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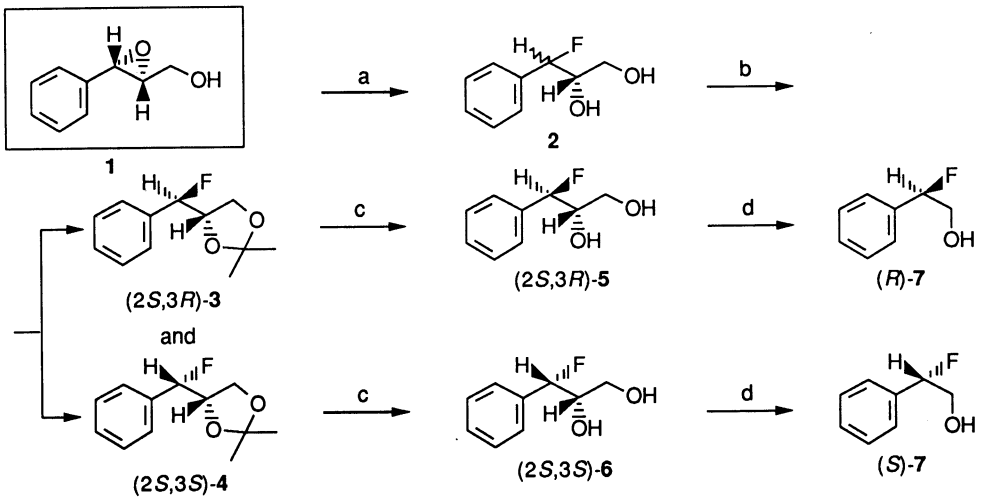
Preparation of Chiral Fluorine Compounds from (2S,3S)-3-Phenylglycidol

Seiichi TAKANO,* Masashi YANASE, and Kunio OGASAWARA
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980

Some potentially useful chiral fluorine compounds have been synthesized starting from (2S,3S)-3-phenylglycidol.

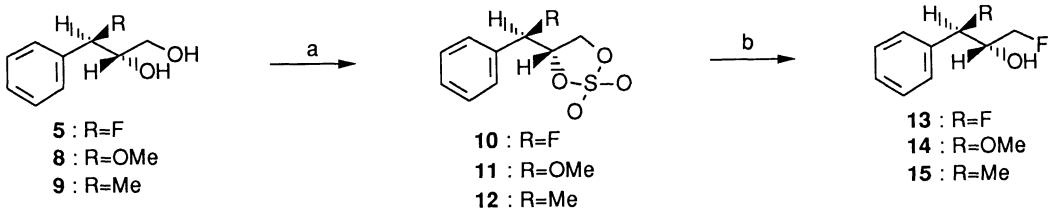
Pronounced biological effects[1] as well as ferroelectric effects[2] are often recognized when hydrogen atoms are replaced by fluorine at an appropriate position. We report here a synthesis of some chiral fluorine compounds which are potentially useful as key building blocks for the construction of a variety of chiral fluorine materials starting from readily accessible (2S,3S)-3-phenylglycidol[3] (**1**).



Scheme 1.
(a) $i\mathrm{Pr}_2\mathrm{NH}\cdot(\mathrm{HF})_3$, 110 °C, 8 h; (b) $\mathrm{Me}_2\mathrm{C(OMe)}_2$, PPTS, acetone, r.t.; (c) 10% HCl-THF (1:5 v/v), r.t.; (d) (i) NaIO_4, aq. MeOH, 0 °C, (ii) NaBH_4, 0 °C.

Heating a mixture of the epoxide[4] **1** and diisopropylamine trihydrofluoride[5,6] (5 equiv.) at 110 °C afforded the fluorodiol **2** in 44% yield as an inseparable mixture of two epimers. None of isolable fluorinated materials could be formed when other fluorinating agents such as hydrogen fluoride pyridine complex,[7] cesium fluoride,[8] tetrabutylammonium fluoride,[9] and silicon tetrafluoride[10] were used in place of diisopropylamine trihydrofluoride. The mixture formed the acetonide which could be readily separated by silica gel column chromatography to give the inversion product[11] (2S,3R)-**3**, $[\alpha]_D^{25}$ -0.19° (c 2.10, $CHCl_3$), and the retention product[11] (2S,3S)-**4**, $[\alpha]_D^{26}$ +33.55° (c 2.40, $CHCl_3$), in yields of 88 and 11%. The stereochemistry of the acetonides was confirmed by correlating them with the known (S)-2-fluoro-2-phenylethanol[12] (**7**), respectively. Thus, acid hydrolysis of **3** gave

the (2S,3R)-fluorodiol **5**, mp 67-68 °C, $[\alpha]_D^{27}$ -19.91° (c 2.24, $CHCl_3$), quantitatively. Similarly, **4** gave the (2S,3S)-fluorodiol **6**, $[\alpha]_D^{22}$ +37.39° (c 2.33, $CHCl_3$), quantitatively. Upon sequential periodate cleavage and borohydride reduction in the same flask both of the above diols yielded the enantiomeric 2-fluoro-2-phenylethanols **7**, respectively. Thus, (2S,3R)-**5** afforded (R)-**7**, $[\alpha]_D^{24}$ -51.75° (c 5.07, $CHCl_3$), in 92% yield and (2S,3S)-**6** afforded (S)-**7**, $[\alpha]_D^{26}$ +50.46° (c 4.72, $CHCl_3$), in 77% yield.



5 : R=F
8 : R=OMe
9 : R=Me

10 : R=F
11 : R=OMe
12 : R=Me

13 : R=F
14 : R=OMe
15 : R=Me

Scheme 2.
(a) $SOCl_2$, CCl_4, r.t. then $RuCl_3 \cdot 3H_2O$, $NaIO_4$, aq. MeCN, 0 °C; (b) n-Bu_4NF (2 equiv.), THF, r.t.

The second fluorine could also be introduced at C_1-center via the cyclic sulfate intermediate employing the method developed by Gao and Sharpless.[13] Thus, the fluorodiol **5** was first transformed into the cyclic sulfate **10**, $[\alpha]_D^{25}$ +8.21° (c 1.10, $CHCl_3$), in 55% yield, with thionyl chloride followed by ruthenium oxide. On reaction with tetrabutylammonium fluoride **10** furnished 1,3-difluoro-3-phenyl-2-propanol **13**, $[\alpha]_D^{26}$ +19.80° (c 3.77, $CHCl_3$), in 82% yield. The same procedure could also transformed two optically pure diols **8** and **9**, readily accessible[14] from **1**, into the corresponding terminal fluorides **14**, $[\alpha]_D^{27}$ +10.97° (c 1.68, $CHCl_3$), and **15**, $[\alpha]_D^{29}$ -116.38° (c 1.54, $CHCl_3$), in 94 and 98% overall yields via the corresponding cyclic sulfates **11**, mp 71-71.5 °C, $[\alpha]_D^{29}$ +6.44° (c 0.96, $CHCl_3$), and **12**, mp 55-55.5 °C, $[\alpha]_D^{27}$ +38.04° (c 1.20, $CHCl_3$), respectively.

References

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4) Optically pure material, mp 50-51 °C, $[\alpha]_D^{26}$ -50.4° (c 2.4, $CHCl_3$), was used.
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