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An Efficient Route for the Preparation of a 21-Fluoro Progestin-16α,17α-Dioxolane, a High-Affinity Ligand for PET Imaging of the Progesterone Receptor

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Two different synthetic routes were explored for the synthesis of fluoro furanyl norprogesterone (FFNP) **1**, a high-affinity ligand for the progesterone receptor (PgR) that is being developed as a PET imaging agent for PgR-positive breast cancer. Both approaches proceed through a key intermediate, triol **5**. The first approach, starting from keto-ketal **2**, employed a dioxenyl group as a synthon for installing a corticosteroid side chain in keto-alcohol **4**. The second approach, starting from propargylic acetate **12b**, involved the application of a two-step method, a Pd(II)-catalyzed oxidative rearrangement followed by a base-catalyzed acetate rearrangement of the intermediate unsaturated acetate **13b**, to generate the requisite corticosteroid side chain in keto-acetate **14b**. This intermediate was further elaborated to the final product **1** via efficient dihydroxylation with potassium permangnate, furan acetalization with scandium triflate, and mesylation and fluorination reactions. The palladium-catalyzed route is considerably more efficient than the dioxene approach for the synthesis of key intermediate triol **5**, and the scandium triflate-catalyzed acetalization, in particular, led to a considerable improvement in the overall yield of the endo furan acetal alcohol **16a**. This route provides a major improvement in the overall yield of the final progestin target, FFNP **1**.

Introduction

Breast cancer is the number one cause of cancer-related deaths in middle-aged women,[1] yet many breast cancers can be successfully treated with the antiestrogens tamoxifen and raloxifene. Currently, monitoring the presence of estrogen receptor (ER) and progesterone receptor (PgR) in tumors is the best method for assessing the hormone responsiveness of breast cancer.[2−4] However, the methods currently used to determine the presence and concentration of ER and PgR in tumors (radioligand binding and immunoassays[5]) require tissue biopsy and are thus invasive. Determining the levels of these receptors noninvasively through radioligand imaging using positron emission tomography (PET) would have a number of advantages.

We have demonstrated that 16α-[^{18}F]fluoroestradiol (FES) is an effective breast tumor ER imaging agent.[6,7] It has been more difficult to develop PET imaging agents for PgR, however. 21-[^{18}F]Fluoro-16α-ethyl-19-norprogesterone, which showed excellent target tissue-selective distribution in rodents,[8] proved to be ineffective in humans because of its rapid reduction to the 20-dihydro progestin by a 20-dehydrogenase.[9,10]

To develop an imaging agent for PgR that would be less prone to the action of 20-dehydrogenases, we examined a number of progestin 16α,17α-ketals and acetals of aromatic carbonyl compounds,[11,12] known to be potent progestins in vivo.[11,13,14] We thought that their bulky substituents near the C-20 carbonyl group would slow

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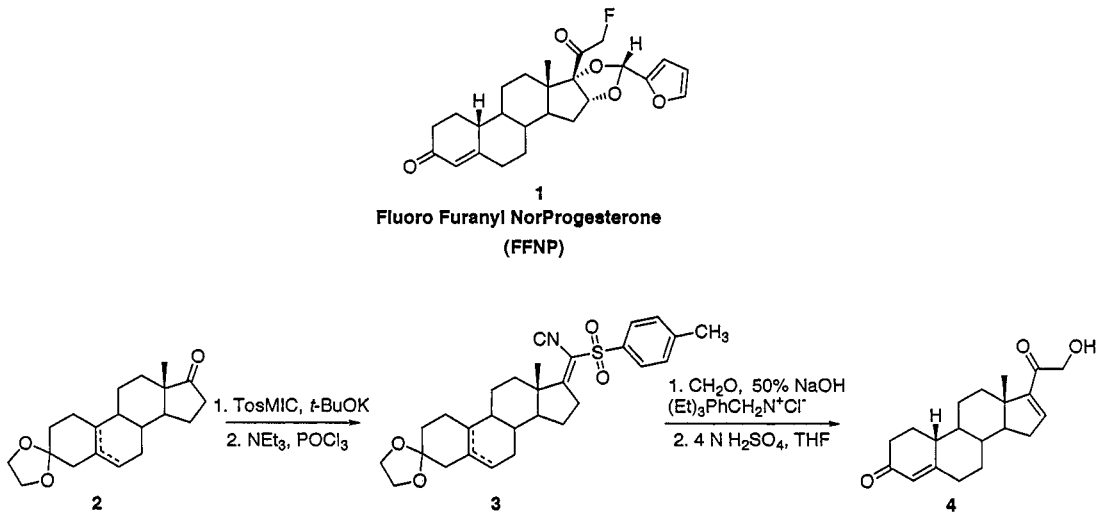
SCHEME 1



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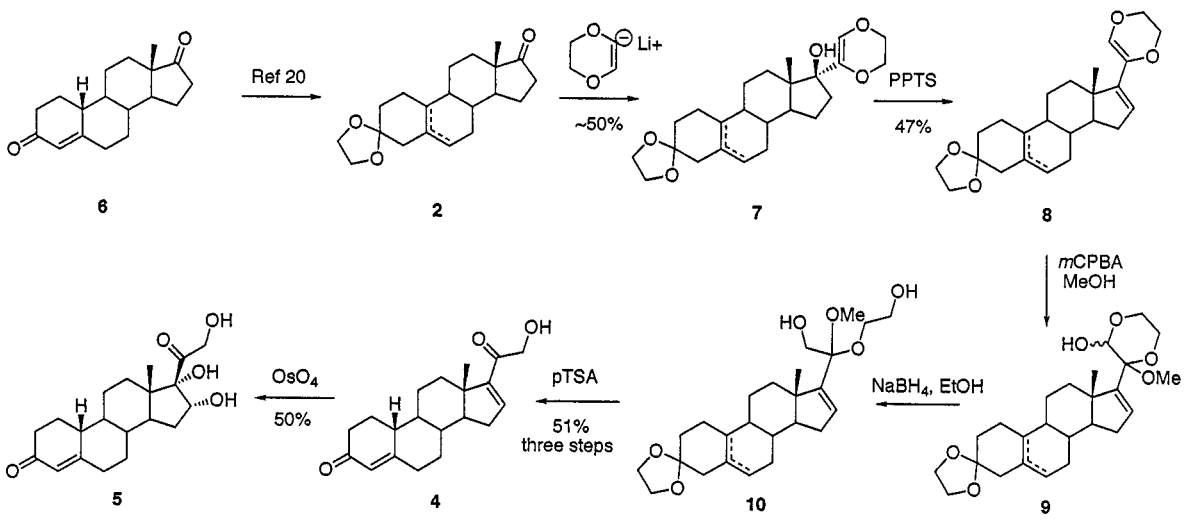

their reduction by the serum 20-dehydrogenases. The most promising progestin derivative for PET imaging we have found is Fluoro Furanyl Norprogesterone (FFNP) **1**,[12] and in preparation for tumor imaging trials in humans, a considerable quantity of this material was needed for sterility, activity, and toxicity studies.

The synthetic method that we originally reported for the preparation of FFNP **1**[11] was very challenging and unfortunately proved to be difficult to reproduce reliably and in satisfactory yields (Scheme 1). A particular problem was the conversion of keto-ketal **2** to toluenesulfonyl isocyanide **3** using a tosylmethyl isocyanide (TosMIC) method,[11,15−18] en route to the generation of the corticosteroid side chain in the intermediate keto-alcohol **4**. Despite several modifications that we made to improve the yield, we found that it was impractical to use this route to prepare FFNP **1** in large quantities.

In this report, we describe two different synthetic routes toward triol **5**, a key intermediate, that we explored to develop an alternative and more efficient synthetic route to FFNP **1**. We also cover significant improvements in other steps of the synthesis.

Results and Discussion

2,3-Dihydro-1,4-dioxene Approach to Key Triol 5. To synthesize triol **5**, the key intermediate for the synthesis of the FFNP **1**, the 1,4-dioxene addition approach of Fetizon et al.,[19] was investigated (Scheme 2), starting from commercially available dione **6**. The 3-ketone group in dione **6** was protected as the ethylene glycol ketal in three steps to furnish compound keto-ketal **2**.[20] The reaction of keto-ketal **2** with 1,4-dioxenyl-lithium at low temperatures furnished tertiary alcohol **7** in ~50% yield. The fact that nearly half of the starting material was recovered after this reaction suggested that the D-ring carbonyl group was undergoing enolization, a common problem with cyclopentanones. Efforts to in-

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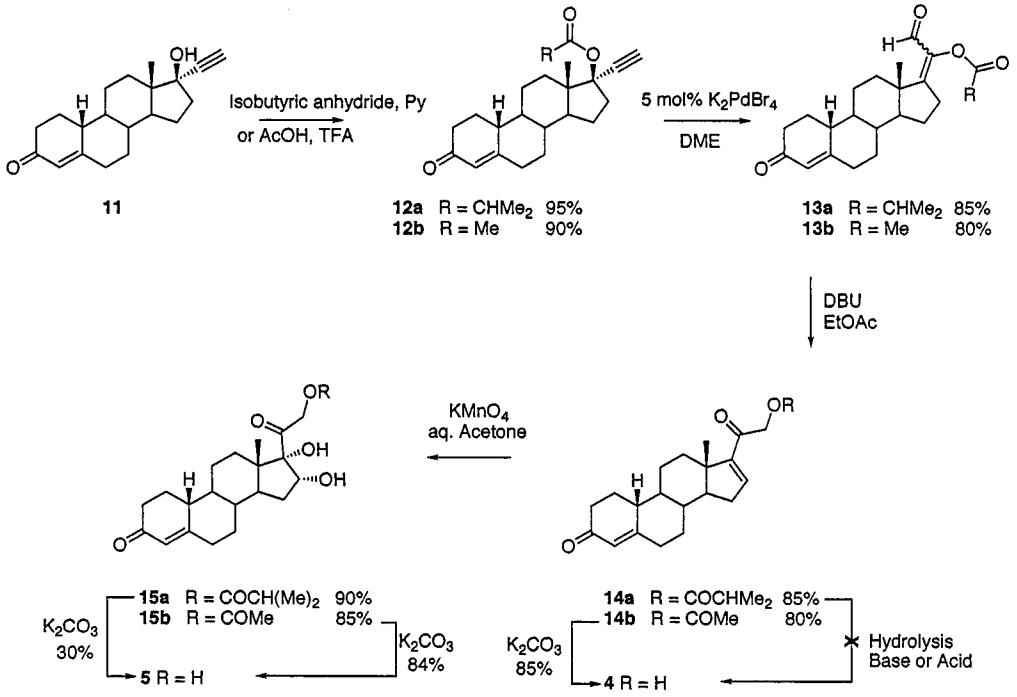
SCHEME 3



crease the yield in the 1,2-addition reaction by adding anhydrous cerium chloride to enhance the electrophilicity of the C-17 carbonyl were unsuccessful.

Dehydration of tertiary alcohol **7** furnished diene **8** in 47% yield. The more electron-rich double bond on the dioxenyl ring was then selectively epoxidized with 1 equiv of *m*-chloroperbenzoic acid (*m*CPBA) and the labile epoxide spontaneously solvolyzed to the hemiacetal-ketal **9**. This intermediate was reduced to the ketal **10**, which was hydrolyzed with *p*-toluenesulfonic acid in moist acetone, to obtain the desired product keto-alcohol **4** (Scheme 2). Dihydroxylation of the $\Delta^{16(17)}$ double bond in keto-alcohol **4** with a stoichiometric amount of osmium tetroxide in pyridine[11] furnished the requisite key intermediate triol **5** in 55% yield. The less hindered $\Delta^{16(17)}$ double bond undergoes oxidation in preference to the $\Delta^{4(5)}$ double bond.

Despite some improvements over the original approach based on the TosMIC route,[11] there are still several drawbacks with this synthetic route, namely, the protection and deprotection sequence of the 3-ketone group in dione **6**, the poor yield in the dioxene 1,2-addition and subsequent elimination reactions, and finally, the low-yielding conversion of diene **8** to keto-alcohol **4**. Thus, for the purpose of producing the desired imaging agent FFNP **1** in larger quantities, we looked further for a shorter and more efficient synthesis.

Pd(II)-Catalyzed Oxidative Rearrangement Approach to Key Triol 5. There are a number of alternative approaches for introducing the 21-hydroxy-16-ene-20-keto (corticosteroid) side chain in steroidal systems that are described in the literature.[21−24] We found the approach based on a palladium-catalyzed rearrangement of propargyl esters[23,24] to be particularly attractive, because it generates the requisite corticosteroid side chain in just three steps, starting from readily available propargylic alcohol precursors. This convenient methodology obviates the need for protection of the 3-keto group (Scheme 3).

Thus, the commercially available steroid propargylic alcohol **11** (norethindrone) was converted to the corresponding propargylic isobutyrate ester **12a**,[25] quantitatively, employing standard conditions, i.e., isobutyric anhydride, pyridine, and a catalytic amount of DMAP. Treatment of this propargylic isobutyrate ester **12a** with 5 mol % potassium tetrabromopalladate and 2 equiv of water in DME in an oxygen atmosphere at 65 °C resulted in the formation of unsaturated isobutyrate **13a** in 85% yield. NMR analysis revealed the presence of an 80:20 mixture of geometrical isomers, but no effort was made to separate them, because both can be converted to the corticosteroid side chain.

Treatment of the unsaturated isobutyrate **13a** with DBU at 55 °C generated the corticosteroid side chain, presumably via a 1,2-acyl transfer on the dienolate intermediate, thereby giving the keto-isobutyrate **14a** in 85% yields. Thus, starting from propargylic alcohol **11**, we could obtain the keto-isobutyrate **14a**, having the necessary side chain, in three steps and in excellent yield. This contrasts with the earlier dioxene approach, wherein the requisite keto-alcohol **4** was obtained from dione **6** in eight steps and in low overall yield (Scheme 2).

We were disconcerted to find, however, that hydrolysis of the isobutyrate ester in keto-isobutyrate **14a** under a

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variety of conditions (both basic and acidic) failed to furnish keto-alcohol **4** in a clean manner and led to extensive decomposition of the starting material. As a result, the required keto-alcohol **4** could be obtained only in very poor yields (<20%) from this precursor.

To circumvent this problem, we repeated the entire reaction sequence with the corresponding acetate, in the hope that it would be easier to hydrolyze this less hindered ester. It is of note that literature reports indicate that the palladium-catalyzed propargyl ester rearrangements do not proceed as effectively with acetates as they do with isobutyrates.[23,24] Nevertheless, we converted propargylic alcohol **11** to the corresponding propargylic acetate ester **12b**[26] and subjected it to the same reaction sequence described for propargylic isobutyrate ester **12a**.

We found, in fact, that the Pd(II)-catalyzed rearrangement of the propargylic acetate ester **12b** gave unsaturated acetate **13b** in 80% yields, and the base-catalyzed acetate transfer also furnished keto-acetate **14b** in similar yields. Furthermore, we were gratified to find that in contrast to the keto-isobutyrate **14a**, the keto-acetate **14b** could be hydrolyzed to keto-alcohol **4** under fairly mild conditions, using potassium carbonate and moist methanol, in 85% yield. Having thus successfully achieved an efficient synthesis of this important intermediate, we turned our attention to improving the yields of subsequent steps.

Because the dihydroxylation of the unprotected keto-alcohol **4** with osmium tetroxide gave the triol **2** in only ~50% yield (Scheme 2), we attempted to improve the efficiency of the $\Delta^{16(17)}$ olefin dihydroxylation, by carrying it out on the protected keto-alcohol, i.e., keto-acetate **14b**. Thus, treatment of keto-acetate **14b** with the cheaper dihydroxylating agent, potassium permanganate in acetone,[27−29] furnished dihydroxy acetate **15b** in 85% yields. Subsequent acetate hydrolysis to give triol **5** was also efficient (84% yield). On the other hand, efforts to hydrolyze isobutyrate ester in dihydroxy isobutyrate **15a** were not so successful (~30% yield). Thus, by this five-step sequence we were able to obtain triol **5** in ~40% overall yield, starting from commercially available propargylic alcohol **11**. By employing the palladium-mediated oxidative rearrangement approach, as well as by using potassium permanganate as a dihydroxylating agent, we obtained nearly a 10-fold increase in the overall yield of the triol **5** compared to the dioxene approach.

Improvements in Furan Acetalization. After having addressed the problem of the efficient synthesis of triol **5**, we turned our attention toward improving the yields of furan acetalization (Table 1). From prior work,[12] it was known that triol **5**, upon treatment with furfural and a catalytic amount of 70% perchloric acid, gave a 1:1 diastereomeric mixture of endo and exo furan acetal alcohols **16a** and **16b**, respectively, in ~40% yields (Scheme 4). With the objective of not only improving this diastereomeric ratio but also improving the overall yield of the reaction, we attempted furan acetalization with a catalytic amount of 70% perchloric acid on the protected dihydroxy acetate **15b**. Unfortunately, this method led to only a very negligible improvement in the yield (45%) and also resulted in the formation of a less favorable 1:2 diastereomeric mixture of endo **17a** and exo **17b** furan acetal acetates.

TABLE 1. Furan Acetalization of Dihydroxy Acetate 15b or Triol 5

compd	R	acid catalyst	endo:exo[a]	yield[b]
15b	Ac	0.023 M 70% $HClO_4$	1:2 (**17a**:**17b**)	55%
5	H	0.023 M 70% $HClO_4$	1:1 (**16a**:**16b**)	45%
15b	Ac	1 mol % $Sc(OTf)_3$	1:6 (**17a**:**17b**)	75%
5	H	1 mol % $Sc(OTf)_3$	1:2 (**16a**:**16b**)	75%
5	H	10 mol % $Sc(OTf)_3$	1:1 (**16a**:**16b**)	80%

[a] Based on the ^1H NMR. [b] Isolated yield.

We imagined that the hydrous Brönsted acid utilized in the acetalization reaction was perhaps responsible for the low yields. Considering this, we wondered whether the use of an anhydrous Lewis acid such as scandium triflate [$Sc(OTf)_3$], a reagent known to be a good catalyst for acetalization,[30] might prove to be more efficient in this reaction. Thus, the furan acetalization was carried out on the protected dihydroxy acetate **15b** with 1 mol % scandium triflate as the catalyst. Unfortunately, this resulted in the formation of a very undesireable 1:6 ratio of endo and exo products **17a** and **17b**, respectively, though the isomeric acetals were obtained in 75% yield. On the other hand, $Sc(OTf)_3$-catalyzed furan acetalization of unprotected triol **5** resulted in the formation of a more favorable 1:2 mixture of endo and exo isomers **16a** and **16b** furan acetal alcohols, respectively, also in similar yield.

It is known that the endo acetal isomer is the thermodynamically more stable product,[13,14] and dioxolone formation should be reversible. Thus, furan acetalization was again attempted on triol **5**, but now with a 10-fold higher concentration of $Sc(OTf)_3$ (10 mol %). Under these conditions, we obtained a 1:1 mixture of endo and exo furan acetal diastereomers in 80% yields. These diastereomers were separated by reversed-phase HPLC to obtain diastereomerically pure endo furan-acetal alcohol **16a**. The undesired exo isomer **16b**, which was also obtained in this purification, could again be equilibrated to a 1:1 mixture of endo and exo furan acetal diastereomers by re-treatment with the $Sc(OTf)_3$ (10 mol %) and furfuraldehyde. Thus, this catalytic route also provided a convenient method for recycling exo furan acetal alcohol **16b** to the desired endo isomer **16a**.

Improvements in the Fluorine Substitution Reaction. Finally, we turned our attention toward improving the final fluorination step. It was observed previously that conversion of the endo furan acetal alcohol **16a** to the corresponding triflate **18a** was very inefficient (~30%), as was conversion of the triflate **18a** to the FFNP **1** (overall yield of 9%).[12] A major problem in this conversion was the fact that the triflate **18a** is very unstable and thus difficult to isolate and purify. Although it is less reactive, we decided to investigate whether the meth-

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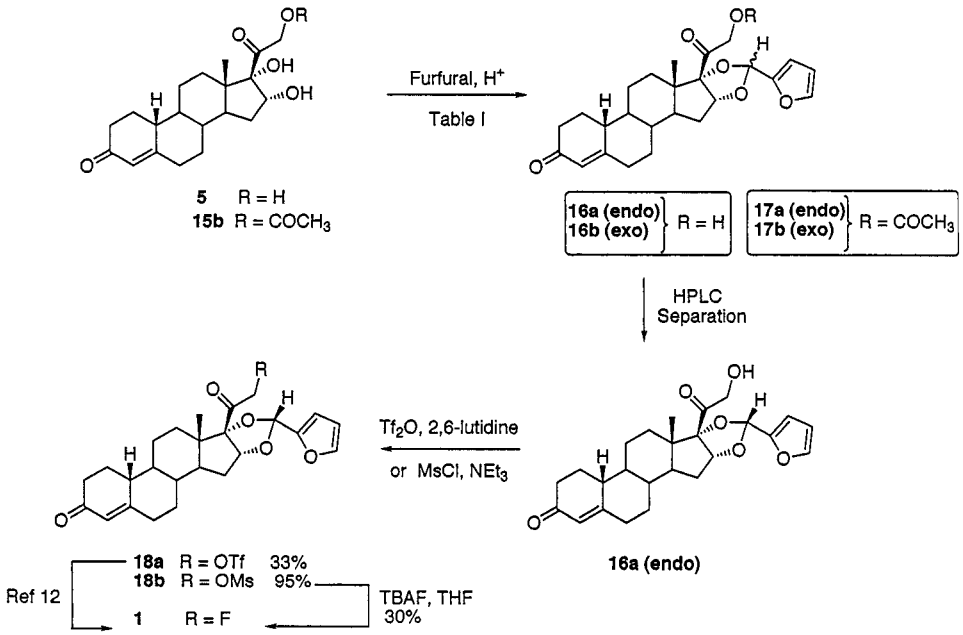
SCHEME 4



anesulfonate (mesylate) **18b** might not be a more suitable intermediate.

Thus, we converted the hydroxy group in endo furan acetal alcohol **16a** to the corresponding mesylate derivative **18b** in more than 90% yield, by treatment with methanesulfonyl chloride and triethylamine. Nucleophilic displacement of the mesylate **18b** with tetrabutylammonium fluoride (TBAF) in DMSO furnished the requisite fluoro compound **1** in only modest yield (ca. 30%, based on the fluoride ion).[31] Nevertheless, this fluorination method constitutes a significant improvement in the overall yield for the conversion of endo furan acetal alcohol **16a** to FFNP **1**.

Conclusion

To address the shortcomings of an earlier route,[11] two different approaches for the synthesis of a precursor for FFNP (**1**), a potential PET imaging agent for progesterone receptors in breast cancer, have been explored. In the first, less efficient approach, a dioxene unit was utilized as the synthon for the requisite progestin side chain. In the second, more efficient approach, a palladium(II)-catalyzed oxidative rearrangement was employed to generate the progestin side chain from a propargylic acetate **12b**. This synthetic route does away with the protection and deprotection protocol of the 3-ketone group, and more importantly, the requisite 21-hydroxy-20-keto-$\Delta^{16(17)}$ system is installed in only three steps starting from commercially available steroid propargylic alcohol **11**. Finally, the acetate-protected 21-hydroxy group in keto-acetate **14b** enables the use of a less toxic, cheaper dihydroxylating agent (potassium permanganate), thereby improving the yield of this step as well. Further improvement in the furan acetalization was obtained by the use of a sufficient quantity of anhydrous scandium triflate as a catalyst. Finally, the efficiency of the fluorination reaction was improved using, in place of the unstable triflate, the more stable mesylate. This latter route enables the synthesis of the precursor for the F-18-labeled FFNP **1** in sufficient quantities for medical imaging studies.

Experimental Section

General Methods. Dioxene,[32] progargylic esters **12a**[25] and **12b**,[26] and keto-ketal **2**[20] were prepared according to the reported procedures. Reaction progress was monitored by analytical thin-layer chromatography. Silica gel used in flash chromatography[33] was 32−63 mm. TLC plates were visualized using short-wave UV light (254 nm), potassium permanganate, or phosphomolybdic acid. Melting points were uncorrected. Standard ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, and the chemical shifts in the NMR spectra are given in the δ scale. Infrared spectra were recorded on a FT-IR spectrometer. MS and HRMS were recorded with either an electron impact (70 eV) or a FAB mass spectrometer. HPLC was performed isocratically (70:30 water−acetonitrile) using a 5 μm ODS partisil column at a 5 mL/min flow rate. Dry THF and CH_2Cl_2 were dried using an alumina column solvent dispensing system. Experimental details for the compounds shown in Scheme 2 (**7**, **8**, **4**) and Scheme 4 (**17a** and **17b**) are given in Supporting Information.

3-Keto-20-isobutanoyloxy-19-norpregna-4,17(20)-dien-21-al (13a). To a stirred solution of propargylic isobutyrate ester **12a** (1.4 g, 3.8 mmol), water (7.6 mmol, 0.137 mL), and DME (18 mL) was added potassium tetrabromopalladate (96 mg, 0.19 mmol). The reaction was heated at 65 °C under an oxygen atmosphere for 3 h. Upon completion of the reaction, the solvent was evaporated, and flash chromatography (3:7 EtOAc−hexane) gave unsaturated isobutyrate **13a** as a yellow viscous oil (1.24 g) in 85% yield. Both ^{1}H and ^{13}C

(31) For the ultimate radiosynthesis of high specific activity [^{18}F]-FFNP **1**, typical alcohol fluorination reagents such as DAST cannot be used. In fact, fluoride ion is the only high specific activity fluorine-18 precursor that is routinely available. Also, because radiofluorination reactions are done with only tracer quantities of (^{18}F) fluoride ion, we have run the displacement reaction with fluoride ion as the limiting reagent, to model the radiolabeling conditions.

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NMR indicated the presence of an 80:20 mixture of geometrical isomers. Major isomer. ^{1}H NMR ($CDCl_3$) δ 9.59 (1 H, s, C*H*O), 5.84 (1 H, br s, olefinic H-4), 1.29 (3 H, d, J = 7 Hz) and 1.27 (3 H, d, J = 7 Hz) CH(CH_3)$_2$, 1.01 (3 H, s, C-18 −CH_3). ^{13}C NMR ($CDCl_3$): δ 199.7, 175, 165.7, 161.2, 124.8, 124.7, 71.9, 52.8, 48.9, 47.0, 42.3, 39.5, 36.4, 35.2, 34.7, 33.7, 30.8, 26.9, 26.5, 26.3, 24.3, 19.0, 18.9. MS (EI): *m*/*z* 384 (M^+). HRMS: calcd for $C_{24}H_{32}O_4$, 384.2300; found, 384.2300.

21-Isobutanoyloxy-19-norpregn-4,16-diene-3,20-dione (14a). To a stirred solution of unsaturated isobutyrate **13a** (0.9 g, 2.33 mmol) in dry ethyl acetate (5 mL) was added DBU (1.16 mmol, 0.17 mL), and the reaction was heated at 60 °C overnight and then cooled. The organic solvent was removed under vacuum. Flash chromatography (2:3 EtOAc−hexane) furnished keto-isobutyrate **14a** (760 mg) as a white amorphous powder in 85% yield. Crystallization (ethyl acetate and hexane) gave colorless crystals, mp 120−121 °C. IR (neat): 1742 (ester C═O), 1673 (unsaturated C═O), 1616 (olefinic), 1586 (olefinic). ^{1}H NMR ($CDCl_3$): δ 6.67 (s, 1 H, olefinic H-16), 5.71 (s, 1 H, olefinic H-4), 4.77 (d, 1 H, J = 16 Hz, H-21), 4.93 (s, 1 H, J = 16.7 Hz), 1.08−1.19 (m, 6H, isopropyl methyl group), 0.87 (s, 3 H, C-18 methyl group). ^{13}C NMR ($CDCl_3$): δ 199.5, 190.4, 176.1, 166.0, 151.5, 143.4, 124.4, 65.1, 54.4, 49.5, 46.5, 42.3, 39.2, 36.2, 35.0, 34.0, 33.4, 32.0, 30.6, 26.2, 25.2, 25.9, 18.7 (2C), 15.7. MS (EI): *m*/*z* 384.3 (M^+). HRMS: calcd for $C_{24}H_{32}O_4$, 384.2300; found, 384.2294. Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39; O, 16.64. Found: C, 74.82; H, 8.60; O, 16.58.

21-Isobutanoyloxy-16α,17α-dihydroxy-19-norpregn-4-ene-3,20-dione (15a). To a stirred solution of keto-isobutyrate **14a** (500 mg, 1.3 mmol) and formic acid (3.3 mmol, 0.126 mL) in acetone (34 mL) at 0 °C was added gradually a solution of potassium permanganate (0.205 g, 1.3 mmol) in water (5.1 mL) and acetone (29 mL). Upon completion of the addition, the reaction was stirred for 5 min and quenched with a 10% aqueous solution of $KHSO_3$ (5 mL). Acetone was removed under vacuum, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by flash chromatography (4:1 EtOAc−hexane) furnished dihydroxy isobutyrate **15a** as white amorphous solid (490 mg) in 90% yield. Recrystallization (dichloromethane/hexane) gave colorless crystals, mp 170−172 °C. IR ($CHCl_3$ film): 3413 (OH), 1738 (C═O), 1724 (C═O), 1660 (C═O). ^{1}H NMR ($CDCl_3$): δ 5.8 (br s, 1H, olefinic H-4), 4.95 (d, 1 H, J = 20 Hz), 4.85 (d, 1 H, J = 20 Hz), 4.85 (t, 1 H, J = 9 Hz, H-16). ^{13}C NMR ($CDCl_3$): δ 206.5, 200.5, 176.9, 166.9, 124.4, 88.5, 72.9, 68.4, 48.7, 48.4, 42.3, 39.8, 36.3, 35.3, 33.6, 33.3, 30.9, 30.2, 26.3, 25.5, 18.9, 18.8. MS (FAB): *m*/*z* 419 $[M + H]^+$. HRMS (FAB): calcd for $C_{24}H_{32}O_4$ $[M + H]^+$, 419.2433; found, 419.2436.

3-Keto-20-acetoxy-estra-4,17(20)-dien-21-al (13b). To a stirred solution of propargylic acetate ester **12b** (4.2 g, 12.3 mmol), water (24.6 mmol, 0.442 mL), and DME (75 mL) was added potassium tetrabromopalladate (619 mg, 1.23 mmol). The mixture was heated at 65 °C under an oxygen atmosphere for 3 h. Workup and purification were the same as those described for compound **13a**, yielding 3.5 g (80%) of the unsaturated acetate ester **13b** as a viscous oil. ^{1}H NMR gave an 80:20 mixture of geometrical isomers. Major isomer. ^{1}H NMR ($CDCl_3$): δ 9.56 (1 H, br s, C*H*O), 5.8 (1 H, br s, olefinic H-4), 3.1−2.75 (2 H, m, H-16), 2.19 (3 H, s, COCH_3), 0.97 (3H, s, C-18 methyl group). ^{13}C NMR ($CDCl_3$): δ 199.6, 183.9, 168.9, 165.7, 161.6, 138.5, 124.6, 52.7, 48.9, 46.9, 42.2, 39.3, 36.3, 35.1, 34.6, 30.7, 26.8, 26.4, 26.7, 24.2, 20.3, 16.1. MS (EI): *m*/*z* 356 (M^+). HRMS: calcd for $C_{22}H_{28}O_4$: 356.1988; found: 356.1982.

21-Acetoxy-19-norpregna-4,16-diene-3,20-dione (14b). To the stirred solution of unsaturated acetate ester **13b** (1 g, 2.8 mmol) in dry ethyl acetate (25 mL) was added DBU (1.4 mmol, 0.2 mL), and the mixture was heated at 60 °C overnight. Workup and purification were as described for compound **14a**, yielding 790 mg (80%) of keto-acetate ester **14b** as white powder. Crystallization (dichloromethane and hexane) gave colorless crystals, mp 167−168 °C. ^{1}H NMR ($CDCl_3$): δ 6.62 (1 H, br s, olefinic H-16), 5.65 (1 H, br s, olefinic H-4), 4.87 (1 H, d, J = 16 Hz, H-21), 4.72 (1 H, d, J = 16 Hz, H-21), 1.99 (3 H, s, acetyl methyl), 0.79 (3 H, s, C-18 methyl). ^{13}C NMR ($CDCl_3$): δ 199.15, 190.0, 169.8, 165.8, 151.1, 143.5, 124.2, 65.2, 54.1, 49.3, 46.3, 42.0, 37.9, 36.0, 34.8, 33.8, 31.9, 30.4, 26.0, 25.7, 20.0, 15.5. MS (EI): *m*/*z* 356 (M^+). HRMS: calcd for $C_{22}H_{28}O_4$, 356.1987; found, 356.1982. Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; O, 17.95. Found: C, 73.80; H, 7.94; O, 18.26.

21-Hydroxy-19-norpregn-4,16-diene-3,20-dione (4). To a solution of keto-acetate ester **14b** (500 mg, 1.4 mmol) in MeOH (7 mL), THF (7 mL), and water (2 drops) was added potassium carbonate (177 mg, 1.4 mmol). The mixture was stirred at room temperature for 15 min. The solvent was then evaporated and the reaction mixture diluted with ethyl acetate (20 mL) and washed with water (2 × 5 mL). The organic layer was washed with brine and dried over sodium sulfate. Evaporation of the organic layer followed by flash chromatography (2:3 EtOAc−hexane) gave keto-alcohol **4** as an off-white crystalline powder (360 mg) in 85% yield, whose spectral data (^{1}H and ^{13}C NMR) were identical to those reported in the literature.[11] Crystallization of the product (dichloromethane and ethyl ether) gave colorless crystals, mp 212−216 °C.[11]

21-Acyloxy-16α,17α-dihydroxy-19-norpregn-4-ene-3,20-dione (15b). To the stirred solution of keto-acetate **14b** (2.1 g, 5.5 mmol) and formic acid (14 mmol, 0.523 mL) in acetone (145 mL) at 0 °C was gradually added a solution of potassium permangnate (0.869 g, 5.5 mmol) in water (21.6 mL) and acetone (122 mL). Workup and purification were as described for compound **15a**, furnishing 1.79 g of dihydroxy-acetate **15b** as a white powder in 85% yield. Crystallization (dichloromethane and hexane) gave colorless crystals, mp 191−193 °C. ^{1}H NMR ($CDCl_3$): δ 5.82 (1 H, br s, olefinic H-4), 5.04 (1H, d, J = 17.8 Hz, H-21), 4.98 (1 H, dd, J = 9.2, 2.14 Hz, H-16), 3.87 (1 H, d, J = 17.8 Hz, H-21), 3.94 (1 H, s, O*H*), 2.16 (3 H, s, COCH_3), 0.73 (3 H, s, H-18). ^{13}C NMR ($CDCl_3$): δ 206, 200.2, 170.8, 166.5, 127.7, 88.5, 73.0, 68.6, 48.7, 48.4, 48.3, 42.4, 39.9, 36.4, 35.3, 33.4, 31.0, 30.3, 26.4, 25.5, 20.5, 14.3. MS (EI): *m*/*z* 390.3 (M^+). HRMS: calcd for $C_{22}H_{30}O_6$, 390.2042; found, 390.2038.

16α,17α,21-Trihydroxy-19-norpregn-4-ene-3,20-dione (5): From Dihydroxy Acetate 15b. To a solution of dihydroxy acetate **15b** (500 mg, 1.28 mmol) in MeOH (7 mL), THF (7 mL), and water (2 drops) was added potassium carbonate (193 mg, 1.28 mmol), and the mixture was stirred at room temperature for 15 min. Upon completion of the reaction, the solvent was evaporated and the residue was diluted with acetone and passed through a pad of silica gel to give triol **5**. Crystallization (acetone and hexane) yielded a white amorphous powder (360 mg) in 84% yield, mp 191−193 °C. [11] Spectral data (^{1}H and ^{13}C NMR) of compound **5** were identical to those reported in the literature.[11] **From Dihydroxy Isobutyrate 15a.** To a solution of dihydroxy isobutyrate **15a** (500 mg, 1.28 mmol) in MeOH (7 mL), THF (7 mL), and water (2 drops) was added potassium carbonate (193 mg, 1.28 mmol), and the mixture was stirred at room temperature for 15 min. Workup and purification were as described above, furnishing triol **5** in 30% yield, whose spectral data (^{1}H and ^{13}C NMR) were identical to those reported in the literature.[11]

16α,17α-[(*R*)-(1′-α-Furylmethylidene)dioxy]-21-hydroxy-19-norpregn-4-ene-3,20-dione (Endo, 16a) and 16α,17α-[(*S*)-(1′-*β*-Furylmethylidene)dioxy]-21-hydroxy-19-norpregn-4-ene-3,20-dione (Exo, 16b): Sc(OTf)$_3$ Method. To a solution of triol **5** (1 mmol) in furfural (6 mL) was added anhydrous magnesium sulfate (50 mg) and a catalytic amount of $Sc(OTf)_3$ (1 or 10 mmol %), and the mixture was stirred at room temperature for 24 h. Evaporation of the solvent in a vacuum followed by flash chromatography (40−80% ethyl acetate in hexane) furnished a mixture of endo and exo hydroxy furan acetal **16a** and **16b** in 75−80% yields. Both ^{1}H and ^{13}C spectral data were identical to those reported in the

literature.[12] **Isomerization of Exo Furan Acetal 16b.** To a solution of pure exo 21-hydroxy furan acetal **16b** (40 mg, 0.11 mmol), which was obtained after reversed-phase HPLC purification of a 1:1 mixture of endo and exo furan acetal alcohols **16a** and **16b**,[12] in furfural (1.5 mL) was added anhydrous magnesium sulfate (25 mg) and a catalytic amount of $Sc(OTf)_3$ (10 mmol %). The reaction was stirred at room temperature for 12 h. Evaporation of the solvent in a vacuum followed by flash chromatography (40−80% ethyl acetate in hexane) furnished 30 mg of a 1:1 mixture of endo and exo furan acetal alcohols **16a** and **16b** in 75% yield. Both ^1H and ^{13}C spectral data were identical to those reported in the literature.[12]

16α,17α-[(*R*)-(1′-α-Furylmethylidene)dioxy]-21[(methyl)sulfonyl]oxy-19-norpregn-4-ene-3,20-dione (Endo, 18b). To a stirred solution of endo furan acetal alcohol **16a** (50 mg, 0.115 mmol) in methylene chloride (1 mL) at −78 °C was added triethylamine (46 mg, 0.46 mmol) followed by methanesulfonyl chloride (16 mg, 0.14 mmol). The reaction mixture was stirred for 20 min, quenched with methanol (0.1 mL), and extracted with ethyl acetate (2 × 10 mL). The organic layer was washed with water (5 mL) and brine and dried over anhydrous sodium sulfate. Evaporation of the organic layer and rapid flash chromatography (30−60% ethyl acetate in hexane) furnished endo furan acetal methanesulfonate **18b** (55 mg) as a white powder in 95% yield. Recrystallization (methanol) gave colorless crystals, mp 193−195 °C. ^1H NMR ($CDCl_3$): δ 7.47 (1 H, dd, J = 1.7 and 0.8 Hz), 6.53 (1 H, dd, J = 3.2 and 0.64 Hz), 6.4 (1 H, dd, J = 3.4 and 1.9 Hz), 5.63 (1 H, s, acetal-H), 5.23 and 5.0 (2 H, d, J = 18.3 Hz, H-21), 5.05 (1 H, J = 5.8 Hz, H-16), 3.25 (3 H, s, sulfonyl-CH_3), 0.77 (3 H, s, C-18 CH_3). ^{13}C NMR ($CDCl_3$): δ 202.5, 199.7, 165.7, 148.1, 143.8, 124.8, 110.4, 110.3, 98.2, 82.8, 71.6, 48.7, 47.9, 47.0, 42.2, 39.4, 36.4, 35.2, 33.1, 31.3, 31.0, 26.5, 25.7, 14.6. MS (EI): m/z 505 (M^+). HRMS: calcd for $C_{26}H_{32}O_8S$, 505.1896; found, 505.1898.

16α,17α-[(*R*)-(1′-α-Furylmethylidene)dioxy]-21[fluoro]-oxy-19-norpregn-4-ene-3,20-dione (Endo, 1). To a stirred solution of the methanesulfonate **18b (**10 mg, 0.019 mmol) in THF (0.5 mL) was added TBAF (15 μL, 0.014 mmol, 1 M solution in THF), and the reaction mixture was heated in a sealed reaction vial at 80 °C for 10 min. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. Evaporation of the solvent and purification of the residue by flash chromatography (30−50% ethyl acetate in hexane) furnished fluorinated compound **1** (2.3 mg) in 30% yield (with respect to TBAF, the limiting reagent). The spectroscopic properties (both ^1H and ^{13}C) were identical to those reported previously.[12]

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Supporting Information Available: Experimental details for the synthesis of compounds keto-alcohol **4**, tertiary alcohol **7**, diene **8**, furan acetal alcohols **16a** and **16b**, furan acetal acetates **17a** and **17b**, and methanesulfonate **18a** are described and ^1H NMR spectra of **7**, **8**, **13a**, **15a**, **13b**, **15b**, a mixture **17a** and **17b**, and **18b** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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