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Stereoselective bromohydrin formation from β-hydroxy sulfoxides mediated by the pendant sulfoxide†‡

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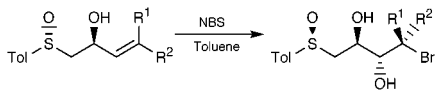
Regio- and stereo-selective bromohydrin formation promoted by a neighbouring sulfinyl moiety is disclosed.

The development of new and efficient methods for regio- and stereo-selective synthesis of biologically active compounds is an active area of research.[1] Our interest in the synthesis of polyhydroxylated sulfoxides and sulfides, *e.g.* Mannostatin A and B, has focussed initially on the stereoselective introduction of chiral centres in appropriate acyclic precursors.

It is well-known that sulfoxides may participate as neighbouring groups in a number of reactions.[2] Sulfoxide group participation in halohydrin formation from cyclic[3] and simple acyclic olefins[4] has been demonstrated, but its potential to produce highly functionalised products with stereochemical control at two adjacent centres in substituted acyclic systems remains unexplored. Here we report the formation of bromohydrins from acyclic β-hydroxy-γ,δ-unsaturated sulfoxides (Scheme 1). The unsaturated β-hydroxy sulfoxide precursors shown in Table 1 were prepared as an epimeric mixture in equimolar proportion and good yield[5] by condensing the lithium anion of (*R*)-(+)-methyl *p*-tolyl sulfoxide[6] **1** with the appropriate aldehydes[7] **2** (Scheme 2). The isomeric hydroxy sulfoxides [(R_S, S_C) and (R_S, R_C)] were separated[8] by chromatography and their configuration assigned unambiguously by comparison of coupling constants for the protons directly bonded to the carbon in the β-hydroxy sulfoxide moiety.[9]

The unsaturated β-hydroxy sulfoxides were reacted with NBS and water in toluene at ambient temperature to afford the bromohydrins in moderate to high stereoselectivity in good yield. Use of solvents like THF, MeCN and CH_2Cl_2 were not satisfactory. The sulfoxide group was envisaged to function as a pendant nucleophile and attack the intermediate bromonium ion, resulting in formation of a cyclic sulfonium salt which could then be hydrolysed by water to afford the bromohydrin (Scheme 3).[4] It is well known that hydrolysis of sulfoxonium salts proceeds with clean inversion on sulfur. Hence in effect the configuration on sulfur would get inverted.[3,10]

As Table 1 indicates, the reaction is general for a variety of γ,δ-unsaturated sulfoxides. According to the literature precedent[11] the reaction of **6a** with NBS is expected to afford **7a** as the predominant product. Contrary to the above expectation the outcome was a 1 : 1 mixture of **7a** and **8a**. The phenyl group in

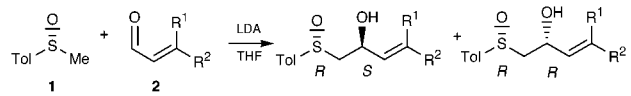


Scheme 1

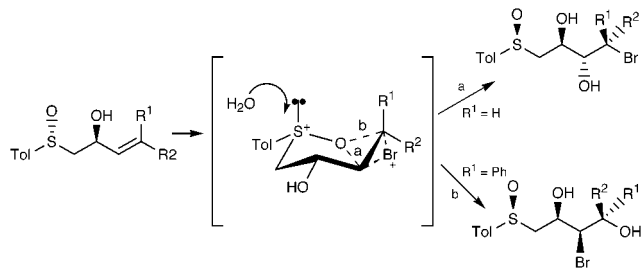
Table 1 Regio- and stereo-selectivity of bromohydrin formation[a]

β-Hydroxy sulfoxide	Products: *Anti* (C-2/C-3)	Products: *Syn* (C-2/C-3)	Yield (%) (*anti* : *syn*)
3a $R^1 = R^2 = H$ **6a** $R^2 = H$, $R^1 = CH_2OTBDPS$	**4a** **7a**	**5a** **8a**	80 (<5:>95)[b] 82 (1:1)[c]
9a $R^2 = H$, $R^1 = Ph$ **12a** $R^1 = H$, $R^2 = Ph$	**10a** **13a**	**11a** **14a**	75 (2:1)[cd] 78 (1:2)[cd]
3b $R^1 = R^2 = H$ **6b** $R^2 = H$, $R^1 = CH_2OTBDPS$	**4b** **7b**	**5b** **8b**	75 (<5:>95)[b] 80 (2:3)[c]
9b $R^2 = H$, $R^1 = Ph$ **12b** $R^1 = H$, $R^2 = Ph$	**10b** **13b**	**11b** **14b**	75 (<5:>95)[bd] 85 (>95:<5)[b]

[a] All reactions were carried out on a 0.25 mmol reaction scale at a concentration of 0.20 M in toluene in the presence of 1.2 equiv. of NBS and 1.7 equiv. of H_2O. [b] Only one isomer was observed in the crude NMR spectrum of the product mixture. [c] Ratio of the isomers determined after separation of the isomers. [d] 10–25% of the product resulting from non-participation of the sulfinyl moiety also observed.



Scheme 2



Scheme 3

† IICT Communication No. 4301.

‡ Experimental and spectral data for species described in this paper are available from the RSC web site, see http://www.rsc.org/suppdata/cc/1999/1845/

the sulfoxides **9a**, **9b**, **12a** and **12b** directs nucleophilic attack on the intermediate bromonium ions to C-4 to afford, regioselectively, products from 6-*endo* opening.[12] It is also apparent that the (R_S, R_C) isomers react to yield products more stereoselectively than the corresponding (R_S, S_C) isomers.

The stereochemical assignments were made by ^{13}C and ^{1}H NMR analysis of the spectra of the acetonides derived from the bromohydrins. The use of ^{13}C NMR data for acetonides of 1,3-diols and 1,2-diols for predicting their relative configurations has been reported by Rychnovsky and co-workers[13] and Dana and co-workers,[14] respectively. The coupling constants of protons on the carbon bearing the hydroxy and bromine in the six-membered ring acetonides reveal stereospecific *trans* addition to the double bond of **9** and **12**.[15] There are ample precedents for overall stereospecific *trans* addition to the double bond with respect to the olefin geometry in a similar reaction, *viz.* halolactonisation.[11] Similarly stereospecific *trans* addition to the double bond should be operative with **3** and **6** also. The sulfoxide group is known to deshield protons in which the S=O bond and the C–H bond are in a 1,3-parallel orientation.[16] The proton on C-2 of the acetonides derived from **5b**, **7b**, **8b**, **11b** and **13b** would occupy a 1,3-parallel orientation, while the proton on C-2 for the isomers **5a**, **7a**, **8a**, **11a** and **13a** would be almost orthogonal to the sulfoxide. A comparison of the chemical shifts for the protons on C-2 of the isomeric sulfoxides supports the configuration assigned to sulfur.

In conclusion, even though the product distribution often shows regio- and stereo-selectivity in a predictable way, striking anomalies are observed which underscore the influence of the sulfoxide group and its configuration on the outcome of the reaction. Experiments bearing on the mechanistic reasons for the observed stereoselectivity will be discussed in a later paper.

Notes and references

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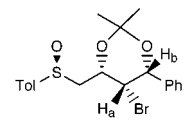
15 For instance, the coupling constants for the protons H_a and H_b in **15** is 1.5 Hz, while in **16** it is 9.52 Hz.



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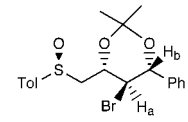

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