Pergamon

Tetrahedron 55 (1999) 4947–4954

TETRAHEDRON

Regio- and Stereoselective Fluorinative Ring-Opening Reaction of Epoxyalcohols by (i-PrO)$_2$TiF$_2$-Et$_4$NF-nHF. Synthesis of Optically Active 3-Fluoro-1,2-diols

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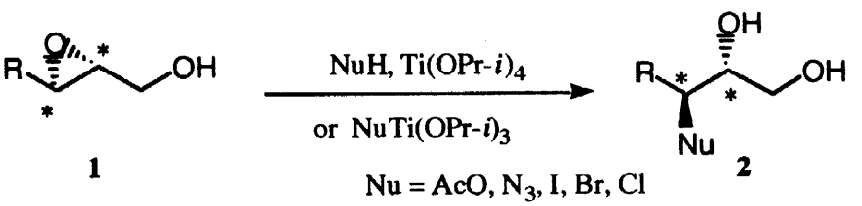
Received 22 January 1999; accepted 22 February 1999

Abstract: Stereo- and regioselective ring opening reaction of epoxyalcohols was achieved by (i-PrO)$_2$TiF$_2$ and Et$_4$NF-nHF under mild conditions. Fluoride attacked the epoxide at the C3 carbon with the inversion of the stereochemistry to give 3-fluoro-1,2-diols selectively. When optically active epoxyalcohols were used as the starting material, the corresponding 3-fluoro-1,2-diols were obtained with high optical purity.

Keywords: asymmetric synthesis; epoxides; halogenation; halohydrins

Introduction

Since the discovery of the asymmetric epoxidation of allylic alcohols,[1] the regio- and stereoselective ring-opening of epoxyalcohols (**1**) by nucleophiles has been studied to prepare chiral diols having functional groups. Such transformations have been achieved using titanium reagents and various nucleophiles which were selectively introduced at the C-3 position of **1** to give the chiral 1,2-diol derivatives (**2**) (eq. 1).[2]



1 **2**

Nu = AcO, N_3, I, Br, Cl (1)

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PII: S0040-4020(99)00180-5

However, the application of this method to the synthesis of chiral fluorodiols (**2**, Nu = F) has been unsuccessful due to the low nucleophilicity of the fluoride ion. In the reaction of **1** with $(i\text{-PrO})_2TiF_2$ (**3**), the epoxy function was attacked by isopropoxide as well as fluoride to give isopropoxy derivatives as by-products (**2**, Nu = OPr-i).[3] Other fluorination reagents such as KHF_2,[4] $Bu_4NH_2F_3$,[5] and R_3N-nHF[6] have been also used for the reaction with **1**, but more severe reaction conditions were generally required which are not favorable for the synthesis of optically pure compounds. We report here that the regio- and stereoselective ring-opening of epoxyalcohols can be achieved under mild conditions using **3** and Bu_4NF-nHF.

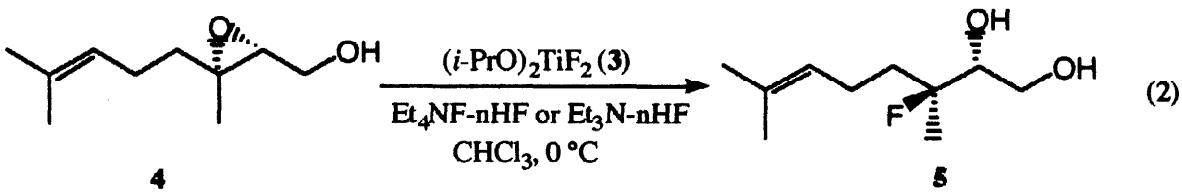
Results and Discussion

Initially, the fluorination reaction of racemic 2,3-epoxygeraniol (**4**) was examined (eq. 2). The reaction of **4** with **3** was completed in 10 h at 0 °C and the expected fluorodiol (**5**) was obtained in 23% yield with 12% yield of the isopropoxy derivative as previously reported[3] (Entry 1 in Table 1). The formation of the isopropoxy derivative could be suppressed by the additional use of the Et_4NF-nHF or Et_3N-nHF complexes with **3**. The best result was obtained when Et_4NF-3HF was used with **3** in $CHCl_3$, and **5** was obtained in 73% yield without the formation of the isopropoxy derivative or the regioisomer (Entry 2).[7] The fluorodiol **5** contained ca. 5% of its diastereoisomer[8] which was formed through the stable tertiary-carbocation during the ring-opening of epoxide.[9]

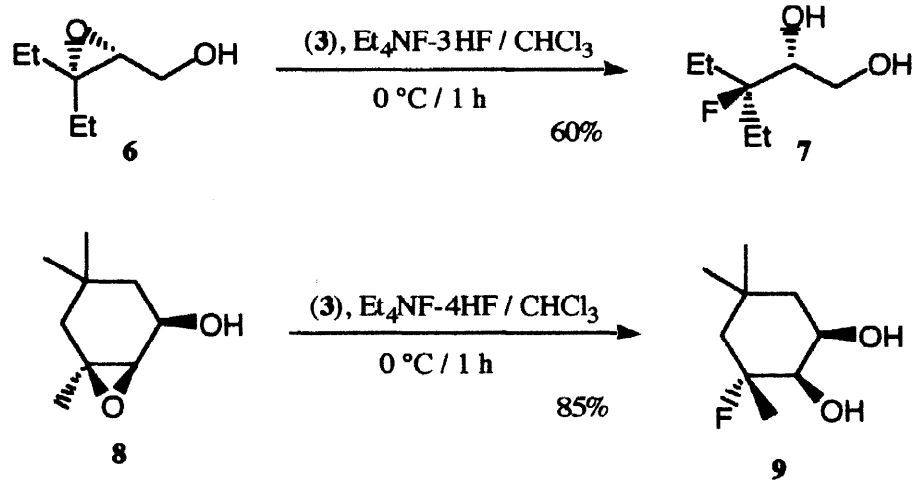
Table 1. Fluorinative Ring Opening Reaction of Epoxygeraniol (**4**)[a]

Entry	Et_3N- or Et_4NF-nHF	Reaction Time/h	Yied of **5**/%[b]
1	—	10	23[c]
2	Et_4NF-3HF	11	73
3	Et_4NF-4HF	2	67
4	Et_4NF-5HF	1	64
5	Et_3N-4HF	1	21
6	Et_3N-5HF	1	58
7	Et_3N-6HF	1	57
8	Et_3N-7HF	1	53

a) The reaction was carried out as shown in a text. b) Isolated yields based on **4**. 5% of diastereoisomer was contained. c) Isopropoxy derivative was also isolated in 12% yield.

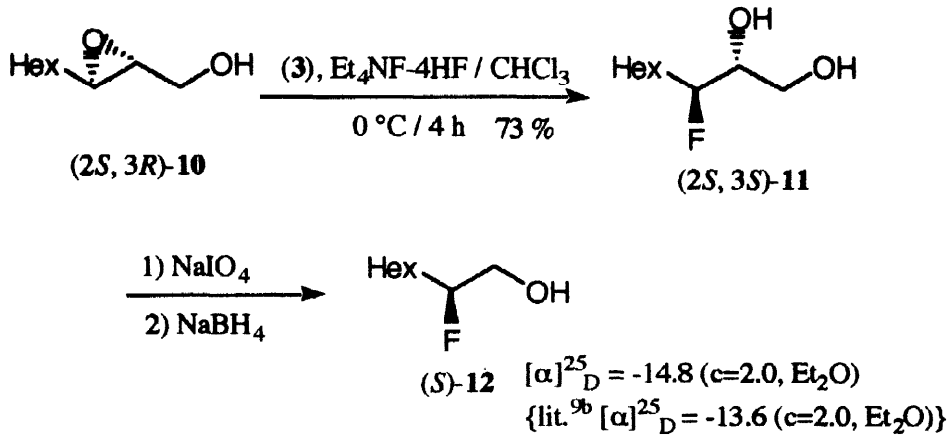


In the reaction of epoxyalcohols (**6**, **8**) with **3** and Et_4NF-3HF or -4HF, only one fluorinated product (**7**, **9**) was selectively obtained (Scheme 1). As a fluorine and a hydroxy group at C-2 have trans-stereochemistry in **9**,[6b] the fluoride attacked the C-3 carbon from the rear side with the inversion of the stereochemistry as previously proposed.[2]



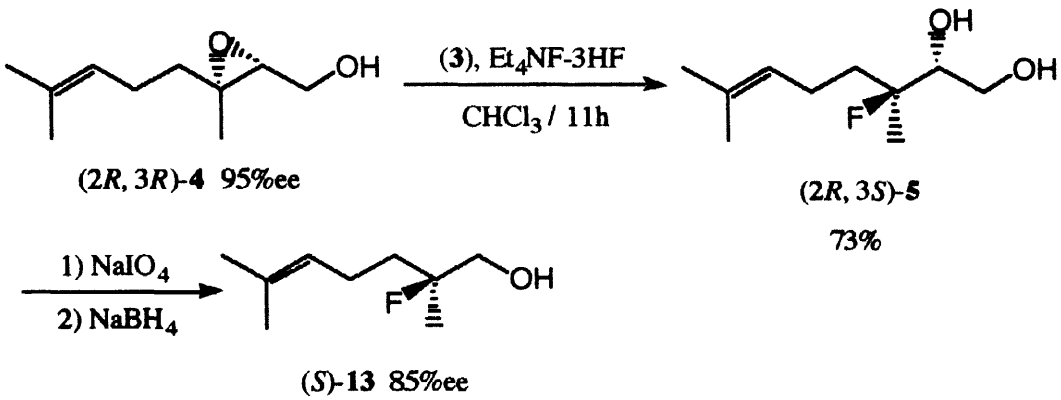
Scheme 1

(2*R*, 3*R*)-2,3-Epoxy-1-nonanol (**10**) of 95 %ee[1] was allowed to react with **3** and Et_4NF-4HF to give a mixture of two regioisomers in a ratio of 10:1. The structure of the main product was determined to be the expected 3-fluoro-1,2-nonanediol (**11**) from the ^1H NMR spectrum of its diacetate.[6a] For the assignment of the absolute configuration, **11** was converted to 2-fluoro-1-octanol (**12**) as shown in Scheme 2.[10] The absolute configuration of **12** was determined to be *S* by comparison of its optical rotation with the reported one[9b] and after converting it to the (*R*)-(+)-MTPA ester,[11] its enantiomeric excess was determined to be 95 %ee which was identical to that of the starting epoxyalcohol **10**. From these results, it was shown that the attack of the fluoride on the epoxy function of **10** mainly occurred at the C-3 carbon from the rear side along with complete inversion of the stereochemistry (Scheme 2).



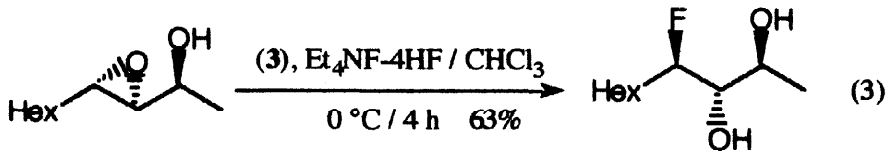
Scheme 2

The reaction of (2*R*, 3*R*)-epoxygeraniol **4** of 95%ee[1] with **3** and Et_4NF-3HF regioselectively proceeded to provide (2*R*, 3*S*)-fluorodiol **5** which was then converted to fluoroalcohol (**13**).[10] The optical purity of **13** was determined to be 85 %ee after conversion to its (*R*)-(+)-MTPA ester,[11] and these results showed that ca. 5 % of the racemization took place at the C-3 carbon of **4** during the fluorination reaction (Scheme 3).[9]



Scheme 3

The fluorination reaction of (2*R*, 3*R*, 4*R*)-3,4-epoxy-2-decanol (**14**) of 98 %ee proceeded with high regio- and stereoselectivities and (2*S*, 3*R*, 4*R*)-4-fluoro-2,3-decanol (**15**) was selectively obtained (>97%ee) (eq. 3).



(3)

(2*S*, 3*R*, 4*S*)-**14** (2*S*, 3*R*, 4*R*)-**15**

Experimental

General. The melting points were measured with a Yanagimoto micro melting-point apparatus and are uncorrected. IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-A400 FT NMR and chemical shifts, δ, are referred to TMS (^{1}H) and $CFCl_3$ (^{19}F) respectively. Optical rotation was measured with a Horiba High Sensitive Polarimeter. FAB- and EI-High-resolution mass spectra were measured on a JEOL JMS-HX110 and JMS-DX303, respectively. Elemental micro analyses were taken by Yanagimoto CHN Corder MT-5. The Et_3N-nHF complexes were prepared from freshly distilled Et_3N and anhydrous HF as previously reported.[12] The Et_4NF-nHF complexes were supplied from Morita Chemical Industries Co. and used without purification. **3** was prepared from $(i\text{-PrO})_4Ti$ and AcF as reported.[3] Chiral epoxy alcohols (2*R*, 3*R*)-**4** and (2*S*, 3*R*)-**10** were prepared in 95%ee from the corresponding unsaturated alcohols by the Sharpless method,[1] and racemic **4**, **6** and **8** were obtained by the oxidation of the corresponding unsaturated alcohols with *m*-CPBA. (2*S*, 3*R*, 4*S*)-**14** of 98%ee was obtained from the racemic 3-decen-2-ol as reported.[13]

3-Fluoro-3,7-dimethyl-6-octen-1,3-diol (5). A $CHCl_3$ solution (3 ml) of **4** (170 mg, 1 mmol) was added at - 20°C to **3** (408 mg, 2 mmol) in $CHCl_3$ (5 ml) and the mixture was stirred for 1 h at the temperature. Then the temperature was allowed to warm to 0°C and Et_4NF-3HF (418 mg, 2 mmol) in $CHCl_3$ (3 ml) was added. The reaction was monitored by TLC and after stirring for 11 h , **4** was completely consumed. The mixture was poured into aq. $NaHCO_3$ and the separated organic layer was washed with 3M HCl. The aqueous layer was extracted with ether and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The ratio of the isomers was determined by ^{19}F NMR before the purification. The product was isolated by column chromatography (silica gel/ hexane:ether = 1:1) in 73 % yield as a mixture of two diastereoisomers (95:5) as a colorless oil: IR (neat) 3400 (-OH) cm^{-1}, ^{1}H NMR δ = 5.10 (1H, t, *J* = 6.83 Hz), 3.62-3.78 (3H, m), 3.17 (brs, 1H), 2.80 (brs, 1H), 2.18-2.05 (2H, m), 1.98-1.42 (m, 2H), 1.69 (3H, s), 1.62 (3H, s), 1.34 (3H, d, *J* = 22.69 Hz). ^{19}F NMR δ = -157.011- -157.342 (0.95F, m), -155.128- -155.261 (0.5F, m). HRMS(EI) Calcd for $C_{10}H_{19}O_2F$: 190.1369. Found. *m/z* 190.1375. Anal. C, 63.13; H, 10.07. Found: C, 63.35; H, 10.08.

(2*R*, 3*S*)-5: $[\alpha]^{25}_D$ = -11.1 (c=20, Et_2O).

3-Ethyl-3-fluoro-1,2-pentandiol (**7**), colorless oil: IR(neat) 3450 (OH) cm^{-1}. ^{1}HNMR δ = 3.83-3.66 (3H, m), 2.75(J = 1H, d), 2.49 (1H, brs), 1.89-1.47 (4H, m), 0.93 (6H, dt, J = 3.7, 7.5 Hz). ^{19}FNMR δ = -167.33--167.08 (1F, m). MS *m/z* 115 (M^+-35) 101 (M^+-Et-HF) 95 (M^+-2H_2O-F) 73 (M^+-2Et-F) 43 (M^+-107). Anal. calcd for $C_7H_{15}O_2F$: C, 55.98; H, 10.07. Found: C, 56.01; H, 10.05.

3-Fluoro-3,5,5-trimethyl-1,2-cyclohexandiol (**9**), white solid; mp 79°C, (ref.[6b] 84°C): IR(nujol) 3450 (OH), 3400 (OH) cm^{-1} ^{1}H NMR δ = 4.17-4.12 (1H, m), 3.72-3.69 (1H, m), 2.45-2.44 (1H, m), 1.90(1H, d, J = 5.4 Hz), 1.54-1.41 (4H, m), 1.41 (3H, d, J = 22.69 Hz),1.04 (3H, s), 0.96 (3H, s). ^{19}FNMR δ = -152.52--152.89 (1F, m). HRMS(EI) Calcd for $C_9H_{17}FO_2$: 176.1213. Found. *m/z* 176.1241.

(2*S*, 3*S*)-3-Fluoro-1,2-nonandiol (**11**), white solid; mp. 52°C: IR(neat) 3304 (-OH) cm^{-1}. ^{1}H NMR δ = 4.51 (1H, m), 4.02-3.72 (3H, m), 2.41 (1H, d, J = 5.1 Hz), 1.88 (1H, s), 1.77-1.30 (10H, m), 0.97 (3H, t, J = 7.3 Hz). ^{19}F NMR: δ = -193.32 - -193.63 (1F, m). HRMS(Fab) Calcd for $C_9H_{20}FO_2$ (M^++1) 179.14474. Found. *m/z* 179.1434. Anal. calcd for $C_9H_{19}FO_2$: C, 60.65; H, 10.74; Found: C, 60.86; H, 10.59. $[\alpha]^{25}_D$ = -11.95 (c=20, Et_2O).

2-Fluoro-1,3-nonandiol (minor isomer), ^{19}F NMR : -195.81 - -196.10 (m).

The conversion of **11** to its diacetate was carried out by the treatment with excess acetic anhydride and *p*-dimethylaminopyridine.[6a] ^{1}H NMR δ = 5.15-5.07 (1H, m), 4.67-4.51 (1H, dm, J = 48.3 Hz), 4.44 (1H, ddd, J = 11.9, 3.0, 1.2 Hz), 4.16 (1H, ddd, J = 12.2, 6.8, 1.2 Hz), 2.11 (3H, s), 2.07 (3H, s), 1.75-1.30 (10H, m), 0.89 (3H, t, J = 6.8Hz).

(*S*)-2-Fluoro-1-octanol (**12**). A THF solution (3 ml) of (2*S*, 3*S*)-**11** (178 mg, 1 mmol) was added to $NaIO_4$ (1.07 g, 5 mmol) in a mixture of THF (7 ml) and water (5 ml) at room temperature. The reaction was completed in 10 min and the product was extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in EtOH (3 ml) and added to $NaBH_4$ (45 mg, 1.2 mmol) in EtOH (8 ml) at room temperature. The mixture was stirred for 1 h and then 3M HCl was slowly added. The product was extracted with ether and the combined organic layers were dried over $MgSO_4$. The purification by column chromatography (silica gel/hexane:ether = 2:1) gave **12** in 65% yield from **11** as a colorless oil: IR(neat) 3279 (-OH) cm^{-1}. ^{1}H NMR δ = 4.57 (1H, m), 3.73-3.63 (2H, m), 2.39 (1H, brs), 1.73-1.30 (10 H, m), 0.89 (3H, t, J = 6.8 Hz). ^{19}F NMR δ = -189.61 - -190.00 (1F, m), MS: *m/z* 129 (M^+-F), 111(M^+-F-H_2O), 102 (M^+-46), 95 (M^+-53), $[\alpha]^{25}_D$ = -14.8 (c=2.0, Et_2O)(lit.[9b] $[\alpha]^{25}_D$ = -13.6 (C=2.0, Et_2O).

The conversion of **12** to its (*R*)-(+)-MTPA ester was carried out by the treatment with (*R*)-(+)-MTPA chloride, triethylamine and *p*-dimethylaminopyridine in CH_2Cl_2.[2f] ^{19}F NMR: δ = -72.93 (0.075F, s), -72.34 (2.925F, s), -187.16 - -187.54 (1F, m).

(*S*)-2-Fluoro-2,6-dimethyl-5-hepten-1-ol (13), colorless oil: IR(neat) 3349 (-OH) cm^{-1}, ^1H NMR: δ = 5.10 (1H, t, J = 7.07 Hz), 3.65-3.51 (2H, m), 2.98 -2.04 (2H, m), 1.91 (1H, brs), 1.69 (3H, s), 1.62 (3H, s), 1.34 (3H, d, J = 21.96 Hz), 1.78-1.58 (2H, m). ^{19}F NMR δ -155.602 - -155.867 (1F, m). HRMS(EI) Calcd for $C_9H_{17}FO$: 160.1263. Found. *m/z* 160.1273. $[\alpha]^{25}_D$ = -1.95 (c=20, Et_2O).

(*R*)-(+)-MTPA ester of **13**: ^{19}F NMR: δ = -72.25 (3F, s), -152.12 - -152.38 (0.075F, m), -152.93 - -153.19 (0.925F, m).

(2*S*, 3*R*, 4*R*)-4-Fluoro-2,3-decandiol (15), colorless oil: IR(neat) 3377 (-OH) cm^{-1}. ^1H NMR δ = 4.44 (1H, m), 4.01-3.97 (1H, m), 3.70-3.68 (1H, m),3.04 (1H, brs), 3.66 (1H, brs), 1.81-1.15 (10H, m), 1.23 (3H, d, J = 6.6 Hz), 0.89 (3H, t, J = 6.7 Hz); ^{19}F NMR δ = -194.10 - -194.40 (1F, m). HRMS (Fab): Calcd for $C_{10}H_{22}FO_2$ (M^++1) 193.1604. Found m/z 193.1597. $[\alpha]^{25}_D$ = +21.2(c=2.0, Et_2O).

Acknowledgements

This work was financially supported by a Grant-in-Aid for Scientific Research (B) from the Japanese Ministry of Education, Science, Sports and Culture. We are grateful to Morita Chemical Industries Co. for their donation of Et_4NF-nHF complexes.

References and Notes

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7. When the Et_4NF-4HF complex alone was used for the reaction with **4**, **5** was obtained only in 3% yield along with a significant amount of unidentified products.
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