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# Synthetically Useful C-4 Fluorinated Building Blocks Bearing a Quaternary Stereocentre

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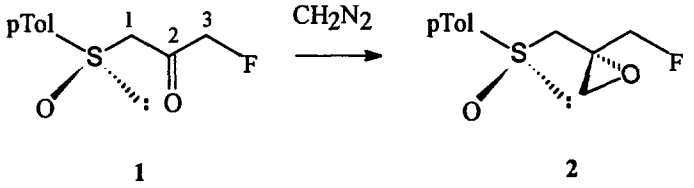
***Abstract:*** *the syntheses of 2-fluoromethyl-2-hydroxymehtyl-, 2-(dimethoxy)methyl-2-fluoromethyl-, and 2-carboxy-2-fluoromethyl oxiranes 5, 7, and 8 through reaction of diazomethane with β-keto-γ-fluorosubstituted sulphoxide 1 followed by Pummerer rearrangement are shown. Selected oxirane opening reactions with nitrogen nucleophiles to give β,γ-dihydroxy-β-fluoromethyl amine 14 and α-hydroxy-α-fluoromethyl-β-amino acid 19 are described.*

The fluorinated chiral building block 1-p-tolylsulphinyl-3-fluoro acetone (**1**) had proven to be a useful chiral synthon[1]. A number of synthetic methodologies based on **1** have been developed for the synthesis of selectively fluorinated organic molecules of biological significance like 4-deoxy-4-fluoromuscarines[2], fluorinated nucleosides[3], fluorinated deoxy sugars[4], and fluorinated carbocycle derivatives[5].

The common key steps in the mentioned synthetic sequences[2-5] were the chain elongation at C-1 or C-3 and the efficient chirality transfer from sulphur to C-2 through hydride reduction of the carbonyl. The only two reactions operating a chain elongation at C-2 of a β-keto-sulphoxide with high asymmetric induction reported so far show limited versatility[6].




**1** **2**

**Scheme 1**

The chain elongation problem at C-2 for chiron **1** can be solved by the asymmetric creation of a quaternary stereocentre through the synthesis of a highly versatile oxirane ring[7] derivative **2** that can subsequently give rise to differently functionalized homochiral tertiary alcohols through oxirane ring opening by nucleophiles (Scheme 1). We have recently described[8] that a methylene group can be transferred from diazomethane to **1** to give the oxirane **2** in high yields and with high diastereoselection and that selective ring opening by several nucleophilic species can be performed.

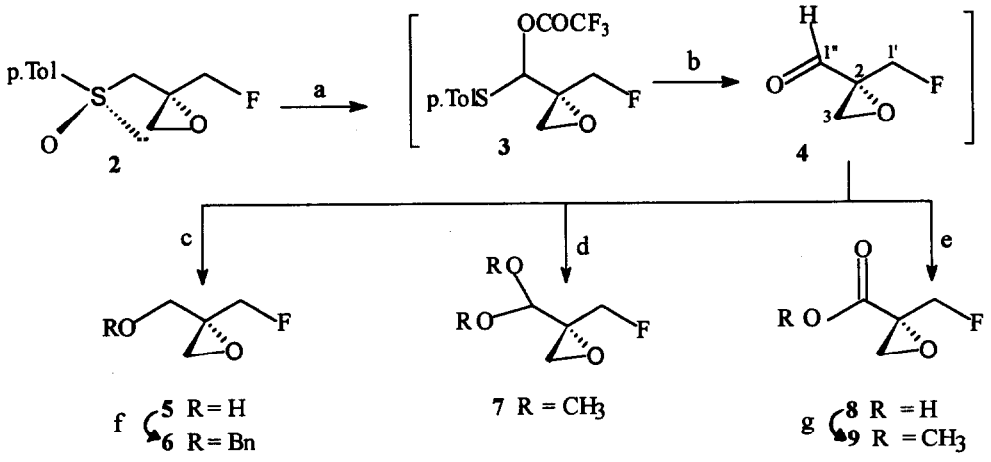
In the present paper we report on oxirane ring-consistent elaborations of the methylene bearing the sulphinyl chiral auxiliary group and on some selected ring opening reactions performed on the sulphur-free derivatives by nitrogen-centered nucleophilic species. The synthesis of 3-amino-2-(fluoromethyl)propan-1,2-diol[9] (**14**) and 3-amino-2-(fluoromethyl)-2-hydroxypropanoic acid[10] (**19**) are described.

## Results and Discussion

Sulphur-free fluorinated oxiranes can be prepared through the Pummerer rearrangement[11] that allows the replacement of the chiral auxiliary sulphinyl group with oxygenated functionalities. Fluorinated α,β-epoxy aldehyde **4**, α,β-epoxy alcohol **5** or ether **6**, α,β-epoxy acetale **7**, α,β-epoxy acid **8** and ester **9** were so prepared as shown in Scheme 2 and the oxirane ring showed to be unaffected by the reaction conditions.

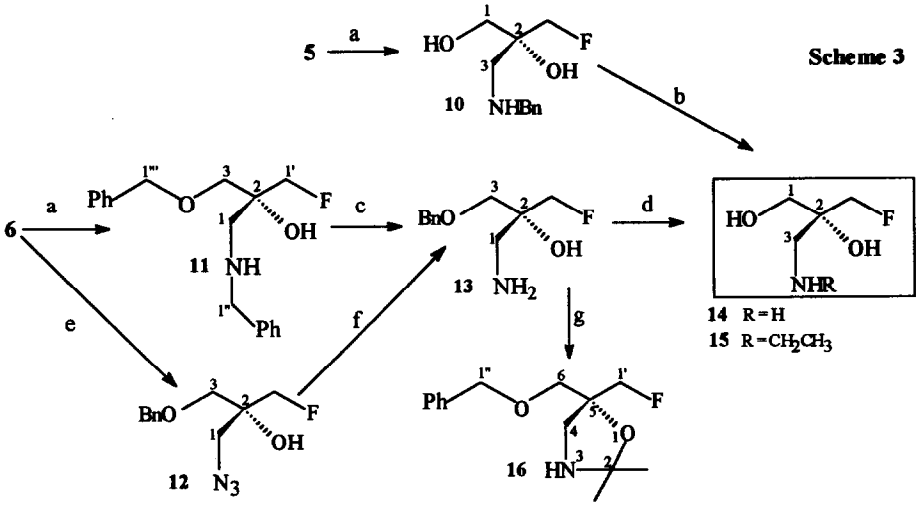
The sulphiyl oxirane **2** was treated with trifluoroacetic anhydride[12] to give the labile intermediate **3** that was cleaved to the free aldehyde **4** by using mercury (II) chloride. Although the isolation and the $^{1}H$ and $^{19}F$ NMR characterizations of the very reactive intermediate aldehyde **4** were performed (see Experimental), it was always submitted *in situ* to the following steps without purification. The reduction of **4** with sodium boro hydride allowed the obtainement of a hydroxyl derivative that could be isolated both as the free epoxy alcohol **5** and as the corresponding benzylether **6**[13] (see Experimental). Treatment of **4** with methanol gave the dimethyl acetal **7**, while treatment of the same intermediate **4** with sodium chlorite as oxidizing agent[14] gave the carboxylic derivative **8**.

**Scheme 2**




**Reagents and Conditions:** a) $(CF_3CO)_2O$, *sym.*-collydine, $CH_3CN$, -20°C; b) $HgCl_2$, $K_2CO_3$, $CH_3CN$, 0°C; c) $NaBH_4$, $(CH_3)_2CHOH$, $CH_3CN$, 0°C; d) $CH_3OH$, 0°C; e) $NaClO_2$, $KH_2PO_4$, $(CH_3)_2C{=}CH_2$, $(CH_3)_3COH$, $H_2O$, 0°C; f) NaH, BnBr, THF, 0°C; g) $CH_2N_2$, ethyl ether, 0°C.

Oxirane ring opening with some selected nitrogen nucleophylic species was performed: (2*S*)-1-amino-3-benzyloxy-2-fluoromethyl-propan-2-ol (**13**) was obtained through nucleophilic opening reaction of the oxirane mojety of **6** performed by sodium azide to give **12** and subsequent reduction of the azido group by lithium aluminium hydride. The nucleophilic ring opening reaction performed by benzylamine gave **11** and the following controlled reductive cleavage (hydrogen atmosphere) catalysed by palladium (0) afforded the labile *O*-benzyl protected derivative **13**. It could be better isolated as the stable acetonide derivative **16** by simple treatment with dimethylketone. A longer action of hydrogen on the *O*-benzyl derivative **13** allowed the cleavage of the other benzylic group giving (2*S*)-3-amino-2-fluoromethyl-propan-1,2-diol (**14**) in 65% yield. The same compound was obtainable from reductive cleavage of the *N*-benzyl derivative **10** which in turn derived from nucleophilic attack on the oxirane ring of the (2*S*)-2-fluoromethyl-2-hydroxymethyl oxirane (**5**) (Scheme 3).



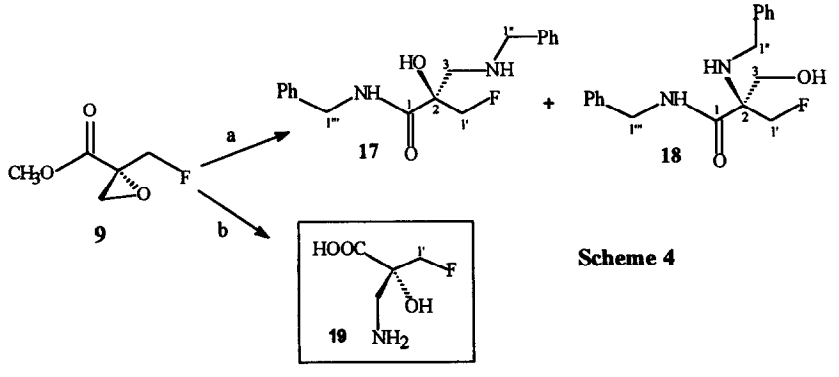
Scheme 3

**Reagents and Conditions:** a) $C_6H_5CH_2NH_2$, r.t.; b) i) R = H: Pd, $H_2$, dioxane , r.t., 3 hours; ii) R = $CH_2CH_3$: Pd, $H_2$, ethanol , r.t., 1 hour; c) Pd, $H_2$, dioxane , r.t., 3 hours; d) i) R = H: Pd, $H_2$, dioxane , r.t., 10 hours; ii) R = $CH_2CH_3$: Pd, $H_2$, ethanol , r.t., 8 hours; e) $NaN_3$, $NH_4Cl$, THF, r.t; f) $LiAlH_4$, ethyl ether, 0°C; g) acetone, r.t.

When reductive debenzylation reaction was run in dioxane as solvent, β,γ-dihydroxy-β-fluoromethyl amine **14** was selectively obtained from both the *N*-benzyl and *O*-benzyl derivatives **10** and **13**. On the other hand, when the reaction was run under the same conditions, but using ethanol as solvent, an approximately one to one mixture of **14** and of the corresponding *N*-ethyl derivative **15** was obtained from **13** in eight hours at room temperature[15].

By reacting the α,β-epoxy carboxylic acid **8** with diazomethane, the corresponding α,β-epoxy methyl ester **9** was obtained[16] which, upon treatment with aqueous ammonium hydroxide and ammonium carbonate,[17] selectively gave α-fluoromethyl-β-amino acid **19** in 60% yield.

The action of benzylamine on **9** afforded a two to one mixture of α-hydroxy-β-amino and β-hydroxy-α-amino benzylamides **17** and **18**, respectively. The obtainement of amides instead of esters following the above mentioned procedure is a very well known process[18] but only the synthesis of α-hydroxy-β-amino amides has been described.



Scheme 4

**Reagents and Conditions**: a) $C_6H_5CH_2NH_2$, THF, r.t.; b) $(NH_4)_2CO_3$, $NH_4OH$, 55°C.

## Structural Assignments

The $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra of compounds **4-19** (Tables 1 and 2, and Experimental) are in agreement with the proposed structures. In particular, the values of 4.6-6.0 Hz observed for the geminal coupling constants of the C-2 protons are diagnostic for the presence of oxirane rings in compounds **4-9**, while the values of 11.3-12.5 Hz observed for the corresponding methylene protons in the remaining products **10-19** imply the opening of the three-membered ring.

Finally, the fact that the above cited methylene protons resonate between 2.74 and 3.19 ppm in compounds **10**, **11**, **13**, **17** and **19** and at 3.73 and 3.83 ppm in compound **18** well accounts for the presence of $CH_2$-N and $CH_2$-O groupings, respectively, thus confirming the formation of β-hydroxy-α-amino- and α-amino-β-hydroxy-derivatives.

## Experimental

***General Details.*** $^{1}H$ and $^{19}F$ NMR spectra were recorded on a Brüker AC 250L spectrometer; chemical shifts are in ppm (δ), tetramethylsilane was used as internal standard ($\delta_H$ and $\delta_C$ = 0.00) for $^{1}H$ and $^{13}C$ nuclei, while $C_6F_6$ was used as internal standard ($\delta_F$ = -162.90) for $^{19}F$ nuclei. $[\alpha]_D$ Values were obtained on a Jasco DIP-181 polarimeter. Melting points are uncorrected and were obtained on a capillary apparatus. Mass spectra were performed with a Hitachi Perkin-Elmer RMU spectrometer. Infrared spectra were recorded on a Perkin-Elmer 177 Grating Infrared Spectrophotometer. Flash chromatographies were performed with silica gel 60 (60-200 μm, Merck) and preparative TLC separations were performed on Merck $60F_{254}$ precoated plates. All reactions were monitored by TLC performed on analytical Merck silica gel $60F_{254}$ TLC plates. Combustion microanalyses were performed by Redox SNC, Cologno M. (Milano). Commercially available reagent-grade solvents and reagents were employed without purification. The synthesis of compound **2** was already described[9].

***Pummerer Rearrangement.*** To a solution of 2-(fluoromethyl)-2-[(4-methylphenylsulphinyl)methyl] oxirane (**2**) (10.0 mmol) and 2,4,6-trimethylpyridine (22.0 mmol) in acetonitrile (40 ml) at -20°C a solution of trifluoroacetic anhydride (20.0 mmol) in the same solvent (10 ml) was added dropwise. The mixture was stirred at room temperature, then pH was adjusted to 7 by adding some solid $K_2CO_3$ and a solution of mercury (II) chloride (30.0 mmol) in acetonitrile (10 ml) was added dropwise at 0°C. White HgS precipitated immediately and, after one hour at room temperature, it was filtered and the clear solution was divided in two amounts: the first one was carefully concentrated and purified by flash chromatography (n-penthane/ethyl ether 1:1) in order to isolate the intermediate aldehyde **4**; EI/MS (70 eV): 104 ($M^+$), 86 ($M^+$-$H_2O$), 75 ($M^+$-$HOC^+$); IR (neat): ν C-O(epox) 870, 920, νC-F 1010, νC=O 1730 $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$) δ: 47.55 (dt, $^{3}J_{C,F}$ = 7.5 Hz, C-3), 59.70 (d, $^{2}J_{C,F}$ = 20.5 Hz, C-2), 79.10 (dt, $^{1}J_{C,F}$ = 174 Hz, C-1'), and 196.42 (d, $^{3}J_{C,F}$ = 4 Hz,C-1"), and the second one was utilized for the following steps.

***Synthesis of (2R)-2-benzyloxymethyl-2-fluoromethyl oxirane (6).*** The solution from above was collected in a flask, cooled to -10°C and $NaBH_4$ (15.0 mmol) in acetonitrile (10 ml) and isobutylalcohol (0.1 ml) were added dropwise. Grey Hg(0) precipitated immediately and was filtered. An amount of the clear solution was evaporated and purified by flash chromatography (n-pentane/ethyl ether 15:85) to give (2*S*)-2-fluoromethyl-2-hydroxymethyl oxirane (**5**) in 70% yield: $[\alpha]_D^{20}$ - 24.6 (c 1.0, $CHCl_3$), $[\alpha]_{365}$ - 89.0 (c 1.0, $CHCl_3$); EI/MS (70 eV): 106 ($M^+$), 76 ($M^+$-$CH_2O$), 75 ($M^+$-$HOH_2C^+$), 31 ($HOH_2C^+$); IR (neat): νC-O(epox) 810, 880, 910, νC-F 1010, νC-O(alcohol) 1040, νO-H 3400 $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$) δ: 48.34 (dt, $^{3}J_{C,F}$ = 6 Hz, C-3), 58.14 (d, $^{2}J_{C,F}$ = 22 Hz, C-2), 60.89 (t, C-1"), and 83.17 (dt, $^{1}J_{C,F}$ = 171.5 Hz,C-1'). *Anal.* Calcd for $C_4H_7O_2F$: C, 45.28; H, 6.65. Found: C, 45.20; H, 6.67. To the remaining clear solution, benzyl bromide (10 ml) was added and the mixture was dropped into a flask containing NaH (15.0 mmol), washed from mineral oil with n-hexane, suspended in THF (10 ml). After total gas evolution, the reaction mixture was poured in an

ice/water bath, the organic layers were extracted in ethyl ether (3 x 10 ml) and dried over anhydrous sodium sulphate. The crude, concentrated under reduced pressure, was purified by flash chromatography (n-penthane/ethyl ether 7:3) to give the oxirane **6** in 60% yield from **2** as a yellowish oil: $[\alpha]_D^{20}$ + 8.8 (c 1.3, $CHCl_3$); EI/MS (70eV): 196 ($M^+$), 119 ($M^+$-$H_5C_6^+$), 107 ($C_6H_5CH_2O^+$), 105 ($M^+$-$C_6H_5CH_2^+$), 91 ($C_6H_5CH_2^+$), 89 ($M^+$-$C_6H_5CH_2O^+$); IR (neat): νC-O(epox) 750, νC-F 1010, νC-H(arom.) 1500, 3020, $\nu CH_2$ 1450, νC-O(ether) 1100 $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$) δ: 48.50 (dt, $^3J_{C,F}$ = 6 Hz, C-3), 56.90 (d, $^2J_{C,F}$ = 22 Hz, C-2), 69.36 (t, C-1"), 73.58 (t, C-1'"), 82.91 (dt, $^1J_{C,F}$ = 172.5 Hz,C-1'), 127.71 (d), 127.88 (d), 128.48 (d), and 137.62 (s) (ArC). *Anal.* Calcd for $C_{11}H_{13}O_2F$: C, 67.33; H, 6.68. Found: C, 67.28; H, 6.65.

***Synthesis of (2R)-2,2-dimethoxymethyl-2-fluoromethyl oxirane (7).*** Mercury(II) chloride (30.0 mmol) was dissolved in methanol (10 ml) and added dropwise to the acetonitrilic solution of **3**. After careful evaporation of the solvent, the crude was purified by flash chromatography (n-penthane/ethyl ether 4:1) to give (2*R*)-2-dimethoxymethyl-2-fluoromethyl oxirane **7** in 60% yield: $[\alpha]_D^{20}$ - 1.5 (c 0.7, $CHCl_3$), $[\alpha]_{365}$ - 2.4 (c 0.7, $CHCl_3$); EI/MS (70 eV): 150 ($M^+$), 119 ($M^+$-$CH_3O^+$), 75 ($M^+$-$C_3H_7O_2^+$). *Anal.* Calcd for $C_6H_{11}O_3F$: C, 47.99; H, 7.38. Found: C, 48.06; H, 7.36.

***Synthesis of (2R)-2-carboxy-2-fluoromethyl oxirane (8).*** Mercury(II) chloride (30.0 mmol) was dissolved in acetonitrile ( 10 ml) and after the same procedure described for **4**, the yellow solution was cooled at -10°C and a solution of $NaClO_2$ (60.0 mmol) and $KH_2PO_4$ (60.0 mmol) in water (40 ml) was added dropwise. An exothermic effect was immediately observed, the light yellow solution was kept at 0°C at pH 2-3 for half an hour, then the solvent was evaporated under reduced pressure, water (10 ml) was added and the organic layers were extracted with ethyl ether (3 x 15 ml), dried over anhydrous sodium sulphate and concentrated in vacuum. The crude was purified by flash chromatography (chloroform/ethyl acetate/acetic acid 1.0:1.0:0.1) to give the carboxylic acid derivative **8** in 94% yield: $[\alpha]_D^{20}$ - 9.1 (c 0.4, $CHCl_3$); EI/MS (70 eV): 120 ($M^+$), 86 ($M^+$-$CH_3F$), 84 ($M^+$-$2H_2O$), 76 ($M^+$-$CO_2$); IR (neat): νC-O(epox) 910, 940, νC-F 1020, νC=O 1740, νO-H 3450 $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$) δ: 49.65 (dt, $^3J_{C,F}$ = 6 Hz, C-3), 55.05 (d, $^2J_{C,F}$ = 22 Hz, C-2), 80.96 (dt, $^1J_{C,F}$ = 174.5 Hz,C-1'), and 173.20 (d, $^3J_{C,F}$ = 3.5 Hz, C-1"). *Anal.* Calcd for $C_4H_5O_3F$: C, 40.01; H, 4.20. Found: C, 40.08; H, 4.15.

Table 1. $^1H$ and $^{19}F$ NMR data[a,b] in $CDCl_3$ for compounds **4-9**.

| Atom | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|
| 3a | 3.28 | 2.98 | 2.85 | 2.95 | 3.21 | 3.18 |
| 3b | 3.19 | 2.85 | 2.84 | 2.82 | 3.12 | 3.04 |
| 1'a | 4.88 | 4.58 | 4.60 | 4.73 | 4.98 | 4.93 |
| 1'b | 4.74 | 4.54 | 4.53 | 4.53 | 4.63 | 4.67 |
| 1"a | 9.00 | 3.93 | 3.70 | 4.46 | | |
| 1"b | | 3.82 | 3.66 | | | |
| OR-1" | | 6.79 | 4.61<br>4.56 | 3.46<br>3.45 | 7.50 | 3.83 |
| F | - 235.83 | - 231.77 | - 231.99 | - 235.74 | - 232.11 | - 231.85 |

[a]The aromatic protons in compound **6** resonate between 7.2 and 7.5 ppm.
[b]The coupling constants observed between the protons of the $H_2$-3, $H_2$-1' and $H_2$-1" methylene groups range between 4.6 and 6.0, 10.4 and 10.8 and 11.1 and 12.5 Hz, respectively, while those observed between F-1' and $H_2$-1' range between 45.3 and 47.5.

***Synthesis of (2R)-2-carboxymethyl-2-fluoromethyl oxirane (9).*** The derivative **8** (10.0 mmol) was dissolved in methanol (10 ml) and an ethereal solution (*c.a.* 0.5 M) of diazomethane was added dropwise at 0°C. After the starting material had completely disappeared (TLC monitored), acetic acid was added dropwise

in order to decompose the excess of $CH_2N_2$. The solvent was evaporated under reduced pressure and the crude was purified by flash chromatography (n-penthane/ethyl ether 2:3) to give the methyl ester **9** in 90% yield: $[\alpha]_D^{20}$ + 4.1 (c 0.6, $CHCl_3$), $[\alpha]_{365}$ + 23.6 (c 0.6, $CHCl_3$); EI/MS (70 eV): 134 ($M^+$), 104 ($M^+$-HCHO), 75 ($M^+$-$CH_3OOC^+$); IR (neat): νC-O(epox) 760, νC-F 1030, νC=O 1730 $cm^{-1}$. *Anal.* Calcd for $C_5H_7O_3F$: C, 44.78; H, 5.26. Found: C, 44.86; H, 5.32.

***Oxirane Ring Opening by Nitrogen Nucleophiles.*** *a) Benzylamine. General Procedure.* To a solution of oxirane (10.0 mmol) in anhydrous THF (10 ml) neat benzylamine (15.0 mmol) was added at room temperature and the reaction was stirred for a period of time depending on the substrate. The solvent was evaporated under reduced pressure and the crude was purified by flash chromatography .

From hydroxymethyl oxirane **5** after 24 hours the chromatographic purification in ethyl acetate gave (2*R*)-3-*N*-benzylamino-2-fluoromethyl-propan-1,2-diol (**10**) in 80% yield: $[\alpha]_D^{20}$ + 7.9 (c 0.8, $CHCl_3$); $[\alpha]_{365}$ + 25.7 (c 0.8, $CHCl_3$); EI/MS (70 eV): 213 ($M^+$), 183 ($M^+$-HCHO), 122 ($M^+$-$C_6H_5CH_2^+$); $^{13}C$ NMR ($CDCl_3$) δ: 51.81 (dt, $^3J_{C,F}$ = 3.5 Hz, C-3), 54.40 (t, C-1"), 65.97 (dt, $^3J_{C,F}$ = 5.5 Hz, C-1), 72.08 (d, $^2J_{C,F}$ = 18.5 Hz, C-2), 85.48 (dt, $^1J_{C,F}$ = 173 Hz, C-1'), 127.54 (d), 128.24 (d), 128.71 (d), and 139.15 (s) (ArC). *Anal.* Calcd for $C_{11}H_{16}NO_2F$: C, 61.95; H, 7.56; N, 6.57. Found: C, 61.98; H, 7.52; N, 6.50.

From oxirane **6** in 48 hours and after purification (n-hexane/ethyl acetate 1:1) (2*R*)-1-*N*-benzylamino-2-fluoromethyl-3-benzyloxy-propan-2-ol (**11**) was obtained in 85% yield: $[\alpha]_D^{20}$ - 8.3 (c 0.8, $CHCl_3$); m.p. 55-57°C (ethyl ether/n-penthane 1:1); EI/MS (70 eV): 303 ($M^+$), 212 ($M^+$-$C_6H_5CH_2^+$), 196 ($M^+$-$C_6H_5CH_2O^+$), 121 ($M^+$-$C_{14}H_{14}^+$); $^{13}C$ NMR ($CDCl_3$) δ: 50.93 (dt, $^3J_{C,F}$ = 3.5 Hz, C-1), 54.31 (t, C-1"), 71.87 (dt, $^3J_{C,F}$ = 5 Hz, C-3), 72.18 (d, $^2J_{C,F}$ = 18.5 Hz, C-2), 73.61 (t, C-1'"), 85.14 (dt, $^1J_{C,F}$ = 1733 Hz, C-1'), 127.15 (d), 127.67 (d), 127.80 (d), 128.03 (d), 128.45 (d), 128.47 (d), 137.83 (s) and 139.89 (s) (ArC). *Anal.* Calcd for: $C_{18}H_{22}NO_2F$: C, 71.26; H, 7.31; N, 4.62. Found: C, 71.13; H, 7.30; N, 4.68.

From carbomethoxy oxirane **9** in three days the chromatographic purification with n-hexane/ethyl acetate 3:7 gave: (2*R*)-3-benzylamino-2-fluoromethyl-2-hydroxy-*N*-benzyl-propionamide (**17**) in 28% yield: $R_F$ 0.35; $[\alpha]_D^{20}$ - 7.1 (c 1.2, $CHCl_3$), $[\alpha]_{365}$ - 32.8 (c 0.9, $CHCl_3$); m.p. 65-67°C (isopropylether); EI/MS (70 eV): 316 ($M^+$), 225 ($M^+$-$C_6H_5CH_2^+$); IR (KBr): νC-F 1100, νC-N 1280, δNH 1540, νC=O 1650, νNH(amine) 3300, ν NH(amide) 3420 $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$) δ: 43.34 (t, C-1'"), 50.80 (dt, $^3J_{C,F}$ = 6.5 Hz, C-3), 53.85 (t, C-1"), 75.54 (d, $^2J_{C,F}$ = 18.5 Hz, C-2), 86.32 (dt, $^1J_{C,F}$ = 176.5 Hz, C-1'), 127.42 (d), 127.56 (d), 128.07 (d), 128.60 (d), 128.71 (d), 137.74 (s), 139.08 (s) (ArC), and 172.07 (d, $^3J_{C,F}$ = 5.5 Hz, C-1). *Anal.* Calcd for $C_{18}H_{21}N_2O_2F$: C, 68.34; H, 6.69; N, 8.85: Found: C, 68.40; H, 6.60; N, 8.80 and (2*R*)-2-benzylamino-2-fluoromethyl-3-hydroxy-*N*-benzyl-propionamide (**18**) in 15% yield: $R_F$ 0.25; $[\alpha]_D^{20}$ - 18.9 (c 0.5, $CHCl_3$); EI/MS (70 eV): 316 ($M^+$), 285 ($M^+$-$CH_3O^+$), 225 ($M^+$-$C_6H_5CH_2^+$). *Anal.* Calcd for $C_{18}H_{21}N_2O_2F$: C, 68.34; H, 6.69; N, 8.85: Found: C, 68.25; H, 6.70; N, 8.82.

*b) $NaN_3$.* To a solution of **6** (10.0 mmol) in ethanol (10 ml) an aqueous (5 ml) solution of $NaN_3$ (12.0 mmol) was added at room temperature. The solution was kept under stirring for 48 hours, ethanol was evaporated and organic layers were extracted from ethyl acetate (3 x 10 ml). The crude was purified by flash chromatography (n-hexane/ethyl ether 7:3) to give (2*R*)-1-azido-2-benzyloxy-3-fluoromethyl-propan-2-ol (**12**) in 76% yield: $[\alpha]_D^{20}$ + 5.4 (c 1.3, $CHCl_3$); EI/MS (70 eV): 239 ($M^+$), 148 ($M^+$-$C_6H_5CH_2^+$), 132 ($M^+$-$C_6H_5CH_2O^+$); *Anal.* Calcd for $C_{11}H_{14}N_3O_2F$: C, 55.22; H, 5.90; N, 17.56: Found: C, 55.20; H, 5.86; N, 17.50.

*c)Ammonium Hydroxide/Ammonium Carbonate.* To a solution of ammonium carbonate (30.0 mmol) and water (0.8 ml) heated at 55°C, a 6N solution of ammonium hydroxide (1.6 ml) was added. The mixture was stirred at 40°C for 30 min., then the carbomethoxy oxirane **9** (6.0 mmol) was added and stirred at 45°C for 3 days and at 55 °C for 12 hours. The solution was concentrated under *vacuum* and the residue was crystallized from ethanol/water to give (2*R*)-3-amino-2-fluoromethyl-2-hydroxy-propionic acid (**19**) in 60% yield: $[\alpha]_D^{20}$ - 3.4 (c 2.0, $H_2O$); $[\alpha]_{365}$ - 9.6 (c 2.0, $H_2O$); m.p. 183-184°C (decarb.) (water/ethanol); EI/MS (70 eV): 137 ($M^+$), 107 ($M^+$-$NH_2CH_2^+$), 93 ($M^+$-$CO_2$); $^1H$ NMR (DMSO-$d_6$) δ: 2.71 and 2.81 (2H, brd, J = 13.0 Hz, $H_2$-3), 4.38 (1H, dd, J = 48.1 and 9.3 Hz, H-1'a), 4.52 (1H, dd, J = 46.9 and 9.3 Hz, H-1'b), and 6.50 (3H, broad

signal, OH-1, OH-2, and $NH_2$-3); $^{19}F$ NMR (DMSO-$d_6$) δ: -227.27 (1F, brdd, J = 48.1 and 46.9 Hz, F-1'); $^{13}C$ NMR (DMSO-$d_6$) δ: 42.80 (dt, $^3J_{C,F}$ = 6.5 Hz, C-3), 75.41 (d, $^2J_{C,F}$ = 18.5 Hz, C-2), 86.07 (dt, $^1J_{C,F}$ = 174 Hz, C-1'), and 174.30 (d, $^3J_{C,F}$ = 4 Hz, C-1). *Anal.* Calcd for $C_4H_8NO_3F$: C, 35.04; H, 5.88; N, 10.21. Found: C, 35.00; H, 5.96; N, 10.10. The same procedure, using ammonium acetate (30.0 mmol) instead of ammonium carbonate, gave identical results.

***Synthesis of (2R)-3-amino-2-fluoromethyl-3-benzyloxy-propan-2-ol (13).*** A solution of the azido derivative **12** (10.0 mmol) in anhydrous ethyl ether (10 ml) was treated with solid $LiAlH_4$ (12.0 mmol): the reaction took place immediately. The reaction mixture was poured into an ice/water bath, the organic layers were extracted with ethyl acetate (3 x 10 ml), dried over anhydrous sodium sulphate and concentrated to dryness. The crude was purified by flash chromatography (n-hexane/ethyl acetate 3:7) to give the amino benzyloxy derivative **13** in 85% yield: $R_F$ = 0.40; $[\alpha]_D^{20}$ - 5.6 (c 0.4, $CH_3OH$). The amino benzyloxy derivative **13** could be easier isolated as acetonide derivative **16** by simply adding dimethylketone at room temperature: $R_F$ = 0.30 in n-hexane/ethyl acetate 3 : 7; $[\alpha]_D^{20}$ - 5.8 (c 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ: 1.38 and 1.39 (6H, s, Me-2), 3.16 and 3.18 (2H, brd, *J* = 12.5 Hz, $H_2$-4), 3.42 (1H, dd, *J* = 9.5 and 2.6 Hz, H-6a), 3.48 (1H, dd, *J* = 9.5 and 1.7 Hz, H-6b), 3.75 (1H, br signal, H-3), 4.37 and 4.41 (2H, dd, *J* = 47.4 and 9.4 Hz, H-1'), 4.52 and 4.56 (2H, d, *J* = 12.0 Hz, H-1"), and 7.2-7.5 (5H, m, ArH); $^{19}F$ NMR ($CDCl_3$) δ: - 231.30; $^{13}C$ NMR (DEPT; $CDCl_3$) δ: 27.29 and 27.36 (q, MeC), 50.72 (dt, $^3J_{C,F}$ = 2 Hz, C-4), 72.45 (dt, $^3J_{C,F}$ = 5 Hz, C-6), 73.61 (t, C-1"), 85.52 (dt, $^1J_{C,F}$ = 174.5 Hz, C-1'), 127.78 (d), 127.90 (d) and 128.48 (d) (ArC).

Table 2. $^1H$ and $^{19}F$ NMR data[a,b] in $CDCl_3$ for compounds **10-15**, **17** and **18**.

| Atom | 10 | 11 | 12 | 13 | 14 | 15 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|
| 1a | 3.62 | 2.78 | 3.42 | 3.08 | 3.62 | 3.68 | | |
| 1b | 3.62 | 2.74 | 3.42 | 3.08 | 3.62 | 3.64 | | |
| 3a | 2.86 | 3.50 | 3.52 | 3.51 | 2.93 | 2.91 | 3.19 | 3.85 |
| 3b | 2.76 | 3.46 | 3.49 | 3.51 | 2.85 | 2.79 | 2.77 | 3.73 |
| 1'a | 4.31 | 4.40 | 4.40 | 4.39 | 4.32 | 4.32 | 4.55 | 4.65 |
| 1'b | 4.27 | 4.36 | 4.39 | 4.39 | 4.30 | 4.28 | 4.44 | 4.55 |
| 1"a | 3.83 | 3.80 | | | | 2.73 | 3.76 | 3.83 |
| 1"b | 3.81 | 3.80 | | | | 2.73 | 3.72 | 3.83 |
| 1"'a | | 4.54 | 4.52 | 4.53 | | | 4.44 | 4.46 |
| 1"'b | | 4.54 | 4.52 | 4.53 | | | 4.44 | 4.46 |
| NHR | 2.25 | 2.40 | | 3.65 | 2.05 | 2.40 | 7.56, 2.50 | 7.30, 2.75 |
| OH | 2.25 | 2.40 | 2.63 | 3.65 | 2.05 | 2.40 | 2.50 | 2.75 |
| F | - 233.28 | - 232.70 | - 233.65 | - 232.86 | - 233.72 | - 233.07 | - 231.98 | - 234.53 |

[a]The aromatic protons resonate between 7.1 and 7.5 ppm and the methyl protons in compound **15** resonate at 1.14 ppm.
[b]The coupling constants observed between the protons of the $CH_2$-N, $CH_2$-O and $CH_2$-F methylene groups range between 12.4 and 13.1, 9.4 and 11.3 and 9.3 and 9.5 Hz, respectively, while those observed between F-1' and $H_2$-1' range between 46.7 and 47.4 Hz.

***Synthesis of (2R)-1-amino-2-fluoromethyl-propan-1,2-diol (14).*** A stirred slurry of **11** (10.0 mmol) in dioxane (10 ml) and of a catalytic amount of Pd/C (10%) was reacted with hydrogen at room temperature. Stirring was continued for 3 hours, a small portion of the reacting mixture was dried under *vacuum*, added with dimethylketone to obtain a product whose $^1H$ and $^{19}F$ NMR spectra were identical to those of the above described 5-benzyloxymethyl-2,2-dimethyl-5-fluoromethyl-1,3-oxazolidine (**16**). The remaining of the reacting mixture was stirred for additional 10 hours, then the solvent was removed under reduced pressure and the crude was submitted to flash chromatographic purification (ethyl ether/methanol 1 : 4) to give (2*R*)-**14** in 65% yield: $R_F$ = 0.40; $[\alpha]_D^{20}$ + 2.3 (c 0.4, $CHCl_3$); $[\alpha]_{365}$ + 5.5 (c 0.4, $CHCl_3$); $[\alpha]_D^{20}$ + 2.1 (c 0.5, ethanol);

$[\alpha]_{365}$ + 13.7 (c 0.5, ethanol); EI/MS (70 eV): 123 ($M^+$), 106 ($M^+$-$NH_3$), 105 ($M^+$-$H_2O$), 92 ($M^+$-$CH_3O^+$). *Anal.* Calcd for $C_4H_{10}NO_2F$: C, 39.02; H, 8.19; N, 11.37. Found: C,39.08; H, 8.13; N, 11.39. The same reaction of debenzylation, carried on in ethanol like solvent, led in 8 hours to an about 1 : 1 mixture of (2*R*)-**14** and (2*R*)-1-ethylamino-2-fluoromethyl-propan-1,2-diol (**15**) in 60% overall yield. The latter compound was purified by flash chromatography in the same eluent ($R_F$ = 0.35): $[\alpha]_D^{20}$ - 2.6 (c 0.6, ethanol).

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