Pergamon

Tetrahedron Letters, Vol. 35, No. 5, pp. 797-800, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0343-I

Ring Opening of 2,3-Epoxy 1-Tosylates to Halohydrins and Subsequent Elaboration to Asymmetrical Alcohols

Chiara Federici, Giuliana Righi*, Leucio Rossi

Centro C.N.R. per lo Studio della Chimica delle Sostanze Organiche Naturali, c/o Dipartimento di Chimica, Università "La Sapienza", P.le A. Moro 5, 00185 Roma,

Carlo Bonini*, Lucia Chiummiento, Maria Funicello

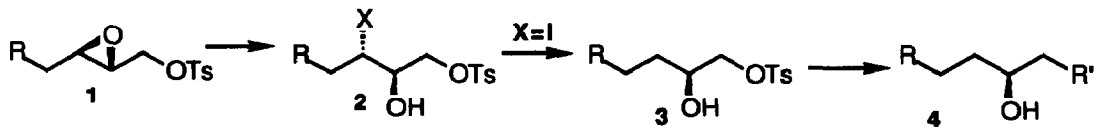
Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza. ITALY

Abstract: 2,3 -epoxy alcohols-1-tosylates are regio and chemoselectively opened to the corresponding 3-halohydrins (I, Br, Cl): the reduction of the iodohydrins to the monoprotected diols and subsequent standard coupling of the tosyl group leads to a straightforward synthesis of optically active naturally occurring pheromones.

2,3 epoxy -1-ol sulphonates can be prepared by standard derivatization or by *in situ* derivatization of the corresponding chiral 2,3 epoxy alcohols.[1] They are quite powerful synthetic intermediates since they possess multiple sites of potential electrophilic reactivity: in some cases carbon nucleophiles, with high selectivity, lead to the epoxide ring opening.[2] The direct tosylate displacement appears more difficult to achieve, due to the similar reactivity of carbons C_1, C_2 and C_3 and it has been performed only with aryloxide nucleophiles[2,3] or in other special cases.[4] To better use the potential tosylate replacement, i.e. for chain elongation, the epoxy ring needs to be chemo and regioselectively opened by a nucleophile which could be subsequently removed easily , as in the case of halogens, preferably iodine . Although the production of halohydrins from epoxides has been largely investigated5, the possibility to prepare the corresponding 3-halo-1,2 diol 1-ol-sulphonates from the 2,3 epoxy sulphonates has been only recently exploited.[6] In this report however (employing two different reagents, one to be prepared "in situ") only the corresponding 3-bromo and 3-chloro halohydrins can be obtained in high regioselectivity, and not the iodohydrins.

Figure 1 shows a possible reaction sequence, starting from 2,3 epoxy -1-tosylate **1**: the obtaining of the the 3-halohydrin **2** (mainly iodohydrin) can be followed by the easy removal of the halogen and then by the coupling of the monotosylated 1,2 diol **3**, leading to optically active alkanols **4** with various substituents.[7]

Figure 1

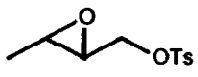
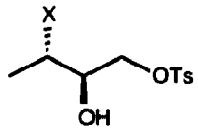
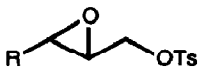
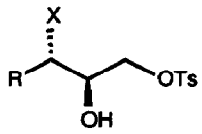
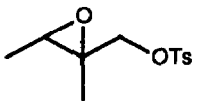
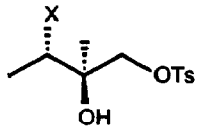
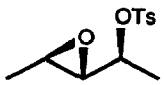
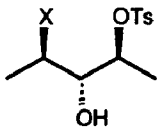
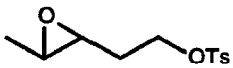
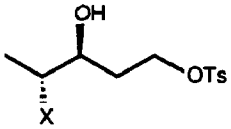
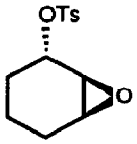
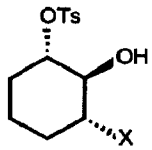


We have also demonstrated that the iodohydrin **2** can eventually be reduced *in situ* by means of nBu_3SnH;[8] this was shown for simple 1,2 epoxides as well as for 2,3 epoxy alcohols. Therefore we have undertaken a further study on 2,3 epoxy tosylates to prepare halohydrins (I, Br, Cl) and also to apply the synthetic sequence shown in figure 1 to the preparation of chiral alcohols like **4**, in high chemo, regio and

chemical yields.

Table 1 shows the results we have obtained with some representative epoxy tosylates[9] employing two different procedures. Firstly we have used our previously reported methodology A(LiX, X=I, Br, Cl, in CH_3CN with Amberlyst 15 resin)[10], which proved to afford the 3-halohydrins easily: this represents the first general method to prepare the 3-halo-1,2-diol tosylates from the corresponding epoxy tosylate with a procedure which appears unbeatable for the rate of the reaction (0.2-1 h), the chemical yields and the extremely simple work up. In all the cases the results are superior to those obtained with the corresponding 2,3 epoxy alcohols,[10] both in chemical yields and regioselectivity. Also 3,4 epoxy tosylate (entry 5) and cyclic *trans* epoxy tosylates (entry 6) gave excellent results expecially for iodohydrins.

Table 1

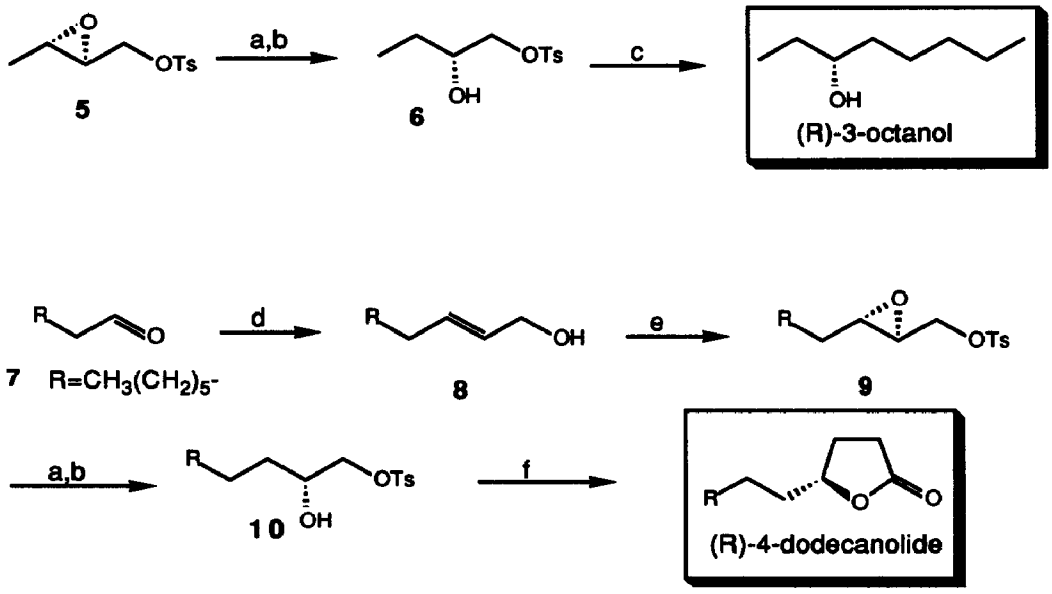
Entry	Epoxy 1- tosylate	Major halohydrins[a]	Methods (yield %)[b] A	B
1			X=I (99%) X=Br (99%) X=Cl (99%)	(98%)
2	 R=C_2H_5, C_4H_9		X=I (99%) X=Br (99%) X=Cl (99%)	(70-82%)
3			X=I (99%)	(50%)
4			X=I (99%)	(35%)
5			X=I (99%) X=Br (55%) X=Cl	(40%)
6			X=I (98%)	(60%)

Method A: LiX in CH_3CN, Amberlyst 15 (ref 9). **Method B**: MgI_2 in toluene (ref. 7).
a. in all the cases the ratio were superior to 99:1, checked by ^1H and ^{13}C-NMR. b. yields referred to isolated products.

With method **B** (MgI_2 in toluene)[8] the results are fair to good: in some cases (entries 3-6) the reactions are very slow and starting material was recovered. An important feature of the easy production of the 3-iodo-1,2-diol-1-tosylates, is the possibility to reduce (in the standard radical conditions, or by the "in situ" methodology [8,11]) the C-I bond. In this way a chemo and regioselective reductive opening of only the oxirane ring in 2,3 epoxy-1-ol-1-tosylates was performed, which is impossible to achieve with the common reducing metal hydrides.[12]

The synthetic utility of such 1,2 diol-1-tosylates was applied to the synthesis of two naturally occurring pheromones (see scheme 1). The above described procedures have been used on the chiral epoxy tosylates **5**[1] (e.e. 94%) and **9**[1] (e.e. 94%, the latter obtained from commercially available aldehyde **7**, by standard omologation to compound **8** and Sharpless A.E.). The chiral tosylate **6** was directly coupled with the appropriate cuprate affording in high yield the corresponding optically active (R)-3-octanol. On the other hand **10** was easily transformed, via the corresponding epoxide,[13] to the (R)-4-dodecanolide.[14]

Scheme1



a. LiI in CH_3CN, Amberlyst 15, r.t. 0.5 h (99%) **b**.nBu_3SnH/AIBN in toluene, 80°C, 2 h (88%).). **c**.nBu_2CuLi, in ether at -78°C, 0.5 h (81%). **d**. $(C_2H_5O)_2POCH_2COOEt$, LiOH, in THF, 0° C, 2h ; DIBAL-H in toluene at -78°C, 1 h (98%). **e**.TBHP in CH_2Cl_2, catalyticTi(OiPr)$_4$ and (+)-L -DET; $(CH_3O)_3P$, DEA, TsCl, (88%). **f**. K_2CO_3 in MeOH, r.t. 1 h; $CH_2(COOEt)_2$ in EtONa; 2N NaOH, 8h, then H_2SO_4 conc. ,reflux, 4 h (78%.).

By our knowledge this approach represents the most straightforward asymmetric synthesis of the title pheromones. A proper choice of the starting epoxy alcohols and of the tosyl replacement would allow the synthesis of all kinds of asymmetrical alcohols, which are not easily obtained by other routes. The 3-halo-1,2-

diol-1-tosylates are also useful intermediates, as was recently demonstrated by the synthesis of halogen containing marine natural products.[15] Studies are underway to effect the tosyl displacement in the presence of a bromine or a chlorine atom, which would allow a new entry into halogenated polyfunctional compounds.

REFERENCES AND NOTES

1. Gao, Y.; Hanson , R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1987**, *109*, 5765-5780.
2. See review on glycidols : Hanson, R.M.; *Chem. Rev.*, **1991**, *91*, 437-475. and ref.1.
3. Klunder, J.M.; Ko, S.Y.; Sharpless, K.B ; *J. Org. Chem.* , **1986**, *51*, 3710-3712 .
4. See for one case of direct tosylate replacement (52% yield): Mori, K.; Ebata, T. *Tetrahedron Lett.*, **1981**, *22*, 4281-4282.
5. See review: Bonini, C.; Righi, G. *Synthesis* , in press.
6. Gao, L.; Saitoh, H.; Feng, F.; Murai, A. *Chemistry Lett.*, **1991**, 1787-1790.
7. The C-1 reactivity of 2,3-epoxy alcohols and derivatives has been scarcely investigated: see for a recent paper: Bonini, C.; Giuliano, C.; Righi, G.; Rossi, L. *Tetrahedron Lett.*, **1992**, *33*, 7209-7212.
8. a) Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.*, **1991**, *56*, 6206-6208. b) Bonini, C. ; Righi, G. *Tetrahedron* , **1992**, *56*, 6206-6208 and references therein.
9. Chiral epoxy alcohols tosylates (entries 1 and 2) have been prepared by standard asymmetric epoxidation and derivatization *in situ* as described in ref. 1. All the other epoxy tosylates (racemic) have been prepared by standard tosylation of the corresponding epoxy alcohols.
10. Bonini, C.; Giuliano, C.; Righi, G.; Rossi, L. *Synthetic Comm.* **1992**, *22*, 1863-1870.
11. The *in situ* reduction of the iodohydrins was performed, following procedure in ref. 8, for entries 1, 2 and 3, with the obtaining of the corresponding 1,2-diols-1-tosylates in 75%, 55% and 60% overall yields respectively.
12. The reduction of 2,3-epoxy alcohol-1-sulphonates was reported to afford the corresponding 2-alkanols with the use of DIBAL-H and other reducing agents (see Chong J.M., *Tetrahedron Lett.*, **1992**, *33*, 33-36).
13. The direct coupling of the compound **10** with diethylmalonate proceeded with lower yields (20-30%).
14. For several approaches to the synthesis of the two pheromones see: Mori, K. in *The Total Synthesis of Natural Products* , ApSimon, J. Ed., John Wiley § Sons Inc., New York, 1992, vol. 9, pp. 108-109, 216-220 and references therein for structure data.
15. Murai, A.; Gao, L. *Tetrahedron Lett.*, **1992**, *33*, 4349-4352.
16. All the compounds show spectroscopical and analytical data in agreement with the structures and the literature data .
17. This work was partially supported by a MURST grant (40%) and a CNR Progetto Finalizzato "Chimica Fine e Secondaria" grant.

(*Received in UK* 27 *September* 1993; *revised* 2 *December* 1993; *accepted* 3 *December* 1993)