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Asymmetric Syntheses of *(S)*-Fenfluramine using Sharpless Epoxidation Methods

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ABSTRACT : We describe one synthesis of (*S*)-fenfluramine and several syntheses of its precursors (*R*)- and (*S*)-1-(meta-trifluoromethylphenyl) propan-2-ols. They were obtained from the asymmetric epoxidation of the primary allylic alcohol **5** and from the kinetic resolution with asymmetric epoxidation of the secondary allylic alcohol **6**.

INTRODUCTION

Fenfluramine, an anorectic agent being a structural analogue of amphetamine without stimulant effects, was first produced as a racemic mixture. The observations that side-effects are due to the action of the (*R*)-enantiomer on dopaminergic transmission and that the (*S*)-enantiomer has the best anorectic power, has led to the marketing of the (*S*)-enantiomer alone, fenfluramine (*S*)-**1**.

During our work on asymmetric synthesis of fenfluramine (*S*)-**1**, we have shown that alcohols (*S*)-**2** and (*R*)-**2** are possible precursors[1,2]. We planned to prepare them from optically active epoxyalcohols **3** and **4**, which could be obtained by asymmetric epoxidation of allylic alcohols **5** and **6** respectively. The Sharpless asymmetric epoxidation of allylic alcohols has been widely used[3,4] since its discovery in 1980[5]. In this paper, we have developed synthetic schemes using the two aspects of this reaction : the asymmetric epoxidation of primary allylic alcohol **5** giving epoxyalcohol **3** and the kinetic resolution with asymmetric epoxidation of secondary allylic alcohol **6** giving epoxyalcohol **4** (Scheme 1) :

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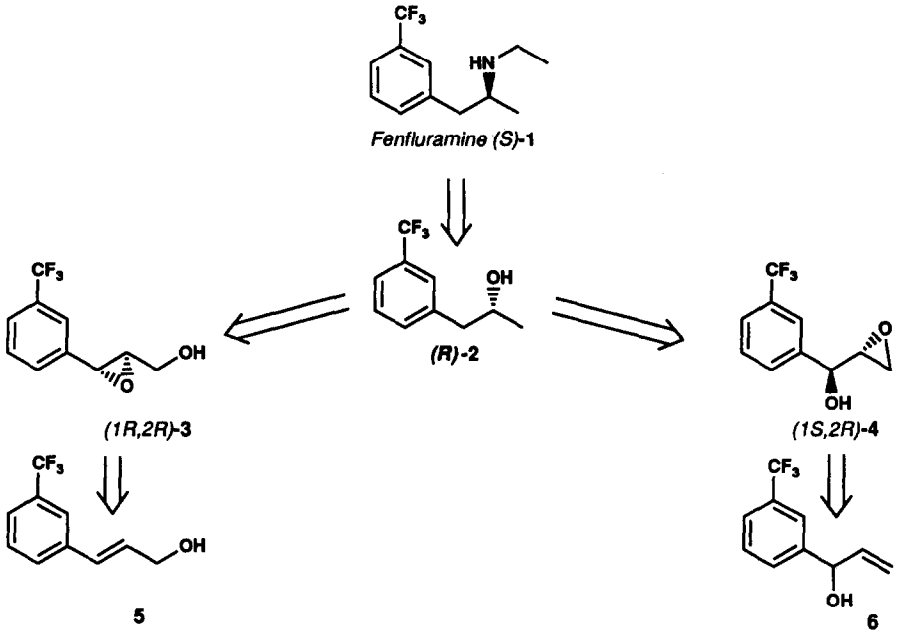
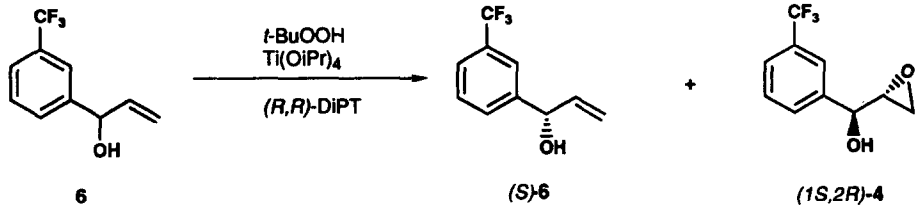


SCHEME 1

KINETIC RESOLUTION OF THE ALLYLIC ALCOHOL 6

Diisopropyl tartrate (DIPT) is the most commonly used tartrate in kinetic resolutions. A rule has been established to predict the configuration of reaction products in relation with the configuration of the starting tartrate[4,6]. We have chosen to use (*R,R*) DIPT in order to obtain the enantiomerically enriched allylic alcohol (*S*)-**6** and the epoxyalcohol (*1S,2R*)-**4**.



The experiments were carried out in methylene chloride, at - 23°C (table 1), first with a stoechiometric quantity of the metallic complex[7] (entries 1 to 3), then with a catalytic quantity[8,9] (entries 4 and 5).

Table 1 : *Kinetic Resolution of Allylic Alcohol 6*

Entry		1	2	3	4	5
complex (eq.)[a]		1.0	1.0	1.0	0.2	0.2
tBuOOH (eq.)		0.6	1.0	2.0	0.7	0.6
reaction time (h)		113	71	141	648	119
(*S*)-**6**	yield (%)	43	44	30	35	46
	GC purity (%)	92	88	81	93	93
	ee (%)[b]	97	72	60	> 99	84
4	yield (%)	48	48	57	54	49
	GC purity (%)	92	92	72	92	95
	erythro/thréo[c]	99/1	99/1	97/3	98/2	98/2
	ee (%)[b,d]	90	90	71	71	87

(a) $Ti(OiPr)_4$ / *(R,R)* DIPT : 1,0/1,2 ; [complex] = 0,1 M

(b) HPLC analysis of MTPA derivative on a silicagel column

(c) HPLC analysis of epoxyalcohol **4** on a silicagel column

(d) predominant isomer : *(1S,2R)*

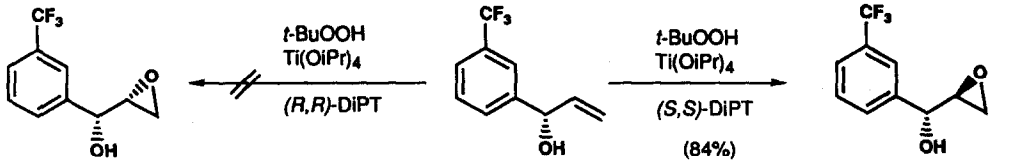
After reaction, a mixture of alcohol **6**, epoxyalcohol **4** and *(R,R)* DIPT was isolated. Tartrate was eliminated by soda hydrolysis, then alcohol (*S*)-**6** and epoxyalcohol *(1S,2R)*-**4** were separated by silicagel chromatography. The percentages of the four possible stereoisomers of **4** and the enantiomeric excess of (*S*)-**6** were determined on their MTPA derivatives by HPLC on a silicagel column [10], whereas the diastereoisomeric composition of **4** was directly obtained by HPLC or ^1H NMR.

Conditions of kinetic resolution (0,6 eq. tBuOOH, entry 1) give the best result : 43 % of alcohol (*S*)-**6** (97 % ee) and 48 % of epoxyalcohol *(1S,2R)*-**4** (99 % erythro, 90 % ee). The same enantioselectivity has been obtained with 1 equivalent of the hydroperoxide (entry 2), in a shorter reaction time, but the enantiomeric excess of the alcohol (*S*)-**6** was lower. With 2 equivalents of the hydroperoxide and a longer reaction time (entry 3), the diastereoselectivity was preserved, but the enantioselectivity was reduced.

With a catalytic quantity (20 %) of complex (entry 5 versus 1), five times less solvant and complex are necessary and only a slight diminution of the enantioselectivity of the epoxidation is observed. If the reaction time is increased (entry 4), the alcohol (*S*)-**6** is optically pure (> 99 % ee), but the optical purity of the epoxyalcohol **4** is shortened (71 % ee.).

In order to exploit the alcohol (*S*)-**6** so obtained, we studied its transformation into *(1R,2R)*-**4** or *(1R,2S)*-**4**, which could lead to the alcohols (*R*)-**2** or (*S*)-**2**. Preliminary attempts at diastereoselective epoxidation of racemic alcohol **6** using the oxidizing agents and catalysts generally employed in this kind of reaction [11-14] (*m*CPBA, *t*BuOOH in presence of $VO(acac)_2$, $Mo(CO)_6$ or $Ti(OiPr)_4$) led to an insufficient diastereoselectivity (best erythro/threo ratio : 81/19).

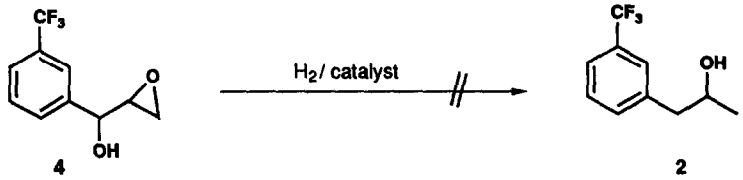
Thus, we decided to use the Sharpless method again:



(1R,2R)-**4** *(S)*-**6** *(1R,2S)*-**4** (ee:97%)

The alcohol (*S*)-**6** was not very reactive with the catalyst prepared starting from (*R,R*)-DIPT. The reaction was slow, the yield low (40 %), the by-products present in large amount and the erythro epoxyalcool (*1R,2S*)-**4** was predominant (erythro/threo = 70/30 by ^{1}H NMR). On the other hand, when (*S,S*)-DIPT was used, the erythro epoxyalcohol (*1R,2S*)-**4** was obtained with satisfactory yield (84 %) and enantiomeric excess (97 %).

We tried to prepare the alcohol **2** from epoxyalcohol **4** by catalytic hydrogenation, realizing the opening of the oxirane on the less substituted side and the hydrogenolysis of the benzylic alcohol function in the same pot :

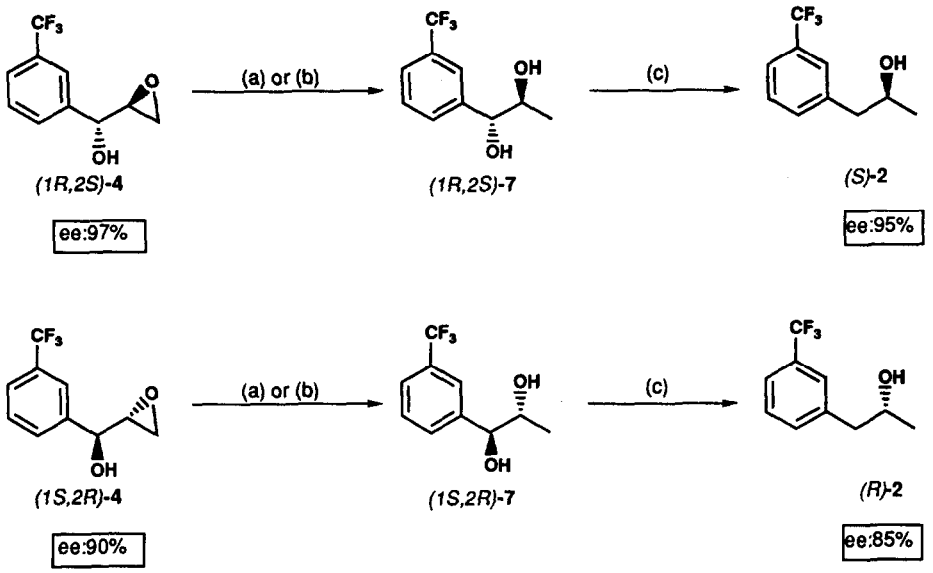


4 **2**

For these two operations, the catalyst of choice is palladium on carbon, at ambient temperature and normal pressure[15]. Nevertheless, benzylic cleavage is facilitated in an acid medium, conditions in which the epoxidic cycle is opened on the more substituted side[15]. For these reasons, attempts to carry out to realize the two reactions in the same pot were unsuccessful. So, the transformation was decomposed into two steps.

Starting from racemic epoxide **4** (erythro/threo = 50/50), the reduction into diol **7** occured regiospecifically with a quantitative yield using molecular hydrogen and 5 % palladium on carbon as catalyst, but satisfactory results were also obtained with lithium aluminium hydride in ether (93 % yield) or sodium borohydride in THF (89 % yield). The hydrogenolysis of diol **7** to alcohol **2** was achieved with 10 % palladium on carbon, after 24 h at 60°C and with 80 % yield. Erythro and threo forms of the epoxy-alcohols **4** and the diols **7** can easily be quantified using ^{1}H NMR. During our numerous tests, we noted that, when the reaction was not complete, the configuration of the unreacted diol **7** was mainly erythro. We have found a similar case in the litterature : benzylic hydrogenolysis of 2,3-dihydroxy-3-phenylpropanoic acid is slower for the erythro form[16].

Starting from optically active epoxides **4**, using the conditions previously defined, reactions were not complete, which was in accordance with the previous observations, our epoxyalcohols and diols being erythro. (scheme 2) However, by increasing the reaction time, the following results were obtained but were not optimized :



(a) H_2, 5 % $Pd/CaCO_3$ (15 % w/w)/ethanol/115 h/20°C (92-94 %)

(b) $LiAlH_4$/ether/-70 to 0°C/3 h (93 %)

(c) H_2, 10 % Pd/C (10 % w/w)/ethanol/92 h/70-75°C (56-58 %).

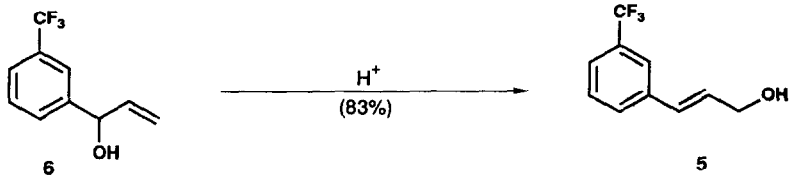
SCHEME 2

The enantiomeric excess of the alcohols **4**, determined by HPLC analysis on a silicagel column of their MTPA derivatives, shows that there is no significant racemization during the two catalytic hydrogenations.

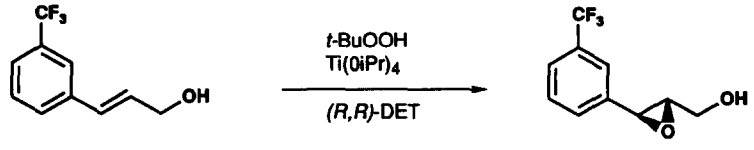
A test of lithium aluminium hydride reduction of the epoxyalcohol (*1R,2S*)-**4** has shown that, in this case, there is no difference in reactivity between the racemic and the chiral product. This could be a convenient alternative to the catalytic reduction to the diol **7**.

ASYMMETRIC EPOXIDATION OF THE ALLYLIC ALCOHOL 5

The alcohol **5** was prepared by allylic transposition of the alcohol **6**, using a 5 % aqueous sulfuric acid solution at 80°C, with 83 % yield. Only the trans isomer was detected[1].



The diethyl tartrate (DET) is the more commonly used tartrate in Sharpless asymmetric epoxidation[3,4]. According to the rule established to predict the configuration of the epoxyalcohol **5**, we used (*R,R*)-DET to obtain the epoxyalcohol (*1S,2S*)-**3** and (*S,S*)-DIPT to obtain its enantiomer. We performed our experiments in methylene choride at -23°C (table 2). Reaction times have not been optimized.



5 *(1S,2S)*-**3**

Table 2 : *Asymmetric Epoxidation of Allylic Alcohol 5*

	Complex [a] (eq.)	Tartrate	tBuOOH (eq.)	Time (h)	Epoxyalcohol 3 yield (%)	GC (%) purity	(*1S,2S*)/(*1R,2R*)[d]	ee(%)
1	1.0[b]	(*R,R*)-DET	2.0	24	61	91	98/2	96
2	0.1[c]	(*R,R*)-DET	1.5	24	82	94	98/2	96
3	0.1[c]	(*S,S*)-DIPT	1.5	15	85	94	4.5/95.5	91

(a) $Ti(OiPr)_4$/Tartrate : 1/1,2

(b) 0,1 M in CH_2Cl_2

(c) 0,02 M in CH_2Cl_2

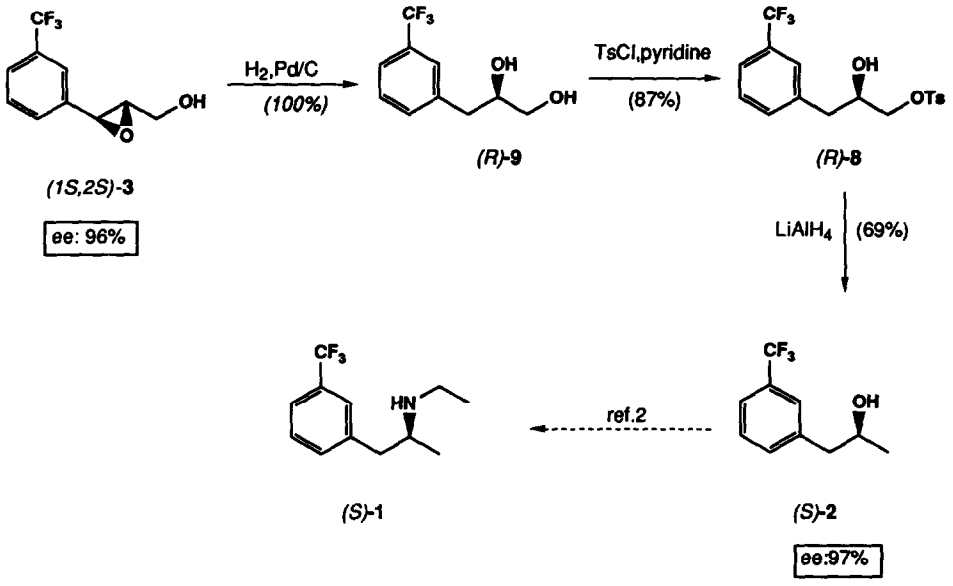
(d) HPLC analysis of the MTPA derivative on a silicagel column

Enantiomeric excess of the epoxy alcohols **3** has been determined by HPLC analysis of their MTPA derivatives, on a silicagel column [10].

With (*R,R*)-DET, the use of a stoechiometric quantity[5] of complex (entry 1) led to a good enantiomeric excess (96 %), but the chemical yield was modest (61 %). It is known that 3-aryl-2,3-epoxy propan-1-ols are very easily opened in the presence of titanium tetrakis isopropylate, giving by-products which usually inhibit the epoxidation[9]. For this reason, we used a catalytic quantity[8,9] of complex (entry 2) in more dilute solutions (complex : 0,02 M instead of 0,1 M). The chemical yield was noticeably better (82 %) and the enantioselectivity not affected. On using DIPT instead of DET (entry 3), a decrease in the enantioselectivity was noted, although this is not generally the case in the litterature.

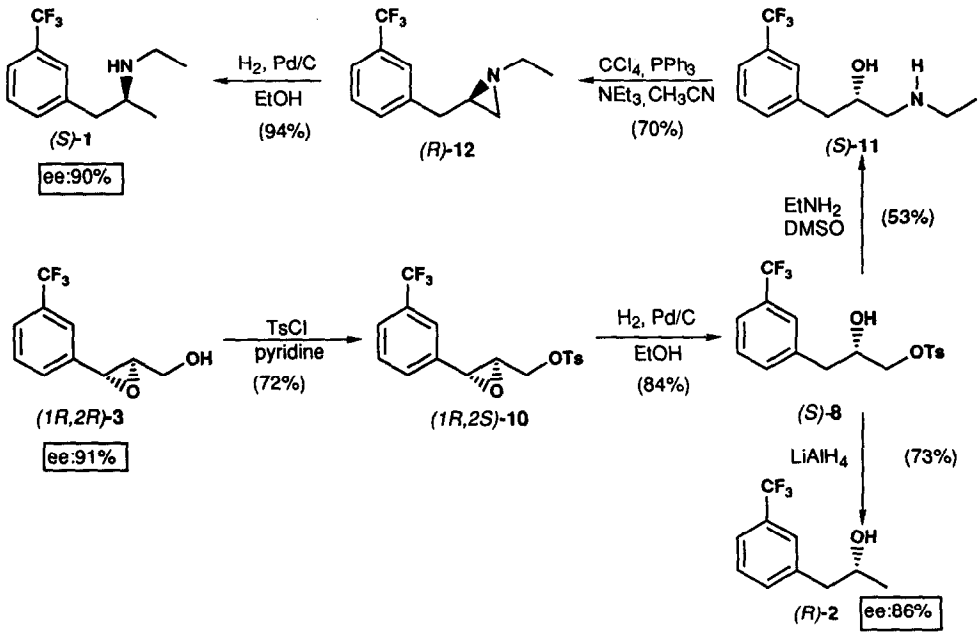
For the transformation of the epoxyalcohols **3** into alcohols **2**, we first used a pathway via epoxyalcohols **4**, but our attemps to isomerize **3** into **4** using the Payne's transposition method[16] were unsuccessful. So, we tested two other paths via tosylates **8**.

The first path, by means of the diol **9**, was evaluated using the epoxy-alcool (*1S,2S*)-**3** (Scheme 3) :



SCHEME 3

The reduction of the epoxyalcohol (*1S,2S*)-**3** into diol (*R*)-**9** was quantitative and regiospecific when using hydrogen and palladium on carbon, at room temperature and normal pressure. No reaction was detected with sodium borohydride in THF at room temperature, and lithium aluminium hydride in ether, after 3 h at 0°C, gave a mixture of the 2 possible diols. Preparation of the tosylate (*R*)-**8**, using tosyl chloride in pyridine[17], followed by reduction of the tosyl moiety with lithium aluminium hydride[18] gave the alcohol (*S*)-**2**, without racemization. Therefore, the by-products were 3-(*meta*-trifluoromethylphenyl) propanol (8 % by G.C.) and 1-(*meta*-trifluoromethylphenyl) propane (2 %). They originated from the reduction of the ditosylate and the monotosylate isomer of **8**, formed during the tosylation of the diol **9**. To circumvent this problem, a second path was studied via the epoxytosylate **10**. It was tested starting from the epoxyalcohol (*1R,2R*)-**3**. (Scheme 4).



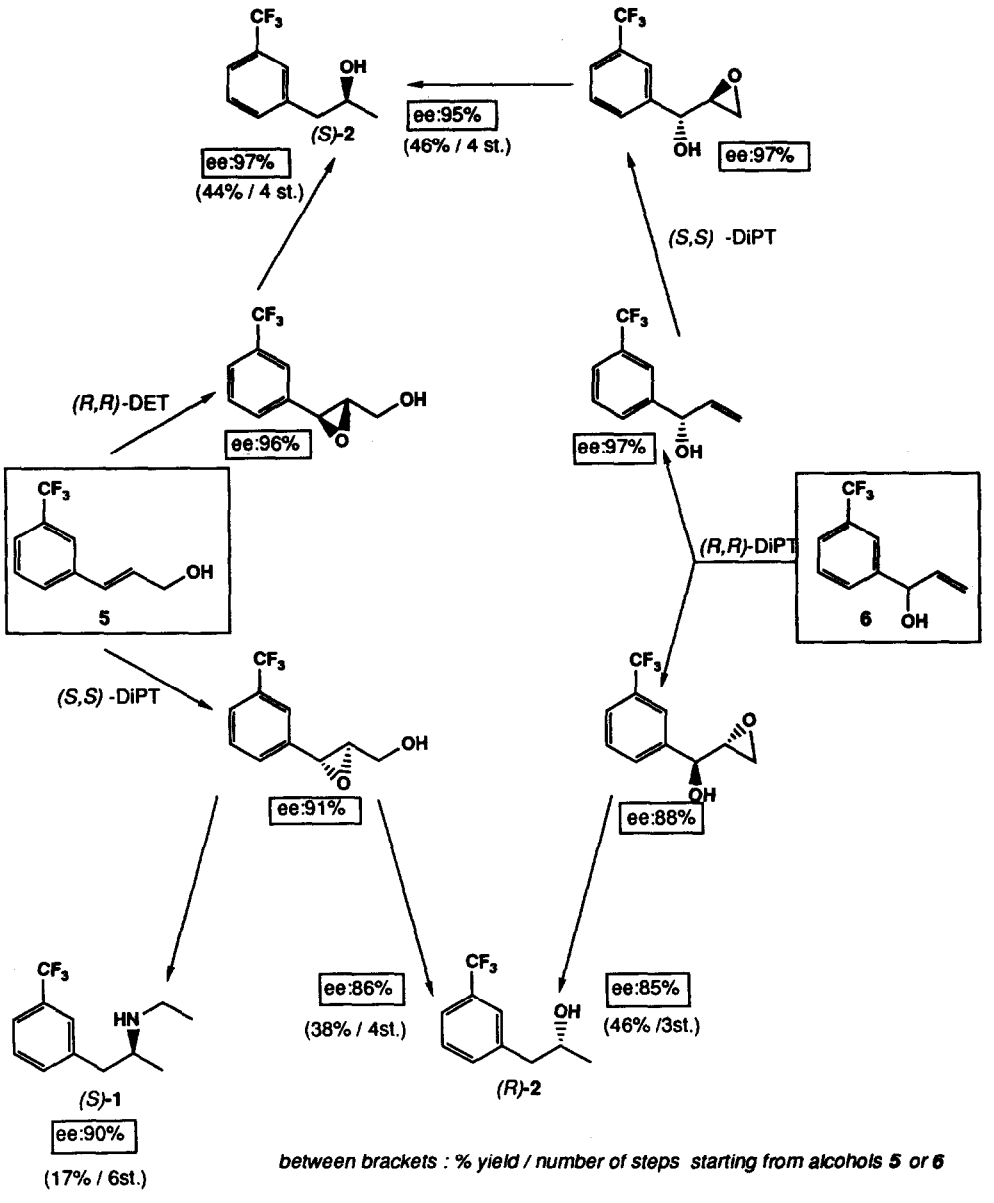
SCHEME 4

Tosylation of the primary alcohol function of (*1R,2R*)-**3** was followed by the regiospecific ring opening of the epoxide at the benzylic position using catalytic hydrogenation. Using lithium aluminium hydride the hydroxytosylate (*S*)-**8** was then reduced into the alcohol (*R*)-**2** which was obtained chemically pure and without significant racemization.

We also achieved a synthesis of fenfluramine (*S*)-**1** starting from the tosylate (*S*)-**8** but without use of the intermediate **2**. The nucleophilic substitution of tosylate (*S*)-**8** by ethylamine gave the amino alcohol (*S*)-**11**. The key steps of this synthetic scheme are the cyclisation of the aminoalcohol (*S*)-**11** into the aziridine (*R*)-**12** and the regiospecific ring opening of the aziridine ring at the less substituted side by catalytic hydrogenation. These two steps have been previously investigated with racemic products[1,2]. The identity of the enantiomeric excesses of starting and final materials, shows no racemization, and shows why the intermediate aziridine is useful for the asymmetric synthesis of (**S**)-fenfluramine, the conservation of the chiral centers during cyclisation of aminoalcohol to aziridine being not proved in the original publication of the method [19]. This pathway can be an alternative for the preparation of chiral secondary amines from chiral aminoalcohols.

CONCLUSION

Using the Sharpless method of asymmetric epoxidation of primary allylic alcohol **5** and kinetic resolution of secondary allylic alcohol **6**, we have achieved several syntheses of the alcohols (*R*)-**2** and (*S*)-**2** and one synthesis of (*S*)-fenfluramine, summarized in the scheme 5 (global yields and numbers of steps are calculated from the starting allylic alcohol **5** or **6**).



SCHEME 5

Asymmetric epoxidation of the primary allylic alcohol **5** seems to be the more promising method because it is much more versatile and leads to products with enantiomeric excesses superior to 95 % when using DET.

Owing to the wide applicability of the Sharpless epoxidation methods, these synthetic schemes could be applied for the asymmetric synthesis of other phenethylalcohols and phenethylamines of the same type.

ACKNOWLEDGEMENTS : This work is a part of the thesis of B. GOUMENT, who gratefully thanks the Society ORIL and the Conseil Régional de Haute Normandie for the grants they have awarded him.

MATERIALS AND METHODS

GENERAL

^{1}H NMR spectra were recorded using a PERKIN ELMER R 12 (60 MHz) or a BRUKER AW 80 (80 MHz) spectrometer, and ^{13}C NMR spectra using a VARIAN CFT 20 (20 MHz) spectrometer. Chemical displacements (δ) are in ppm and, unless otherwise specified, the solvent is $CDCl_3$ and the internal standard TMS.

Concerning ^{13}C NMR spectra : our spectrometer did not enable us to realize spectra uncoupled from both proton and fluor at the same time. The carbon of CF_3 (q, $^{1}J_{CF} = 271,1$ Hz) and the carbon in α position of CF_3 (q, $^{2}J_{CF} = 32,3$ Hz) are very difficult to distinguish or are not visible. They are never indicated. On the other hand, the 2 carbons in β position of CF_3 are very typical (q, $^{3}J_{CF} = 3,9$ Hz).

IR spectra were recorded using a PERKIN ELMER 377 spectrometer. Optical rotations were measured with a PERKIN ELMER 241 polarimeter, using a 1 ml (1 dm path length) quartz cell. Melting points were determined on a REICHERT WME Koffler apparatus. Microanalyses were performed by "le service de microanalyses de l'INSA de ROUEN".

Gas chromatography analyses were performed using a GIRDEL series 30 chromatograph with a flame ionisation detector. We used a 30 % SE 30 + 1 % triethanolamine on chromosorb W AW 80-100 mesh column (0,75 m ; maximal utilization temperature : 150°C).

Liquid chromatography analyses were performed either with a HPLC Chromatem 800 set from TOUZART and MATIGNON made of 2 CHROMATEM 380 pumps and a SHIMADZU SPD-2A detector with variable wavelength, or a HPLC BECKMAN set made of a BECKMAN 110B pump and a BECKMAN 160 detector with fixed wavelength (254 nm). We used a Lichrosorb Si60 (5 mm) MERCK column (25 cm x 4.6 mm), with the following eluants :

- Hexane/THF 99,9/0,1 (2 ml/min) for MTPA's derivative of alcohol **6**.
- Hexane/THF 99,5/0,5 (2 ml/min) for MTPA's derivative of alcohol **2**
- Hexane/THF 96/4 (1,5 ml/min) for MTPA's derivative of epoxy-alcohol **3**
- Hexane/THF 97,5/2,5 (2 ml/min) for MTPA's derivative of epoxy-alcohol **4**
- Hexane/isopropanol 99/1 (2 ml/min) for epoxy-alcohol **4**
- Hexane/isopropanol 98/2 (1 ml/min) for camphanylated derivative of amine **1**

Percentages of compounds were calculated with a SHIMADZU C-R1B integrator.

Analytical TLC analyses were carried out on MERCK Kieselgel 254 GF plates (0,25 mm thick). The revelation was obtained by UV (254 nm) or by an ethanolic solution of vanilin.

230-400 mesh MERCK Kieselgel 60 was used for column flash chromatography.

Anhydrous THF and diethyl ether were distilled on sodium and benzophenone ketyl just before use. Methylene chloride was distilled and filtered through basic alumina. DMSO was dried on potassium

hydroxide, distilled on barium oxide, then stored on 3 A molecular sieves. Acetonitrile was dried and distilled on calcium hydride. Anhydrous RPE ethanol (CARLO ERBA) was used as received. Pyridin and acetone were distilled before use. *(R,R)* and *(S,S)* DIPT were obtained from JANSSEN. *(R,R)* DET was prepared from *(R,R)* tartaric acid according to the BADOCHE method [20]. *Tert*-butyl hydroperoxide solution in methylene chloride was prepared, titrated and stored as proposed by SHARPLESS and Coll. [8].

SYNTHETIC SCHEMES USING ASYMMETRIC EPOXIDATION OF SECONDARY ALLYLIC ALCOHOL 6

RACEMIC EPOXY-ALCOHOL 4 :

1-(meta-Trifluoromethylphenyl)-2-propen-1-ol 6 : This product was supplied us by ORIL.

BP : 45-47°C/0.1 mmHg

IR (film) : 1648 cm^{-1} (C=C) and 3350 cm^{-1} (OH)

^1H NMR : 4.10 (s, 1 mobile H, exchanged with D_2O) ; 5.10-6.35 (m, 5H) ; 750-7.70 (m, 4H)

^{13}C NMR : 74.5 (d) ; 115.8 (t) ; 122.9 (d) ; 124.2 (d) ; 128.7 (d) ; 129.6 (d) ; 139.3 (d) ; 143.4 (s).

1-(meta-Trifluoromethylphenyl)-2,3-epoxypropan-1-ol 4 : 80 % *meta*-chloroperoxybenzoic acid (25.85 g ; 1.1 eq) was added in 5 min to alcohol **6** (22 g, 108.9 mmol) in methylene chloride (200 ml), then refluxed 5 h. After cooling, the precipitate was filtered and the organic phase was washed successively with a 10 % aqueous solution of sodium sulfite (50 ml), a saturated aqueous solution of sodium carbonate (3 x 100 ml) and brine (100 ml), then dried (magnesium sulfate), concentrated, distilled (99-103°C/0.3 mmHg) and flash chromatographied (eluant : petroleum ether/ethyl ether 90/10 to 50/50) to give epoxy-alcohol **4** (14.8 g ; 62 % yield ; 96 % GC ; erythro/threo : 50/50).

IR (film) : 3420 cm^{-1} (OH)

^1H NMR : 2.60-3.30 (m, 4H, including 1 H exchanged with D_2O) ; 4.52 (d, J = 5.3 Hz, 0.5H, threo) ; 4.95 (d, J = 2.7 Hz, 0.5H, erythro) ; 7.60-7.70 (m, 4H).

^{13}C NMR : 43.5 (t) ; 45.2 (t) ; 54.7 (d) ; 55.7 (d) ; 70.3 (d) ; 73.7 (d) ; 122.9 (d) ; 124.8 (d) ; 128.9 (d) ; 129.5 (d) ; 140.5 (s) ; 140.9 (s)

ASYMMETRIC EPOXIDATION OF RACEMIC ALLYLIC ALCOHOL 6

With a stoechiometric quantity of complex (entry 1 table 1) : (R,R)-DIPT (10.6 g ; 1.2 eq) in methylene chloride (370 ml) was cooled to -20°C. With a syringe were added sequentially titanium tetra *iso*-propoxide (11.25 ml, 1 eq) in 3 min, allylic alcohol **6** (7.64 g ; 37.8 mmol) in methylene chloride (8 ml) in 5 min and *tert*-butyl hydroperoxide (4,0 N in methylene chloride ; 5.65 ml ; 0.6 eq) in 10 min. The mixture was stirred for 30 min, stored at -23°C during 113 h, then poured into precooled (-25°C) acetone (380 ml) containing water (15 ml), and stirred for 5 h at room temperature. Magnesium sulfate (3 g) was added, stirring was continued for 20 min and the mixture was filtered through celite (545 PROLABO). The crude product (a mixture of tartrate, allylic alcohol **6** and epoxy-alcohol **4**) was diluted in ethyl ether (200 ml), cooled (0°C) and a precooled (0°C) 1N solution of soda (150 ml) saturated with sodium chloride was added. After 2 h 30 stirring at 0°C, the aqueous phase was separated and extracted with ethyl ether (2 x 150 ml). The combined organic phases were dried over magnesium sulfate, then concentrated and flash chromatographied (eluant : petroleum

ether/ethyl ether 90/10 to 0/100). Allylic alcohol (S)-**6** (3.27 g ; 43 % yield ; 92 % GC) and epoxy-alcohol *(1S,2R)*-**4** (3.92 g ; 48 % yield ; 92 % GC) were eluted successively.

Allylic alcohol *(S)*-**6** : $[\alpha]_D^{23}$ = +15.5° (c = 2.15 ; $CHCl_3$)

HPLC analysis of its MTPA derivative : *S/R* = 98.5/1.5 (ee : 97 %)

Epoxy-alcohol *(1S,2R)*-**4** :

^1H NMR : 2.45-3.00 (m, 3H) ; 3.05-3.30 (m, 1H) ; 4.90 (d, J = 3.0 Hz, 1H) ; 7.50-7.70 (m, 4H)

^{13}C MNR : 43.5 (t) ; 54.7 (d) ; 70.5 (d) ; 122.9 (d) ; 124.6 (d) ; 128.7 (d) ; 129.6 (d) ; 140.7 (s)

$[\alpha]_D^{23}$ = +61.8 (c = 2.41 ; $CHCl_3$)

HPLC analysis of its MTPA derivative : 94.5 % *(1S, 2R)*

With a catalytic quantity of complex (entry 5 table 1) : *(R,R)* -DIPT (0.29 g ; 0.24 eq) and powdered activated 4 A molecular sieves (200 mg ; 20 % by weight) in methylene chloride (9 ml) were cooled to -10°C. Titanium tetra *iso*-propoxide (0.31 ml, 0.2 eq) and *tert*-butyl hydroperoxide (3.92 N in methylene chloride ; 0.79 ml ; 0.6 eq) were added sequentially with a syringe. After 20 min at -10°C, the mixture was cooled to -20°C and allylic alcohol **6** (1.04 g ; 5.14 mmol) in methylene chloride (1 ml) was added in 4 min. The mixture was stirred for 15 min, maintained at -23°C during 119 h, then treated as previously described to give allylic alcohol *(S)*-**6** (474 mg ; 46 % yield ; 93 % GC) and epoxy-alcohol *(1S,2R)*-**4** (545 mg ; 49 % yield ; 95 % GC).

Allylic alcohol *(S)*-**6** :

$[\alpha]_D^{24}$ = +14.4° (c = 1.17 ; $CHCl_3$)

HPLC analysis of its MTPA derivative : *S/R* = 92/8 (ee : 84 %)

Epoxy-alcohol *(1S,2R)*-**4**

$[\alpha]_D^{24}$ = +59.4° (c = 2.06 ; $CHCl_3$)

HPLC analysis of its MTPA derivative : 91.5 % *(1S,2R)*.

EPOXYDATION OF CHIRAL ALLYLIC ALCOHOL (S)-6 :

(1R,2S)-1-(meta-Trifluoromethylphenyl)-2,3-epoxypropan-1-ol **4** *:* We proceeded as described previously, for 113 h at -23°C, starting from 1.06 g (5.25 mmol) of alcohol *(S)*-**6** (97 % ee), 1.56 ml (1.0 eq) of titanium tetra *iso*-propoxide, 1.48 g (1,2 eq) of *(S,S)* DIPT and 1.45 ml of *tert*-butyl hydroperoxyde (4.0 N in methylene chloride ; 1.1 eq) in 52 ml of methylene chloride. 965 mg of epoxy-alcohol *(1R,2S)*-**4** (84 % yield ; 88 % GC) was obtained after flash chromatography.

$[\alpha]_D^{24}$ = -61.9° (c = 2.79 ; $CHCl_3$)

HPLC analysis of its MTPA derivative : 98.5 % *(1R, 2S)*..

With *(R,R)* -DIPT, we used the same method with 2 eq. *tert*-butyl hydroperoxide to obtain epoxy-alcohol **4** (41 % yield ; 61 % GC).

^1H NMR : erythro/threo = 70/30

HPLC analysis of its MTPA derivative : 68 % *(1R, 2S)* and 3 % *(1S, 2R)* (erythro)

28 % *(1R, 2R)* and <1 % *(1S, 2S)* (threo)

CONVERSION OF EPOXY-ALCOHOLS 4 IN ALCOHOLS 2 :

1-(meta-Trifluoromethylphenyl)-1.2-propanediol **7** *using catalytic hydrogenation :*

Racemic diol **7** (typical experiment) : 5 % palladium on calcium carbonate (460 mg ; 12.6 % by weight) was added to racemic epoxy-alcohol **4** (3.65 g ; 16.7 mmol ; erythro/threo : 50/50) in ethanol (22 ml). After

vigourous stirring at room temperature and normal pressure of hydrogen for 46 h, the catalyst was filtered, washed with ethanol (20 ml) and the combined organic phases were concentrated to give diol **7** (3.65 g ; 99 % yield ; 96 % GC ; erythro/threo : 50/50).

IR (film) : 3380 cm^{-1} (OH)

^1H NMR : 0.97 (d, 3H) ; 3,10-4.15 (m, 3H including 2H exchanged with D_2O) ; 4.35 (d, J = 7.1 Hz), 0.5 H) ; 4.68 (d, J = 4.0 Hz, 0.5 H) ; 7.35-7.70 (m, 4H).

^{13}C NMR : 16.1 (q) ; 18,.4 (q) ; 71.0 (d) ; 71.8 (d) ; 76.3 (d) ; 78.5 (d) ; 123.3 (d+d) ; 124.1 (d) ; 124.7 (d) ; 128.5 (d) ; 128.8 (d) ; 129.8 (d) ; 130.1 (d) ; 141.3 (s) ; 142.0 (s).

Microanalysis : $C_{10}H_{11}F_3O_2$ Calc. % C 54.55 H 5.04

Found % 54.2 5.0

Optically active diols **7** : We used the same method starting from 810 mg epoxy-alcohol *(1R, 2S)*-**4** (97 % ee) and 122 mg (15 % by weight) of catalyst in 5 ml ethanol. The reaction time at room temperature was increased to 115 h to give 748 mg of erythro diol *(1R, 2S)*-**7** (92 % yield ; 91 % GC).

^1H NMR : 0.95 (d, J = 7.2 Hz, 3H) ; 3.45 (large s, 2H exchanged with D_2O) ; 3.75-4.15 (m, 1H) ; 4.70 (d, J = 4.0 Hz, 1H) ; 7.40-7.70 (m, 4H)

^{13}C NMR : 16.5 (q) ; 71.5 (d) ; 76.9 (d) ; 123.7 (d) ; 124.7 (d) ; 128.9 (d) ; 130.4 (d) ; 141.9 (s)

$[\alpha]_D^{23}$ = -13.9° (c = 1.88 ; MeOH)

Using the same method, epoxy-alcohol *(1S, 2R)*-**4** (90 % ee) gave erythro diol *(1S,2R)*-**7** (94 % yield ; 92 % GC).

$[\alpha]_D^{23}$ = +13.3° (c = 1.73 ; MeOH)

1-(meta-Trifluoromethylphenyl)-1,2-propanediol **7** *using lithium aluminium hydride reduction :*

Racemic diol **7** (typical experiment) : Epoxy-alcohol **4** (441 mg ; 2.02 mmol) in ethyl ether (1 ml) was added in 8 min to lithium aluminium hydride (82 mg ; 2.1 mmol) in ethylether (5 ml) at -70°C. After 1 h at -70°C, the reaction mixture was heated to 0°C in 3 h and quenched with a saturated aqueous solution of ammonium chloride (2.5 ml). After stirring for 1 h at room temperature and addition of water (2.5 ml), it was filtered and the solid was washed with ethyl ether (20 ml). The aqueous phase was separated and extracted with ethyl ether (2 x 20 ml). The combined ethereal phases were dried (magnesium sulfate) and concentrated to give diol **7** (416 mg, 93 % yield ; 97 % GC).

Diol *(1R, 2S)*-**7** : We used the same method starting from 451 mg of epoxy-alcohol *(1R, 2S)*-**4** (97 % ee) and obtained 356 mg of diol *(1R, 2S)*-**7** (78 % yield ; 94 % GC).

$[\alpha]_D^{25}$ = + 13,0° (c = 1,76 ; MeOH).

1-(meta-Trifluoromethylphenyl)-2-propanol **2** *:*

Racemic products (typical experiment) : 10 % palladium on carbon (26 mg ; 12 % by weight) was added to diol **7** (213 mg ; 0.967 mmol ; erythro/threo : 50/50) in ethanol (5 ml). After vigourous stirring at 60°C and normal pressure of hydrogen for 24 h, the catalyst was filtered, washed with ethanol (20 ml) and the combined organic phases were concentrated to give alcohol **2** (157 mg ; 80 % yield ; 94 % GC) (it contained 2 % 3-(*meta*-trifluoromethylphenyl) propan-1-ol and 3 % *meta*-trifluoromethylphenyl propane).

Optically active products : We used the same method starting from 720 mg diol *(1R, 2S)*-**7** (prepared from epoxy-alcohol with 97 % ee) and 72 mg (10 % by weight) of catalyst in 5 ml ethanol. The reaction time and temperature were increased to 115 h and 70-75°C, respectively, to give after flash chromatography (eluant:

petroleum ether/ethyl ether 95/5 to 80/20) alcohol *(S)*-**2** (370 mg ; 56 % yield ; 95 % GC ; 3 % 3-(*meta*-trifluoromethylphenyl)propan-1-ol).
$[\alpha]_D^{21}$ = + 24.9° (c = 2.25 ; $CHCl_3$).
HPLC analysis of its MTPA derivative : *R/S* = 97.5/2.5 (ee : 95 %).

Using the same method, diol *(1S, 2R)*-**7** (prepared from epoxy-alcohol *(1S, 2R)*-**4** with 90 % ee) gave alcohol *(R)*-**2** (58 % yield ; 95 % GC ; 2 % 3-(*meta*-trifluoromethylphenyl) propan-1-ol).
$[\alpha]_D^{21}$ = - 23.9° (c = 2.12 ; $CHCl_3$)
HPLC analysis of its MTPA derivative : *R/S* = 92.5/7.5 (ee : 85 %).

SYNTHETIC SCHEME USING ASYMMETRIC EPOXIDATION OF PRIMARY ALLYLIC ALCOHOL 5

RACEMIC EPOXY-ALCOHOL 3 :

1-(meta-Trifluoromethylphenyl) 1-propen-3-ol **5** *:* Alcohol **6** (6.28 g ; 31.1 mmol) in a 5 % aqueous solution of sulfuric acid (78 ml) was heated at 75-80°C for 8 h under vigourous stirring (alcohols **5** and **6** are not soluble in the reaction mixture). After cooling, the aqueous phase was extracted with ethyl ether (3 x 25 ml). The combined ethereal phases were washed with brine (15 ml)., dried (magnesium sulfate), concentrated and flash chromatographied (eluant : petroleum ether/ethyl ether 98/2 to 50/50) to give alcohol **5** (5.21 g ; 83 % yield ; 98 % GC).
IR (film) : 1655 cm^{-1} (C=C) and 3320 cm^{-1} (OH)
^1H NMR : 2,.85 (s, 1 mobile H exchanged with D_2O) ; 4.17 (d, J = 4.0 Hz, 2H) ; 6.00-6.70 (m, 2H) ; 7.20-7.50 (m, 4H).
^{13}C NMR : 62.8 (t) ; 122,.8 (d) ; 123.9 (d) ; 128.8 (d) ; 128.9 (d) ; 129.2 (d) ; 130.3 (d) ; 137.3 (s).
Microanalysis : $C_{10}H_9F_3O$ Calc % C 59.41 H 4.49
Found % 59.2 4.4

1-(meta-Trifluoromethylphenyl) 1,2-epoxy 3-propanol **3** *:* We proceeded as previously described for epoxy-alcohol **4** starting from allylic alcohol **5** (600 mg ; 2.97 mmol) in methylene chloride (10 ml), 4 h to reflux. After flash chromatography (eluant : petroleum ether/ethyl ether 90/10 to 50/50), it gave epoxy-alcohol **3** (419 mg ; 65 % yield ; 92 % GC).
IR (film) : 3380 cm-1 (OH)
^1H NMR : 2.30 (s large, 1 mobile H exchanged with D_2O) ; 3.05-3.25 (m, 1H) ; 3.60-4.20 (m, 3H) ; 7.30-7.60 (m, 4H).
^{13}C NMR : 54.8 (d) ; 60.6 (t) ; 62.7 (d) ; 122,.2 (d) ; 124.8 (d) ; 128.8 (d+d) ; 137.9 (s).

ASYMMETRIC EPOXIDATION OF ALLYLIC ALCOHOL **5** *:*

With a stoechiometric quantity of complex (entry 1 table 2) : (R,R) -DET (1.24 g ; 1.2 eq) in methylene chloride (48 ml) was cooled to -23°C. With a syringe were added sequentially titanium tetra *iso*-propoxide (1.49 ml, 1 eq) in 3 min and, after 10 min, allylic alcohol **5** (1.01 g ; 4.99 mmol) in methylene chloride (2 ml) in 6 min and *tert*-butyl hydroperoxide (3.92 N in methylene chloride ; 2.54 ml ; 2.0 eq) in 8 min. The mixture was stirred for 15 min, maintained at -23°C for 24h, then a 10 % aqueous tartaric acid solution (12 ml) was added. After 30 min, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The organic phase was separated, washed with water (10 ml), dried (magnesium sulfate) and concentrated. The

crude product (a mixture of tartrate and epoxy-alcohol **3**) was diluted in ethyl ether (15 ml), cooled (0°C) and a precooled (0°C) 1N solution of soda (10 ml) saturated with sodium chloride was added. After 2 h stirring at 0°C, the aqueous phase was separated and extracted with ethyl ether (2 x 20 ml). The combined organic phases were dried (magnesium sulfate), then concentrated and flash chromatographied (eluant : petroleum ether/ethyl ether 90/10 to 50/50) to give epoxy-alcohol *(1S,2S)*-**3** (668 mg ; 61 % yield ; 92 % GC)
$[\alpha]_D^{23}$ = -42.6° (c = 2.08 ; $CHCl_3$).
HPLC analysis of its MTPA derivative : *(1S,2S) / (1R,2R)* = 98.1/1.9 (ee : 96 %).

With a catalytic quantity of complex (entry 2 table 2) : (R,R) -DET (124 mg ; 0.12 eq) in methylene chloride (23 ml) was cooled to -23°C. With a syringe were added sequentially titanium tetra *iso*-propoxide (0,147 ml, 0,1 eq) in 2 min and, after 15 min, allylic alcohol **5** (994 mg ; 4.92 mmol) in methylene chloride (2 ml) in 6 min and *tert*-butyl hydroperoxide (3.92 N in methylene chloride ; 1.88 ml ; 1.5 eq) in 8 min. The mixture was stirred for 15 min, maintained at -23°C for 24h, then treated as previously described to give epoxy-alcohol *(1S,2S)*-**3** (880 mg ; 82 % yield ; 94 % GC).
$[\alpha]_D^{23}$ = -38.0° (c = 2.14 ; $CHCl_3$).
HPLC analysis of its MTPA derivative : *(1S,2S)/(1R,2R)* = 98/2 (ee : 96 %)

Using the same method, with *(S,S)* DIPT (entry 3 table 2), after 15 h at -23°C, a product with 91 % enantiomeric excess was obtained.

SYNTHESIS AND REACTIONS OF TOSYLATE (S)-**8** *:*

1-(meta-Trifluoromethylphenyl) 1,2-epoxy 3-tosyloxy propane (1R,2S)-**10** **:** Tosyl chloride (578 mg ; 1.5 eq) was added in 3 portions in 5 min to epoxy-alcohol *(1R,2R)*-**3** (440 mg; 2.02 mmol ; 91 % ee) in pyridine (4 ml). The reaction mixture was stirred for 10 min, stored for 18 h at 0°C, then poured into a 50/50 mixture of water and crushed ice (15 g). The aqueous phase was extracted with ethyl ether (2 x 25 ml). The combined ethereal phases were washed successively with a saturated aqueous solution of copper sulfate (10 ml), brine (10 ml) and water (5 ml), then dried (magnesium sulfate), concentrated and flash chromatographied (eluant : petroleum ether/ethyl ether 90/10 to 80/20) to give tosylate *(1R,2S)*-**10** (542 mg ; 72 % yield) as an oil.
^1H NMR : 2.40 (s, 3H) ; 3.05-3.25 (m, 1H) ; 3.82 (d, J = 1.8 Hz, 1H) ; 4.00-4.50 (m, 2H) ; 7.10-7.90 (m, 8H).
^{13}C NMR : 21.1 (q) ; 55.2 (d) ; 58.5 (d) ; 68.9 (t) ; 122.1 (d) ; 124.9 (d) ; 127.6 (d) ; 128.9 (d) ; 129.7 (d) ; 136.7 (s) ; 145.1 (s)

Microanalysis : $C_{17}H_{15}F_3O_4S$	Calc. %	C 54.84	H 4.06
	Found %	55.1	4.2

$[\alpha]_D^{23}$ = +34.9° (c = 1.36 ; $CHCl_3$).

1-(meta-Trifluoromethylphenyl) 3-tosyloxy 2-propanol (S)-**8** *:* 5 % palladium on carbon (52 mg ; 10 % by weight) was added to tosylate *(1R,2S)*-**10** (522 mg ; 1,40 mmol) in ethanol (5 ml). After vigourous stirring at 21°C and normal pressure of hydrogen for 24 h, the catalyst was filtered, washed with ethanol (20 ml) and the combined organic phases were concentrated. The crude product (which contained a solid) was taken in methylene chloride (25 ml), washed with brine (5 ml), dried (magnesium sulfate) and concentrated to give tosylate (*S*)-**8** (442 mg ; 84 % yield) as an oil analytically pure.
IR (film) : 3520 cm^{-1} (OH)

^{1}H NMR : 2.37 (s, 3H) ; 2.75 (d, J = 5.5 Hz, 2H) ; 2.97 (s, 1H exchanged with D_2O) ; 3.80-4.20 (m, 3H) ; 7.10-7.90 (m, 8H)

^{13}C NMR : 21.1 (q) ; 38.5 (t) ; 69.5 (d) ; 72.4 (t) ; 123.1 (d) ; 125.6 (d) ; 127.6 (d) ; 128.6 (d) ; 129.7 (d) ; 132.6 (d) ; 137.9 (s) ; 145.0 (s)

Microanalysis : $C_{17}H_{17}F_3O_4S$	Calc %	C 54.54	H 4.58
	Found %	55.0	4.6

$[\alpha]_D^{24}$ = +2.8° (c = 1.16 ; $CHCl_3$).

Synthesis of alcohol (R)-2 from tosylate (S)-8 : Tosylate (*S*)-**8** (412 mg ; 1.1 mmol) in ethyl ether (1 ml) was added in 6 min to lithium aluminium hydride (83 mg ; 2.2 mmol) in ethyl ether (5 ml) at 21°C. The reaction mixture was stirred for 1h30 at room temperature, quenched with a saturated aqueous solution of ammonium chloride (2 ml), stirred for 1h30, filtered and solid was washed with water (2 ml). The aqueous phase was separated and extracted with ethyl ether (3 x 10 ml). The combined ethereal phases were dried (magnesium sulfate) and concentrated to give alcohol (*R*)-**2** (164 mg ; 73 % yield ; 100 % GC).

IR (film) : 3380 cm-1 (OH)

^{1}H NMR : 1.18 (d, J = 6.0 Hz, 3H) ; 2.40 (1H exchanged with D_20) ; 2.75 (d, J = 6.0 Hz, 2H) ; 4.00 (sextuplet, J = 6.0 Hz, 1H) ; 7.35-7.55 (m, 4H)

^{13}C NMR : 22.5 (q) ; 45.0 (t) ; 68.2 (d) ; 122.8 (d) ; 125.8 (d) ; 128.5 (d) ; 132.6 (d) ; 139.6 (s)

Optical rotations at 23°C (C = 2.43 ; $CHCl_3$) :

λ (nm)	589	578	546	436	365
[α] λ	-22.1°	-23.1°	-26.6°	-48.4°	-83.3°

HPLC analysis of its MTPA derivativce : R/S = 93/7 (ee : 86 %)

*1-(meta-Trifluoromethylphenyl) 3-ethylamino 2-propanol (S)-***11** *:* Anhydrous ethylamine (07 ml ; 4 eq) was added to tosylate (*S*)-**8** (1003 mg ; 2.68 mmol) in DMSO (5 ml) in an autoclave. The mixture was heated 45 min at 60°C, then cooled and poured in 3N aqueous hydrochloric acid (10 ml). Aqueous phase was extracted with ethyl ether (2 x 25 ml), then basified with 10 N soda (5 ml) and extracted with ethyl ether (3 x 25 ml). The combined ethereal phases were washed with water (10 ml), dried (magnesium sulfate) and concentrated to give aminoalcohol (*S*)-**11** (354 mg ; 53 % yield ; 95 % GC).

^{1}H NMR : 1.00 (t, J = 7.3 Hz, 3H) ; 2.20-2.80 (m, 8H, including 2 mobile H exchanged with D_2O) ; 3.60-3.95 (m, 1H) ; 7.30-7.55 (m, 4H)

^{13}C NMR : 14.4 (q) ; 41.4 (t) ; 43.4 (t) ; 54.5 (t) ; 69.7 (d) ; 122.7 (d) ; 125.8 (d) ; 128.3 (d) ; 132.6 (d) ; 139.7 (s)

$[\alpha]_D^{23}$ = +8.5° (c = 1.06 ; $CHCl_3$).

*1-Ethyl 2-(meta-trifluoromethylbenzyl) aziridine (R)-***12** *:* Triethylamine (143 mg ; 1 eq), tetrachloromethane (217 mg ; 1 eq) and triphenylphosphine (430 mg ; 1.15 eq) were added to amino alcohol (*S*)-**11** (349 mg ; 1.41 mmol) in acetonitrile (1,5 ml) at room temperature. The reaction mixture was heated 4 h at 45°C. The precipitate was filtered and washed with acetonitrile (2 ml). The combined organic phases were

concentrated, then triturated with petroleum ether (4 x 10 ml). The combined organic phases were concentrated and distilled to give aziridine (*R*)-**12** (226 mg ; 70 % yield ; 98 % GC).

^{1}H NMR : 1.00 (t, J = 6.7 Hz, 3H) ; 1.20-1.80 (m, 3H) ; 1.95-2.55 (m, 2H) ; 2.75 (d, J = 5.3 Hz, 2H) ; 7.40-7.70 (m, 4H)

^{13}C NMR : 14.0 (q) ; 33.2 (t) ; 38.9 (t) ; 39.9 (d) ; 54.9 (t) ; 122.8 (d) ; 125.1 (d) ; 128.5 (d) ; 131.9 (d) ; 140.5 (s)

Optical rotations at 25°C (C = 0,90 ; $CHCl_3$) :

λ (nm)	589	578	546	436	365
[α] λ	+5,3°	+5,5°	+6,6°	+13,1°	+25,2°

*1-(meta-Trifluoromethylphenyl) 2-ethylamino propane (S)-***1** *(dexfenfluramine) :* 5 % palladium on carbon (23 mg ; 10 % by weight) was added to aziridine (*R*)-**12** (226 mg ; 1.45 mol) in ethanol (4 ml). After vigourous stirring at 20°C and normal pressure of hydrogen for 16h, the catalyst was filtered, washed with ethanol (20 ml) and the combined organic phases were concentrated to give fenfluramine (*S*)-**1** (205 mg ; 90 % yield ; 94 % GC).

^{1}H NMR : 0.90-1.25 (m, 7H including 1 mobile H exchanged with D_2O) ; 2.40-3.20 (m, 5H) ; 7.40-7.60 (m, 4H).

^{13}C NMR : 14.6 (q) ; 19.3 (q) ; 40.7 (t) ; 42.7 (t) ; 53.7 (d) ; 122.2 (d) ; 125.2 (d) ; 128.0 (d) ; 132.0 (d) ; 140.0 (s)

HPLC analysis of its camphanylated derivative : S/R = 95/5 (ee : 90 %)

1-(meta-TRIFLUOROMETHYLPHENYL) 2,3-PROPANEDIOL (R)-9 :

Using lithium aluminium hydride reduction : Epoxy alcohol (*1S,2S*)-**3** (168 mg ; 0.77 mmol ; 96 % ee) in ethyl ether (1 ml) was added in 15 min to lithium aluminium hydride (59 mg ; 1.5 mmol) in ethyl ether (3 ml) at 0°C. The reaction mixture was stirred for 3 h at 0°C, quenched at 0°C with a saturated aqueous solution of ammonium chloride (2 ml), stirred for 2 h at room temperature, filtered and the solid was washed with water (2 ml) and ethyl ether (10 ml). The aqueous phase was separated and extracted with ethyl ether (2 x 15 ml). The combined ethereal phases were dried (magnesium sulfate) and concentrated to give impure diol **9** (148 mg ; 87 % crude yield).

GC analysis : 62 % diol **9**, 19 % 1-(meta-trifluoromethylphenyl) 1,3-propanediol, 2 % epoxy-alcohol **3**, 10 % heavy product and 7 % minor products.

Using catalytic hydrogenation : 5 % palladium on carbon (21 mg ; 10 % by weight) was added to epoxy-alcohol (*1S,2S*)-**3** (211 mg ; 0.97 mmol ; 96 % ee) in ethanol (5 ml). After vigourous stirring at 20°C and normal pressure of hydrogen for 19h, the catalyst was filtered, washed with ethanol (20 ml) and the combined organic phases were concentrated to give diol (*R*)-**9** (213 mg ; 100 % yield ; 95 % GC).

MP : 80-81°C (Köfler)

IR (nujol) : 3180-3280 cm^{-1} (OH)

^{1}H NMR : 2.72 (d, J = 6.4 Hz, 2H) ; 3.20-4.00 (m, 5H) ; 7.20-7.55 (m, 4H)

^{13}C NMR : 39.1 (t) ; 65.6 (t) ; 72.6 (d) ; 123.2 (d) ; 125.8 (d) ; 128.7 (d) ; 132.6 (d) ; 138.9 (s)

$[\alpha]_D^{24}$ = +25.9° (c = 0.96 ; MeOH).

1-(meta-TRIFLUOROMETHYLPHENYL)-2-PROPANOL (S)-2 FROM DIOL (R)-9

Tosyl chloride (340 mg ; 2,0 eq) was added in 3 portions in 5 min to diol *(R)*-**9** (196 mg ; 0.89 mmol) in pyridine (5 ml). The reaction mixture was stirred for 14h30 at 0°C, then poured in a 50/50 mixture of water and crushed ice (15 g). The aqueous phase was extracted with ethyl ether (3 x 20 ml). The combined ethereal phases were washed with 1 N aqueous hydrochloric acid (15 ml) and brine (10 ml), then dried (magnesium sulfate), concentrated and flash chromatographied (eluant : petroleum ether/ethyl ether 80/20) to give tosylate *(R)*-**8** (289 mg ; 87 % yield). This product was reduced with lithium aluminium hydride as described for tosylate (*S*)-**8** (except 3 h at 21°C) to give alcohol (*S*)-**2** (69 % yield).

GC analysis : 86 % alcohol (*S*)-**2**, 8 % 3-(*meta*-trifluoromethylphenyl) propanol, 2 % *meta*-trifluoromethylphenyl propane and 3 % heavy product.

HPLC analysis of its MTPA derivative : $S/R = 98.5/1.5$ (ee : 97 %).

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