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Synthesis of High-specific-radioactivity 4- and 6-[^{18}F]fluorometaraminol- PET Tracers for the Adrenergic Nervous System of the Heart

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Abstract—Fluorine-18- ($t_{1/2}$ 109.8 min) and carbon-11 ($t_{1/2}$ 20.4 min)-labeled norepinephrine analogues have been found previously to be useful positron-emission-tomography (PET) radioligands to map adrenergic nerve terminals of the heart. Metaraminol ((1*R*,2*S*)-2-amino-1-(3-hydroxyphenyl)-1-propanol) is a metabolically stable structural analogue of norepinephrine and possesses high affinity towards the norepinephrine transporter and the vesicular monoamine transporter. This paper presents the radiosynthesis of new positron-emission-tomography halogeno analogues of metaraminol labeled with high specific radioactivity. Firstly, fluorine-18-labeled 4-fluorometaraminol (4-[^{18}F]FMR or (1*R*,2*S*)-2-amino-1-(4-[^{18}F]fluoro-3-hydroxyphenyl)-1-propanol) and its three other stereoisomers were prepared based on the following key steps: (a) condensation of the corresponding no-carrier-added labeled fluorobenzaldehyde with nitroethane, and (b) HPLC (C18 and chiral) resolution of the diastereomeric product mixture into the four individual enantiomers. Secondly, the corresponding 6-fluoro analogues, fluorine-18-labeled 6-fluorometaraminol (6-[^{18}F]FMR or (1*R*,2*S*)-2-amino-1-(2-[^{18}F]fluoro-5-hydroxyphenyl)-1-propanol) and its three other enantiomers, were prepared in an analogous way. Typically, 0.48–0.55 GBq of 4-[^{18}F]FMR and 0.14–0.15 GBq of 6-[^{18}F]FMR could be obtained after 120–160 min total synthesis time, with a specific radioactivity of 56–106 GBq/μmol. Furthermore, the synthesis of racemic 4-fluorometaraminol and 6-fluorometaraminol as reference compounds was performed, as well as independent chiral syntheses of the optically active (1*R*,2*S*) enantiomers. For the chiral syntheses, the key step was an electrophilic fluorination with acetyl hypofluorite of (1*R*,2*S*)-configurated organometallic derivatives of metaraminol. Tissue distribution studies in rats suggested that both 4-[^{18}F]FMR and 6-[^{18}F]FMR display similar affinity towards the presynaptic adrenergic nerve terminal in the heart. From a practical point of view, 4-[^{18}F]FMR appeared to be the more attractive candidate for future PET investigations, due to higher radiochemical yields.

Introduction

Sympathetic cardiac innervation plays a key role in the evolution of heart disease—such as congestive heart failure, myocardial infarction,—hypertrophy and diabetes—and is a major target of many therapeutic agents. Norepinephrine (NE, **1**) (Fig. 1) is the endogenous neurotransmitter of the sympathetic nervous system. Its physiological behavior involves several steps: synthesis by the axons, accumulation of the neurotransmitter in nerve terminals, release into the synaptic cleft and binding to the receptor inducing the physiological response by the effector. The final step is metabolism and/or re-uptake of the neurotransmitter. In humans, the re-uptake system plays a major function for inactivation of NE. Presynaptic function—i.e., release and re-uptake of the neurotransmitter—can be assessed using 'false adrenergic neurotransmitters' in positron emission tomography (PET), a high-resolution-, sensitive- and non-invasive imaging technique.[1–6] Sympathetic neurons take up circulating NE by the neuronal norepinephrine transporter (uptake-1), followed by storage in neuronal vesicles by the vesicular monoamine transporter. The uptake-2 system is located in myocardial

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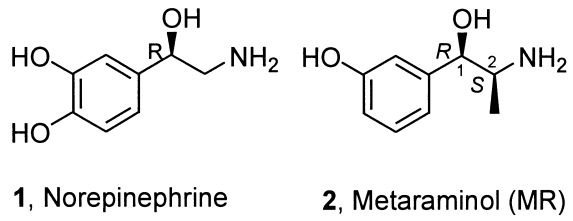


Figure 1. Chemical structures of norepinephrine (**1**) and metaraminol (**2**).

myocytes and is quantitatively not important in humans. NE uptake is a reliable indicator of neuronal integrity.[7]

Metaraminol (**2**, (1*R*,2*S*)-2-amino-1-(3-hydroxyphenyl)-1-propanol or MR) is a metabolically stable structural analogue of NE (**1**).[8] This 'false neurotransmitter' possesses optimal characteristics for a myocardial neuronal marker, since it displays high affinity towards both the norepinephrine transporter and the vesicular monoamine transporter.[9] Radiolabeled metaraminol and a series of analogues have been prepared and assessed for their suitability to map adrenergic nerve terminals of the heart with PET.[10–16] From these emerged 6-[^{18}F]fluorometaraminol (6-[^{18}F]FMR or (1*R*,2*S*)-2-amino-1-(2-[^{18}F]fluoro-5-hydroxyphenyl)-1-propanol, [^{18}F]-(1*R*,2*S*)-**4**) (Fig. 2) as a potential candidate with first promising in vivo results in animals.[10–13] The radiosynthesis was achieved by electrophilic substitution of the corresponding acetoxymercurio derivative using carrier-added acetyl hypo[^{18}F]fluorite.[10] The relatively low specific radioactivity (typically 0.04–0.56 GBq/μmol) obtained for this tracer suggested that the doses to be used would be too high—inducing a significant increase in blood pressure—to allow its clinical use in patients with heart failure.

Recently, carbon-11-labeled metaraminol has been prepared by condensation of 3-hydroxybenzaldehyde with [^{11}C]nitroethane.[15,17] Benzaldehydes can be labeled with no-carrier-added fluorine-18 by nucleophilic aromatic substitution,[18] leading to high-specific-radioactivity fluoro derivatives. This approach has already been successfully applied to the synthesis of labeled catecholamines, such as [^{18}F]fluoronorepinephrine[19] and [^{18}F]fluorodopamine.[20]

This paper presents the radiosynthesis of new positron-emission-tomography halogeno analogues of metaraminol. Firstly, fluorine-18-labeled 4-fluorometaraminol (4-[^{18}F]FMR or (1*R*,2*S*)-2-amino-1-(4-[^{18}F]fluoro-3-hydroxyphenyl)-1-propanol ([^{18}F]-(1*R*,2*S*)-**3**)) (Fig. 2) and its three other stereoisomers were prepared based on the following key steps: (a) condensation of the corresponding no-carrier-added labeled fluorobenzaldehyde with nitroethane, and (b) HPLC resolution of the diastereomeric product mixture into the four individual enantiomers. Secondly, the corresponding 6-fluoro analogues, fluorine-18-labeled 6-fluorometaraminol (6-[^{18}F]FMR or (1*R*,2*S*)-2-amino-1-(2-[^{18}F]fluoro-5-hydroxyphenyl)-1-propanol ([^{18}F]-(1*R*,2*S*)-**4**)) (Fig. 2) and its three other enantiomers, were prepared in an analogous way. Furthermore, the synthesis of racemic 4-FMR (**3**) and 6-FMR (**4**) as reference compounds was performed as well as independent chiral syntheses of the optically active, enantiomerically pure stereoisomers (1*R*,2*S*)-**3** and (1*R*,2*S*)-**4**.

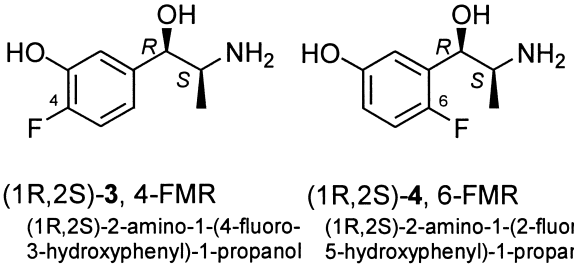


Figure 2. Chemical structures of 4-FMR ((1*R*,2*S*)-**3**) and 6-FMR ((1*R*,2*S*)-**4**).

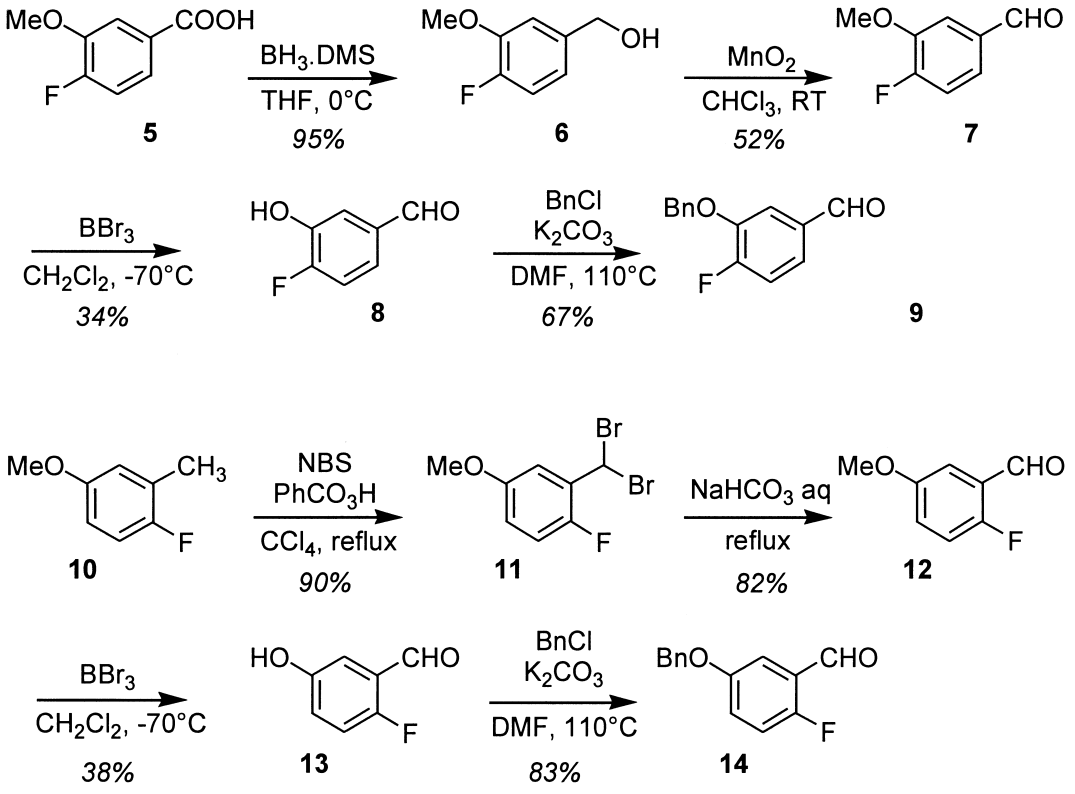
Finally, this paper presents a preliminary radiopharmacological characterization of 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**) and the other three stereoisomers. Their suitability to map sympathetic nerves of the heart was evaluated and compared with 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**).

Results and Discussion

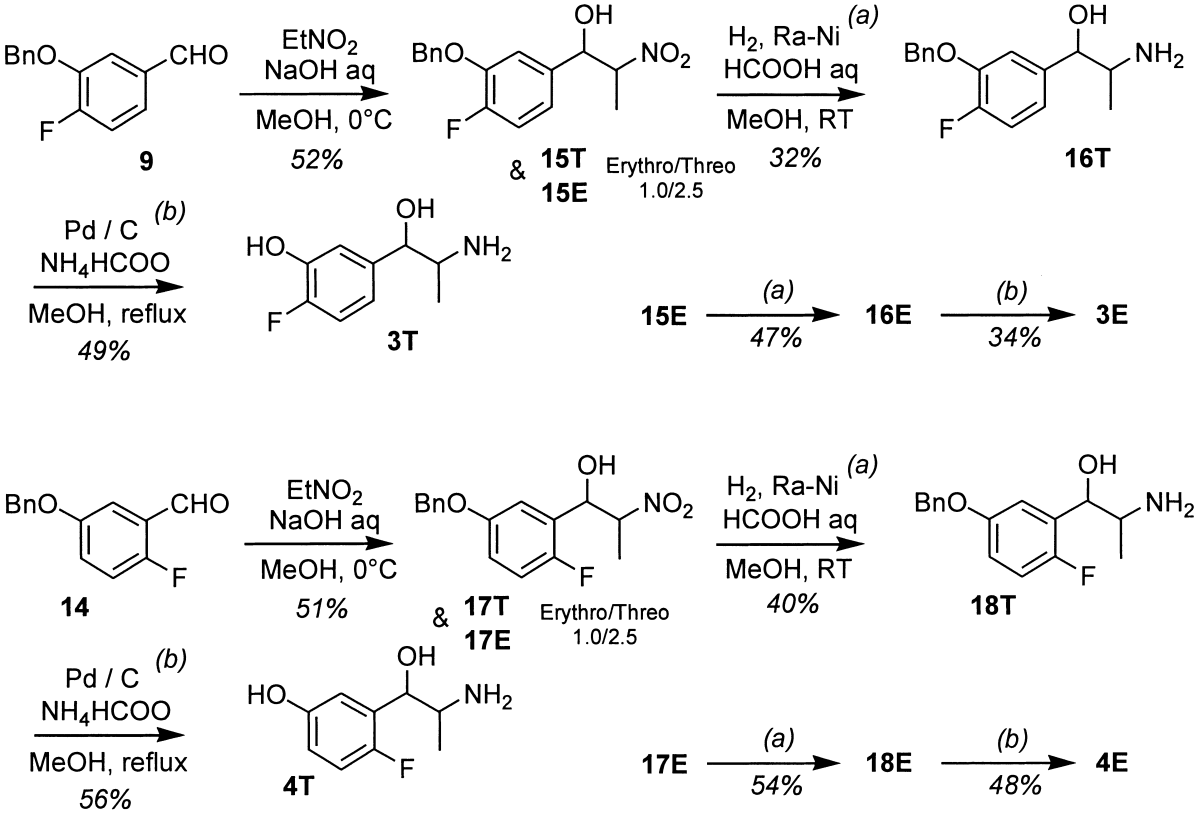
Chemistry

Preparation of racemic 4-FMR (3, or 2-amino-1-(4-fluoro-3-hydroxyphenyl)-1-propanol) and racemic 6-FMR (4, or 2-amino-1-(2-fluoro-5-hydroxyphenyl)-1-propanol). 3-Benzyloxy-4-fluorobenzaldehyde (**9**) and 5-benzyloxy-2-fluorobenzaldehyde (**14**) were used as starting material for the synthesis of racemic 4-FMR (**3**, or 2-amino-1-(4-fluoro-3-hydroxyphenyl)-1-propanol) and racemic 6-FMR (**4**, or 2-amino-1-(2-fluoro-5-hydroxyphenyl)-1-propanol), respectively. Benzaldehydes **9** and **14** were prepared according to Scheme 1.

For the synthesis of **9**, commercially available 4-fluoro-3-methoxybenzoic acid (**5**) was reduced with borane dimethyl sulfide complex to afford the intermediate benzyl alcohol **6** in 95% yield. Compound **6** was oxidized with manganese dioxide to give, in 52% yield, the corresponding benzaldehyde **7**. The phenolic methyl ether was cleaved by reaction with BBr_3[21] to obtain free phenol **8** in 34% yield. Intermediate **8** was subsequently reacted with benzyl chloride to afford finally the desired benzyl-protected fluorobenzaldehyde derivative **9** in 67% yield. The synthesis of compound **14**, the 6-fluoro isomer of **9**, started from commercially available 4-fluoro-3-methylanisole (**10**). In an initial attempt (not shown in Scheme 1), potassium peroxydisulfate ($K_2S_2O_8$), a reagent reported to be suitable for oxidation of toluenes to benzaldehydes,[22] was tested for the synthesis of aldehyde **12** from **10**. However, the only product that could be isolated from the reaction mixture was identified as methyl-1,4-benzoquinone by ^{1}H- and ^{13}C NMR comparison with the commercially available product (Aldrich, structure not shown). This quickly let us



Scheme 1. Synthesis of 3-benzyloxy-4-fluorobenzaldehyde (**9**) and 5-benzyloxy-2-fluorobenzaldehyde (**14**).



Scheme 2. Preparation of *erythro*/*threo* 4-FMR (**3E**/**3T**) and *erythro*/*threo* 6-FMR (**4E**/**4T**).

abandon this pathway in favor of the indirect approach depicted in Scheme 1. Instead of direct oxidation of **10**, the toluene was first brominated with *N*-bromosuccinimide to afford dibromotoluene **11** (90% yield).[23] Derivative **11** was subsequently hydrolyzed by use of aq $NaHCO_3$ to give benzaldehyde **12** in good yield (82%). In an analogous way, as described above for the preparation of **9**, the methoxy group in **12** was replaced by a benzyloxy group to give finally **14** in a yield of 32%.

Base-catalyzed (NaOH) condensation of benzaldehydes **9** and **14** with nitroethane in ice-cooled CH_3OH afforded the corresponding β-nitroalcohols **15** and **17**, both in about 50% yield (Scheme 2).[24] As two asymmetric carbon atoms were introduced into the molecule at this step of the synthesis, the formed nitroalcohols represented racemic diasteromeric mixtures, *erythro*-**15E** and-**17E** (1*R*,2*S* and 1*S*,2*R*) and *threo*-**15T** and-**17T** (1*R*,2*R* and 1*S*,2*S*), respectively. Diastereomers possess different physicochemical properties, and *erythro*/*threo* product mixtures could thus be conveniently separated by semipreparative normal-phase HPLC. In the 4- as well as in the 6-substituted series, the formation of the *threo* product predominated over *erythro*, in a ratio of around 2:1. Interestingly, performance of the reaction at ambient temperature favored the *threo* product even more (*threo*:*erythro*, 3:1).

The reaction sequence was continued for each racemic diastereomer separately (Scheme 2). Raney-nickel-catalyzed reduction of the NO_2 function[25] in 4-fluoro-substituted compounds **15E** (*erythro*) and **15T** (*threo*), and 6-fluoro-substituted compounds **17E** (*erythro*) and **17T** (*threo*) with H_2 in a mixture of CH_3OH and formic acid afforded the corresponding β-aminoalcohols **16E**, **16T**, **18E** and **18T**, respectively (30–50% yield). Without formic acid in the reaction mixture yields were substantially lower. Surprisingly, the benzyl protective group in these intermediates was left unaffected by the reaction, even though this type of protective group is normally cleaved under reductive conditions.[21] The cleavage of the benzyl ethers was finally achieved with NH_4HCOO and palladium catalyst to yield the *erythro*- and *threo* forms of 4-FMR (**3E** and **3T**) and 6-FMR (**4E** and **4T**), respectively. Each racemic diastereomer was resolved by chiral HPLC (using a semipreparative ChromTech AB Chiral-CBH column), which afforded all possible enantiomers of these analogues (Fig. 3) (Scheme 3). A similar chiral HPLC method for the resolution of metaraminol (**2**) and the other three stereoisomers from the racemic mixture has been described previously in the literature.[26]

Preparation of optically pure 4-FMR ((1*R*,2*S*)-3, or (1*R*,2*S*)-2-amino-1-(4-fluoro-3-hydroxyphenyl)-1-propanol) and optically pure 6-FMR ((1*R*,2*S*)-4, or (1*R*,2*S*)-2-amino-1-(2-fluoro-5-hydroxyphenyl)-1-propanol). Metaraminol (**2**) is the (1*R*,2*S*)-configurated and pharmacologically most potent enantiomer of 2-amino-1-(3-hydroxyphenyl)-1-propanol (Fig. 3).[27] In order to identify the (1*R*,2*S*) enantiomers of both the 4-fluoro and the 6-fluoro analogues of MR (**3** and **4**), we independently synthesized the correspondingly configurated products, starting from commercially available metaraminol (**2**) (Scheme 4).

For the 4-substituted series, **2** was selectively iodinated in the 4-position of the aromatic ring (using I_2 in aq NH_4OH/EtOH) according to a literature method to afford 4-iodometaraminol **19** (57% yield).[11] The NH_2- and phenolic OH group were then simultaneously protected with di-*tert*-butyl dicarbonate in dioxane/H_2O and aq NaOH[28] to yield di-Boc-protected derivative **20** in 30% yield. Treatment of **20** with hexamethyldistannane and tetrakis(triphenylphosphine)palladium gave organotin compound **21** in good yield (75%).[29] Organotin derivatives are reported to react readily with electrophilic fluorinating agents, such as F_2 or acetyl hypofluorite (AcOF), to afford the corresponding fluoro analogues.[30] No product could be isolated from the reaction mixture when diluted F_2 was directly used as the fluorinating agent. We therefore generated AcOF on-line from F_2 by a gas-phase method reported in the

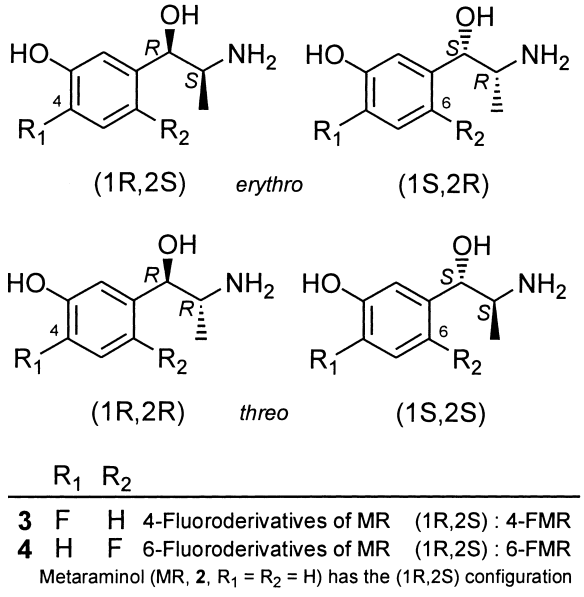
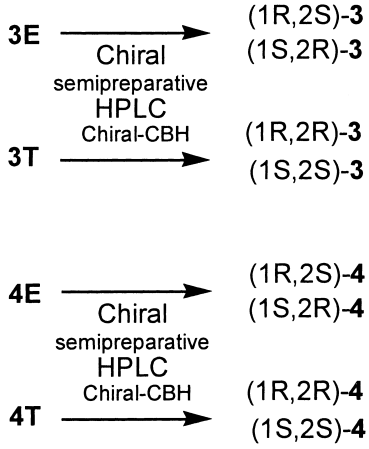


Figure 3. Chemical structures of the four enantiomers of both the 4- and the 6-fluoroderivatives of metaraminol.

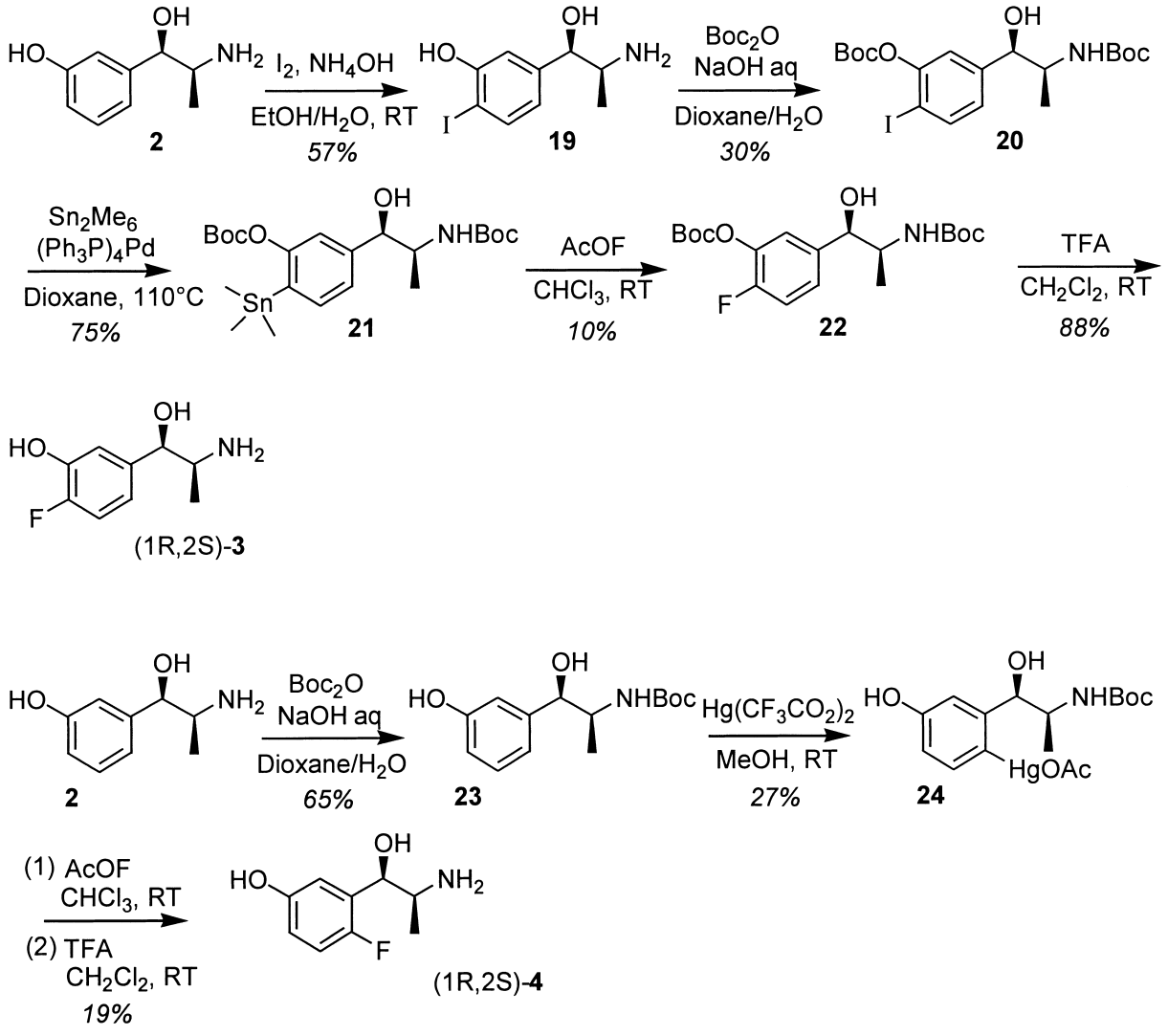


Scheme 3. Chiral HPLC resolution of 4-FMR ((1*R*,2*S*)-**3**) and 6-FMR ((1*R*,2*S*)-**4**).

literature.[31] Acetyl hypofluorite is known to be a milder alternative to F_2 that affords good product yields in fluorodemetallation reactions of aromatic compounds.[32] However, in our case the yield of fluoro intermediate **22** was relatively low (10%). Deprotection of compound **22** with TFA in CH_2Cl_2 occurred smoothly (88% yield) and afforded 4-FMR ((1*R*,2*S*)-**3**) as the final product. 4-FMR ((1*R*,2*S*)-**3**) co-eluted on chiral HPLC with one of the two enantiomers of the *erythro* racemate **3E** (obtained in the racemic synthesis described earlier), thus unambiguously assigning the (1*R*,2*S*) enantiomer in the racemic mixture.

For the synthesis of 6-FMR ((1*R*,2*S*)-**4**), starting material metaraminol (**2**) was first Boc-protected on the NH_2 function[28] to yield derivative **23** in good yield (65%) (Scheme 4). Treatment of **23** with mercuric trifluoroacetate, according to a method published in the literature, selectively afforded the 6-substituted trifluoroacetoxymercurio analogue **24**.[10,33] As described before, organometallic compound **24** was fluorinated with AcOF to give, after deprotection with TFA, the desired 6-fluoro-substituted product 6-FMR ((1*R*,2*S*)-**4**). 6-FMR ((1*R*,2*S*)-**4**) co-eluted on chiral HPLC with one of the two enantiomers of the *erythro* racemate **4E** (obtained in the racemic synthesis described earlier), thus unambiguously assigning the (1*R*,2*S*) enantiomer in the racemic mixture.

Preparation of the precursors for fluorine-18 labeling of racemic 4-FMR and racemic 6-FMR: trimethylanilinium triflates 26 and 30 and nitrobenzaldehydes 28 and 32. Fluorobenzaldehyde derivatives **9** and **14** (Scheme 5) gave easy access to the corresponding trimethylanilinium trifluoromethanesulfonates (triflates) **26** and **30** to be used in the radiosynthesis as precursors for [^{18}F]fluoride incorporation. Fluoro- for dimethylamino substitution with $Me_2NH.HCl$, K_2CO_3 in refluxing DMSO/H_2O afforded intermediates **25** and **29** in 85 and 66% yield, respectively. Trimethylanilinium triflates **26** and **30** were prepared from **25** and **29**, in 71 and 46% yield, respectively, by methylation of the Me_2N groups with methyl triflate.[34] Derivatives **28** and **32**, the corresponding nitro precursors, were prepared by simple benzyl protection of the phenolic OH functions in commercially available **27** and **31**, in 40–45% yield (Scheme 5).



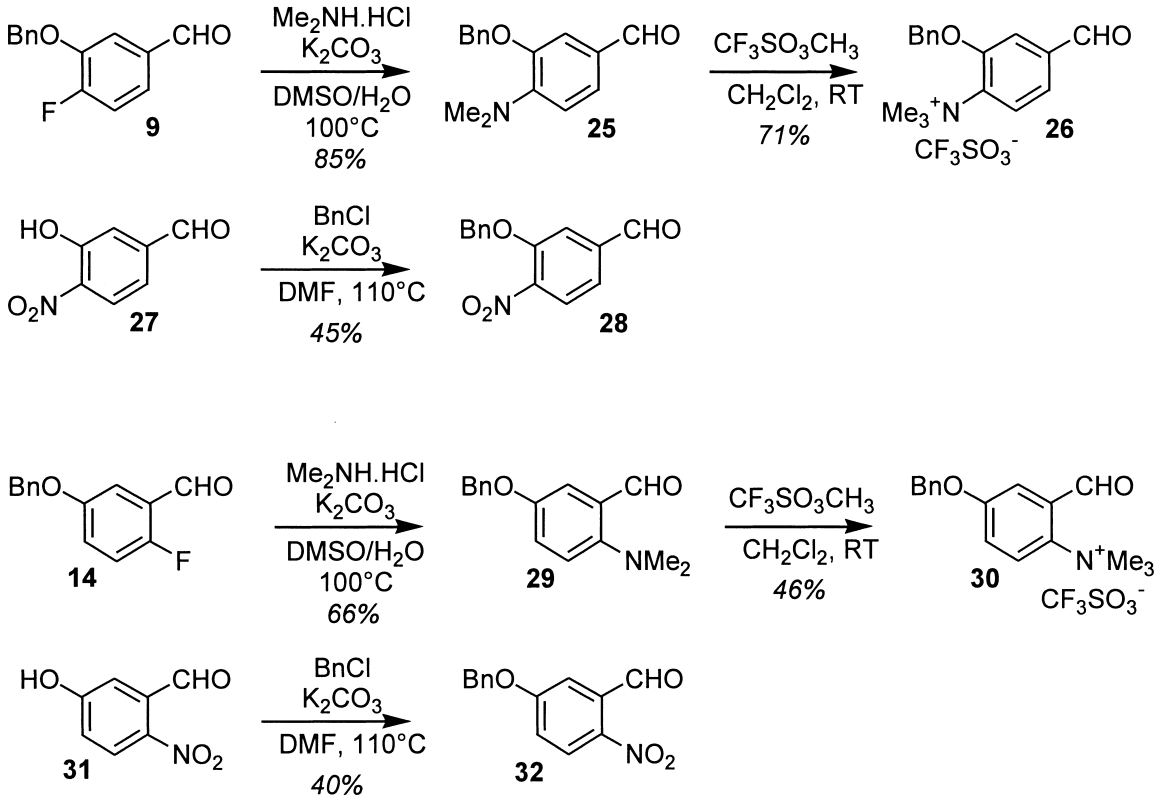
Scheme 4. Preparation of optically pure 4-FMR ((1*R*,2*S*)-**3**) and 6-FMR ((1*R*,2*S*)-**4**).

Radiochemistry

Nucleophilic substitution, by means of cyclotron-produced, no-carrier-added [^{18}F]fluoride ion is the method of choice for the synthesis of high-specific-radioactivity fluorine-18-labeled ($t_{1/2}$ 109.8 min) radioligands for PET. However, many biologically interesting compounds, such as catecholamines, are not activated for this type of reaction due to the presence of electron-donating substituents in the aromatic nucleus. In this case, a common strategy involves fluorine-18 labeling of chemically activated precursor molecules that are, in the subsequent reaction steps, converted into the compounds of interest. Examples for this approach are given by the syntheses of [^{18}F]fluoronorepinephrine and [^{18}F]fluorodopamine reported in the literature.[19,20] The approach for the radiosynthesis of [^{18}F]fluorometaraminol, presented in this work, is derived from the previously published preparation of [^{11}C]metaraminol starting from 3-hydroxybenzaldehyde and [^{11}C]nitroethane.[15]

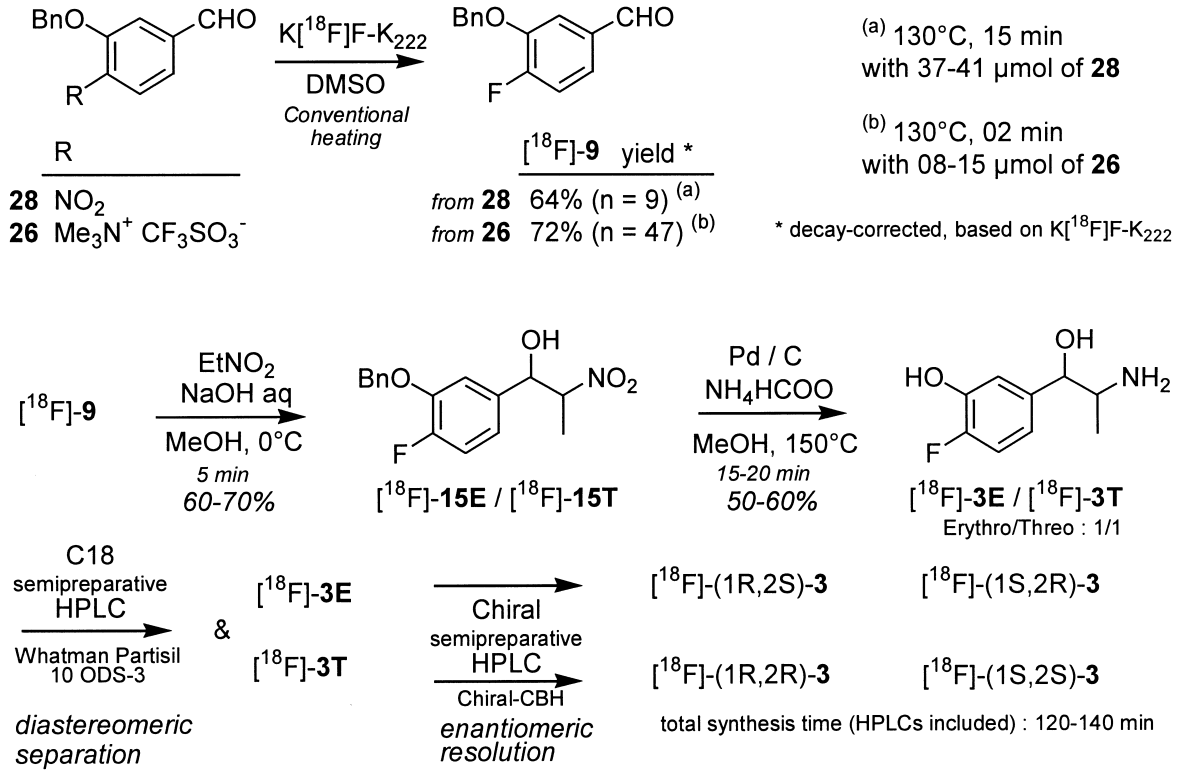
Preparation of racemic 4-[^{18}F]FMR ([^{18}F]-3, or 2-amino-1-(4-[^{18}F]fluoro-3-hydroxyphenyl)-1-propanol) and racemic 6-[^{18}F]FMR ([^{18}F]-4, or 2-amino-1-(2-[^{18}F]fluoro-5-hydroxyphenyl)-1-propanol). Racemic 4-[^{18}F]FMR ([^{18}F]-**3**, 2-amino-1-(4-[^{18}F]fluoro-3-hydroxyphenyl)-1-propanol) was prepared in three steps from precursor benzaldehydes bearing either a nitro leaving group (**28**) or a trimethylanilinium leaving group (**26**) (Scheme 6). Racemic 6-[^{18}F]FMR ([^{18}F]-**4**, 2-amino-1-(2-[^{18}F]fluoro-5-hydroxyphenyl)-1-propanol) was prepared in an analogous way from the nitro derivative **32** or trimethylanilinium triflate **30** (Scheme 7).

Step 1: incorporation of fluorine-18. The first step consisted of the introduction of fluorine-18 into the 4- or 6-position of the aromatic ring using no-carrier-added nucleophilic aromatic substitution with K[^{18}F]F-K_{222} in DMSO (Schemes 6 and 7). The trimethylanilinium group has not only a high potential as a leaving group for incorporation of [^{18}F]fluoride into an aromatic ring but also facilitates precursor-product separation due to its ionic nature.[34] The phenolic OH groups in the precursor benzaldehydes needed to be protected, as commercially available free phenols **27** and **31** (structures shown in Scheme 5) afforded no product at all in the reaction with K[^{18}F]F-K_{222}. The benzyl group was preferred to other groups, such as methyl groups, due to its fast and easy removal by catalytic hydrogenation.[21] The 4-NO_2 precursor **28** (19.5 μmol), when heated with [^{18}F]fluoride at 130 °C during 15 min, gave an average radiochemical yield of 52%. Increase of precursor amount to 39 μmol improved the yield to 64%, while prolongation of reaction time had no effect. The corresponding 4-substituted $^{+}NMe_3$ precursor **26** was better than the NO_2 analogue, with an incorporation yield of 72% achieved within only 2 min heating at 130 °C (using 11.9 μmol precursor). In addition to that, the reaction could be performed in the same tube as the one for drying the K[^{18}F]F-K_{222} complex, simply by addition of the precursor dissolved in DMSO. It is noteworthy that a prolonged reaction time caused a drop in yield, probably due to the volatility of the formed

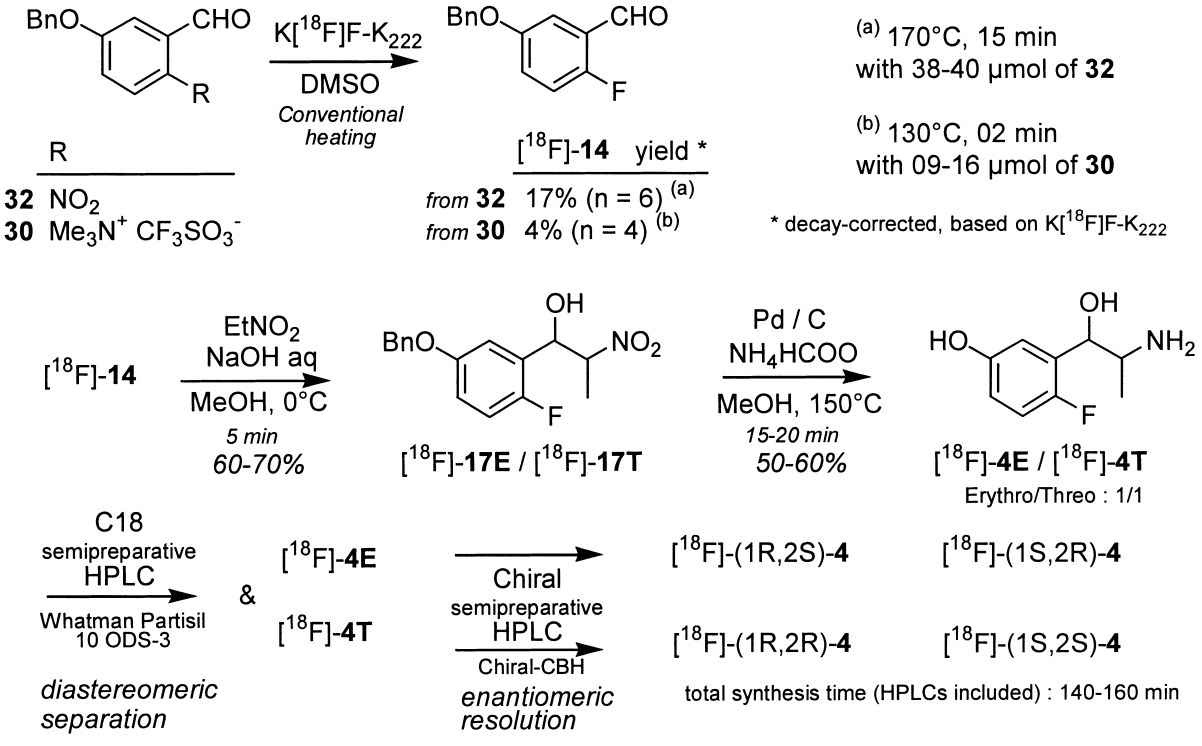


Scheme 5. Preparation of the precursors for fluorine-18 labeling: trimethylanilinium triflates **26** and **30** and nitrobenzaldehydes **28** and **32**.

[^{18}F]fluorobenzaldehyde [^{18}F]-**9** in combination with the unsealed reaction tube. Interestingly, in case of the 6-substituted [^{18}F]fluorobenzaldehyde [^{18}F]-**14**, the NO_2 precursor was more effective than the corresponding $^{+}NMe_3$ precursor. From NO_2 compound **32** an average yield of 17% could be obtained, while $^{+}NMe_3$ precursor **30** gave only 4% of product. The comparatively low yield of [^{18}F]fluorobenzaldehyde in case of the 6-substituted precursor might be explained by formation of CH_3[^{18}F]F as a side product, due to nucleophilic attack of fluoride at one of the methyl groups born by the ammonium function.[35] For both types of leaving



Scheme 6. Preparation of racemic 4-[^{18}F]FMR ([^{18}F]-**3**, or 2-amino-1-(4-[^{18}F]fluoro-3-hydroxyphenyl)-1-propanol).



Scheme 7. Preparation of racemic 6-[^{18}F]FMR ([^{18}F]-**4**, or 2-amino-1-(2-[^{18}F]fluoro-5-hydroxyphenyl)-1-propanol).

groups, the 6-position in the aromatic ring seemed to be significantly less activated for nucleophilic aromatic substitution as compared to the 4-position. These findings are consistent with literature results where similar substrates had been subjected to no-carrier-added nucleophilic substitutions with fluorine-18.

Step 2: condensation of the fluorine-18-labeled benzaldehydes with nitroethane. After C_{18} Sep-Pak purification, benzaldehydes [^{18}F]-**9** and [^{18}F]-**14** were in analogy to the synthesis of reference compounds, converted into the corresponding nitroalcohols ([^{18}F]-**15E**/**T** and [^{18}F]-**17E**/**T**), by base-catalyzed condensation with nitroethane (Schemes 6 and 7). In contrast to the published synthesis of [^{11}C]metaraminol, where tetrabutylammonium fluoride was used as the base,[15] better yields were achieved, in our case, with NaOH.[24] Condensation reactions were completed within 5 min and conversion yields (determined by analytical HPLC) averaged 60–70%. Unlike the preparation of reference material, *erythro*:*threo* ratios were in both cases 1:1 ([^{18}F]-**15E**/[^{18}F]-**15T** and [^{18}F]-**17E**/[^{18}F]-**17T**: 50/50), as deducted from the *erythro*:*threo* ratios of final [^{18}F]-**3** and [^{18}F]-**4**.

Step 3: reduction and resolution of all stereoisomers. Palladium catalyst and NH_4HCOO in CH_3OH was then added to the crude reaction mixtures of [^{18}F]-**15E**/[^{18}F]-**15T** and [^{18}F]-**17E**/[^{18}F]-**17T**, followed by heating at 150 °C for 15–20 min. These reaction conditions resulted in simultaneous reduction of NO_2 groups and cleavage of benzyl ethers, thus affording directly, in one step, racemic 4-[^{18}F]FMR ([^{18}F]-**3**) and 6-[^{18}F]FMR ([^{18}F]-**4**), respectively, in 50–60% radiochemical yield (corrected for decay and based on nitroalcohols). Alternatively, use of 30% aq HCOOH and Raney nickel catalyst was tried out for the reduction, as in the synthesis of [^{11}C]metaraminol,[15] but led to unsatisfactory yields of product.

Crude product mixtures [^{18}F]-**3** and [^{18}F]-**4** were subsequently, after filtration and removal of remaining CH_3OH by heating under a N_2 stream, separated into the two *erythro*- and *threo* racemates by semipreparative HPLC (using a Whatman Partisil 10 ODS-3 C18 column). Two fractions with equal amounts of radioactivity and 4–5 min difference in retention times were collected, with *erythro* (**3E** and **4E**) eluting in both cases before *threo* (**3T** and **4T**). Resolution into individual enantiomers was accomplished by chiral HPLC with a semipreparative ChromTech AB Chiral-CBH column. Due to the sensitivity of the chiral HPLC column, the individual fractions from the first HPLC had to be concentrated to dryness and re-dissolved in mobile phase prior to injection. When *erythro*/*threo* mixtures were directly injected into chiral HPLC no baseline separation of the stereoisomers was achieved. The (1*R*,2*S*) enantiomers, 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**) and 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**), respectively, were identified by co-elution with the corresponding reference compounds. The mobile phase of chiral HPLC (phosphate buffer, pH 6.5) was suitable for direct administration in the rat experiments and did not have to be removed. The whole synthesis procedure (including the first HPLC purification) was fully automated on a computer-assisted Zymate® robot system (Zymark Corporation, USA).

Typical radiosynthesis. In the case of the radiosynthesis of racemic 4-[^{18}F]FMR ([^{18}F]-**3**), productions started from $^{+}NMe_3$ precursor **26**, while for the radiosynthesis of racemic 6-[^{18}F]FMR ([^{18}F]-**4**), the NO_2 precursor **32** was preferred. Typically, starting from a 20.3–24.0 GBq fluorine-18 cyclotron production batch (20 μA, 30 min, 36,000 μC) the synthesis of racemic [^{18}F]-**3** yielded around 0.48–0.55 GBq of each enantiomer within a total synthesis time (HPLC purification included) of 120–140 min. For racemic [^{18}F]-**4**, starting from a similar fluorine-18 cyclotron production batch afforded 0.14–0.15 GBq of each enantiomer within 140–160 min synthesis time. Specific radioactivity ranged from 56–106 GBq/μmol at the end of synthesis. This specific radioactivity meant a 100- to 200-fold improvement compared to the electrophilic pathway reported in the literature[10] and should thus exclude pharmacological side effects of the radioligand.

During the preparation of this manuscript, an alternative radiochemical synthesis of 4-[^{18}F]FMR was developed at the *Institut für Nuklearchemie* (Forschungszentrum Jülich, Germany) and appeared in the literature both as an abstract at the *XIIth International Symposium on Radiopharmaceutical Chemistry* and as an internal report.[36,37] These authors described an approach starting from 4-(2-*N*,*N*-dibenzylaminopropionyl)-2-benzyloxyphenyl-1-*N*,*N*,*N*-trimethylanilinium triflate as a precursor. Following no-carrier-added nucleophilic aromatic substitution, a partially stereoselective reduction and final deprotection step were performed. C18 and chiral HPLC purification finally afforded 4-[^{18}F]FMR.

Pharmacology

The high-specific-radioactivity synthetic approach used for the preparation of fluorometaraminol derivatives [^{18}F]-**3** and [^{18}F]-**4** afforded for each analogue all four possible enantiomers. Tissue distribution studies in rat were performed with the 4-fluorometaraminol derivatives ([^{18}F]-**3**) to evaluate their capability of mapping cardiac sympathetic nerve terminals. These results were compared with those obtained with 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**) as this MR analogue (labeled with low specific radioactivity) had previously been found to be a suitable neuronal marker[10–12] (Table 1).

Among the four enantiomers of [^{18}F]-**3**, only two compounds had a significantly high cardiac uptake: the (1*R*,2*S*) enantiomer (same configuration as MR,% I.D./g: 2.93 at 20 min) and one enantiomer of the *threo* racemate (configuration not identified,% I.D./g: 2.35 at 20 min). The other two enantiomers (namely *erythro*-(1*S*,2*R*), and the second, unidentified enantiomer of the *threo* racemate) had a twice as low myocardial uptake (% I.D./g: 0.72 and 0.80, respectively, at 20 min). In the spleen, another organ with rich sympathetic innervation in rodents, the same two first above-mentioned enantiomers

Table 1. Tissue distribution studies in rats

Time	4-[^{18}F]Fluoro derivatives of MR (2-amino-1-(4-[^{18}F]fluoro-3-hydroxyphenyl)-1-propanol) *erythro* racemate [^{18}F]-**3E**		*threo* racemate [^{18}F]-**3T**		6-[^{18}F]FMR [^{18}F]-**4**
min	1*R*,2*S*	1*S*,2*R*	1*S*,2*S**	1*R*,2*R**	1*R*,2*S*
Heart					
5	3.08±0.28	1.70±0.02	3.10±0.30	1.60±0.14	–
10	3.18±1.26	0.85±0.05	3.40±0.20	1.16±0.14	–
20	2.93±0.04	0.72±0.14	2.35±0.25	0.80±0.07	2.96±0.17
60	1.64±0.37	0.13±0.01	1.54±0.38	0.26±0.05	–
Spleen					
5	0.80±0.12	0.73±0.20	1.02±0.40	0.58±0.08	–
10	0.58±0.03	0.42±0.04	0.92±0.14	0.70±0.14	–
20	1.09±0.23	0.59±0.05	0.81±0.08	0.54±0.09	0.80±0.35
60	0.73±0.16	0.15±0.01	0.64±0.05	0.28±0.07	–
Lung					
5	1.53±0.28	2.79±0.50	4.50±0.98	1.68±0.27	–
10	0.85±0.13	0.87±0.14	1.42±0.41	1.08±0.06	–
20	0.67±0.10	0.92±0.11	1.04±0.27	0.66±0.12	0.73±0.10
60	0.39±0.03	0.41±0.10	0.75±0.06	0.60±0.15	–

Adult male Sprague–Dawley rats weighing 200 g were each injected with 1.1–1.2 MBq (27–29 pmol; specific radioactivity, 40.7 GBq/μmol) of optically pure enantiomers of 4-[^{18}F]FMR ([^{18}F]-**3**) in the tail vein. The rats were sacrificed at selected time points after injection of the radiotracer ($n=3$ per time point). Tissues of different organs (heart, spleen and lung) were rapidly removed, blotted and weighed. Radioactivity of the samples was measured in a γ-counter and tissue concentrations were expressed as percent of injected dose per gram of tissue (% I.D./g)±standard deviation. For direct comparison, 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**) was injected (0.9–1.1 MBq; 24–29 pmol; specific radioactivity, 37 GBq/μmol) and rats ($n=3$) were sacrificed at 20 minutes after injection. Tissue samples of the different organs were removed and evaluated as described above.
*Interchangeable assignment.

showed significant organ uptake (% I.D./g: 1.09 and 0.81, respectively, at 20 min) and retention whereas rapid clearance was observed for the other two enantiomers (% I.D./g: 0.59 and 0.54, respectively, at 20 min). These findings are in good agreement with a previous study on the sympathomimetic activity of individual metaraminol stereoisomers.[27] In that study, the (1*S*,2*R*) enantiomer was found to be the least potent stereoisomer, whereas both *threo* enantiomers exhibited some sympathomimetic activity (about one tenth of the activity of the (1*R*,2*S*) enantiomer and the (1*S*,2*S*) enantiomer being more potent than the (1*R*,2*R*) enantiomer). For the two compounds showing high heart and spleen uptake, the % I.D./g in the target cardiac tissue was still measurable at 90 min (% I.D./g: 0.82±0.5 and 0.55±0.5, respectively; data not shown in Table 1) and the plot of myocardial time radioactivity curves was similar and gave a calculated half life of one hour. For the other two enantiomers, the activity had practically washed out completely at 90 min. All enantiomers exhibited rapid blood clearance. Comparably high myocardium over blood radioactivity ratios were found for the two enantiomers of interest from the time of tracer injection up to one hour (values of 24–27, at 10 min post-injection). However, only the (1*R*,2*S*)-enantiomer ([^{18}F]-(1*R*,2*S*)-**3** or 4-[^{18}F]FMR) showed a high myocardium over lung ratio (a value of 4, 10 min post-injection), a highly favorable feature for PET imaging of the heart. Furthermore, the distribution pattern of 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**) closely paralleled that of 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**), with comparably high radioactivity concentrations in both heart and spleen. These latter findings were consistent with previously published results for low-specific-radioactivity labeled 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**).[10–12]

Additional experiments to prove the neuronal selectivity in the heart of 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**) for the NE transporter have been carried out and results have been presented elsewhere.[38] Serotonin and dopamine transporters (SERT and DAT, respectively) are hardly expressed in the cardiac tissue. The selective binding of 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**) in the heart for the NE transporter has been demonstrated in vivo in both rats and dogs: e.g. in a PET experiment, pretreatment of a dog with desipramine (a tricyclic antidepressant that blocks the neuronal NE transporter) reduced by 90% the myocardial uptake of 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**).[38]

Conclusion

A three-step synthetic route to high-specific-radioactivity fluorine-18-labeled metaraminol derivatives was developed. Products are in the form of diastereomeric mixtures and are resolved into individual stereoisomers by C18 and chiral HPLC. The fluorine-18 label could be introduced both into the 4-and the 6-position of the aromatic ring, leading to 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**) and 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**). Moreover, this approach overcomes the problem of low-specific-radioactivity labeled 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**), prohibiting its safe use in humans. Typically, optically pure 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**) could be obtained in practical amounts of 0.48–0.55 GBq (specific radioactivity, 56–106 GBq/μmol) within a total synthesis time of

120–140 min (including HPLC purification). 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**, 0.14–0.15 GBq) could be obtained within 140–160 min synthesis time in an analogous way. Preliminary radiopharmacological studies suggested that changing the position of the fluorine-18 label in the metaraminol aromatic ring (from the 6- to the 4-position) does not affect tracer uptake into heart tissue. Both tracers, 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**) and 6-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**4**) seemed to display similar affinity to the presynaptic adrenergic nerve terminal. Additional experiments will be performed to prove the neuronal selectivity of 4-[^{18}F]FMR uptake. From a practical point of view, 4-[^{18}F]FMR ([^{18}F]-(1*R*,2*S*)-**3**) appeared to be the more attractive candidate for future PET investigation of the adrenergic nervous system, due to higher radiochemical yields obtained in the synthesis.

Experimental

General

Chemicals were purchased from standard commercial sources (Aldrich, Fluka or Sigma France) and were used without further purification unless stated otherwise. (−)-Metaraminol (**2**) bitartrate and 4-fluoro-3-methoxybenzoic acid (**5**) were purchased from Sigma and Interchim, France, respectively. TLC was run on pre-coated plates of silica gel 60F_{254} (Merck). The compounds were localized at 254 nm using a UV lamp and/or by dipping the TLC plates into an aq $KMnO_4$ solution (1%) and heating on a hot plate. Radioactive spots were detected using a Berthold TraceMaster 20 automatic TLC linear analyzer. Flash chromatography was conducted on silica gel 63–200 μm (Merck) at 0.3 bar (compressed air). HPLCs were run on a system equipped with a Waters 510 HPLC pump and either of the following two Waters UV detectors: models 440 (single-wavelength) or 486 (multi-wavelength). Alternatively, a Waters 600 HPLC pump controlled by a Waters 600S Controller together with a Shimadzu SPD-10A UV detector (multi-wavelength) were used. The effluent was also monitored for radioactivity with a Geiger-Müller counter. The HPLC columns and conditions were for **A** [Column, Waters μBondapak C18 (300×7.8 mm); porosity, 10 μm; temperature, rt; UV detection at λ: 280 nm]; for **B** [Column, Zorbax RX-SIL (250×9.4 mm); porosity, 5 μm; temperature, rt; UV detection at λ: 280 nm]; for **C** [Column, Whatman Partisil 10 ODS-3 C18 (500×9.4 mm); porosity, 10 μm; temperature, rt; UV detection at λ: 254 nm]; and for **D** [Column, ChromTech AB Chiral-CBH (150×10 mm); porosity, 5 μm; temperature, rt; UV detection at λ: 280 nm]. Specific radioactivity was determined by comparison of the UV absorbance from semipreparative HPLC (system **C**) with that of known amounts of reference compounds.

NMR spectra were recorded on a Bruker AMX (300 MHz) apparatus using the hydrogenated residue of the deuteriated solvents (CD_2Cl_2, δ = 5.32 ppm; CD_3OD, δ = 4.78 and 3.35 ppm; DMSO-d_6, δ = 2.50 ppm) and/or TMS as internal standards for ^{1}H NMR as well as the deuteriated solvents (CD_2Cl_2, δ = 53.8 ppm ; CD_3OD, δ = 49.3 ppm; DMSO-d_6, δ = 39.5 ppm) and/or TMS as internal standards for ^{13}C NMR. The chemical shifts (δ) are reported in ppm, downfield from TMS (s, bs, b, d, bd, t, bt, m for singlet, broad singlet, broad, doublet, broad doublet, triplet, broad triplet and multiplet respectively). The mass spectra (MS), DCI/NH_4^+ and EI, were measured on a Nermag R10-10 apparatus.

Radiosyntheses including the first semipreparative HPLC purification were performed in a 5 cm-lead-shielded confinement using a computer-assisted Zymate® robot system (Zymark Corporation, USA).

Chemistry

4-Fluoro-3-methoxybenzyl alcohol (6). To a solution of 4-fluoro-3-methoxybenzoic acid (**5**, 6.5 g, 38.1 mmol) in freshly distilled THF (100 mL), cooled to 0 °C, borane dimethyl sulfide complex in THF (10.1 M, 20 mL, 202 mmol, 5.6 eq) was slowly added and the mixture was stirred overnight at rt. After slow addition of 60 mL of ice/H_2O and stirring at rt for 30 min the mixture was extracted with diethyl ether. The combined organic layers were washed with saturated aq $NaHCO_3$, H_2O and brine, dried ($MgSO_4$) and concentrated to dryness to give compound **6** (5.7 g, 95% yield) in the form of a yellowish oil. An aliquot of the product was purified by silica gel flash chromatography (CH_2Cl_2:diethyl ether, 96:4) for analytical purposes to afford pure **6**: R_f 0.30-0.35 (CH_2Cl_2:diethyl ether, 95:5); R_f 0.10–0.15 (heptane:EtOAc, 20:10); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 3.82 (s, 3H), 4.54 (s, 2H), 6.80 (dd, *J* 6.0 & 3.0 Hz, 1H), 6.95–7.05 (b, 2H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 56.4 [CH_3], 64.8 [CH_2], 112.5 [CH], 116.0 [CH, $J_{F\text{-}C}$ 15.1 Hz], 119.3 [CH], 138.1 [C], 148.1 [C, $J_{F\text{-}C}$ < 10 Hz,], 152.1 [C, $J_{F\text{-}C}$ 249.0 Hz,]; MS (DCI/NH_4^+) $C_8H_9FO_2$, 174 [M + NH_4^+].

4-Fluoro-3-methoxybenzaldehyde (7). To a solution of **6** (5.5 g, 35.2 mmol) in $CHCl_3$ (500 mL) MnO_2 (115 g, 1.3 mol, 37 equiv) was added and the resulting mixture was stirred overnight at rt. Filtration and removal of solvent yielded **7** (2.8 g, 52% yield) in the form of yellowish crystals: R_f 0.40–0.45 (heptane:EtOAc, 20:10); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 3.95 (s, 3H), 7.24 (dd, *J* 10.7 Hz & 8.2 Hz, 1H), 7.45 (ddd, *J* 8.2, 4.5 & 1.9 Hz, 1H), 7.52 (dd, *J* 8.3 Hz & 1.8 Hz, 1H), 9.90 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 56.7 [CH_3], 112.3 [CH], 116.8 [CH, $J_{F\text{-}C}$ 15.0 Hz], 125.3 [CH, $J_{F\text{-}C}$ 7.5 Hz,], 133.9 [C], 149.2 [C, $J_{F\text{-}C}$ < 10 Hz], 156.7 [C, $J_{F\text{-}C}$ 256.6 Hz], 191.0 [CH]; MS (DCI/NH_4^+) $C_8H_7FO_2$, 172 [M + NH_4^+].

4-Fluoro-3-dibromomethylanisole (11). To a solution of 4-fluoro-3-methylanisole (**10**, 5.1 g, 36.4 mmol) in CCl_4 (200 mL) *N*-bromosuccinimide (16.2 g, 91 mmol, 2.5 equiv) and benzoyl peroxide (200 mg, 0.85 mmol) were added and the reaction mixture was refluxed overnight. The mixture was cooled and filtered and the filtrate was concentrated to dryness to give **11** (9.7 g, 90% yield) as a yellow oil. Silica gel flash chromatography purification (heptane:EtOAc, 95:5) of an aliquot (for analytical purposes) afforded analytically pure **11**: R_f 0.50–0.55 (heptane:EtOAc, 20:10); R_f 0.30–0.35 (heptane:EtOAc, 95:5); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 3.81 (s, 3H), 6.87

(ddd, *J* 9.3, 4.1 & 3.1 Hz, 1H), 6.93 (s, 1H), 6.96 (d, *J* 9.2 Hz, 1H), 7.28 (dd, *J* 6.0 Hz & 3.1 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 32.8 [CH], 56.3 [CH_3], 114.7 [CH], 116.6 [CH, $J_{F\text{-}C}$ 22.6 Hz], 117.7 [CH, $J_{F\text{-}C}$ 7.5 Hz], 129.9 [C, $J_{F\text{-}C}$ 15 Hz], 151.4 [C, $J_{F\text{-}C}$ 241.5 Hz], 156.6 [C]; MS (EI) $C_8H_7Br_2FO$, 300, 298, 296 [M^+], 219, 217 [M^+-Br].

2-Fluoro-5-methoxybenzaldehyde (12). Compound **11** (9.0 g, 30.1 mmol) was refluxed overnight in saturated aq $NaHCO_3$ (100 mL). The reaction mixture was cooled and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to dryness to afford **12** (3.8 g, 82% yield) in the form of a red oil. An aliquot of the product was purified by silica gel flash chromatography (pentane: EtOAc, 97:3) for analytical purposes to afford pure **12**: R_f 0.45–0.50 (heptane:EtOAc, 20:10); R_f 0.15–0.20 (heptane:EtOAc, 95:5); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 3.82 (s, 3H), 7.05–7.20 (b, 2H), 7.28 (dd, *J* 4.9 & 2.8 Hz, 1H), 10.30 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 56.3 [CH_3], 110.6 [CH], 117.9 [CH, $J_{F\text{-}C}$ 22.6 Hz], 123.7 [CH, $J_{F\text{-}C}$ 7.6 Hz], 124.6 [C, $J_{F\text{-}C}$ < 7 Hz], 156.5 [C], 159.9 [C, $J_{F\text{-}C}$ 249.1 Hz], 187.2 [CH]; MS (EI) $C_8H_7FO_2$, 154 [M^+].

General procedure for cleavage of phenolic methyl ethers with BBr_3. A solution of the methoxy derivative in CH_2Cl_2 (100 mL) was cooled to −70 °C and BBr_3 (1.0 M in CH_2Cl_2, 2 to 3 equiv) was added. The reaction mixture was stirred overnight without further cooling. After slow addition of ice/H_2O (100 mL) and stirring for 1 h the layers were separated and the organic phase was washed with saturated aq $NaHCO_3$. The organic phase was then extracted with 2 M aq NaOH. The combined aqueous layers were acidified with concentrated HCl and re-extracted with CH_2Cl_2. The organic layers were washed with brine, dried (Na_2SO_4) and concentrated to dryness to afford the corresponding free phenol.

4-Fluoro-3-hydroxybenzaldehyde (8). Using the methyl ether cleavage procedure described above and starting from compound **7** (4.5 g, 29.2 mmol) afforded **8** (1.4 g, 34% yield) in the form of orange crystals. A sample of **8** was purified by silica gel flash chromatography (pentane: EtOAc, 85:15–75:25) for analytical purposes: R_f 0.25–0.30 (heptane/EtOAc, 20/10); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 5.80 (b, $w_{1/2}$ 75 Hz, 1H), 7.26 (t, *J* 9.0 Hz, 1H), 7.44 (ddd, *J* 8.0, 6.0 & 3.0 Hz, 1H), 7.53 (dd, *J* 6.0 & 3.0 Hz, 1H), 9.89 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 116.9 [CH, $J_{F\text{-}C}$ 19.6 Hz], 118.0 [CH], 124.2 [CH], 134.1 [C], 145.1 [C], 155.6 [C, $J_{F\text{-}C}$ 249.9 Hz], 191.3 [CH]; MS (DCI/NH_4^+) $C_7H_5FO_2$, 158 [$M + NH_4^+$]; MS (EI), 140 [M^+], 111 [M^+-CHO].

2-Fluoro-5-hydroxybenzaldehyde (13). Using the methyl ether cleavage procedure described above and starting from compound **12** (5 g, 32.4 mmol) afforded **13** (1.7 g, 38% yield) in the form of yellow crystals. A sample of **13** was purified by silica gel flash chromatography (pentane:EtOAc, 85:15–75:25) for analytical purposes: R_f 0.25–0.30 (heptane:EtOAc, 20:10); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 6.38 (b, $w_{1/2}$ 11.2 Hz, 1H), 7.00–7.20 (b, 2H), 7.32 (dd, *J* 5.1 & 3.0 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 113.7 [CH], 118.0 [CH, $J_{F\text{-}C}$ 22.6 Hz], 124.4 [CH, $J_{F\text{-}C}$ 7.5 Hz], 124.7 [C], 153.0 [C], 159.8 [C, $J_{F\text{-}C}$ 249.1 Hz], 188.3 [CH]; MS (DCI/NH_4^+) $C_7H_5FO_2$, 158 [$M + NH_4^+$].

General procedure for benzyl protection of phenols. To a solution of the hydroxybenzaldehyde derivative in freshly distilled DMF (10 mL) K_2CO_3 (1.1 equiv) and benzyl chloride (2 equiv) were added and the reaction mixture was heated at 110 °C for 3 h. The cooled mixture was then diluted with H_2O (100 mL). Extraction with CH_2Cl_2, washing with brine, drying ($MgSO_4$) and concentration yielded the crude benzyl-protected phenol.

3-Benzyloxy-4-fluorobenzaldehyde (9). The benzylation procedure described above was used with **8** (1.3 g, 9.3 mmol) and afforded, after silica gel flash chromatography (pentane:EtOAc, 93:7–92:8), pure **9** (1.4 g, 67% yield) in the form of white crystals: R_f 0.45–0.50 (heptane:EtOAc, 20:10); Rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH/CH_3OH: 40:60; flow rate: 4 mL/min): 6–7 min; rt (HPLC B; eluent: heptane:EtOAc: 85:15; flow rate: 5 mL/min): 5–6 min; ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 5.18 (s, 2H), 7.25 (dd, *J* 9.5 & 9.0 Hz, 1H), 7.30–7.50 (b, 6H), 7.57 (dd, *J* 9.0 & 3.0 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 71.6 [CH_2], 114.2 [CH], 117.0 [CH, $J_{F\text{-}C}$ 19.6 Hz], 125.5 [CH, $J_{F\text{-}C}$ 8.0 Hz], 128.1 [CH], 128.8 [CH], 129.1 [CH], 133.8 [C], 136.3 [C], 148.0 [C, $J_{F\text{-}C}$ < 7 Hz], 156.3 [C, $J_{F\text{-}C}$ 255.9 Hz, C], 190.8 [CH]; MS (DCI/NH_4^+) $C_{14}H_{11}FO_2$, 248 [$M + NH_4^+$].

5-Benzyloxy-2-fluorobenzaldehyde (14). The benzylation procedure described above was used with **13** (1.6 g, 7.9 mmol) and gave after purification by silica gel flash chromatography (pentane:EtOAc, 96:4) pure **14** (1.5 g, 83% yield) in the form of yellowish crystals: R_f 0.45–0.50 (heptane:EtOAc, 20:10); rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH:CH_3OH: 40:60; flow rate: 4 mL/min): 8–9 min; rt (HPLC B; eluent: heptane:EtOAc: 95:5; flow rate: 5 mL/min): 5–6 min; ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 5.06 (s, 2H), 7.11 (t, *J* 9.0 Hz, 1H), 7.22 (ddd, *J* 9.0, 4.0 & 3.0 Hz, 1H), 7.30–7.45 (b, 6H), 10.29 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 71.1 [CH_2], 111.9 [CH], 117.9 [CH, $J_{F\text{-}C}$ 22.6 Hz], 124.4 [CH, $J_{F\text{-}C}$ 8.5 Hz], 128.0 [CH], 128.6 [CH], 129.0 [CH], 136.8 [C], 155.6 [C], 159.9 [C, $J_{F\text{-}C}$ 251.3 Hz], 187.1 [CH]; MS (DCI/NH_4^+) $C_{14}H_{11}FO_2$, 248 [$M + NH_4^+$].

3-Benzyloxy-4-nitrobenzaldehyde (28). The benzylation procedure described above was used with 3-hydroxy-4-nitrobenzaldehyde (**27**, 2.0 g, 11.96 mmol) and gave after purification by silica gel flash chromatography (heptane:EtOAc, 80:20) pure **28** (1.4 g, 45% yield) in the form of yellowish crystals: R_f 0.3–0.35 (heptane:EtOAc, 20:10); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 5.29 (s, 2H), 7.30–7.50 (b, 5H), 7.53 (dd, *J* 8.1 & 1.2 Hz, 1H), 7.65 (d, *J* 1.2 Hz, 1H), 7.90 (d, *J* 8.1 Hz, 1H), 10.0 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 71.9 [CH_2], 114.6 [CH], 122.9 [CH], 126.3 [CH], 127.7 [CH], 128.9 [CH], 129.1 [CH], 135.5 [C], 140.1 [C], 143.4 [C], 152.3 [C], 190.7 [CH]; MS (DCI/NH_4^+) $C_{14}H_{11}NO_4$, 275 [$M + NH_4^+$]; MS (EI), 257 [M^+].

5-Benzyloxy-2-nitrobenzaldehyde (32). The benzylation procedure described above was used with 5-hydroxy-2-nitrobenzaldehyde (**31**, 1.0 g, 5.98 mmol) and gave after purification by silica gel flash chromatography (heptane:EtOAc, 80:20) pure **32** (0.62 g, 40% yield) in the form of yellowish crystals: R_f 0.40–0.45 (heptane:EtOAc, 20:10); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 5.20 (s, 2H), 7.21 (dd, *J* 9.1 & 2.8 Hz, 1H), 7.30–7.50 (b, 6H), 8.12 (d, *J* 9.0 Hz, 1H), 10.4 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 71.5 [CH_2], 114.7 [CH], 119.3 [CH], 127.6 [CH], 128.0 [CH], 128.9 [CH], 129.1 [CH], 134.8 [C], 135.7 [C], 142.7 [C], 163.6 [C], 188.8 [CH]; MS (DCI/NH_4^+) $C_{14}H_{11}NO_4$, 275 [$M+NH_4^+$], 258 [$M+H^+$].

General procedure for dimethylamino/fluoro substitution. To a solution of the fluorobenzaldehyde derivative in a mixture of freshly distilled DMSO:H_2O (2.5:1, 10 mL), K_2CO_3 (1 equiv) and dimethylamine hydrochloride (1.4 equiv) were added. The reaction mixture was heated overnight at 100 °C, cooled, diluted with H_2O (25 mL) and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated to dryness to afford the crude dimethylamino derivative.

3-Benzyloxy-4-*N,N*-dimethylaminobenzaldehyde (25). The substitution procedure described above was used with **9** (0.5 g, 2.16 mmol) and gave after purification by silica gel flash chromatography (heptane:EtOAc, 94:6) pure **25** (0.47 g, 85% yield) in the form of yellow crystals: R_f 0.30–0.35 (heptane:EtOAc, 20:10); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 2.82 (s, 6H), 4.95 (s, 2H), 6.74 (d, *J* 9.0 Hz, 1H), 7.20–7.50 (b, 7H), 9.71 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 42.9 [CH_3], 71.2 [CH_2], 111.9 [CH], 116.7 [CH], 127.2 [CH], 128.2 [CH], 128.6 [CH], 129.1 [CH], 129.8 [C], 137.4 [C], 148.9 [C], 150.8 [C], 190.7 [CH]; MS (DCI/NH_4^+) $C_{16}H_{17}NO_2$, 256 [$M+H^+$].

5-Benzyloxy-2-*N,N*-dimethylaminobenzaldehyde (29). The substitution procedure described above was used with **14** (1.2 g, 5.2 mmol) and gave after purification by silica gel flash chromatography (pentane:EtOAc, 98:2–97:3) pure **29** (0.85 g, 66% yield) in the form of yellow crystals: R_f 0.30–0.35 (heptane:EtOAc, 20:10); ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 2.86 (s, 6H), 5.10 (s, 2H), 7.16 (t, *J* 9.0 Hz, 1H), 7.22 (dd, *J* 8.7 & 2.7 Hz, 1H), 7.30–7.55 (b, 6H), 10.41 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 46.5 [CH_3], 70.7 [CH_2], 113.0 [CH], 120.6 [CH], 123.0 [CH], 127.8 [CH], 128.3 [CH], 128.8 [CH], 129.4 [C], 137.3 [C], 151.6 [C], 154.2 [C], 191.3 [CH]; MS (DCI/NH_4^+) $C_{16}H_{17}NO_2$, 256 [$M+H^+$].

General procedure for preparation of trifluoromethanesulfonates from dimethylamino compounds. To a solution of the dimethylamino derivative in CH_2Cl_2 (10 mL) methyl trifluoromethanesulfonate (2 equiv) was added and the reaction mixture was stirred overnight at rt. After addition of heptane (50 mL) the formed precipitate was washed several times with diethyl ether. Drying under vacuum afforded the corresponding trifluoromethanesulfonate.

2-Benzyloxy-4-formyl-*N,N,N*-trimethylanilinium trifluoromethanesulfonate (26). The quaternization procedure described above was used with **25** (0.22 g, 0.86 mmol) and afforded pure **26** (256 mg, 71% yield) in the form of white crystals: R_f 0.0 (heptane:EtOAc, 20:10); ^{1}H NMR (DMSO-d_6, 298.0 K) δ 3.70 (s, 9H), 5.49 (s, 2H), 7.35–7.55 (b, 3H), 7.60 (d, *J* 6.0 Hz, 2H), 7.75 (d, *J* 6.0 Hz, 1H), 7.97 (s, 1H), 8.09 (d, *J* 9.0 Hz, 1H), 10.10 (s, 1H); ^{13}C NMR (DMSO-d_6, 298.0 K) δ 55.1 [CH_3], 71.5 [CH_2], 115.0 [CH], 120.2 [C, $J_{F\text{-}C}$ 264 Hz, quadruplet], 122.7 [CH], 123.4 [CH], 128.4 [CH], 128.6 [CH], 128.8 [CH], 135.1 [C], 137.4 [C], 138.3 [C], 151.4 (C), 192.0 [CH].

4-Benzyloxy-2-formyl-*N,N,N*-trimethylanilinium trifluoromethanesulfonate (30). The quaternization procedure described above was used with **29** (0.3 g, 1.2 mmol) and afforded pure **30** (276 mg, 46% yield) in the form of white crystals: R_f 0.0 (heptane:EtOAc, 20:10); ^{1}H NMR (DMSO-d_6, 298.0 K) δ 3.72 (s, 9H), 5.32 (s, 2H), 7.30–7.60 (b, 7H), 7.97 (b, 1H), 10.15 (s, 1H); ^{13}C NMR (DMSO-d_6, 298.0 K) δ 56.9 [CH_3], 70.0 [CH_2], 119.3 [CH], 120.1 [C, $J_{F\text{-}C}$ 263 Hz, quadruplet], 124.3 [CH], 127.0 [CH], 127.8 [CH], 128.2 [CH], 128.5 [CH], 131.1 [C], 135.9 [C], 137.0 [C], 159.0 [C], 192.9 [CH].

General procedure for coupling of benzaldehyde derivatives with nitroethane. To a solution of the benzaldehyde derivative in CH_3OH (50 mL), cooled to 0 °C, nitroethane (2 equiv) and aq NaOH (10 M, 3.7 mmol) were added and the resulting solution was stirred at 0 °C for 80 min. After addition of aq CH_3COOH (2%, v/v, 50 mL) the reaction mixture was stirred at rt for another 30 min. The CH_3OH was removed under vacuum and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to dryness to afford the crude, racemic mixture of the corresponding nitroalcohol. After purification by silica gel flash chromatography the product mixture was resolved into the respective diastereomeric racemates (*erythro* & *threo*) by semipreparative HPLC.

***Erythro*- and *threo*-1-(3-benzyloxy-4-fluorophenyl)-2-nitro-1-propanol (15E/15T).** The coupling procedure described above was used with **9** (0.86 g, 3.72 mmol) and afforded after purification by silica gel flash chromatography (heptane:EtOAc, 90:10) the crude product (**15E**/**15T**) in the form of a yellow oil. Semipreparative HPLC was used to separate the corresponding *erythro* racemate (**15E**, rt 10–11 min) from the *threo* racemate (**15T**, rt 9–10 min) [HPLC B; eluent: heptane/EtOAc: 85:15; flow rate: 5 mL/min]. Concentration of HPLC fractions to dryness afforded **15E** (171 mg, 16% yield) and **15T** (393 mg, 36% yield) in the form of colorless oils: **15E** (*erythro*): R_f 0.45–0.50 (heptane:EtOAc, 50:50); rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH/CH_3OH: 40:60; flow rate: 4 mL/min): 5–6 min; Rt (HPLC B; eluent: heptane:EtOAc: 85:15; flow rate: 5 mL/min): 10–11 min; ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 1.38 (d, *J* 6.0 Hz, 3H), 2.87 (bd, $w_{1/2}$ 11 Hz, 1H), 4.61 (m, 1H), 5.11 (s, 2H), 5.30 (bs, $w_{1/2}$ 12 Hz, 1H), 6.89 (m, 1H), 7.00–7.15 (b, 2H), 7.25–7.50 (b, 5H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 12.2 [CH_3], 71.7 [CH_2], 73.8 [CH], 87.7 [CH], 113.8 [CH], 116.6 [CH, $J_{F\text{-}C}$ 19 Hz], 119.2 [CH, $J_{F\text{-}C}$ 7 Hz], 128.1 [CH], 128.7 [CH], 129.0 [CH], 135.6 [C], 136.7 [C],

147.1 [C, $J_{F\text{-}C}$ 11 Hz], 152.9 [C, $J_{F\text{-}C}$ 245 Hz]; MS (DCI/NH_4^+) $C_{16}H_{16}FNO_4$, 323 [$M+NH_4^+$]. **15T** (*threo*): R_f 0.45–0.50 (heptane:EtOAc, 50:50); Rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH:CH_3OH: 40:60; flow rate: 4 mL/min): 5–6 min; rt (HPLC B; eluent: heptane:EtOAc: 85:15; flow rate: 5 mL/min): 9–10 min; ^1H NMR (CD_2Cl_2, 298.0 K) δ 1.22 (d, *J* 6.0 Hz, 3H), 2.70 (bs, $w_{1/2}$ 11 Hz, 1H), 4.66 (m, 1H), 4.94 (d, *J* 9.0 Hz, 1H), 5.13 (s, 2H), 6.92 (m, 1H), 7.00–7.15 (b, 2H), 7.30–7.55 (b, 5H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 16.6 [CH_3], 71.7 [CH_2], 76.2 [CH], 88.9 [CH], 114.4 [CH], 116.8 [CH, $J_{F\text{-}C}$ 20 Hz], 120.4 [CH, $J_{F\text{-}C}$ 7 Hz], 128.1 [CH], 128.7 [CH], 129.0 [CH], 135.3 [C], 136.6 [C], 147.4 [C, $J_{F\text{-}C}$ 11 Hz,], 153.4 [C, $J_{F\text{-}C}$ 246 Hz]; MS (DCI/NH_4^+) $C_{16}H_{16}FNO_4$, 323 [$M+NH_4^+$].

***Erythro*- and *threo*-1-(5-benzyloxy-2-fluorophenyl)-2-nitro-1-propanol (17E/17T).** The coupling procedure described above was used with **14** (0.53 g, 2.27 mmol) and yielded after purification by silica gel flash chromatography (heptane:EtOAc, 96:4–94:6) the crude product (**17E**/**17T**). Semipreparative HPLC was used to separate the corresponding *erythro* racemate (**17E**, rt 11.5–12.0 min) from the *threo* racemate (**17T**, rt 10.5–11.0 min) [HPLC B; eluent: heptane:EtOAc: 92.5:7.5; flow rate: 5 mL/min]. Concentration of HPLC fractions to dryness afforded **17E** (106 mg, 15% yield) and **15T** (247 mg, 36% yield) in the form of colorless oils: **17E** (*erythro*): R_f 0.50–0.55 (heptane/EtOAc, 50/50); Rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH:CH_3OH: 40:60; flow rate: 4 mL/min): 6–7 min; rt (HPLC B; eluent: heptane:EtOAc: 92.5:7.5; flow rate: 5 mL/min): 11.5–12.0 min; ^1H NMR (CD_2Cl_2, 298.0 K) δ 1.37 (d, *J* 6.6 Hz, 3H), 3.01 (bd, $w_{1/2}$ 13 Hz, 1H), 4.74 (m, 1H), 5.01 (s, 2H), 5.63 (bs, $w_{1/2}$ 11 Hz, 1H), 6.87 (m, 1H), 6.97 (t, *J* 9.6 Hz, 1H), 7.12 (dd, *J* 5.7 & 3.3 Hz, 1H), 6.95–7.10 (b, 2H), 7.25–7.45 (b, 5H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 11.8 [CH_3], 68.8 [CH], 71.0 [CH_2], 85.6 [CH], 114.1 [CH], 116.2 [CH], 116.4 [CH, $J_{F\text{-}C}$ 12 Hz], 127.1 [C, $J_{F\text{-}C}$ 14 Hz], 128.0 [CH], 128.4 [CH], 128.9 [CH], 137.1 [C], 154.0 [C, $J_{F\text{-}C}$ 237 Hz], 155.6 [C]; MS (DCI/NH_4^+) $C_{16}H_{16}FNO_4$, 323 [$M+NH_4^+$]. **17T** (*threo*): R_f 0.50–0.55 (heptane:EtOAc, 50:50); Rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH:CH_3OH: 40:60; flow rate: 4 mL/min): 6–7 min; rt (HPLC B; eluent: heptane: EtOAc: 92.5:7.5; flow rate: 5 mL/min): 10.5–11.0 min; ^1H NMR (CD_2Cl_2, 298.0 K) δ 1.29 (d, *J* 6.6 Hz, 3H), 3.11 (bs, $w_{1/2}$ 12 Hz, 1H), 4.76 (m, 1H), 4.97 (s, 2H), 5.25 (b, $w_{1/2}$ 10 Hz, 1H), 6.89 (m, 1H), 6.95–7.05 (b, 2H), 7.25–7.45 (b, 5H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 16.1 [CH_3], 70.3 [CH], 71.0 [CH_2], 88.3 [CH], 114.3 [CH, $J_{F\text{-}C}$ < 3.0 Hz], 116.7 [CH, $J_{F\text{-}C}$ 24 Hz], 117.0 [CH, $J_{F\text{-}C}$ 8 Hz], 126.7 [C, $J_{F\text{-}C}$ 15 Hz], 128.0 [CH], 128.5 [CH], 128.9 [CH], 137.0 [C], 154.8 [C, $J_{F\text{-}C}$ 238 Hz], 155.6 [C]; MS (DCI/NH_4^+) $C_{16}H_{16}FNO_4$, 323 [$M+NH_4^+$].

General procedure for the reduction of nitroalcohols. To a solution of the nitroalcohol (*erythro*- or *threo* racemate) in CH_3OH (20 mL) and aq formic acid (30%, v/v, 1.5 mL), Raney nickel (50% slurry in H_2O, 40–50 mg) was added. The reaction mixture was put under H_2 and stirred at rt until all starting material had been consumed. After removal of hydrogen the reaction mixture was filtered. The CH_3OH was removed under vacuum and the aqueous residue made alkaline with NH_4OH (28%) and extracted with EtOAc. After washing with brine, drying ($MgSO_4$) and concentration to dryness the crude amine was obtained.

***Erythro*-2-amino-1-(3-benzyloxy-4-fluorophenyl)-1-propanol (16E).** The hydrogenation procedure described above was used with **15E** (0.17 g, 0.56 mmol) and yielded after purification by silica gel flash chromatography (CH_2Cl_2:CH_3OH:Et_3N, 100:0:0.05–95:5:0.05) pure **16E** (72 mg, 47% yield) in the form of white crystals: R_f 0.10–0.15 (CH_2Cl_2:CH_3OH:Et_3N, 70:30:0.05); rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH:CH_3OH: 60:40; flow rate: 4 mL/min): 11.5–12.5 min; ^1H NMR (CD_2Cl_2, 298.0 K) δ 0.82 (d, *J* 6.3 Hz, 3H), 3.00 (b, $w_{1/2}$ 15 Hz, 2H), 3.05 (b, $w_{1/2}$ 10 Hz, 1H), 4.49 (d, *J* 3.3 Hz, 1H), 5.08 (s, 2H), 6.80 (b, $w_{1/2}$ 15 Hz, 1H), 6.95–7.10 (b, 2H), 7.25–7.50 (b, 5H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 17.3 [CH_3], 52.5 [CH], 71.6 [CH_2], 76.2 [CH], 114.2 [CH], 115.9 [CH, $J_{F\text{-}C}$ 19 Hz], 119.6 [CH, $J_{F\text{-}C}$ 7 Hz], 128.1 [CH], 128.5 [CH], 128.9 [CH], 137.0 [C], 138.6 [C], 146.7 [C, $J_{F\text{-}C}$ 11 Hz], 152.3 [C, $J_{F\text{-}C}$ 243 Hz]; MS (DCI/NH_4^+) $C_{16}H_{18}FNO_2$, 276 [$M+H^+$].

***Threo*-2-amino-1-(3-benzyloxy-4-fluorophenyl)-1-propanol (16T).** The hydrogenation procedure described above was used with **15T** (0.39 g, 1.29 mmol) and yielded after purification by silica gel flash chromatography (CH_2Cl_2:CH_3OH:Et_3N, 100:0:0.05–90:10:0.05) pure **16T** (115 mg, 32% yield) in the form of white crystals: R_f 0.10–0.15 (CH_2Cl_2:CH_3OH:Et_3N, 70:30:0.05); rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH:CH_3OH: 60:40; flow rate: 4 mL/min): 11.5–12.5 min; ^1H NMR (CD_2Cl_2, 298.0 K) δ 0.95 (d, *J* 5.7 Hz, 3H), 2.84 (b, $w_{1/2}$ 15 Hz, 2H), 2.90 (b, $w_{1/2}$ 10 Hz, 1H), 4.15 (d, *J* 5.7 Hz, 1H), 5.10 (s, 2H), 6.86 (b, $w_{1/2}$ 15 Hz, 1H), 6.95–7.10 (b, 2H), 7.25–7.50 (b, 5H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 19.9 [CH_3], 53.6 [CH], 71.6 [CH_2], 78.0 [CH], 114.3 [CH], 116.1 [CH, $J_{F\text{-}C}$ 19 Hz], 119.9 [CH, $J_{F\text{-}C}$ 6 Hz], 128.1 [CH], 128.5 [CH], 128.9 [CH], 137.0 [C], 139.7 [C], 146.9 [C, $J_{F\text{-}C}$ 11 Hz], 152.5 [C, $J_{F\text{-}C}$ 243 Hz]; MS (DCI/NH_4^+) $C_{16}H_{18}FNO_2$, 276 [$M+H^+$].

***Erythro*-2-amino-1-(5-benzyloxy-2-fluorophenyl)-1-propanol (18E).** The hydrogenation procedure described above was used with **17E** (88 mg, 0.29 mmol) and yielded after purification by silica gel flash chromatography (CH_2Cl_2:CH_3OH:Et_3N, 100:0:0.05–95:5:0.05) pure **18E** (43 mg, 54% yield) in the form of white crystals: R_f 0.15–0.20 (CH_2Cl_2:CH_3OH:Et_3N, 70:30:0.05); rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH:CH_3OH: 60:40; flow rate: 4 mL/min): 12.5–13.5 min; ^1H NMR (CD_2Cl_2, 298.0 K) δ 0.86 (d, *J* 6.3 Hz, 3H), 2.37 (b, $w_{1/2}$ 20 Hz, 2H), 3.20 (bt, $w_{1/2}$ 10 Hz, 1H), 4.83 (d, *J* 2.7 Hz, 1H), 5.02 (s, 2H), 6.80 (dd, *J* 8.4 Hz & 3.6 Hz, 1H), 6.91 (t, *J* 9.0 Hz, 1H), 7.11 (b, $w_{1/2}$ 10 Hz, 1H), 7.25–7.50 (b, 5H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 17.5 [CH_3], 51.1 [CH], 70.9 [CH_2], 70.9 [CH], 114.4 [CH, $J_{F\text{-}C}$ < 5 Hz], 115.0 [CH, $J_{F\text{-}C}$ 7 Hz], 115.7 [CH, $J_{F\text{-}C}$ 24 Hz], 127.9 [CH], 128.3 [CH], 128.9 [CH], 130.1 [C, $J_{F\text{-}C}$ 16 Hz], 137.5 [C], 154.7 [C, $J_{F\text{-}C}$ 236 Hz, C], 155.3 [C]; MS (DCI/NH_4^+) $C_{16}H_{18}FNO_2$, 276 [$M+H^+$].

***Threo*-2-amino-1-(5-benzyloxy-2-fluorophenyl)-1-propanol (18T).** The hydrogenation procedure described above was used with **17T** (0.2 g, 0.66 mmol) and afforded after purification by silica gel flash chromatography (CH_2Cl_2/CH_3OH:Et_3N, 100:0:0.05–95:5:0.05) pure **18T** (73 mg, 40% yield) in the form of white crystals: R_f 0.15–0.20 (CH_2Cl_2:CH_3OH:Et_3N, 70:30:0.05); Rt (HPLC A; eluent: 1% (v/v) aq CH_3COOH:CH_3OH: 60:40; flow rate: 4 mL/min): 12.5–13.5 min; ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 0.98 (d, *J* 6.3 Hz, 3H), 2.83 (b, $w_{1/2}$ 15 Hz, 2H), 3.00 (m, *J* 6.3 Hz, 1H), 4.55 (d, *J* 6.0 Hz, 1H), 4.99 (s, 2H), 6.79 (dd, *J* 6.9 Hz & 3.3 Hz, 1H), 6.90 (t, *J* 9.3 Hz, 1H), 7.05 (dd, *J* 5.1 Hz & 3.0 Hz, 1H), 7.25–7.45 (b, 5H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 19.8 [CH_3], 52.7 [CH], 70.9 [CH_2], 71.9 [CH], 114.2 [CH], 115.2 [CH, $J_{F\text{-}C}$ 7 Hz], 116.0 [CH, $J_{F\text{-}C}$ 24 Hz], 128.0 [CH], 128.3 [CH], 128.9 [CH], 131.4 [C, $J_{F\text{-}C}$ 15 Hz], 137.5 [C], 154.9 [C, $J_{F\text{-}C}$ 236 Hz], 155.4 [C]; MS (DCI/NH_4^+) $C_{16}H_{18}FNO_2$, 276 [M + H$^+$].

General procedure for reductive cleavage of phenolic benzyl ethers. To a solution of the benzyl-protected metaraminol derivative (*erythro*- or *threo* racemate) in CH_3OH (10 mL), ammonium formate (3 equiv) and palladium on carbon (10% Pd, 50–60 mg) were added. The reaction mixture was refluxed for 30 min, and then cooled, filtered and concentrated to afford an oily residue that was purified by semipreparative HPLC. The fraction containing the product was reduced in volume under vacuum to 10 mL, made alkaline with NH_4OH (28%) and extracted with EtOAc. After washing with brine, drying ($MgSO_4$) and concentration to dryness the pure, deprotected metaraminol derivative was obtained.

***Erythro*-2-amino-1-(4-fluoro-3-hydroxyphenyl)-1-propanol (*erythro*-4-FMR, 3E).** The cleavage procedure described above was used with **16E** (60 mg, 0.22 mmol) and afforded after semipreparative HPLC purification [HPLC A; eluent: 50 mM aq NaH_2PO_4/EtOH: 99:1; flow rate: 6 mL/min] pure **3E** (14 mg, 34% yield, Rt 5.0–6.0 min) in the form of a white solid: R_f 0.05–0.10 ($CHCl_3$:CH_3OH:28% NH_4OH 70:30:1); Rt (HPLC A; eluent: 50 mM aq NaH_2PO_4:EtOH: 99:1; flow rate: 6 mL/min): 5.0–6.0 min; rt (HPLC C; eluent: 1% (v/v) aq CH_3COOH; flow rate: 6 mL/min): 14–15 min; rt (HPLC D; eluent: 40 mM Na_3PO_4:EtOH, 95:5, adjusted to pH 6.5 (with aq 5 M NaOH) and containing 50 μM disodium EDTA; flow rate: 4 mL/min): 7.5–8.0 min & 6.0–6.5 min; ^{1}H NMR (CD_3OD, 298.0 K) δ 1.06 (d, *J* 6.0 Hz, 3H), 3.18 (m, *J* 5.4 Hz, 1H), 4.55 (d, *J* 3.0 Hz, 1H), 6.70–6.80 (b, 1H), 6.94 (dd, *J* 8.7 Hz & 1.8 Hz, 1H), 7.01 (dd, *J* 11.0 Hz & 8.4 Hz, 1H); ^{13}C NMR (CD_3OD, 298.0 K) δ 15.6 [CH_3], 53.5 [CH], 76.3 [CH], 116.5 [CH, $J_{F\text{-}C}$ 19 Hz], 117.3 [CH], 118.2 [CH, $J_{F\text{-}C}$ 6 Hz], 139.1 [C], 146.9 [C, $J_{F\text{-}C}$ 13 Hz], 152.7 [C, $J_{F\text{-}C}$ 239 Hz]; MS (DCI/NH_4^+) $C_9H_{12}FNO_2$, 203 [M + NH_4^+], 186 [M + H$^+$].

***Threo*-2-amino-1-(4-fluoro-3-hydroxyphenyl)-1-propanol (*threo*-4-FMR, 3T).** The cleavage procedure described above was used with **16T** (85 mg, 0.31 mmol) and afforded after semipreparative HPLC purification [HPLC A; eluent: 50 mM aq NaH_2PO_4:EtOH: 99:1; flow rate: 6 mL/min] pure **3T** (28 mg, 49% yield, Rt 6.0–7.0 min) in the form of a white solid: R_f 0.05–0.10 ($CHCl_3$:CH_3OH:28% NH_4OH 70:30:1); rt (HPLC A; eluent: 50 mM aq NaH_2PO_4/EtOH: 99:1; flow rate: 6 mL/min): 6.0–7.0 min; Rt (HPLC C; eluent: 1% (v/v) aq CH_3COOH; flow rate: 6 mL/min): 18–19 min; rt (HPLC D; eluent: 40 mM Na_3PO_4:EtOH, 95:5, adjusted to pH 6.5 (with aq 5 M NaOH) and containing 50 μM disodium EDTA; flow rate: 4 mL/min): 15.0–16.0 min & 7.5–8.0 min; ^{1}H NMR (CD_3OD, 298.0 K) δ 0.94 (d, *J* 6.6 Hz, 3H), 3.02 (m, 1H), 4.19 (d, *J* 7.8 Hz, 1H), 6.67 (b, 1H), 6.89 (dd, *J* 8.7 Hz & 2.0 Hz, 1H), 6.96 (dd, *J* 11.0 Hz & 8.4 Hz, 1H); ^{13}C NMR (CD_3OD, 298.0 K) δ 18.0 [CH_3], 54.1 [CH], 79.0 [CH], 116.4 [CH, $J_{F\text{-}C}$ 19 Hz], 117.8 [CH], 117.9 [CH], 140.0 [C], 148.0 [C, $J_{F\text{-}C}$ 14 Hz], 153.3 [C, $J_{F\text{-}C}$ 238 Hz]; MS (DCI/NH_4^+) $C_9H_{12}FNO_2$, 203 [M + NH_4^+], 186 [M + H$^+$].

***Erythro*-2-amino-1-(2-fluoro-5-hydroxyphenyl)-1-propanol (*erythro*-6-FMR, 4E).** The cleavage procedure described above was used with **18E** (60 mg, 0.22 mmol) and afforded after semipreparative HPLC purification [HPLC A; eluent: 50 mM aq NaH_2PO_4:EtOH: 99:1; flow rate: 6 mL/min] pure **4E** (19 mg, 48% yield, Rt 7.0–7.5 min) in the form of a white solid: R_f 0.15–0.20 ($CHCl_3$/CH_3OH/28% NH_4OH 70:30:1); rt (HPLC A; eluent: 50 mM aq NaH_2PO_4:EtOH: 99:1; flow rate: 6 mL/min): 7.0–7.5 min; rt (HPLC C; eluent: 1% (v/v) aq CH_3COOH; flow rate: 6 mL/min): 20.5–21.5 min; rt (HPLC D; eluent: 40 mM Na_3PO_4:EtOH, 95:5, adjusted to pH 6.5 (with aq 5 M NaOH) and containing 50 μM disodium EDTA; flow rate: 4 mL/min): 6.5–7.0 min & 4.5–5.0 min; ^{1}H NMR (CD_3OD, 298.0 K) δ 1.02 (d, *J* 6.0 Hz, 3H), 3.15 (m, 1H), 4.86 (m, partially hidden by solvent, 1H), 6.67 (m, 1H), 6.87 (t, *J* 9.0 Hz, 1H), 6.94 (m, 1H); ^{13}C NMR (CD_3OD, 298.0 K) δ 16.7 [CH_3], 52.3 [CH], 71.8 (CH), 115.4 [CH, $J_{F\text{-}C}$ < 5 Hz], 116.2 [CH, $J_{F\text{-}C}$ 8 Hz], 116.5 [CH, $J_{F\text{-}C}$ 24 Hz], 130.8 [C, $J_{F\text{-}C}$ 15 Hz], 154.8 [C, $J_{F\text{-}C}$ 232 Hz], 155.0 [C]; MS (DCI/NH_4^+) $C_9H_{12}FNO_2$, 203 [M + NH_4^+], 186 [M + H$^+$].

***Threo*-2-amino-1-(2-fluoro-5-hydroxyphenyl)-1-propanol (*threo*-6-FMR, 4T).** The cleavage procedure described above was used with **18T** (35 mg, 0.13 mmol) and afforded after semipreparative HPLC purification [HPLC A; eluent: 50 mM aq NaH_2PO_4:EtOH: 99:1; flow rate: 6 mL/min] pure **4T** (13 mg, 56% yield, rt 8.0–8.5 min) in the form of a white solid: R_f 0.15–0.20 ($CHCl_3$:CH_3OH: 28% NH_4OH 70:30:1); Rt (HPLC A; eluent: 50 mM aq NaH_2PO_4:EtOH: 99:1; flow rate: 6 mL/min): 8.0–8.5 min; rt (HPLC C; eluent: 1% (v/v) aq CH_3COOH; flow rate: 6 mL/min): 25.0–27.0 min; rt (HPLC D; eluent: 40 mM Na_3PO_4:EtOH, 95:5, adjusted to pH 6.5 (with aq 5 M NaOH) and containing 50 μM disodium EDTA; flow rate: 4 mL/min): 6.0–7.0 min & 5.0–5.5 min; ^{1}H NMR (CD_3OD, 298.0 K) δ 0.96 (d, *J* 6.0 Hz, 3H), 3.01 (m, 1H), 4.57 (d, *J* 6.0 Hz, 1H), 6.67 (m, 1H), 6.80–6.95 (m, 2H); ^{13}C NMR (CD_3OD, 298.0 K) δ 18.3 [CH_3], 53.6 [CH], 73.0 [CH], 115.2 [CH, $J_{F\text{-}C}$ < 5 Hz], 116.4 [CH, $J_{F\text{-}C}$ < 5 Hz], 116.5 [CH, $J_{F\text{-}C}$ 24 Hz], 131.6 [C, $J_{F\text{-}C}$ 15 Hz], 155.0 [C, $J_{F\text{-}C}$ 233 Hz], 155.1 [C]; $C_9H_{12}FNO_2$, 203 [M + NH_4^+], 186 [M + H$^+$].

(1*R*,2*S*)-2-Amino-1-(3-hydroxy-4-iodophenyl)-1-propanol (4-iodometaraminol, 19). To a solution of metaraminol (**2**) bitartrate (2 g, 6.3 mmol) in NH_4OH (10 M, 200 mL) iodine (1.6 g, 6.5 mmol) dissolved in absolute EtOH (120 mL) was added dropwise over a period of 45 min. The reaction mixture was stirred in the dark at rt for 12 h. The EtOH was then removed under vacuum and the aqueous residue extracted with EtOAc. Drying of the combined organic layers ($MgSO_4$) and concentration to dryness afforded a yellow solid that was purified by silica gel flash chromatography ($CHCl_3$:CH_3OH: 28% NH_4OH, 80:20:1) to give **19** (1.0 g, 57% yield) in the form of a white solid: R_f 0.15–0.20 ($CHCl_3$:CH_3OH: 28% NH_4OH, 80:20:1); ^1H NMR (CD_3OD, 295.0 K) δ 1.07 (d, *J* 6.6 Hz, 3H), 3.36 (m, 1H), 4.75 (d, *J* 3.6 Hz, 1H), 6.61 (d, *J* 8.1 Hz, 1H), 6.92 (s, 1H), 7.63 (d, *J* 8.1 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 13.9 [CH_3], 50.1 [CH], 74.5 [CH], 84.3 [C], 114.2 [CH], 120.2 [CH], 140.5 [CH], 144.3 [C], 158.8 [C]; MS (DCI/NH_4^+) $C_9H_{12}INO_2$, 294 [$M+H^+$].

General procedure for the Boc protection of amino- and phenolic hydroxyl functions in metaraminol derivatives. To an ice-cooled solution of the metaraminol derivative in dioxane:H_2O (2:1, 30 mL) and aq NaOH (2 M, 1–2 equiv), di-*tert*-butyl dicarbonate (1 or 2 equiv, depending on the number of Boc groups to be introduced) dissolved in dioxane (10 mL) was added dropwise. The reaction mixture was stirred overnight at rt. The volume was reduced under vacuum and the residue extracted with EtOAc. Washing of the combined organic layers with brine, drying (Na_2SO_4) and concentration to dryness afforded the crude Boc-protected compound.

(1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)-1-(3-*tert*-butoxycarbonyloxy-4-iodophenyl)-1-propanol (20). Following the Boc protection procedure described above, **19** (0.54 g, 1.8 mmol) was reacted with di-*tert*-butyl dicarbonate (0.78 g, 3.6 mmol, 2 equiv) which afforded after purification by silica gel flash chromatography (heptane:EtOAc, 80:20–70:30) **20** (0.26 g, 30% yield) in the form of white crystals as well as the corresponding mono-protected *N*-Boc derivative (10% yield) as a side product. **20**: ^1H NMR (CD_2Cl_2, 298.0 K) δ 0.93 (d, *J* 9.0 Hz, 3H), 1.41 (s, 9H), 1.54 (s, 9H), 4.72 (bt, 1H), 4.97 (d, *J* 9.0 Hz, 1H), 6.95 (d, *J* 6.0 Hz, 1H), 7.17 (s, 1H), 7.75 (d, *J* 6.0 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ:14.6 [CH_3], 27.8 [CH_3], 28.5 [CH_3], 52.2 [CH], 76.0 [CH], 79.9 [C], 84.3 [C], 88.8 [C], 121.2 [CH], 126.0 [CH], 139.1 [CH], 144.4 [C], 151.2 [C], 151.5 [C], 156.6 [C]; MS (DCI/NH_4^+), $C_{19}H_{28}INO_6$, 511 [$M+NH_4^+$], 494 [$M+H^+$].

Side product: (1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)-1-(3-hydroxy-4-iodophenyl)-1- propanol: ^1H NMR (CD_2Cl_2, 298.0 K) δ 0.93 (d, *J* 6.0 Hz, 3H), 1.39 (s, 9H), 4.71 (b, 1H), 5.08 (bd, 1H), 6.59 (d, *J* 6.0 Hz, 1H), 6.96 (s, 1H), 7.59 (d, *J* 6.0 Hz, 1H), 7.71 (s, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 14.7 [CH_3], 28.5 [CH_3], 52.1 [CH], 76.0 [CH], 80.5 [C], 83.3 [C], 113.4 [CH], 120.3 [CH], 128.8 [CH], 143.6 [C], 155.8 [C], 156.8 [C]; MS (DCI/NH_4^+), $C_{14}H_{20}INO_4$, 411 [$M+NH_4^+$], 394 [$M+H^+$].

(1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)-1-(3-hydroxyphenyl)-1-propanol (23). Following the Boc protection procedure described above, metaraminol (**2**) bitartrate (2 g, 6.3 mmol) was reacted with di-*tert*-butyl dicarbonate (1.4 g, 6.3 mmol, 1 equiv) which afforded after purification by silica gel flash chromatography (heptane:EtOAc, 75:25–60:40) **23** (1.1 g, 65% yield) in the form of white crystals: ^1H NMR (CD_2Cl_2, 298.0 K) δ 0.94 (d, *J* 6.0 Hz, 3H), 1.42 (s, 9H), 4.73 (bt, 1H), 5.20 (bd, 1H), 6.73 (dd, *J* 7.8 Hz & 1.8 Hz, 1H), 6.81 (d, *J* 7.8 Hz, 1H), 6.86 (s, 1H), 7.13 (t, *J* 7.8 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 14.5 [CH_3], 28.6 [CH_3], 52.4 [CH], 76.3 [CH], 79.6 [C], 113.7 [CH], 114.6 [CH], 117.8 [CH], 129.4 [CH], 143.8 [C], 156.4 [C], 157.4 [C]; MS (DCI/NH_4^+), $C_{14}H_{21}NO_4$, 268 [$M+H^+$].

(1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)-1-(3-*tert*-butoxycarbonyloxy-4-trimethylstannylphenyl)-1-propanol (21). To a solution of **20** (0.5 g, 1.01 mmol) in dioxane (20 mL) tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) and hexamethyldistannane (0.39 g, 1.2 mmol) were added. The reaction mixture was refluxed under nitrogen for 5 h, cooled and filtered. The filtrate was diluted with 100 mL of EtOAc, washed with H_2O and brine, dried ($MgSO_4$) and concentrated to dryness to afford a yellow oil that was purified by silica gel flash chromatography (heptane:EtOAc, 90:10–80:20) to give **21** (400 mg, 75% yield) in the form of white crystals: ^1H NMR (CD_2Cl_2, 298.0 K) δ 0.30 (s, with tin satellites $J^2_{Sn\text{-}H}$ 57.0 Hz, 9H), 0.94 (d, *J* 6.0 Hz, 3H), 1.42 (s, 9H), 1.52 (s, 9H), 4.76 (bt, 1H), 4.89 (d, *J* 6.0 Hz, 1H), 7.11 (s, 1H), 7.15 (d, *J* 6.0 Hz, 1H), 7.41 (d, *J* 6.0 Hz, 1H). ^{13}C NMR (CD_2Cl_2, 298.0 K) δ −9.1 [CH_3, with tin satellites $J^1_{Sn\text{-}C}$ 361 Hz], 14.8 [CH_3], 27.9 [CH_3], 28.5 [CH_3], 52.4 [CH], 76.4 [CH], 79.8 [C], 83.4 [C], 119.7 [CH], 124.2 [CH], 133.0 [C], 136.4 [C & CH], 144.2 [C], 152.7 [C], 156.6 [C]; MS (DCI/NH_4^+), $C_{22}H_{37}NO_6Sn$, 553, 551, 549, 548, 547, 546, 545 [$M+NH_4^+$], and 536, 534, 532, 531, 530, 529, 528 [$M+H^+$] for Sn isotopes of 124, 122, 120, 119, 118, 117 and 116 respectively.

(1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)-1-(2-acetoxymercurio-5-hydroxyphenyl)-1-propanol (24). To a solution of **23** (0.55 g, 2.1 mmol) in CH_3OH (10 mL) mercuric trifluoroacetate (0.44 g, 1.0 mmol) was added. The reaction mixture was stirred for 24 h at rt and concentrated to dryness. A white solid was obtained that was purified by silica gel flash chromatography ($CHCl_3$: EtOH:100% CH_3COOH, 94:4:0.01–94:6:0.01) to afford **24** (150 mg, 27% yield) in the form of white crystals: ^1H NMR (CD_3OD, 298.0 K) δ 1.04 (d, *J* 6.0 Hz, 3H), 1.39 (s, 9H), 2.02 (s, 3H), 3.74 (m, 1H), 4.71 (b, 1H), 6.67 (dd, *J* 9.0 Hz & 3.0 Hz, 1H), 6.83 (d, *J* 3.0 Hz, 1H), 7.18 (d, *J* 9.0 Hz, 1H); ^{13}C NMR (CD_3OD, 298.0 K) δ 14.6 [CH_3], 23.1 [CH_3], 28.8 [CH_3], 53.9 [CH], 77.8 [CH], 80.1 [C], 115.6 [CH], 115.9 [CH], 138.8 [CH], 150.0 [C], 157.6 [C], 158.7 [C], 178.9 [C].

General procedure for electrophilic fluorination of organometallic derivatives. Through a solution of the organometallic compound in $CHCl_3$ (20 mL), acetyl hypofluorite (1 equiv, generated by passing F_2 (1.62% in Ne)

through a glass column containing 10 g of a CH_3COOK:CH_3COOH (1:1.5) complex) was bubbled over a period of 30 min. The reaction mixture was then diluted with CH_2Cl_2, washed with aq $Na_2S_2O_3$ (0.1 M), H_2O and brine, dried (Na_2SO_4) and concentrated to dryness to afford the crude fluoro derivative.

(1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)-1-(3-*tert*-butoxycarbonyloxy-4-fluorophenyl)-1-propanol (22). The fluorination procedure described above was used with **21** (186 mg, 0.35 mmol) and afforded after semipreparative HPLC purification (HPLC B; eluent: heptane:EtOAc: 80:20; flow rate: 5 mL/min) pure **22** (13 mg, 10% yield, Rt 9.0–10.0 min) in the form of white crystals: Rt (HPLC B; eluent: heptane:EtOAc: 80:20; flow rate: 5 mL/min): 9.0–10.0 min; ^{1}H NMR (CD_2Cl_2, 298.0 K) δ 0.97 (d, *J* 6.9 Hz, 3H), 1.44 (s, 9H), 1.53 (s, 9H), 3.93 (m, $w_{1/2}$ 15 Hz, 1H), 4.63 (d, *J* 6.0 Hz, 1H), 4.79 (bs, $w_{1/2}$ 7 Hz, 1H), 7.05–7.20 (b, 2H), 7.21 (d, *J* 7.8 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 298.0 K) δ 15.2 [CH_3], 27.7 [CH_3], 28.5 [CH_3], 52.6 [CH], 76.5 [CH], 80.2 [C], 84.5 [C], 116.4 [CH, $J_{F\text{-}C}$ 19 Hz], 122.2 [CH], 125.3 [CH], 138.4 [C], 138.7 [C, $J_{F\text{-}C}$ 13 Hz], 151.2 [C], 153.8 [C, $J_{F\text{-}C}$ 247 Hz], 157.0 [C]; MS (DCI/NH_4^+), $C_{19}H_{28}FNO_6$, 386 [M + H$^+$].

General procedure for TFA deprotection of Boc groups. To a solution of the Boc-protected metaraminol derivative in CH_2Cl_2 (5 mL), TFA (99%, 1 mL) was added and the reaction mixture was stirred at rt for 2 h. The solution was then concentrated to dryness under repeated addition of CH_2Cl_2 to afford the crude TFA salt of the desired product.

(1*R*,2*S*)-2-Amino-1-(4-fluoro-3-hydroxyphenyl)-1-propanol ((1*R*,2*S*)-3). The deprotection procedure described above was used with **22** (10 mg, 0.026 mmol) and afforded the TFA salt of (1*R*,2*S*)-**3** (7 mg, 88% yield) in the form of a white solid. HPLC retention times (HPLC C and D) of (1*R*,2*S*)-**3** were compared with those of compounds **3E** and **3T** obtained in the synthesis described before to identify the diastereomers and to assign the (1*R*,2*S*) enantiomer: rt (HPLC C; eluent: 1% (v/v) aq CH_3COOH; flow rate: 6 mL/min): 14–15 min; rt (HPLC D; eluent: 40 mM Na_3PO_4:EtOH, 95:5, adjusted to pH 6.5 (with aq 5 M NaOH) and containing 50 μM disodium EDTA; flow rate: 4 mL/min): 7.5–8.0 min; NMR and MS data were identical with those of **3E**.

(1*R*,2*S*)-2-Amino-1-(2-fluoro-5-hydroxyphenyl)-1-propanol ((1*R*,2*S*)-4). Following the fluorination and deprotection procedures described above, **24** (115 mg, 0.23 mmol) afforded directly crude (1*R*,2*S*)-**4**. The Boc-protected intermediate was not isolated. The product was purified by semipreparative HPLC (HPLC C; eluent: 1% (v/v) aq CH_3COOH; flow rate: 6 mL/min). The fraction containing the product (rt 20.5–21.5 min) was reduced in volume to 10 mL, made alkaline with NH_4OH (28%) and extracted with EtOAc. After washing with brine, drying (Na_2SO_4) and concentration to dryness pure (1*R*,2*S*)-**4** was obtained in the form of a yellow oil (8 mg, 19% yield). HPLC retention times (HPLC C and D) of (1*R*,2*S*)-**4** were compared with those of compounds **4E** and **4T** obtained in the synthesis described earlier to identify the diastereomers and to assign the (1*R*,2*S*) enantiomer: rt (HPLC C; eluent: 1% (v/v) aq CH_3COOH; flow rate: 6 mL/min): 20.5–21.5 min; rt (HPLC D; eluent: 40 mM Na_3PO_4:EtOH, 95:5, adjusted to pH 6.5 (with aq 5 M NaOH) and containing 50 μM disodium EDTA; flow rate: 4 mL/min): 6.5–7.0 min; NMR and MS data were identical with those of **4E**.

Radiochemistry

Production of aqueous [^{18}F]fluoride. No-carrier-added aqueous [^{18}F]fluoride ion was produced on a CGR-MeV 520 cyclotron by irradiation of a 2 mL water target using a 17 MeV proton beam on 95% enriched [^{18}O]water [^{18}O(p,n)^{18}F] and was transferred to the appropriate hot cell. Typical production: 20.3–24.0 GBq of [^{18}F]F$^-$ at the end of bombardment for a 20 μA, 30 min (36,000 μC) irradiation. A complete description of the target hardware and operation can be found elsewhere.[39,40]

Preparation of the K[^{18}F]F-K_{222} complex. For recovery and recycling of the [^{18}O]water, the 2 mL of aqueous [^{18}F]fluoride obtained from the target were forced through a glass column containing 20–50 mg of an anion exchange resin (AG 1-X8, Bio-Rad 100–200 mesh, ionic form: chloride, washed with aq $NaHCO_3$ (1 M, 5 mL) and then rinsed with 15 mL of H_2O) by He pressure (1.5–2.0 bar). Helium was blown through the column to remove the last traces of [^{18}O]water. The [^{18}F]fluoride ion was eluted from the column using 1.0 mL of aq K_2CO_3 (4.5 mg/mL) into a Vacutainer® tube containing 12–16 mg of Kryptofix® K_{222} (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane). The resulting solution was concentrated to dryness at 145–150 °C under a nitrogen stream for 10 min to afford the no-carrier-added K[^{18}F]F-K_{222} complex as a creamy, yellow and semi-solid residue.

Nucleophilic exchange reaction using trimethylanilinium trifluoromethanesulfonates as precursors. *N* μmol of the labeling precursor *P* dissolved in freshly distilled DMSO (0.6 mL) were added into the tube containing the K[^{18}F]F-K_{222} complex. The reaction mixture was vortexed for 30 sec and then heated during a time *t* at 130 °C. The reaction tube was cooled in a water bath and the remaining radioactivity was measured. Between 85 and 95% of the initial radioactivity were usually still present. The often darkly colored reaction mixture was analyzed by radio TLC. The incorporation yields were calculated from the TLC radiochromatogram and defined as the [^{18}F]fluorobenzaldehyde derivative over total fluorine-18 activity area ratio [SiO_2-TLC, eluent: heptane:EtOAc: 50:50, R_f: 3-benzyloxy-4-[^{18}F]fluorobenzaldehyde ([^{18}F]-**9**): 0.55–0.60; R_f : 5-benzyloxy-2-[^{18}F]fluorobenzaldehyde ([^{18}F]-**14**): 0.55–0.60 and R_f: [^{18}F]fluoride ion: 0.0]. After addition of H_2O (3 mL) the reaction mixture was passed through a C_{18} Sep-Pak® cartridge (Waters). The cartridge was washed with H_2O (10 mL) and partially dried for 30 s by application of a nitrogen stream.

P/(*N*): 2-benzyloxy-4-formyl-*N,N,N*-trimethylanilinium trifluoromethanesulfonate (**26**) and 4-benzyloxy-2-formyl-*N,N,N*-trimethylanilinium trifluoromethanesulfonate (**30**)/ 11.9 or 23.8 μmol; *t*: 0.5–5 min.

Nucleophilic exchange reaction using nitro precursors. The K[^{18}F]F-K_{222} complex obtained after concentration to dryness was dissolved in 0.2 mL freshly distilled DMSO and transferred to a 2 mL reaction vial containing *N* μmol of the labeling precursor *P*. The evaporation tube was rinsed twice with 0.2 mL DMSO which was then added to the reaction mixture. Re-solubilization efficiencies were about 80–95% of the original [^{18}F]fluoride ion. The reaction vial was tightly sealed with a Teflon cap and heated in a heating block without stirring at a temperature *T* for *t* min. Cooling, determination of incorporation yields, dilution with H_2O and Sep-Pak purification were performed as described above.

P/(*N*): 3-benzyloxy-4-nitrobenzaldehyde (**28**) and 5-benzyloxy-2-nitrobenzaldehyde (**32**)/19.5 or 39 μmol; *T*: 130 °C or 170 °C; *t*: 15 or 20 min.

Preparation of racemic 4-[^{18}F]FMR ([^{18}F]-3) and racemic 6-[^{18}F]FMR ([^{18}F]-4) and resolution into stereoisomers. The [^{18}F]fluorobenzaldehyde derivative ([^{18}F]-**9**, [^{18}F]-**14**) was eluted from the Sep-Pak cartridge with 1.5 mL of ice-cooled CH_3OH into a reaction vial containing an ice-cooled mixture of nitroethane (50 μL, 0.92 mmol) and aq NaOH (2.5 M, 50 μL, 0.13 mmol) in CH_3OH (100 μL). The incorporation yields, now determined after the Sep-Pak elution as the ratio of the CH_3OH-eluted radioactivity over the total eluted radioactivity (DMSO/H_2O and CH_3OH), were consistently comparable to the yields estimated by radio TLC. The reaction vial was left to stand at rt for 5 min. The reaction was then quenched by addition of formic acid (99%, 50 μL, 1.3 mmol) and the conversion of the [^{18}F]fluorobenzaldehyde derivatives [^{18}F]-**9** and [^{18}F]-**14** into the corresponding ^{18}F-labeled nitroalcohols [^{18}F]-**15** and [^{18}F]-**17**, respectively, was determined by analyzing an aliquot of the reaction mixture on HPLC (HPLC A; eluent: 1% (v/v) aq CH_3COOH:CH_3OH: 40:60; flow rate: 4 mL/min; rt: [^{18}F]-**9**: 6–7 min; rt: [^{18}F]-**14**: 8–9 min; rt: [^{18}F]-**15**: 5–6 min; rt: [^{18}F]-**17**: 6–7 min). The reaction mixture was transferred into a new reaction vial containing palladium on carbon (10% Pd, 30–40 mg). After addition of a freshly prepared solution of NH_4HCOO in CH_3OH (1 M, 1.5 mL) the reaction vessel was sealed and heated at 150 °C for 15–20 min. After cooling in a water bath the reaction mixture was filtered through a C_{18} Sep-Pak® cartridge (Waters) and the filter residue was washed with CH_3OH (2×0.5 mL). The filtrate containing crude racemic 4-[^{18}F]FMR ([^{18}F]-**3**) or racemic 6-[^{18}F]FMR ([^{18}F]-**4**) was gently concentrated to dryness at 70 °C under a nitrogen stream (7–8 min). The residue was then re-dissolved in aq CH_3COOH (1%, v/v, 1 mL) and injected into the semipreparative HPLC system for purification and separation into the respective two diastereomeric racemates (HPLC C; eluent: 1% (v/v) aq CH_3COOH; flow rate: 6 mL/min; rt: [^{18}F]-**3E** (*erythro*): 14–15 min; rt: [^{18}F]-**3T** (*threo*): 18–19 min; rt: [^{18}F]-**4E** (*erythro*): 20.5–21.5 min; Rt: [^{18}F]-**4T** (*threo*): 25–27 min). The fraction (6–8 mL) containing the desired diastereomeric racemate was concentrated to dryness under vacuum and redissolved in 0.5 mL sodium phosphate buffer (40 mM, pH = 6.5). The solution was injected into the semipreparative chiral HPLC system for resolution into the respective two enantiomers (HPLC D; eluent: 40 mM Na_3PO_4/ EtOH, 95:5, adjusted to pH 6.5 (with aq 5 M NaOH) and containing 50 μM disodium EDTA; flow rate: 4 mL/min; rt: [^{18}F]-(1*R*,2*S*)-**3**: 7.5–8.0 min; rt: [^{18}F]-(1*S*,2*R*)-**3**: 6.0–6.5 min; [^{18}F]-**3T** (*threo*) gave two peaks (not assigned) at rt: 15.0–16.0 & rt: 7.5–8.0 min, respectively; rt: [^{18}F]-(1*R*,2*S*)-**4**: 6.5–7.0 min; rt: [^{18}F]-(1*S*,2*R*)-**4**: 4.5–5.0 min; [^{18}F]-**4T** (*threo*) gave two peaks (not assigned) at rt: 6.0–7.0 min & Rt: 5.0–5.5 min, respectively).

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