N.C.A. ^{18}F-LABELLED NOREPHEDRINE DERIVATIVES VIA α-AMINOPROPIOPHENONES

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Summary

N-protected 2-amino-1-([^{18}F]fluorophenyl)-1-propanones are interesting fluorine-18 labelled intermediates to synthesize potential PET-tracers for mapping the adrenergic nervous system of the heart. Several N-protected α-aminoalkylarylketones were prepared to examine the direct nucleophilic n.c.a. ^{18}F-fluorination of these carbonyl activated precursors. The influence of different protecting groups, the kind of leaving group and the stereoselective reduction of the keto function have been investigated in order to optimize the radiotracer production. It was shown that the ^{18}F-substitution of the para-trimethylammonium group, e.g. of N-dibenzylated propiophenone, leads to radiochemical yields of up to 60%. The stereoselective reduction of the carbonyl function with formation of the n.c.a. erythro 2-N,N-dibenzylamino-1-(4-[^{18}F]fluorophenyl)-1-propanol was performed using BH$_3$·THF. The diastereomeric excess was about 80 %. Hydrogenolytical debenzylation was achieved with ammonium formiate in presence of palladium on charcoal to give the 4-[^{18}F]fluoronorephedrine with a radiochemical yield of 15-20% within a total time of 60 min.

Introduction

Several no-carrier-added fluorine-18 labelled synthons like ^{18}F-substituted benzonitriles (1), benzophenones (2) and benzaldehydes (3) are key intermediates in multi-step syntheses of radiopharmaceuticals (4, 5, 6). These activated aromatic compounds allow the n.c.a. nucleophilic aromatic ^{18}F-fluorination under formation of suitable ^{18}F-labelled synthons which are useful to synthesize radiotracers of more complex structure not accessible via direct nucleophilic substitution.

The present paper describes the n.c.a. ^{18}F-labelling of α-aminoalkylarylketones yielding a new fluorine-18 labelled synthon which can selectively be reduced forming the corresponding β-amino alcohol as outlined in scheme 1. The aim was to develop a new synthetic pathway for the preparation of [^{18}F]fluoronorepinephrine derivatives especially [^{18}F]fluorometaraminol ([^{18}F]FMR). [^{18}F]FMR has been shown to be useful as a diagnostic tool for the cardiac innervation using PET (7).

Labelling methods described for the synthesis of n.c.a. [^{18}F]norepinephrine analogues so far showed significant disadvantages because multi-step reactions were indispensable (8).

Besides the direct nucleophilic ^{18}F-labelling of γ-aminoarylalkylketones (9) the corresponding ^{18}F-fluorination of α-aminoarylalkylketones via n.c.a. nucleophilic substitution has not yet been described. The ^{18}F-fluorination of the N-protected

X = leaving group
R = protecting group

three or erythro isomers
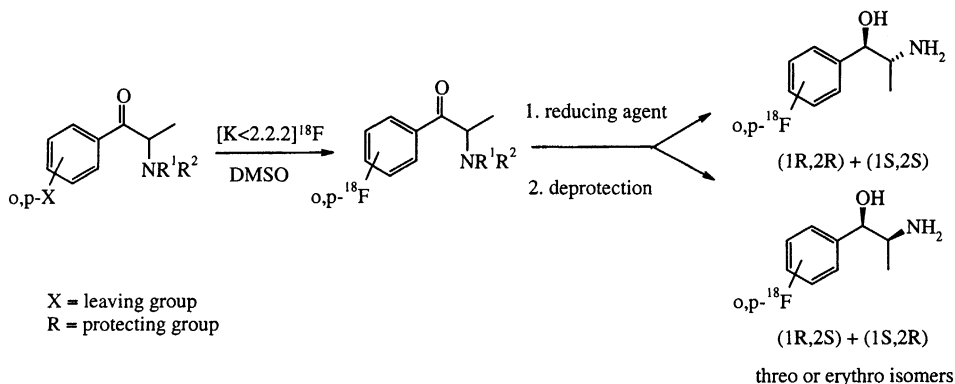
Scheme 1: Preparation of n.c.a. ^{18}F-labelled norephedrine derivatives via α-amino-propiophenones

standard compound, 2-amino-1-(fluorophenyl)-1-propanone, was studied in detail to get sufficient information about the necessary precursor design for ¹⁸F-labelling. Although the ¹⁸F-for-¹⁹F substitution yields no product of high molar radioactivity the isotopic substitution reaction was useful to prove the stability of different precursors under labelling conditions. Furthermore, the influence of the protecting groups on the radiochemical yield and the stereoselectivity of the subsequent reduction of the phenone step could be investigated.

Results and Discussion

Precursor syntheses

The halogen containing α-aminoarylalkylpropiophenones were synthesized according to scheme 2 starting with the o-fluoro-, p-fluoro- and p-chloro-propiophenone **1**, respectively.

The phenones were brominated in the α-position via standard methods and transferred either to the amine hydrochlorides **3** or dibenzylaminated with formation of the protected α-aminopropiophenone derivatives **4**, **7** and **8**. The amines were obtained using a modified Staudinger-reaction starting from the appropriate azide (10) followed by reduction with triethyl phosphite. The trimethylammonium group
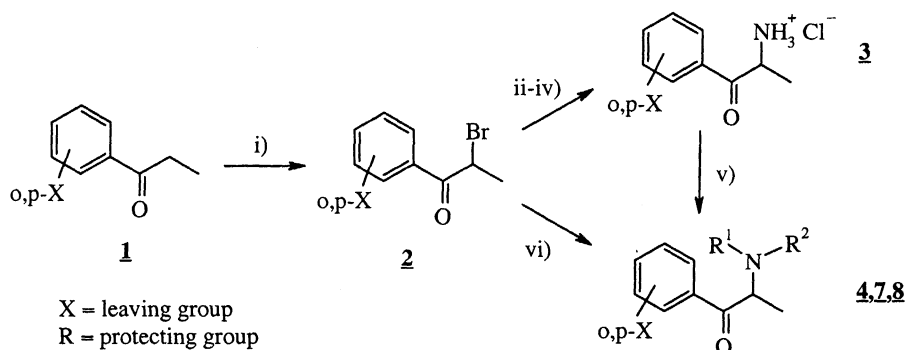

Scheme 2: Syntheses of α-aminopropiophenone precursors (**4a-f, 7, 8**)

X = F, Cl; R¹ = benzyl, acetyl, benzoyl, trityl; R² = H, benzyl;

i) Br₂, ii) NaN₃, iii) triethylphosphite, iv) HCl₍g₎, v) protecting group, base, vi) dialkylamine

was introduced as shown in scheme 3 (11) leading to the precursor **5** for the no-carrier-added ^{18}F-fluorination. Quaternisation of the aliphatic amino function with methyltriflate is excluded due to the bulky N-benzyl groups. In the case of N-acetyl or N-tert.-butoxycarbonyl protected compounds the quaternisation of the N,N-dimethylaniline moiety failed, while the strong methylating agent methyl trifluoromethansulfonate leads to the methylation of the amide function with formation of compounds not useful for ^{18}F-labelling.
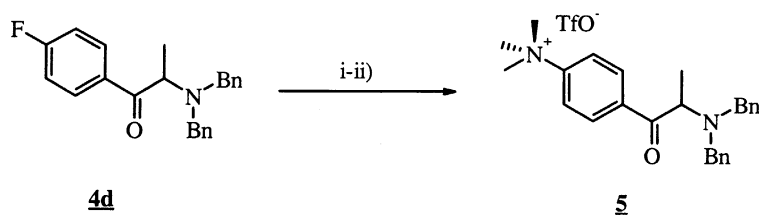
Scheme 3:   Synthesis   of   4-[2-(dibenzylaminopropionyl)]phenyl-N,N,N-trimethyl
             ammonium trifluoromethansulfonate **5**
             i) (CH₃)₂NH, K₂CO₃, ii) methyl triflate

The stereoselectivity of the keto reduction was investigated based on the reference compound 2-N,N-dibenzylamino-1-(4-fluorophenyl)-1-propanone (**4d**). Reduction using sodium borohydride leads quantitatively to the corresponding threo-isomer (for review see 12) whereas the more interesting erythro-isomer was obtained with borane in tetrahydrofuran. The reduction is finished within 15 min yielding the corresponding carbinol with a diastereomeric ratio of 4:1 (erythro/threo).

Nucleophilic ^{18}F-for-^{19}F substitution

In a first set of experiments precursor **4d** was used to study the influence of reaction solvent, time and cryptate system on the nucleophilic ^{18}F-substitution. The aim was to prove the general suitability of this carbonyl activated aromatic model structure of α-amino(fluoro)arylalkylketones for nucleophilic aromatic ^{18}F-fluorination.

The labelling reaction can be performed in various dipolar aprotic solvents such as DMSO, DMF and N,N-dimethylacetamide. DMSO, however, is obviously the best solvent with an optimum precursor concentration of 80 mmol/l as shown in figure 1.
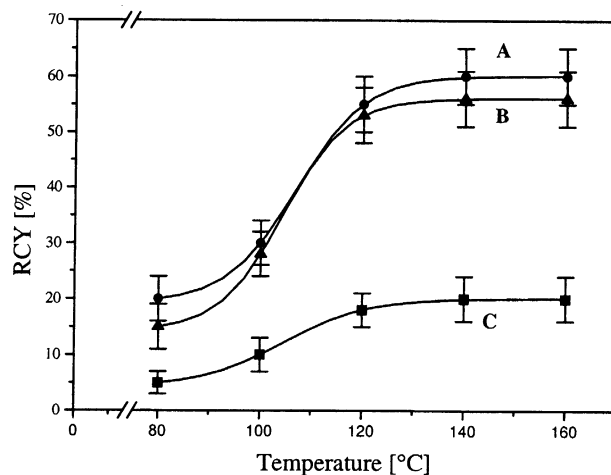
Figure 1: Temperature dependence of the isotopic exchange on 2-N,N-
dibenzylamino-1-(4-fluorophenyl)-1-propanone (**4d**) in different solvents
*A = DMSO, B = DMF, C= N,N-dimethylacetamide, [2.2.2] = 50 mmol/l,
[K$_2$CO$_3$] = 25 mmol/l, [2-N,N-dibenzylamino-1-(4-fluorophenyl)-1-
propanone] = 80 mmol/l, 0.5 ml solvent*

A maximum radiochemical yield of about 60% was obtained within 10 min using the
carbonate cryptate whereas the less basic oxalate cryptate [K⊂222]$_2$C$_2$O$_4$ leads only
to a value of 40 % within 20 min at 120°C, as graphically depicted in figure 2.

As summarized in table 1, a comparison of different N-protecting groups shows that
the radiochemical yield of the ^{18}F-for-^{19}F exchange is about 50% for the N-acetyl-,
N-benzoyl- and N,N-dibenzyl-2-amino-1-(4-fluorophenyl)-1-propanone (**4b,d,g**)
whereas the ^{18}F-fluorination of the N-Boc- and N-trityl-protected compounds (**4c** and
4f) is less efficient by a factor of about 3 and 10, respectively. In contrast to the para
^{18}F-exchange ortho-substitution is only effective with the dibenzyl-protected
precursor **4e** but not the N-acetyl protected one **4a**. This is probably due to a
hydrogen bond interaction between the amide group and the fluorine atom.

N.c.a. nucleophilic fluorination of propiophenone derivatives

The reaction conditions evaluated for the ^{18}F-for-^{19}F substitution were transferred to
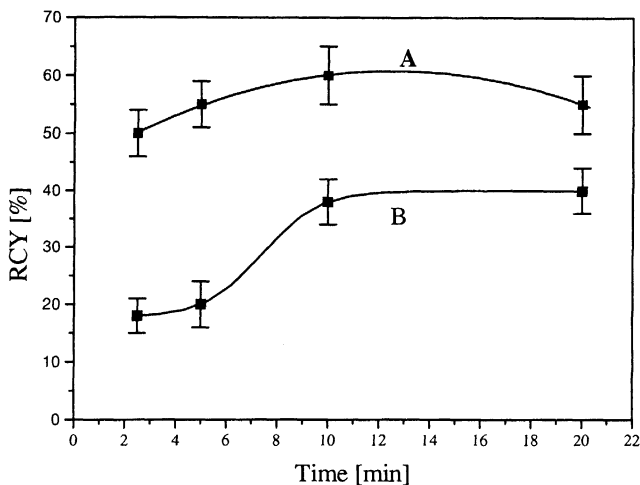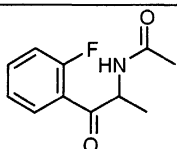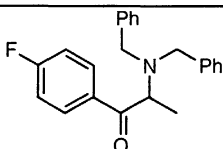the no-carrier-added ^{18}F-fluorination of propiophenone derivatives with different
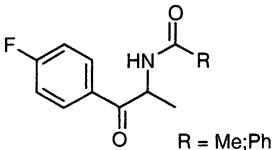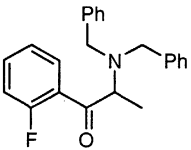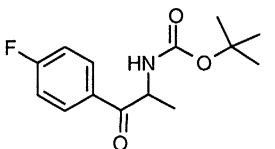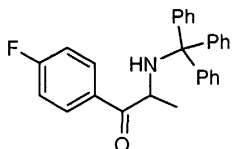
Figure 2:   Time dependence of the RCY of 2-N,N-dibenzylamino-1-(4-[^{18}F]fluoro-
phenyl)-1-propanone

*A = Kryptofix/carbonate; B= Kryptofix/oxalate, [2-N,N-dibenzylamino-
1-(4-fluorophenyl)-1-propanone (__4d__)] = 80 mmol/l, [2.2.2] = 50
mmol/l, [K$_2$CO$_3$] = 25 mmol/l, 0.5 ml DMSO, 140°C, n.c.a.
[^{18}F]fluoride*

leaving groups according to table 2. Although the NO$_2$-group is a potent leaving
group for n.c.a. nucleophilic aromatic ^{18}F-fluorination (14), 2-N-benzoylamino-1-(4-
nitrophenyl)-1-propanone __6__ was not fluorinated either using the carbonate cryptate or
the less basic oxalate complex. This is due to the fact that the precursor is very
unstable under the labelling conditions applied leading to a total destruction within a
few minutes.
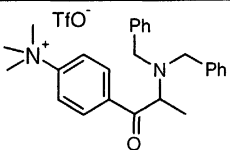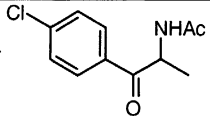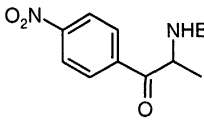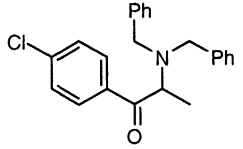
However, the ^{18}F-for-N(CH$_3$)$_3$ displacement of 4-(2-N,N-dibenzylamino)propionyl-
phenyl-1-N,N,N-trimethylammonium triflate (__5__) yielded 50-55% of n.c.a. 2-N,N-
dibenzylamino-1-(4-[^{18}F]fluorphenyl)-1-propanone in DMSO at 140°C within 5 min.
The ^{18}F-for-chloro exchange was performed using the N-acetyl- and N,N-dibenzyl-
propiophenones (__7__, __8__). The labelling conditions applied had to be more harsh
according to the less nucleofugic properties of the chloro substituent thus leading to
a RCY of 15% only at 160°C within 30 min for __8__ and of about 10% obtained with
the acetylated precursor __7__, respectively.

Table 1: ^{18}F-for-^{19}F substitution on N-protected α-amino-fluoropropiophenones

	precursor	RCY [%]		precursor	RCY [%]
4a		15 ± 5	**4d**		55 ± 5
4b,g		50 ± 5	**4e**		50 ± 5
4c		15 ± 5	**4f**		5 ± 3

Reaction conditions: 0.5 mL DMSO, [educt] = 80 mmol/l, [2.2.2.] = 50 mmol/l,

[K$_2$CO$_3$] = 25 mmol/l, 5 min, n.c.a. [^{18}F]fluoride

Table 2: N.c.a. ^{18}F-for-X substitution on N-protected α-aminopropiophenones

	precursor	RCY [%]		precursor	RCY [%]
5		55 ± 5	**7**		10 ± 3
6		0	**8**		20 ± 3

Reaction conditions: 500 μl DMSO, [educt] = 40 μmol/mL, [2.2.2] = 50 mmol/l,

[K$_2$CO$_3$] = 25 mmol/l, 140 –160°C, n.c.a. [^{18}F]fluoride

The formation of [^{18}F]fluoromethane is a potential side reaction of ^{18}F-for-N(CH$_3$)$_3$ displacement. It is favoured by weakly activating groups (14) or by sterical hindrance as in case of ortho substituted propiophenone (15). Therefore a ^{18}F-for-N(CH$_3$)$_3$ exchange on 2-(2-N,N-dibenzylamino)propionylphenyl-1-N,N,N-trimethyl-ammonium triflate seemed not to be successful and was not performed.

Stereoselective carbonyl reduction

The stereoselective synthesis of ^{18}F-labelled norephedrin [^{18}F]**9a,b** via keto activated nucleophilic aromatic fluorination of propiophenone derivatives requires a reduction of the keto-function with diastereoselective formation of the carbinol. Reduction of 2-N,N-dibenzylamino-1-(4-[^{18}F]fluorophenyl)-1-propanone [^{18}F]**4d** with sodium boronate leads to the formation of the threo isomers (1R,1R and 1S,2S) within 10 min. Consecutive debenzylation of the N-protected threo-4-[^{18}F]fluoronorephedrine [^{18}F]**9a** takes place within 15 min in presence of palladium on charcoal using ammonium formate as hydrogen source yielding the racemic threo-4-[^{18}F]fluoronorephedrine with 20 to 25%.

A diastereomeric mixture of the threo and erythro compounds is obtained if the reduction is performed with borane in THF. The radiochemical yield is in the range of 15 to 20% and the diasteremeric ratio of erythro to threo is 4:1. The reaction time required in total is about 60 min (scheme 5).

(1R,2R) + (1S,2S)
threo isomer (20 %)
[^{18}F]**9a**

(1R,2S) + (1S,2R)
erythro isomer (80 %)
[^{18}F]**9b**
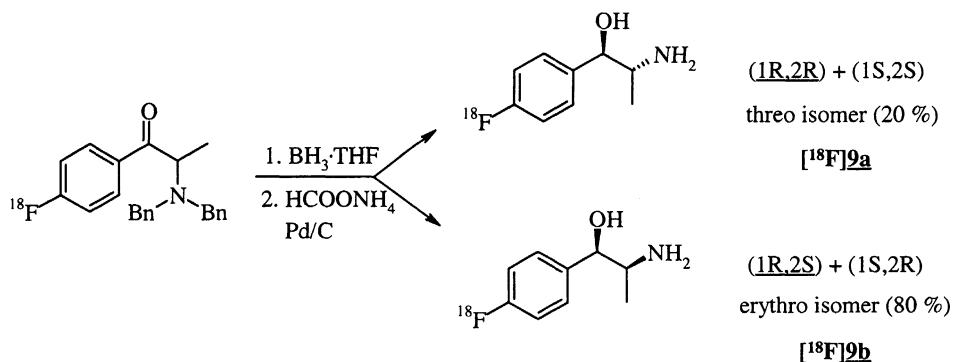
Scheme 5: Synthesis of n.c.a. erythro- and threo-4-[^{18}F]fluoronorephedrine [^{18}F]**9a,b**

Conclusion

The possibility of the aromatic ^{18}F-labelling of 2-amino-1-(fluorophenyl)-1-propanone derivatives was studied with different protecting groups at the amino function. In the case of a ^{18}F-for-^{19}F substitution a good RCY on para-substituted phenones was obtained using N-dibenzylated and N-acetyl protected precursors using optimized labelling conditions. Transferred to other leaving groups for n.c.a. labelling only a ^{18}F-for-$N(CH_3)_3$ displacement on N-dibenzylated precursors gave satisfactory radiochemical yields of 50-55 %.

Reduction experiments on labelled α-aminoarylalkylketones were performed with n.c.a. 2-N,N-dibenzylamino-1-(4-[^{18}F]fluorophenyl)-1-propanone in the presence of the precursor. Stereoselective reduction of the carbonyl function can be achieved either with $NaBH_4$ with nearly exclusive formation of the threo-isomer or with borane in THF, yielding predominantly the erythro-isomer (diastereomeric excess 80%). Cleavage of benzyl groups was optimally accomplished with ammonium formate in presence of palladium on charcoal. Thus, ^{18}F-labelled sympathomimetics of norephedrine structure can be synthesized in radiochemical yields of 15-20 % within 60 min.

Experimental

Materials and methods

All reagents and anhydrous solvents were purchased from Aldrich or Fluka Chemical Company. Sep-Pak™ C-18 plus-cartridges were purchased from Waters and EN-cartridges from Merck. Thin layer chromatography (TLC) was run on precoated plates of silica gel 60F254 (Merck). The compounds were detected at 254 nm. Analytical HPLC was performed on the following systems: HPLC Sykam (S1000) pump, Knauer UV/VIS-detector (type 97) with a constant wavelength of 254 nm and a EG&G ACE Mate™ radioactivity detector. RadioTLC chromatograms were detected on a Packard Instant Imager™. ^{1}H NMR spectra were recorded on a Bruker Avance (200 MHz) apparatus using TMS as an internal standard. The chemical shifts

are reported in ppm, downfield from TMS (s, d, t, m, b for singlet, doublet, triplet, multiplet and broad, respectively). The mass spectra (MS), EI, were measured on a Infinnigan Automass III apparatus. High resolution mass spectra were recorded on a Finnigan MAT 900 ST apparatus (Universität zu Köln). IR spectra (KBr pellets) were measured using a Shimadzu (IR-440) spectrometer. Melting points are uncorrected and were determined on a Mettler FP-61 apparatus in open capillaries.

General procedure of bromination

A few drops of bromine were added to 20 mmol of a given alkyl-1-(haloaryl)ketone dissolved in 40 mL CCl₄ until the reaction started. Then 20 mmol of bromine were added dropwise and the solvent was removed after 2 h. The α-brominated products were used without further purification.

General procedure to prepare haloarylaminoketones

40 mmol of sodium azide were added to 20 mmol of 2-bromoalkyl-1-(haloaryl)ketone in 20 mL acetonitrile and heated at 60° C for 3 h. The reaction course was monitored by TLC. The solution was cooled, water was added and extracted 3 times with 15 mL of ether. The organic solution was dried over Na_2SO_4 and evaporated to dryness. The product was solubilized in 40 mL of toluene, 20 mmol of triethyl phosphite was added dropwise at 0° C and left overnight at room temperature. The solution was saturated with dry hydrogen chloride and again allowed to stand overnight at room temperature. The mixture was evaporated to dryness, 20 mL of dry ether was added and the mixture stored at -20°C for 24 h. The precipitated amine hydrochloride was isolated by suction, washed with ether, and dried in vacuum over sodium hydroxide.

2-Amino-1-(4-fluorophenyl)-1-propanone hydrochloride: mp.: 215-218°C, Lit. 217-218°C (16); ¹H-NMR (d₆-DMSO): δ 7.8 (4H, m, Ar-H), 8.70 (1H, s, -NH₃), 5.13 (1H, m, -CH), 1.45 (3H, d, -CH₃); IR (KBr, cm⁻¹): 1688 (C=O).

2-Amino-1-(2-fluorophenyl)-1-propanone hydrochloride: mp.: 160°C; ¹H-NMR (d₆-DMSO): δ (4H, m, Ar-H), 8.65 (1H, s, -NH₃), 4.80 (1H, m, -CH), 1.43 (3H, d, -CH₃); IR (KBr, cm⁻¹): 1693 (C=O).

2-Amino-1-(4-chlorophenyl)-1-propanone hydrochloride: mp.: 218-220°C; Lit. 220-222°C (16); ^{1}H-NMR (d$_6$-DMSO): δ 7.68 (4H, m, Ar-H), 8.65 (1H, s, -NH$_3$), 5.14 (1H, m, -CH), 1.44 (3H, d, -CH$_3$); IR (KBr, cm^{-1}): 1687 (C=O).

General procedure of N-acetylation

15 mL of ice water and 15 mmol of acetic anhydride were added to 15 mmol of 2-amino-1-(4-fluorophenyl)-1-ethanone hydrochloride and neutralized with sodium carbonate. The products were extracted with ethyl acetate and the organic phase neutralized by washing with a solution of NaHCO$_3$. The solvent was evaporated after drying with Na$_2$SO$_4$ and the residue crystallized from ethyl acetate/n-hexane (50/50) (V/V).

2-N-Acetylamino-1-(2-fluorophenyl)-1-propanone **4a**: mp.: 56°C; ^{1}H-NMR (CDCl$_3$): δ 7.55 (4H, m, Ar-H), 6.65 (1H, s, N-H), 5.43 (1H, m, -CH), 2.1 (3H, s, N-CH$_3$), 1.43 (3H, d, -CH$_3$); ^{13}C NMR (CDCl$_3$) δ 197.86, 170.17, 161.95, 123.19 (C), 135.89, 131.60, 117.31 (=CH), 54.42 (CH-N), 23.64, 18.86 (CH$_3$); ^{19}F-NMR(CDCl$_3$): δ -109.43; MS (relative intensity): 209 (M$^+$, 3), 123 (10), 86 (20), 44 (100); HR-MS calculated for C$_{11}$H$_{12}$FNO$_2$: 210.0930; found 210.0930; IR (KBr, cm^{-1}): 1688, 1647 (C=O).

2-N-Acetylamino-1-(4-fluorophenyl)-1-propanone **4b**: mp: 94-96°C, Lit. 95-96°C (16); ^{1}H-NMR (CDCl$_3$): δ 7.59 (4H, m, Ar-H), 6.8 (1H, s, N-H), 5.54 (1H, m, -CH), 2.04 (3H, s, CO-CH$_3$), 1.40 (3H, d, -CH$_3$); ^{13}C NMR (CDCl$_3$) δ 198.09, 170.03, 165.56, 130.75 (C), 131.87, 116.51 (=CH), 50.23 (CH-N), 23.61, 19.95 (CH$_3$); ^{19}F-NMR(CDCl$_3$): δ -103.38;); MS (relative intensity): 209 (M$^+$, 3), 123 (10), 86 (20), 44 (100); IR (KBr, cm^{-1}): 1682, 1643 (C=O).

2-N-Acetylamino-1-(4-chlorophenyl)-1-propanone **7**: mp.: 104-105°C, Lit. 106-107°C (16); ^{1}H-NMR (CDCl$_3$): δ 7.64 (4H, m, Ar-H), 6.7 (1H, s, N-H), 5.55 (1H, m, -CH), 2.08 (3H, s, CO-CH$_3$), 1.44 (3H, d, -CH$_3$); ^{13}C NMR (CDCl$_3$) δ 198.49, 169.95, 140.91, 132.65 (C), 130.54, 129.68 (=CH), 50.35 (CH-N), 23.70, 20.02 (CH$_3$); MS (relative intensity): 225 (M$^+$, ^{35}Cl, 5), 139 (^{35}Cl, 10), 111 (^{35}Cl, 15), 86 (45), 75 (29), 44 (100); IR (KBr, cm^{-1}) 1636 (C=O).

2-N-tert.-Butoxycarbonylamino-1-(4-fluorophenyl)-1-propanone **4c**

1 g (4.9 mmol) of 2-amino-1-(4-fluorophenyl)-1-propanone hydrochloride dissolved in 40 mL of DMF was mixed with 1.11 g (5.1 mmol) of di-tert.-butyldicarbonate and 1.4 mL (10 mmol) of triethylamine. The solution was stirred overnight, quenched with 15 mL of water. Ether (3 x 10 mL) was added, the organic layers were separated, washed three times with brine, dried over Na_2SO_4 and evaporated to dryness. Yield 76 %. mp.: 107°C. ^{1}H-NMR (CDCl$_3$): δ 7.58 (4H, m, Ar-H), 5.63 (1H, d, NH), 5.26 (1H, m, -CH), 1.43 (9H, s, C(CH$_3$)$_3$), 1.38 (3H, d, -CH$_3$); ^{13}C NMR(CDCl$_3$) δ 198.34, 166.41, 155.56, 131.06, 80.13 (C), 131.52, 116.39 (=$\underline{C}$H), 51.31 ($\underline{C}$H-N), 28.73, 20.04 ($\underline{C}$H$_3$); ^{19}F-NMR(CDCl$_3$): δ -104.38; MS (relative intensity): 267 (M$^+$, < 1), 194 (1), 123 (15), 95 (25), 75 (15), 57 (100); HR-MS calculated for C$_{14}$H$_{18}$FNO$_3$: 290.1168; found 290.1164; IR (KBr, cm^{-1}): 1671 (C=O).

1-(4-Fluorophenyl)-2-N-tritylamino-1-propanone **4f**

0.5 g (2.45 mmol) of 2-amino-1-(4-fluorophenyl)-1-propanone hydrochloride was dissolved in 10 mL of DMF and 0.68 g (2.45 mmol) of chlorotriphenylmethane and 0.68 mL (5 mmol) of triethylamine was added. After stirring for 3 h, 10 mL of ether and 15 mL of water were added. The organic layer was separated, washed three times with a brine solution, dried over Na_2SO_4 and distilled off. The product was crystallized from petrol ether yielding 850 mg (85 %) of yellow crystals. mp.: 171°C. ^{1}H-NMR (CDCl$_3$): δ 7.28 (4H, m, Ar-H), 4.39 (1H, q, -CH-), 3.33 (1H, b, NH), 1.52 (3H, d, -CH$_3$); ^{13}C NMR(CDCl$_3$) δ 202.00, 165.88, 146.83, 71.91 (C), 131.00, 129.52, 128.28, 126.99, 115.51 (=$\underline{C}$H), 53.30 ($\underline{C}$H-N), 22.34 ($\underline{C}$H$_3$); ^{19}F-NMR(CDCl$_3$): δ -105.95; MS (relative intensity): 409 (M$^+$, < 1), 243 (100), 165 (45), 123 (35), 95 (50); HR-MS calculated for C$_{28}$H$_{24}$FNO: 432.1740; found 432.1741; IR (KBr, cm^{-1}): 1677 (C=O).

General procedure of N,N-dibenzylamination

10 mmol of 2-bromoalkyl-1-(haloaryl)ketone solubilized in 30 mL of acetonitrile was added to 20 mmol of dibenzylamine and heated at 60° C. The reaction was

finished after 5 to 6 hours. The dibenzylamino hydrobromide was filtered off and the organic solvent evaporated under reduced pressure. The residue was solubilized in a mixture of 20 mL of water and 10 mL of ether. The organic layer was separated and the aqueous phase extracted again with ether (2 x 10 mL). The organic layers were combined, washed with water, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column using ether-n-hexane (50:50).

2-N,N-Dibenzylamino-1-(4-fluorophenyl)-1-propanone **4d**: yield: 85 %, mp.: 55°C. ^{1}H-NMR (CDCl$_3$): δ: 7.25 (14H, m, Ar-H), 4.26 (1H, q, -CH), 3.6 (4H, J$_{AB}$ = 13.4 Hz, -CH$_2$-), 1.30 (3H, d, -CH$_3$);); ^{13}C NMR (CDCl$_3$): δ 200.42, 165.83, 144.91, 139.52 (C), 132.13, 129.78, 129.21, 128.73, 115.52 (=$\underline{C}$H), 57.55 ($\underline{C}$H-N), 54.71 ($\underline{C}$H$_2$-N), 8.13 ($\underline{C}$H$_3$); ^{19}F-NMR(CDCl$_3$): δ -106.40; MS (relative intensity): 347 (M$^+$, < 1), 224 (40), 91 (100); HR-MS calculated for C$_{23}$H$_{22}$FNO: 348.1764; found 348.1761; IR (KBr, cm^{-1}): 1679 (C=O).

2-N,N-Dibenzylamino-1-(2-fluorophenyl)-1-propanone **4e**: yield: 75 %, mp. (hydrochloride): 163°C; ^{1}H-NMR (CDCl$_3$): δ 7.25 (14H, m, Ar-H), 4.25 (1H, q, -CH), 3.63 (4H, J$_{AB}$ = -13.6 Hz, -CH$_2$), 1.30 (3H, d, -CH$_3$); ^{13}C NMR(CDCl$_3$) δ 202.74, 160.89, 144.88, 139.64 (C), 133.53, 130.72, 129.41, 128.59, 127.51, 124.54, 116.58 (=$\underline{C}$H), 61.74 ($\underline{C}$H-N), 54.94 ($\underline{C}$H$_2$-N), 9.20 ($\underline{C}$H$_3$); ^{19}F-NMR(CDCl$_3$): δ -104.38;); MS (relative intensity): 347 (M$^+$, < 1), 224 (40), 91 (100); HR-MS calculated for C$_{23}$H$_{22}$FNO: 348.1764; found 348.1759; IR (KBr, cm^{-1}): 1694 (C=O).

1-(4-Chlorophenyl)-2-N,N-dibenzylamino-1-propanone **8**: Yield: 61%, mp.: 61°C. ^{1}H-NMR (CDCl$_3$): δ 7.25 (14H, m, Ar-H), 4.20 (1H, q, -CH), 3.50 (4H, J$_{AB}$ = -13.4 Hz, -CH$_2$), 1.20 (3H, d, -CH$_3$); ^{13}C NMR (CDCl$_3$): δ 200.66, 139.44, 139.24, 135.38 (C), 130.97, 129.81, 128.77, 128.08, 127.79 (=$\underline{C}$H), 57.58 ($\underline{C}$H-N), 54.73 ($\underline{C}$H$_2$-N), 7.98 ($\underline{C}$H$_3$); MS (relative intensity): 363 (M$^+$, ^{35}Cl, < 1), 224 (100), 91 (100); HR-MS calculated for C$_{23}$H$_{22}$ClNO: 363.8868; found 363.8865; IR (KBr, cm^{-1}): 1677 (C=O).

2-N,N-Dibenzylamino-1-(4-N,N-dimethylaminophenyl)-1-propanone

A mixture of 0.5 g (1.55 mmol) 2-N,N-dibenzylamino-1-(4-fluorphenyl)propan-1-one, 0,16 g (2 mmol) dimethylamine hydrochloride and 0.55 g (4 mmol) of K$_2$CO$_3$ in 25 mL of DMSO and 10 mL of water was stirred and heated to reflux overnight.

After cooling at room temperature the solution was diluted using 20 mL of water and extracted three times with 15 mL of ether. The ether phase was washed with water, dried over Na_2SO_4, evaporated and purified on a silica gel column (ether/n-hexane (50:50) yielding 0.25 g (44 %) 2-N,N-dibenzylamino-1-(4-N,N-dimethylamino-phenyl)-1-propanone. mp.: 126°C; ^{1}H-NMR (CDCl$_3$): δ 7.08 (14H, m, Ar-H), 4.33 (1H, q, -CH), 3.7 (4H, J$_{AB}$ = 13.9 Hz, -CH$_2$-), 2.93 (6H, s, N(CH$_3$)$_2$)), 1.33 (3H, d, -CH$_3$);); ^{13}C NMR(CDCl$_3$): δ 200.01, 153.67, 140.42, 125.07, 139.64 (C), 131.59, 129.63, 128.57, 127.35 (=CH), 110.75 (CH$_3$-N), 54.72 (CH$_2$-N), 10.63 (CH$_3$); MS (relative intensity): 372 (M$^+$, < 1), 281 (< 1), 224 (10), 91 (100); HR-MS calculated for $C_{25}H_{28}N_2O$: 373.2280; found 373.2279; IR (KBr, cm^{-1}): 1661 (C=O).

4-(2-N,N-Dibenzylamino)propionylphenyl-1-N,N,N-trimethylammonium trifluorome-thanesulfonate **5**

120 mg (0.32 mmol) of methyl trifluoromethanesulphonate was added dropwise to a stirred solution of 110 mg (0.32 mmol) of 2-N,N-dibenzylamino-1-(4-N,N-dimethylaminophenyl)-1-propanone in 10 mL of CH$_2$Cl$_2$ at ambient temperature. After 3 h the solution was cooled and 50 mL n-hexane was added. The precipitate was filtered of, washed with ether and dried under reduced pressure. It was used without further purification. Yield: 55%, mp.: 61°C; ^{1}H-NMR (d$_6$-DMSO): δ: 7.58 (14H, m, Ar-H), 4.35 (1H, q, -CH), 3.68 (9H, s, N(CH$_3$)$_3$), 3.54 (4H, s, CH$_2$-Ph), 1.30 (3H, d, -CH$_3$); HR-MS calculated for $C_{25}H_{28}N_2O$: 387.5449; found 387.5445; IR (KBr, cm^{-1}): 1686 (C=O).

2-N-Benzoylamino-1-(4-fluorophenyl)-1-propanone and *2-N-Benzoylamino-1-(4-nitrophenyl)-1-propanone* **4g**, **6**

The compounds were synthesized according to Steglich et al. (17) starting from 6.2 mmol 4-fluorobenzoic acid chloride and 4-nitrobenzoic acid chloride, respectively. Besides 2.6 g (13.66 mmol) of N-benzoylalanine was heated with 50 mL acetic anhydride for 3 h at 80°C. 3-benzoyl-5-methyloxazolone was obtained after evaporation of the acetic anhydride under reduced pressure.

2-N-Benzoylamino-1-(4-fluorphenyl)-1-propanone: 0.7 g, mp.: 118°C; ^{1}H-NMR (CDCl$_3$): δ: 10.9 (2H, d, NH$_2$), 7.60 (9H, m, Ar-H), 5.75 (1H, m, -CH), 1.55 (3H, d, -CH$_3$); ^{13}C NMR(CDCl$_3$) δ: 198.09, 167.07, 166.65, 134.44, 130.75 (C), 132.10, 131.88, 129.03, 127.51, 116.61 (=$\underline{C}$H), 50.78 ($\underline{C}$H-N), 20.21 ($\underline{C}$H$_3$); MS (relative intensity): 271 (M+, 1), 148 (25), 105 (90), 77 (100); HR-MS calculated for C$_{16}$H$_{14}$FNO$_2$: 272.1087; found 272.1090; IR (KBr, cm^{-1}): 1647(C=O).

2-N-Benzoylamino-1-(4-nitrophenyl)-1-propanone: 0.74 g, mp.: 129°C; ^{1}H-NMR (CDCl$_3$): δ: 7.80 (9H, m, Ar-H), 7.2 (2H, d, -NH$_2$), 5.8 (1H, C-H), 1.55 (3H, d, -CH$_3$); ^{13}C NMR(CDCl$_3$) δ: 198.51, 167.24, 151.13, 139.19 (C), 132.40, 130.26, 129.11, 127.52, 124.54 (=$\underline{C}$H), 51.29 ($\underline{C}$-N), 19.45 ($\underline{C}$H$_3$); MS (relative intensity): 298 (M$^+$, < 1), 254 (4), 224 (2), 105 (100), 77 (70); HR-MS calculated for C$_{16}$H$_{14}$N$_2$O$_4$: 299.1032; found 299.1030; IR (KBr, cm^{-1}): 1691(C=O).

threo-2-Dibenzylamino-1-(4-fluorophenyl)propanol (**9b**)

0.69 g (2 mmol) of 2-N,N-dibenzylamino-1-(4-fluorophenyl)propanone (**4d**) was dissolved in 15 mL of ethanol and dropwise added to a suspension of 0.15 g (4 mmol) sodium borohydride in 50 mL of ethanol. After stirring for 6 h the reaction mixture was treated with 50 mL of 1 M hydrochloric acid. After removing the solvent, 20 mL of water was added and extracted with 2 x 20 mL ether. The solution was dried over Na$_2$SO$_4$ and the solvent evaporated. Threo-2-N,N-dibenzylamino-1-(4-fluorophenyl)propanol was obtained thereafter by flash chromatography (silica gel: ether/n-hexane (1:4)) as a colourless solid. mp. 138°C. ^{1}H-NMR (CDCl$_3$): δ 7.10 (14H, m, Ar-H), 5.10 (1H, b, OH), 4.33 (1H, d, -CH-O), 3.63 (4H, J$_{AB}$ 13.2 Hz, -CH$_2$-Ph), 2.75 (1H, m, N-CH-), 0.88 (3H, -CH$_3$); ^{13}C NMR(CDCl$_3$) δ 162.76, 139.10, 138.26, (C), 129.58, 129.26, 129.06, 127.87, 115.48 (=$\underline{C}$H), 74.22 ($\underline{C}$-O), 60.71 ($\underline{C}$H$_2$-N), 53.81 ($\underline{C}$-N), 8.17 ($\underline{C}$H$_3$); ^{19}F-NMR(CDCl$_3$): δ -115.41; MS (relative intensity): 349 (M$^+$, < 1), 224 (100), 91 (100); HR-MS calculated for C$_{23}$H$_{24}$FNO: 350.1920; found 350.1923.

erythro-2-Dibenzylamino-1-(4-fluorophenyl)propanol (**9a**)

0.69 g (2 mmol) of 2-N,N-dibenzylamino-1-(4-fluorophenyl)propanone (**4d**) was dissolved in 15 mL of THF and a solution of 4 mmol of BH$_3$·THF in THF was added

dropwise. After heating under reflux for 2 h the reaction mixture was treated with 50 mL of 1 M hydrochloric acid. After removal of the solvent the residue was taken up in 20 mL of water, extracted with 2 x 20 mL of ether and dried over Na_2SO_4. After removing the solvent, 20 mL of water was added and extracted with 2 x 20 mL ether. 2-N,N-dibenzylamino-1-(4-fluorophenyl)propanol was purified by flash chromatography (silica gel: ether/n-hexane (1:4)) yielding a colorless oil. mp. (hydrochloride): 188°C. ^{1}H-NMR (CDCl$_3$): δ 7.26 (14H, m, Ar-H), 4.71 (1H, d, -CH-O), 3.72 (4H, J_{AB} 13.9 Hz, -CH$_2$-Ph), 3.05 (1H, b, OH), 3.14 (1H, m, N-CH-), 1.32 (3H, -CH$_3$); ^{13}C NMR(CDCl$_3$) δ 162.67, 140.29, 139.69 (C), 129.27, 129.10, 128.89, 127.54, 115.30 (=$\underline{C}$H), 75.70 ($\underline{C}$-O), 55.00 ($\underline{C}$H$_2$-N), 58.83 ($\underline{C}$-N), 9.54 ($\underline{C}$H$_3$); ^{19}F-NMR(CDCl$_3$): δ -115.52; MS (relative intensity): 349 (M$^+$, < 1), 224 (100), 91 (100); HR-MS calculated for C$_{23}$H$_{24}$FNO: 350.1920; found 350.1922.

General procedure of debenzylation

0.35 g (1 mmol) of 2-N,N-dibenzylamino-1-(4-fluorophenyl)propanol was dissolved in 15 mL of methanol, 0.45 g of 10 % palladium on charcoal and 0.32 g (5 mmol) of ammonium formate were added and refluxed for 1 h. The suspension was filtered and the charcoal washed with methanol. The combined solutions were evaporated to dryness. The residue was dissolved in 10 mL of 2-propanol and refluxed for 30 min in presence of 1 mL of ether containing about 1 mmol of HCl. The solution was filtered and the product precipitated by adding 10-20 mL of ether.

erythro-2-amino-1-(4-fluorophenyl)propanol·HCl **10a**: mp.: 221°C. Lit. 220-221°C (16); ^{1}H-NMR (d$_6$-DMSO): δ: 8.34 (3H, b, $^+$N$\underline{H}_3$), 7.36 (4H, m, Ar-H), 6.19 (1H, d, C$\underline{H}$-O), 5.09 (1H, m, N-C$\underline{H}$), 0.96 (3H, d, -CH$_3$), ^{13}C NMR(d$_6$-DMSO) δ 162.23, 138.28 (C), 128.78, 115.76 (=$\underline{C}$H), 71.56 ($\underline{C}$-O), 52.77 ($\underline{C}$-N), 12.20 ($\underline{C}$H$_3$);. ^{19}F-NMR(d$_6$-DMSO): δ -116.05.

threo-2-amino-1-(4-fluorophenyl)propanol·HCl **10b**: mp: 178°C. Lit. 187-188°C (16); ^{1}H-NMR (d$_6$-DMSO): δ: 8.44 (3H, b, $^+$N$\underline{H}_3$), δ: 7.35 (4H, m, Ar-H), 4.55 (1H, d, C$\underline{H}$-O), 2.85 (1H, m, N-C$\underline{H}$), 0.80 (3H, d, -CH$_3$); ^{13}C NMR(d$_6$-DMSO) δ 162.59, 138.47 (C), 129.42, 115.96 (=$\underline{C}$H), 74.38 ($\underline{C}$-O), 53.23 ($\underline{C}$-N), 15.74 ($\underline{C}$H$_3$);. ^{19}F-NMR(d$_6$-DMSO): δ -115.02.

N.c.a. nucleophilic fluorination

N.c.a. [^{18}F]fluoride was produced via the ^{18}O(p,n)^{18}F nuclear reaction by bombardment of isotopically enriched [^{18}O]water with 17 MeV protons at the JSW cyclotron BC 1710. The aqueous [^{18}F]fluoride solution (10-50 µL, 75-375 MBq) was filled into a 5 mL conical vial (Reactivial) containing 1 mL of acetonitrile, 10 mg of Kryptofix® 2.2.2., 13 µl of a 1 M potassium carbonate solution. The solvent was evaporated under a stream of argon at 90°C and 900 mbar. The azeotropic drying step was repeated using 1 mL of dry acetonitrile, followed by evaporation at 40-50 mbar for 5 min. The dry cryptate was dissolved in 0.5 mL of DMSO containing the appropriate amount of precursor and heated under isochoric conditions.

Stereoselective reduction

9 mL of water were added to the reaction mixture and then passed through a conditioned Sep-Pak™ C-18 plus-cartridge (Waters) combined with an EN-cartridge (Merck), which was prewashed with 10 mL of ethanol followed by 10 mL of water. The products adsorbed on the solid phase were eluted with 4 mL of acetonitrile and evaporated under a stream of argon. The azeotropic drying step was repeated twice with each 1 mL of acetonitrile, followed by evaporation for 5 min at 40-50 mbar. In the case of erythro isomer the residue was diluted with 1 mL THF, mixed with 100-200 µl of 1 M BH$_3$·THF solution and heated at 66°C for 15 min. The reduction of the carbonyl function with formation of the threo isomer was carried out with 0.1 mmol of NaBH$_4$ in 0.5 mL ethanol within 10 min. The solvents were evaporated and the residue hydrolysed in presence of 1 to 2 mL of 1 M hydrochloric acid. The N-protected 4-[^{18}F]fluoronorephedrine was diluted with water and passed through Sep-Pak™ C18 cartridge. The product adsorbed on the solid phase was eluted using 1-2 mL methanol and debenzylated using ammonium formate in presence of palladium on charcoal at 60°C within 15 min. The radiochemical yield of n.c.a. 4-[^{18}F]fluoronorephedrine was 15-20%. The molar activity was >74 TBq/mmol.

HPLC-analyses

The final characterization of the diastereomers of n.c.a. 4-[^{18}F]fluoronorephedrine was performed using a Multosorb® RP-18 Select B 5 µl (250 x 4 mm) column with

an eluant consisting of ethanol/water/acetic acid (10:87.5:2.5) and 2.5 g ammonium acetate with a flow of 1 mL/min. The k' value for the erythro and threo isomer was 4.8 and 5.0, respectively.

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