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Research Article

Synthesis of 4-[^{18}F]fluoroiodobenzene and its application in sonogashira cross-coupling reactions

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Summary

The first application of a Sonogashira cross-coupling reaction in ^{18}F chemistry has been developed. The reaction was exemplified by the cross-coupling of terminal alkynes (ethynylcyclopentyl carbinol **6**, 17α-ethynyl-3,17β-estradiol **7** and 17α-ethynyl-3-methoxy-3,17β-estradiol **8**) with 4-[^{18}F]fluoroiodobenzene. 4,4′-Diiododiaryliodonium salts were used as precursors for the synthesis of 4-[^{18}F]fluoroiodobenzene, enabling the convenient access to 4-[^{18}F]fluoroiodobenzene in 13–70% yield using conventional heating or microwave activation. The Sonogashira cross-coupling of 4-[^{18}F]fluoroiodobenzene with terminal alkynes gave the corresponding 4-[^{18}F]fluorophenylethynyl-substituted compounds **[^{18}F]-9**, **[^{18}F]-10** and **[^{18}F]-13** in yields up to 88% within 20 min of starting from 4-[^{18}F]fluoroiodobenzene. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: [^{18}F]fluoroiodobenzene; sonogashira cross-coupling; ^{18}F-labelled steroids

Introduction

The extensive development of novel radiolabelling techniques with the short-lived positron emitters ^{11}C and ^{18}F represents a fundamental but challenging task. With regard to the special requirements encountered

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by the synthesis of PET radiotracers special attention has to be paid to rapid, selective and functional group-tolerating reactions. In this connection the use of catalysts such as enzymes or transition metal complexes have proved to be particularly valuable tools in the rapid and efficient syntheses of a wide variety of ^{11}C-labelled radiotracers.[1–6] Hence, the application of copper- and palladium-mediated cross-coupling reactions for distinct ^{11}C–C bond forming reactions has significantly extended the number of ^{11}C-labelled compounds.

However, only a few attempts have been made to adopt the recent advances in transition-metal catalysed reactions to the synthesis of ^{18}F-labelled radiotracers.[7–10] The palladium-catalysed cross-coupling reactions of organometallic compounds like Grignard reagents, tin, or boron derivatives with organic halides suggests the use of ^{18}F-labelled aryl halides as the coupling partners. This approach can be regarded as a general method for the mild and efficient introduction of a 4-[^{18}F]fluorophenyl group into a wide variety of complex functionalized target molecules. The 4-fluorophenyl group is a common structural component found in many fluorinated drugs. The beneficial effect of a fluoroaryl group in drug design and development with regard to drug metabolism, in vivo activity and stability has been reviewed recently.[11,12] The first few reports on the synthesis of ^{18}F-labelled radiotracers via palladium-mediated cross-coupling reactions have mainly exploited the Stille reaction[7–9] and in one case a Hartwig–Buchwald *N*-arylation reaction.[10] The reaction of vinyl or aryl tin reagents with 4-[^{18}F]fluoro-bromobenzene or 4-[^{18}F]fluoroiodobenzene led to the formation of 4-[^{18}F]fluorostyrenes, 4-[^{18}F]fluoro-biphenyls and the nicotinic acetylcholine receptor ligand 9-(4′-[^{18}F]fluoro-phenyl)cytisine.[7–9] The reaction of a piperazine derivative with 4-[^{18}F]fluorobromobenzene according to a Hartwig-Buchwald *N*-arylation protocol provided the 5-HT$_{2A}$ receptor antagonist [^{18}F]RP 62203.[10] (Figure 1).

The synthesis of 4-[^{18}F]fluorohalobenzenes can be accomplished via three different routes. The one-step synthesis of 4-[^{18}F]fluoroiodobenzene starting from 4-iodophenyltrimethylammonium triflate only gives low yields (5–10%, decay-corrected) due to the formation of large amounts of [^{18}F]fluoromethane originating from a competitive nucleophilic aliphatic substitution reaction.[7] Alternatively, 4-[^{18}F]fluorobromobenzene can be synthesized in a two-step process comprising the nucleophilic fluorination of 5-bromo-2-nitrobenzaldehyde and subsequent reductive decarbonylation with Wilkinson catalyst.[7,13] A third

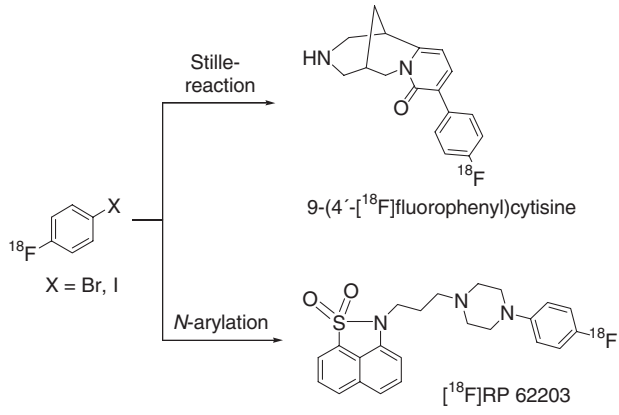

Figure 1. Cross-coupling reactions with 4-[^{18}F]fluorohalobenzenes

approach for the synthesis of 4-[^{18}F]fluorohalobenzenes consists of the thermal decomposition of diaryliodonium salts in the presence of [^{18}F]fluoride.[14–17] This route was shown to be very efficient in the synthesis of several [^{18}F]fluoroarenes in moderate to high radiochemical yields.

Recently we have developed a modified Sonogashira-like reaction for the cross-coupling of terminal alkynes with the readily available ^{11}C labelling precursor [^{11}C]MeI.[18] In this paper we describe for the first time Sonogashira cross-coupling reactions in ^{18}F chemistry. For this purpose we have developed a convenient route to 4-[^{18}F]fluoroiodobenzene via symmetrical diiododiphenyliodonium salts in order to circumvent the regioselectivity problems encountered in the ^{18}F-labelling when non-symmetrical iodonium salts are used.[14–16] The Sonogashira reaction[19] was exemplified by reacting 4-[^{18}F]fluoroiodobenzene with terminal alkynes (ethynylcyclopentyl carbinol **6**, 17α-ethynyl-3,17β-estradiol **7** and 17α-ethynyl-3,17β-estradiol-3-methylether **8**) to form the corresponding 4-[^{18}F]fluorophenylethynyl-substituted compounds **[^{18}F]-9**, **[^{18}F]-10** and **[^{18}F]-13**.

Results and discussion

Synthesis of 4,4′-diiododiphenyliodonium salts **2**, **3** *and* **5**

The syntheses of symmetrical 4,4′-diiododiphenyliodonium salts **2**, **3** and **5** were accomplished via two different routes, being the coupling of iodobenzene with iodyl sulfate **1**[20,21] in sulfuric acid and the

condensation of 4-iodo-1-(diacetoxyiodo)benzene **4** with iodobenzene in the presence of trifluoromethane sulfuric acid (Figure 2).

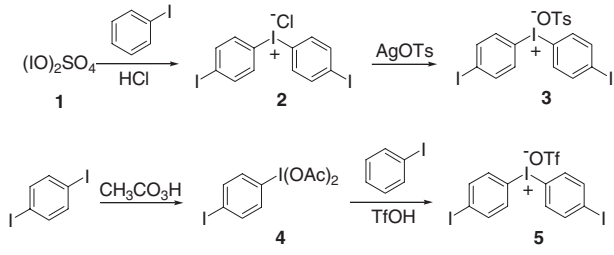

Figure 2. Synthesis of 4,4′-diiododiphenyliodonium salts

The first approach started from iodyl sulfate **1** and its subsequent reaction with iodobenzene followed by HCl to form 4,4′-diiododiphenyl-iodonium chloride **2** in 37% yield. The chloride ion was replaced with the tosylate anion by refluxing the chloride salt **2** in methanol with silver tosylate to yield 25% of 4,4′-diiododiphenyliodonium tosylate **3**. An alternative route was employed by refluxing 1,4-diiodobenzene with peracetic acid to give 4-iodo-1-(diacetoxyiodo)benzene **4** in 63% isolated yield. This compound was treated with trifluorosulfonic acid and iodobenzene to give 4,4′-diiodo-diphenyliodonium triflate **5** in 32% yield.

Synthesis of reference compounds

The syntheses of the 4-fluorophenylethynyl-substituted compounds **9**, **10** and **13** were accomplished by employing a Sonogashira cross-coupling reaction of 4-fluoroiodobenzene with the corresponding terminal alkynes **6**, **7** and **8** in the presence of CuI and $Pd[PPh_3]_4$ as catalysts and triethylamine as the base. The desired cross-coupled products **9**, **10** and **13** could be obtained in high yields of 78–94% after purification by flash chromatography.

The thermal decomposition of the diiododiphenyliodonium salts in the presence of [^{18}F]fluoride to form 4-[^{18}F]fluoroiodobenzene leads to rather large amounts of iodobenzene and 1,4-diiodobenzene as non-radioactive by-products. Therefore, we also set up the syntheses of 17α-phenylethynyl-3,17β-estradiol **11** and 17α-(4-iodophenylethynyl)-3,17β-estradiol **12** to prove the expected competitive reaction of iodobenzene and 1,4-diiodobenzene in the Sonogashira cross-coupling of 17α-ethynyl-3,17β-estradiol **8** with 4-[^{18}F]fluoroiodobenzene. The reaction

of iodobenzene and 1,4-diiodobenzene with 17α-ethynyl-3,17β-estradiol **8** was accomplished according to a similar Sonogashira reaction employed for the synthesis of compounds **8**, **9** and **10**, yielding 96% of **11** and 59% of **12**, respectively.

The syntheses of all reference compounds via a Sonogashira cross-coupling reaction are depicted in Figure 3.

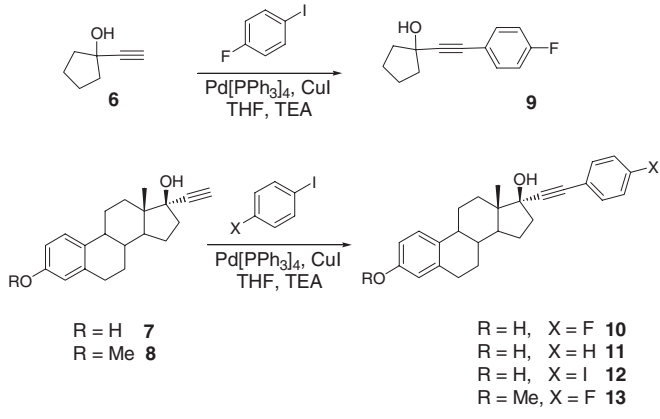

Figure 3. Synthesis of reference compounds

Synthesis of 4-[^{18}F]fluoroiodobenzene

The symmetrical 4,4′-diiododiphenyliodonium salts **2**, **3** and **5** were used as precursors for radiofluorinations with [^{18}F]fluoride to yield 4-[^{18}F]fluoroiodobenzene as the only radioactive product along with non-reacted [^{18}F]fluoride. The conventional heating was carried out in a sealed vial containing the iodonium salt (20 mg) and resolubilized [^{18}F]KF in an aprotic solvent (DMF, DMSO or acetonitrile) using an oil bath at different temperatures for 40 min. Alternatively, microwave activation at 120 W for 5 min was used (Figure 4).

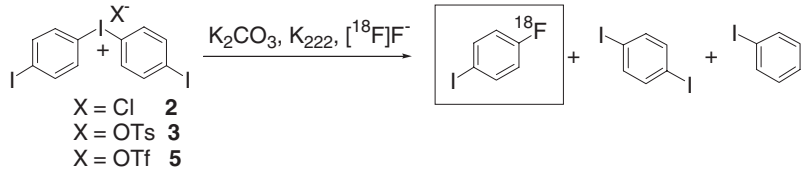

Figure 4. Radiosynthesis of 4-[^{18}F]fluoroiodobenzene

By varying the counter anion (chloride, tosylate and triflate) of the diiododiphenyliodonium salts, the reaction temperature (80, 100, 120, 140, 160°C and microwave activation) and the solvent (acetonitrile, DMF and DMSO) the radiochemical yield of 4-[^{18}F]fluoroiodobenzene could reach up to 70%. The yield of 4-[^{18}F]fluoroiodobenzene was determined by radio-TLC. The results are given in Table 1.

Table 1. Reaction conditions for the synthesis of 4-[^{18}F]fluoroiodobenzene.

Run	Precursor	X	Solvent	Temperature/ microwave (MW) (°C)	Yield of 4-[^{18}F] fluoroiodobenzene (%)
1	**2**	Cl	CH_3CN	80	0.5–1.0
2	**2**	Cl	CH_3CN	100	1.6–3.0
3	**2**	Cl	CH_3CN	120	1.3–2.8
4	**2**	Cl	DMF	100	3–12
5	**2**	Cl	DMF	120	8–19
6	**2**	Cl	DMF	140	13–63
7	**2**	Cl	DMF	160	15–52
8	**2**	Cl	DMSO	140	0.5–1.0
9	**3**	OTs	CH_3CN	100	0.5–2.5
10	**3**	OTs	DMF	140	21–46
11	**5**	OTf	CH_3CN	80	0.5–1.0
12	**5**	OTf	CH_3CN	100	2.5–5
13	**5**	OTf	DMF	140	11–22
14	**5**	OTf	DMSO	140	0.5–1.0
15	**2**	Cl	DMF	MW	15–70
16	**5**	OTf	DMF	MW	16–37

The summary clearly shows the important influence of temperature and solvent on the radiochemical yield, showing a maximum at 140°C with DMF as the solvent (runs 4–7,10,13). This finding agrees with the results obtained by Gail *et al.* [16] since high reaction temperatures seem to be essential for an efficient thermal decomposition of diaryliodonium salts in a highly polar aprotic solvent. However, the reported high radiochemical yields of several [^{18}F]fluoroarenes in the reaction of [^{18}F]fluoride with diaryliodonium salts in acetonitrile as the solvent using lower reaction temperatures (80–100°C)[15] could not be reproduced (runs 1, 2, 9, 11 and 12). In our experiments acetonitrile always gave considerable lower yields than DMF. Surprisingly, DMSO as an otherwise very efficient polar aprotic solvent gave only very low radiochemical yields of 4-[^{18}F]fluoroiodobenzene (runs 8 and 14), being less than 1%.

The influence of the diiododiphenyliodonium salt counter anion (chloride, tosylate and triflate) on the radiochemical yield was also

studied. Despite the better solubility of tosylate precursor **3** and triflate precursor **5** in DMF the obtained radiochemical yields are in the same range or even slightly higher when the less DMF-soluble chloride precursor **2** was used (runs 6, 10 and 13). However, starting from chloride precursor **2** the radiochemical yields are obtained over a wide range, from 13 to 63% (run 6). The obtained radiochemical yields using tosylate precursor **3** (run 10) and triflate precursor **5** (run 13) are more reproducible, ranging from 21–46% and 11–22%, respectively.

Microwave activation did not further improve the radiochemical yield of 4-[^{18}F]fluoroiodobenzene (runs 15 and 16), but the reduction of reaction time from 40 to 5 min is of great advantage in the work with the short-lived positron emitter ^{18}F. Again, the radiochemical yields obtained with chloride precursor **2** vary widely, from 15 to 70%.

The 4-[^{18}F]fluoroiodobenzene was purified by solid phase extraction (SPE) to provide a radiochemically pure product ($>95\%$) suitable for subsequent Sonogashira cross-coupling reactions with terminal alkynes.

It is of great importance to mention that in all our experiments with symmetrical diiododiphenyl iodonium salts **2**, **3** and **5** the formation of 1,4-diiodobenzene and iodobenzene as non-radioactive by-products was observed. This finding has not been reported yet in the literature dealing with the synthesis of [^{18}F]fluoroarenes via thermal decomposition of non-symmetrical diaryliodonium salts. Therefore, we also set up an experiment using the non-symmetrical iodonium salt 4-iodophenyl(tolyl) triflate in the radiolabelling with [^{18}F]fluoride in DMF at 140°C for 40 min. As expected we found [^{18}F]fluoroiodobenzene as the only radioactive product (10–15% yield) along with 1,4-diiodobenzene, iodobenzene and 4-iodotoluene as non-radioactive by-products originating from thermal decomposition of the iodonium salt.

The non-radioactive iodoarene by-products could not be removed by solid phase extraction. Since we were starting from symmetrical diiododiphenyliodonium salts the formation of 1,4-diiodobenzene and iodobenzene as by-products is inevitable. Hence, they will act as competitive ligands in the subsequent Sonogashira cross-coupling reaction of terminal alkynes **6**, **7** and **8** with 4-[^{18}F]fluoroiodobenzene.

Sonogashira cross-coupling reactions with 4-[^{18}F]fluoroiodobenzene

SPE-purified 4-[^{18}F]fluoriodobenzene (50–150 MBq) was used in the palladium–copper catalysed Sonogashira cross-coupling with terminal alkynes **6**, **7** and **8** (Figure 5).

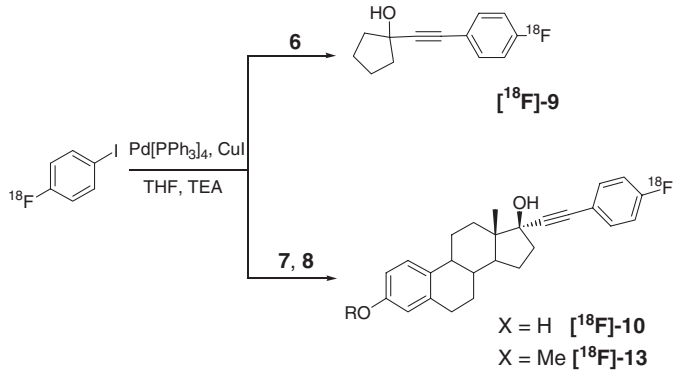

Figure 5. Sonogashira cross-coupling with 4-[^{18}F]fluoroiodobenzene

The reactions were performed in a sealed vial at 110°C for 20 min using THF as the solvent and triethylamine as the base. The obtained radiochemical yields were determined by monitoring the conversion of 4-[^{18}F]fluoroiodobenzene into the corresponding cross-coupled products. 85% of 4-[^{18}F]fluoroiodobenzene was converted into cross-coupled product **[^{18}F]-9**, 65–88% into **[^{18}F]-10** and 34–64% into **[^{18}F]-13**, respectively. Lowering the reaction temperature to 60°C did not lead to any product formation. Also the use of triethylamine as the solvent and the base gave no cross-coupled products. The optimum amount of components in the cross-coupling reaction was found to be about 3 mg for each component. Higher amounts of catalyst (CuI and Pd[PPh$_3$]$_4$) and terminal alkynes did not further improve the radiochemical yields.

The competitive cross-coupling reaction of 1,4-diiodobenzene and iodobenzene originating from the synthesis of 4-[^{18}F]fluoroiodobenzene was studied by the reaction of 4-[^{18}F]fluoroiodobenzene with 17α-ethynyl-3,17β-estradiol **8**. The corresponding cross-coupled products **11** and **12** could be identified by comparing the retention times of pure reference compounds with the HPLC-trace of the reaction mixture. As expected, the phenylethynyl compound **11** and 4-iodophenylethynyl compound **12** could be found in the UV-trace of the HPLC-chromatogram of the reaction mixture, showing retention times of 8.7 and 14.7 min, respectively. The retention time of the desired ^{18}F-labelled cross-coupling product **[^{18}F]-10** was found to be 9.1 min.

The strong electron-withdrawing effect of the fluorine atom and the trace amounts of 4-[^{18}F]fluoroiodobenzene make this ligand probably the most reactive partner in the Sonogashira cross-coupling cycle resulting in moderate to high radiochemical yields of 34–88%. However,

when the presented Sonogashira reaction is aimed at ^{18}F-labelled receptor-binding ligands, the effective specific radioactivity[24] will probably be low, since the exact separation of the [^{18}F]fluorophenylethynyl compound from the non-radioactive phenylethynyl compound was found to be very challenging. All our attempts to achieve a sufficient separation of **[^{18}F]-10** from **11** by varying the RP-HPLC-separation conditions have failed.

To circumvent that problem it will be necessary to develope an approach to synthesize radiochemically and chemically pure 4-[^{18}F]fluoroiodobenzene. In this respect the substitution of 4-[^{18}F]fluoroiodobenzene with [^{18}F]fluorobromobenzene could be an attractive alternative. [^{18}F]fluorobromobenzene can be synthesized in high radiochemical and chemical purity.[7,13] Investigations on the application of [^{18}F]fluorobromobenzene in the Sonogashira reaction are currently in progress.

Conclusions

We have developed a novel approach for a transition-metal mediated carbon–carbon bond formation in ^{18}F chemistry, being the Sonogashira cross-coupling of terminal alkynes with 4-[^{18}F]fluoroiodobenzene. The reaction proceeds in sufficient radiochemical yields in short reaction times, and the reaction is compatible with functional groups such as hydroxyl. However, the utilized 4-[^{18}F]fluoroiodobenzene is contaminated with 1,4-diiodobenzene and iodobenzene, causing competitive cross-coupling reactions which result in the formation of non-radioactive by-products which interfere with the separation process. An alternative approach using radiochemically and chemically pure 4-[^{18}F]fluorobromobenzene is currently under investigation.

Experimental

General

^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra were recorded on a Varian Inova-400 at 400, 100 and 376 MHz, respectively. Chemical shifts (δ) are determined relative to the solvent and converted to the TMS scale. The ^{13}C-NMR data of steroids are reported as: chemical shift (assignment of

carbon atom according to steroid numbering). Elemental analysis were obtained on a LECO CHNS 932 elemental analyser. 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. Flash chromatography was conducted according to Still *et al.*[22] using MERCK silica gel (mesh size 230–400 ASTM). Thin-layer chromatography (TLC) was performed on Merck silica gel F-254 plastic plates, with visualization under UV (254 nm).

All chemicals were obtained from commercial suppliers of reagent grade and used without further purification. Reactions using microwave activation were performed with a MICROWELL 10 oven (Labwell AB).

Chemical synthesis

4,4′-*Diiododiphenyliodonium chloride* **2**. A mixture of concentrated sulfuric acid (15 ml) and 30% fumic sulfuric acid (30 ml) was added to iodine (12.7 g, 50 mmol) under stirring. Then a mixture of concentrated sulfuric acid (4 ml), 65% fumic sulfuric acid (2 ml), and 100% fumic nitric acid (6.5 ml) was slowly added. The reaction mixture was stirred at 70–80°C for 1.5 h, at which time yellow crystals of iodyl sulfate **1** precipitated. The mixture was then cooled to 0°C, and iodobenzene (51 g, 250 mmol) was slowly added. The mixture was stirred at 45°C for 2 h and then cooled to 0°C. Water was very carefully added in small portions. The nitrogen oxides were removed by a gentle stream of nitrogen. The product, a brown oil, was collected, dissolved in methanol, and crystallized as the chloride salt **2** by dropwise addition of concentrated hydrochloric acid. Yield: 52.6 g (37%). Melting point 198–200°C. Analytically calculated for $C_{12}H_8ClI_3$: C, 25.36; H, 1.42. Found: C, 24.93; H, 1.18.

4,4′-*Diiododiphenyliodonium tosylate* **3**. 4,4′-Diiododiphenyiodonium chloride **2** (2.84 g, 5.0 mmol) and AgOTs (1.4 g, 5.0 mmol) were refluxed in methanol (100 ml) for 30 min. The mixture was filtered hot, and the filtrate was evaporated to a final volume of 5 ml. Diethyl ether was added, and the white precipitate was filtered off and dried under vacuum to give 0.9 g (25%) of **3** as a white solid. Melting point 152–154°C. ^{1}H-NMR ($DMSO_{d6}$): δ 3.84 (s, 3H; CH_3), 7.06 (*d*, $J = 8.2$ Hz, 2H; Ar-H), 7.43 (*d*, $J = 8.2$ Hz, 2H; Ar-H), 7.81 (*d*, $J = 8.7$ Hz, 4H; Ar-H), 7.93 (*d*,

$J = 8.7$ Hz, 4H; Ar-H). ^{13}C-NMR ($DMSO_{d6}$): δ 21.14, 100.62, 116.50, 125.80, 128.46, 137.15, 138.18, 140.64, 145.57. Analytically calculated for $C_{19}H_{15}I_3O_3S$: C, 32.41; H, 2.15; S 4.55. Found: C, 31.96; H, 2.49; S, 4.76.

4-*Iodo-1-(diacetoxyiodo)-benzene* **4**. 1,4-diiodobenzene (3.29 g, 10 mmol) was suspended under stirring in 40% peracetic acid (19 ml). The mixture was carefully warmed up to 40°C and after refluxing a yellow precipitate was formed. After cooling the precipitate was filtered off and washed with acetic acid. The product was re-crystallized from acetic acid/acetic anhydride (4:1) to give 2.84 g (63%) of **4** as a white solid. Melting point 170–172°C. ^{1}H-NMR ($DMSO_{d6}$): δ 1.89 (s, 6H; CH_3), 7.49 (m, 4H; Ar-H). Analytically calculated for $C_{10}H_{10}I_2O_4$: C, 26.81; H, 2.25. Found: C, 26.50; H, 2.47.

4, 4′-*Diiododiphenyliodonium triflate* **5**. 4-Iodo-1-(diacetoxyiodo)-benzene **4** (582 mg, 1.3 mmol) was suspended in dry dichloromethane (20 ml) and cooled to −30°C while stirring under nitrogen. Then trifluoro-methane sulfonic acid (230 µl, 2.6 mmol) was added dropwise over 2 h. The mixture was warmed up to 0°C and stirring was continued for 1 h at 0°C. During this time a clear yellow solution was produced. After re-cooling to −30°C iodobenzene (265 mg, 1.3 mmol) in dichloromethane (1 ml) was added, and the mixture was stirred at ambient temperature overnight. The yellow solution was evaporated under vacuum and the residue was treated with diethyl ether. The white solid was filtered off, washed with diethyl ether and dried to give 287 mg (32%) of **5**. Melting point 185–187°C. ^{1}H-NMR ($DMSO_{d6}$): δ 7.88 (d, 4H; Ar-H), 7.98 (m, 4H; Ar-H), ^{13}C-NMR ($DMSO_{d6}$): 131.81, 135.18, 136.77, 140.40. Analytically calculated for $C_{13}H_8F_3I_3O_3S$: C, 22.90; H, 1.18; S, 4.70. Found: C, 22.48; H, 1.05; S, 4.57. LRMS (ESI positive) 532.6 [M-OTf].

General procedure for the Sonogashira cross-coupling reaction to give compounds **9**, **10**, **11**, **12** *and* **13**. A solution of the terminal alkyne (**6**, **7** and **8**, 1 mmol), the iodoarene (1,4-fluoroiodobenzene, iodobenzene or 1,4-diiodobenzene, 1 mmol), CuI (0.04 mmol) and $Pd[PPh_3]_4$ (0.02 mmol) was refluxed in THF (5 ml) and triethylamine (5 ml) for 3 h under an argon atmosphere. After cooling the solvent was evaporated and the residue was purified by flash chromatography (50% EtOAc/hexane) to give the corresponding cross-coupled products.

4-*fluorophenylethynyl-cyclopentylcarbinol* **9**. Yield: 88%. Melting point 39-41°C. ^{1}H-NMR ($CDCl_3$): δ 1.75-1.90 (m, 4H; $2 \times CH_2$), 2.00–2.06 (m, 4H; $2 \times CH_2$), 6.98 (m, 2H; Ar–H), 7.39 (m, 2H; Ar–H). ^{13}C-NMR ($CDCl_3$): 23.48, 42.49, 74.84, 82.03, 92.51, 115.47 (d, $J_{CF} = 21.4$ Hz), 118.92 (d, $J_{CF} = 3.0$ Hz), 133.44 (d, $J_{CF} = 9.2$ Hz), 162.38 (d, $J_{CF} = 250.2$ Hz). ^{19}F-NMR ($CDCl_3$): δ -111.65 (dt, $J = 18.9$ Hz, $J = 5.4$ Hz).

17α-*(4-fluorophenylethynyl)-3,17β-estradiol* **10**. Yield: 94%. Melting point 85–88°C. ^{1}H-NMR ($CDCl_3$): 0.93 (s, 3H; 18-CH_3), 2.81 (m, 2H; 6α/6β-H), 6.56 (d, $J = 2.5$ Hz, 1H; 4-H), 6.63 (dd, $J = 8.6$ Hz, $J = 2.5$ Hz, 1H; 2-H), 7.00 (m, 2H; Ar–H), 7.16 (d, $J = 8.6$ Hz, 1H; 1-H), 7.42 (m, 2H; Ar–H). ^{13}C-NMR ($CDCl_3$): 12.86(18), 22.56(15), 26.20(11) 26.95(7), 29.19(8), 32.89(12), 39.04(16), 39.44(6) 43.33(9), 47.20(13), 49.33(14), 78.54(17), 82.96(C≡C), 94,72(C≡C), 112.70(2), 114.88(4), 115.64 (d, $J_{CF} = 22.0$ Hz), 119.32, 126.05(1), 130.21(10), 133.42 (d, $J_{CF} = 8.3$ Hz), 137.10(5), 154.87(3), 162.84 (d, $J_{CF} = 245.8$ Hz). ^{19}F-NMR ($CDCl_3$): -111.48 (quint. $J = 5.4$ Hz). Analytically calculated for $C_{26}H_{27}FO_2$: C, 79.97; H, 6.97. Found: C, 80.06; H, 6.84. LRMS (ESI positive) 413.0 [M + Na].

17α-*(phenylethynyl)-3,17β-estradiol* **11**. Yield: 96%. Melting point 155-157°C. ^{1}H-NMR ($DMSO_{d6}$): 0.81 (s, 3H; CH_3), 2.70 (m, 2H; 6α/6β-H), 5.46 (s, 1H; 17-OH), 6.43 (d, $J = 2.5$ Hz, 1H; 4-H), 6.51 (dd, $J = 8.6$ Hz, $J = 2.5$ Hz, 1H; 2-H), 7.06 (d, $J = 8.6$ Hz, 1H; 1-H), 7.34–7.37 (m, 3H; Ar–H), 7.38–7.42 (m, 2H; Ar–H), 8.99 (s, 1H; 3-OH), ^{13}C-NMR ($DMSO_{d6}$): 12.83(18), 22.51(15), 26.16(11), 26.91(7), 29.13(8), 32.84(12), 38.84(16), 39.21(6), 43.31(9), 47.17(13), 49.29(14), 78.50(17), 83.94(C≡C), 94.97(C≡C), 112.65(2), 114.81(4), 122.85, 126.03(1), 128.06, 128.53, 130.40, 131.11(10), 137.04(5), 154.82(3). Analytically calculated for $C_{26}H_{28}O_2$: C,83.83; H,7.58. Found: C,83.21; H,7.32. LRMS (ESI positive) 373.5 [M + H].

17α-*(4-iodophenylethynyl)-3,17β-estradiol* **12**. Yield: 59%. Melting point 219–222°C. ^{1}H-NMR ($DMSO_{d6}$): 0.79 (s, 3H; CH_3), 2.69 (m, 2H; 6α/6β-H), 5.48 (s, 1H; 17-OH), 6.42 (d, $J = 2.2$ Hz, 1H; 4-H), 6.50 (dd, $J = 8.3$ Hz, $J = 2.2$ Hz, 1H; 2-H), 7.05 (d, $J = 8.3$ Hz, 1H; 1-H), 7.19 and 7.71 (2d of AA′BB′system, $J = 8.3$ Hz, 4H; Ar–H), 8.97 (s, 1H; 3-OH), ^{13}C-NMR ($DMSO_{d6}$): 12.88(18), 22.58(15), 26.20(11), 26.98(7), 29.20(8), 32.92(12), 38.73(16), 39.19(6), 43.35(9), 47.25(13), 49.39(14),

78.62(17), 83.25(C≡C), 94.58(C≡C), 96.51, 112.73(2), 114.91(4), 122.37, 126.10(1), 130.20, 132.96(10), 137.13(5), 137.44, 154.89(3). Analytically calculated for $C_{26}H_{27}O_2I$: C, 62.66; H, 5.46. Found: C, 62.61; H, 5.55. LRMS (ESI positive) 520.9 [M + H].

17α-*(4-fluorophenylethynyl)-3,17β-estradiol-3-methylether* **13**. Yield: 78%. Melting point 52–54°C. ^{1}H-NMR ($CDCl_3$): 0.94 (s, 3H; 18-CH_3), 2.87 (m, 2H; 6α/6β-H), 3.78 (s, 3H; OCH_3), 6.65 (d, J = 2.9 Hz, 1H; 4-H), 6.74 (dd, J = 8.6 Hz, J = 2.9 Hz, 1H; 2-H), 7.01 (m, 2H; Ar–H), 7.23 (d, J = 8.6 Hz, 1H; 1-H), 7.45 (m, 2H; Ar–H), ^{13}C-NMR ($CDCl_3$): 12.86(18), 22.89(15), 26.44(11), 27.23(7), 29.81(8), 33.06(12), 39.01(16), 39.44(6), 43.62(9), 47.57(13), 49.76(14), 55.15(3-OCH_3), 80.27(17), 85.14(C≡C), 92.68(C≡C), 111.45(2), 113.74(4), 115.66 (d, J_{CF} = 22.0 Hz), 118.99, 126.59(1), 132.70(10), 133.80 (d, J_{CF} = 8.3 Hz) 138.19(5), 157.66(3), 161.44 (d, J_{CF} = 248,1 Hz). ^{19}F-NMR ($CDCl_3$): -111.42 (m). Analytically calculated for $C_{27}H_{29}O_2F$: C, 80.17; H, 7.23. Found: C, 79.91; H, 6.93. LRMS (ESI positive) 426.9 [M + H].

Radiochemical syntheses

No-carrier-added aqueous [^{18}F]fluoride ion was produced in a 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 (300–700 MBq) was accomplished as described by Coenen *et al.*[23] with Kryptofix® 2.2.2 and K_2CO_3 in a conical vial and azeotropically removing water with acetonitrile in a stream of nitrogen. Finally the dried [^{18}F]KF was resolubilized in an appropriate volume of anhydrous solvent (acetonitrile, DMSO or DMF). HPLC analyses were carried out with a Phenomenex RP 18 column (LUNA C18(2) 4.6 × 250 mm, 5 μm) using an indicated isocratic eluent with a flow rate of 1.0 ml/min. The products were monitored by UV detector L4500 (Merck, Hitachi) at 254 nm and by γ-detection with a scintillation detector GABI (X-RAYTEST). For radio-TLC detection a BAS 2000 scanner (FUJIX) was used.

General procedure for the synthesis of 4-[^{18}F]fluoroiodobenzene

The dried [^{18}F]KF (300–700 MBq) in 1 ml of solvent (acetonitrile, DMF or DMSO) was heated in a sealed conical vial in the presence of 4,4′-diiododiphenyliodonium salts **2**, **3** or **5** (20 mg) by means of an oil bath at the indicated temperatures for 40 min or mirowaved for 5 min at

120 W. The mixture was diluted with water (10 ml) and passed through a Chromafix RP18 cartridge (200 mg, pre-conditioned with 5 ml ethanol and 10 ml water). The cartridge was washed with water (5 ml), dried with a stream of nitrogen and the 4-[^{18}F]fluoroiodobenzene (50–150 MBq) was eluted from the cartridge using THF (2 ml). Radio-TLC: $R_f = 0.4-0.5$, hexane). HPLC-analysis: acetonitrile/water (80/20), $t_R = 6.5$ min, acetonitrile/water (70/30), $t_R = 9.8$ min.

General procedure for the Sonogashira reaction with 4-[^{18}F]fluoroiodobenzene

A vial containing the terminal alkyne **6**, **7** or **8** (3 mg), CuI (3 mg), $Pd[PPh_3]_4$ (3 mg), triethylamine (1 ml) and 4-[^{18}F]fluoroiodobenzene (50–150 MBq in 2 ml THF) was sealed and heated in an oil bath (110°C) for 20 min. After cooling aliquots were taken for radio-HPLC analysis.

4-*[^{18}F]fluorophenylethynyl-cyclopentylcarbinol [^{18}F]-9*. Yield: 85%, radio-HPLC-analysis: acetonitrile/water (70/30), $t_R = 3.1$ min.

17α-*(4-[^{18}F]fluorophenylethynyl)-3,17β-estradiol [^{18}F]-10*. Yield: 65–88%, radio-HPLC-analysis: acetonitrile/water (70/30), $t_R = 9.1$ min.

17α-*(4-[^{18}F]fluorophenylethynyl)-3,17β-estradiol-3-methylether [^{18}F]-***13***. Yield: 34–64%. radio-HPLC-analysis: acetonitrile/water (80/20), $t_R = 14.2$ min.

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