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No-carrier-added (NCA) synthesis of 6-[^{18}F]fluoro-L-DOPA using 3,5,6,7,8,8a-hexahydro-7,7,8a-trimethyl-[6S-(6α, 8α, 8αβ)]-6,8-methano-2H-1,4-benzoxazin-2-one.

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Summary

3,5,6,7,8,8a-Hexahydro-7,7,8a-trimethyl-[6S-(6α,8α,8αβ)]-6,8-methano-2H-1,4-benzoxazino-2-one (**2**) was investigated as chiral auxiliary for asymmetric NCA nucleophilic synthesis of 6-[^{18}F]Fluoro-L-DOPA. Direct condensation of 3,4-dimethoxy-2-[^{18}F]fluorobenzaldehyde (**1a**) or 6-[^{18}F]fluoropiperonal (**1b**) in the presence of NaH with **2** gave the corresponding [^{18}F]-3-[(2-fluorophenyl)methylene]-3,5,6,7,8,8a-hexahydro-7,7,8a-trimethyl-[6S-(3Z,3α,6α,8α,8αβ)]-6,8-methano-2H-1,4-benzoxazin-2-one derivative **3a** or **3b** as a single stereoisomer. L-Selectride® promoted hydrogenation of the olefinic double bond of these derivatives, in presence of tert-butyl alcohol, afforded the corresponding [^{18}F]-3-[(2-fluorophenyl)methyl]-3,5,6,7,8,8a-hexahydro-7,7,8a-trimethyl-[3S-(3α,6α,8α,8αβ)]-6,8-methano-2H-1,4-benzoxazin-2-one derivatives (**4a**,**b**) without affecting the

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orientation of diastereofacial discrimination. Deprotection of the derivatives **4a,b** yielded 6-[^{18}F]fluoro-L-DOPA (e.e. >90%, 3% radiochemical yield (EOB), total synthesis time 125 min, specific activity >2000 mCi/μ mol). Direct deprotection/reduction of the compounds **3a,b** provides the enantiomeric mixture of 6-[^{18}F]fluoro-D,L-DOPA (10-12% radiochemical yield) and, after chiral separation, 6-[^{18}F]fluoro-L-DOPA (e.e. 98%, 4-5% radiochemical yield).
A "cold" enantioselective synthesis of 6-fluoro-L-DOPA has been effected with total chemical yield 15% (e.e. 93.4%).

Key Words: 6-[^{18}F]fluoro-L-DOPA, enantioselective synthesis, positron emission tomography, dopamine, radio tracer.

Introduction

Positron emission tomography has been used with some success to evaluate the dopamine system in vivo. Although many radio-labelled tracers have been utilized (1 - 17), most studies have utilized 6-[^{18}F]fluoro-L-DOPA. As a tracer, this compound may provide useful information about dopamine system function as it is metabolized in an identical fashion to DOPA (18-21).

Regioselective electrophilic fluorination (via $^{18}F_2$) is still the method of choice for preparation of clinical doses of 6-[^{18}F]fluoro-L-DOPA. However, most PET centers do not have the equipment for production of $^{18}F_2$ which is a logistic limitation for widespread use of 6-[^{18}F]fluoro-L-DOPA. Several procedures have been recently developed to produce 6-[^{18}F]fluoro-L-DOPA via nucleophilic substitution with widely available [^{18}F]fluoride (21-24). Semi-remote modification of the non-enantioselective synthesis through 2-phenyl-5-oxazolone (22) has been used at our PET center for routine preparation of 6-[^{18}F]fluoro-L-DOPA for the past year with the average radiochemical yield of 4.5% (EOB) (Figure 1):

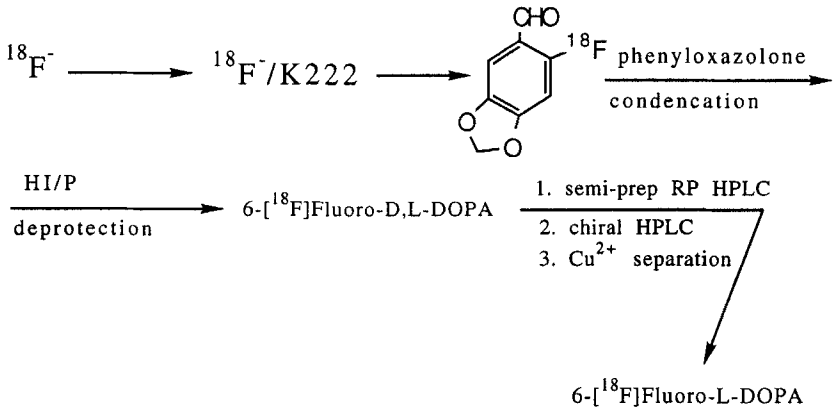

Figure 1: NCA non-enantioselective synthesis of 6-[^{18}F]Fluoro-L-DOPA

The theoretical maximal yield of 6-[^{18}F]fluoro-L-DOPA in this synthesis is 50% since the intermediate product is a racemic mixture. The purification procedure requires a chiral semi-prep HPLC separation of the D,L-mixture and subsequent separation of copper ions from the final product solution. An enantioselective procedure (24) provides 6-[^{18}F]fluoro-L-DOPA in 96% e.e. (Figure 2). However, the complex nature of this multi-step synthetic strategy precludes the production of clinical quantities of 6-[^{18}F]fluoro-L-DOPA at most PET centers.

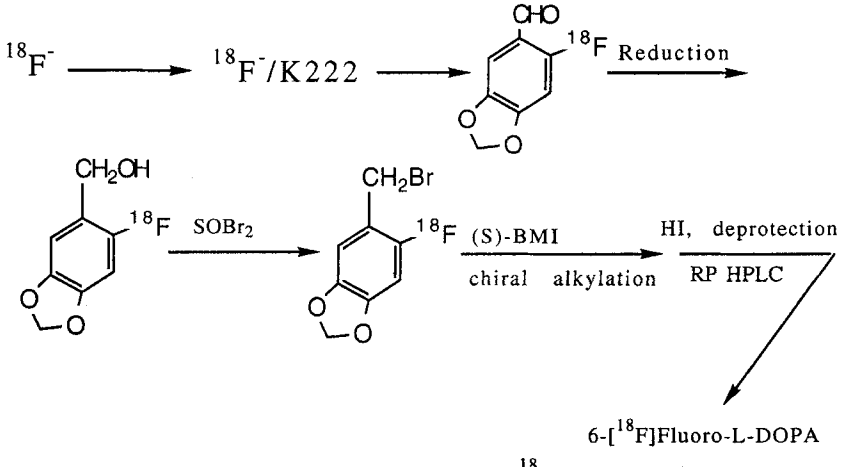

Figure 2: NCA enantioselective synthesis of 6-[^{18}F]Fluoro-L-DOPA

Reliable and simple NCA enantioselective synthesis of 6-[^{18}F]fluoro-L-DOPA continues to be a limiting factor for the more wide-spread use of this tracer. We believed that a shorter enantioselective synthesis could be developed if ^{18}F-labeled benzaldehydes were directly involved in the condensation with an asymmetric inductor. It seemed to us that the most attractive synthesis would be a chiral variant of the 2-phenyl-5-oxazolone procedure. Herein we report a new enantioselective method of 6-[^{18}F]fluoro-L-DOPA preparation based on this strategy.

Results and Discussion

3,5,6,7,8,8a-Hexahydro-7,7,8a-trimethyl-[6S-(6a,8a,8ab)]-6,8-methano-2H-1,4-benzoxazino-2-one (2 ("lactone")) was reported recently as an efficient agent for the enantioselective preparation of amino acids in e.e.>95% from corresponding aldehydes (25). Our initial experiments showed the feasibility of synthesizing of 6-fluoro-L-DOPA from the lactone (2) and 3,4-dimethoxy-2-fluorobenzaldehyde (1) (Figure 3):

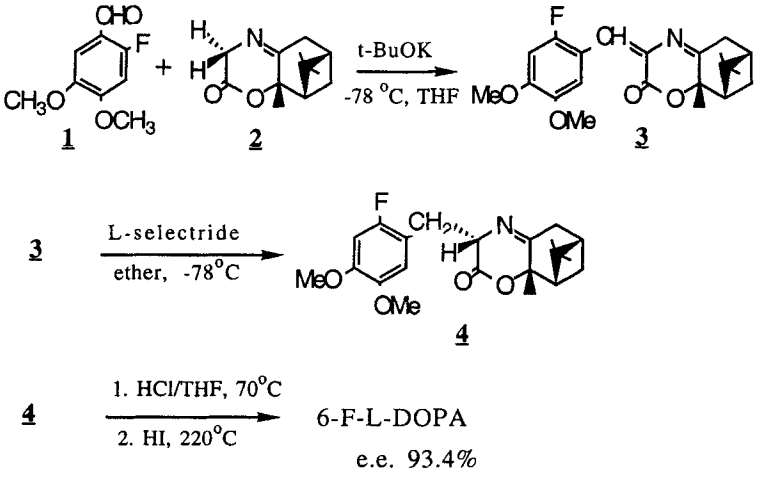

Figure 3: "Cold" asymmetric synthesis of 6-F-L-DOPA

The "lactone" **2** easily reacted with 3,4-dimethoxy-2-fluorobenzaldehyde **1** in the presence of t-BuOK to furnish 3-[(2-fluoro-4,5-dimethoxyphenyl)methylene]-3,5,6,7,8,8a-hexahydro-7,7,8a-trimethyl-[6S-(3Z,3α,6α,8α,8αβ)]-6,8-methano-2H-1,4-benzoxazin-2-one (**3**) as a single reaction product. Careful L-selectride® promoted hydrogenation of the olefinic bond of **3** gave the corresponding aminoacid derivative **4**. The yield of **4** is very sensitive to reaction conditions and may be associated with cleavage of the C-F bond and/or Claisen condensation of the intermediate enolate. In the ^{1}H-NMR spectrum of **4**, the splitting of the proton α to the benzyl group indicates that the hydrogen entered the same face to the gem dimethyl group since the proton shows homoallylic coupling (25,26). The structure of the compounds **3** and **4** were confirmed with ^{1}H-NMR and high resolution mass-spectra. Followed acidic cleavage of **4** afforded 6-fluoro-L-DOPA in 15% overall yield in e.e. 93.4%.

For the preparation of corresponding [^{18}F]labeled benzaldehyde we chose commercially available 6-nitropiperonal or 3,4-dimethoxy-2-nitrobenzaldehyde as starting agents. Initial experiments were performed with 3,4-dimethoxy-2-nitrobenzaldehyde since compounds **1**, **3** and **4** were prepared and purified as chromatographic standards (Figure 4). However, 6-nitropiperonal used as the precursor gave a better yield of final product due to smooth deprotection.

3,4-dimethoxy-2-[^{18}F]-fluorobenzaldehyde (**1a**) or 6-[^{18}F]fluoropiperonal (**1b**) was prepared from non-carrier-added [^{18}F]fluoride as previously described (22) with an average yield 55% (EOB). Traces of water in [^{18}F] fluorobenzaldehyde solution were removed by passing it through a $MgSO_4$ disposable cartridge. Knoevenagel condensation of lactone **2** with benzaldehydes **1a** or **1b** in the presence of t-BuOK gave the corresponding [^{18}F]labeled α,β-didehydroderivatives **3a**,**b** in moderate yield. Dramatic improvement

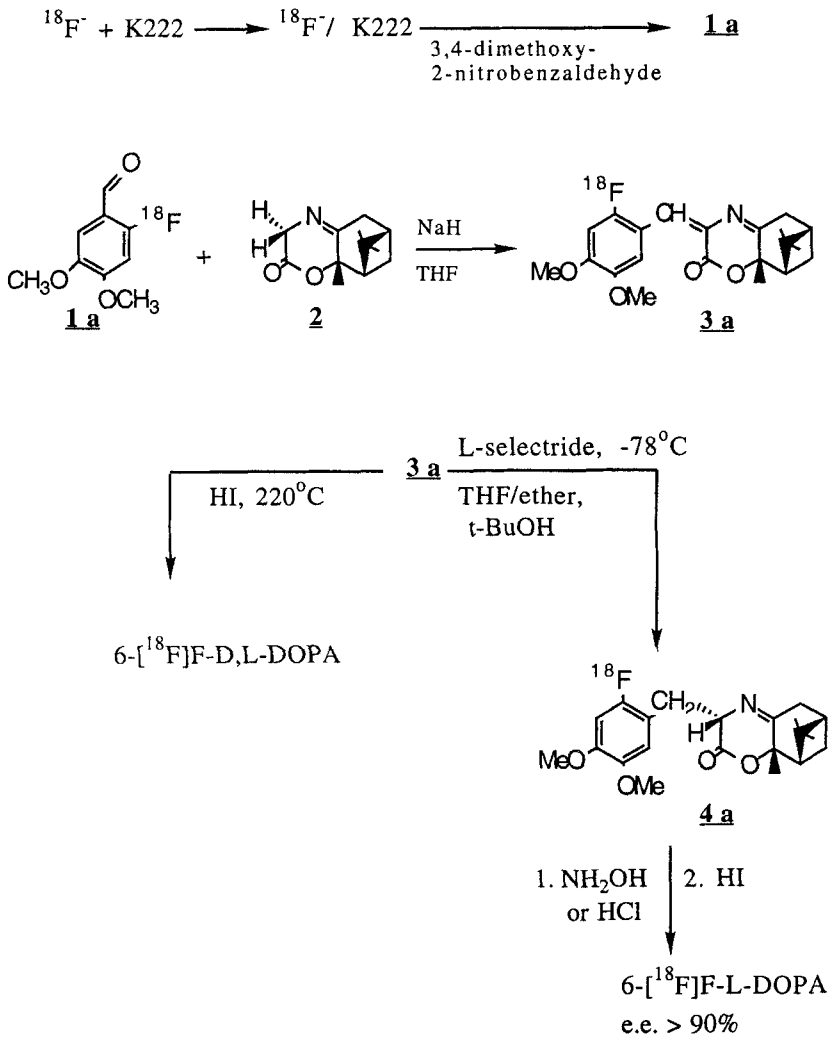

Figure 4: NCA synthesis of 6-[^{18}F]Fluoro-L-DOPA via lactone, **2**

of the condensation yield (up to 80%, corrected to **1a**) took place when NaH was used as the base. In this case the reaction did not require a dry ice cooling bath. Before the next step was performed the reaction mixture was quenched by passing it through an Al_2O_3 disposable cartridge. After such purification the THF solutions of **3a,b** were 90% radiochemically pure (each solution contained about 10% of corresponding ^{18}F-benzaldehyde).

Treatment of **3a** with acidic hydroxylamine solution and subsequent deprotection/reduction with hydriodic acid afforded an enantiomeric mixture of 6-[^{18}F]fluoro-D,L-DOPA which could be separated by chiral HPLC (22). Without optimization the decay corrected radiochemical yield of the D,L-mixture was 10-12% and the yield of 6-[^{18}F]fluoro-L-DOPA was 4-5%.

Enantioselective reduction of **3a,b** with L-selectride® was not straightforward. The reduction was very sensitive to reaction conditions and was accompanied, especially when using of excess of reducting agent, by the formation of non-identified radiolabeled by-products which may be associated with a decomposition reaction and/or Claisen condensation of intermediate enolate. Such by-products were observed during L-selectride promoted reduction of α,β-unsaturated esters (27). The formation of labeled by-products was partially suppressed when t-butyl alcohol was used as the proton donor. On the other hand, prolonged reaction time was required for complete reduction of **3** if a stoichiometric amount of L-selectride® was used. Unreacted **3a,b** in the reduction mixture was not acceptable due to its subsequent conversion to racemic 6-[^{18}F]fluoro-D,L-DOPA. (6-[^{18}F]fluoro-L-DOPA was formed in e.e. 15%-89% when the reaction mixture contained some unreacted **3a**). Because 6-[^{18}F]fluoro-L-DOPA used in PET studies must have an e.e.>90%, we made some effort to drive the reduction of **3a** to completion using a large excess of L-selectride® without incurring significant decomposition of the reduction product **4a**. The results of these experiments are shown in Table.

The final product was prepared with a total radiochemical yield of 3% (EOB) in e.e. 90-91% and synthesis time was 125 minutes. The NCA enantioselective procedure described here is a relatively convenient approach to 6-[^{18}F]fluoro-L-DOPA. Direct condensation of ^{18}F-benzaldehydes (**1a,b**) with the inductor of chirality allows one to decrease the number of chemical steps. In accordance with the

Table. Effect of reduction conditions for **3a** on the yield and enantiomeric purity of 6-[^{18}F]fluoro-L-DOPA†

L-selectride, mmol	Temperature, °C	Time, min	Yield of **4a**, %*♦	^{18}F-L-DOPA yield (EOB), %**	e.e. of ^{18}F-L-DOPA, %
0.1	-78	30	6	0.6	15
0.2	-78	15	52	0.54	42
0.4	-78	5			
	20	5	9	0.1	91
0.4	0	10	16	0.34	90
0.4	-78	5	88	1.51	83
0.4	-78	10	96	2.98	89
0.4	-78	15	47	0.53	90.5
0.5	-78	8	72	1.54	69
0.5	-78	9	83	1.73	81
0.5	-78	10	95	2.91	90.8
0.5	-78	10.5	78	1.17	90.4
0.5	-78	11	62	0.58	91
0.5	-78	15	12	0.12	90

† General procedure: tert-Butyl alcohol (0.2 mL) was added to the 10 mL V-vial containing the THF/ether solution of **3a**, and the whole solution was chilled. 1M solution of L-selectride® was added to the cooled solution and reaction mixture was stirred for 5-30 min. Hydroxylamine solution (1.5 mL) was added to the chilled reaction mixture. Organic solvent was partially evaporated and hydriodic acid (57%, 1.5 mL) was added. This mixture was refluxed for 15 min and chilled. Solution of NaOH (6N, 1 mL) was added and the mixture was passed through a C18 Sep-Pak. The Sep-Pak was washed with semi-prep mobile phase and the combined eluate was injected on to a semi-prep Magnum column. The peak corresponding to radioactive F-DOPA was collected and the solvent was evaporated to dryness. The residue was redissolved in mobile phase (*A*) and analyzed with chiral and analytical HPLC.

* The yield was determined by analytical HPLC; ** The radiochemical yield of deprotection step was not greater than 20%; ♦ The yield was decay corrected to **3a**

previous literature (25), the "lactone" procedure provides amino acids in e.e.>95%. We will continue optimisation of the 6-[^{18}F]fluoro-L-DOPA preparation to improve radiochemical yield and enantiomeric purity in order to use this procedure for PET studies.

Experimental

All reagents used were ACS or HPLC purity grade. ^{1}H-NMR spectra were recorded on a Nicolet 360-2 (Spectral Data Services, Inc.); chemical shifts (δ) were recorded in parts per million down field from TMS. High resolution mass-spectra (EI) was recorded on a Finnigan MAT 95 (University of Minnesota Mass Spectroscopy Laboratory). High performance liquid chromatographic analysis and purification were performed with two Spectra-Physics IsoChrom LC pumps, an in-line fixed wavelength (254 nm) detector, Waters 440 or tunable absorbance HPLC detector, Waters 486 (220 nm, for determination of specific activity), and a single two inch NaI crystal radioactive detector. HPLC chromatograms were recorded by a Rainin Dynamax dual channel control/interface module connected to a Macintosh computer with appropriate program software (Dynamax - version 1.4). HPLC conditions:

A. Semipreparative purification of FDOPA were completed on an Partisil 10 ODS-3 Magnum-9 column (500 x 9.4 mm), eluant: $CH_3COOH/CH_3CN/H_2O$ 0.2/3/97, flow 3.5 mL/min.

Chiral semipreparative purification and chiral HPLC analysis were completed on an Serva Chiral=SI 100 L-ProCu columns (250 x 4.6 mm):

B. chiral semiprep HPLC eluant: 0.05M NaH_2PO_4/ 0.85mM $CuSO_4$, pH 4.0, flow 1.5 mL/min,

C. analytical chiral HPLC eluant: 0.05M NaH_2PO_4/ 0.4mM $CuSO_4$, pH 4.0, flow 1.5 mL/min.

Chemical and radiochemical purity were determined using an Alltech 10 μ C-18 Econosil column (250 x 4.6 mm):

D. The following conditions were used for identification of compounds **1**, **1a**, **3**, **3a**, **4** and **4a** : CH_3CN/ 0.1M ammonium formate buffer 75/25; flow rate 1.5 mL/min),

F. Determination of radiochemical purity of final ^{18}FDOPA: step gradient: 0.2% aqueous CH_3COOH; 15 min, 100% acetonitrile; flow 1.5 ml/min.

A dose calibrator (Capintec CRC-712M) was used for all radioactivity measurements. $^{18}F^-$ was produced with an 11 MeV negative ion cyclotron (Siemens).

Ultra high purity argon was used as a sweep gas for all syntheses.

3-[(2-fluoro-4,5-dimethoxyphenyl)methylene]-3,5,6,7,8,8a-hexahydro-7,7,8a-trimethyl-[6S-(3Z,3α,6α,8α,8αβ)]-6,8-methano-2H-1,4-benzoxazin-2-one, **3**

A solution of 1M t-BuOK (1 mmol) in dry THF was added under argon at -78 °C to a stirred solution of lactone (26), (**2**, 1 mmol) in dry THF (6 mL) and this mixture was stirred for 40 min. A solution of 3,4-dimethoxy-2-fluorobenzaldehyde (28), **1** (1 mmol) in dry THF (3 mL) was added at same temperature. The mixture was stirred at -78 °C for 1 hour and reaction was monitored by analytical RP HPLC (*D*, R_t 6.1 min).. The solvent was evaporated to dryness by rotory evaporator (bath temperature 40 °C). Separation of the residue by flash chromatography (silica gel, column 20x350 mm, $CHCl_3$/ether 1/1) gave analytically pure **3a** (0.8 mmol, 80%) as a yellow solid.

MS, m/z (rel. intensity), [M^+]: 373.1716 (100%), calculated for $C_{21}H_{24}NFO_4$: M 373.1689. ^{1}H-NMR, $CDCl_3$ (δ, ppm):1.09 (3H, s), 1.35 (1H, d, J=11.1Hz), 1.42 (3H, s), 1.62 (3H, s), 2.20 (2H, m), 2.45 (1H, m), 2.95 (2H, m), 3.90 (3H, s), 3.91 (3H, s), 6.65 (ArH-3, d, J_{HF}^{ortho} 11.5 Hz), 7.55(1H, s), 8.12 (ArH-6, d, J_{HF}^{meta} 7.0 Hz).

3-[(2-fluoro-4,5-dimethoxyphenyl)methyl]-3,5,6,7,8,8a-hexahydro-7,7,8a-trimethyl-[3S-(3α,6α,8α,8αβ)]-6,8-methano-2H-1,4-benzoxazin-2-one, **4**

A 1.0 M solution of L-selectride® in dry THF (Aldrich, 0.46 mmol, 0.46 mL) was added under argon at -78°C to a stirred solution of **3**

(85 mg, 0.23 mmol) in dry ether (6 mL). The chilled reaction mixture was stirred for 75 min and saturated aqueous NH_4Cl solution (1 mL) was added to terminate reduction. The mixture was extracted by ether; and the ether solution was washed with water and was dried over anhydrous $MgSO_4$. After ether evaporation **4** was afforded as a single diastereoisomer (by ^{1}H-NMR) with 75% yield. Additional purification was performed by flash chromatography (silica gel, column 20x350 mm, ether/hexane 7/3). The reaction mixture was monitored using C18 HPLC (*D*, R_t 4.1 min).

MS, m/z (rel. intensity), [M^+]: 375,1841 (98%), calculated for $C_{21}H_{26}NFO_4$: M:375.1846 . ^{1}H-NMR, $CDCl_3$ (δ, ppm):1.02 (3H, s), 1.15 (1H, d, J=11.2 Hz), 1.38 (3H, s), 1.60 (3H, s), 2.00-2.22 (2H, m), 2.35 (1H, m), 2.62-2.73 (1H, m), 2.81-2.88 (1H, m), 3.07 (1H, dd), 3.51 (1H, dd), 3.84 (3H, s), 3.86 (3H, s), 4.26 (1H, m), 6.62 (1H, d), 6.94 (1H, d).

6-Fluoro-L-DOPA

3-[(2-Fluoro-3,4-dimethoxyphenyl)methyl]-3,5,6,7,8,8a-hexahydro-7,7,8a-trimethyl-[3S-(3α,6α,8α,8αβ)]-6,8-methano-2H-1,4-benzoxazin-2-one, **4** (0.1 mmol) was dissolved in THF (0.5 mL) and 6N HCl (3 mL) were added. The mixture refluxed at 80-95°C for 4 h and the solvent was evaporated to approximately 0.5 mL. Hydriodic acid (3 mL, 57%, stabilized) was added and the solution was stirred at 220°C for 40 min and was then evaporated to dryness. The residue was redissolved in 0.2% CH_3COOH (3 mL), passed through C18 SEP-PAK and the cartridge was washed with 0.2% CH_3COOH (2 mL). Separation of final product was performed with semi-prep HPLC (*A*, R_t 13 min) to afford 0.025 mmol 6-fluoro-L-DOPA as mobile phase solution (e.e. 93.4% determined with chiral HPLC, *C*, R_t^L 11-12 min, R_t^D 4 min). Yield: 25% (determined with C18 HPLC, *F*, R_t 11 min). 6-Fluoro-D,L-DOPA as HPLC standard was prepared accordingly to the procedure of Lemaire at al. (24).

6-[^{18}F]Fluoro-L-DOPA

1.Enantioselective procedure:

3,4-Dimethoxy-2-[^{18}F]fluorobenzaldehyde (**1a**) or 6-[^{18}F]fluoropiperonal (**1b**) were synthesized with no-carrier-added complex [K/Kryptofix 222]$^{+}$^{18}F^{-} as previously described (22).

Condensation:

A solution of 3,5,6,7,8,8a-Hexahydro-7,7,8a-trimethyl-[6S-(6α,8α,8αβ)]-6,8-methano-2H-1,4-benzoxazino-2-one, **2** (40 mg) in dry THF (1 mL) was stirred with NaH (3-5 mg) for 10 min in a 10 mL V-vial. A solution of [^{18}F]labeled benzaldehyde derivative **1a** or **1b** in dry THF (1.5 mL) was added into the same vial, the mixture was stirred for 20 min, passed through a glass wool cartridge and a Waters alumina (N) Sep-Pak. Both cartridges were washed with dry ether (2 x 1 mL) to yield a solution of **3a**,**b** in THF/ether mixture.

Reduction:

tert-Butyl alcohol (0.2 mL) was added to the 10 mL V-vial containing the THF/ether solution of **3a** or **3b**, and the viale was chilled in a dry ice/acetone bath. 1M solution of L-selectride® (Aldrich) (0.5 mL) was added to the cooled solution and the mixture was stirred for 10 minutes. (When the precursor **1a** was used the reaction mixture was monitored by RP HPLC (*D*), the radioactive peaks of **3a** and **4a** showed the same retention times (RP HPLC) as **3** and **4**, respectively).

Deprotection:

First method - Hydroxylamine solution (1.5 mL, NH_2OHx$HCl/CH_3COOH/EtOH/H_2O$ 8.75/50/50/100)was added to the chilled solutions of **4a** or **4b** . Organic solvent was partly evaporated (oil bath, 140^{o}C, argon flow) and hydriodic acid (57%, stabilized, 1.5 mL) was added. This mixture was refluxed (oil bath, 220 ^{o}C, argon flow) for 15 min and chilled using a dry ice/acetone bath. The cold bath was removed, 6N NaOH solution (1 mL) was added and the solution was passed through a C18 Sep-Pak. The Sep-Pak was

washed with semi-prep mobile phase (*A*, 2 x 1 mL) and the combined eluate was injected on to a semi-prep Magnum column. The peak corresponding to radioactive F-DOPA was collected (R_t 12-13 min) and the solvent was evaporated to dryness. The residue was redissolved in mobile phase (*A*) and analyzed with chiral and analytical HPLC.

Second method - 6N HCl (1 mL) was added to the chilled reaction vial. Organic solvent was partly evaporated (oil bath, 140°C, argon flow) and hydriodic acid (57%, stabilized, 1.5 mL) was added. Subsequent steps were the same as for the first method.

2. Non-enantioselective procedure

The solution of **3b** was prepared as described above. The solvent was partly evaporated and hydroxylamine solution (1 mL) added. The organic solvents were evaporated under a stream of argon at 140°C. Hydriodic acid (57%, stabilized, 1.5 mL) was added, the remaining steps were the same as for the first method. The solution of 6-[^{18}F]fluoro-D,L-DOPA (2 mL) was injected on to a chiral column (*B*). 6-[^{18}F]Fluoro-L-DOPA peak with Rt 14-18 min was collected and copper salt was removed by passing through a Waters Accell Plus CM Sep-Pak cartridge. The cartridge was washed with saline (2x1 mL) to yield 6-[^{18}F]fluoro-L-DOPA in e.e. >98%.

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