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Research Article

Synthesis of ^{18}F-labelled stilbenes from 4-(^{18}F)fluorobenzaldehyde using the Horner–Wadsworth–Emmons reaction

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Abstract: The first application of the Horner–Wadsworth–Emmons reaction in ^{18}F-chemistry is described. This carbonyl-olefination reaction was performed via a 'multi-step/one-pot' reaction by the coupling of benzylic phosphonic acid esters (3,5-bis-methoxymethoxybenzyl)-phosphonic acid diethyl ester **2e**, (4-methoxymethoxybenzyl)-phosphonic acid diethyl ester **3e** and (4-dimethyl-aminobenzyl)phosphonic acid diethyl ester **4d**) with 4-[^{18}F]fluorobenzaldehyde to give the corresponding ^{18}F-labelled stilbenes **[^{18}F]2g**, **[^{18}F]3g** and **[^{18}F]4e** exclusively as the expected *E*-isomers. The radiochemical yields ranged from 9% to 22% (based upon [^{18}F]fluoride, including HPLC purification). The specific activity reached up to 90 GBq/μmol. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: ^{18}F-labelled stilbenes; [^{18}F]fluorobenzaldehyde; Horner–Wadsworth–Emmons reaction

Introduction

The synthesis of ^{18}F-labelled PET tracers is mainly based on the use of n.c.a. [^{18}F]fluoride. Although favoured, the direct single-step radiolabelling of compounds with [^{18}F]fluoride is not always applicable due to the required harsh reaction conditions and the structural and electronic character of the given molecules. Alternatively, radiolabelling of organic molecules can be accomplished via build-up syntheses involving secondary labelling precursors, such as ^{18}F-labelled alkyl- or aryl fluorides.[1] A very prominent and frequently used secondary labelling precursor is 4-[^{18}F]fluorobenzaldehyde. 4-[^{18}F]Fluorobenzaldehyde has successfully been applied in various reductive amination reactions to give ^{18}F-labelled radiotracers like 4-[^{18}F]fluorobenzyldexetimide,[2] 4-[^{18}F]fluorobenzyltrozamicol[3] or a nonpeptide chemokine receptor CCR1 antagonist.[4] Moreover, 4-[^{18}F]fluorobenzaldehyde is an useful starting material for the synthesis of other secondary labelling precursors like 4-[^{18}F]fluorobenzylic alcohol and 4-[^{18}F]fluorobenzyl halides.[1]

Beside reductive aminations with 4-[^{18}F]fluorobenzaldehyde, several carbonyl olefination reactions based on ^{18}F-labelled benzaldehydes have been explored. Thus, a Knoevenagel reaction with ^{18}F-labelled benzaldehyde was used for the synthesis of the amino acid L-4-[^{18}F]fluorophenylalanine.[5] Other C–H acidic phosphorous-containing compounds have been coupled with ^{18}F-labelled aldehydes according to Wittig-type reactions giving reasonable radiochemical yields of a mixture of *E*/*Z*-isomers.[6]

The coupling of phosphonic acid esters with carbonyl compounds, also referred to as the Horner–Wadsworth–Emmons reaction, represents another powerful carbonyl olefination reaction successfully applied for a long time in organic synthesis.[7] In contrast to the related Wittig-type reactions the Horner–Wadsworth–Emmons reaction opens a convenient synthesis route for C–C double bonds, exhibiting *E*-configuration exclusively (Figure 1).

In this paper, we describe the application of the Horner–Wadsworth–Emmons reaction as novel labelling technique in ^{18}F-chemistry. Various ^{18}F-labelled *E*-configured stilbenes could be synthesized through the coupling of several benzylic phosphonic acid esters with readily available 4-[^{18}F]fluorobenzaldehyde as secondary labelling precursor.

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Results and discussion

Synthesis of labelling precursors and reference compounds

The benzylic phosphonates **2e**, **3e** and **4d** were synthesized starting from 3,5-dihydroxybenzoic acid methyl ester **2a**, 4-hydroxybenzoic acid methyl ester **3a**[8] and 1-bromomethyl-4-nitrobenzene **4a** (Figures 2 and 3).

Compounds **2a** and **3a** were subjected to standard reaction conditions using methoxymethyl chloride (MOMCl) and diisopropylethylamine (DIPEA) in refluxing THF to give the corresponding MOM-ethers **2b** and **3b** in very good yields greater than 90%. Reduction of the ester group in **2a** and **3a** with $LiAlH_4$ in Et_2O according to Sun *et al.*[9] afforded benzylic alcohols **2c** and **3c** in 92% and 98% chemical yield, respectively. Conversion of benzylic alcohols **2c** and **3c** into benzyl bromides **2d** and **3d** was achieved using *N*-bromosuccinimide in the presence of triphenylphosphine in DMF in 56% and 45% yield[10] Bromide **2d** was converted into phosphonic acid ester **2e** according to a Michaelis–Arbuzov reaction[11] using conventional heating with an excess of triethylphosphite. This procedure afforded compound **2e** in 65% yield. For the synthesis of phosphonate **3e**, the reaction of benzylic bromide **3d** was carried out with equimolar triethylphosphite by means of microwave activation.[12] Compared to the synthesis of compound **2e** via conventional heating (65% yield) the rapid heating technique in the microwave-mediated synthesis of compound **3e** proceeds in significant higher chemical yields of 83%. Moreover, the use of equimolar amounts of triethylphosphite also facilitated purification by flash-chromatography.

A microwave-assisted Michaelis–Arbuzov reaction was also applied within the reaction sequence for the synthesis of phosphonate **4d**. Thus, commercially available benzylic bromide **4a** was treated with equimolar amounts of triethylphosphite under microwave activation to give compound **4b** in 70% yield. The nitro group in phosphonic acid ester **4b** was reduced with $SnCl_2$ under acidic conditions to give the corresponding aniline derivative **4c** in 95% yield.[13] Reductive amination of amine **4c** with sodium borohydride and formaldehyde provided *N,N*-dimethylated compound **4d** as labelling precursor in 60% yield.[14] The overall chemical yields for the syntheses of labelling precursors **2e**, **3e** and **4d** were 33%, 34% and 40%, respectively.

Fluorophenyl group-containing stilbenes **2g**, **3g** and **4e** as reference compounds were synthesized based upon the Horner–Wadsworth–Emmons reaction as the key step followed by acidic hydrolysis of the MOM-ether groups in case of MOM-ether protected stilbenes **2f** and **3f**[15,16] (Figure 4).

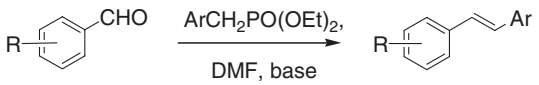
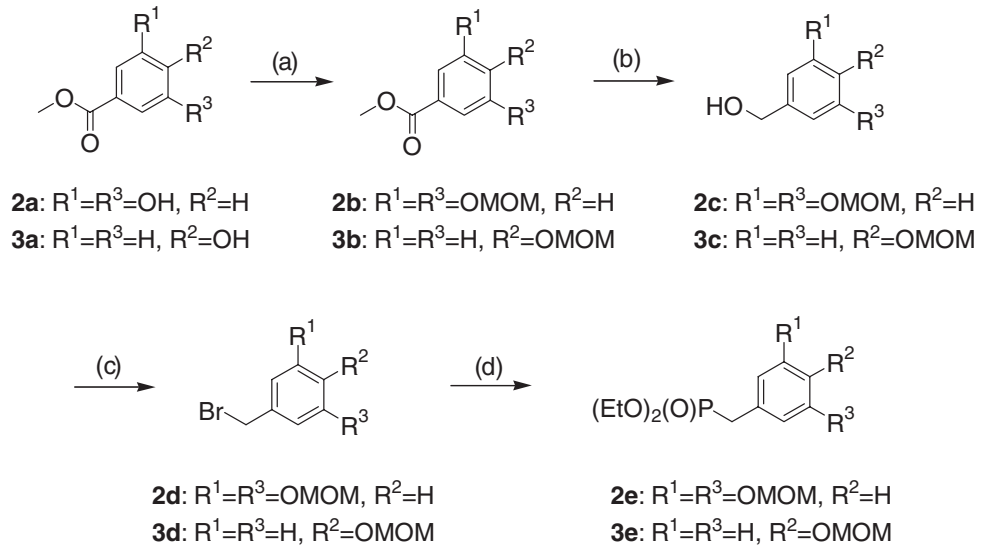


Figure 1 Horner–Wadsworth–Emmons reaction between substituted benzaldehydes and benzylic phosphonic acid diesters.



2a: R^1=R^3=OH, R^2=H
3a: R^1=R^3=H, R^2=OH
2b: R^1=R^3=OMOM, R^2=H
3b: R^1=R^3=H, R^2=OMOM
2c: R^1=R^3=OMOM, R^2=H
3c: R^1=R^3=H, R^2=OMOM
2d: R^1=R^3=OMOM, R^2=H
3d: R^1=R^3=H, R^2=OMOM
2e: R^1=R^3=OMOM, R^2=H
3e: R^1=R^3=H, R^2=OMOM

Figure 2 Synthesis of phosphonate precursors **2e** and **3e**: (a) DIPEA, MOMCl, THF, reflux, 6–24 h, (**2b**, 99%), (**3b**, 92%); (b) $LiAlH_4$, Et_2O, 0–25°C, 1–2 h, (**2c**, 92%), (**3c**, 98%); (c) NBS, PPh_3, DMF, 60°C, 1 h, (**2d**, 56%), (**3d**, 45%); (d) $P(OEt)_3$, 160°C, 3 h, (**2e**, 65%) or microwave, 200 W, 15 min, (**3e**, 83%).

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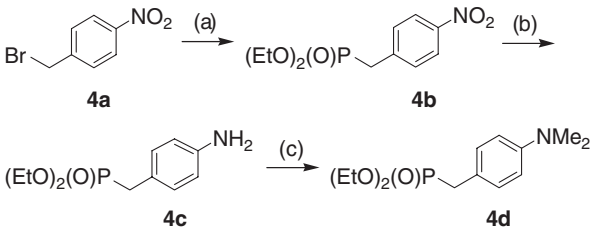

Figure 3 Synthesis of phosphonate precursor **4d**: (a) $P(OEt)_3$, microwave, 150 W, 3 min, 70%; (b) $SnCl_2 \cdot 2H_2O$, HCl, EtOH, reflux, 2 h, 95%; (c) $NaBH_4$, HCHO, H^+, THF, 25°C, 30 min, 60%.

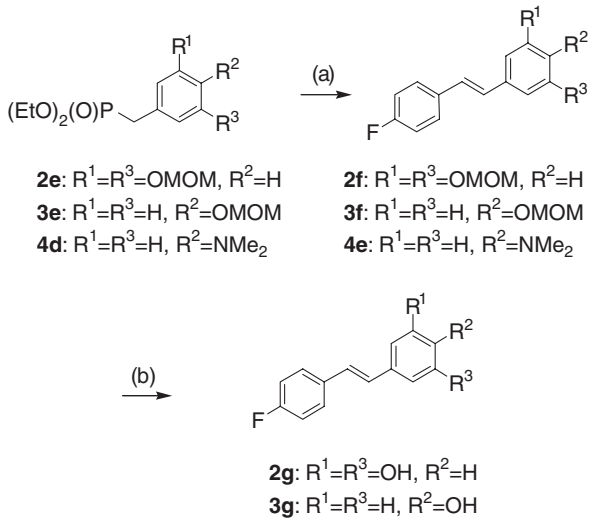

Figure 4 Synthesis of reference compounds **2g**, **3g** and **4e**: (a) 4-Fluorobenzaldehyde, KO^{t}Bu, DMF, 25°C, 10–60 min, >99% (**2f**), 90% (**3f** and **4e**); (b) H^+, MeOH, 25–60°C, 30–120 min, 93% (**2g**), 99% (**3g**).

Treatment of the phosphonic acid esters **2e**, **3e** and **4d** with potassium *tert*-butoxide as base in DMF resulted in the formation of the corresponding carbanions, which was visible by a color change of the reaction mixture from colorless to dark orange-red. Then, 4-fluorobenzaldehyde as the electrophile was added, and stilbenes **2f**, **3f** and **4e** were obtained in excellent chemical yields of 99% and 90%, respectively, after purification by means of flash-chromatography. Deprotection of the MOM-ether derivatives **2f** and **3f** under acidic conditions gave compounds **2g** and **3g** in high yields 93% and 99%.

The ^{1}H-NMR data confirm the *E*-configuration. The measured $^3J_{(H,H)}$-coupling constants of the olefinic protons for compounds **2g**, **3g** and **4e** are in the range of 16.1–16.5 Hz. These large coupling constants are in agreement with the expected *E*-configuration. The ^{1}H-NMR spectra showed no evidence for a significant formation (>5%) of the corresponding *Z*-isomers.

Synthesis of ^{18}F-labelled stilbenes

The radiochemical 'multi-step/one-pot' syntheses of the ^{18}F-labelled stilbenes according to Horner–Wadsworth–Emmons reaction commenced with the synthesis of readily available 4-[^{18}F]fluorobenzaldehyde using 4-trimethylammoniumbenzaldehyde triflate as the labelling precursor. The content of 4-[^{18}F]fluorobenzaldehyde in the reaction mixture varied between 60% and 80% as determined by radio-TLC analysis. Laborious and challenging SPE- or HPLC-based purification of 4-[^{18}F]fluorobenzaldehyde was not applied. DMF proved to be a suitable solvent for both, the radiosynthesis of 4-[^{18}F]fluorobenzaldehyde and performance of the Horner–Wadsworth–Emmons reaction. Therefore, the reaction could be carried out as a multistep/one pot reaction in a remotely controlled synthesis apparatus.

A solution of one equivalent phosphonic acid esters **2e**, **3e** or **4d** and 2.5 equivalents of potassium *tert*-butoxide in DMF was added to the reaction mixture containing 4-[^{18}F]fluorobenzaldehyde. The carbonyl olefination reaction was carried out at 60°C for 15 min to give stilbene compounds **[^{18}F]2g**, **[^{18}F]3g** and **[^{18}F]4e**. Prolongation of the reaction time did not enhance the formation of the coupling product as monitored by radio-TLC analysis. In case of MOM-ether protected stilbenes **[^{18}F]2f** and **[^{18}F]3f** an additional reaction step was necessary to remove the protecting groups. Addition of 3 M HCl to the reaction mixture and stirring for 20 min at 60°C gave the ^{18}F-labelled phenolic stilbenes **[^{18}F]2g** and **[^{18}F]3g**. The entire reaction sequence is depicted in Figure 5.

The results of the accomplished radiochemical syntheses in terms of synthesis times, achieved radiochemical yields and radiochemical purities are summarized Table 1.

All reactions were carried out in a remotely controlled synthesis apparatus. This allows the convenient and safe handling of large amounts of radioactivity. The performed three-steps/one pot (compounds **[^{18}F]2g** and **[^{18}F]3g**) or two-steps/one pot (compound **[^{18}F]4e**) reaction sequences gave reasonable amounts of the desired products after purification by means of semi-preparative HPLC. The identity of the compounds was confirmed by co-injection of the reference compounds onto analytical HPLC. The specific activities reached up to 90 GBq/μmol at the end-of-synthesis. In a typical experiments, starting from 3780 MBq of [^{18}F]fluoride 370 MBq of the desired stilbene **[^{18}F]4e** within 135 min including HPLC purification could be obtained. The

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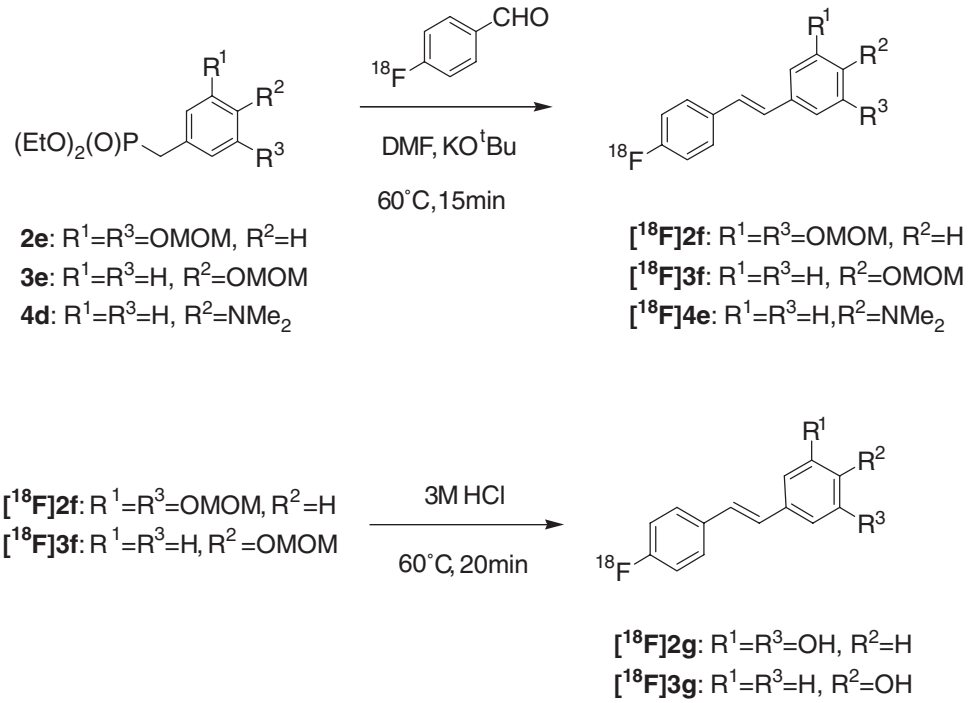

Figure 5 Synthesis of ^{18}F-labelled stilbenes via a Horner–Wadsworth–Emmons reaction between [^{18}F]fluorobenzaldehyde and benzylic phosphonates.

Table 1 Experimental data for the radiochemical syntheses of ^{18}F-labelled stilbenes using the Horner–Wadsworth–Emmons reaction

Product	Reaction steps	Radiochemical yield[a] (%)	Radiochemical purity[b] (%)	Synthesis time (min)
[^{18}F]2g (*n*=5)	Three	8–22	>90	120–130
[^{18}F]3g (*n*=6)	Three	5–9	>92	140–170
[^{18}F]4e (*n*=4)	Two	11–17	>95	110–140

[a] Decay-corrected, based upon to [^{18}F]fluoride.
[b] Detected by analytical HPLC (**[^{18}F]3g**) or radio-TLC (**[^{18}F]2g** and **[^{18}F]4e**).

achieved radiochemical purities and specific activities are suitable for further radiopharmacological studies.

The successful application Horner–Wadsworth–Emmons coupling reaction of phosphonic acid esters with the readily available 4-[^{18}F]fluorobenzaldehyde as secondary labelling precursor to give stilbene compounds **[^{18}F]2g**, **[^{18}F]3g** and **[^{18}F]4e** represents a novel radiolabelling technique in ^{18}F-chemistry for the convenient synthesis of *E*-configured stilbenes. The exclusive formation of the *E*-isomers makes laborious separation of undesired *Z*-isomers unnecessary as otherwise observed in Wittig-type reactions. Thus, the described method opens a convenient access to a large number of ^{18}F-labelled compounds bearing an *E*-configured stilbene backbone. In this connection the Horner–Wadsworth–Emmons coupling reaction with 4-[^{18}F]fluorobenzaldehyde should represent an interesting alternative to the synthesis of ^{18}F-labelled stilbenes via direct nucleophilic substitution of nitro-substituted *E*- and *Z*-stilbenes as recently reported by Gao *et al.*[17]

The reaction may be applied for the synthesis of polyphenolic compounds and aromatic amines bearing an *E*-configured stilbene backbone as pharmaceutically interesting compounds. Thus, several *E*-configured stilbene-based polyphenols are known to be potential anticancer compounds.[18,19] In the case of amine group-containing stilbene compound **[^{18}F]4e**, structural comparable stilbenes were investigated by Kung *et al.*[20] as potential ligands to bind to Aβ-plaques found in the brain of patients with the neurodegenerative Alzheimer's disease. Preliminary radiopharmacological studies including small animal

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PET of compound **[^{18}F]4e** in normal rats showed promising brain uptake (unpublished data). Further detailed radiopharmacological characterization of compound **[^{18}F]4e** is currently in progress.

Experimental

General

All reactions were performed under nitrogen atmosphere with oven-dried glassware. Tetrahydrofuran was distilled from sodium/benzophenone prior to use. 4-Trimethylammoniumbenzaldehyde triflate and 4-[^{18}F]fluorobenzaldehyde were synthesized according to Wilson *et al.*[2] Substances **2b–2g** were synthesized according to Gester *et al.*[21] and substance **3a** was prepared according to Patel *et al.*[8] All other starting materials and reagents were obtained commercially and used without further purification. Reactions using microwave irradiation were performed with a MICROWELL 10 oven (Labwell AB). Analytical thin-layer chromatography was carried out on Merck silica gel F-254 plates with UV-visualization. Flash chromatography was performed using Merck silica gel (230–400 mesh) according to Still *et al.*[22] ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR and ^{31}P-NMR spectra were recorded on a Varian Inova-400 at 400, 100, 376 and 162 MHz, respectively. Chemical shifts (δ) are determined relative to the solvent and converted to the TMS scale. Elemental analyses were obtained on a LECO CHNS 932 elemental analyzer. Mass spectra were obtained on a Quattro/LC mass spectrometer (Micromass) by electrospray ionisation. Melting points were determined on a Galen III melting point apparatus (Cambridge Instruments) and are uncorrected.

Chemical syntheses

Methyl-4-(methoxymethoxy)benzoate 3b. To a stirred solution of 4-hydroxybenzoic acid methyl ester **3a** (4.23 g, 27.8 mmol) in THF (150 ml) was added DIPEA (5.36 g, 41.5 mmol) and MOMCl (3.39 g, 42.1 mmol). The mixture was stirred at reflux for 6 h. If monitoring by TLC shows an incomplete conversion of the starting material, another portions of DIPEA (1.5 eq.) and MOMCl (1.5 eq.) were added to the reaction mixture. After end of reaction, water (300 ml) was added carefully. The mixture was extracted with CH_2Cl_2 (1×100 ml, 3×50 ml), and the combined organic layers were washed with brine (100 ml), water (100 ml) and dried over Na_2SO_4. Evaporation of the solvent gave the protected MOM-ether **3b** as colorless oil, which was used without further purification. Yield: 4.99 g (92%). R_f = 0.56 (ethyl acetate/petroleum ether 50/50). ^{1}H-NMR ($CDCl_3$): δ 3.47 (s, 3 H, -$OCH_2OC\mathbf{H}_3$), 3.88 (s, 3 H, -$CO(OCH_3)$), 5.21 (s, 2 H, -$OC\mathbf{H}_2OCH_3$), 7.04 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H), 7.98 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 51.84, 56.16, 94.00, 115.54, 123.52, 131.44, 160.86, 166.69. Analytically calculated for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16; O, 32.62. Found: C, 61.38; H, 6.35; O, 32.27. LRMS (ESI positive) 197 [M+H], 151 [M-CH_2OCH_3].

(4-(Methoxymethoxy)phenyl)methanol 3c. To a cooled (0°C) solution of $LiAlH_4$ (7.7 ml 1 M in Et_2O, 7.7 mmol) in Et_2O (15 ml) was added the MOM-ether **3b** (1.24 g, 6.33 mmol) in Et_2O (20 ml) while stirring. The reaction mixture was warmed up to room temperature and stirring was continued for 2 h. After carefully quenching with water (5 ml), the ethereal layer was separated, washed with brine (30 ml) and dried over Na_2SO_4. Solvent evaporation gave the alcohol **3c** as colorless oil, which was used in following reactions without purification. Yield: 1.05 g (98%). R_f = 0.31 (ethyl acetate/petroleum ether 50/50). ^{1}H-NMR ($CDCl_3$): δ 1.76 (s, br, 1 H, -$CH_2O\mathbf{H}$), 3.47 (s, 3 H, -$OCH_2OC\mathbf{H}_3$), 4.61 (s, 2 H, -$C\mathbf{H}_2OH$), 5.17 (s, 2 H, -$OC\mathbf{H}_2OCH_3$), 7.03 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H), 7.29 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 55.93, 64.92, 94.38, 116.29, 128.52, 134.34, 156.73. Analytically calculated for $C_9H_{12}O_3$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.49; H, 7.30; O, 28.21. LRMS (ESI positive) 169 [M+H], 123 [M-CH_2OCH_3].

1-(bromomethyl)-4-(methoxymethoxy)benzene 3d. To a stirred solution of the alcohol **3c** (2.00 g, 11.9 mmol) and PPh_3 (6.24 g, 23.8 mmol) in DMF (30 ml) was added *N*-bromosuccinimide (NBS) (4.23 g, 23.8 mmol) in portions. The reaction mixture was warmed up to 60°C and stirring was continued for 1 h. Because of the hydrolysis of the product in different aqueous work-ups, the solution was concentrated under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/petroleum ether 50/50). The benzylic bromide **3d** was obtained as a pale yellow oil. Yield: 1.25 g (45%). R_f = 0.63 (ethyl acetate/petroleum ether 50/50). ^{1}H-NMR ($CDCl_3$): δ 3.47 (s, 3 H, -$OCH_2OC\mathbf{H}_3$), 4.49 (s, 2 H, -CH_2Br), 5.18 (s, 2 H, -$OC\mathbf{H}_2OCH_3$), 7.00 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H), 7.32 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 33.68, 56.01, 94.26, 116.41, 130.38, 131.09, 157.24. Analytically calculated for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80; O, 13.85. Found: C, 47.04; H, 4.99; O, 13.56.

Diethyl (4-(methoxymethoxy)benzyl)phosphonate 3e. A mixture of the bromide **3d** (775 mg, 3.35 mmol) and phosphorous acid triethyl ester ($P(OEt)_3$) (557 mg,

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3.35 mmol) was heated in a tightly closed reaction vessel for 15 min at 200 W in a microwave (MICROWELL 10, Labwell AB). After cooling to room temperature the solution was diluted with ethyl acetate (3 ml) and purified by flash chromatography (100% ethyl acetate) to give the phosphonate **3e** as a nearly colorless oil. Yield: 801 mg (83%). R_f = 0.25 (100% ethyl acetate). ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, 6 H, $^3J_{(H,H)}$ = 6.8 Hz, -$CH_2PO(OCH_2C\mathbf{H}_3)_2$), 3.08 (d, 2 H, $^2J_{(H,P)}$ = 21.0 Hz, -$C\mathbf{H}_2PO(OCH_2CH_3)_2$), 3.46 (s, 3 H, -$OCH_2OC\mathbf{H}_3$), 4.00 (m, 4 H, $^3J_{(H,H)} \approx {}^3J_{(H,P)}$ = 6.8 Hz, -$CH_2PO(OC\mathbf{H}_2CH_3)_2$), 5.14 (s, 2 H, -$OC\mathbf{H}_2OCH_3$), 6.97 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H), 7.20 (dd, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, $^4J_{(H,P)}$ = 2.4 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 16.34 (d, $^3J_{(C,P)}$ = 6.1 Hz), 32.78 (d, $^1J_{(C,P)}$ = 138.9 Hz), 55.91, 62.01 (d, $^2J_{(C,P)}$ = 7.6 Hz), 94.42, 116.31 (d, $^4J_{(C,P)}$ = 3.1 Hz), 124.71 (d, $^2J_{(C,P)}$ = 7.6 Hz), 130.70 (d, $^3J_{(C,P)}$ = 6.1 Hz), 156.17. ^{31}P-NMR ($CDCl_3$): δ 27.77. Analytically calculated for $C_{13}H_{21}O_5P$: C, 54.16; H, 7.34. Found: C, 53.82; H, 7.05. LRMS (ESI positive) 289 [M+H], 152 [M+H-$PO(OEt)_2$].

1-Fluoro-4-(*E*)-2-(4-(methoxymethoxy)phenyl)ethenylbenzene 3f. A solution of the phosphonic acid ester **3e** (100 mg, 0.347 mmol) and 4-fluorobenzaldehyde (44 mg, 0.355 mmol) in DMF (3 ml) was added to a stirred solution of KO^tBu (100 mg, 0.891 mmol) in DMF (3 ml), at the same time the reaction mixture changes from colorless to dark orange indicating the deprotonation of the methylene unit. Stirring was continued at room temperature for 30 min.The reaction mixture was poured onto crushed ice and extracted with CH_2Cl_2 (2 × 10 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by flash chromatography (ethyl acetate/petroleum ether 50/50) to give the protected fluorostilbene **3f** as a pale yellow oil. Yield: 81 mg (90%). R_f = 0.63 (ethyl acetate/petroleum ether 50/50). ^{1}H-NMR ($CDCl_3$): δ 3.50 (s, 3 H, -$OCH_2OC\mathbf{H}_3$), 5.20 (s, 2 H, -$OC\mathbf{H}_2OCH_3$), 6.95 (AB quartet, Δν = 10.4 Hz, 1 H, $^3J_{(H,H)}$ = 16.5 Hz), 6.98 (AB quartet, Δν = 10.4 Hz, 1 H, $^3J_{(H,H)}$ = 16.5 Hz), 7.04 (m, 4 H, Ar-H), 7.45 (m, 4 H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 56.01, 94.35, 115.52 (d, $^2J_{(C,F)}$ = 22.9 Hz), 116.41, 125.83, 127.57, 127.69 (d, $^3J_{(C,F)}$ = 7.6 Hz), 127.85, 131.06, 133.67 (d, $^4J_{(C,F)}$ = 3.1 Hz), 156.86, 162.09 (d, $^1J_{(C,F)}$ = 245.7 Hz). ^{19}F-NMR ($CDCl_3$): δ -115.17. Analytically calculated for $C_{16}H_{15}FO_2$: C, 74.40; H, 5.85. Found: C, 74.64; H, 6.07. LRMS (ESI positive) 259 [M+H], 239 [M-F].

4-((*E*)-2-(4-Fluorophenyl)ethenyl)phenol 3g. To a stirred solution of the fluorostilbene **3f** (51 mg, 0.198 mmol) in methanol (MeOH) (15 ml) was added 3 M HCl (1 ml). Stirring was continued at 60°C for 2 h. Then saturated $NaHCO_3$-solution (5 ml) was added to the reaction mixture and MeOH was evaporated. After extracting the reaction mixture with ethyl acetate (3 × 10 ml) the combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether 50/50) to give the *E*-fluorostilbene **3g** (*E*/*Z*-ratio >95%, determined by ^{1}H-NMR spectroscopy) as white crystals. Yield: 42 mg (99%). R_f = 0.51 (ethyl acetate/petroleum ether 50/50), R_f = 0.2 (ethyl acetate/petroleum ether 20/40). Melting point 183–185°C. ^{1}H-NMR ($DMSO_{d6}$): δ 6.77 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H), 7.01 (AB quartet, Δν = 29.9 Hz, 1 H, $^3J_{(H,H)}$ = 16.3 Hz), 7.08 (AB quartet, Δν = 29.9 Hz, 1 H, $^3J_{(H,H)}$ = 16.3 Hz), 7.16 (t, 2 H, $^3J_{(H,H)} \approx {}^3J_{(H,F)}$ = 8.8 Hz, Ar-H), 7.41 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H), 7.57 (dd, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, $^4J_{(H,F)}$ = 5.4 Hz, Ar-H), 9.61 (s, br, 1 H, -OH). ^{13}C-NMR ($DMSO_{d6}$): δ 115.40 (d, $^2J_{(C,F)}$ = 19.8 Hz), 115.50, 123.86, 127.72 (d, $^3J_{(C,F)}$ = 9.2 Hz), 127.77, 127.95, 128.28, 134.07 (d, $^4J_{(C,F)}$ = 3.1 Hz), 157.25, 161.19 (d, $^1J_{(C,F)}$ = 244.1 Hz). ^{19}F-NMR ($DMSO_{d6}$): δ -115.66. Analytically calculated for $C_{14}H_{11}FO$: C, 78.49; H, 5.18. Found: C, 78.55; H, 5.36. LRMS (ESI positive) 215 [M+H].

Diethyl (4-nitrobenzyl)phosphonate 4b. A mixture of 1-bromomethyl-4-nitrobenzene (**4a**) (4.39 g, 20.3 mmol) and phosphorous acid triethyl ester ($P(OEt)_3$) (3.37 g, 20.3 mmol) was heated in a tightly closed reaction vessel for 3 min at 150 W in a microwave (MICROWELL 10, Labwell AB). After cooling to room temperature the solution was diluted with ethyl acetate (10 ml) and purified by flash chromatography (100% ethyl acetate) to give the phosphonate **4b** as a colorless oil. Yield: 3.86 g (70%). R_f = 0.32 (100% ethyl acetate). ^{1}H-NMR ($CDCl_3$): δ 1.26 (t, 6 H, $^3J_{(H,H)}$ = 7.1 Hz, -$CH_2PO(OCH_2C\mathbf{H}_3)_2$), 3.24 (d, 2 H, $^2J_{(H,P)}$ = 22.3 Hz, -$C\mathbf{H}_2PO(OCH_2CH_3)_2$), 4.04 (m, 4 H, $^3J_{(H,H)} \approx {}^3J_{(H,P)}$ = 7.1 Hz, -$CH_2PO(OC\mathbf{H}_2CH_3)_2$), 7.46 (dd, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, $^4J_{(H,P)}$ = 2.5 Hz, Ar-H), 8.17 (d, 2 H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 16.34 (d, $^3J_{(C,P)}$ = 6.1 Hz), 33.92 (d, $^1J_{(C,P)}$ = 137.3 Hz), 62.40 (d, $^2J_{(C,P)}$ = 6.1 Hz), 123.66 (d, $^4J_{(C,P)}$ = 3.1 Hz), 130.58 (d, $^3J_{(C,P)}$ = 6.1 Hz), 139.67 (d, $^2J_{(C,P)}$ = 9.2 Hz). ^{31}P-NMR ($CDCl_3$): δ 25.19. Analytically calculated for $C_{11}H_{16}NO_5P$: C, 48.36; H, 5.90; N, 5.13. Found: C, 48.58; H, 6.18; N, 4.73. LRMS (ESI positive) 274 [M+H], 137 [M+H-$PO(OEt)_2$].

Diethyl (4-aminobenzyl)phosphonate 4c. To a stirred solution of the phosphonate **4b** (3.86 g, 14.1 mmol) in EtOH (120 ml) at room temperature was added $SnCl_2 \cdot 2H_2O$ (15.94 g, 70.6 mmol) in portions, following by the addition of conc. HCl (5.7 ml). The reaction

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mixture was heated for 2 h under reflux, cooled down to room temperature and adjusted to pH 8–9 by the addition of 1 M NaOH (approx. 200 ml). After extraction with CH_2Cl_2 (1×100 ml, 3×50 ml) the combined organic layers were washed with water (100 ml) and brine (100 ml), dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified by flash chromatography (100% ethyl acetate) to provide the phosphonic acid ester **4c** as a pale yellow solid. Yield: 3.25 g (95%). R_f = 0.14 (100% ethyl acetate). Melting point 93–95°C. ^{1}H-NMR ($DMSO_{d6}$): δ 1.15 (t, 6H, $^3J_{(H,H)}$ = 7.1 Hz, -$CH_2PO(OCH_2C\mathbf{H}_3)_2$), 2.97 (d, 2H, $^2J_{(H,P)}$ = 20.5 Hz, -$C\mathbf{H}_2PO(OCH_2CH_3)_2$), 3.90 (m, 4H, $^3J_{(H,H)} \approx {}^3J_{(H,P)}$ = 7.1 Hz, -$CH_2PO(OC\mathbf{H}_2CH_3)_2$), 4.95 (s, br, 2H, -$NH_2$), 6.48 (d, 2H, $^3J_{(H,H)}$ = 8.6 Hz, Ar-H), 6.90 (dd, 2H, $^3J_{(H,H)}$ = 8.6 Hz, $^4J_{(H,P)}$ = 2.0 Hz, Ar-H). ^{13}C-NMR ($DMSO_{d6}$): δ 16.23 (d, $^3J_{(C,P)}$ = 4.6 Hz), 31.31 (d, $^1J_{(C,P)}$ = 135.8 Hz), 61.13 (d, $^2J_{(C,P)}$ = 6.1 Hz), 113.79 (d, $^4J_{(C,P)}$ = 3.1 Hz), 118.27 (d, $^2J_{(C,P)}$ = 9.2 Hz), 130.13 (d, $^3J_{(C,P)}$ = 7.6 Hz), 147.18. ^{31}P-NMR ($DMSO_{d6}$): δ 28.55. Analytically calculated for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.46; N, 5.76. Found: C, 54.07; H, 7.68; N, 5.33. LRMS (ESI positive) 244 [M+H], 107 [M+H-$PO(OEt)_2$].

Diethyl (4-(dimethylamino)benzyl)phosphonate 4d. One half of a solution of the primary amine **4c** (1.50 g, 6.17 mmol) and $NaBH_4$ (1.36 g, 36.0 mmol) in dry tetrahydrofurane (THF) (15 ml) was added slowly at room temperature to a well stirred solution of formaldehyde (1.9 ml, 36% in water, 1.09 g/ml, 0.746 g, 24.8 mmol) and 3 M H_2SO_4 (1.6 ml) in THF (15 ml), following by careful addition of 3 M H_2SO_4 (1.6 ml) and finally the remaining half of the amine-$NaBH_4$-solution. After stirring for 30 min at room temperature, the reaction mixture was diluted with water (10 ml) and 1 M NaOH (20 ml) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2×20 ml). The combined organic layers were washed with brine (20 ml), dried over Na_2SO_4, filtered and the solvent was evaporated. The crude product was purified by flash chromatography (100% ethyl acetate) to provide the methylated amine **4d** as a pale yellow oil. Yield: 1.00 g (60%). R_f = 0.25 (100% ethyl acetate). ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 6H, $^3J_{(H,H)}$ = 7.1 Hz, -$CH_2PO(OCH_2C\mathbf{H}_3)_2$), 2.91 (s, 6H, -$N(CH_3)_2$), 3.04 (d, 2H, $^2J_{(H,P)}$ = 20.9 Hz, -$C\mathbf{H}_2PO(OCH_2CH_3)_2$), 3.98 (m, 4H, $^3J_{(H,H)} \approx {}^3J_{(H,P)}$ = 7.1 Hz, -$CH_2PO(OC\mathbf{H}_2CH_3)_2$), 6.68 (d, 2H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H), 7.14 (dd, 2H, $^3J_{(H,H)}$ = 8.8 Hz, $^4J_{(H,P)}$ = 2.6 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 16.34 (d, $^3J_{(C,P)}$ = 6.1 Hz), 32.47 (d, $^1J_{(C,P)}$ = 138.9 Hz), 40.66, 61.90 (d, $^2J_{(C,P)}$ = 6.1 Hz), 112.82, 118.96, 130.27 (d, $^3J_{(C,P)}$ = 7.6 Hz), 149.39. ^{31}P-NMR ($CDCl_3$): δ 28.43. LRMS (ESI positive) 272 [M+H].

4-((*E*)-2-(4-fluorophenyl)ethenyl)-*N*,*N*-dimethylaniline 4e. A solution of the phosphonate **4d** (100 mg, 0.369 mmol) and 4-fluorobenzaldehyde (46 mg, 0.371 mmol) in dimethylformamide (DMF) (3 ml) was added to a stirred solution of KO^tBu (103 mg, 0.918 mmol) in DMF (3 ml), at the same time the color of the reaction mixture changed from colorless to reddish-brown indicative of the formation of the carbanion. Stirring was continued at room temperature for 10 min. The reaction mixture was poured onto crushed ice and extracted with CH_2Cl_2 (2×20 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by flash chromatography (ethyl acetate/petroleum ether 50/50) to give the *E*-fluorostilbene **4e** (*E*/*Z*-ratio >95%, determined by ^{1}H-NMR spectroscopy) as pale yellow crystals. Yield: 80 mg (90%). R_f = 0.62 (ethyl acetate/petroleum ether 50/50), R_f = 0.40 (ethyl acetate/petroleum ether 20/40). Melting point 194–196°C. ^{1}H-NMR ($CDCl_3$): δ 3.00 (s, 6H, -$N(CH_3)_2$), 6.74 (d, br, 2H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H), 6.88 (AB quartett, $\Delta\upsilon$ = 30.6 Hz, 1H, $^3J_{(H,H)}$ = 16.2 Hz), 6.96 (AB quartett, $\Delta\upsilon$ = 30.6 Hz, 1H, $^3J_{(H,H)}$ = 16.2 Hz), 7.03 (t, 2H, $^3J_{(H,H)} \approx {}^3J_{(H,F)}$ = 8.8 Hz, Ar-H), 7.41 (d, 2H, $^3J_{(H,H)}$ = 8.8 Hz, Ar-H), 7.44 (dd, 2H, $^3J_{(H,H)}$ = 8.8 Hz, $^4J_{(H,F)}$ = 5.5 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 40.55, 112.51, 115.42 (d, $^2J_{(C,F)}$ = 21.4 Hz), 123.22, 127.34 (d, $^3J_{(C,F)}$ = 7.6 Hz), 127.47, 128.46, 134.25, 161.78 (d, $^1J_{(C,F)}$ = 245.7 Hz). ^{19}F-NMR ($CDCl_3$): δ-116.16. Analytically calculated for $C_{16}H_{16}FN$: C, 79.64; H, 6.68; N, 5.80. Found: C, 79.90; H, 6.81; N, 5.47. LRMS (ESI positive) 242 [M+H].

Radiochemical syntheses

No-carrier-added aqueous [^{18}F]fluoride was produced in an IBA CYCLONE 18/9 cyclotron by irradiation of [^{18}O]H_2O via the ^{18}O(p,n)^{18}F nuclear reaction. Resolubilization of the aqueous [^{18}F]fluoride was accomplished with Kryptofix®2.2.2 and K_2CO_3 in an automated nucleophilic fluorination module (GE Medical Systems, former Nuclear Interface, Uppsala, Sweden). 4-[^{18}F]Fluorobenzaldehyde was synthesized according to Wilson *et al.*[20] starting from 4-trimethylammoniumbenzaldehyde triflate.

HPLC analyses were carried out with a Supelco Supelcosil™ LC-18S column (250×4.6 mm, 5 μm) and a Phenomenex Luna® C18(2) column (250×4.6 mm, 5 μm) using an isocratic eluent (acetonitrile/0.1 M ammonium formate, 60/40 and 70/30, respectively) at flow rates of 1 ml/min. The products were monitored by an UV detector L4500 (Merck, Hitachi) at 250 nm and by γ-detection with a scintillation detector GABI Star (Raytest). Semi-preparative HPLC was performed with a Hamilton PRP®-1 column (250×10 mm, 10 μm) and a Phenomenex

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Luna® C18(2) column (250 × 10 mm, 10 μm) using isocratic elution with acetonitrile/0.1 M ammonium formate at flow rates of 3 ml/min. Radio thin-layer chromatography was carried out on Merck silica gel F-254 plates. For radio-TLC detection a BAS 2000 scanner (Fuji) was used.

General procedure for the synthesis of 5-((*E*)-2-(4-(^{18}F)Fluorophenyl)ethenyl)-1,3-benzenediol (^{18}F)2g and 4-((*E*)-2-(4-(^{18}F)Fluorophenyl)ethenyl)phenol (^{18}F)3g

Cyclotron produced [^{18}F]HF (8140 MBq and 2940 MBq) was dried in a remotely controlled fluorination module. Then, 4-trimethyl-ammoniumbenzaldehyd triflate (15 mg, 47.9 μmol) dissolved in DMF (1 ml) was added and the reaction mixture was heated at 120°C for 15 min (step one). After cooling the reaction vessel to 60°C, phosphonate precursor **2e** (10 mg, 28.7 μmol) or **3e** (14 mg, 48.6 μmol) and KO^{t}Bu (2.5 eq.) dissolved in DMF (1.5 ml) were added to the reaction mixture. The coupling-reaction (step two) was carried out for 15 min. To remove the MOM-ether protecting groups, 3 M HCl (2 ml) was added. After 20 min at 60°C (step three), the mixture was diluted with H_2O (10 ml) and passed through a Merck LiChrolut® RP-18 cartridge (500 mg). The cartridge was washed with water (5 ml) and the product was eluted from the cartridge with acetonitrile (3 ml) and subjected onto a semi-preparative HPLC column.

5-((*E*)-2-(4-(^{18}f)fluorophenyl)ethenyl)-1,3-benzenediol (^{18}F)2g

Semi-preparative HPLC: Hamilton PRP®-1 column, eluent: acetonitrile/0.1 M ammonium formate 50/50. The fraction eluting at 18.0–20.0 min was collected, diluted with water (30 ml) and passed through a Macherey-Nagel Chromafix® C18ec cartridge. The cartridge was washed with water (5 ml) and the product was finally eluted from the cartridge with 1 ml of EtOH. Radio-HPLC: t_R = 10.8 min (Supelco Supelcosil™ LC-18S, acetonitrile/0.1 M ammonium formate 40/60), radio-TLC: R_f = 0.35 (ethyl acetate/petroleum ether 50/50).

4-((*E*)-2-(4-(^{18}f)fluorophenyl)ethenyl)phenol (^{18}F)3g

Semi-preparative HPLC: Hamilton PRP®-1 column, eluent: acetonitrile/0.1 M ammonium formate 60/40). The fraction eluting at 16.0–18.0 min was collected, diluted with water (30 ml) and passed through a Macherey-Nagel Chromafix® C18ec cartridge. The cartridge was washed with water (5 ml) and the product was finally eluted from this cartridge with 1 ml of EtOH. Radio-HPLC: t_R = 7.9 min (Phenomenex Luna® C18(2), acetonitrile/0.1 M ammonium formate 70/30), radio-TLC: R_f = 0.22 (ethyl acetate/petroleum ether 20/40).

4-((*E*)-2-(4-(^{18}f)fluorophenyl)ethenyl)-*N*^{1},*N*^{1}-dimethylaniline (^{18}F)4e

Cyclotron produced [^{18}F]HF (3780 MBq) was dried in a remotely controlled radiofluorination module. Then, 4-trimethylammonium-benzaldehyd triflate (15 mg, 47.9 μmol) dissolved in DMF (1 ml) was added and the reaction mixture was heated at 120°C for 15 min (step one). After cooling the reaction vessel to 60°C, phosphonate precursor **4d** (13 mg, 47.9 μmol) and KO^{t}Bu (13 mg, 115.9 μmol) dissolved in DMF (1.5 ml) were added to the reaction mixture. The coupling-reaction (step two) was carried out for 15 min.The mixture was diluted with H_2O (10 ml) and passed through a Merck LiChrolut® RP-18 cartridge (500 mg). The cartridge was washed with water (5 ml) and the product was eluted from the cartridge with acetonitrile (3 ml) and subjected onto a semi-preparative HPLC column (Phenomenex Luna® C18(2), eluent: acetonitrile/0.1 M ammonium formate 70/30). The fraction eluting at 31.0–33.0 min was collected, diluted with water (30 ml) and passed through a Macherey-Nagel Chromafix® C18ec cartridge. The cartridge was washed with water (5 ml) and the product was finally eluted from this cartridge with 1 ml of EtOH. Radio-HPLC: t_R = 17.6 min (Phenomenex Luna® C18(2), acetonitrile/0.1 M ammonium formate 70/30), radio-TLC: R_f = 0.40 (ethyl acetate/petroleum ether 20/40).

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