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ASYMMETRIC EPOXIDATION OF FLUORINATED ALLYLIC ALCOHOLS

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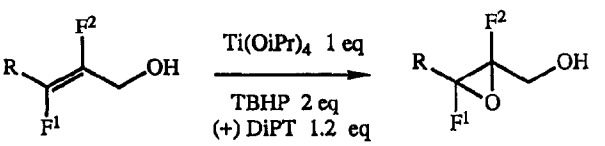
Abstract - The asymmetric epoxidation of an α, β-difluoro primary allylic alcohol, and of two α-fluoro secondary allylic alcohols follows the pattern known with non fluorinated analogs. The fluoro epoxides thus formed can be transformed into chiral α-ketols and into an α-fluoroacid.

The selective substitution of a hydrogen atom by a fluorine atom is used extensively for the study of enzymatic processes, and the need for chiral fluorinated substrates is increasing. We have already used the Sharpless method[1] to prepare fluorinated epoxides[2] from the corresponding allylic alcohols, which were prepared according to Dubuffet et al[3].
We report here our first results concerning the enantioselective epoxidation of a primary α,β-difluoro, and of two secondary α-fluoro allylic alcohols.

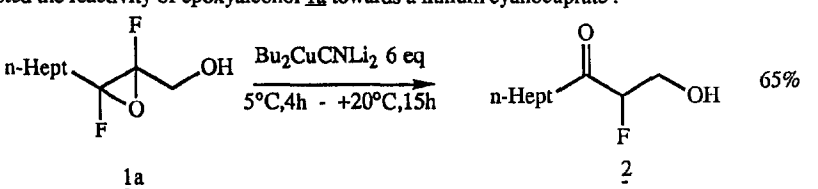
α,β-difluoro primary allylic alcohol.

By using slightly modified conditions of ref[4] we could isolate the first chiral fluoroepoxyalcohol 1a with 80% e.e.



1a R= n-Hept (81%; e.e.=80%)

This result was obtained when a stoichiometric amount of titanium tetraisopropoxide was used at -38°C for 72h. The observed e.e. is slightly inferior to that obtained in the hydrocarbon series (H for F^1, F^2) although the temperature was lowered purposedly. With a catalytic amount (5%) of the titanium alkoxide, in the presence of molecular sieves[4] the e.e. drops to 10% (chemical yield 76%). When R = Ph, the product 1b is particularly unstable and an evaluation of its e.e. could not be made.
We have tested the reactivity of epoxyalcohol 1a towards a lithium cyanocuprate :

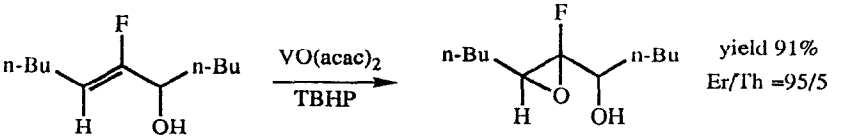


1a 2

However, the overall process is a reduction, which we interpret by way of an intermediate Cu^{III} complex[5], so that 2 is totally racemized. (Nevertheless, this reaction can be useful for the preparation of 3-keto-2-fluoroalkan-1-ols of difficult access)[6]. The poor reactivity of 1a, towards several electrophiles tested, led us to study the case of monofluorinated analogs.

Secondary α-fluoroallylic alcohols.

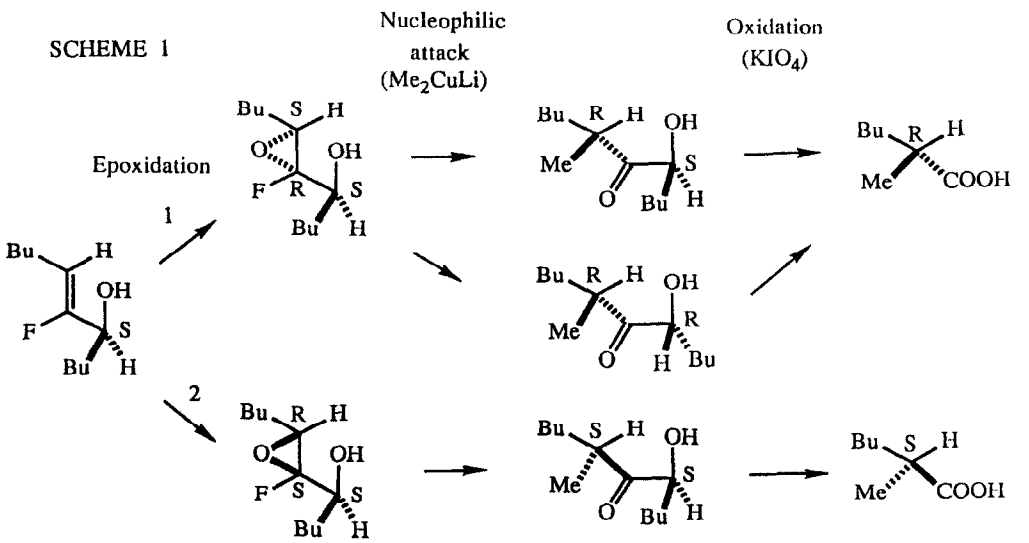
We have shown previously[2] that the epoxidation of these alcohols by tertiobutylhydroperoxide (TBHP) in the presence of vanadylacetylacetonate or titanium tetraisopropoxide leads to a remarkable diastereoselection (as compared to what is generally observed when no fluorine atom is present[1]).



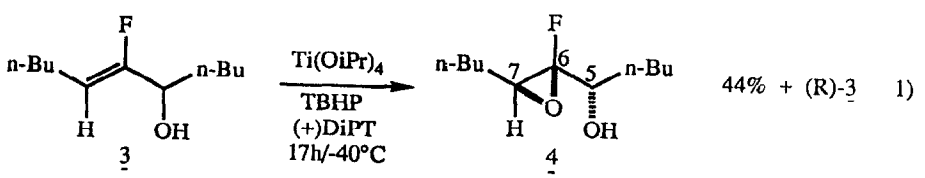
We have shown that the major isomer was the erythro one (for the sake of clarity, and for comparisons, we use the terms erythro-threo here considering F atoms analogous to H atoms).

When the same substrate is now submitted to a kinetic resolution according to Sharpless[4], a chiral epoxyalcohol is isolated. Its configuration is ascertained via two further reactions, namely (i) organocuprate attack, and (ii) oxidative cleavage of the ketol thus obtained (see scheme 1).

SCHEME 1



First step : epoxidation of 3.



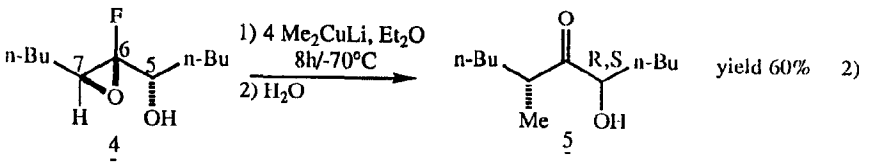
No evolution of the reaction is observed after 17 h at -40°C. The ratio of 3/4 is nearly 50/50 (from G.L.C.). The two products could not be separated, so that we submitted the mixture to ozonolysis, and obtained a 44% isolated yield of pure 4 (from 3). 4 is shown to be the erythro isomer by comparison of its ^{19}F NMR spectrum (δF = -94.9 ppm/Ph-CF_3) to those of authentic samples already prepared[2] (erythro : same value, and threo δ_F = -93.8 ppm). No trace of the latter is discernible in the spectrum of 4.

Since the following steps will lead (v.i) to a unique (R)-2-methyl hexanoic acid, one can conclude that, in the presence of (+) DIPT, the only attack occurs from "below" the plane of the alcohol (using Sharpless drawing ref 1) see way 1 on scheme 1, as it does with the non-fluorinated alcohol, and that C^5 and C^7 are both of (S) configuration in 4. At -20°C, the same reaction leads to a lower ratio : 81/19 of the erythro isomer.

Longer reaction times at -40°C do not promote the formation of threo 4. It thus appears that the relative rate of the reactions of (R) -3 and (S) - 3 are extremely different.

Second step : nucleophilic attack of 4

Lithium dimethyl cuprate was used for a typical S_N2 reaction of ring opening. We anticipated a regioselective attack on C^7 due to the driving force of a departing fluoride anion in that case (equation 2) :

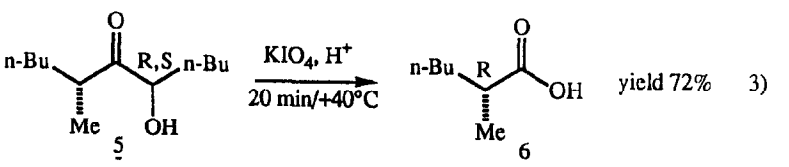


Indeed, after 8 h at -70°C, 5 was the major product obtained, with some unreacted epoxyalcohol 4, and a side product which we have not been able to identify. Longer reaction times, or a higher temperature led only to an increase of this by product.

When 4 (erythro/threo = 95/5) is formed from diastereoselective epoxidation of 3 (v.s.) and submitted to the same cuprate attack, the resulting alcohols 5' can be derivatized to the corresponding phosphites by 2-dimethylamino-2, 3, 3a, 4, 5, 6, 7, 7a octahydro-1,3 dimethyl-1H-1, 2, 3 benzodiazaphosphole (3aR, 7aR)[7] and compared to the corresponding phosphite of 5 obtained from enantioselection (eq 2). The ^{31}P NMR spectrum of 5' shows four signals : two major ones corresponding to the erythro isomers of 5 at δ = 147.33 and δ = 142.71 ppm (from H_3PO_4)., and two minor ones corresponding to the threo isomers at δ = 146.91 ppm and δ = 143.00 ppm. The ratio between the two types of signals is 85/15. The spectrum of the derivatized ketol obtained via eq 2 displays only two signals : a major one at 142.71 ppm corresponding to the erythroketol (S)-5 (R)-7 5 and a minor one at 146.91 ppm corresponding to the threo isomer (R)-5, (R)-7 5. Thus, contrary to our expectation, a single isomer is not obtained. We interpret this fact by a rapid enolisation of the ketol in the reaction medium, leading to an epimerisation of carbon 5. (A comparative study with Mosher's esters of 5 led to similar results, but the resolution was not as good as in the case of the phosphorous reagent).

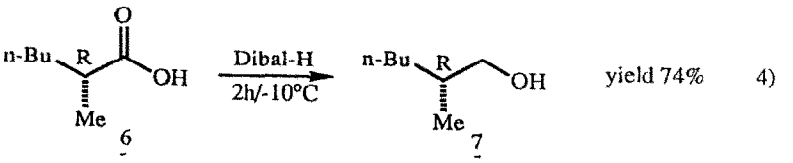
Third step : oxidative cleavage.

Notwithstanding this latter drawback, compound 5 is cleaved by potassium periodate in acidic medium (eq 3) :



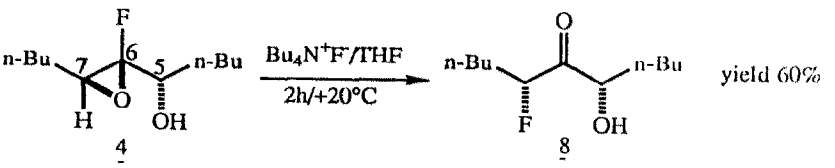
The absolute configuration of 6 is established by comparison of its specific rotation with known values[8-10] of the (R) acid : $[\alpha]_D^{27} = -17.4$ (neat). lit $[\alpha]_D^{20} = -16.3$[8], -13.1[9], -16.7[10]

The optical purity of 6 is measured after reduction to the primary alcohol 7 and comparison of the ^1H NMR spectrum of its Mosher's ester, with those of the racemic alcohol obtained from the commercially available racemic acid. Only one diastereoisomer is descernible (e.e. > 95% for 6) :



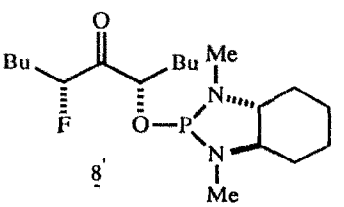
6 7 yield 74% 4)

Chiral fluoroepoxide 4 can be opened by fluoride anions : the reaction is fast at room temperature.



4 8 yield 60%

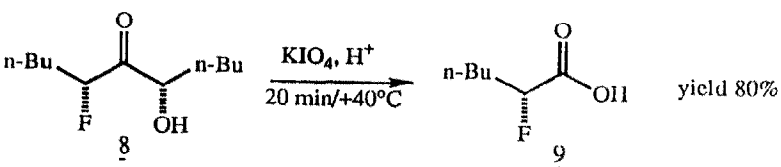
In this case, the low basicity of the nucleophile cannot promote any epimerisation of the formed fluoroketol 8, in contrast to the case where cuprates were used. The optical purity of 8 was determined in the same way as for ketol 5 : derivatization to phosphite 8'.



8'

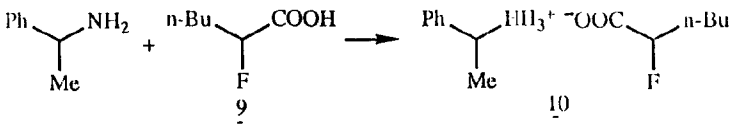
Whose ^{31}P NMR spectrum shows one single signal δ = 139.59 ppm (from H_3PO_4) corresponding to the erythro isomer (S) - 5 (R) - 7 8 (e.e > 95%) whereas the ketol prepared from diastereoselective epoxidation of 3 shows four signal : two major ones at δ = 144.77 ppm and δ = 139.59 ppm (from H_3PO_4), and two minor ones at δ = 146.36 ppm and δ = 138.11 ppm.

The cleavage of ketol 8 by potassium periodate generates α-fluoro hexanoic acid (R) - 9 $[\alpha]_D^{25} = +14.06$ (c = 1.7, $CHCl_3$). This configuration is attributed by analogy with the preceeding case :



8 9 yield 80%

The corresponding (S) acid has been recently disclosed $[\alpha]_D^{25} = -13.8°$ (c = 1.7, $CHCl_3$) and was prepared by enzyme catalyzed kinetic resolution[11]. The optical purity of 9 is determined by ^1H NMR of the ammonium salt 10 derived from 9 and (R) - (+) - α-methylbenzylamine. Only one diastereoisomer is observed (e.e > 95%).



In summary : a primary α,β-difluoroallylic alcohol can be epoxidized with good enantiomeric excess, but the epoxide is rather reluctant to nucleophilic attack, whereas a secondary α-fluoro allylic alcohol leads to an excellent kinetic resolution : the formed fluoroepoxide is easily opened by cuprates or fluoride anions. Several other nucleophiles are presently tested in this laboratory to take advantage of the bis electrophilic nature of these epoxides.

Experimental part.

NMR spectra were recorded using Jeol FX 90 and GSX 400 and Bruker AC 200 spectrometers ($CDCl_3$, TMS, δ ppm, J(Hz) for ^1H, ^{13}C and ^{31}P (H_3PO_4) or $CDCl_3$, $C_6H_5CF_3$, δ (ppm), J(Hz) for ^{19}F). IR spectra were recorded as films using a Perkin-Elmer 457 spectrometer (NaCl, cm^{-1}). Specific rotations were measured on a Perkin-Elmer 141 polarimeter. G.L.C. were recorded on a Carlo-Erba 4100 chromatograph (glass column 2 meters SE 30 10%) and on a Carlo-Erba 2150 spectrometer (capillary column 0V 101) connected to a Hitachi D 2000 integrator.

Preparation of epoxyalcohols 1a and 1b.

To a mixture of 0.1 g of molecular sieves 4Å and 4.56 g (19.5 mmol) of L-(+)-diisopropyltartrate in 20 ml of methylene chloride are successively added at -25°C : 3.98 g (14 mmol) of titanium tetraisopropoxide , then 2.52 g (28 mmol) of t-butylhydroperoxide. The mixture is then stirred for 30 min at this temperature. 14 mmol of 2,3-difluorodec-2-en-1-ol (2.69 g) for 1a, or of 1,2-difluoro-3-phenylpropen-1-ol (2,38 g) for 1b dissolved in 2 ml methylene chloride, are then added. After stirring for 72 h at -38°C, the mixture is hydrolyzed with a solution of 1 g $FeSO_4$ and 0.3 g tartaric acid in 30 ml of water. The biphasic system is stirred during 20 min then decanted. The aqueous phase is extracted (2 x 10 ml ether). The organic phases are mixed, and treated with 4 ml of a 30% sodium hydroxide solution (1 h at 0°C). The mixture is extracted again with ether, the organic phase is dried over sodium sulfate and the products are separated by flash chromatography (cyclohexane/ethyl acetate = 90/10). Thus we obtained 2.36 g of 1a (yield : 81%). The enantiomeric excess is determined according to Mosher[12], by integration of the CF_3 signals. The peaks corresponding to the two diastereoisomers are separated by $\Delta\delta = 0{,}030$ ppm.

2,3-epoxy-2,3-difluoro decan-1-ol trans 1a

Yield : 81% e.e. = 80%

^{19}F NMR : -73.7 (td, F^1), J(FH) = 19.1, J(FF) = 10.8 ; -83.5 (ddd, F^2), J(FH) = 18.0 and 14.5, J(FF) = 10.8

^1H NMR : 0.9 (t,3H) 1.2-1.45 (m,8H) 1.6 (q,2H) 1.95-2.15 (m,2H) 3.35 (s,OH) ; 4.0 (dd,H) J(HF) = J(HH) = 13.2 4.1 (dd,H) J(HF) = 14.5 J(HH) = 13.2

^{13}C NMR : 28.7 (dd,C_6H_{13}-$\underline{C}H_2$) J(CF) = 26.3 and 2.6 59.4 (dd,$\underline{C}H_2OH$) J(CF) = 30.4 and 2.2 96.7 (dd,$\underline{C}F$), J(CF) = 279.8 and 18.8 98.4 (dd,$\underline{C}F$) J(CF) = 277.7 and 18.9

2,3-epoxy-2,3-difluoro-3-phenyl propan-1-ol trans 1b

Yield (estimated) ≈ 80%, very unstable product.

^{19}F NMR: -73.5 (d,F^1) J(FF) = 9.2 ; - 83.1 (ddd,F^2) J(FH) = 17.2 and 14.5 J(FF) = 9.2

^1H NMR : 3.0 (s,$\underline{OH}$) 4.2(dd,H) J(HF) = 17.2 J(HH) = 13.3 ; 4.3 (dd,H), J(HF) = 14.5 J(HH) = 13.3 7.5 (m,5H)

^{13}C NMR : 59.9 (dd,$\underline{C}H_2OH$) J(CF) = 30.5 and 3.1 ; 96.89 (dd,$\underline{C}F$) J(CF) = 282.6 and 21.9 ; 96.92 (dd,$\underline{C}F$) J(CF) = 275.3 and 18.6

2-fluorodecan-1-ol-3-one 2

To dilithium dibutylcyanocuprate[13] (6 mmol) in 30 ml ether at -40°C are added 0.21 g (1 mmol) of epoxyalcohol 1a. The mixture is allowed to warm to -5°C and stirred for 4 h, then to + 20°C and stirred for 15 h. Hydrolysis is performed at 0°C by a solution of ammonium chloride/ammonia. The aqueous phase is extracted with ether. The organic phases are collected, washed with brine then dried over magnesium sulfate. The product (1,23 g, 65%) is purified by flash-chromatography (cyclohexane/ethyl acetate = 80/20). IR : 3420, 1740

^{19}F NMR : -135.9 (dtt) J(FH) = 48.9, 24.4 and 2.5

^1H NMR : 0.9 (t,3H) 1.3 (m,8H) 1.6 (q,2H) 2.6 (tdd,2H) J(HH) = 7.2 and 3.0 ; J(HF) = 2.5 4.0 (dd,2H) J(HF) = 24.4 J(HH) = 3.7 4.85 (dt,H) J(HF) = 48.9 J(HH) = 3.7

^{13}C NMR : 62.75 (d,$\underline{C}H_2OH$) J(CF) = 21.1 96.1 (d,$\underline{C}F$) J(CF) = 186.8 209.2 (d,$\underline{C}O$) J(CF) = 24.6

Anal. calcd for $C_{10}H_{19}FO_2$ (190,25) ; C, 63.13 ; H, 10.07. Found : C, 62.98 ; H, 9.94.

6,7-epoxy-6-fluoroundecan-5-ol 4.

Molecular sieves 3Å (0.85 g) and L-(+) diisopropyltartrate (0.53 g, 2.25 mmol) are added at +20°C, to a solution of alcohol 3 (2.82 g, 15 mmol) in 15 ml of methylenechloride. The mixture is cooled to -40°C, and titanium tetraisopropoxide (0.42 g, 1.5 mmol) is added. After stirring for 10 min, t-butylhydroperoxide (0..94 g, 10.5 mmol) are added. The mixture is stirred 17 h. at -40°C, then hydrolyzed and worked up as described for 1a and 1b. In a first step, the mixture 4 + 3 is isolated by flash chromatography (cyclohexane/ethylacetate = 80/20). This mixture is then disolved in methylene chloride (15 ml) and cooled to -70°C. A stream of ozone is introduced until the solution turns blue. The temperature is raised to -10°C : the mixture becomes colorless and is submitted to rotary evaporation. The product is purified by flash chromatography (cyclohexane/ethylacetate : 80/20) 1,35 g of 4 are thus isolated (yield 44%). 4 has already been described[2]. The ^{19}F NMR spectrum displays only one doublet J_{HF} = 6.9 at -94.9 ppm.

7-methyl undecan-5-ol-6-one 5

The epoxy alcohol 4 (1 mmol) is added at -70°C to a solution of lithium dimethyl cuprate (4 mmol) in 20 ml of ether. After stirring 8 h., the mixture is hydrolysed by a solution of ammonium chloride/ammonia (2/1), then extracted with ether. The organic phases are collected and washed with brine and dried over magnesium sulfate. Flash vacuum chromatography (cyclohexane/ethyl acetate = 80/20) gives 0,12 g (60%) of 5. IR : 3470, 1710

^1H NMR : 0.9 (2t,6H) 1.12 (d,3H) 1.2-1.9 (2m,12H) ; 2,75 (m,H) 3.6 (m,$\underline{OH}$) 4.3 (m,H)

^{13}C NMR : 13.9, 17.8, 22.6, 22.8, 27.4, 29.6, 31.9, 33.4 ; 41.6 ($\underline{C}$H-Me), 75.1 ($\underline{C}$HOH), 216.2 ($\underline{C}$O)

Anal. Calcd for $C_{12}H_{24}O_2$ (200.31) : C, 71.95 ; H, 12.07. Found : C, 71.82 ; H, 11.90

The configuration of carbon 5 is established by comparison of the ^1H NMR spectra of the Mosher's ether of 5, (spectrum II) and of cetol 5' obtained by diastereoselective oxidation via vanadyle acetylacetate (spectrum I).
Spectrum I displays, inter alia :

- Two doublets of doublets of same intensity corresponding to the two erythro isomers : 85% one dd at 5.24 ppm ; J = 9.3 and 3.4 : one dd at 5.28 ppm ; J = 8.8 and 3.8
- Two doublets of doublets of some intensity corresponding to threo isomers : 15% : one dd at 5.15 ppm ; J = 8.4 and 4.2 ; one dd at 5.18 ppm ; J = 7.8 and 5.1

In spectrum II the only discernible signals are : one dd at 5.28 ppm (erythro) 86% ; one dd at 5.18 pp (threo) 14%. This ketol 5 is a mixture of two diastereoisomers (R,S) (85%) and (R,R) (15%).

2-methyl hexanoic acid 6

Potassium periodate (0.46 g, 2 mmol) and 12 ml 1N sulfuric acid are added to ketol 5 (0.4 g, 2 mmol) in 15 ml ethanol at + 40°C. After stirring 20 min at + 40°C, then 15 h at +20°C, the mixture is hydrolysed and extracted with ether (2 x 10 ml). The acid is separated by an acid-base treatment. The final organic layer is dried over magnesium sulfate : 0.19 g (yield : 72%) of 6 are obtained. The corresponding data are in accordance with those of the literature.

Determination of the optical purity of 6

Acid 6 (0.13 g, 1 mmol) in 10 ml of ether is treated 2 h at -10°C by three equivalents of Dibal-H 1N (3 ml, 3 mmol). The mixture is hydrolysed with water and extracted with ether. The organic layer is neutralized with sodium hydrogenocarbonate, washed with brine, and dried over magnesium sulfate.
The alcohol 7 is purified by flash chromatography (cyclohexane/ethyl acetate) = 80/20) 0.085 g are obtained (yield 74%). In the same way commercially available acid 6 (racemic form) is reduced, and the Moshers' esters of both alcohols are prepared and their ^1H NMR spectra are compared, particularly the -CH_2-OH protons.
The racemic alcohol leads to two diastereoisomers (1/1) respectively :
D^1 : δ : 4.07 dd,1H ; J_{HH} = 10.5 and 6.7δ : 4.23 dd,1H ; J_{HH} = 10.5 and 5.7 the two hydrogens are well separated and D^2 : δ 4.15 (2d, 2H, $J_{HH} \approx 5.5$) the two hydrogens are almost equivalent .
In the Mosher ester of 6 from equation 4, only the signals corresponding to D^1 (corresponding to the (R)-alcohol) can be detected.

7-fluoro undecan-5-ol-6-one 8

To a solution of epoxy alcohol 4 (0.21 g, 1 mmol) in 10 ml of THF was added $Bu_4N^+F^-$/THF (1 mmol) et 0°C. The reaction mixture was then stirred at + 20°C for 2 h, hydrolyzed with water and extracted with ether. The organic phases are collected and washed with brine and dried over magnesium sulfate. Flash vacuum chromatography (cyclohexane/ethyl acetate = 80/20) gives 0.2 g (60%) of 8.
Bp : 120°C/0.4 Torr. $[\alpha]_D^{25}$ = + 128.84 (c = 6.9, $CHCl_3$). IR : 3460, 1720, 1460
^{19}F NMR : -134.7 (dt) J(FH) = 49.6 and 25.2
^1H NMR : 0.9(t,6H) 1.2-1.6(m,8H) 1.8-2.0(m,4H) 3.2(m,OH) 4.6(m,H) 5.0(ddd,H) J(HF) = 49.6 J(HH) = 7.7 and 4.5

^{13}C NMR : 13.45, 13.54, 22.3, 22.4, 26.85, 27.2, 31.8, 33.3, 74.2, 94.9(d,CF) J(CF) = 180.2, 211.7(d,CO) J(CF) = 25.7

Anal. Calcd. for $C_{11}H_{21}FO_2$ (204.28) ; C, 64.67 ; H, 10.36. Found : C, 64.21 ; H, 10.12.

2-fluoro hexanoic acid 9

Prepared in the same way as 6

Yield : 80%. $[\alpha]_D^{25}$ = + 14.06 (c = 1.7, $CHCl_3$). IR : 2500-3400, 1730

^{19}F NMR : -129.1(dt) J(FH) = 51 and 25

^1H NMR : 0.9(t,3H) 1.4-1.6(2m,4H) 1.8-2.0(m,2H) 4.95(ddd,H) J(HF) = 49.1, 7.1, 4.4, 7.6(m,OH)

^{13}C NMR : 13.8, 22.3, 26.6(d) J(CF) = 2.7, 32.1(d) J(CF) = 20.8, 88.7(d,CF) J(CF) = 183.96, 174.1(d,CO) J(CF) = 24.17.

Determination of optical purity of 9

Racemic acid 9', obtained by diastereoselection, is reacted wich (R) - (+) - α-methyl benzylamine. The proton geminal to the fluorine atom displays two signals in ^1H NMR(ddd) corresponding to the diastereoisomers RR (at δ = 4.41 ppm) and RS (at δ = 4.36 ppm). The ammonium salt derived from 9 shows only the former signal.

Acknowledgements

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