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REACTIONS OF 2,3-EPOXYHALIDES. SYNTHESIS OF OPTICALLY ACTIVE ALLYLIC ALCOHOLS AND HOMOALLYLIC EPOXIDES

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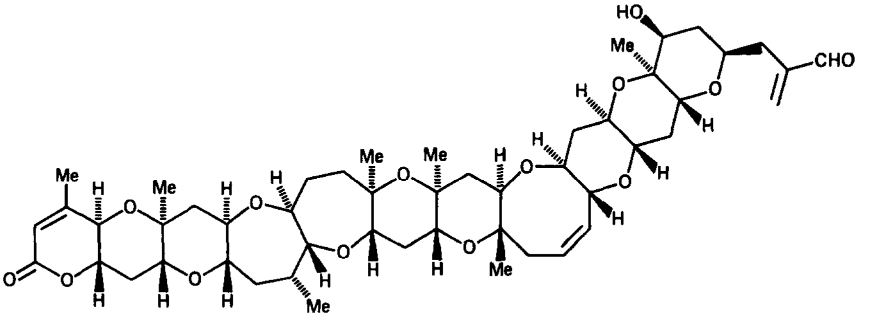
Summary: *Mild and efficient reactions for the conversion of optically active 2,3-epoxyhalides to optically active allylic alcohols and optically active epoxides are described.*

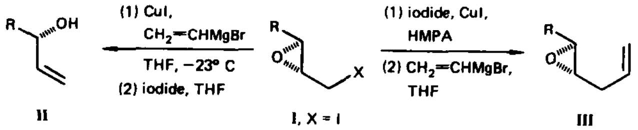
In conjunction with a program directed towards the total synthesis of ionophores and brevetoxin B[2] we had the opportunity to examine the chemistry of 2-haloepoxides (I)



Brevetoxin B

readily available in optically active form by Sharpless asymmetric epoxidation[3] of allylic alcohols followed by conventional manipulation[4,5] of the primary hydroxyl. We now wish to describe synthetically useful methods for the conversion of such intermediates to (a) optically active allylic alcohols (II) and (b) optically active homoallylic epoxides (III) (Scheme 1).

Scheme 1



The crucial observation was made when a THF solution of iodide 6 (Table 1) was dropwise added to a preformed (10 mins.) mixture of CH_2=CHMgBr and CuI (2 eq. each) in THF at -23^{o}C leading cleanly to the allylic alcohol 6a (90% yield), whereas modification of these conditions to dropwise addition of CH_2=CHMgBr (2 eq.) to a mixture of iodide 6, CuI (0.1 eq.) and HMPA (4.0 eq.) in THF at -23^{o}C, led almost exclusively, to the substitution product homoallylic epoxide 6c (85% yield).[6,7] It was later found that formation of the vinyl alcohols could also be realized in a more convenient way by treatment of I (Scheme 1, X=I, Br) with NaI (2.5 eq.) and Zn dust (3.0 eq.) in refluxing MeOH (Method B) or by exposure of I (Scheme 1, X=I, Br, Cl) to nBuLi (2.5 eq.) in THF at -23^{o}C (Method A).

Tables 1 and 2 demonstrate the versatility, mildness and efficiency of the above two processes. *Coupled with the power of the Sharpless asymmetric epoxidation,*[3] *this* methodology could deliver a variety of highly functionalized and enriched chiral building blocks of either enantiomeric form.

The following experimental procedures are representative for the two reactions described herein.

Preparation of 5c from 5. To a mixture of iodide 6 (1.0 mmole), CuI (0.1 mmole) and HMPA (4.0 mmole) in dry THF (1 ml) at -23^{o}C under argon was added CH_2=CHMgBr (1M THF solution; 2.0 mmole). After stirring at -23^{o}C for 15 mins. the reaction was quenched (Et_2O-NH_4Cl aq.) and after warming to room temperature, the usual work-up and silica flash column chromatography afforded compound 6c[8] as a colorless oil in 85% yield, R_f=0.24 (silica, 20% Et_2O in petroleum ether).

Preparation of 4a from 4 by Method B. A mixture of bromide 4 (1.0 mmole), NaI (2.5 eq.) and purified Zn dust (3.0 eq.) in absolute MeOH (5 ml) was refluxed under argon for 3.5 hrs. The cooled reaction mixture was then diluted with Et_2O (50 ml), filtered and the solution washed with H_2O, NaCl saturated aq. solution and dried ($MgSO_4$). After evaporation and silica flash column chromatography compound 4a[9] was obtained in 91% yield as a colorless oil, R_f=0.45 (silica, 50% Et_2O in petroleum ether. Analysis of this material by Mosher ester[10] formation ((-)-α-methoxy-α-(trifluoro methyl)phenylacetic acid, DCC, DMAP cat., THF, 25^{o}C, 6 hrs) and ^{1}H NMR spectroscopy revealed 93% ee.

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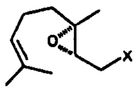
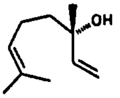
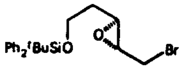
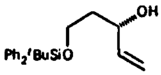
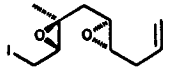
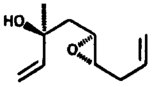
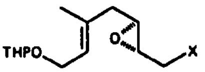
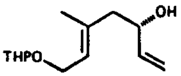
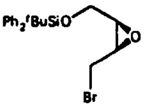
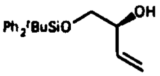
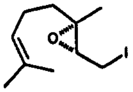
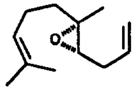
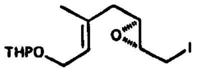
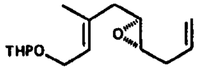
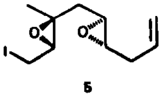
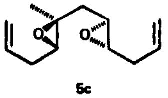
Table 1. Synthesis of Optically Active Allylic Alcohols

Entry	*Substrate*	*Product*	*Method*	*Yield (percent)*
				
1	1, X = Cl	1a	A B	92 0
2	2, X = Br		A B	93 95
3	3, X = I		A B	95 98
4		 4a	B	91
5		 5a	B	100
				
6	6, X = Br	6a	B	90
7	7, X = Cl		A	89
8	 8	 8a	B	86

Method A: *n* BuLi, THF, −23° C; Method B: Zn dust NaI (omitted in entries 3 and 5) MeOH, reflux.

Table 2. Synthesis of Optically Active Homoallylic Epoxides

Entry	*Substrate*	*Product*	*Yield (percent)*
1	 3	 3c	74
2	 6	 6c	83
3	 5	 5c	85

Conditions: $CH_2{=}CHMgBr$ (2.0 eq) in THF added to iodide, CuI (0.1 eq), HMPA (4.0 eq), THF, −23° C.

References and Notes

1. Fellow of the A. P. Sloan Foundation, 1979-1983; recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980-1985; J. S. Guggenheim Fellow, 1984.

2. Y.-Y. Lin, M. Risk, M. S. Ray, D. van Engen, J. Clardy, J. Golik, J. C. James, K. Nakanishi, *J. Am. Chem. Soc.*, 103, 6773 (1981).

3. (a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.*, 102, 5975 (1980); See also recent reviews: (b) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, K. B. Sharpless, *J. Am. Chem. Soc.*, 103, 6237 (1981); (c) K. B. Sharpless, C.H. Behrens, T. Katsuki, A. W. M. Lee, V. S. Martin, M. Takatani, S. M. Viti, F. J. Walker, S. S. Woodward, *Pure & Appl. Chem.*, 55, 589 (1983); (d) C. H. Behrens, K. B. Sharpless, *Aldrichimica Acta*, 16, 67 (1983).

4. The halides used in this work were prepared from the corresponding epoxyalcohols by tosylation followed by displacement with NaI, LiBr or LiCl. Alternatively, the bromides and chlorides could be prepared directly from the epoxyalcohols by standard procedures.

5. New compounds were characterized by ^{1}H NMR, IR, mass spec and analytical or exact mass data. Yields referred to spectroscopically and chromatographically homogeneous materials.

6. For a related procedure leading to substituted alkenes by displacement of aliphatic halides with vinyl Grignard reagents in the presence of CuI see: F. Derguini-Boumechal, G. Liustremelle, *Tetrahedron Lett.* 3225, 1976. In the case of 6, however, this procedure led to a mixture of 6a and 6c (*ca* 1:1).

7. These results are presumably a consequence of the known ability of transition metal salts to promote metal-halogen exchange: L. I. Zakharkin, O. Y. Okhlobystin, K. A. Bilevitch, *J. Organomett. Chem.* 2, 309 (1964). Although complexation of HMPA with organocuprates tends to decrease their reactivity, the diminished oxirane/cuprate interaction should favor, as observed, the displacement reaction.

8. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 5.82 (m, 2H, CH=), 5.04-5.20 (m, 4H, $C\underline{H}_2$=), 2.84 (m, 2H, $C\underline{H}_2$-CH=), 1.80 (dd, J=15,5Hz, 1H, $C\underline{H}_2$), 1.63 (dd, J=16, 7Hz, 1H, $C\underline{H}_2$).

9. ^{1}H NMR (250 MHz, $CDCl_3$, δ): 7.68 (m, 4H, Ph), 7.40 (m, 6H, Ph), 5.91 (ddd, J=16, 10, 6Hz, 1H, CH=), 5.30 (d, J=16Hz, 1H, $C\underline{H}_2$=), 5.12 (d, J=10Hz, 1H, $C\underline{H}_2$=), 4.44 (m, 1H, CH-O), 3.86 (m, 2H, $C\underline{H}_2$-O), 3.11 (d, J=4Hz, 1H, O$\underline{H}$), 1.78 (m, 2H, $C\underline{H}_2$), 1.05 (s, 9H, ^{t}Bu).

10. J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.*, 34, 2543 (1969).

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