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Research Article

Preparation of 4-[^{11}C]methylmetaraminol, a potential PET tracer for assessment of myocardial sympathetic innervation

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Summary

The false adrenergic neurotransmitter [^{11}C]*meta*-hydroxyephedrine ([^{11}C]HED) is currently the PET tracer of choice for assessment of myocardial sympathetic innervation. The molecule is metabolised in the 4-position of the aromatic ring. The resulting radiolabelled metabolites need to be measured in order to obtain an arterial input function. Our aim was the development of a PET tracer with an increased metabolic stability relative to [^{11}C]HED. We selected 4-methylmetaraminol as a candidate molecule for radiolabelling with ^{11}C ($t_{1/2}$ 20.4 min). Our radiosynthetic approach towards 4-[^{11}C]methylmetaraminol involved a palladium-catalyzed cross-coupling reaction of a protected 4-trimethylstannyl derivative of metaraminol with [^{11}C]methyl iodide followed by removal of the protective groups. 4-[^{11}C]methylmetaraminol was obtained in a final decay-corrected radiochemical yield of 20–25% within a synthesis

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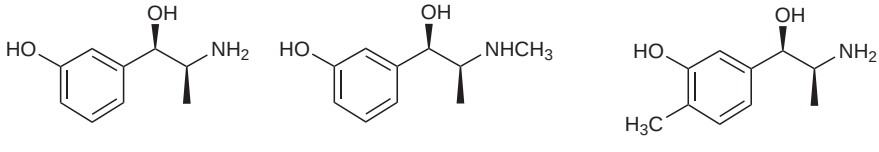
time of 60–80 min. The specific radioactivity at the end of the synthesis ranged from 18–37 to GBq/μmol. The unlabelled reference molecule, 4-methylmetaraminol, was prepared in a 5-step synthesis starting from metaraminol. A biological evaluation of 4-[^{11}C]methylmetaraminol is in progress and the results will be reported elsewhere.

Key Words: 4-[^{11}C]methylmetaraminol; sympathetic nervous system; heart; positron emission tomography; stille coupling

Introduction

Metaraminol ((1*R*,2*S*)-2-amino-1-(3-hydroxyphenyl)-1-propanol, **1**, Figure 1) is a structural analogue of norepinephrine, the endogenous neurotransmitter of the sympathetic nervous system. Due to a high affinity towards presynaptic uptake mechanisms (Michaelis–Menten constant, K_m, for uptake into rabbit heart slices: 1.0 μM[1]) and its metabolic stability **1** has served as a lead structure for developing PET tracers to assess cardiac sympathetic innervation.[2,3] The molecule was initially labelled with ^{18}F in an electrophilic radiolabelling approach.[4,5] However, this approach suffered from low specific radioactivity of the radiotracer (0.04–0.56 GBq/μmol[4]), which consequently did not permit a safe use in human applications. More recently, labelling approaches with ^{11}C or no-carrier-added ^{18}F have been elaborated[6–9]; however, these approaches are rather complex as they involve multi-step reactions and enantiomeric resolution. The *N*-methyl analogue of **1**, [^{11}C]*meta*-hydroxyephedrine ([^{11}C]HED, Figure 1), can be synthesized by simple methylation of **1** with [^{11}C]methyl iodide and has therefore become the PET tracer of choice for cardiac neuronal imaging.[10,11]

The lack of the catechol function and the presence of an α-methyl group render both **1** and [^{11}C]HED resistant against metabolism by



Metaraminol (**1**) *Meta*-hydroxyephedrine (HED) 4-Methylmetaraminol (**2**)

Figure 1. Chemical structures of metaraminol (1), *meta*-hydroxyephedrine (HED) and 4-methylmetaraminol (2)

catechol-*O*-methyl transferase and monoamine oxidase, the two main enzymes responsible for metabolic degradation of catecholamines.[12] Nevertheless, a considerable number of radiolabelled metabolites occur in human plasma following intravenous administration of [^{11}C]HED (about 48% of total radioactivity in human plasma at 20 min after injection of [^{11}C]HED represents radiolabelled metabolites[11]), thus making the routine determination of plasma metabolites necessary.[10] The metabolic degradation of [^{11}C]HED is assumed to occur by hydroxylation in the 4-position of the aromatic ring.[12–14] From this perspective we considered the introduction of a substituent in the 4-position of compound **1** as a promising strategy for obtaining a PET tracer with improved metabolic stability. We selected the 4-methyl derivative of **1**, 4-methylmetaraminol (**2**, Figure 1), as a candidate molecule for labelling with carbon-11 ($t_{1/2}$ 20.4 min).

In this work, we report the carbon-11 radiolabelling of **2** *via* a palladium-catalyzed cross-coupling reaction of a stannylated derivative of **1** with [^{11}C]methyl iodide.

Results and discussion

Compound **2** was synthesized as shown in Figure 2. Commercially available **1** was first iodinated with I_2 in NH_4OH/EtOH/H_2O according to a literature procedure to obtain 4-iodometaraminol (**3**) in an yield of 85% (5). Compound **3** was then treated with benzyl chloride to afford tribenzyl derivative **4** in 18% non-optimized yield. The benzyl protective group was chosen because of its stability and fast and easy removal by catalytic hydrogenation.[15] In order to determine the position of the benzyl protective groups, nuclear overhauser effect spectroscopy experiments were run in $CDCl_3$. These experiments showed a correlation peak between the region for the methylene protons ($\delta = 4.7$–4.9 ppm) and the proton in the 2-position of the aromatic ring ($\delta = 6.67$ ppm), thus indicating the benzyl protective group to be located on the phenolic hydroxyl group and not on the benzyl alcohol. The proton attached to the benzyl alcohol ($\delta = 4.66$ ppm) showed correlation between protons in both the 2- and 6-positions ($\delta = 6.67$ and 6.58 ppm, respectively) of the aromatic ring. Derivative **4** was converted into the trimethylstannyl compound **5** by reaction with hexamethyldistannane (Sn_2Me_6) and tetrakis(triphenylphosphine)palladium(0) [$(Ph_3P)_4Pd$] in 61% yield (9). Compound **5** was

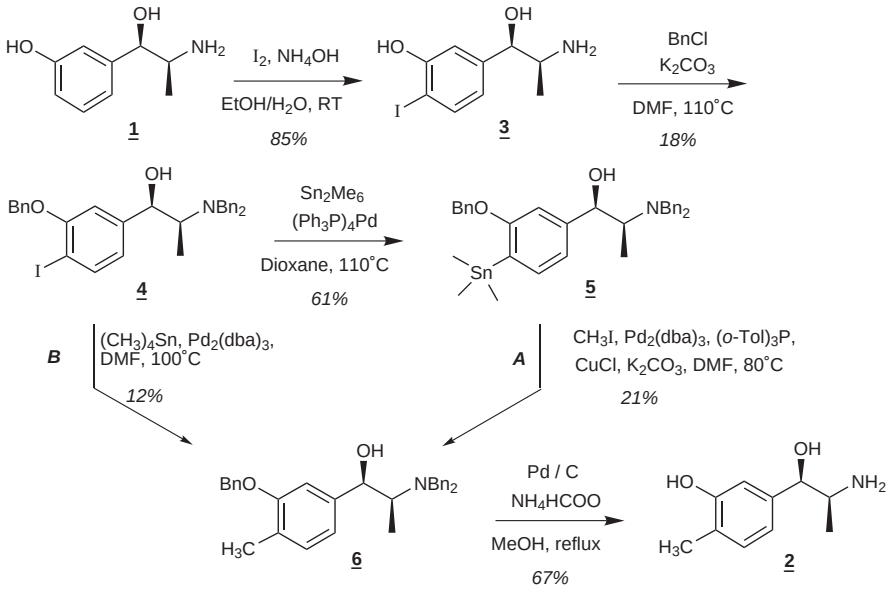


Figure 2. Synthesis of labelling precursor 5 and unlabelled reference molecule 4-methylmetaraminol (2)

then reacted with methyl iodide catalyzed by tris(dibenzylideneacetone)-dipalladium(0) [$Pd_2(dba)_3$] and tri(*o*-tolyl)phosphine [$(o\text{-Tol})_3P$] together with copper(I) chloride (CuCl) and potassium carbonate (K_2CO_3) in DMF, which afforded the 4-methyl-substituted compound **6** in 21% yield.[16] Alternatively, **4** was reacted with tetramethyltin [$(CH_3)_4Sn$] and $Pd_2(dba)_3$ to give **6** in a yield of 12% (Figure 2). The removal of the benzyl protective groups was accomplished by refluxing **6** in CH_3OH with ammonium formate and palladium on charcoal to give **2** in a yield of 67%.

For the radiolabelling, a pathway was pursued that involves a palladium-catalyzed reaction between an organic stannane and a halide resulting in ^{11}C–C bond formation (Stille coupling, Figure 3).[16] This pathway has previously been used for the synthesis of various other PET radiotracers.[17–20] Derivative **5** was reacted for 10 min at 110°C with [^{11}C]CH_3I in DMF containing a mixture of $Pd_2(dba)_3$, $(o\text{-Tol})_3P$, CuCl and K_2CO_3, which corresponds to the optimized radiolabelling conditions described by Björkman *et al.*,[18] to afford intermediate [^{11}C]-**6** in an incorporation yield of 30–40%. After purification by solid-phase extraction [^{11}C]-**6** was deprotected with NH_4HCOO/Pd(0) in CH_3OH (>90% conversion yield) to give, after semipreparative high performance liquid chromatography (HPLC) purification, radiochemically

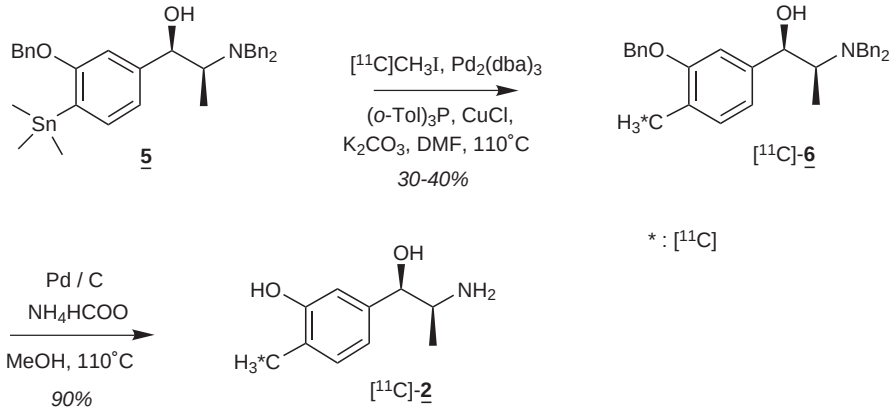


Figure 3. Radiosynthesis of 4-[^{11}C]methylmetaraminol ([^{11}C]-2)

and chemically pure (>95%) [^{11}C]-**2**. Compound [^{11}C]-**6** as well as [^{11}C]-**2** coeluted with authentic samples of unlabelled **6** and **2**, respectively. The final decay-corrected radiochemical yield of [^{11}C]-**2** was 20–25% and the total synthesis time including HPLC purification ranged from 60 to 80 min. The specific radioactivity at the end of the synthesis was 18–37 GBq/μmol.

Experimental

General

Radiochemistry. [^{11}C]CO_2 was produced at the Karolinska Hospital/Institute with a Scanditronix MC-16 cyclotron and at the Uppsala University PET Centre with a Scanditronix MC-17 cyclotron using the ^{14}N(p,α)^{11}C reaction. [^{11}C]CH_3I was prepared from [^{11}C]CO_2 either (A) *via* [^{11}C]CH_4 by catalytic gas-phase iodination in a GEMS MeI PETtrace MicroLab (Karolinska)[21] or (B) *via* [^{11}C]CH_3OH using a semiautomated system for production of radiopharmaceuticals (Uppsala).[22,23]

HPLC was performed using a Beckman 126 pump and a Beckman 166 UV detector in series with a β^+-flow detector. Data collections were performed using a Beckman System Gold Chromatography Software Package for semipreparative HPLC and a Beckman System Nouveau Chromatography Software Package for analytical HPLC. A C-18 Beckman Ultrasphere ODS 5 μm (250 × 10 mm) column was used for semipreparative HPLC and a Beckman Ultrasphere ODS 5 μm

(250 × 4.6 mm) column was used for analytical HPLC. Mobile phases were 50 mM aqueous NaH_2PO_4 (A), methanol (B) and acetonitrile (C). The HPLC was performed at room temperature and the wavelength for UV-detection was 280 nm. The semipreparative HPLC purification of the crude reaction mixture was performed at a flow rate of 4 ml/min with the following gradient time program: 0–3 min, (A:B, v:v) 90:10 isocratic; 3–8 min, (A:B) 90:10–55:45; 8–14 min, (A:B) 55:45 isocratic; 14–16 min, (A:B) 55:45–5/95; 16–20 min, (A:B) 5:95 isocratic. Analytical HPLC was performed at a flow rate of 1.5 ml/min employing the following gradient time programs. Method A: 0–5 min, (A:C, v:v) 40:60 isocratic; 5–6 min, (A:C) 40:60–30:70; 6–10 min, (A:C) 30:70 isocratic. Method B: 0–4 min, (A:C, v:v) 95:5 isocratic; 4–10 min, (A:C) 95:5–80:20; 10–12 min, (A:C) 80:20–5:95; 12–15 min, (A:C) 5:95 isocratic.

Chemistry. (-)-Metaraminol (**1**) bitartrate was purchased from Sigma-Aldrich, Sweden AB. Other chemicals were obtained from standard commercial sources and were of analytical grade. Analytical TLC was run on pre-coated plates of silica gel 60 F_{254} (Merck). The compounds were localized using an UV-lamp at 254 nm and/or by dipping the TLC plates into an aqueous $KMnO_4$ solution (1%) and heating on a hot plate. Flash chromatography was conducted on silicagel of 63–200 μm (Merck). ^{1}H NMR spectra were recorded on Bruker DRX500 or DRX600 spectrometers using the hydrogenated residue of the deuteriated solvents ($CDCl_3$, $\delta = 7.24$ ppm; DMSO-d_6, $\delta = 2.49$ ppm) and/or TMS as internal standards. The chemical shifts (δ) are reported in ppm, downfield from TMS (s, d, dd, bd, t, m, bm for singlet, doublet, doublet of doublet, broad doublet, triplet, multiplet and broad multiplet, respectively). Electro spray time of flight mass spectra (TOF MS ES+) were recorded on an AutoSpec-OATOFFPD (Micromass, Manchester, UK) double focusing high resolution tandem mass spectrometer.

Chemistry

(1R,2S)-2-amino-1-(3-hydroxy-4-iodophenyl)-1-propanol (4-iodometaraminol, **3**). To a solution of metaraminol (**1**) bitartrate (2 g, 6.3 mmol) in NH_4OH (10 M, 200 ml), iodine (1.6 g, 6.5 mmol) dissolved in absolute ethanol (120 ml) was added dropwise over a period of 45 min. The reaction mixture was stirred in the dark at room temperature for 12 h.

The ethanol was then removed under vacuum and the aqueous residue extracted with ethyl acetate. After washing of the combined organic layers with brine and drying (Na_2SO_4) concentration to dryness afforded the title compound (1.6 g, 85% yield) in the form of a yellowish solid. Compound **3** was used in the following step without further purification: R_f 0.15–0.20 ($CHCl_3$/CH_3OH/28% NH_4OH, 80/20/1); ^{1}H NMR (DMSO-d_6) δ 0.93 (d, J 7.6 Hz, 3 H), 2.93 (m, 1 H), 4.31 (d, J 6.1 Hz, 1 H), 6.62 (d, J 7.1 Hz, 1 H), 6.98 (s, 1 H), 7.65 (d, J 7.1 Hz, 1 H); TOF MS ES+ ($C_9H_{12}INO_2$):294.0 [M + H$^+$].

*(1R,2S)-2-N,N-dibenzylamino-1-(3-benzyloxy-4-iodophenyl)-1-propanol (**4**)*. To a solution of compound **3** (1.6 g, 5.5 mmol) in DMF (20 ml) K_2CO_3 (1.3 g, 10 mmol) and benzyl chloride (3.5 g, 27.5 mmol) were added and the reaction mixture was heated at 100°C for 2 h. The reaction mixture was cooled and diluted with H_2O (100 ml). Extraction with CH_2Cl_2, washing of the combined organic layers with brine, drying (Na_2SO_4) and concentration to dryness yielded a dark oil. Silica gel flash chromatography purification (heptane/ethyl acetate, 95/5–90/10) afforded the title compound (0.57 g, 18% yield) in the form of fluffy white crystals: R_f 0.40–0.45 (heptane/ethyl acetate, 80/20); ^{1}H NMR ($CDCl_3$) δ 1.11 (d, J 6.9 Hz, 3 H), 3.06 (m, J 6.5 Hz), 3.47 (d, J 14.1 Hz, 2 H), 3.71 (d, J 14.1 Hz, 2 H), 4.66 (d, J 6.5 Hz, 1 H), 4.77 (d, J 11.7 Hz, 1 H), 4.89 (d, J 11.7 Hz, 1 H), 6.58 (dd, J 8.1 Hz & 1.6 Hz, 1 H), 6.67 (d, J 1.6 Hz, 1 H), 7.15–7.50 (m, 15 H), 7.68 (d, J 8.1 Hz, 1 H); TOF MS ES+ ($C_{30}H_{30}INO_2$) : 564.0 [M + H$^+$].

*(1R,2S)-2-N,N-dibenzylamino-1-(3-benzyloxy-4-trimethylstannylphenyl)-1-propanol (**5**)*. To a solution of **4** (0.45 g, 0.8 mmol) in dioxane (20 ml) tetrakis(triphenylphosphine)palladium (49 mg, 0.043 mmol) and hexamethyldistannane (0.34 g, 1.0 mmol) were added. The reaction mixture was refluxed under nitrogen overnight, cooled and filtered. The filtrate was diluted with ethyl acetate (100 ml), washed with H_2O and brine, dried (Na_2SO_4) and concentrated to dryness to afford a yellow oil that was purified by silica gel flash chromatography (heptane/EtOAc, 100/0–90/10) to give the title compound (293 mg, 61% yield) in the form of white crystals: R_f 0.50–0.55 (heptane/ethyl acetate, 80/20); ^{1}H NMR ($CDCl_3$) δ 0.21 (s, with tin satellites: ^2J[^{119}Sn–H] 56.2 Hz & ^2J[^{117}Sn–H] 53.5 Hz, 9 H), 1.15 (d, J 6.7 Hz, 3 H), 3.08 (m, J 6.8 Hz, 1 H), 3.51 (d, J 14.0 Hz, 2 H), 3.75 (d, J 14.0 Hz, 2 H), 4.70 (d, J 11.0 Hz, 1 H), 4.75 (d, J 6.0 Hz, 1 H), 4.79 (d, J 11.0 Hz, 1 H), 6.69 (s, with tin satellites: ^2J[Sn–H]

18.2 Hz, 1 H), 6.85 (dd, *J* 7.8 and 1.3 Hz, 1 H), 7.10–7.75 (m, 16 H); TOF MS ES+ ($C_{33}H_{39}NO_2Sn$) : 606.1, 604.1, 602.1, 601.1, 600.1, 599.1, 598.1 [$M+H^+$] for Sn isotopes of 124, 122, 120, 119, 118, 117 and 116, respectively.

*(1R,2S)-)-2-N,N-dibenzylamino-1-(3-benzyloxy-4-methylphenyl)-1-propanol (***6***).* Approach A: Tris(dibenzylideneacetone)dipalladium(0) (3.0 mg, 3.4 μmol), tri(*o*-tolyl)phosphine (4.0 mg, 13.4 μmol), copper(I) chloride (1.4 mg, 14.1 μmol) and potassium carbonate (1.8 mg, 13.0 μmol) were dissolved in DMF (0.3 ml) and the solution was stirred and purged with N_2 for 30 min at room temperature. Then compound **5** (32 mg, 53.3 μmol) dissolved in DMF (0.2 ml) and methyl iodide (142 mg, 1.0 mmol) were added and the mixture heated at 80°C for 24 h. The reaction mixture was then cooled, diluted with H_2O (10 ml) and extracted with CH_2Cl_2. After washing of the combined organic layers with brine, drying (Na_2SO_4) and concentration to dryness, a brownish solid was obtained. The crude product was purified by semipreparative HPLC [column: Waters μBondapak C18 (300 × 7.8 mm, 10 μm); eluent: 0.01 M aqueous phosphoric acid/acetonitrile 50/50; flow rate: 6 ml/min; UV detection at λ:280 nm]. The product was collected at *R*t 6.0–6.5 min. The combined HPLC fractions were made alkaline with aqueous ammonia, the acetonitrile removed *in vacuo* and the aqueous residue extracted with CH_2Cl_2. Washing with brine, drying (Na_2SO_4) and concentration to dryness yielded pure title compound (5 mg, 21% yield) in the form of a white solid: R_f 0.45–0.50 (heptane/ethyl acetate, 80/20); ^{1}H NMR ($CDCl_3$) δ 1.13 (d, *J* 6.7 Hz, 3 H), 2.27 (s, 3 H), 3.08 (m, *J* 6.4 Hz, 1 H), 3.47 (d, *J* 13.8 Hz, 2 H), 3.72 (d, *J* 13.8 Hz, 2 H), 4.70 (d, *J* 6.4 Hz, 1 H), 4.72 (d, *J* 11.3 Hz, 1 H), 4.83 (d, *J* 11.3 Hz, 1 H), 6.70 (d, *J* 0.7 Hz, 1 H), 6.73 (dd, *J* 7.8 and 0.7 Hz, 1 H), 7.08 (d, *J* 7.8 Hz, 1 H), 7.15–7.45 (m, 15 H); TOF MS ES+ ($C_{31}H_{33}NO_2$): 452.2 [$M+H^+$].

Approach B: Tris(dibenzylideneacetone)dipalladium(0) (7 mg, 7.9 μmol) and tetramethyltin (78 mg, 436 μmol) were dissolved in DMF (0.3 ml). The solution was stirred and purged with N_2 for 30 min at room temperature. Then, compound **4** (41 mg, 72.8 μmol) dissolved in DMF (0.2 ml) was added and the mixture heated at 100°C for 2 days. Work up of the reaction and semipreparative HPLC purification were performed as described under approach A to yield pure compound **6** (4 mg, 12% yield).

(1R,2S)-2-amino-1-(3-hydroxy-4-methylphenyl)-1-propanol (4-methylmetaraminol, **2***)*. To a solution of compound **6** (15 mg, 33.3 μmol) in CH_3OH (5 ml), ammonium formate (40 mg, 0.63 mmol) and palladium on carbon (5% Pd, 10–20 mg) were added. The reaction mixture was refluxed for 2 h, and then cooled, filtered and concentrated to dryness to afford the title compound (4 mg, 67% yield) as an oily residue: ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J 6.5 Hz, 3 H), 2.25 (s, 3 H), 3.20 (bm, $w_{1/2}$ 11 Hz, 1 H), 4.48 (bd, $w_{1/2}$ 12 Hz, 1 H), 6.76 (d, J 7.6 Hz, 1 H), 6.80 (s, 1 H), 7.08 (d, J 7.6 Hz, 1 H); TOF MS ES+ ($C_{10}H_{15}NO_2$): 182.2 [$M+H^+$].

Radiochemistry

*(1R,2S)-2-N,N-dibenzylamino-1-(3-benzyloxy-4-[^{11}C]methylphenyl)-1-propanol ([^{11}C]-***6***)*. A solution of tris(dibenzylideneacetone)dipalladium(0) (1.2 mg, 1.3 μmol) and tri(*o*-tolyl)phosphine (1.5 mg, 4.9 μmol) in DMF (200 μl) was prepared in a dry 0.8 ml septum-equipped vial and purged with N_2 gas for 5 min. [^{11}C]CH_3I was passed through a Sicapent drying tower and trapped in the solution at room temperature. After trapping, the solution was transferred to a septum-equipped vial containing compound **5** (1.6 mg, 2.7 μmol), copper(I) chloride (1.2 mg, 12.1 μmol) and potassium carbonate (1.4 mg, 10.1 μmol) dissolved in DMF (100 μl). The latter mixture had been dissolved in DMF and purged with N_2 just prior to the transfer of the trapped [^{11}C]CH_3I. The reaction vial was then shaken vigorously and heated at 110°C for 10 min. The conversion of [^{11}C]CH_3I into [^{11}C]-**6** was determined by analysing an aliquot of the reaction mixture on analytical HPLC [method A: Rt ([^{11}C]-**6**) 7.5–8 min, Rt ([^{11}C]CH_3I) 2–3 min (void volume)].

*(1R,2S)-2-amino-1-(3-hydroxy-4-[^{11}C]methylphenyl)-1-propanol (4-[^{11}C]methylmetaraminol, [^{11}C]-***2***)*. The reaction mixture from the Stille coupling was diluted with H_2O (3.5 ml) and passed through a Supelco LC-18 cartridge that had been washed with methanol (10 ml) and H_2O (20 ml) prior to use. The cartridge was washed with H_2O (1.5 ml) and eluted with methanol (2 ml) into a vial containing ammonium formate (40 mg, 0.63 mmol) and palladium on carbon (5% Pd, 10–20 mg). The vial was sealed and heated for 10 min at 110°C. The conversion of [^{11}C]-**6** into [^{11}C]-**2** was determined on analytical HPLC [method A: Rt ([^{11}C]-**6**) 7.5–8.0 min, Rt ([^{11}C]-**2**) 2–3 min (void volume); method B: Rt ([^{11}C]-**2**) 9.5–10.0 min]. The reaction mixture was filtered

over a Supelco LC-18 cartridge that was then washed with methanol (3 ml). The filtrate was concentrated to dryness under vacuum, dissolved in 50 mM aqueous NaH_2PO_4/methanol (90/10, 4 ml) and injected on the semipreparative HPLC system. Derivative [^{11}C]-**2** was collected at Rt 10–12 min. The methanol from the HPLC fraction was removed *in vacuo* and the aqueous residue passed through a Millipore filter (0.22 μm). The radiochemical purity and specific radioactivity of [^{11}C]-**2** were determined by HPLC (method B: Rt ([^{11}C]-**2**) 9.5–10.0 min).

Conclusion

With the aim to develop a metabolically stable PET tracer to assess myocardial sympathetic innervation 4-[^{11}C]methylmetaraminol ([^{11}C]-**2**) was prepared by a 2-step radiochemical pathway.

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