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Highly Regioselective Ring Opening of 2,3-Epoxy Alcohol Methanesulfonates

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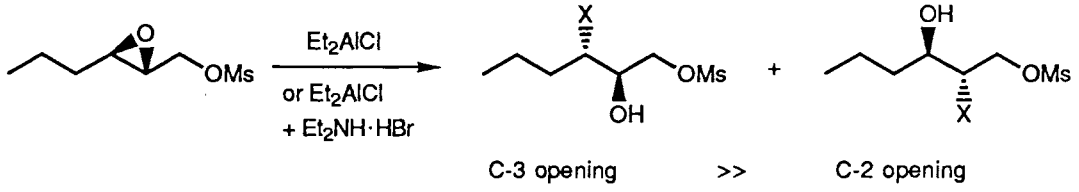
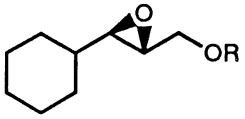
Reaction of 2,3-epoxy-1-ol methanesulfonates with diethylaluminum chloride or with the mixture of diethylaluminum chloride and diethylamine hydrobromide in dichloromethane gave rise to regioselectively the corresponding 3-chloro- and 3-bromo-1,2-diol 1-methanesulfonates, respectively, in excellent yields.

During the course of the synthetic studies on halogenated marine natural products, we have recently found an efficient procedure for titanium-mediated ring openings of 2,3-[1,2] and 3,4-epoxy-1-ols[2] at the 3- and 4-positions, respectively, using diethylamine hydrohalides as sources of halide nucleophiles. Since then, we have further studied to improve the regioselectivity. We describe herein the more effective procedure of the regioselective opening reaction of 2,3-epoxy-1-ols and its derivatives. A general procedure is as follows: (Method A) diethylaluminum chloride (Et_2AlCl, 1.5 mmol) was added dropwise to a solution of 2,3-epoxy-1-ol or its derivative (1.0 mmol) in dichloromethane (CH_2Cl_2, 8 ml) at -55 °C, and stirred for an appropriate period (see Table 1); (Method B) Et_2AlCl (1.5 mmol) and diethylamine hydrobromide ($Et_2NH{\cdot}HBr$, 3.0 mmol) was stirred in CH_2Cl_2 (4 ml) at 20 °C for 15 min., and then cooled to -15 °C. A solution of 2,3-epoxy-1-ol or its derivative (1.0 mmol) in CH_2Cl_2 (4 ml) was added and stirred for an appropriate period (see Table 1). The reaction proceeded by procedures A or B was quenched with 5% hydrochloric acid (HCl), and the mixture was diluted with ethyl acetate, washed with 5% HCl, 10% aq sodium carbonate solution, and saturated brine. After drying over anhydrous sodium sulfate, the solvent was evaporated to afford the residue, which was peracetylated for estimation of the ratio of C-3- to C-2-opening. The results were summarized in Table 1. The data



indicate that (i) every reaction proceeded with a high regioselectivity of C-3 opening in a S_N2 fashion; (ii) the sulfonyl esters resulted in preferable opening at the C-3 position

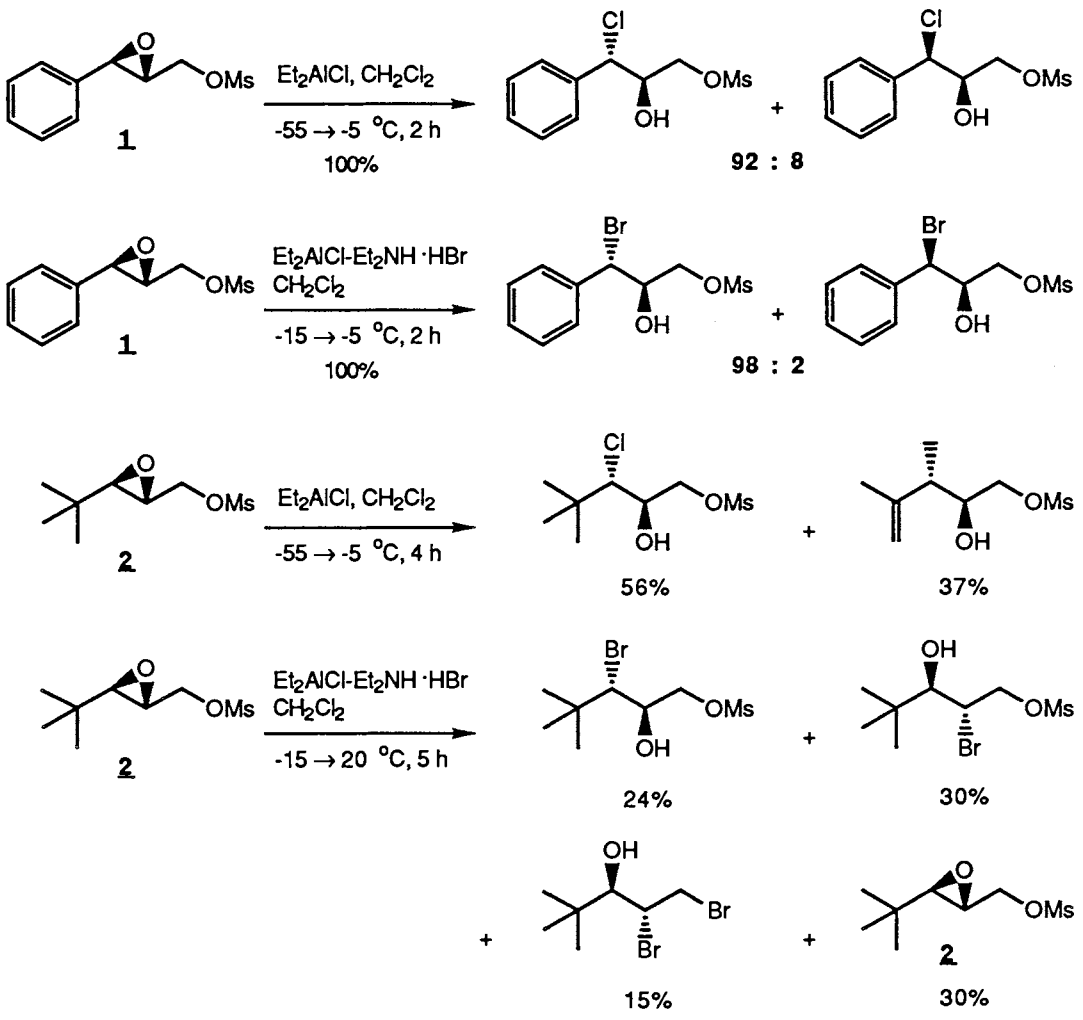
Table 1. Ring Openings of 2,3-Epoxy-1-ols and Their Derivatives

Epoxy alcohols or its derivatives	Method	Temperature °C	Time h	Regioselectivity C-3/C-2[a]	Yield %
					
R=H	A	-55 → 0	3	160/1	98
R=H	B	-15 → -5	2	96/4	95
R=Ms[b]	A	-55 → -5	2	200/1	99
R=Ms	B	-15 → -5	2	120/1	100
R=Ts[c]	A	-55 → -5	2	210/1	99
R=Ts	B	-15 → -5	2	160/1	100
R=TBS[d]	A	-55 → 5	4	135/1	86
R=TBS	B	-55 → 5	4	160/1	95
					
R=H	A	-55 → 0	3	89/11	85
R=H	B	-15 → 0	3	89/11	88
R=Ms	A	-55 → 0	3	140/1	99
R=Ms	B	-15 → -5	2	98/2	100
					
R=Ms	A	-55 → 5	4	100/0	100
R=Ms	B	-15 → 5	4	97/3	100

a) The ratio was based determined by ^{1}H NMR (400 MHz) after peracetylation. b) Ms denotes methanesulfonyl. c) Ts denotes toluenesulfonyl. d) TBS denotes *t*-butyldimethylsilyl.

comparing to the original alcohols; (iii) the secondary alkyl group at C-4 did not give any influence on the reaction course.

We have then checked the scope and limitation of these new reactions by using the methanesulfonates (mesylates) of 2,3-epoxy-1-ols as depicted in Scheme 1. When the compound (1) was used as the starting material, the method A gave rise to the (92:8) ratio of the inversion and retention products opening at the C-3 position, while the method B afforded the (98:2) ratio of the requisite opening. On the other hand,

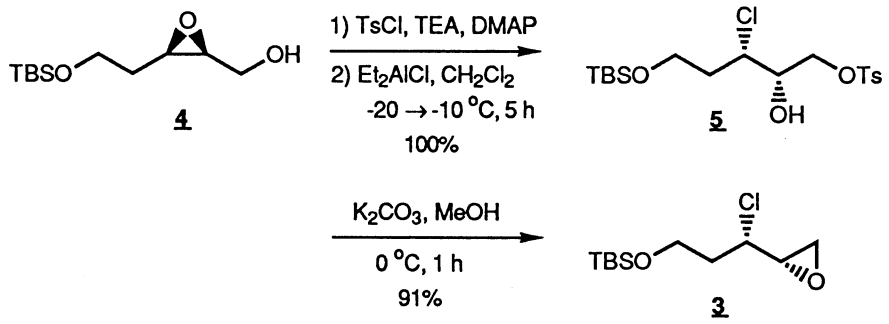


Scheme 1.

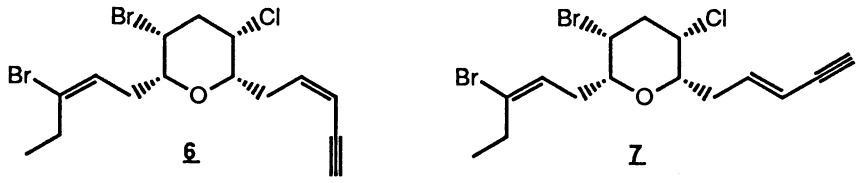
when the compound (2) was reacted by the method A, the yield of the desired chlorohydrin decreased to 56% with a formation of 1,2-rearranged product of a methyl group. On treatment with the method B, the compound (2) yielded the desired bromohydrin in only 24% yield, along with the C-2 opening compounds in 45% combined yield. These results reveal that the bulkiness at the C-4 position would have a tendency to decrease the yield of the aimed C-3 opening product for the steric hindrance when the halogeno-nucleophile attacks the oxirane ring from the backside. Further studies on directing to propose a mechanistic scheme are in due course. In the method B, the active reagent might be diethylaluminum bromide. Since it is generally difficult to prepare and handle the reagent experimentally,[3] this procedure would provide the *in situ* preparation of the reagent. We are now characterizing the net active species in this combined reagent.

These new reaction procedures are facile to handle and would provide highly efficient entry to the construction of various marine natural products containing chlorine or bromine atoms. We applied these results to preparation of the valuable

segment (3) for the synthesis of some marine natural products as shown below (Scheme 2). Thus the readily available (2*S*,3*R*)-4-*t*-butyldimethylsilyloxy-2,3-epoxypentan-1-ol (4) was tosylated in a usual manner, and treated with Et_2AlCl in CH_2Cl_2 at -20 °C to -10 °C during 5 h to afford exclusively (2*S*,3*S*)-4-*t*-butyldimethylsilyloxy-3-chloropentane-1,2-diol 1-tosylate (5) in an almost 100% yield. Compound 5 was reacted with potassium carbonate in methyl alcohol at 0 °C for 1 h to give 3 in 91% yield. Total synthesis of (-)-dactylyne (6) and (-)-isodactylyne (7) starting from the compound (3) is now under investigation.



Scheme 2.



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