 0.5 M/MeOH) were added and the mixture stirred at 0 °C for 1 h, quenched with water (5 mL), and extracted with CH_2Cl_2. The residue was chromatographed [ether / hexane (1 : 9)] to give 142 mg of pure epoxide **17** (94%).

Epoxide **23** has been used previously for the synthesis of platelet activating factor (PAF), a potent proinflammatory agent.[10] Note that the preparation of *bis*-thionocarbonates **30** and **35** and their conversion to the *bis*-iodo derivatives **31**, **32** and **36**, **37** worked very well considering the degree of complexity.[3c] Except for **21**, entry 2, we have been unable to detect any secondary iodo derivative in all these cases.[11] We have also

Table

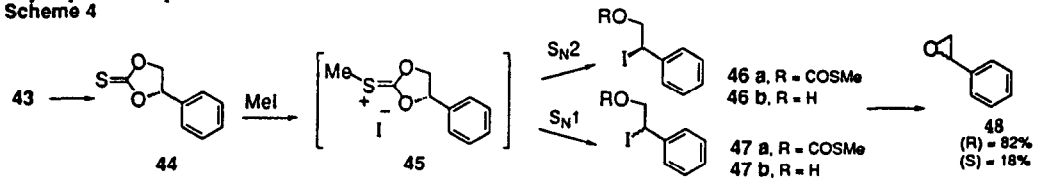
Entry	Diol	Thionocarbonate	% Yield	Primary[b] Iodo deriv.	% Yield	Epoxide[b]	% Yield
1	11	12	95	14 16	99 98	17	97 (94%)[c]
2	19	 20	96	 21 : R = COSMe 22 : R = H	99 97	 23	99 (93%)[c]
3	24	 25	94	 26 : R = COSMe 27 : R = H	96 94	 28	98 (90%)[c]
4	29	 30	91	 31 : R = COSMe 32 : R = H	99 93	 33	99
5	34	 35	91	 36 : R = COSMe 37 : R = H	99 95	 38	97
6	39	 40	93	 41 : R = COSMe 42 : R = H	99 99		

a) For all diols, entries 1, 2 and 3, the one-pot reaction for the preparation of the epoxide or the hydroxy iodide is recommended for best yields. For the more complex (tetraols **29** and **34**), the stepwise procedure is recommended for optimal yield. Except for **12**[7] all thionocarbonates, primary iodo derivatives, hydroxy iodides are new compounds and have been characterized by spectroscopic techniques, NMR, IR, HRMS. b) Spectroscopic data of epoxides **17**, **23**, **28**, **33**, and **38** matched literature values,[4,12] epoxides **17**, **28**, and **38** were compared with authentic samples. c) Numbers in parenthesis refer to the overall yield of the one-pot reaction.

selected a 6-membered ring thionocarbonate **39**, entry 6, and found no difference in reactivity as compared to the 5-membered ring system.

We are assuming that reactive intermediates, such as **13**, shown in Scheme 3, are attacked by a bulky iodide anion exclusively on the primary carbon. However, when we performed the MeI reaction on the phenyl-substituted thionocarbonate **44** we found that we have reversed the regioselectivity of the iodide introduction (Scheme 4).[13] This, we assume, is due to the strong electronegative effect of the phenyl ring, resulting in a preferential attack by the iodide on the benzylic carbon. In addition, chiral HPLC analysis[14] of epoxide **48** shows that it is partially racemized, indicating that some S_N1 reaction leading to a benzylic cation may have occurred. Alternatively, double inversion caused by an iodide attack on the initially-formed iodohydrin **46a** may explain the epimerization.[8b]

Scheme 4



In summary, we have developed an efficient one-pot reaction to convert *vic* diols to iodohydrins and epoxides with total retention of stereochemistry. This method has been applied to complex tetraol carbohydrates.

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9. Generally we used 5 mL solvent per mmol; in the preparation of 25, 35 and 40 we used 5 fold dilution for optimal yield.
10. Cimetiere, B.; Jacob, L.; Julia, M. *Tetrahedron Lett.* 1986, *27*, 6329.
11. Extent of absolute purity determined by NMR analysis. In the case of 21, entry 2, less than 0.5% of the secondary iodide could be detected. Representative spectroscopic data of 14 and 16 follows. **Compound 14**: IR (neat) ν 1719.3 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 5.70 (d, *J* = 3.5 Hz, 1H), 4.95 (m, 1H), 4.75 (t, *J* = 4.1 Hz, 1H), 4.30 (m, 1H), 3.48 (dd, *J* = 4.1 and 11 Hz, 1H), 3.33 (dd, *J* = 6.9 and 11 Hz, 1H), 2.38 (s, 3H), 2.20 (dd, *J* = 4.6 and 13.4 Hz, 1H), 1.80 (m, 1H), 1.53 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 171.2, 111.7, 105.6, 80.2, 78.2, 76.1, 35.3, 26.8, 26.2, 13.6, 3.6. DEPT 135 ($CDCl_3$) δ 35.3 (CH_2) and 3.6 (CH_2). HREIMS calc for (M-CH_3) 372.9606, obsd 372.9604. **Compound 16**: ^1H NMR ($CDCl_3$) δ 5.8 (d, *J* = 3.6 Hz, 1H), 4.75 (t, *J* = 4.1 Hz, 1H), 4.25 (dt, *J* = 4.8 and 5.3 Hz, 1H), 3.75 (dt, *J* = 3.3 and 4.5 Hz, 1H), 3.32 (dd, *J* = 4.1 and 10.4 Hz, 1H), 3.20 (dd, *J* = 7.7 and 10.4 Hz, 1H), 2.50 (d, *J* = 4.3 Hz, OH), 2.18 (dd, *J* = 4.5 and 13.4 Hz, 1H), 1.80 (ddd, *J* = 4.7, 10.6 and 13.5 Hz, 1H), 1.5 (s, 3 H), 1.31 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 111.5, 105.3, 80.4, 79.5, 72.0, 33.7, 26.7, 26.1, 9.3.
12. Le Merrer, Y.; Dureault, A.; Gravier, C.; Languin, D.; Depezay, J. C. *Tetrahedron Lett.* 1985, *26*, 319.
13. Similar reversal of the regioselectivity was previously observed by Sharpless *et al* (reference 5).
14. The ratio of R and S enantiomers was determined by HPLC using chiracel OD 4.6 X 250 mm column, hexane:isopropanol (99.75 : 0.25), flow rate 0.4 mL/min. When MeI treatment on thionocarbonate 44 was performed at room temperature the ratio of R and S becomes 95 : 5. Sharpless *et al* did not observe epimerization in the conversion of 43 to 48 using their cyclic *ortho* acetate method (reference 5).

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