Bromine- and Iodine-Substituted 16α,17α-Dioxolane Progestins for Breast Tumor Imaging and Radiotherapy: Synthesis and Receptor Binding Affinity

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Progesterone receptors (PRs) are present in many breast tumors, and their levels are increased by certain endocrine therapies. We describe the synthesis and PR binding affinities of a series of bromine- and iodine-substituted 16α,17α-dioxolane progestins, some of which, when appropriately radiolabeled, are potential agents for diagnostic imaging of PR-positive breast tumors using positron emission tomography (PET) and for radiotherapy. These compounds were synthesized from halogenated furanyl, phenyl, and thiophenyl aldehydes and a progestin 16α,17α,21-triol (**5**) in the presence of $HClO_4$ or $Sc(OTf)_3$ in high yields under optimized conditions. A new reagent, perfluoro-1-butanesulfonyl fluoride (PBSF), was used to convert the C-21 OH to F in high yields. The relative binding affinities (RBAs) of the most promising compounds for the PR (RBA of R5020 = 100) were 16α,17α-[(*R*)-1′-α-(5-bromofurylmethylidene)dioxyl]-21-hydroxy-19-norpregn-4-ene-3,20-dione (*endo*-**6**; RBA = 65 and moderate lipophilicity), 21-fluoro-16α,17α-[(*R*)-1′-α-(5-iodofurylmethylidene)dioxyl]-19-norpregn-4-ene-3,20-dione (*endo*-**14**; RBA = 40) and 21-fluoro-16α,17α-[(*S*)-1′-β-(4-iodophenylmethylidene)dioxyl]-19-norpregn-4-ene-3,20-dione (*exo*-**16**; RBA = 34).

Introduction

Steroid receptors are found in a number of endocrine-responsive cancers, estrogen receptors (ERs), and progesterone receptors (PRs)[a] in many breast tumors, and androgen receptors (ARs) in most prostate cancers. These receptors serve as targets for endocrine therapies of these cancers, but they also can be used as targets for diagnostic imaging and radiotherapy. Diagnostic imaging can be achieved by the administration of a suitably radiolabeled ligand (an estrogen, progestin, or androgen for their cognate receptor, ER, PR, or AR, respectively) that accumulates in the receptor-positive tumor, where it can be detected and quantified by imaging. Such images can sometimes be used to predict whether hormone therapy will be effective.[1,2] In a related manner, a hormone receptor ligand labeled with a different radionuclide (e.g., an Auger electron emitting isotope) that accumulates in a tumor through a receptor-mediated uptake process can deliver a cytotoxic dose of high linear energy transfer (LET) radiation selectively to the tumor cells, ablating the tumor while limiting widespread radiation toxicity. Therefore, the development of such hormone receptor ligands for both diagnostic imaging and radiotherapy is a promising area of great current interest.

Diagnostic imaging of breast and prostate tumors by positron emission tomography (PET) is well established and has been achieved using steroids labeled with fluorine-18. Most extensive are studies in breast cancer using 16α-[^{18}F]fluoroestradiol (FES),[2] and in prostate cancer using 16β-[^{18}F]fluoro-5α-dihydrotestosterone (FDHT).[3] Although a number of steroids labeled with bromine and iodine radioisotopes have been prepared,[4] their use in imaging studies, particularly in humans, has been more limited.[4f] These agents have been studied quite extensively, however, in terms of their potential for selective radiotherapy.

It was shown by Bronzert, Lippman, and Hochberg that 16α-[^{125}I]iodoestradiol was selectively cytotoxic to human mammary cancer cells (MCF-7) when bound to ER.[5] Similar experiments were reported by Bloomer et al. using [^{125}I]iodotamoxifen and various I-125 and I-123 labeled estrogens.[6] A number of bromine- and iodine-substituted estrogens have been developed by DeSombre and co-workers for selective radiotherapy, and they have quantified both chromosome damage and cell survival following the exposure of ER+ cells to 17α-[^{123}I]iodovinyl-11β-methoxyestradiol.[7] DeSombre and others also determined the mean lethal dose for I-123 or Br-77 to be 300−600 decays per cell, and they established that the radiation damage from the electron shakeoff following the decay of these isotopes was spatially limited to a sphere of ca. 10 Å radius.[8,9] These experiments establish the feasibility of using various Auger electron-emitting isotopes for selective cellular therapy.

Other Auger electron-emitting halogens, namely iodine-124 and bromine-76, decay with a significant amount of positron emission, a characteristic that allows for diagnostic PET imaging to be used to complement their use in radiotherapy. All of these radionuclides have a half-life that is sufficiently long to permit target tissue-selective distribution while being sufficiently short so that the bulk of the dose can be delivered to the tissue prior to metabolism and elimination of the radiopharmaceutical. It is of note that in order for radiolabeled steroids to be used successfully for diagnostic imaging or therapy, the labeled ligand must maintain very high affinity for its receptor, with low binding for other nonspecific sites.

In applications in breast tumor imaging and therapy, a PR-based radioligand has some potential advantages over an ER-

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[a] Abbreviations used: PR, progesterone receptor; ER, estrogen receptor; AR, androgen receptor; RBA, relative binding affinity; PET, positron emission tomography; LET, linear energy transfer; R5020, promegestone; FES, 16α-fluoroestradiol; FDHT, 16β-fluoro-5α-dihydrotestosterone; FFNP, fluoro furanyl norprogesterone, compound **1**; PBSF, perfluoro-1-butanesulfonyl fluoride; EtOAc, ethyl acetate; endo/exo refer to the stereochemistry at the acetal carbon; $Sc(OTf)_3$, scandium trifluoromethanesulfonate; PM3, B3LYP, computational methods; TBAF, tetrabutylammonium fluoride; DAST, diethylaminosulfur trifluoride; TMS, tetramethylsilane; ESI, Electrospray ionization.

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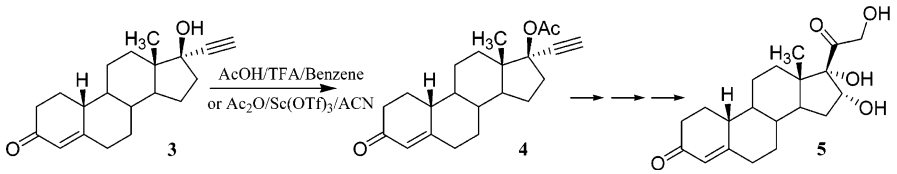
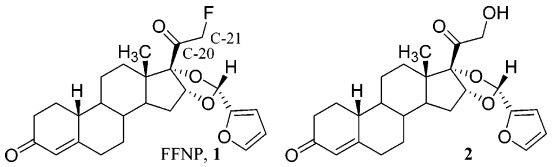
Scheme 1



based one: (1) there is a better correlation between PR status and hormonal responsiveness than there is with ER status;[10] (2) a PR-based ligand could be used after the initiation of antiestrogen hormonal therapy, whereas an ER-based one would not be useful when tumor ER is saturated by the hormonal agent.[11] Moreover, (3) PR-based ligands may benefit from the increased PR levels induced by the transient agonistic effect of tamoxifen during the initial course of tamoxifen treatment of breast tumor.[12]



Based on what is known about the structure-affinity relationships of PR ligands, a good candidate molecule for labeling with bromine or iodine should have a skeleton related to fluoro furanyl norprogesterone (FFNP) **1**.[13] This compound appears to have promise as an agent for PET imaging,[13] and it is being developed for this purpose. FFNP has a high relative binding affinity to PR (190% relative to R5020 = 100%), low nonspecific binding (log $P_{o/w}$ = 3.87), and high binding selectivity index (the ratio of PR binding affinity to nonspecific binding). In tissue biodistribution studies in estrogen-primed immature female Sprague−Dawley rats, FFNP demonstrated high PR-selective uptake in the principal target tissues, uterus and ovaries, and relatively low uptake in fat and bone. Also, the metabolism at the 20-position in FFNP is likely to be less than that in other 20-fluoroprogestins,[13b] because the bulk of the 16α,17α-furanyl group protects the C-20 ketone from attack by steroid dehydrogenases. In addition to these favorable pharmacokinetic and pharmacodynamic attributes, the 16α,17α-dioxolane group of FFNP (and its C-21 OH precursor, **2**) provides a convenient aromatic site where bromine or iodine can be introduced easily by electrophilic substitution reactions. These haloarenes are much more stable than would be the corresponding 21-iodo or bromo analogues, which are reactive α-haloketones.

In this report, we describe the synthesis of a series of 16α,17α-dioxolane bromine- and iodine-substituted and C-21 hydroxyl- or fluoride-substituted norprogesterones that have a skeleton similar to that of FFNP and a determination of their relative binding affinities to PR. The norprogesterone with a 5-bromofuranyl system (*endo*-**6**) has good binding affinity and moderate lipophilicity and thus appears to be a promising PR ligand for radiobromine labeling for diagnostic imaging and radiotherapy purposes.

Results and Discussion

Synthesis of a Key Precursor, Norprogesterone Triol 5. The key intermediate in the synthesis of FFNP and its analogues is the 19-norprogesterone 16α,17α,21-triol **5**, which was synthesized from commercially available 17α-ethynyl-nortestosterone (**3**, 19-norethindrone) according to our recently reported method,[14] with some modification, as shown in Scheme 1. In the previously reported method,[14] acetylation to prepare **4** was carried out in refluxing benzene with acetic acid and trifluoroacetic anhydride (TFA) as catalyst, which formed the mixed anhydride as the active acylating agent. We had difficulty in reproducibly obtaining the high yield reported for this transformation.[14,15] We believe this is due to the low boiling point of TFA, which makes formation of the mixed anhydride inefficient.

Because scandium trifluoromethanesulfonate $Sc(OTf)_3$ is reported to be an extremely active acylation catalyst[16] as well as acetalization catalyst,[17] this acylation reaction was carried out with acetic anhydride using $Sc(OTf)_3$ as catalyst. The reaction went smoothly in CH_3CN at ambient temperature and gave a 90% yield within 1 h. This yield is comparable to the reported one,[14] but this reaction is much easier to carry out. Therefore, with this modification, the key intermediate triol **5** was synthesized according to the reported route.[14]

Formation of the Norprogesterone 16α,17α-Acetal. The acetalization of the norprogesterone triol **5** was carried out with the corresponding aldehyde in the presence of 70% $HClO_4$, according to the procedure of Fried,[18] or $Sc(OTf)_3$ as reported by us.[14] Formation of the dioxolane ring generates a new stereogenic center, so that a mixture of endo and exo diastereomers is produced, as shown in Scheme 2. In early studies on the formation of progestin 16α,17α-dioxolanes, Fried[18] showed that with aromatic aldehydes the endo isomer was more stable; the less stable exo isomer was kinetically preferred (low acid, short time), whereas the more stable one was thermodynamically preferred (high acid, longer time).

In the presence of $HClO_4$, we found previously that triol **5** gave nearly 1:1 mixtures of diastereomers when reacted with furfural under a variety of conditions,[13,14] but that when $Sc(OTf)_3$ was used as catalyst, exo isomers were obtained as the major products at low catalyst level (1 mol %), whereas 1:1 endo/exo mixtures were produced at high catalyst level (10 mol %) level and longer reaction time.[14] In the presence of both catalysts, isomerization between endo and exo was observed by ^1H NMR and ^{19}F NMR in the case of $HClO_4$[19] or by direct conversion from exo isomer to endo isomer in the case of $Sc(OTf)_3$.[14] Our results for the acetalization with the halogen substituted aldehydes are shown in Table 1.

In the reactions in which $HClO_4$ was used as catalyst, a nearly 1:1 of endo and exo diastereomers were obtained, which is the same as that reported for furfural.[13,14,18] When we tried the acetalization with bromofurfural under the same conditions as for furfural, however, using 10 mol % $Sc(OTf)_3$ as catalyst in an attempt to get a 1:1 mixture of endo/exo isomers,[14] almost all of the expected product decomposed after 20 h, even though it appeared that product **6** was being formed when the reaction was followed by TLC.

Therefore, we limited the reaction time to a couple hours, at which point triol **5** was consumed. Under these conditions with 10 mol % $Sc(OTf)_3$, the endo and exo isomers were obtained in a 1:2 ratio for the furfural analogues; by contrast, the

Scheme 2

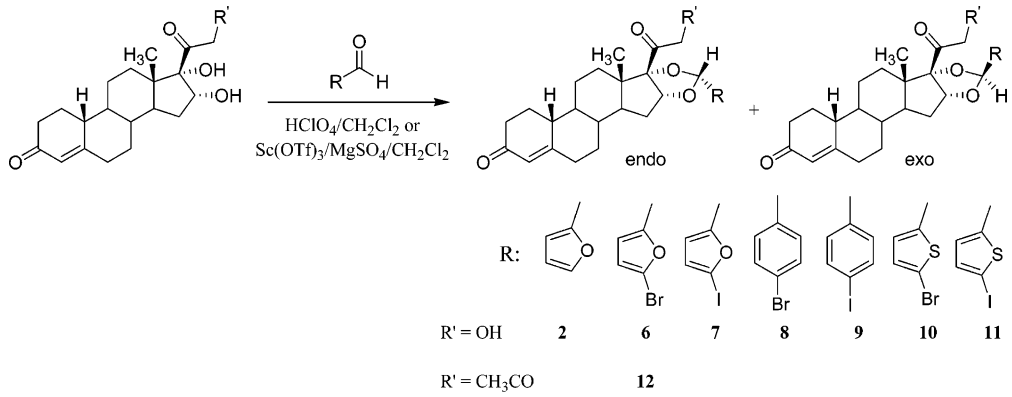


Table 1. Acetalization of Norprogesterone Triol **5**

			catalyst					
entry	compd	ratio triol:aldehyde	$HClO_4$ (M)	$Sc(OTf)_3$ (% M)	reaction time (min)	ratio[a] endo/exo	yield[b] (%)	ΔH^c (endo − exo) (kcal/mol)
1	**2**	in furfural	0.04		70	50/50	64	2.6 (0.11)
2				12	80	37/63	92	
3	**6**	1:10	0.04		50	42/58	95	1.8
4		1:20		12	120	36/64	69	
5		1:22		12	20 h	-	0	
6	**7**	1:8	0.04		45	2/3	90	1.7
7		1:8	0.08		60	45/54	90	
8	**8**	1:10	0.04		60	52/48	83	1.1
9		1:20		12	120	54/45	81	
10	**9**	1:7	0.04		45	55/44	98	1.1
11		1:15		12	90	55/44	78	
12	**10**	1:18		10	240	70/30	80	1.6
13	**11**	1:13		12	80	65/35	81	1.6
14	**12**	1:22		12	210	1/2	70	1.1

[a] The ratio is reported as HPLC integration ratio. [b] The yield is reported as isolated yield of the endo/exo isomers. [c] Geometry was optimized at the PM3 (or B3LYP) level using Spartan for Windows software package,and ΔH was calculated from the heat of formation of the geometry-optimized compound.

benzaldehyde analogues gave a 1:1 ratio, and the thiophene carboxaldehyde analogues gave a 2:1 ratio.

Because of the unusual behavior of the acetalization reaction, we studied this transformation further in a model system. Using *cis*-1,2-cyclopentanediol instead of the norprogesterone triol **5**, we attempted to establish reaction conditions for the acetalization with bromofurfural. Surprisingly, we found that $Sc(OTf)_3$ did not catalyze this acetalization at all, yet the reaction proceeded smoothly in the presence of $HClO_4$. This observation indicates that $HClO_4$ is a strong catalyst, in that both the acetalization and isomerization are very fast with this reagent, whereas $Sc(OTf)_3$ is a mild catalyst, resulting in slow formation of mixtures of the endo and exo isomers and being slow in effecting their isomerization.

Computational calculations at the semiempirical PM3 level and density function B3LYP level indicate that the endo isomer of acetal **2** is the more stable one, but only by <2 kcal/mol. Therefore, in the presence of the strong catalyst, $HClO_4$, the endo/exo diastereomers form in nearly a 1:1 ratio due to the fast acetalization and isomerization, whereas $Sc(OTf)_3$ affords kinetically controlled products under the reaction conditions.

After understanding the difference resulting from the two catalysts, we made further efforts to optimize the acetalization to obtain a high yield. We found that this acetal is not very stable under acidic conditions; in fact, it even appears to decompose slowly on a silica gel column or in aqueous solution. Therefore, we bypassed the aqueous workup and loaded the reaction mixture (2 mL in CH_2Cl_2) directly onto a silica gel column to quench the reaction. The isomer mixture could then be isolated quickly, in very good yields, by flash chromatography.

The pure diastereomers are obtained by preparative reversed phase HPLC, and the stereochemistry of the newly formed stereogenic center was assigned by an analysis of the ^{1}H NMR of the C-21 protons: those of the exo isomers are shifted upfield by about 0.5 ppm because of shielding by the aromatic ring.[20] This assignment is consistent with the HPLC retention times of the endo/exo isomers, where the endo isomers elute faster, as expected based on greater shielding of the polar functionality. All the acetals synthesized show the same ^{1}H NMR pattern of C-21 protons, and all of the endo isomers eluted faster than exo isomers.

Conversion of the Norprogestin Acetal C-21 OH to C-21 F. Previously, we obtained FFNP **1** from the precursor C-21 alcohol **2** via a triflate[13] or mesylate[14] intermediate with an overall yield of 9% and ca. 30%, respectively. The conversion took place via a nucleophilic substitution on the triflate or mesylate with tetrabutylammonium fluoride (TBAF) in THF. Because of these low yields, however, we found this route to be impractical for the synthesis of the ring-halogenated acetals and looked for an alternative method. We first tried the widely used fluorinating reagent, diethylaminosulfur trifluoride (DAST), but it did not give a clean reaction. This is not surprising because the byproduct, HF, makes the reaction mixture highly acidic.

Huffman[21] reported a direct and convenient conversion of alcohols to fluorides using a combination of perfluoro-1-butanesulfonyl fluoride (PBSF)/$NEt_3(HF)_3$/NEt_3 in THF or CH_3-

Scheme 3

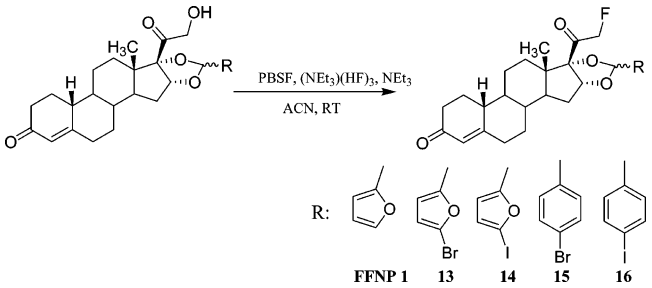


Table 2. Conversion of C-21 OH to C-21 F Using PBSF

starting material	product	reaction time (h)	yield (%)
2 (endo)	**1** (FFNP)	3	85
2 (exo)	**1** (exo)	3	81
6 (endo)	**13** (endo)	3	80
6 (exo)	**13** (exo)	3	90
7 (endo)	**14**(endo)	2.8	75
7 (exo)	**14** (exo)	2.8	92
8 (endo)	**15** (endo)	3	83
8 (exo)	**15** (exo)	3	83
9 (endo)	**16** (endo)	3	81
9 (exo)	**16** (exo)	4	80

CN. The conversion takes place under nearly neutral conditions, which are favorable to our highly acid-labile acetals. We used the reported optimized reaction conditions, that is 1:2:6:2 of alcohol/$NEt_3(HF)_3$/NEt_3/PBSF, to convert the C-21 OH to C-21 F, and we found that the reaction proceeded smoothly in CH_3-CN at ambient temperature in high yields, as shown in Scheme 3 and Table 2. Activation of this S_N2 reaction by the C-20 ketone undoubtedly contributed to these good yields.

Progestin Receptor Binding Affinities. The relative binding affinities of the new compounds we have prepared as ligands for the PR were determined by a competitive radiometric binding assay using [^{3}H]R5020 as tracer and R5020 as a standard, as previously described.[22] The binding affinities are expressed as relative binding affinity (RBA) values, with the RBA of the R5020 standard set to 100 (R5020 binds to PR with a K_d of 0.4 nM). The values given are the average ± range or SD of two or more independent determinations. The results are shown in Table 3 together with the octanol/water partition coefficient calculated using ACD software.

First, the RBA values of the two known compounds **1** and FFNP (**2**), previously determined using rat uterine PR (entries 3 and 4),[22] were determined again here with human recombinant PR (entries 1 and 2), which is commercially available. The binding affinities are very similar in both systems. Therefore, the other ligands were assayed using human recombinant PR rather than the rat uterine PR.

Generally, 16α or 17α substitutents are expected to enhance the binding of ligands to the PR.[23] All the bromine- and iodine-substituted progestin ligands synthesized show binding affinities to PR that range from poor to good, but none are as high as those of the fluorine-substituted dioxolane ligands reported previously.[13,19] This could be due both to the greater bulk of the bromine and iodine atoms, as well as to their electronic effects.

We[13,19,20] and others[18] have shown that when the 16α,17α-dioxolane aromatic substituent is endo, the PR binding affinity is better than when it is exo. The higher affinity of the endo isomer, however, does not hold for all of the phenyl ligands. The exo isomer binds better than the endo for compounds **9**, **15**, and **16**, especially for compound **16**, for which exo isomer (RBA = 34) has a 5-fold higher affinity compared to the endo isomer (RBA = 6.4). In fact, the exo isomer of **16** could be a good candidate for labeling with iodine.

On the basis of the compounds synthesized previously,[13] we expected that the conversion of C-21 substituent from OH to F would enhance the binding affinity considerably. For example, this conversion results in a ca. 4-fold increase in the case of compounds **2** (C-21 OH) and **1** (C-21 F). For the bromine- and iodine-substituted ligands, the increase in binding affinity for this conversion was observed for all exo isomers: the increase was only 2-fold for the bromofuranyl derivatives (exo isomer **6** to **13**) and 4-fold for the iodofuranyl derivatives (exo isomer **7** to **14**), but the increase was 10-fold for the bromophenyl derivatives (exo isomer **8** to **15**) and 20-fold for the iodophenyl ones (exo isomer **9** to **16**).

Not all of the endo isomers benefit from the C-21 OH to F conversion. The binding affinity increased for those with iodine substituents (endo isomer **7** and **9**), but it decreased for those with bromine substituents (endo isomer **6** and **8**). The endo isomer of **14** shows good binding affinity, and it could also be a good candidate for iodine labeling. The conversion of C-21 OH to C-21 acetyl decreases the binding affinity, so the acetyl analogues do not merit further consideration.

Comparing bromine and iodine analogues with the same aromatic ring systems, the bromo-substituted ones have better binding affinity than the iodo-substituted ones in the endo series, but this is reversed in the exo series. When the aromatic ring structures are compared, the furanyl group furnishes the best binding affinity, while thiophenyl group gives the worst results.

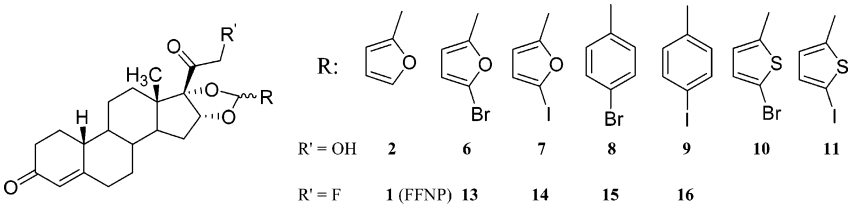
Because the lipophilicity of a steroidal ligand is directly related to its binding affinity for low-affinity, non specific sites,[24] the octanol/water partition coefficients values (log $P_{o/w}$) were calculated, and the results are shown in Table 3, along with those measured previously by an experimental method for comparison.[13] It is clear that compound **6** has the lowest lipophilicity among the bromine- and iodine-substituted ligands. The phenyl ligands have the highest lipophilicity.

In terms of binding affinity to PR and lipophilicity, the endo isomer of compound **6** has the best binding affinity for PR with the least lipophilicity. Thus, the endo epimer of **6**, along with the endo epimer of **14** and the exo epimer of **16** are most likely to meet our requirement for radiolabeling for both diagnostic imaging and radiotherapy purpose. Further study of radiolabeling is underway and will be reported separately.

Conclusion

We have synthesized a series of bromine- and iodine-substituted 16α,17α-dioxolane progestins, potential agents—with proper radiolabeling—for diagnostic imaging using positron emission tomography (PET) or for radiotherapy. These compounds were synthesized from the halogenated aromatic aldehydes and the key 19-norprogestin 6α,17α,21-triol **5** in the presence of $HClO_4$ or $Sc(OTf)_3$, using a procedure that was carefully optimized to achieve high yields. Conversion of the C-21 substituent from OH to F was effected in high yield by a combination of perfluoro-1-butanesulfonyl fluoride (PBSF), $(NEt_3)(HF)_3$, and NEt_3. The binding affinities of these compounds for human progesterone receptor (PR) were determined using a competitive radiometric binding assay. On the basis of PR binding affinity and lipophilicity (estimated from the calculated octanol−water partition coefficient), 16α,17α-[(*R*)-1′-α-(5-bromofurylmethylidene)dioxyl]-21-hydroxy-19-norpregn-4-ene-3,20-dione (*endo*-**6**) (having a relative binding affinity of 65 compared to 100 for the standard R5020) was determined to be the most promising agent, along with 21-fluoro-16α,17α-

Table 3. Progesterone Receptor Binding Affinities and Octanol−Water Partition Coefficients



		relative binding affinity					relative binding affinity		
entry	compd	endo	exo	log $P_{o/w}$[b]	entry	compd	endo	exo	log $P_{o/w}$
1	**2**	53 ± 15	2.4 ± 0.5	4.15 ± 0.69 (3.78/4.01)[c]	2	**1**	180 ± 40	5.0 ± 0.9	4.40 ± 0.82 (3.87/4.11)[c]
3	**2**[a]	55 ± 19	2.5 ± 0.9		4	**1**[a]	190 ± 22	11 ± 4	
5	**6**	65 ± 6	2.3 ± 0.3	5.09 ± 0.84	6	**13**	24 ± 4	4.4 ± 1.1	5.34 ± 0.89
7	**7**	23 ± 3	2.6 ± 0.2	5.48 ± 0.75	8	**14**	40 ± 6	9.0 ± 0.8	5.73 ± 0.85
9	**8**	23 ± 4	0.41 ± 0.09	5.76 ± 0.73	10	**15**	3.9 ± 1.7	4.7 ± 0.8	6.01 ± 0.85
11	**9**	0.81 ± 0.14	1.8 ± 0.6	6.02 ± 0.73	12	**16**	6.4 ± 1.4	34 ± 4	6.27 ± 0.85
13	**10**	5.2 ± 0.7	1.7 ± 0.8	5.52 ± 0.78	14	**11**	3.2 ± 0.7	0.95 ± 0.25	6.00 ± 0.76
15	**12**	7.1 ± 0.1	1.4 ± 0.2	6.21 ± 0.86					

[a] Determined using rat uterine PR. [b] Calculated using ACD LogP software. [c] Measured by HPLC, see ref 13.

[(*R*)-1′-α-(5-iodofurylmethylidene)dioxyl]-19-norpregn-4-ene-3,20-dione (*endo*-**14**) (RBA = 40) and 21-fluoro-16α,17α-[(*S*)-1′-*β*-(4-iodophenylmethylidene)dioxyl]-19-norpregn-4-ene-3,20-dione (*exo*-**16**) (RBA = 34). These compounds are planned for further study.

Experimental Section

All chemicals were obtained from standard commercial sources and used without further purification. All reactions were carried out by standard air-free and moisture-free techniques under an inert argon atmosphere with dry solvents unless otherwise stated. Flash column chromatography was conducted using Scientific Adsorbents, Inc. silica gel, 60A, "40 Micron Flash" (32−63 μm). Melting points were determined using MEL-TEMP 3.0 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity-300 (300 MHz) NMR spectrometer. All chemical shifts were reported a part per million (ppm) downfield from tetramethylsilane (TMS). Chloroform-*d* was used as solvent, and the residual $CHCl_3$ solvent peak at δ 7.25 ppm was used as an internal standard. All coupling constants (*J*) are given in Hertz (Hz). Splitting patterns are typically described as follows: s, singlet; d, doublet; t, triplet; m, multiplet. ^{19}F NMR spectra were recorded at 282.22 MHz, and chemical shifts are reported as ppm upfield from an external $CFCl_3$ standard. High-pressure liquid chromatography (HPLC) was performed with UV detection at 254 nm with acetonitrile and water as mobile phase using Alltech Altima C18 250 × 22 mm preparative column for separation and Altech Altima C18 250 × 4.6 mm analytical column for analysis. Elemental analyses (C, H) were determined by Atlantic Microlab, Inc. ESI/MS was performed on a Waters ZQ 4000 single quadrupole mass spectrometer equipped with an electrospray ionization (ESI) LC-MS interface. 5-Iodothiophene-2-carboxaldehyde[25] and 5-iodofurane-2-carboxaldehyde[26] were synthesized according to literature procedures.

Synthesis of Progargylic Ester (4). To a stirred mixture of 2.0 g (6.7 mmol) **3** and 160 mg (0.33 mmol) $Sc(OTf)_3$ in 40 mL dry CH_3CN was added 850 μL (8.3 mmol) acetic anhydride. The reaction mixture became homogeneous in 10 min, and almost all of **3** was consumed in 1 h according to TLC. Upon completion of the reaction, the mixture was diluted with 100 mL ethyl acetate and washed with saturated $NaHCO_3$ and NaCl solution. Solvent was evaporated and flash chromatography (1:4 EtOAc/hexane, R_f = 0.1) gave 1.97 g **4** as white solid in 86% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.84 (s, 1H), 2.05 (s, 3H, $COCH_3$), 0.93 (s, 3H, CH_3).

General Procedure: Synthesis of 16α,17α-dioxolane Derivatives Using $HClO_4$ as Catalyst. Into a 5 mL dry round-bottom flask equipped with a magnetic stirring bar and septum were loaded 100 mg triol **5**, 10-fold excess of the corresponding aromatic aldehyde, and 2 mL dry CH_2Cl_2, followed by addition of 7 μL 70% $HClO_4$ via a syringe. The reaction mixture became brown in color, and the triol solid dissolved in CH_2Cl_2 gradually during the reaction. The reaction was checked by TLC, and usually it was complete within 1 h. Upon completion of the reaction, the reaction mixture was loaded onto a silica gel column directly to quench the reaction and for purification. The excess of aldehyde was eluted using 1:1 EtOAc/hexane, and the two isomers were eluted using 7:3 EtOAc/hexane. After removal of solvents under reduced pressure, the isomer mixture was purified further using reversed phase C18 preparative HPLC with CH_3CN and water as mobile phase. Pure isomer was obtained by removing HPLC solvents under vacuum (<10 Torr) at ambient temperature. The yield for the mixture before HPLC purification was around 90%.

General Procedure: Synthesis of 16α,17α-Dioxolane Derivatives Using $Sc(OTf)_3$ as Catalyst. Into a 5 mL dry round-bottom flask equipped with a magnetic stirring bar and septum were loaded 100 mg triol **5**, 10−20-fold excess of the corresponding aromatic aldehyde, 10% mmol $Sc(OTf)_3$, 100 mg anhydrous magnesium sulfate, and 2 mL dry CH_2Cl_2. The reaction mixture was stirred at ambient temperature and checked by TLC. Upon completion of the reaction, the reaction mixture was loaded onto a silica gel column directly for purification. The excess of aldehyde was eluted using 1:1 EtOAc/hexane, and the two isomers were eluted using 7:3 EtOAc/hexane. After removal of solvents under reduced pressure, the isomer mixture was purified further using reversed phase C18 preparative HPLC with CH_3CN and water as mobile phase. Pure isomer was obtained by removing HPLC solvents under vacuum (<10 Torr) at ambient temperature.

General Procedure: Fluorination Using Perfluoro-1-butanesulfonyl Fluoride (PBSF). Into a 10 mL dry round-bottom flask equipped with a magnetic stirring bar and septum were loaded 0.064 mmol 21-hydroxy acetal derivative and 6 mL CH_3CN, followed by 22.5 μL (0.127 mmol) PBSF, 53.4 μL (0.38 mmol) NEt_3, and 20.7 μL (0.127 mmol) $(NEt_3)(HF)_3$. The reaction mixture was stirred at room temperature for 3 h to complete the reaction. Solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography using 1:1 EtOAc/hexane to afford the product as white solids in 80% to 90% yield.

Data for *endo*-6. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.48 (d, 1H, *J* = 3.3 Hz), 6.31 (d, 1H, *J* = 3.3 Hz), 5.85 (s, 1H), 5.55 (s, 1H), 5.08 (d, 1H, *J* = 5.7 Hz), 4.48 (AB, q, 2H, $\Delta\upsilon$ = 0.32 ppm, *J* = 20.4 Hz), 3.0 (s, br, 1H), 2.6−0.8 (m, 18H), 0.72 (s, 3H); mp. 155.3−156.0 °C; Elemental analysis: Calcd for $C_{25}H_{29}BrO_6 + H_2O$

(522.13): C 57.37, H 5.97; Found: C 57.11, H 5.85. MS (ESI): *m*/*z* 526.84 ($M^+ + 23$).

Data for *exo*-6. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.29 (d, 1H, $J = 3.3$ Hz), 6.23 (d, 1H, $J = 3.3$ Hz), 6.11 (s, 1H), 5.84 (s, 1H), 5.31 (d, 1H, $J = 6.0$ Hz), 4.21 (AB, q, 2H, $\Delta\upsilon = 0.18$ ppm, $J = 20.1$ Hz), 2.6−0.8 (m, 18H), 0.72 (s, 3H); mp. 150.0−151.0 °C; Elemental analysis: Calcd for $C_{25}H_{29}BrO_6$ (504.11): C 59.41, H 5.78; Found: C 59.14, H 5.90; MS (ESI): *m*/*z* 526.74 ($M^+ + 23$).

Data for *endo*-7. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.54 (d, 1H, $J = 3.3$ Hz), 6.43 (d, 1H, $J = 3.3$ Hz), 5.85 (s, 1H), 5.59 (s, 1H), 5.08 (d, 1H, $J = 5.4$ Hz), 4.48 (AB, qd, 2H, $\Delta\upsilon = 0.32$ ppm, $J = 4.5$, 20.1 Hz), 2.98 (t, 1H, $J = 4.8$ Hz), 2.6−0.8 (m, 18H), 0.73 (s, 3H); mp. 135 °C decomposition; Elemental analysis: Calcd for $C_{25}H_{29}IO_6 + H_2O$ (570.11): C 52.64, H 5.48; Found: C 52.96, H 5.20; MS (ESI): *m*/*z* 574.76 ($M^+ + 23$).

Data for *exo*-7. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.46 (d, 1H, $J = 3.3$ Hz), 6.23 (d, 1H, $J = 3.3$ Hz), 6.15 (s, 1H), 5.85 (s, 1H), 5.32 (d, 1H, $J = 5.7$ Hz), 4.19 (AB, qd, 2H, $\Delta\upsilon = 0.16$ ppm, $J = 4.2$, 20.1 Hz), 2.83 (t, 1H, $J = 4.8$ Hz) 2.6−0.8 (m, 18H), 0.73 (s, 3H); mp. 145 °C decomposition; Elemental analysis: Calcd for $C_{25}H_{29}IO_6 + H_2O$ (570.11): C 52.64, H 5.48; Found: C 52.81, H 5.17; MS (ESI): *m*/*z* 574.76 ($M^+ + 23$).

Data for *endo*-8. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.53 (d, 2H, $J = 8.7$ Hz), 7.33 (d, 2H, $J = 8.1$ Hz), 5.84 (s, 1H), 5.43 (s, 1H), 5.08 (d, 1H, $J = 5.4$ Hz), 4.49 (AB, q, 2H, $\Delta\upsilon = 0.32$ ppm, $J = 20.4$ Hz), 2.6−0.8 (m, 18H), 0.73 (s, 3H); mp. 133.5−135.0 °C; Elemental analysis: Calcd for $C_{27}H_{31}BrO_5 + 0.5\ H_2O$ (523.14): C 61.83, H 6.15; Found: C 62.14, H 6.20; MS (ESI): *m*/*z* 514.87 ($M^+ + 1$).

Data for *exo*-8. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.49 (d, 2H, $J = 6.6$ Hz), 7.20 (d, 2H, $J = 6.9$ Hz), 6.11 (s, 1H), 5.85 (s, 1H), 5.40 (d, 1H, $J = 6.3$ Hz), 4.20 (AB, q, 2H, $\Delta\upsilon = 0.19$ ppm, $J = 20.1$ Hz), 2.6−0.9 (m, 18H), 0.75 (s, 3H); mp. 215.0−219.0 °C; Elemental analysis: Calcd for $C_{27}H_{31}BrO_5$ (514.14): C 62.92, H 6.06; Found: C 62.87, H 6.20; MS (ESI): *m*/*z* 514.81 ($M^+ + 1$).

Data for *endo*-9. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.75 (d, 2H, $J = 8.7$ Hz), 7.19 (d, 2H, $J = 8.1$ Hz), 5.84 (s, 1H), 5.42 (s, 1H), 5.08 (d, 1H, $J = 5.4$ Hz), 4.49 (AB, q, 2H, $\Delta\upsilon = 0.32$ ppm, $J = 20.4$ Hz), 3.0 (s, br, 1H), 2.6−0.8 (m, 18H), 0.73 (s, 3H); mp. 239.5−241.9 °C; Elemental analysis: Calcd for $C_{27}H_{31}IO_5 + 0.5\ H_2O$ (571.45): C 56.75, H 5.64; Found: C 56.96, H 5.63; MS (ESI): *m*/*z* 584.83 ($M^+ + 23$).

Data for *exo*-9. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.69 (d, 2H, $J = 8.1$ Hz), 7.06 (d, 2H, $J = 8.4$ Hz), 6.09 (s, 1H), 5.85 (s, 1H), 5.40 (d, 1H, $J = 6.0$ Hz), 4.19 (AB, q, 2H, $\Delta\upsilon = 0.19$ ppm, $J = 19.8$ Hz), 2.6−0.9 (m, 18H), 0.75 (s, 3H); mp. 239.0−241.0 °C; Elemental analysis: Calcd for $C_{27}H_{31}IO_5$ (562.12): C 57.66, H 5.56; Found: C57.38, H 5.57; MS (ESI): *m*/*z* 584.70 ($M^+ + 23$).

Data for *endo*-10. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.96 (d, 1H, $J = 3.9$ Hz), 6.92 (d, 1H, $J = 3.6$ Hz), 5.87 (s, 1H), 5.71 (s, 1H), 5.06 (d, 1H, $J = 5.4$ Hz), 4.48 (AB, q, 2H, $\Delta\upsilon = 0.33$ ppm, $J = 20.4$ Hz), 3.0 (s, br, 1H), 2.6−0.8 (m, 18H), 0.72 (s, 3H); mp. 131.5−134.4 °C; Elemental analysis: Calcd for $C_{25}H_{29}BrO_5S$ (520.09): C 57.58, H 5.61; Found: C 57.41, H 5.68; MS (ESI): *m*/*z* 542.75 ($M^+ + 23$).

Data for *exo*-10. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.92 (d, 1H, $J = 3.6$ Hz), 6.86 (d, 1H, $J = 3.9$ Hz), 6.29 (s, 1H), 5.85 (s, 1H), 5.37 (d, 1H, $J = 6.3$ Hz), 4.33 (AB, qd, 2H, $\Delta\upsilon = 0.35$ ppm, $J = 3.9$, 20.4 Hz), 2.6−0.8 (m, 18H), 0.75 (s, 3H); mp. 206.4−208.4 °C; Elemental analysis: Calcd for $C_{25}H_{29}BrO_5S + 0.5\ H_2O$ (529.09): C 56.60, H 5.70; Found: C 56.36, H 5.66; MS (ESI): *m*/*z* 542.85 ($M^+ + 23$).

Data for *endo*-11. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.15 (d, 1H, $J = 3.9$ Hz), 6.83 (d, 1H, $J = 3.6$ Hz), 5.87 (s, 1H), 5.75 (s, 1H), 5.06 (d, 1H, $J = 5.4$ Hz), 4.48 (AB, q, 2H, $\Delta\upsilon = 0.33$ ppm, $J = 20.4$ Hz), 2.6−0.8 (m, 18H), 0.72 (s, 3H); mp. 174.0−175.3 °C; Elemental analysis: Calcd for $C_{25}H_{29}IO_5S$ (568.5): C 52.82, H 5.14; Found: C 52.87, H 5.11; MS (ESI): *m*/*z* 591.1 ($M^+ + 23$).

Data for *exo*-11. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.11 (d, 1H, $J = 3.6$ Hz), 6.78 (d, 1H, $J = 3.6$ Hz), 6.33 (s, 1H), 5.85 (s, 1H), 5.37 (d, 1H, $J = 5.7$ Hz), 4.33 (AB, q, 2H, $\Delta\upsilon = 0.35$ ppm, $J = 20.1$ Hz), 2.9 (br, 1H), 2.6−0.8 (m, 18H), 0.75 (s, 3H); mp. 199.0−201.0 °C; Elemental analysis: Calcd for $C_{25}H_{29}IO_5S$ (568.5): C 52.82, H 5.14; Found: C 52.80, H 5.30; MS (ESI): *m*/*z* 591.1 ($M^+ + 23$).

Data for *endo*-12. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.50 (d, 1H, $J = 3.3$ Hz), 6.32 (d, 1H, $J = 3.3$ Hz), 5.85 (s, 1H), 5.63 (s, 1H), 5.05 (d, 1H, $J = 5.7$ Hz), 4.92 (AB, q, 2H, $\Delta\upsilon = 0.12$ ppm, $J = 18.0$ Hz), 2.6−0.8 (m, 18H), 2.19 (s, 3H), 0.77 (s, 3H); Elemental analysis: Calcd for $C_{27}H_{31}BrO_7$ (546.13): C 59.24, H 5.71; Found: C 59.11, H 5.72; MS (ESI): *m*/*z* 569.08 ($M^+ + 23$).

Data for *exo*-12. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.34 (d, 1H, $J = 3.3$ Hz), 6.27 (d, 1H, $J = 3.3$ Hz), 6.11 (s, 1H), 5.84 (s, 1H), 5.27 (d, 1H, $J = 5.7$ Hz), 4.68 (AB, q, 2H, $\Delta\upsilon = 0.0.38$ ppm, $J = 17.4$ Hz), 2.6−0.8 (m, 18H), 2.15 (s, 3H), 0.72 (s, 3H); mp. 157.9−160.2°C; Elemental analysis: Calcd for $C_{27}H_{31}BrO_7$ (546.13): C 59.24, H 5.71; Found: C 59.10, H 5.61; MS (ESI): *m*/*z* 569.10 ($M^+ + 23$).

Data for *endo*-13. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.49 (d, 1H, $J = 3.3$ Hz), 6.31 (d, 1H, $J = 3.3$ Hz), 5.85 (s, 1H), 5.58 (s, 1H), 5.27 (d, 1H, $J = 55.2$, $J_{H-F} = 17.1$ Hz), 5.11 (d, 1H, $J = 54.9$, $J_{H-F} = 17.4$ Hz), 5.09 (d, 1H, $J = 5.4$ Hz), 2.6−0.8 (m, 18H), 0.77 (s, 3H); ^{19}F ($CDCl_3$, 282.4 MHz) δ: − 56.88 (t, $J = 47.3$ Hz); mp. 156.1−158.1 °C; Elemental analysis: Calcd for $C_{25}H_{28}BrFO_5 + 2\ H_2O$ (542.13): C 55.26, H 5.94; Found: C 54.90, H 5.33; MS (ESI): *m*/*z* 529.08 ($M^+ + 23$). HRMS: Calcd for $C_{25}H_{28}BrFO_5 + Na^+$, 529.1002; found, 529.0996.

Data for *exo*-13. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.32 (d, 1H, $J = 3.3$ Hz), 6.25 (d, 1H, $J = 3.3$ Hz), 6.09 (s, 1H), 5.83 (s, 1H), 5.28 (d, 1H, $J = 6.0$ Hz), 5.00 (d, 1H, $J = 12.6$, $J_{H-F} = 17.1$ Hz), 4.85 (d, 1H, $J = 12.6$, $J_{H-F} = 17.1$ Hz), 2.6−0.8 (m, 18H), 0.77 (s, 3H); ^{19}F ($CDCl_3$, 282.4 MHz) δ: − 56.49 (t, $J = 47.3$ Hz); mp. 183.8−184.6 °C; Elemental analysis: Calcd for $C_{25}H_{28}BrFO_5$ (506.11): C 59.18, H 5.56. Found: C 58.63, H 5.65; MS (ESI): *m*/*z* 529.08 ($M^+ + 23$). HRMS: Calcd for $C_{25}H_{28}BrFO_5 + Na^+$, 529.1002; found, 529.0976.

Data for *endo*-14. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.54 (d, 1H, $J = 3.3$ Hz), 6.42 (d, 1H, $J = 3.3$ Hz), 5.85 (s, 1H), 5.62 (s, 1H), 5.27 (d, 1H, $J = 55.2$, $J_{H-F} = 17.1$ Hz), 5.11 (d, 1H, $J = 55.5$, $J_{H-F} = 17.4$ Hz), 5.09 (d, 1H, $J = 5.7$ Hz), 2.6−0.8 (m, 18H), 0.77 (s, 3H); ^{19}F ($CDCl_3$, 282.4 MHz) δ: − 56.88 (t, $J = 48.9$ Hz); mp. 170.6−171.6 °C; Elemental analysis: Calcd for $C_{25}H_{28}FIO_5$ (554.10): C 54.16, H 5.09; Found: C54.22, H 5.33; MS (ESI): *m*/*z* 576.89 ($M^+ + 23$).

Data for *exo*-14. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.47 (d, 1H, $J = 3.63$ Hz), 6.26 (d, 1H, $J = 3.63$ Hz), 6.13 (s, 1H), 5.83 (s, 1H), 5.28 (d, 1H, $J = 3.0$ Hz),4.98 (d, 1H, $J = 6.6$, $J_{H-F} = 17.1$ Hz), 4.82 (d, 1H, $J = 6.6$, $J_{H-F} = 17.1$ Hz), 2.6−0.8 (m, 18H), 0.77 (s, 3H); ^{19}F ($CDCl_3$, 282.4 MHz) δ: − 56.48 (t, $J = 48.8$ Hz); mp. 150 °C decomposition; MS (ESI): *m*/*z* 576.89 ($M^+ + 23$). HRMS: Calcd for $C_{25}H_{28}FIO_5 + H^+$, 555.1044; found, 555.1066.

Data for *endo*-15. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.54 (d, 2H, $J = 8.4$ Hz), 7.33 (d, 2H, $J = 8.4$ Hz), 5.84 (s, 1H), 5.46 (s, 1H), 5.27 (d, 1H, $J = 52.5$, $J_{H-F} = 17$ Hz), 5.11 (d, 1H, $J = 52.5$, $J_{H-F} = 17$ Hz), 5.09 (d, 1H, $J = 5.4$ Hz), 2.6−0.8 (m, 18H), 0.77 (s, 3H); ^{19}F ($CDCl_3$, 282.4 MHz) δ: − 56.88 (t, $J = 48.9$ Hz); mp. 148.0−152.0 °C; Elemental analysis: Calcd for $C_{27}H_{30}BrFO_4$ (516.13): C 62.67, H 5.84; Found: C 62.74, H 6.09; MS (ESI): *m*/*z* 539.09 ($M^+ + 23$).

Data for *exo*-15. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.50 (d, 2H, $J = 8.7$ Hz), 7.21 (d, 2H, $J = 8.1$ Hz), 6.10 (s, 1H), 5.84 (s, 1H), 5.40 (d, 1H, $J = 6.3$ Hz), 4.93 (d, 1H, $J = 2.7$, $J_{H-F} = 17.4$ Hz), 4.77 (d, 1H, $J = 2.7$, $J_{H-F} = 17.4$ Hz), 2.6−0.8 (m, 18H), 0.79 (s, 3H); ^{19}F ($CDCl_3$, 282.4 MHz) δ: − 55.58 (t, $J = 48.9$ Hz); mp. 156.7−162.3 °C; Elemental analysis: Calcd for $C_{27}H_{30}BrFO_4$ (516.13): C 62.67, H 5.84; Found: C 62.68, H 6.06; MS (ESI): *m*/*z* 539.09 ($M^+ + 23$).

Data for *endo*-16. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.75 (d, 2H, $J = 8.4$ Hz), 7.18 (d, 2H, $J = 8.4$ Hz), 5.83 (s, 1H), 5.45 (s, 1H), 5.27 (d, 1H, $J = 52.2$, $J_{H-F} = 17.1$ Hz), 5.11 (d, 1H, $J = 52.2$, $J_{H-F} = 17.1$ Hz), 5.08 (d, 1H, $J = 5.7$ Hz), 2.6−0.8 (m, 18H), 0.77

(s, 3H); ^{19}F ($CDCl_3$, 282.4 MHz) δ: − 56.89 (t, J = 48.9 Hz); mp. 181.6−185.0 °C; Elemental analysis: Calcd for $C_{27}H_{30}FIO_4$ (564.12): C 57.45, H 5.36; Found: C56.80, H 5.44; MS (ESI): m/z 587.10 (M^+ + 23).

Data for *exo*-16. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.71 (d, 2H, J = 8.7 Hz), 7.07 (d, 2H, J = 8.1 Hz), 6.08 (s, 1H), 5.84 (s, 1H), 5.39 (d, 1H, J = 6.0 Hz), 4.93 (d, 1H, J = 2.7, J_{H-F} = 17.1 Hz), 4.77 (d, 1H, J = 2.7, J_{H-F} = 17.1 Hz), 2.6−0.8 (m, 18H), 0.79 (s, 3H); ^{19}F ($CDCl_3$, 282.4 MHz) δ: − 55.58 (t, J = 48.9 Hz); mp. 190.4−194.2 °C; Elemental analysis: Calcd for $C_{27}H_{30}FIO_4$ (564.12): C 57.45, H 5.36; Found: C57.68, H 5.59; MS (ESI): m/z 587.04 (M^+ + 23).

Progesterone Receptor Binding Affinity Assays. Relative binding affinities were determined by a competitive radiometric binding assay as previously described,[19] using 10 nM [^{3}H]R5020 as tracer ([17α-methyl-3H]-promegestone) (Perkin-Elmer, Boston, MA), unlabeled R5020 as standard, and purified full length progesterone receptor B from PanVera/Invitrogen (Carlsbad, CA). Incubations were for 18−24 h at 0 °C. Hydroxyapatite (BioRad, Hercules, CA) was used to absorb the receptor−ligand complexes, and free ligand was removed by washing with cold buffer. The binding affinities are expressed as relative binding affinity values with the RBA of R5020 set to 100%. The values given are the average ± range or SD of two or more independent determinations. R5020 binds to PR with a K_d of 0.4 nM.

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Supporting Information Available: Elemental analyses and mass spectrometry data of compound **6**−**16**, HPLC conditions for separation of isomers of compound **6**−**12**. ^{1}H NMR spectra of compound **6**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org

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