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Determination of the enantiomeric purity and the configuration of β-aminoalcohols using (*R*)-2-fluorophenylacetic acid (AFPA) and fluorine-19 NMR: application to β-blockers

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Abstract

A method has been developed for determining the enantiomeric purity and the absolute configuration of β-aminoalcohols of type $ArOCH_2CH(OH)CH_2NHR$ (R = *i*Pr, *t*Bu). To determine enantiomeric purity, the amine function was first protected by a benzyl group, then the compound formed was esterified using the acid chloride of (*R*)-2-fluorophenylacetic acid (AFPA). The ^{19}F NMR analysis of the derivative obtained revealed the presence of two distinctly separate signals (~2.5 ppm), the one for the *RS*–*SR* pair being the most deshielded. The configuration was determined directly on the aminoalcohol by using the acid. In stoichiometric conditions, when R = *i*Pr, the amide function was obtained very preponderantly. The ^{19}F NMR spectrum of the amide presented four distinct signals when derivatization was carried out by means of a reaction between the (±)-β-aminoalcohol and the (*R*)-AFPA. The extreme signals, which were over 3.5 ppm apart, did not belong to the same diastereomer. With R = *t*Bu essentially the ester function was obtained. The first studies revealed the presence of two signals, though not as clearly separated as in the previous cases. Each experiment was simple to perform, and purification was not necessary. Mosher's acid gave unsatisfactory results in each case.

1. Introduction

Determination of the enantiomeric purity and the absolute configuration of a compound is now of particular importance when synthesizing chiral molecules where one enantiomer is of biological interest. For example, in the case of β-blockers of type $ArOCH_2CH(OH)CH_2NHR$,

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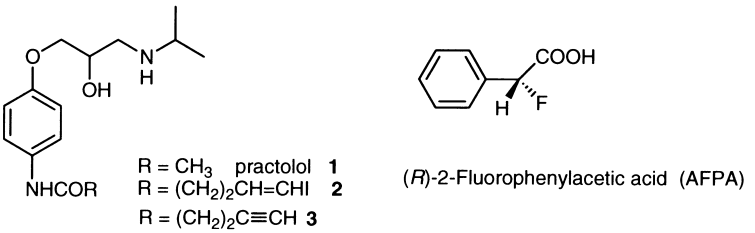
which have to be synthesized, the carbon carrying the alcohol function is stereogenic and only the *S* enantiomer is sufficiently active.

Numerous determination methods exist, using a variety of techniques such as polarimetry, chromatography and NMR.[1] In the latter case, the most interesting aspect is the condensation of a chiral derivatization agent with the compound being studied. A certain number of chiral acids or acid chlorides with a general structure ArCXYCOOH have proved to be very useful in studies of chiral alcohols and amines.

o-Methylmandelic acid ($X = CH_3O$, $Y = H$)[2–6] and especially 2-methoxy-2-trifluorophenylacetic acid (MTPA) ($X = CH_3O$, $Y = CF_3$) proposed by Mosher in 1969 have been widely used.[2,4,7–12] The latter, which has the advantage of not causing racemization during derivatization, can also be used in ^{19}F NMR studies. This possibility is of interest for a number of reasons. In particular, the difference in $\Delta\delta_F$ chemical displacement is greater than $\Delta\delta_H$ and the signals obtained are in a clear zone.

However, MTPA also has certain disadvantages: its reactivity is not always sufficient, for steric reasons.[10,16,17] In addition, the results obtained from NMR of the proton or fluorine are not always reliable.[10,18] Finally, on the one hand, the binding of fluorine atoms to a carbon adjacent to the stereogenic carbon (rather than on it), and, on the other hand, long distance coupling between the methoxy hydrogens and the fluorines (broadening of the signals)[7,19] are not favourable. 2-Fluorophenylacetic acid (AFPA) ($X = F$, $Y = H$) has the advantage of having a fluorine atom which is directly bound to the stereogenic carbon and consequently more sensitive to diastereotopic magnetic differences. The rare studies performed, using the *R* configuration of this acid, have shown that the $\Delta\delta_F$ values observed are in most cases very significant and that racemization does not occur during esterification.[20,21]

In the context of our studies on β-blockers, we synthesized the *S* isomer of an iodinated analogue **2** of practolol **1** via **3** (Scheme 1).[22] Preliminary biological studies revealed this analogue **2** to be of considerable interest.[23,24] In order to determine the enantiomeric purity obtained during the synthesis of **2**, we had to develop *a determination method which would overcome a problem of chemoselectivity inherent to β-aminoalcohols*, namely the presence in the β position of two often closely related reactivity functions. We used the chloride of 2-fluorophenylacetic acid. For comparative purposes, we also performed the same reactions with the chloride of Mosher acid.



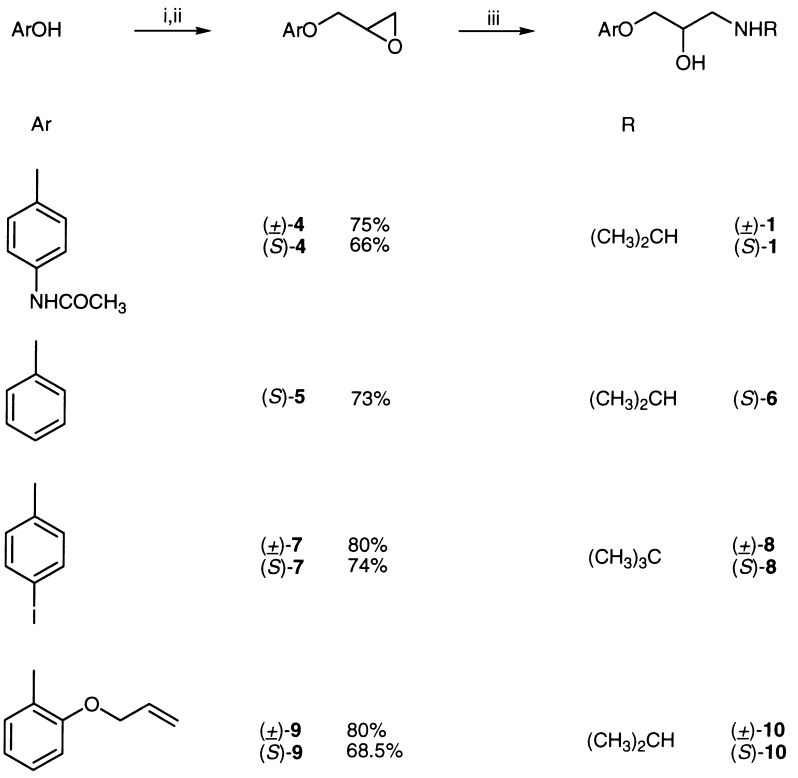
Scheme 1.

Moreover, from the studies already mentioned, it can be concluded that MTPA, AFPA and *o*-methylmandelic acid can be used to determine the configuration of secondary chiral alcohols and aminoalcohols carrying a chiral carbon in the α position of the nitrogen. We therefore decided to find out whether this same method could also be used to determine the configuration in the case of β-aminoalcohols of which β-blockers are a part.

2. Results and discussion

2.1. Synthesis of compounds

The compounds synthesized for this study were obtained according to Scheme 2.

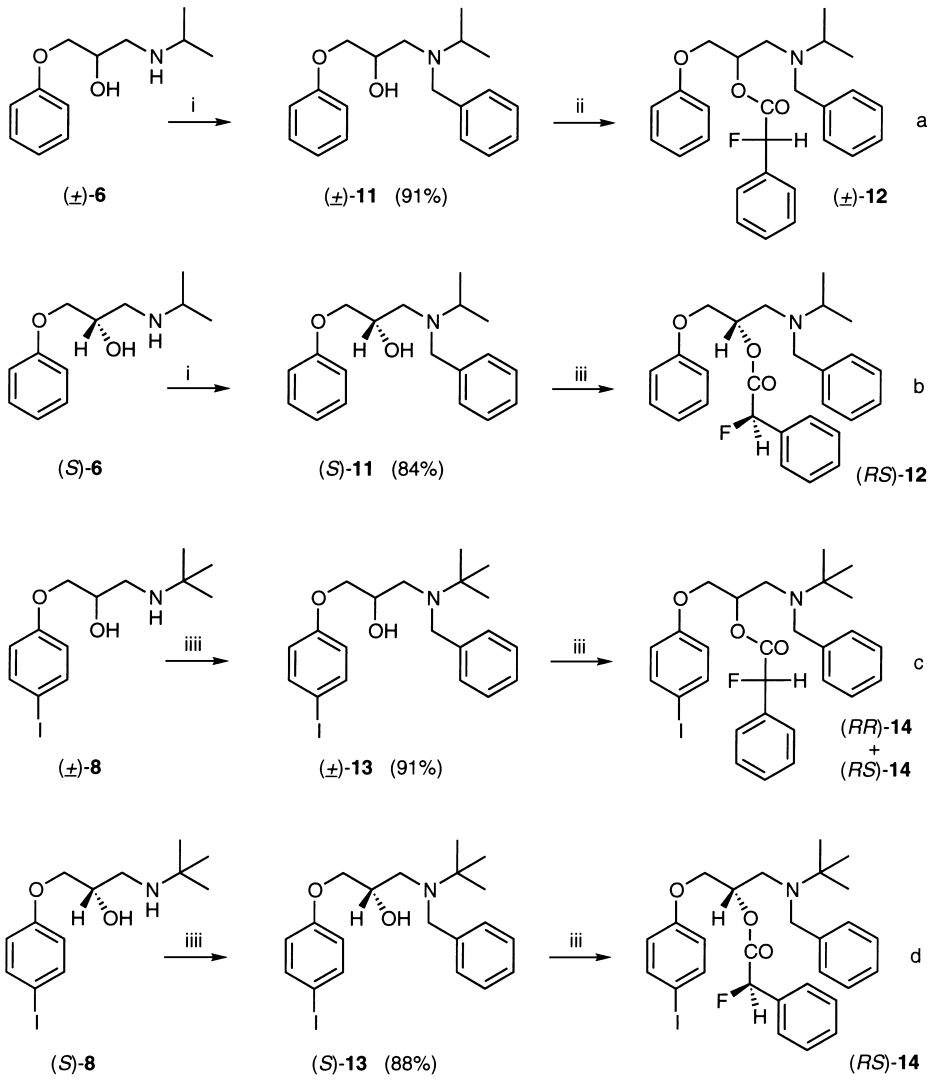


Scheme 2. Reagents: (i) NaH, DMF, 0°C; (ii) (±)- or (*S*)-glycidyl tosylate; (iii) amine, isopropanol, reflux

2.2. Determination of enantiomeric purity

The method was developed on the simple model compound (±)-**6** (Scheme 3). Obviously, it was necessary during the derivatization to obtain a total reaction, and for one function only. Determination of enantiomeric purity thus involved a preliminary step to protect one of the functions. After various tests, protection of the amine function by the benzyl group was found to give the best results.[25,26]

Esterification was performed from the acid chlorides with an acid chloride:alcohol ratio of 3:2. A first experiment performed on (±)-**11** with the chloride of the racemic fluorophenylacetic acid (Scheme 3a) showed, after workup, a very simple ^{19}F NMR spectrum (recorded in chloroform): two signals situated at –15.78 and –18.30 ppm, *of different intensity* (54:46). A second experiment performed using the same conditions with the *R* acid chloride revealed the presence of two



Scheme 3. Reagents: (i) $C_6H_5CH_2Cl$, K_2CO_3, CH_3CN, reflux; (ii) (±)-$C_6H_5CFHCOCl$, pyridine, rt; (iii) (*R*)-$C_6H_5CFHCOCl$, pyridine, rt; (iiii) $C_6H_5CH_2Br$, K_2CO_3, CH_3CN, reflux

signals, *of the same intensity* in this case, at –15.88 and –18.36 ppm. Finally, a third experiment, performed with the *S* acid chloride, gave the same results: the presence of two signals *of the same intensity* at –15.82 and –18.32. Together, these three experiments confirmed that the esterification was complete. It was thus quite possible, because of the significant difference (≅2.5 ppm) between the diastereomeric signals that were formed, to determine the enantiomeric purity (with the precision of the NMR) of the starting β-aminoalcohols. The method leads to a very good correlation when applied to **2** (–15.94 and –18.36) or to **3** (–15.91 and –18.40).[26] The esterification performed from (*S*)-**11** (Scheme 3b) made it possible to determine the position of the signal of each pair of enantiomers *RS–SR* and *RR–SS*. The first pair was found to have the most deshielded signal.

The chlorides of Mosher's acid did not give the desired esters, most likely for reasons of bulkiness: the proton NMR spectrum of the crude reaction mixture recorded after 15 h revealed no signal at 5.2 ppm (characteristic of $>CHOCO$).

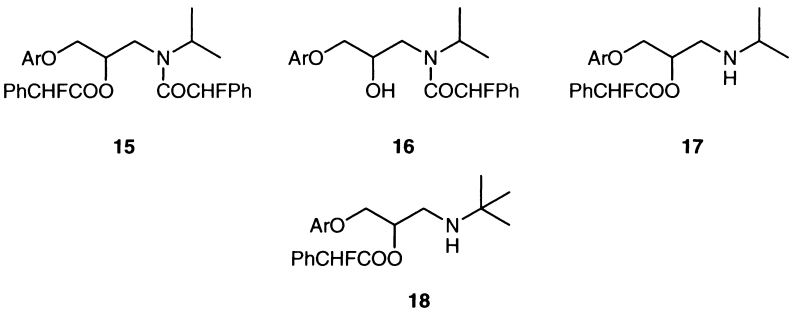
A great many β-blockers have a tertiobutyl group bound to nitrogen in the place of the isopropyl. By applying the reactions performed from (±)-**6** to (±)-**8** we were able to conclude that it was also possible to determine the enantiomeric purity when the nitrogen carries a tertiobutyl group: the ^{19}F spectrum in $CHCl_3$ of esters **14** obtained by the action of the *R* acid chloride on (±)-**13** (Scheme 3c) presented two signals at –16.39 and –18.44 ppm, in other words very close to those of (*RS*)-**12** and (*RR*)-**12**. Their intensity ratio here was also 54:46. The position at –16.40 ppm of the signal obtained after esterification of (*S*)-**8** (Scheme 3d) indicated that the enantiomer pair *RS*–*SR* again had the most deshielded signal.

2.3. Determination of configuration

In this case, the approach to the problem was simplified: the intensity ratio of the two signals did not have to be determined, but simply the position of the signal corresponding to each *R* or *S* isomer. The identification, discussed in the previous paragraph, of two distinctly separate signals in the case of the *N*-benzylesters could also be used to determine the configuration of the starting β-aminoalcohol. But it was decided to try and develop a simpler method which would not require protection of a function or the use of the acid chloride, which required preparation. To do this, we started with the model compound (±)-**6**.

Direct action of the fluorinated acid was first envisaged, since it gives rise to the formation of ammonium salts only. Unfortunately, in ^{19}F NMR, these salts presented only one fairly broad signal, both with Mosher's acid and with 2-fluorophenylacetic acid, contrary to what may be observed during the reaction between α-methylbenzylamine and AFPA.[20]

The action of the fluorinated acid on the β-aminoalcohol in the presence of dicyclohexylcarbodiimide (DCC) and a catalyst was then envisaged. In this case, we expected to observe the simultaneous formation of the amide and ester functions. The results obtained would be positive if, on the one hand, the zones where signals were present did not overlap, and, on the other hand, at least one of the functions gave rise to the presence of distinctly separate signals. By reacting (±)-**6** with a large excess of the chloride of racemic fluorophenylacetic acid, which led to **15**, we were able to identify the zones corresponding to the signals of the amides **16** and esters **17** (Scheme 4). In dimethylsulfoxide, used because of the low solubility of β-blockers often observed in chloroform, these zones extended, respectively, from –3.4 to –7.9 ppm and from –10.8 to –14.5



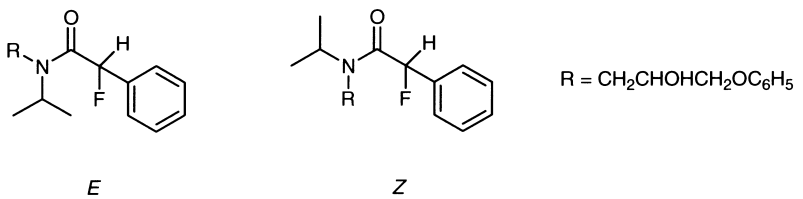
Scheme 4.

ppm using C_6F_6 as a reference. When we worked with stoichiometric amounts of (*R*)-2-fluorophenylacetic acid in the presence of DCC and hydroxybenzotriazole (HOBT) the very preponderant formation of the (*RR*)-**16** and (*RS*)-**16** amides was observed. The spectra were also recorded in other solvents (Table 1). In each case, the presence of four distinct signals was observed after the suppression of the H–F coupling. The subsequent studies were carried out in methanol. Each *RR* or *RS* configuration of the amide **16** was thus demonstrated by the presence of two fluorine-NMR signals. They correspond to the *Z* and *E* conformers (Scheme 5).[5,19] The latter result from a rotation, which is slow in relation to the NMR time scale, around the amide bond. In order to determine the position of the signals corresponding to each enantiomer of (±)-**6**, an experiment was carried out with (*S*)-**6**. The two signals of the (*RS*)-**16** isomer obtained were situated at –3.04 and –3.68 ppm, in other words more deshielded than those of the (*RR*)-**16** isomer. A study of molecular modelling, which is in the course of publication, allowed us to partly justify the position of the different signals: the signal at –6.59 ppm corresponds to the *RR*(*Z*) form and the one at –4.24 ppm to the *RR*(*E*) form. This last one is clearly predominant and its percentage varies with the solvent: methanol (75), acetone (87.5), acetonitrile (84.5).

The reaction carried out under the same conditions with Mosher's acid gave much less decisive results. No matter what solvent was used, the four good signals were never completely separate. The biggest difference between the extremes was 0.71 ppm in methanol.

Table 1
δ_F values of signals (and $\Delta\delta_F$ differences between these signals) observed for amides **16** ($Ar = C_6H_5$) in different solvents. Internal reference: C_6F_6

Solvent	δ_F	$\Delta\delta_F$
Acetonitrile	-2.97	
	-3.47	0.50
	-3.67	0.20
	-6.90	3.23
Acetone	-4.02	
	-4.37	0.35
	-5.15	0.78
	-7.71	2.56
Chloroform	-5.09	
	-7.00	1.91
	-8.30	1.30
	-9.14	0.84
DMSO	-3.39	
	-4.26	0.87
	-4.30	0.04
	-7.79	3.49
Methanol	-3.10	
	-3.74	0.64
	-4.24	0.50
	-6.59	2.35

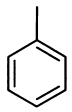
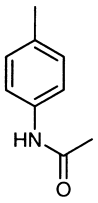
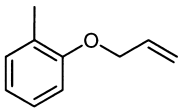
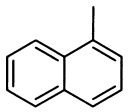
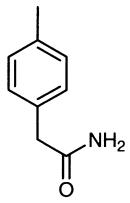
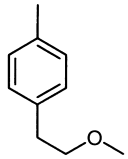
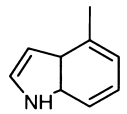


E *Z*

Scheme 5.

These results, which can be used for establishing a correlation between the δ_F values observed and the *R* and *S* configurations of the β-aminoalcohols, needed to be confirmed. The aryl group of β-blockers is in fact generally substituted, which was not the case for (±)-**6**; this may influence the results. The reaction was thus extended to six β-blockers substituted in various ways: practolol **1** and oxprenolol **10** (in racemic and *S* forms) prepared according to Scheme 1, propranolol (racemic and *S*), atenolol, metoprolol and pindolol, which are available commercially. The results are shown in Table 2. It can be seen from Table 2 that for the different derivatives each signal was situated in a narrow δ_F range and there was a correlation between the δ_F values and the absolute configuration: the *RS*-isomer presented the most deshielded signals (except for **10**). Both of the extreme signals thus corresponded to a different configuration. The difference between these signals—at least 3.5 ppm—was such that they could be used to determine the *R* or *S* configuration of the β-aminoalcohols and in particular of the β-blockers with the structure $ArOCH_2$-$CHOHCH_2NHiPr$.

Table 2
Chemical displacement of fluorine signals in amides **16**. Solvent: methanol. Internal reference: C_6F_6

Ar	 **6**	 Practolol	 Oxprenolol	 Propranolol	 Atenolol	 Metoprolol	 Pindolol
δF (±)	-3.10 -3.74 -4.24 -6.59	-3.00 -3.64 -4.11 -6.57	-2.97 -4.13 -4.37 -6.47	-2.97 -3.70 -4.10 -6.61	-3.13 -3.72 -4.27 -6.57	-3.11 -3.73 -4.21 -6.47	-2.97 -3.84 -4.04 -6.64
δF (*S*)	-3.04 -3.68	-3.04 -3.67	-2.91 -4.34	-2.92 -3.68			

Here again, as with **6**, the *E* conformer clearly predominates in the case of the *RR* configuration. One cannot, however, establish a valid correlation between the importance of the *E*:*Z* ratio and the substituent (nature or position) in the cycle, as the results below show. With the *para* substituent the following percentages of *E* conformer can be observed: 81 (practolol), 74 (atenolol) and 72 (metoprolol). With the *ortho* substituent the results are very similar: 80 (propranolol), 73 (oxprenolol) and 70 (pindolol). In the case of the *RS* isomer, for which the determination of the position of each conformer is in progress, one arrives at the same conclusion. In effect, there is practically equality of percentage between the two forms for oxprenolol (50), propranolol (51), atenolol and **6** (52). The other three compounds show a slightly greater difference (57% of predominant conformer). In each case the most deshielded signal is the less important. As with the *RR* isomer, it is therefore not possible to establish a correlation between the percentage of the predominant form and the substitution in the aromatic cycle.

When the nitrogen carried a tertiobutyl, as in the case of (±)-**8**, it was observed that the derivatization carried out in the same conditions as for (±)-**6** led to the extremely preponderant formation of the *RS* and *RR* esters **18** (Scheme 4), for obvious steric reasons. The spectra plotted in the same solvents as previously gave the values shown in Table 3. It can be seen that the results are not as clear as in the case of amides **16**. Only acetone, chloroform and DMSO gave sufficient differences between the two expected signals for there to be some hope of being able to determine the configuration of the initial aminoalcohol. Unlike the case of the amides, it is not possible to generalize on the basis of these results. Further studies are needed on compounds where the aromatic cycle is substituted in different ways. Such studies are now under way. Even so, these first results are very encouraging.

Table 3
Fluorine chemical shift in esters **18**

Solvent	δ_F	$\Delta\delta_F$
Acetonitrile	-12.95 -13.03	0.08
Acetone	-12.87 -13.55	0.68
Chloroform	-17.04 -17.68	0.64
DMSO	-11.71` -12.22	0.51
Methanol	-14.69 -14.73	0.04

3. Conclusion

We developed a method for determining the enantiomeric purity and configuration of β-aminoalcohols with the structure $ArOCH_2CH(OH)CH_2NHR$ (R = *i*Pr or *t*Bu) using ^{19}F NMR. The derivatization agent used, 2-fluorophenylacetic acid or its chloride, made it possible to obtain very simple spectra with distinctly separate signals. For determination of enantiomeric purity, after protection of the amine function by a benzyl group, the ester spectrum obtained presented essentially two signals separated by at least 2.5 ppm. For determination of the configuration, the direct action of the acid on the aminoalcohol led to the very preponderant formation of amide (R = *i*Pr) or ester (R = *t*Bu). In the first case, the spectrum presented four distinctly separate signals in various solvents. The two extreme signals, which did not belong to the same diastereomer compound, were at least 3.5 ppm apart. The presence or absence of one of these two signals can thus be used to determine the configuration of the β-aminoalcohol unambiguously. The method was successfully applied to six β-blockers. With R = *t*Bu, the first results obtained were positive, but they must be completed with further studies. From a practical standpoint, a complete derivatization reaction was not required to determine the configuration; the running of this reaction and workup were very simple, without final purification.

4. Experimental

Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl under argon immediately prior to use. Pyridine and acetonitrile were dried by reflux over and distillation from CaH_2. DMF was freshly distilled from BaO. All epoxidations, amide and ester formations were conducted under an atmosphere of argon. TLC was performed on Merck aluminium precoated plates of silica gel 60F-254 (detection by UV and by spraying with phosphomolybdic acid—5% in ethanol—followed by heating). Column chromatography was carried out on a Merck kieselgel 60 (0.063–0.20 mm) using the same eluting system as for TLC, unless otherwise noted.

Uncorrected melting points were determined on a Büchi melting point apparatus. Optical rotations were determined at the sodium D line with a Perkin–Elmer 341 polarimeter. Infrared spectra were recorded on a Nicolet impact 400 spectrophotometer. NMR spectra were recorded on a Brüker AC 200 spectrometer using Me_4Si as internal reference for ^1H NMR spectra, $CDCl_3$ for ^{13}C NMR and C_6F_6 for ^{19}F NMR spectra. Coupling constants (J) are given in hertz. Elemental analyses were determined by the Service Central d'Analyses du CNRS (Vernaison, France).

General procedure for the epoxidation reaction. To a slurry of NaH in dry DMF at 0°C was added dropwise a solution of the phenol in DMF. When the H_2 evolution stopped, glycidyl tosylate in DMF was added dropwise. After complete consumption of the phenol at rt, the solvent was very carefully removed and the resulting crude product dissolved in EtOAc. The organic layer was washed three times with water, then dried, concentrated in vacuo and the residue purified by column chromatography.

4.1. (±)-3-(4-Acetamidophenoxy)-1,2-epoxypropane (±)-4[27,28]

4-Acetamidophenol (7.55 g, 50 mmol), NaH (2.20 g, 55 mmol), (±)-glycidyl tosylate (11.40 g, 50 mmol) and DMF (100 mL) gave, after column chromatography ($CHCl_3$:MeOH, 97:3), 7.7 g (75%) of epoxide (±)-**4** as a white solid: mp 112–113°C (lit.:[27,28] 110°C); ^1H NMR (200 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.73–2.77 (dd, H, J = 4.8 and 2.6 Hz), 2.88–2.92 (2 overlapping d, H), 3.30–3.38 (m, H), 3.86–3.95 (dd, H, J = 10.9 and 5.8 Hz), 4.16–4.24 (dd, H, J = 10.9 and 3.1 Hz), 6.82–6.87 (d, 2H, J = 8.9 Hz), 7.36–7.41 (d, 2H, J = 8.9 Hz), 7.48 (s, H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.2, 44.6, 50.1, 69.0, 114.9, 121.8, 131.5, 155.1, 168.6.

4.2. (S)-3-(4-Acetamidophenoxy)-1,2-epoxypropane (S)-4[29]

4-Acetamidophenol (0.755 g, 5 mmol), NaH (0.22 g, 5.5 mmol) and (*S*)-glycidyl tosylate (1.14 g, 5 mmol) in DMF (15 mL) furnished 0.700 g (66%) of (*S*)-**4** as a white solid: mp 108–110°C (lit.:[29] 104–106°C for the *R* isomer); $[\alpha]_D^{20} = 9.6$ (*c* 1.02, MeOH) [lit.:[29] $[\alpha]_{365}^{25} = -18.5$ (*c* 2.0, EtOH) for the *R* isomer].

4.3. (S)-1,2-Epoxy-3-phenoxypropane (S)-5

Phenol (0.5 g, 5.32 mmol), NaH (0.23 g, 6 mmol) and (*S*)-glycidyl tosylate (1.21 g, 5.30 mmol) in DMF (15 mL) gave (*S*)-**5** (0.573 g, 73%) as an oil after chromatography (cyclohexane:EtOAc, 6:2); $[\alpha]_D = 5.2$ (*c* 1.15, $CHCl_3$).

4.4. (±)-3-(4-Iodophenoxy)-1,2-epoxypropane (±)-7[30]

4-Iodophenol (3.3 g, 15 mmol), NaH (0.72 g, 18 mmol) and (±)-glycidyl tosylate (4 g, 18 mmol) in DMF (25 mL) furnished after column chromatography ($CHCl_3$:MeOH, 9:1) (±)-**7** (3.32 g, 80%) as a white solid: mp 67–68°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.71–2.76 (dd, H, J = 4.8 and 2.7 Hz), 2.87–2.92 (overlapping dd, H), 3.28–3.37 (m, H), 3.85–3.93 (dd, H, J = 11.0 and 5.8 Hz), 4.16–4.23 (dd, H, J = 11.0 Hz and 3.1 Hz), 6.67–6.71 (d, 2H, J = 8.6 Hz), 7.51–7.57 (d, 2H, J = 8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.58, 49.9, 68.8, 83.4, 117.0, 138.2, 158.3.

4.5. (S)-3-(4-Iodophenoxy)-1,2-epoxypropane (S)-7

4-Iodophenol (0.44 g, 2 mmol), NaH (0.088 g, 2.2 mmol) and (*S*)-glycidyl tosylate (0.456 g, 2 mmol) in DMF (25 mL) furnished after purification 0.41 g (74%) of (*S*)-**7** as a solid: mp 58–60°C; $[\alpha]_D^{20} = 9.1$ (*c* 1.01, MeOH).

4.6. (±)-3-(2-Allyloxyphenoxy)-1,2-epoxypropane (±)-9[31,32]

Catechol monoallylether[33] (1.5 g, 10 mmol), HNa (0.44 g, 11 mmol) and (±)-glycidyl tosylate (2.28 g, 10 mmol) in DMF (50 mL in all) furnished after chromatography (cyclohexane:EtOAc, 8:2) 1.65 g (80%) of (±)-**9** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.73–2.77 (dd, H, J = 5.0 and 2.6 Hz), 2.85–2.90 (overlapping dd, H), 3.31–3.42 (m, H), 3.99–4.07 (dd, H, J = 11.3 and 5.5 Hz), 4.21–4.29 (dd, H, J = 11.3 and 3.4 Hz), 5.29–5.47 (m, 2H), 5.98–6.18 (m, H), 6.88–6.99 (m, 4H); ^{13}C NMR (50MHz, $CDCl_3$) δ 44.5, 50.1, 69.7, 70.1, 114.3, 114.9, 117.3, 121.2, 121.8, 133.3, 148.4, 148.6.

4.7. (S)-3-(2-Allyloxyphenoxy)-1,2-epoxypropane (S)-9

Starting from the same quantities as for (±)-**9**, 1.41 g (68.5%) of (*S*)-**9** was obtained as an oil; $[\alpha]_D^{20} = 13.55$ (*c* 1.07, MeOH).

Preparation of the aminoalcohols: general procedure. A solution of the epoxide and the chosen amine (10 equiv.) in isopropanol was heated to reflux. After complete consumption of the epoxide (TLC), the solvent was evaporated to dryness, the residue powdered, and stirred in ether or pentane at rt. After filtration the compound was recovered as a white powder. The yield was always higher than 90%. The aminoalcohol could also be purified by column chromatography.

4.8. (±)-1-Isopropylamino-3-phenoxypropan-2-ol (±)-6[34,35]

(±)-1,2-Epoxy-3-phenoxypropane (22.5 g, 0.15 mol) and isopropylamine (60 g) in isopropanol (150 mL) gave after treatment with pentane 30.1 g (96%) of (±)-**6**: mp 92.5–94°C.[36] ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 and 1.06, (d, 6H, J = 6.2 Hz), 2.64–2.95 (m, 5H), 3.91–4.09 (m, 3H), 6.85–7.00 (m, 3H), 7.21–7.34 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.9, 23.1, 48.9, 49.3, 68.3, 70.4, 114.6, 120.9, 129.4, 158.6.

*4.9. (S)-1-Isopropylamino-3-phenoxypropan-2-ol (S)-**6***

(*S*)-**5** (570 mg, 3.8 mmol) and isopropylamine (3.36 g, 57 mmol) in isopropanol (30 mL) gave, after chromatography (EtOAc:MeOH, 6:4), (*S*)-**6** (575 mg, 72%) as a white powder: mp 42–43.5°C; $[\alpha]_D^{25} = -7.8$ (*c* 1.05, $CHCl_3$).

*4.10. (±)-3-(4-Acetamidophenoxy)-1-(isopropylamino)propan-2-ol (practolol) (±)-**1**[28]*

Mp 140–142°C (lit.:[28] 142–143°C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06–1.09 (d, 6H, J = 6.2 Hz), 2.14 (s, 3H), 2.40 (br s, 2H), 2.65–3.00 (m, 3H), 3.80–4.10 (m, 3H), 6,85 (d, 2H, J = 9.0 Hz), 7.32 (s, H), 7.36 (d, 2H, J = 9.0 Hz); ^{13}C NMR (50 Hz, $CDCl_3$) δ 22.4, 22.6, 23.6, 50.3, 50.9, 69.6, 72.2, 115.6, 122.9, 133.2, 156.9, 171.3.

*4.11. (S)-3-(4-Acetamidophenoxy)-1-(isopropylamino)propan-2-ol (S)-**1**[29]*

Mp 132–134°C; $[\alpha]_D^{25} = -2.42$ (*c* 0.99, EtOH) [lit.:[29] $[\alpha]_D^{25} = \pm 4.3$ (*c* 1.0, EtOH) for *R* isomer].

*4.12. (±)-1-*tert*-Butylamino-3-(4-iodophenoxy)propan-2-ol (±)-**8**[36]*

Mp 96–97°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.13 (s, H), 2.61–2.74 (m, 2H), 2.78–2.91 (m, 4H), 3.86–4.02 (m, 2H), 6.64–6.73 (dt, 2H, J = 8,9 Hz and 2.0 Hz), 7.50–7.59 (dt, 2H, J = 8.9 and 2.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.8, 44.7, 50.6, 68.3, 70.6, 82.9, 116.8, 138.0, 158.5.

*4.13. (S)-1-*tert*-Butylamino-3-(4-iodophenoxy)propan-2-ol (S)-**8***

Mp 72–74°C; $[\alpha]_D^{20} = 2.61$ (*c* 1.07, $CHCl_3$).

*4.14. (±)-3-(2-Allyloxyphenoxy)-1-(isopropylamino)propan-2-ol (oxprenolol) (±)-**10** [32]*

Mp 77–78°C (lit.:[32] 78–80°C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05–1.09 (d, 6H, J = 6.2 Hz), 2.69–2.88 (m, 5H), 3.94–4.20 (m, 3H), 4.54–4.58 (m, 2H), 5.22–5.47 (m, 2H), 5.97–6.16 (m, 4H), 6.83–6.98 (m, 4H); ^{13}C NMR (50 MHZ, $CDCl_3$) δ 22.9, 48.8, 49.3, 68.4, 69.8, 73.0, 114.2, 115.3, 117.7, 121.5, 121.9, 133.3, 148.7, 148.9.

*4.15. (S)-3-(2-Allyloxyphenoxy)-1-(isopropylamino)propan-2-ol (S)-**10**[31]*

Mp 56–58°C; $[\alpha]_D^{20} = -2.57$ (*c* 1.05, $CHCl_3$).

*4.16. (±)-1-(N-Benzyl)isopropylamino-3-phenoxypropan-2-ol (±)-**11***

A solution of (±)-**6** (1 g, 4.78 mmol) and benzyl chloride (0.847 g, 6.69 mmol) in anhydrous acetonitrile (30 mL) was refluxed under argon in the presence of dry potassium carbonate (0.926 g, 6.69 mmol). After completion of the reaction, and monitoring by TLC (cyclohexane:acetone, 4.5:0.5), the solid was filtered and rinsed with CH_2Cl_2. The filtrate was concentrated in vacuo and the residue purified by chromatography to give 1.30 g (91%) of (±)-**11** as a viscous yellowish oil. IR (neat) 3444 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01–1.09 (2d, 6H, J = 6.6 Hz), 2.58–2.64

(m, 2H), 2.98 (sept, H, J = 6.6 Hz), 3.52–3.75 (2d, 2H, J = 13.8 Hz), 3.87–3.95 (m, 3H), 6.85–6.96 (m, 3H), 7.19–7.31 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 19.6, 50.1, 51.9, 54.8, 66.1, 70.3, 114.5, 120.8, 127.1, 128.4, 128.6, 129.3, 158.8. Anal. calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.01; H, 8.60; N, 4.54.

4.17. (S)-1-(N-Benzyl)isopropylamino-3-phenoxypropan-2-ol (S)-11

Aminoalcohol (*S*)-**6** (100 mg, 0.48 mmol), benzyl chloride (84.7 mg, 0.67 mmol), acetonitrile (5 mL) and dry K_2CO_3 (93 mg, 0.67 mmol) gave (*S*)-**11** (120 mg, 84%) after chromatography (cyclohexane:EtOAc:MeOH, 8.5:1:0.5) as a viscous oil. $[\alpha]_D^{20} = -17.2$ (*c* 1.15, $CHCl_3$).

4.18. (±)-1-(N-Benzyl)tert-butylamino-3-(4-iodophenoxy)propan-2-ol (±)-13

The procedure was the same as for (±)-**11**. Aminoalcohol (±)-**8** (80 mg, 0.21 mmol), benzyl bromide (70 mg, 0.42 mmol), acetonitrile (8 mL) and dry K_2CO_3 (57 mg, 0.42 mmol) furnished after chromatography (cyclohexane:EtOAc, 4.5:0.5) 82 mg (91%) of (±)-**13** as an oil. IR (neat) 3432; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 9H), 2.64–2.85 (m, 2H), 3.2 (s, H), 3.40–3.49 (m, H), 3.52–3.59 (d, H, J = 14.4 Hz), 3.65–3.68 (m, 2H), 3.68–3.82 (d, H, J = 14.4 Hz), 6.55–6.61 (d, 2H, J = 9 Hz), 7.20–7.30 (m, 5H), 7.44–7.52 (d, 2H, J = 9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.4, 53.6, 55.8, 66.9, 70.3, 82.8, 116.9, 127.0, 128.5, 138.0, 141.6, 158.6. Anal. calcd for $C_{20}H_{26}INO_2$: 54.67; H, 5.92; I, 28.93; N, 3.19. Found: C, 54.83; H, 6.14; I, 27.32; N, 3.11.

4.19. (S)-1-(N-Benzyl)tert-butylamino-3-(4-iodophenoxy)propan-2-ol (S)-13

Aminoalcohol (*S*)-**8** (100 mg, 0.286 mmol), benzyl bromide (73 mg, 0.42 mmol), acetonitrile (5 mL) and dry K_2CO_3 (60 mg, 0.43 mmol) gave (*S*)-**13** (100 mg, 88%) after chromatography (cyclohexane:EtOAc:MeOH, 8.5:1:0.5) as a viscous oil. $[\alpha]_D^{20} = 5.0$ (*c* 1.00, $CHCl_3$).

4.20. 1-(N-Benzyl)isopropylamino-3-phenoxyprop-2-yl 2-fluorophenylacetate 12

To a solution of (±)-**11** (35 mg, 0.12 mmol) in anhydrous CH_2Cl_2 at rt, under argon, was added (*R*)-2-fluorophenylacetyl chloride (40 mg, 0.23 mmol) and pyridine (9 mL). After complete consumption of the starting material (TLC; cyclohexane:acetone, 9:1) the reaction mixture was washed first with an $NaHCO_3$ saturated aqueous solution, then with water until neutrality. The organic layer was dried and the solvent evaporated. The residue was dissolved in the NMR solvent. The esterification of (±)-**13** or (*S*)-**13** followed the same way to give isomers **14**.

4.21. 1-(N-Isopropyl-α-fluorotoluenecarboxamido)-3-phenoxyprop-2-yl 2-fluorophenyl acetate 15

To a solution of (±)-**6** (42 mg, 0.2 mmol) and (*R*)-α-fluorophenylacetyl chloride (173 mg, 1 mmol) in THF:acetonitrile (1:1, 10 mL) was added triethylamine (101 mg, 1 mmol). A precipitate appeared and the reaction—monitored by TLC (methanol:$CHCl_3$, 3:7)—was finished after 1 hour. The precipitate was filtered and the solvent removed in vacuo to dryness. The residue was dissolved in CH_2Cl_2 (20 mL) and the solution washed with 5% $NaHCO_3$. After drying and evaporation of the solvent, the residue was dissolved in deuterated DMSO for NMR measures.

Reaction of AFPA (or MTPA) with the aminoalcohols in the presence of DCC and HOBT: general procedure. A solution of the aminoalcohol (0.1 mmol), AFPA (0.1 mmol), DCC (0.11 mmol) and HOBT (0.11 mmol) in THF:acetonitrile (1:1) was stirred at rt. After consumption of the starting aminoalcohol, monitored by TLC (methanol:$CHCl_3$, 3:7), the reaction mixture was filtered and the solvents evaporated to dryness. The residue was dissolved in the proper solvent for ^{19}F NMR.

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