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NO-CARRIER-ADDED (NCA) ARYL [^{18}F]FLUORIDES VIA THE NUCLEOPHILIC AROMATIC SUBSTITUTION OF ELECTRON-RICH AROMATIC RINGS

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SUMMARY

Nucleophilic aromatic substitution by [^{18}F]fluoride ion has been demonstrated on rings containing electron donating groups in addition to the necessary electron withdrawing and leaving groups. The reaction of $^{18}F^-$ with a series of aromatic nitro aldehydes having protected hydroxyl substituents on the ring was studied. The reactivity of the aromatic ring towards nucleophilic substitution to give ^{18}F-labeled aromatic fluoroaldehyde derivatives is correlated with electron density at the reaction center. The effect of a number of protected hydroxyl substituents is reported. ^{13}C-NMR was used as a sensitive probe for the changes in electron distribution at the ring carbon atoms. Radiochemical yield correlates with ppm values at the reaction center. This methodology has been applied to the synthesis of no-carrier-added (NCA) 6-[^{18}F]fluoro-L-DOPA. The extention of this strategy to the syntheses of other labeled pharmaceuticals appears promising.

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INTRODUCTION

Nucleophilic aromatic substitution by fluoride ion has become one of the most useful labeling techniques utilizing fluorine-18, a positron emitter with a 110 minute half life. The mechanism and conditions necessary for successful substitution were the subject of a series of papers [1 - 4] and these techniques now have widespread application in the original or modified form [5-7] The leaving group in the substitution reaction on an aromatic ring is usually nitro or $-^{+}NMe_3$ and the necessary electron withdrawing group to effect the reaction can be RCO, CN, NO_2 etc. However, there are numerous important radiopharmaceuticals with electron donating substituents in addition to the electron withdrawing substituents which can make the substitution reaction proceed in low yield or be ineffective. To name a few of such multifunctional aromatic compounds we can include fluorine-18 labeled 6-fluoro-L-DOPA [8] and 4-fluoro-m-tyrosine [9 - 11] used to study dopamine metabolism in the brain, 2-fluorotyrosine for studying in vivo protein metabolism [12] and 6-fluoronorepinephrine [13, 14] and 6-fluoro-metaraminol [15] for studying adrenergic receptors and myocardial innervation. To date, the practical synthetic route for a number of these molecules involved the use of the electrophilic fluorinating reagents either fluorine-18 labeled elemental fluorine or acetylhypofluorite [8, 15, 16]. The use of these two reagents results in low specific activity and direct fluorination usually produces a mixture of fluorinated products.

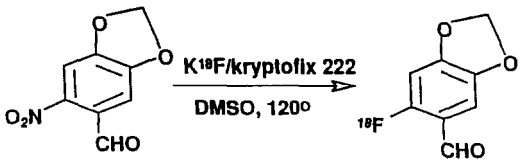
The considerable importance of [^{18}F]fluoride ion for labeling radiopharmaceuticals and the biomolecules used in Positron Emission Tomography (PET) research has lead us to investigate the feasibility of using nucleophilic aromatic substitution by [^{18}F]fluoride ion as a more general method applicable to aromatic substitution when both electron donating and electron withdrawing substituents are present on the aromatic ring. Thus a series of compounds with hydroxyl groups suitably protected were studied using no-carrier-added (NCA) $^{18}F^{-}$ as the labeling nucleophile.

The implications of this substitution from a mechanistic point of view as well as an efficacious labeling method are presented.

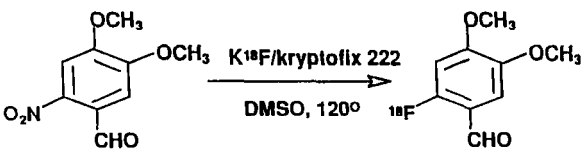
As an example of this method, the synthesis of 6-[^{18}F]fluoro-L-DOPA is described.

RESULTS AND DISCUSSION

In studying nucleophilic substitution using NCA $^{18}F^-$ obtained from the ^{18}O (p,n) ^{18}F reaction on enriched water, a striking difference in radiochemical yield between 6-nitropiperonal and 6-nitroveratraldehyde was noted; 6-[^{18}F]fluoropiperonal and 6-[^{18}F]fluoroveratraldehyde were obtained in 51% and 23% yield, respectively.



Radiochemical Yield: 51 %

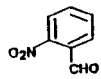
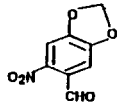
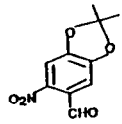
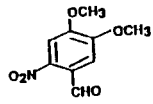
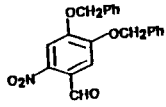
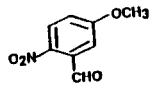
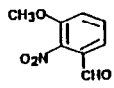
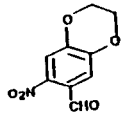
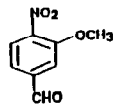


Radiochemical Yield: 23 %

This suggested that the hydroxyl protecting group plays an important role in controlling the reactivity of the aromatic ring towards nucleophilic substitution and prompted us to carry out an investigation on the effects which different protecting groups have on this reaction (Table I). When there was no electron donating group on the ring, the radiochemical yield for nucleophilic substitution was the highest. When the dihydroxy groups were protected as 1,3-benzodioxolanes (compound **B** & **C**), the yields were still good, but when protected as dialkyl groups (compound **D** & **E**), the yields

TABLE 1

Structural Effects of Various Protecting Groups on Radiochemical Yields in Nucleophilic Substitution with NCA $^{18}F^-$

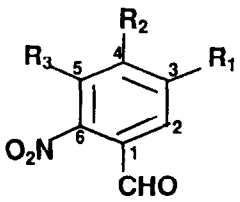
Compound		Radiochemical Yield (EOB)
(A)		78%
(B)		51%
(C)		42%
(D)		23%
(E)		24%
(F)		5%
(G)		23%
(H)		0%
(I)		35%

decreased. In the case of only one methoxy group *para* to the nitro group (compound **F**), only a 5% yield was obtained However, a single methoxy *ortho* to the nitro group (compound **G**) gave the ^{18}F-labeled product in 23% yield. 1,4-Benzodioxan-6-carboxyaldehyde (compound **H**) was essentially inert to nucleophilic substitution while compound **I** which has a nitro group *para* to the formyl group, afforded a 35% yield of product

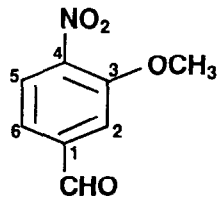
To probe the electron density at the reaction center, an approach [17, 18] that has been suggested for the electron donating effect on unhindered and crowded anisoles may be applied. The methoxy groups of unhindered anisoles tend to lie in the aromatic plane with an Ar-O-Me bond angle of 117-118^{o}, a value near that is expected for sp^2-hybridized oxygen. This arrangement has the optimum overlap between the oxygen p-type lone pair orbital and the aromatic π system. In crowded anisoles, nonbonded interactions may force the CH_3 of the methoxy group out of the aromatic plane. The hybridization of the oxygen then approaches sp^3 and the overlap decreases. As a consequence there will be a lowering of the π-electron densities at the *para* carbon atoms, a phenomenon which was verified by ^{13}C-NMR chemical shift Since a similar crowding and rehybridization mechanism could explain the relative reactivities of the compounds in our series, we examined their ^{13}C-NMR spectra in order to test this hypothesis. ^{13}C-NMR analysis was applied to detect experimentally the changes in electron distribution at the ring carbon atoms of a series of aromatic nitroaldehydes with different hydroxyl protecting groups (Table II). For the structurally similar compounds **A** through **F**, a good correlation (Figure I) between ^{13}C chemical shifts and radiochemical yields was obtained by plotting the chemical shifts of the reaction center (where the nitro group is attached) against the corresponding radiochemical yield (from Table I). This suggested that a downfield chemical shift (larger ppm value) at the reaction center should indicate a lower electron density and therefore result in a higher radiochemical yield for nucleophilic substitution. The fact that three cases (compounds **G**, **H**, **I**) fell off

TABLE II

^{13}C Chemical Shifts of the Ring Carbon Atoms



A-H



I

Compound / ^{13}C Chemical Shifts*	A	B	C	D	E	F	G	H	I
1	131.33	128.18	127.77	125.49	125.55	134.32	128.10	126.14	143 31
2	129.58	107.48	107.34	109 74	111 88	113 29	122.23	118.08	112.68
3	134.00*	152.21*	151.92*	153 21*	152.79*	163.99	131 66	148.12*	152 96
4	133.65*	151.50*	151.17*	152.39*	151.80*	118.46	118 57	146.94*	139 67
5	124.43	105.05	104.92	107.17	109.42	127 17	151.07	114 58	125.79
6	149.58	146 08	145.76	143 80	143.65	142.24	140 10	123.70	122 42

* 0.5 M solutions in $CDCl_3$.

* Interchangable

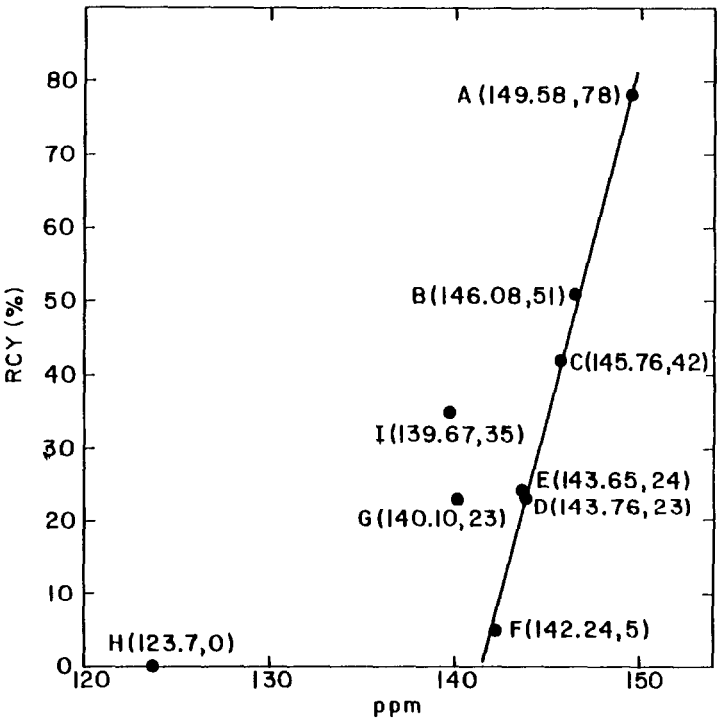


Fig. 1 Correlation between the ^{13}C chemical shift of the reaction center and the radiochemical yiel

the straight correlation line could be ascribed to the fact that compounds **G**-**I** were structurally different from compounds **A** through **F**. That is, in the case of compound **G**, instead of having a *meta* or *para* methoxy group relative to the nitro group, it has an *ortho* methoxy group which, being more hindered, should be less able to donate electrons, thus affording a higher yield than compound **F**. Compound **H** was expected to be unreactive to nucleophilic substitution since the reaction center possessed a relatively high electron density indicated by a smaller ppm value in its ^{13}C-NMR (26 ppm further upfield than that observed for the corresponding carbon in compound **A**). A better yield was obtained for compound **I** than for compound **G** As compound **I** has a NO_2 group *para* to the formyl group, the higher yield suggests increased reactivity towards nucleophilic substitution due to less steric hindrance.

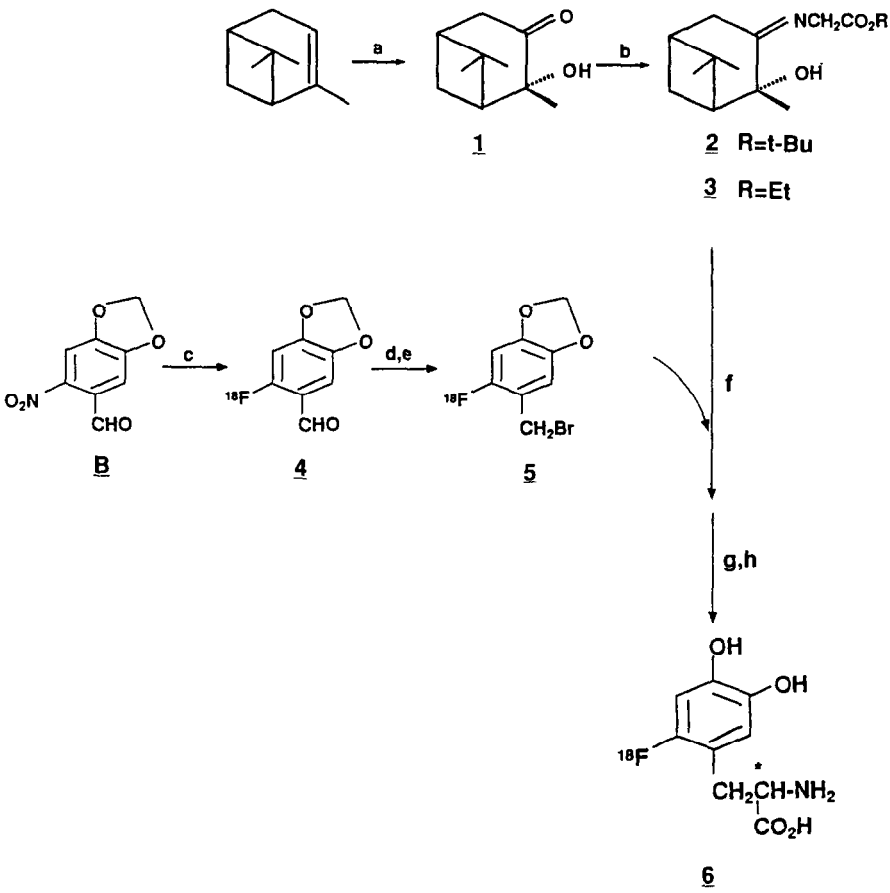
The identification of the structural requirements for effecting the nucleophilic aromatic substitution reaction in moderate yield holds the promise of the synthesis of useful radiotracers through elaboration of the aldehyde moiety. From the work described above, we have identified 6-[^{18}F]fluoro-L-DOPA, 6-[^{18}F]fluoro-norepinephrine, 4-[^{18}F]fluoro-m-tyrosine as promising candidates and have applied this methodology toward the synthesis of 6-[^{18}F]fluoro-L-DOPA (Scheme I). This no-carrier-added radiotracer was prepared from asymmetric alkylation of a chiral synthon [19, 20] glycine ester derivatives **2** or **3**, with 6-[^{18}F]fluoro-piperonyl bromide **5** (Scheme I). The chiral synthon was prepared from chiral ketol **1** [21] which was itself derived from (-)-α-pinene and a glycine ester The ^{18}F labeled bromide was prepared using nucleophilic displacement of the activated nitro group of 6-nitropiperonal by NCA $^{18}F^-$, followed by reduction with $LiAlH_4$ and bromination with $SOBr_2$. The alkylation was carried out using anhydrous conditions in THF with 2,2,6,6,-tetramethylpiperidyllithium as base Upon deprotection, the product was assayed by HPLC and was found to contain 6-[^{18}F]fluoro-L-DOPA in approx 12% overall radiochemical yield (EOB)

The radiosynthesis involved five steps displacement by $^{18}F^-$, hydride reduction, bromination, alkylation and hydrolysis. The unoptimized yields and synthesis times for individual steps are listed in Table III The specific activity and enantiomeric purity of the final product are currently being determined.

In the preparation of 6-[^{18}F]fluoro-L-DOPA, hydrolysis of the dioxolane ring proved to be a major problem. Since it is known that the relative rates of acid catalyzed hydrolysis [22] of some dioxolanes are 2,2-dimethyldioxolane 2-methyldioxolane· dioxolane = 50,000 · 5,000 · 1, we prepared 2,2,-dimethyl-benzodioxolane **C** (Scheme II) and found that the deprotection was more efficient; a shorter reaction time was required and a cleaner conversion was obtained.

EXPERIMENTAL

Except compound **C** (see synthetic Scheme II), compounds **A-I** used in the comparative studies were either purchased from Aldrich or prepared by the routine



a. $KMnO_4$, 90% Acetone/ H_2O;

b. $BF_3 \cdot Et_2O$/benzene, $H_2NCH_2CO_2R$;

c. $K^{18}F$, Kryptofix 222; d,$LiAlH_4$; e, $SOBr_2$,pyr.;

f. LiTMP/ THF; g. NH_2OH,HCl; h. HPLC

Scheme I. Asymmetric Synthesis of NCA 6-[^{18}F]Fluoro-L-DOPA (6)

TABLE III

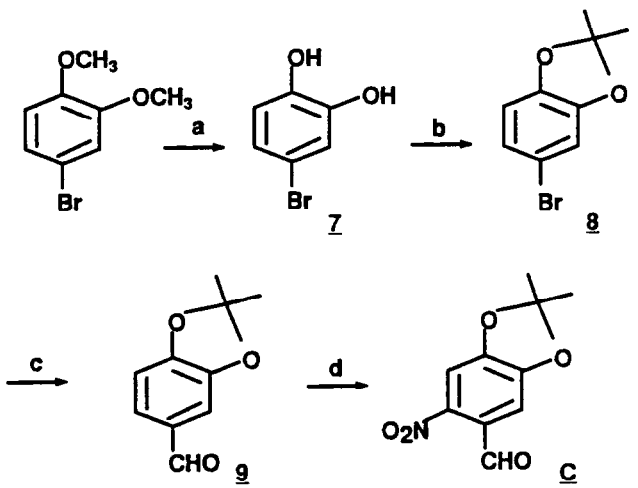
Synthesis of 6-[^{18}F]Fluoro-L-Dopa

Radio-Synthesis Step	Nucleophilic Substitution	Reduction	Bromination	Alkylation & Deprotection	Overall
Synthesis Time (Min)	10	5	5	50	100-110
RCY % (EOB)	45-50%	40-50%	35-43%	----	12%

* The yield and synthesis time were not optimized.

procedure for methylation (K_2CO_3/MeI/EtOH)[23] or nitration [24] (as described for the synthesis of compound C) from the commercially available precursors. ^{13}C NMR spectra of aromatic nitroaldehydes were recorded with a Brucker 300 MHz as 0.5 M solutions in deuteriochloroform.

(1S)-(-)-α-pinene, 6-nitropiperonal, boron tribromide, glycine ethyl ester, lithium aluminum hydride (1 M in diethyl ether) and thionyl bromide were obtained from Aldrich. Glycine *t*-butyl ester was purchased from Sigma Chemical Company. Hydroxylamine (free base) was obtained from Southwestern Analytic Chemicals, Inc. ^1H NMR spectra were also recorded with a Brucker 300 MHz in $CDCl_3$ using TMS as internal reference. Mass spectra were recored with a Finnegan-Mat GC-MS 5100 mass spectrometer using electron impact ionization at 70 eV



a. BBr_3/CH_2Cl_2;b,ACETONE,PTSA/BENZENE
c, Mg, DMF/THF;d, HNO_3

Scheme II. Synthesis of 3,4-O-Isopropylidene-6-Nitro-Benzaldehyde(C)

Nucleophilic aromatic fluorination with NCA ^{18}F

NCA $^{18}F^-$ ion for displacement was prepared by dissolving 4 mg of K_2CO_3 and 20 mg of Kryptofix 222 in aqueous $H^{18}F$ solution, prepared from the ^{18}O (p,n) ^{18}F reaction in a small volume $H_2{}^{18}O$ target. The aqueous solution was evaporated in a Pyrex vessel at 120° while purging with a slow stream of nitrogen, and then coevaporated to dryness with acetonitrile The comparative studies with compounds having different protecting groups were carried out using 2 mCi $^{18}F^-$ in each case.

A solution of the aromatic substrate (0.051 mmol) in 0.3 mL of dry DMSO was added to dried $K^{18}F$/Kryptofix 222 The mixture was stirred at 120° for 10 min, quenched by adding water (3 mL) and extracted with CH_2Cl_2 (2 x 2 mL). The CH_2Cl_2 extracts were dried by passing through a K_2CO_3 column. The activities of the aqueous and organic layers were then measured in a scintillation counter (Picker Nuclear Inc.) to determine the fraction of the $^{18}F^-$ activity incorporated into the organic products. The radiochemical purity of the ^{18}F-labeled product(s) from the organic layer was assayed by thin layer chromatography (30% ethyl acetate/hexane) and radio HPLC (Berthold Radioactivity Monitor, Model LB 503 flow scintillation counter). The HPLC analyses were performed on a phenomenex column (Ultremex 5 sil, 250 x 4.6 mm), eluting with a mixture of hexane : CH_2Cl_2. *i*-PrOH = 80 : 20 : 0.5 In each case, a single product was obtained (radiochemical purity was greater than 99%) The retention times for ^{18}F compounds using a radiodetector and nitrocompounds using a UV detector are listed in Table IV

Synthesis of (+)-2-Hydroxypinan-3-one (1) and [(+)-2-Hydroxy-pinanyl-3-idene]glycine t-butyl ester (2) or ethyl ester (3)

Compounds (1), (2) and (3) were synthesized according to Refs. 19 and 21. Compound (1) was purified by distillation to give a colorless oil, bp_{15} 119-120° C (lit. [19]

TABLE IV

Retention Time for Nitroaldehydes and the Corresponding ^{18}F-Labeled Products

Compound	A	B	C	D	E	F	G	H	I
I*(min)	7.2	9.2	5.8	18.4	6.3	7.7	13.31	16.78	17.2
II*(min)	5.4	6.9	5.7	16.9	6.4	5.9	6.7	---	8.1

I*: Retention time of nitroaldehydes on UV detector.

II*: Retention time of the corresponding ^{18}F-labeled products on radiodetector.

bp_{15} 118-119° C). ^{1}H-NMR ($CDCl_3$) 2.62-1.65 (m, 7H), 1.38 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 0.88 (s, 3H, CH_3) Compounds (2) and (3) were purified by column chromatography ^{1}H-NMR ($CDCl_3$) of 2, δ 4.23 (q, 2H), 4 16 (d, 2H), 2 70-1.55 (m, 7H), 1.52 (s, 3H), 1.33 (s, 3H), 1.30 (t, 3H), 0.87 (s, 3H). ^{1}H-NMR ($CDCl_3$) of 3, δ 4.08 (d, 2H), 2 70-1.55 (m, 7H), 1.52 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H), 0.87 (s, 3H).

Synthesis of NCA 6-[^{18}F]Piperonyl Bromide (5)

The K^{18}F/kryptofix 222 was prepared as described above A solution of p-nitropiperonal 4 (10 mg) in 0.3 mL of dry DMSO was added to the dried K^{18}F/kryptofix 222. The mixture was stirred at 120° for 5 min, cooled in an ice bath, and then 0.2 mL of 1 M lithium aluminum hydride in diethyl ether was added. The resulting mixture was stirred at room temperature for 10 min, cooled in an ice bath, and then 1 mL of saturated $NaCl_{(aq)}$ was added. After the mixture was extracted with ether (3 X 1 mL), the combined extracts were dried by passing through K_2CO_3 and concentrated to give approx. 1 mL solution. Pyridine (0.04 mL) and thionyl bromide (0.04 mL) were added sequentially The reaction mixture was stirred at room temperature for 5 min, then diluted with 1 mL of ice water and extracted with ether (2 x 1 mL). The combined ether layers were dried by passing through K_2CO_3 The solvent was then evaporated and the residue taken up in 0 3 mL of dry THF. The solution of 6-[^{18}F]piperonyl bromide 5 was analyzed by thin layer chromatography (silica, 7·3 hexane : ethyl acetate; 6-[^{18}F]piperonyl alcohol R_F = 0.24, 6-[^{18}F]piperonyl bromide R_F = 0.68) The labeled bromide was used for the alkylation step without further purification.

Alkylation of the Schiff Base (2) with 6-[^{18}F]Piperonyl Bromide (5)

[(+)-2-Hydroxypipanyl-3-idene]glycine ethyl ester 3 (25-50 mg, 9 8- 19 7 x 10^{-5} mol) and 2,2,6,6-tetramethyl-pipendyl-lithium (2.4- 4 9 x 10^{-4} mol) in THF, total volume 0.6-0.8 mL, was cooled to -78° C with dry ice/acetone. The solution of crude [6-^{18}F]piperonyl bromide 5 in THF was then added to the mixture of the Schiff base anion freshly prepared as described above The resulting mixture was stirred for 15 min at -

78° C, and the solution of crude product was analyzed by TLC (silica gel, 6:4 hexane:ethyl acetate). The alkylation product was deprotected without isolation.

Synthesis of 6-[^{18}F]Fluoro-L-DOPA (6)

The alkylation reaction was quenched at -78° C by adding 0.6 M hydroxylamine acetate in 70% aqueous ethanol (0 4 mL), followed by addition of concentrated HCl (3 mL) and then heated in a closed vessel (fitted with a 0.2 mm tube to release pressure) at 125° C for 30 min.

Analytical HPLC of the product was carried out on a Phenomenex NH_2 column (100 x 4.6 mm, particle size 5 um) under the following conditions: flow 1.0 mL/min, CH_3CN : 0.01 M KH_2PO_4 = 65 : 35, pH 3.60, 254 nm; or on a Phenomenex ODS column (250 x 4.6 mm) eluting with 0 1% CH_3COOH (1.8 mL/min, 280 nm). The radioactive peak corresponding to 6-[^{18}F]fluoroDOPA had the same retention time as an authentic, inactive sample (time corrected for time delay between mass detector and radiodetector). This sequence was also carried out with 3,4-O-isopropylidine-6-nitrobenzaldehyde (**C**). Deprotection of this compound was effected.

Synthesis of 3,4-dihydroxybromobenzene (7)

4-Bromoveratrole (30 g, 0 138 mol) was placed in a three-neck reaction flask and cooled in an ice bath. Boron tribromide [25] (1.0 M in CH_2Cl_2, 0.2 mol) was slowly introduced through a dropping funnel. After the addition was complete, the reaction mixture was refluxed overnight (20 h). The solution was chilled to 0° C and water was added slowly. The residue was hydrolyzed with a minimum amount of 10 % $NaOH_{(aq)}$. The resulting solution was acidified with hydrochloric acid and extracted with ether. The extracts were washed with H_2O and brine, then dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford compound **7** (24 g, 92 %). The product was used in the next step without purification (only one spot by TLC). ^{1}H-NMR ($CDCl_3$) δ 7.02 (d, 1 H, J_{meta} = 2.26 Hz), 6.92 (dd, J_{ortho} = 8.45 Hz, J_{meta} = 2.26 Hz), 6.74 (d, J_{ortho} = 8.45 Hz).

Synthesis of 3,4-O-isopropylidenebromobenzene (8)

Catechol 7 (10 g), acetone (30 mL, excess), *p*-toluenesulfonic acid (150 mg) and benzene (30 mL) were heated under reflux for 72 h [26] The condensed azeotrope was percolated through a bed of molecular sieves (Linde, 1/16" pellets) before returning solvent/acetone to the flask The solvent was removed using a rotary evaporator and the reaction mixture was purified by column chromatography ($CHCl_3$/hexane) to afford compound 8 (3 0 g, 25%) The starting material (7.0 g) was recovered (by eluting with ethyl acetate/hexane) and could be reused. ^{1}H-NMR ($CDCl_3$) δ 6.90 (dd, 1 H, J_{ortho} = 8.12 Hz, J_{meta} = 1.98 Hz), 6.86 (d, 1H, J_{meta} = 1.98 Hz), 6.60 (d, 1H, J_{ortho} = 8 12 Hz), 1.67 (s, 6H).

Synthesis of 3,4-O-isopropylidenebenzaldehyde (9)

A solution of bromide 8 (1.7 g, 7.42 mmol) in dry THF was added dropwise to a suspension of magnesium metal turnings (231 mg, 9.5 mmol) in dry THF (10 mL). During the addition, two drops of 1,2-dibromoethane was added to initiate the reaction and the reaction mixture was stirred at 40-45^0 C for 1-2 h. The solution was cooled in an ice bath and DMF (0 83 mL, 10 71 mmol) was added dropwise The mixture was stirred for one hour and was warmed to room temperature. The reaction was quenched by careful addition of 10% $HCl_{(aq)}$ and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with 10% $HCl_{(aq)}$, H_2O, brine, then dried and concentrated to afford a yellow oil, which was purified by column chromatography ($CHCl_3$/hexane) to yield compound 9 (1.2 g, 91%) ^{1}H-NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.37 (dd, 1H, J_{ortho} = 7.94 Hz, J_{meta} = 1 4 Hz), 7.26 (d, 1H, J_{meta} = 1.4 Hz), 6 84 (d, 1H, J_{ortho} = 7 94 Hz), 1 72 (s, 6H). MS, m/e (rel intensity): 178 (M^+, 51), 163 (100), 138 (20), 137 (66), 109 (7), 91 (3), 43 (10).

Synthesis of 3,4-O-isopropylidene-6-nitrobenzaldehyde (C)

Aldehyde 9 (800 mg, 4.49 mmol) was added dropwise with stirring to 9 mL of 55% nitric acid at O^0 C over a period of ten minutes. The reaction mixture was stirred

for 1 h at 30-35° C, then cooled in an ice bath, diluted with ice water (15 mL) and extracted with ethyl acetate (2 x 10 mL). The extracts were washed with H_2O (3 x 5 mL), dried ($MgSO_4$) and concentrated to give the product **C** as a yellow solid. The crude product was purified by column chromatography (ethyl acetate/hexane) and afforded **C** (930 mg, 93%) ^{1}H-NMR ($CDCl_3$) δ 10.3 (s, 1H), 7.45 (s, 1H), 7.27 (s, 1H), 1.77 (s, 6H) MS, m/e (rel. intensity): 223 (M^+, 27), 208 (12), 193 (27), 153 (100), 134 (20), 107 (16), 79 (11), 41 (20).

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