# Synthesis of 2-[$^{18}$F]Fluoroestradiol, a Potential Diagnostic Imaging Agent for Breast Cancer: Strategies to Achieve Nucleophilic Substitution of an Electron-Rich Aromatic Ring with [$^{18}$F]F$^-$

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To improve the pharmacokinetics of fluorine-18 labeled estrogens to be used as receptor-based imaging agents for the identification and staging of estrogen-receptor-positive breast carcinoma, we wanted to synthesize 2-[$^{18}$F]fluoroestradiol. This compound has high affinity for the estrogen receptor and also binds very well to sex hormone binding globulin, a protein thought to protect estrogens from metabolism and deliver them to target tissues. We anticipated that this compound might have increased tumor uptake and reduced uptake in the liver. The synthesis of a [$^{18}$F]fluoroaryl estrogen at the high specific activity, no-carrier-added level requires the use of [$^{18}$F]F$^-$ as a precursor. Several strategies were explored for the synthesis of a [$^{18}$F]fluoroaryl estrogen. The synthesis of 2-[$^{18}$F]fluoroestradiol was eventually achieved by [$^{18}$F]fluoride ion displacement of a trimethylammonium leaving group at C-2 of an estrogen, with additional activation being provided by a 6-keto group which was subsequently removed by reduction. Incorporation yields of fluorine-18 were between 20% and 50%. The potential of this new radiopharmaceutical as an imaging agent is being evaluated in an appropriate animal model.

## I. Introduction

The level of estrogen receptors (ER) in human breast carcinoma has been shown to be a significant prognostic indicator for the disease and is used to guide the selection of the most appropriate therapeutic regimen for breast cancer patients.[1] Normally, the ER concentration in a breast tumor is determined by in vitro ligand binding or immunoassay of a tumor biopsy sample.[2] Limitations of these assays,[3] coupled with the search for noninvasive diagnostic methods, have prompted the synthesis and evaluation of radiolabeled estrogens as potential tracers for the in vivo assessment of tumor ER concentration by imaging methods.[4] The most promising agent studied to date is 16α-[$^{18}$F]fluoroestradiol (FES). In human studies, the uptake of radiolabeled FES into breast tumors, as measured by positron emission tomography (PET), correlates closely with the ER concentration measured by in vitro ligand binding assays.[5,6] Tumor uptake of FES also appears to be a significant predictor of the success of hormone therapy.[7,8] Despite the preliminary success of FES, however, an imaging agent with higher tumor-to-background-tissue activity ratios is desirable, as it would extend the utility of this agent to smaller tumors and lower ER levels.

In an attempt to increase the tumor-to-blood uptake ratios, second generation imaging agents related to FES were designed to have reduced binding to serum proteins.[9,10] In this design paradigm, high binding affinity for sex hormone binding globulin (SHBG) in particular was to be avoided, because it was believed that binding to this protein rendered the imaging agent unavailable for binding to ER.[11] However, recent evidence suggests that SHBG actually delivers estrogens to ER-rich tissues, while protecting them from metabolism,[12−17] suggesting that high binding affinity of an estrogen-based imaging agent for this protein may in fact be desired. Empirical observation has supported this theory, as an agent (16β-

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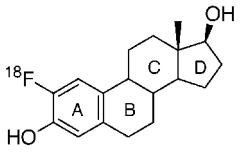
[18F]fluoromoxestrol or β-FMOX) which was designed to possess low relative binding affinity for SHBG (RBA = 0.037% vs estradiol = 100%)[19] performed poorly in imaging biopsy-confirmed ER+ human breast carcinoma compared to FES,[18] which has a 260-fold greater affinity (RBA = 9.5%)[19] for SHBG than that of β-FMOX. It is equally notable that in vivo evaluation in rats showed β-FMOX to be superior to FES in terms of target-to-blood activity ratio.[10] However, rats do not possess SHBG and are therefore a poor model for predicting the behavior of these compounds in humans.[20−22]

To evaluate the potentially beneficial role of SHBG binding in the biodistribution of ER-binding radiopharmaceuticals, we became interested in preparing an imaging agent that had high binding affinity for both ER and SHBG. Estradiol substituted with fluorine-18 on the aromatic A-ring at the 2-position, 2-[18F]fluoroestradiol (**1**, 2-$FE_2$), provides an agent with high affinity for both



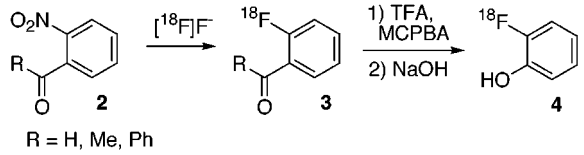

2-[18F]Fluoroestradiol (2-$FE_2$) (**1**)

ER (RBA = 87% vs estradiol = 100%)[23] and SHBG (RBA = 3700%).[24] C-2 substitution with larger halogens such as bromine also provides a steroid with high affinity for SHBG, but the bulk of the larger halogen markedly reduces binding to ER.[23] Additionally, use of the positron-emitting fluorine-18 isotope allows for tumor imaging using PET. The challenge inherent in the synthesis of this steroid imaging agent arises from the requirement for radiolabeling it at high specific activity, as is needed for receptor-based imaging.[23] For practical purposes, this means that radiolabeling needs to be based on [18F]-fluoride ion ([18F]F−), a reagent which is conveniently available at the no-carrier-added level (not mixed with the stable isotope, fluorine-19). However, [18F]F− is a relatively poor nucleophile,[27,28] and its incorporation into the electron-rich phenolic A-ring of estradiol provides a formidable synthetic challenge. [18F]Fluorine ([18F]F+), an electrophile well-suited for labeling electron-rich aromatic rings, has only recently begun to be produced at specific activity levels sufficiently high for receptor-based imaging and is not presently a practical alternative.[11,25,26]

## II. Results and Discussion

A number of strategies have been developed for the incorporation of [18F]F− into an electron-rich aromatic ring.[27,29−37] However, few methods have proved to be useful for the synthesis of an *o*-fluorophenol at high specific activity, and none have been used for the preparation of a fluorine-18 labeled phenol of complex structure, such as **1**. We will describe four distinct approaches that we have investigated for the synthesis of **1**, the last of which was successful. Some of these approaches were studied only at the level of simpler model systems.

**Scheme 1**




R = H, Me, Ph

***o*-Nitrobenzaldehyde Route.** One group accomplished the synthesis of *o*-[18F]fluorophenol (**4**) itself, albeit in low overall yield, by [18F]F− displacement of the nitro group from an *o*-nitrobenzaldehyde or acetophenone precursor **2** (Scheme 1).[31] The corresponding *o*-[18F]fluoro carbonyl derivative **3** was then converted to **4** via a Baeyer−Villager oxidation, followed by alkaline hydrolysis.

Synthesis of the appropriate precursor to 2-[18F]fluoroestradiol (**1**) required for this approach was accomplished efficiently in four steps (Scheme 2). The phenolic hydroxyl group of estradiol (**5**) was selectively converted into the trifluoromethanesulfonate ester (triflate) **6** by treatment with *p*-nitrophenyltriflate.[38] The 17β-alcohol was then protected as the pivaloate ester (**7**) by treatment of triflate **6** with pivaloyl chloride. Palladium-catalyzed carbonylative coupling of triflate **7** in the presence of $Et_3$-SiH afforded aldehyde **8**. Nitration with $HNO_3/H_2SO_4$ provided only the desired 2- and 4-nitro isomers, **9a** and **9b**, respectively, with none of the 1-nitro isomer being formed. Although this might be considered somewhat suprising, considering the meta-directing nature of the aromatic aldehyde, in our work with A-ring substituted estrogens, we have found that many reactions at C-1 are often constrained, most likely by the great steric bulk of the C-11 methylene unit (E. Hostetler, unpublished).

Reaction of either of the nitro aldehydes **9a** or **9b** with either $^n$Bu$_4$N[18F]F ([18F]TBAF) or [18F]KF/[2.2.2]Kryptofix (K2.2.2) in DMSO at temperatures up to 150 °C failed to produce any fluorine-18 labeled product. RadioTLC analysis showed all radioactivity remained at the origin, indicating the activity remained in its original form as [18F]F− and thus did not incorporate. While it is not certain why the more complex *o*-nitrobenzaldehydes **9a**

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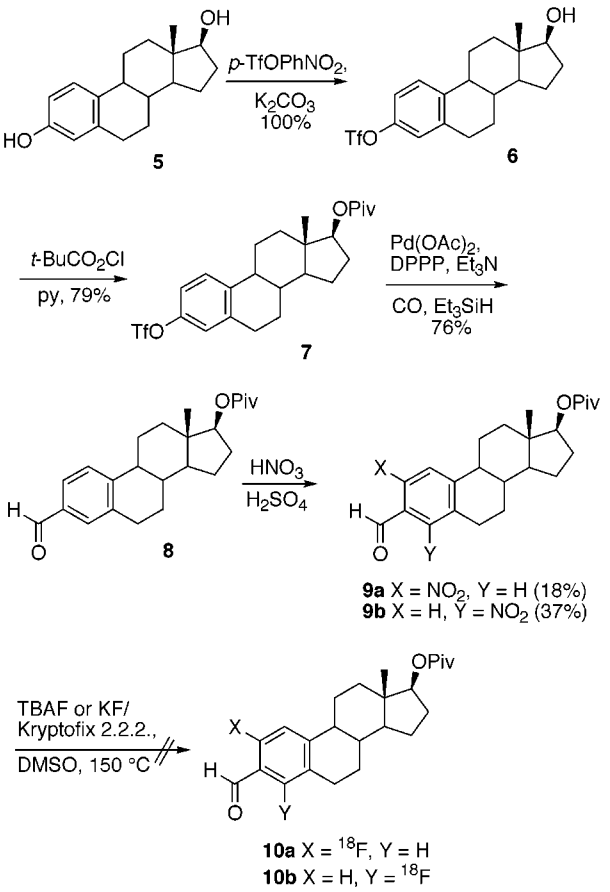
**Scheme 2**




and **9b** failed in the same reaction that succeeded with the simpler systems (**2**), the additional electron donation by the alkyl substituents at the meta and para positions of the estrogen systems (**9a** and **9b**) undoubtedly contributed to their reduced reactivity.

**Aryldiazosulfide Precursors.** From earlier work in our laboratories, there was precedent for the incorporation of fluoride ion into simple aromatic systems via the silver-promoted decomposition of para-substituted aryldiazosulfides, including reaction with the electron-rich *p*-methoxy-substituted derivative.[32] However, in these earlier studies, we were not able to achieve fluorine incorporation when a methoxy group was located ortho to the diazosulfide. We thought, perhaps, that by positioning an electron-withdrawing (activating) substituent para to the diazosulfide, we might counteract the detrimental effect of the ortho-electron-donating substituent, thereby facilitating the incorporation of fluoride ion into the ring. A model system was synthesized to test this strategy (Scheme 3).

Diazotization of aniline **11**[39] with $HBF_4/NaNO_2$ provided the stable diazonium tetrafluoroborate salt, which was not isolated but reacted in situ with thiophenol at neutral pH to form aryldiazosulfide **12**. This provided an aryldiazosulfide precursor in which the electron-donating nature of the *o*-methoxy group was balanced by the presence of an electron-withdrawing ketone situated at the para position.

Unfortunately, incorporation of fluorine from decomposition of diazosulfide **12** was never observed under a variety of conditions (Scheme 3). Different sources of $F^-$

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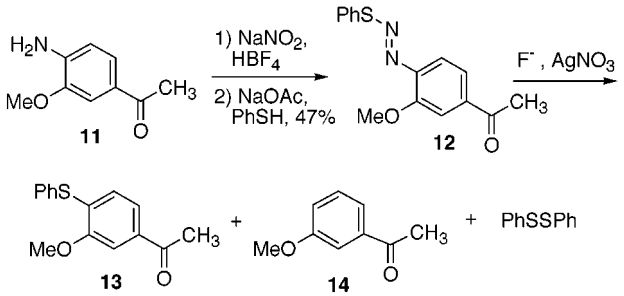
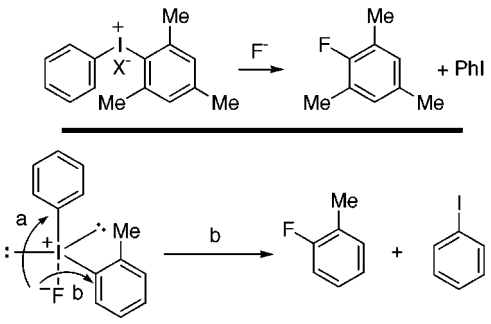
**Scheme 3**




**Scheme 4**




were used, including HF·pyridine, TBAF, and KF/K2.2.2. Varying the temperature from 0 °C to reflux in several different solvents, including benzene, toluene, and DMF, also failed to effect any incorporation of fluorine, as judged by $^{19}F$ NMR. The major products observed were those commonly seen from thermally or photochemically induced decomposition of aryldiazosulfides, including phenyl disulfide, the thiophenol coupled product (**13**), and the reduced aryldiazosulfide (**14**).[40] Because we had previously succeeded in effecting fluorinations by this approach in a simple *p*-methoxy-substituted model, it is likely that a nonelectronic factor is responsible for the lack of fluoride incorporation in this model system. For example, it is possible that the methoxy group is acting as a hydride donor, quenching the extremely reactive aryl cation produced upon decomposition of the aryl diazosulfide in an $S_N1$ manner.

**Aryliodonium Ion Precursors.** Recently, aryliodonium salts have been used as leaving groups in the nucleophilic substitution of simple unactivated aromatic systems by $[^{18}F]F^-$.[41] When an aryliodonium salt is used as a leaving group on an aromatic ring, the nucleophile has a choice of displacing either of the two arenes. Following the trend of $S_NAr$, the nucleophile always prefers attacking the less electron-rich arene in the case of para-substituted diaryliodonium salts.[42] However, in the case of ortho-substituted diaryliodonium salts, the ortho-substituted arene is preferentially attacked by the nucleophile, even if it is more electron-rich.[42] This preference increases further for doubly ortho-substituted arenes (Scheme 4, top).[41]

This "ortho effect" can be explained by examining the arrangement of the substituents around the proposed trigonal bipyramidal geometry of the transition state

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(41) Shah, A.; Pike, V. W.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, *13*, 2043−2046.

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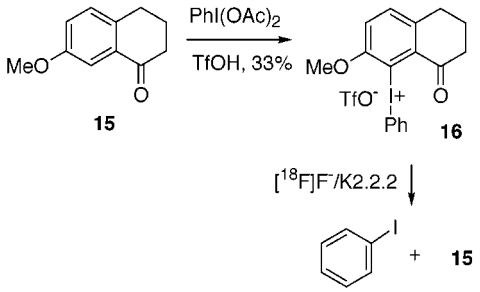
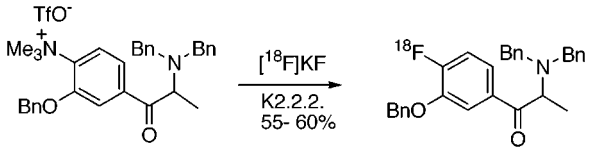
**Scheme 5**




**Scheme 6**



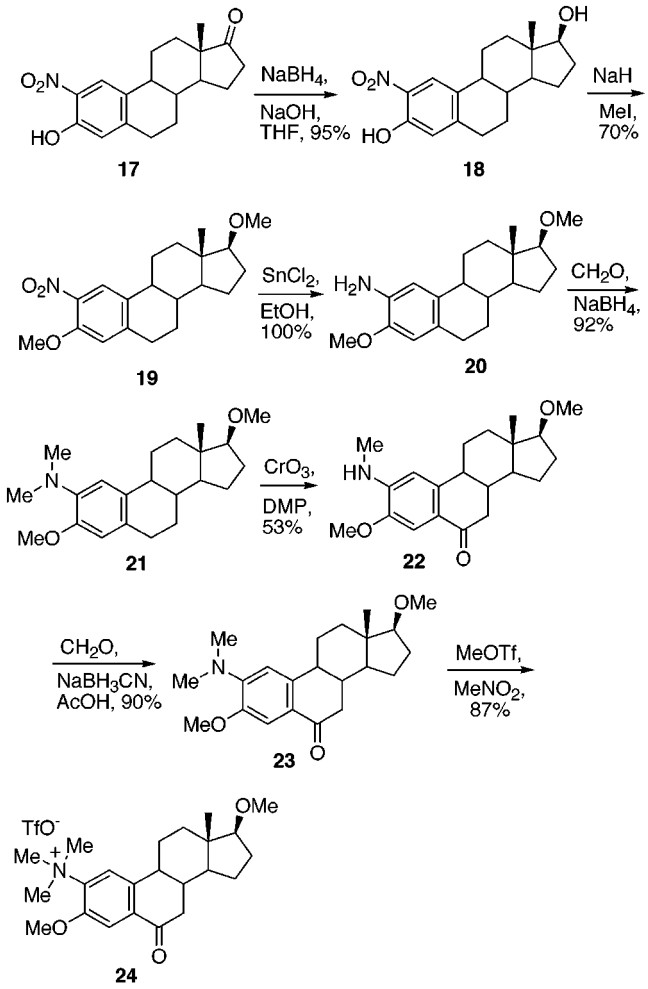

(Scheme 4, bottom).[42] The incoming nucleophile approaches along an axial trajectory, from which it is in proximity only to attack an equatorially disposed arene. Because the more bulky ortho-substituted arene prefers to occupy a less sterically congested equatorial position, with the less bulky arene occupying the other axial position, it is the more proximal ortho-substituted arene that undergoes substitution (i.e., trajectory b is preferred to a).

Because we wished to take advantage of this ortho effect in the synthesis of our target compound **1**, we constructed a simple model system (Scheme 5) with which we could study the reaction of [$^{18}$F]F$^-$ with potential precursors for **1**. Reaction of 7-methoxytetralone (**15**) with iodobenzene diacetate in triflic acid[43] formed the 8-substituted regioisomer **16** regioselectively. This system provides a nice mimic of the A and B rings of estradiol. The steroid-like half of the diaryliodonium salt is doubly ortho-substituted, which should favor the attack of the fluoride anion on the A-ring, according to the analysis above. The benzylic carbonyl group serves to activate the A-ring further toward substitution, because the methoxy group is strongly electron donating.

However, reaction of diaryliodonium salt **16** with [$^{18}$F]-TBAF or [$^{18}$F]KF/K2.2.2 in $CH_3CN$ or DMF at 100 °C did not produce any of the desired fluorinated product. Only starting material and reduced tetralone (**15**) were recovered. The formation of reduced arenes from reaction of [$^{18}$F]F$^-$ with diaryliodonium salts is consistent with published data.[41] Again, it is possible that other reactions, such as hydrogen atom donation by the methoxy group or solvent, are intervening in this more complex precursor, interrupting the fluoride displacement process.

**Activated Trimethylammonium Triflate Precursors.** The use of trimethylammonium triflate salts as leaving groups on aromatic rings has been widely utilized in fluoride ion nucleophilic aromatic substitution reactions.[44] Until recently, however, there was no precedent for the use of the trimethylammonium group to incorporate [$^{18}$F]F$^-$ ortho to a protected phenol. Ermert et al. were able to achieve good levels of incorporation in a system (Scheme 6) which we felt could be adapted to the synthesis of **1**.[45] This system requires the presence of an electron-withdrawing group para to the trimethylammonium group to provide sufficient activation of the aromatic ring for substitution. In the case of our desired target compound, this activating group must then be removed after the incorporation of the fluoride ion.

**Scheme 7**




Synthesis of the trimethylammonium salt precursor for 2-[$^{18}$F]fluoroestradiol (Scheme 7) began with the reduction of 2-nitroestrone[46] (**17**) by treatment with $NaBH_4$/NaOH.[46] This provided the 17$\beta$-hydroxy compound **18** with no competing reduction of the nitro group. Diol **18** was protected as the dimethyl ether **19**, and the aniline **20** was obtained quantitatively by reduction of the nitro group of **19** with $SnCl_2$/EtOH. Reductive methylation of aniline **20** with $NaBH_4/CH_2O$ afforded the *N*,*N*-dimethylamino derivative **21** in high yield. Treatment of dimethylamine **21** with $CrO_3$/DMP at −78 °C provided the 6-oxo compound **22** in moderate yield. Monodemethylation of the amine was concurrent with the oxidation, so *N*-methylamine **22** was remethylated using the mild Borch conditions[47] to provide *N*,*N*-dimethylamine **23**. Treatment of amine **23** with MeOTf in $MeNO_2$ provided trimethylammonium triflate salt **24** in 87% yield.

**Radiochemical Synthesis.** Upon treatment of the trimethylammonium salt **24** with [$^{18}$F]TBAF in DMSO

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(44) Haka, M. S.; Kilbourn, M. R.; Watkins, G. L.; Toorongian, S. A. *J. Labelled Compd. Radiopharm.* **1989**, *27*, 823−833.
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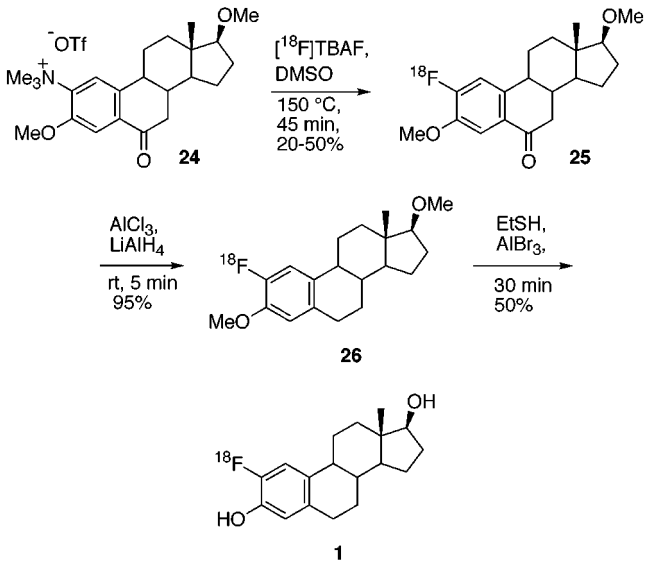
(47) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673−1676.

**Scheme 8**




at 150 °C for 45 min, we were successful in achieving levels of [$^{18}$F]fluoride incorporation between 20% and 50% (Scheme 8). Upon completion of the reaction, radioactivity which could not be accounted for (ca. 10−20% of total) was assumed to have been lost as [$^{18}$F]fluoromethane resulting from attack of [$^{18}$F]F$^-$ on one of the methyl groups of the trimethylammonium salt or as [$^{18}$F]fluorobutane from decomposition of [$^{18}$F]TBAF. A significant portion of the unincorporated radioactivity remained unreacted. The use of [$^{18}$F]KF/K2.2.2 did not afford higher incorporation yields. A specially designed microwave cavity has been shown to significantly improve yields while greatly reducing the time necessary to effect incorporation of a radiotracer in some related fluoride ion displacement reactions.[48] However, the use of this microwave cavity in place of heating at 150 °C in an oil bath did not facilitate fluoride incorporation.

The subsequent steps necessary to convert the fluorinated product to 2-[$^{18}$F]fluoroestradiol (**1**) proceeded as desired. Ketone **25** was quickly purified by passage through a short column of silica gel. Treatment with $LiAlH_4$ in the presence of anhydrous $AlCl_3$ in diethyl ether reduced the benzylic ketone to the corresponding hydrocarbon **26** in nearly quantitative yield within 5 min. The reaction was quenched, and the organic layer was separated and dried by passage through a silica gel plug. Deprotection of the dimethyl ether **26** was achieved upon reaction with anhydrous $AlBr_3$ in EtSH for 30 min, providing the target compound **1** in 50% yield. A slightly less polar byproduct, which did not correspond with the monodeprotected steroid, was readily removed by preparative HPLC.

The identity of **1** was confirmed by co-injection with an authentic sample of 2-fluoroestradiol[49] on both reversed-phase and normal-phase analytical HPLC systems; the radioactive peak coeluted with the UV peak of the standard in both cases. A competitive receptor-based assay[9] of the decayed product indicated an effective specific activity of 1110 Ci/mmol, which is greater than the 1000 Ci/mmol desired for a receptor-based imaging agent.[23]

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## III. Conclusion

Several strategies were investigated in our attempts to synthesize an *o*-[$^{18}$F]fluorophenol for the purpose of evaluating the potential breast cancer imaging agent 2-[$^{18}$F]fluoroestradiol (**1**). Only methods using [$^{18}$F]F$^-$ are practical due to the requirement of high specific activity fluorine-18. Only one literature synthesis uses a nucleophilic source of fluoride[50] to synthesize 2-fluoroestradiol, and this route was found to be unsuitable for use with [$^{18}$F]F$^-$.[37] The synthesis of **1** was eventually achieved by [$^{18}$F]F$^-$ displacement of an *o*-methoxy trimethylammonium triflate salt which was activated by a para-positioned carbonyl group. Incorporation yields ranged between 20% and 50%. Subsequent deoxygenation and deprotection provided **1** in overall yields (decay corrected) between 10% and 24%. The specific activity of the purified product was determined to be sufficiently high (1110 Ci/mmol) for study of a receptor-based system. The high affinity of **1** for SHBG, a serum protein believed to facilitate delivery and reduce metabolism of estrogens such as **1**, may provide an improved breast cancer imaging agent in terms of target-to-nontarget tissue uptake. In vivo evaluation of this compound is underway.

## Experimental Section

**General Methods.** $^1$H and $^{13}$C NMR spectra were obtained at 400 or 500 MHz. Mass spectra were obtained by one of the following ionization techniques: fast atom bombardment (FAB), electron impact (EI), chemical ionization (CI), or electrospray ionization (ESI). Melting points are uncorrected. All solvents were dried and distilled under $N_2$ prior to use. Flash chromatography was performed with Woelm silica gel (0.040−0.063 mm). All reactions were performed under a nitrogen atmosphere. For general radiochemical procedures, see ref 6. The radiochemical yields are decay corrected and refer to the amount of purified radioactive product as a percent of the initial reaction activity.

Unless described otherwise, the normal reaction workup procedure was as follows. Following the reaction quench, the aqueous layer was extracted with (solvent), and the combined organic layers were washed with water and brine and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration, and the filtrate was evaporated under reduced pressure to afford the crude product.

**3-Trifluoromethanesulfonyloxy-17$\beta$-hydroxy-estra-1,3,5-(10)-triene (6).** Estradiol (3.93 g, 14.4 mmol) was dissolved in DMF (50 mL). $K_2CO_3$ (3.99 g, 28.8 mmol) was added followed by *p*-nitrophenyl triflate (4.30 g, 15.9 mmol), and the reaction was stirred for 2 h at room temperature. Water (200 mL) and ether (75 mL) were added, and the aqueous layer was separated. The organic layer was washed with 1 N HCl, 1 N NaOH × 3, water, and brine and was dried ($MgSO_4$). The solvent was evaporated in vacuo to give 5.83 g (100%) of a pale yellow solid which was used without further purification: mp 123−125 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.78 (s, 3H), 1.17−1.58 (m, 7H), 1.71 (m, 1H), 1.86−2.37 (m, 5H), 2.87 (m, 2H), 3.73 (t, $J$ = 8.6 Hz, 1H), 6.96 (d, $J$ = 2.4 Hz, 1H), 7.00 (dd, $J$ = 8.5, 2.7 Hz, 1H), 7.33 (d, $J$ = 8.5 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 10.9, 22.9, 25.9, 26.6, 29.4, 30.3, 36.4, 38.1, 43.0, 43.9, 49.9, 81.5, 117.9, 118.6 (q, $J$ = 321 Hz), 121.0, 127.0, 139.4, 140.7, 147.3; MS (EI) 404 ($M^+$, 70); HRMS calcd for $C_{19}H_{23}F_3SO_4$ 404.126895, found 404.126804.

**3-Trifluoromethanesulfonyloxy-17$\beta$-trimethylacetoxy-estra-1,3,5(10)-triene (7).** Triflate **6** (2.72 g, 6.73 mmol) was dissolved in pyridine (10 mL) and cooled to 0 °C. Pivaloyl chloride (0.971 mL, 7.88 mmol) was added, and the reaction was stirred at room temperature for 24 h. Water (200 mL) and

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ether (75 mL) were added, and the aqueous layer was separated. The organic layer was washed with 1 N HCl, saturated $CuSO_4 \times 3$, water, and brine and was dried ($MgSO_4$). The organic layer was evaporated in vacuo, and the residue was recrystallized from EtOH to afford 2.60 g (79%) of fine, white needles: mp 101−104 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.85 (s, 3H), 1.21 (s, 9H), 1.20−1.60 (m, 7H), 1.78 (m, 1H), 1.90 (m, 2H), 2.25 (m, 3H), 2.89 (dd, $J$ = 8.8, 4.2 Hz, 2H), 4.66 (dd, 8.0, 7.8 Hz, 1H), 6.96, (d, $J$ = 2.7 Hz, 1H), 7.01 (dd, $J$ = 8.6, 1.6 Hz, 1H), 7.32 (d, $J$ = 8.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 12.0, 23.2, 25.9, 26.7, 27.1, 27.5, 29.5, 36.8, 37.9, 38.9, 43.0, 43.9, 49.8, 82.1, 118.1, 118.8 (q, $J$ = 321 Hz), 121.1, 127.2, 139.4, 140.8, 147.5, 178.6; MS (EI) 488 ($M^+$, 19). Anal. Calcd for $C_{24}H_{31}F_3SO_5$: C, 59.00; H, 6.40. Found: C, 58.87; H, 6.44.

**3-Carboxy-17$\beta$-trimethylacetoxy-estra-1,3,5(10)-triene (8).** Triflate **7** (136 mg, 0.278 mmol) was dissolved in DMF (1.25 mL), and the solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times). $Pd(OAc)_2$ (3.6 mg, 0.008 mmol) and bis(diphenylphosphino)propane (dppp) (6.6 mg 0.008 mmol) were added, and the solution was heated to 70 °C. Carbon monoxide was rapidly bubbled through the yellow-brown solution until the color changed to black-brown and then was continued to bubble at a slow rate for a few additional minutes. $Et_3N$ (0.155 mL, 1.11 mmol) was added dropwise via syringe with stirring followed by the slow addition of $Et_3SiH$ (0.089 mL, 0.557 mmol) via syringe over 20 min. The reaction was stirred at 70 °C overnight and diluted with water (50 mL). The aqueous layer was separated; the organic layer was washed with 1 N HCl, water, saturated $NaHCO_3$, and brine and was dried ($MgSO_4$). The solvent was removed in vacuo to afford a crude oil. The excess $Et_3SiH$ was removed via high vacuum, and the residue was suspended in 3:1 $CH_2Cl_2$/hexanes and loaded onto a short silica gel column. The column was eluted with 3:1 $CH_2Cl_2$/hexanes, then 1:1 $CH_2Cl_2$/hexanes, and then $CH_2Cl_2$ to afford 78 mg (76%) of a white solid: mp 107−108 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.84 (s, 3H), 1.20 (s, 9H), 1.30−1.60 (m, 7H), 1.78 (m, 1H), 1.92 (m, 2H), 2.18−2.38 (m, 3H), 2.93 (dd, $J$ = 9.9, 6.6 Hz, 2H), 4.66 (t, $J$ = 7.9 Hz, 1H), 7.43 (d, $J$ = 8.0 Hz, 1H), 7.57 (s, 1H), 7.62 (d, $J$ = 8.0 Hz, 1H), 9.92 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 12.0, 23.3, 25.8, 26.9, 27.2, 27.5, 29.3, 36.9, 37.9, 38.9, 43.0, 44.7, 50.0, 82.1, 126.1, 127.1, 130.3, 134.1, 137.7, 147.7, 178.6, 192.4; MS (EI) 368 ($M^+$, 24); Anal. Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 77.84; H, 8.82.

**2-Nitro-3-carboxy-17$\beta$-trimethylacetoxy-estra-1,3,5(10)-triene (9a) and 4-Nitro-3-carboxy-17$\beta$-trimethylacetoxy-estra-1,3,5(10)-triene (9b).** Aldehyde **8** (336 mg, 0.913 mmol) was dissolved in concentrated $H_2SO_4$ (4 mL). The solution was cooled to 0 °C with an ice bath, and a solution of concentrated $HNO_3$ (0.056 mL) in concentrated $H_2SO_4$ (0.102 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 2 h. Water was added (20 mL), and normal workup (EtOAc) afforded a crude orange solid. Flash chromatography (compound was loaded onto column with $CH_2Cl_2$ and eluted with 4:1 hexanes/EtOAc) provided 139 mg (37%) of a yellow solid (**9b**) and 68 mg (18%) of a yellow solid (**9a**). Analytical samples were recrystallized from EtOH/petroleum ether to give fine yellow needles.

**9a**: mp 145.0−146.0 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.86 (s, 3H), 1.21 (s, 9H), 1.30−1.61 (m, 7H), 1.78 (m, 1H), 1.90−2.03 (m, 2H), 2.20−2.41 (m, 3H), 3.30 (m, 2H), 4.68 (dd, $J$ = 9.1 7.9 Hz, 1H), 7.64 (s, 1H), 8.03 (s, 1H), 10.40 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 12.0, 23.2, 25.7, 26.4, 27.2, 27.5, 29.4, 36.6, 37.5, 38.9, 42.9, 44.3, 49.8, 81.9, 121.9, 128.7, 129.9, 144.4, 147.4, 147.5, 178.6, 188.6; MS (EI) 413 ($M^+$, 47); HRMS calcd for $C_{24}H_{31}NO_5$ 413.220223, found 413.219949.

**9b**: mp 211.0−212.0 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.86 (s, 3H), 1.21 (s, 9H), 1.30−1.61 (m, 7H), 1.78 (m, 1H), 1.90−2.03 (m, 2H), 2.23 (m, 1H), 2.35 (m, 2H), 2.81 (m, 2H), 4.68 (dd, $J$ = 9.2, 7.9 Hz, 1H), 7.60 (d, $J$ = 8.1 Hz, 1H), 7.73 (d, $J$ = 8.1 Hz, 1H), 9.88 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 12.0, 23.2, 25.8, 26.0, 27.2, 27.5, 36.7, 37.1, 38.9, 42.9, 44.9, 49.8, 81.8, 124.6, 127.7, 128.3, 129.0, 150.0, 150.7, 178.6, 187.0; MS (EI) 413 ($M^+$, 3); HRMS calcd for $C_{24}H_{31}NO_5$ 413.220223, found 413.219570.

**3-Methoxy-4-phenylsulfidediazoacetophenone (12).** To a solution of **11** (74 mg, 0.448 mmol) in EtOH (2 mL) cooled by an ice−acetone bath was added 10% $HBF_4$ (2.0 mL) dropwise. A solution of $NaNO_2$ (34 mg, 0.493 mmol) in water (0.5 mL) was added dropwise, and the solution was stirred at 0 °C for 1 h. The reaction vessel was covered with aluminum foil so that no light could penetrate, and a solution of thiophenol (51 $\mu$L, 0.493 mmol) in EtOH (1 mL), cooled to 0 °C, was added followed by 25% aqueous NaOAc (cooled to 4 °C) until the solution was neutral. Cold dioxane was added to redissolve the oil which had separated out of the solution, and the bright orange reaction was stirred at 0 °C for 30 min. The reaction was diluted with water and extracted with ether. The ether layer was separated and dried ($Na_2SO_4$), and the solvent was removed in vacuo at room temperature, with the flask covered with aluminum foil to keep out light. The resulting red oil was purified by flash chromatography to yield a bright yellow oil (60 mg, 47%) which solidified upon refrigeration: mp 72−75 °C (dec) $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.60 (s, 3H), 4.02 (s, 3H), 7.28 (d, $J$ = 8.5 Hz, 1H), 7.46 (m, 4H), 7.63 (d, $J$ = 1.6 Hz, 1H), 7.71 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 26.7, 56.3, 111.8, 117.0, 121.4, 129.1, 129.2, 130.4, 134.4, 138.8, 144.1, 154.8, 197.2; MS (CI) 273 ($M^+$ + H, 28), 245 ($M^+$ + H − 28 ($N_2$), 100); Anal. Calcd for $C_{15}H_{14}O_2N_2S$ C, 62.92; H, 4.93. Found: C, 62.66; H, 5.04.

**7-Methoxy-8-phenyliodotriflate tetralone (16).** To a suspension of iodobenzene diacetate (612 mg, 1.9 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C was added trifluoromethanesulfonic acid (0.336 mL, 3.8 mmol). The ice bath was removed, and the suspension was stirred for 1 h, during which time the reaction became homogeneous. The bright yellow solution was cooled to 0 °C, and a solution of 7-methoxytetralone (**15**) (352 mg, 2.0 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise with stirring. The brown reaction was stirred 10 h, after which the solvent was removed. The dark viscous residue was triturated with ether and filtered. The gray solid was washed with ether and recrystallized from $CH_2Cl_2$/ether to give 353 mg (33%) of light gray needles: mp 175.0−176.0 °C; $^1$H NMR (400 MHz, $d_6$-acetone) $\delta$ 2.21 (p, $J$ = 6.6 Hz, 2H), 2.86 (t, $J$ = 6.6 Hz, 2H), 3.04 (t, $J$ = 6.1 Hz, 2H), 3.37 (s, 3H), 7.21 (d, $J$ = 8.5 Hz, 1H), 7.47 (t, $J$ = 7.8 Hz, 2H), 7.55 (d, $J$ = 8.3 Hz, 1H), 7.63 (t, $J$ = 7.5 Hz, 1H), 7.98 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz, $d_6$-acetone) $\delta$ 22.4, 28.8, 37.7, 56.1, 98.5, 114.9, 119.8, 131.3, 131.5, 132.1, 134.9, 135.6, 141.5, 157.1, 199.6; MS (FAB) 379 ($M^+$, 32). Anal. Calcd for $C_{18}H_{16}O_5F_3IS$ C, 40.93; H, 3.05. Found: C, 40.62; H, 3.12.

**2-Nitroestra-1,3,5(10)-triene (18).** 2-Nitroestrone[46] (3.50 g, 11.1 mmol) was dissolved in THF (275 mL) and added dropwise to a stirred solution of $NaBH_4$ (6.72 g, 178 mmol), 1 N NaOH (44 mL), $H_2O$ (33 mL), and THF (220 mL). The mixture was refluxed for 30 min and cooled to 0 °C, and 1 N HCl was added with stirring until the reaction was acidic. The THF was removed in vacuo, and the aqueous portion was extracted with EtOAc. The extracts were dried ($MgSO_4$) and evaporated to provide 3.9 g (95%) of a yellow solid which was used without further purification: mp 168−170 °C (lit.[46] 169−171 °C) $^1$H NMR (400 MHz, $d_6$-DMSO), $\delta$ 0.65 (s, 3H), 1.02−2.25 (m, 13H), 2. 78 (m, 2H), 3.50 (t, $J$ = 8.1 Hz, 1H), 4.53 (bs, 1H), 6.81 (s, 1H), 7.73 (s, 1H); MS (EI, 70 eV) 317 ($M^+$, 84), 258 (100).

**2-Nitro-3,17$\beta$-dimethoxy-estra-1,3,5(10)-triene (19).** Diol **18** (1.07 g, 3.40 mmol) was dissolved in DMF (20 mL). Sodium hydride powder (632 mg of a 60% dispersion in mineral oil, 15.8 mmol) was washed with hexanes 3 times to remove any oil and was added to the reaction. Methyl iodide (1.9 mL, 31.5 mmol) was added, and the reaction was stirred for 3 h. The reaction was quenched by addition of MeOH (10 mL) followed by addition of water (100 mL). Normal workup (ether) provided 1.21 g of a crude solid. Recrystallization from EtOH/$H_2O$ afforded 816 mg (70%) of a yellow solid: mp 205−207 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.77 (s, 3H), 1.20−2.24 (m, 13H), 2.89 (m, 2H), 3.30 (t, $J$ = 8.2 Hz, 1H), 3.36 (s, 3H), 3.90 (s, 3H), 6.75 (s, 1H), 7.80 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 11.5, 23.0, 26.2, 26.7, 27.7, 30.0, 37.7, 38.1, 43.1, 43.4, 50.1, 56.4, 57.9, 90.6, 113.5, 123.1, 133.1, 137.2, 144.8, 151.0; MS

(EI) 345 ($M^+$, 5), 205 (100). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.30; H, 8.00; N, 4.06.

**2-Amino-3,17$\beta$-dimethoxy-estra-1,3,5(10)-triene (20).** The nitro dimethyl ether **19** (1.11 g, 3.22 mmol) was dissolved in EtOH (150 mL). $SnCl_2 \cdot 2H_2O$ (3.63 g, 16.1 mmol) was added, and the reaction was stirred at 70 °C for 12 h. The reaction was diluted with water (100 mL) and saturated $NaHCO_3$ (100 mL). Normal workup (EtOAc) afforded 1.0 g (100%) of a yellow foam which was used without further purification. An analytical sample was recrystallized from $CH_3CN$ to give pale yellow needles: mp 130−131 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.80 (s, 3H), 1.18−1.60 (m, 7H), 1.70 (m, 1H), 1.88 (m, 1H), 2.04−2.25 (m, 4H), 2.74−2.85 (m, 2H), 3.32 (t, $J$ = 8.2 Hz, 1H), 3.40 (s, 3H), 3.67 (s, 2H), 3.83 (s, 3H), 6.52 (s, 1H), 6.69 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 11.6, 23.1, 26.6, 27.5, 27.8, 29.3, 38.2, 38.7, 43.3, 44.0, 50.3, 55.5, 57.9, 90.9, 111.0, 112.4, 126.5, 132.6, 133.8, 145.7; MS (EI), 315 ($M^+$, 100). Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.17; H, 9.36; N, 4.63.

**2-*N*,*N*-Dimethylamino-3,17$\beta$-dimethoxy-estra-1,3,5(10)-triene (21).** Aniline **20** (100 mg, 0.317 mmol) was dissolved in THF (5 mL), and finely crushed $NaBH_4$ (168 mg, 4.43 mmol) was added. In a separate flask containing aqueous 38% $CH_2O$ (0.5 mL, 6.0 mmol) was added aqueous $H_2SO_4$ (0.4 mL of 3.0 M, 0.13 mmol). This solution was cooled to 0 °C with an ice bath, and the slurry of the aniline **20** and $NaBH_4$ was added in portions, causing vigorous evolution of gas. The reaction was stirred for 1 h at room temperature, after which methanol (10 mL) and water (50 mL) were added. Normal workup (ether) afforded 100 mg (92%) of a crude white solid which was used without further purification. An analytical sample was recrystallized from MeOH to give white needles: mp 92−93 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.79 (s, 3H), 1.20−1.60 (m, 7H), 1.70 (m, 2H), 1.90 (m, 1H), 2.06 (m, 1H), 2.21 (m, 1H), 2.30 (m, 1H), 2.76 (s, 6H), 2.82 (m, 2H), 3.32 (t, $J$ = 8.2 Hz, 1H), 3.38, (s, 3H), 3.85 (s, 3H), 6.57 (s, 1H), 6.90 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 11.6, 23.0, 26.6, 27.4, 27.8, 29.4, 38.1, 38.7, 43.2, 43.6 × 2, 44.2, 50.3, 55.3, 57.9, 90.8, 111.4, 115.4, 130.7, 132.0, 140.1, 150.5; MS (EI) 343 ($M^+$, 100). Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 77.15; H, 9.79; N, 4.17.

**2-*N*-Methylamino-6-oxo-3,17$\beta$-demethoxy-estra-1,3,5-(10)-triene (22).** Dry $CrO_3$ (225 mg, 2.25 mmol) was suspended in $CH_2Cl_2$ and cooled to −20 °C in a dry ice/$CCl_4$ bath. 3,5-Dimethylpyrazole (211 mg, 2.19 mmol) was added, and the suspension was stirred for 1 h until homogeneous. The solution was cooled to −78 °C, amine **21** (75 mg, 0.219 mmol) was added as a solution in $CH_2Cl_2$, and the reaction was stirred for 5 min. The reaction was applied directly to the top of a silica gel column and eluted with hexanes/EtOAc (2:1) to afford 40 mg (53%) of a yellow foamy solid. An analytical sample was obtained by recrystallization from $CH_3CN$ to give pale yellow prisms: mp 197.0−198.0 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.79 (s, 3H), 1.20−2.44 (m, 13H), 2.61 (dd, $J$ = 16.7, 3.6 Hz, 1H), 2.91 (d, $J$ = 4.4 Hz, 2H), 3.29 (t, $J$ = 8.3 Hz, 1H), 3.35 (s, 3H), 3.84 (s, 3H), 4.82 (bs, 1H), 6.42 (s, 1H), 7.40 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 11.2, 22.7, 25.4, 27.4, 29.5, 37.4, 39.9, 42.8, 43.0, 43.4, 50.1, 55.5, 57.7, 90.2, 103.4, 106.3, 121.1, 143.2, 144.1, 144.7, 196.2; MS (EI) 343 ($M^+$, 100); HRMS calcd for $C_{21}H_{29}NO_3$ 343.214744, found 343.214600. Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.37; H, 8.49; N, 4.01.

**2-*N*,*N*-Dimethylamino-6-oxo-3,17$\beta$-dimethoxy-estra-1,3,5(10)-triene (23).** The monomethylamine **22** (125 mg, 0.364 mmol) was dissolved in 7 mL THF/$CH_3CN$ (2:5). Formaldehyde (0.5 mL, 37% in $H_2O$) and $NaBH_3CN$ (69 mg, 1.09 mmol) were added with stirring. Glacial acetic acid was added periodically to maintain a slightly acidic pH. The reaction was stirred at 50 °C for 1 h, and water was added. Normal workup (ether) afforded a crude yellow solid. Purification by flash chromatography (2:1 hexanes/EtOAc) yielded 114 mg (88%) of a white solid: mp 118−120 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.79 (s, 3H), 1.20−1.70 (m, 6H), 1.83−2.12 (m, 3H), 2.17 (dd, $J$ = 17.0, 13.5 Hz, 1H), 2.33 (m, 1H), 2.42 (td, $J$ = 11.2, 4.5 Hz, 1H), 2.65 (dd, $J$ = 16.7, 3.4 Hz, 1H), 2.90 (s, 6H), 3.31 (t, $J$ = 8.3 Hz, 1H), 3.35 (s, 3H), 3.89 (s, 3H), 6.79 (s, 1H), 7.49 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 11.4, 22.8, 25.5, 27.5, 37.5, 40.0, 43.0, 43.1, 43.7, 50.2, 55.6, 57.9, 90.4, 108.8, 113.2, 125.7, 141.4, 147.4, 149.9, 197.0; MS (EI) 357 ($M^+$, 93); HRMS calcd for $C_{22}H_{31}NO_3$ 357.230394, found 357.230400. Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92. Found: C, 73.95; H, 8.75; N, 3.90.

**2-*N*,*N*,*N*-Trimethylammoniumtriflate-6-oxo-3,17-dimethoxy-estra-1,3,5(10)-triene (24).** *N*,*N*-Dimethylamine **23** (16 mg, 0.045 mmol) was dissolved in $CH_3NO_2$ (0.50 mL). Methyl trifluoromethanesulfonate (6.1 $\mu$L, 0.054 mmol) was added via syringe, and the reaction was stirred for 10 min. The solvent was evaporated, and the residue was dried under high vacuum to give 20 mg (87%) of trimethylammonium salt **24**, which was used without further purification: mp 127−129 °C; $^1$H NMR (500 MHz, $d_6$-acetone) $\delta$ 0.78 (s, 3H), 1.37 (dt, $J$ = 11.3, 6.0, 1H) 1.43−1.75 (5H), 1.93−2.12 (m, 3H), 2.37 (dd, $J$ = 17.0, 13.5 Hz, 1H), 2.52 (m, 1H), 2.66 (m, 2H), 3.30 (s, 3H), 3.34 (t, $J$ = 8.6 Hz, 1H), 3.96 (s, 9H), 4.19 (s, 3H), 7.79 (s, 1H), 7.95 (s, 1H); $^{13}$C NMR (500 MHz, $d_6$-acetone) $\delta$ 11.8, 23.4, 26.1, 28.2, 38.0, 40.7, 43.5, 43.8, 44.0, 50.5, 56.5, 57.4, 57.9, 90.8, 112.8, 120.7, 135.7, 138.2, 141.3, 151.6, 196.3; $^{19}$F NMR (400 MHz, $d_6$-acetone) $\delta$ −80.1; MS (ESI) 373 ($M^+$, 100).

**2-[$^{18}$F]Fluoroestradiol (1).** Approximately 200 mCi of [$^{18}$F]-fluoride was resolubilized by the addition of tetrabutylammonium hydroxide (2.88 $\mu$mol, 1.0 M in $H_2O$) to proton bombarded [$^{18}$O]$H_2O$. Water was removed by four azeotropic distillations at 110 °C with MeCN (0.5 mL) under a stream of $N_2$. The resulting [$^{18}$F]TBAF was transferred with DMSO (55 $\mu$L) to a 0.6 mL reactivial containing **24** (2 mg, 3.84 $\mu$mol). The reactivial was sealed with a Teflon-lined cap and heated at 150 °C for 45 min to effect incorporation. The reaction was diluted with ethyl acetate (300 $\mu$L) and applied to a silica "plug" (a Pasteur pipet with ca. 150 mg silica gel atop a Kimwipe plug) and eluted (7:3 hexanes/EtOAc) into a flask. Incorporation yields ranged from 20% to 50% ($n$ = 20).[51] Analysis of the product by radioTLC ($R_f$ = 0.29; 7:3 hexanes/EtOAc) indicated 100% radiochemical purity.

The eluent containing ketone **25** was evaporated in vacuo and diethyl ether (1 mL) and a stir bar were added to the flask. Upon addition of $AlCl_3$ (ca. 25 mg) the reaction developed a light green color. The flask was capped with a septa and stirred. $LiAlH_4$ (0.75 mL, 1.0 M in diethyl ether) was added dropwise via syringe, causing evolution of gas and disappearance of the green color. Complete reduction of the carbonyl was effected upon stirring for 5 min. The reaction was quenched by dropwise addition of EtOAc (1 mL) followed by 6 N HCl (300 $\mu$L) and water (2 mL). Analysis of the crude reaction by radioTLC ($R_f$ = 0.49; 7:3 hexanes/EtOAc) indicated 100% radiochemical purity. The aqueous layer was removed via pipet, and the organic layer was dried by elution through a silica plug (7:3 hexanes/EtOAc; 0.5 mL × 3) into a flask.

The eluent from the silica plug was removed in vacuo, and EtSH (300 $\mu$L) was added to the radioactive residue. Anhydrous $AlBr_3$ (ca. 50 mg) was added to an oven-dried flask containing EtSH (1.0 mL) and was stirred 10 min. The EtSH solution of dimethyl ether **26** was added to the flask via syringe. After 30 min of stirring at room temperature, the reaction was quenched by dropwise addition of 6 N HCl followed by addition of water (1.0 mL). Ether (3.0 mL) was added to extract the aqueous layer, which was then removed via pipet. The organic layer was evaporated in vacuo, and the residue was dissolved in $CH_2Cl_2$, applied to a $MgSO_4$ plug, and eluted with 1:1 $CH_2Cl_2$/hexanes (0.5 mL × 4). Extent of reaction was determined by radioTLC ($R_f$ = 0.17; 7:3 hexanes/EtOAc). Purification was performed on normal phase semi-

(51) It is of note that attempts to accomplish the transformation of **24** to **25** with unlabeled TBAF gave less than 5% of the unlabeled analogue of the fluoroproduct **25**. Fluorination reactions that are inefficient with respect to the organic reactant may still proceed in reasonable radiochemical yield when they are performed with tracer levels of fluorine-18 labeled precursors. In this case, the organic reactant is present in a vast excess, and the yield is based on the incorporation of fluorine-18 activity.

preparative HPLC (30% 1:19 2-propanol/$CH_2Cl_2$, 70% hexanes) using a silica column (Mag 9, 0.9 cm × 50 cm, Whatman) under isocratic conditions at 5 mL/min, and the eluent was monitored by UV (254 nm) and radioactivity (NaI/Tl) detection. Fractions containing the first major radioactive peak ($t_R$ = 33 min) were pooled, and an aliquot of **1** was co-injected with authentic nonradioactive 2-fluoroestradiol[49] on analytical HPLC to confirm the identity. Typical quantities of purified **1** ranged from 1 to 2 mCi starting with 200 mCi [$^{18}$F]$F^-$.

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