Synthesis and Biological Evaluation of [^{18}F]Bicalutamide, 4-[^{76}Br]Bromobicalutamide, and 4-[^{76}Br]Bromo-thiobicalutamide as Non-Steroidal Androgens for Prostate Cancer Imaging

Ephraim E. Parent,[†] Carmen S. Dence,[‡] Carl Jenks,[‡] Terry L. Sharp,[‡] Michael J. Welch,[‡] and John A. Katzenellenbogen*[,†]

Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801, and Washington University School of Medicine, Saint Louis, Missouri 63110

Received July 19, 2006

Androgen receptors (AR) are overexpressed in most primary and metastatic prostate cancers. To develop a nonsteroidal AR-mediated imaging agent, we synthesized and radiolabeled several analogs of the potent antiandrogen bicalutamide: [^{18}F]bicalutamide, 4-[^{76}Br]bromobicalutamide, and [^{76}Br]bromo-thiobicalutamide. Two of these analogs, 4-[^{76}Br]bromobicalutamide and [^{76}Br]bromo-thiobicalutamide, were found to have a substantially increased affinity for the androgen receptor (AR) compared to that of bicalutamide. The synthesis of [^{18}F]bicalutamide utilized a pseudocarrier approach to effect addition of a carbanion generated from tracer-level amounts of a radiolabeled precursor to an unlabeled carbonyl precursor. 4-[^{76}Br]Bromobicalutamide and [^{76}Br]bromo-thiobicalutamide were labeled through electrophilic bromination of a tributylstannane precursor. The former could be prepared in high specific activity, and its tissue distribution was tested in vivo. Androgen target tissue uptake was evident in castrated adult male rats; however, in DES-treated, AR-positive, tumor-bearing male mice, tumor uptake was low.

Introduction

Prostate cancer is the second leading cause of cancer death in men in the United States,[1] and it has been directly linked to the androgen receptor (AR)[a] in most cases. Androgen ablation monotherapy, surgical or chemical castration with nonsteroidal antiandrogens such as flutamide (**1**) and bicalutamide (**2**), is the principal initial treatment for progressive prostate cancer and results in the regression of most androgen-dependent tumors.[2] Many men eventually fail androgen ablation therapy, however, and die of recurrent androgen-independent prostate cancer (AIPC).

In our efforts to develop agents for the in vivo imaging of androgen receptor (AR) in prostate cancers by positron emission tomography (PET), we and others have prepared steroidal[3−5] and nonsteroidal[6,7] AR ligands labeled with fluorine-18. Several of these ^{18}F-labeled *steroidal* androgens show tissue distribution in chemically castrated rats that is consistent with their uptake by an AR-dependent process, namely, selective target tissue (prostate) accumulation that is effectively blocked by coadministration of a blocking dose of unlabeled androgen.[3,5] One of the agents we have developed, 16β-[^{18}F]fluoro-5α-dihydrotestosterone (FDHT), has proved to be an effective agent for PET imaging of AR-positive prostate tumors in humans.[8,9]

Despite androgen deprivation therapy, most patients will experience disease progression to AIPC,[10] a stage at which only a small fraction of tumors respond to secondary hormonal therapies, including treatment with nonsteroidal antiandrogens.[11] In fact, at this stage treatment with an antiandrogen often leads to increased tumor growth.[12−14] Although the cause of this antiandrogen activation is not known, it is believed to be due to changes in the androgen signaling cascade.[15] Therefore, PET imaging agents that are close structural analogs of the nonsteroidal antiandrogen compounds used in second-line hormone therapy, namely, flutamide and bicalutamide, might be particularly useful because failure of these agents generally presages the onset of unmanageable disease. The development of effective PET imaging agents based on such nonsteroidal androgens, however, has proved to be a challenge.[16−18]

The nonsteroidal antiandrogen bicalutamide is the leading antiandrogen used for the treatment of prostate cancer. Nonsteroidal antiandrogens, such as flutamide and bicalutamide, are often referred to as "pure antiandrogens" because they bind exclusively to the AR and, therefore, are devoid of antigonadotropic, antiestrogenic, and progestational effects (Figure 1).[19] Bicalutamide is a racemic mixture,[20,21] with the R enantiomer having 30-fold higher binding affinity than the S isomer.[22] In this study, we describe the syntheses of ^{18}F and ^{76}Br-labeled androgen receptor ligands based on the bicalutamide core: [^{18}F]bicalutamide, 4-[^{76}Br]bromobicalutamide, and [^{76}Br]bromo-thiobicalutamide, the last being based on thiobicalutamide, a bicalutamide analog reported to have improved AR binding affinity.[23] We determined the AR binding affinity of these compounds and related analogs, and we determined the metabolic stability and tissue biodistribution of 4-[^{76}Br]bromobicalutamide in rats and tumor-bearing mice.

Results

Chemistry. Linear Synthesis of Bicalutamide (1). Our first attempt to develop a synthesis of bicalutamide suitable for radiolabeling involved a linear synthetic route, shown in Scheme 1. 4-Cyano-3-trifluoromethyl-aniline (**5**) was condensed with pyruvic acid chloride[24] to produce ketoamide **6** in 27% yield.[21] The keto moiety of **6** was attacked by the anion of amine **12,**[25] which was formed using either lithium diisopropyl amide (LDA) or *n*-BuLi, to afford anilide **7** in 30%. Anilide **7** was protected with acetyl chloride to give the corresponding ester (**8**),[26] and then N-methylated with methyl trifluoromethanesulfonate[27,28] to form the ammonium salt **9** in 53% and 66% yields, respectively.

* Corresponding author. Phone: 217-333-6310. E-mail: jkatzene@uiuc.edu.
[†] University of Illinois.
[‡] Washington University School of Medicine.

[a] Abbreviations: AR, androgen receptor; AIPC, androgen-independent prostate cancer; PET, positron emission tomography; FDHT, 16β-[^{18}F]-fluoro-5α-dihydrotestosterone; LDA, lithium diisopropyl amide; TBAF, tetrabutylammonium fluoride; RBA, relative binding affinity; DHT, dihydrotestosterone.

10.1021/jm060847r CCC: $37.00
Published on Web 01/20/2007

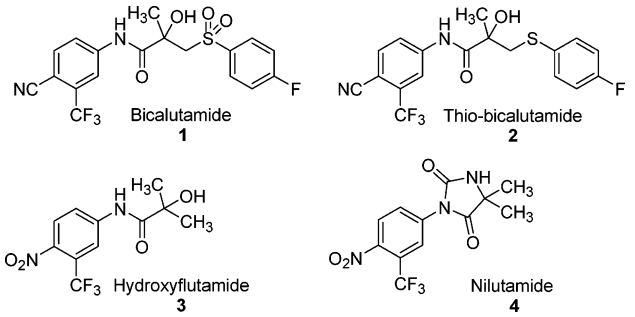


Figure 1. Bicalutamide and other nonsteroidal anilide AR antagonists.

Whereas treatment of the labeling precursor **9** with either tetrabutylammonium fluoride (TBAF), KF/kryptofix[2.2.2], or CsF/ionic liquid, did result in the incorporation of fluorine into the desired sulfone activated ring, it simultaneously led to the unwanted formation of isomeric alkene by products **10ab**.[29,30] These elimination products are believed to arise from the deprotonation of the anilide nitrogen of **9** by fluoride, producing a reactive amide anion that extracts a hydrogen vicinal to the acetate ester to furnish the observed alkene products. Several attempts were made either to protect the anilide nitrogen or to change the acetate protecting group to prevent this undesired elimination reaction; however, in none of these cases were we successful in producing a labeling precursor that did not undergo this side reaction. Additionally, although there are literature reports of using a sulfonyl substituent to activate the displacement of a nitro group at a para position,[31−33] we were unable to achieve fluoride ion displacement of either the nitro analog of ammonium salt **9** or the nitro group in 4-nitrophenyl methyl sulfone itself.

Convergent Synthesis of Bicalutamide (1). Because of these complications, the linear synthesis of [^{18}F]bicalutamide was abandoned in favor of an alternative, convergent approach (Scheme 2), in the hope that protection and elimination of the hydroxyl group could be avoided. Methyl sulfone **11** was treated with iodomethane to produce dimethylamine **12** in 89% yield.[34] The ammonium salt (**13**) was produced by the reaction of amine **12** with methyl trifluoromethanesulfonate in 31% yield.[27] Treatment of labeling precursor **13** with TBAF yielded the fluorophenyl sulfone **14** in 87% yield.[29] This product was deprotonated using *n*-BuLi at −78 °C and then combined with keto amide **6** to form bicalutamide in 95% yield. This synthesis proceeded in an overall yield of 23%, and the bicalutamide produced by this approach was found to be identical to an authentic commercially available sample by HPLC and NMR. Use of this synthetic route at the tracer level, however, was unsuccessful because we were unable to get tracer levels of [^{18}F]-fluorophenyl sulfone (^{18}F-**14**) to react with ketoamide **6**.

Because of problems encountered in the tracer-level radiochemical synthesis of 4-[^{18}F]bicalutamide using this convergent synthesis, we modified our synthetic route to include a pseudocarrier. Pseudocarriers are often beneficial to a synthesis when a reactive intermediate generated from tracer levels of the radiolabeled component undergoes quenching from adventitious water, which appeared to be the case here with the anion derived from the [^{18}F]fluorophenyl sulfone (^{18}F-**14**).

4-(*t*-Butyl)phenyl methyl sulfone (**16**, Scheme 3) serves as an effective pseudocarrier analog of sulfone **14** for the bicalutamide synthesis by this convergent approach. Its reactivity for anion generation and carbonyl addition is essentially the same as that of the fluorophenyl sulfone **14**, yet the bicalutamide product analog that it produces (**17**) is considerably more lipophilic and thus is readily separable from bicalutamide by HPLC under reverse-phase conditions.

The pseudocarrier *t*-butylphenyl methyl sulfone (**16**) was synthesized from 4-(*t*-butyl)phenyl mercaptan (**15**) in two steps and in 75% yield, as shown in Scheme 3.[35,36] This analog was then treated with *n*-BuLi to generate the corresponding anion, which reacted with keto amide **6** to afford the *t*-butyl analog of bicalutamide (**17**) in 28%. The overall yield of this sequence was 21%. This approach was investigated for the preparation of fluorine-18 labeled material (below).

Synthesis of 4-Bromobicalutamide (19). The difficulty in synthesizing no-carrier-added [^{18}F]bicalutamide encouraged us to examine the properties of some bromine analogs of bicalutamide: 4-bromobicalutmaide (**19**) and 4-bromo-thiobicalutamide (**23**). Bromine has several properties that make it a synthetically appealing element for radiolabeling. Bromide ion can be easily oxidized to create hypobromite, using either a peracid[37,38] or chloramine-T,[39,40] and this electrophilic bromination species can be incorporated into a variety of aromatic rings.[41] Thus, we found peracid oxidation of bromide ion to be an extremely efficient and reliable method for incorporating this halogen into the aforementioned sulfone-activated ring on suitable precursors (Scheme 4).

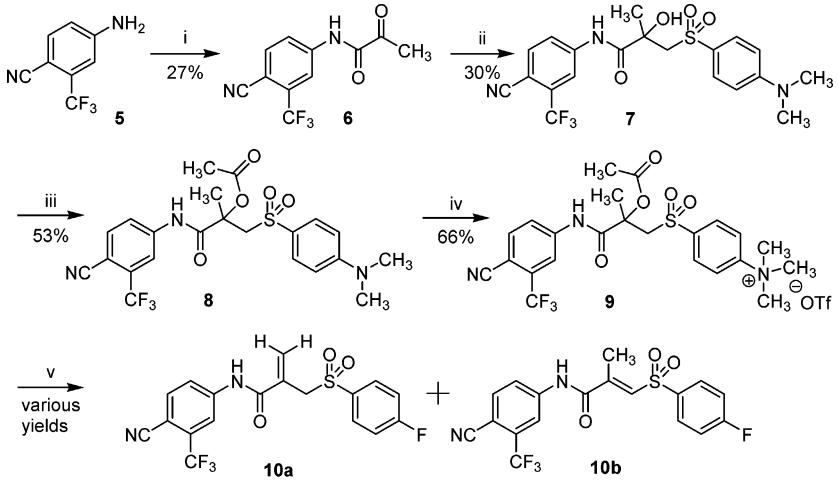
An authentic sample of 4-bromobicalutamide was synthesized as shown in Scheme 4. Bromophenyl sulfone **18** was treated with *n*-BuLi to form the corresponding anion, which was then reacted with ketoamide **6** to form 4-bromobicalutamide (**19**) in 78% yield. Palladium coupling with bis-(tributyltin)[42] gave in 28% yield the precursor **20** suitable for radiolabeling. Ammonium bromide was oxidized to hypobromite in a solution of 10% HOOAc/HOAc,[41] and this electrophile was then used to effect an aryl destannylation reaction with the tin precursor (**20**), reforming the desired final product (**19**) in 84% yield. The overall yield of 4-bromobicalutamide by this approach was 18%. This route was also investigated for preparing radiolabeled material (below).

Synthesis of 4-Bromo-thiobicalutamide (23). The ease with which 4-bromobicalutamide could be prepared by this route encouraged us to also explore the possibility of labeling 4 -bromo-thiobicalutamide. Thiobicalutamide (**2**) is reported to have a 10-fold higher binding affinity for the AR than its sulfone analog, bicalutamide.[23] 4-Bromo-thiobicalutamide was synthesized as shown in Scheme 5.

Primary amine **5** was condensed with methacroyl chloride to form the acrylanilide **21**,[43] which was then treated with performic acid to afford the epoxide **22**[44] in 59% and 88% yields, respectively. Epoxide **22** was reacted with 4-bromothiophenol to give 4-bromo-thiobicalutamide **23** in 61% yield.[44] 4-Bromo-thiobicalutamide **23** underwent palladium-mediated coupling to form alkyl tin **24** in a 12% yield. Labeling precursor **24** reacted readily with hypobromite, formed by oxidation of NH_4Br in 1.6% HOOAc/HOAc, to give a mixture of the sulfoxide **25** and sulfone **19**.

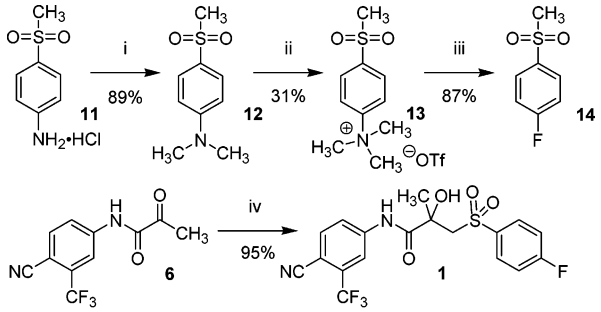
The observed oxidation of the sulfide to the sulfoxide and sulfone was expected and unavoidable.[45] Fortunately, whereas sulfones are difficult to reduce, sulfoxide compounds can be reduced relatively easily because of the nucleophilic nature of the sulfoxide oxygen, which can be covalently bound to electrophilic species, producing an oxosulfonium species that undergoes reduction by S−O bond scission.[46] To obtain sulfide **23**, it was necessary to reduce sulfoxide **25** under the conditions consistent with work on the tracer level (i.e., normal atmosphere, H_2O). Diethyl chlorophosphite has been shown to reduce sulfoxides in excellent yields at room temperature and to do so

Scheme 1. Attempted Synthesis of Bicalutamide



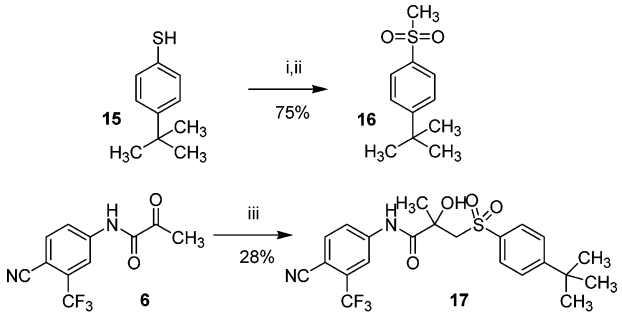
(i) Cl_2CHOCH_3, pyruvic acid, CH_2Cl_2. (ii) Amine **12,** *n*-BuLi, THF. (iii) Acetyl Chloride, DMAP, pyr. (iv) MeOTf, CH_2Cl_2. (v) TBAF, DMSO.

Scheme 2. Convergent Synthesis of Bicalutamide



(i) NaH, CH_3I, HMPA, THF. (ii) MeOTf, CH_2Cl_2. (iii) TBAF, DMSO, 90 °C. (iv) **14**, *n*-BuLi, THF, -78 °C.

Scheme 3. Pseudocarrier Synthesis and Reaction to Form the Bicalutamide Analog

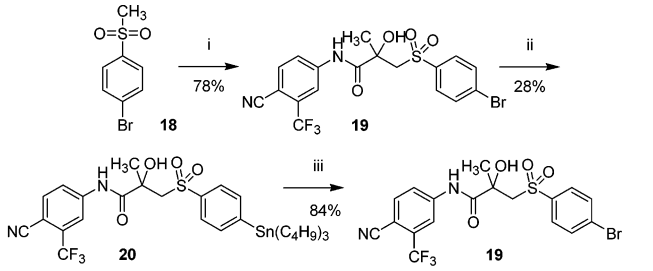


(i) CH_3I, NaOH, H_2O. (ii) mCPBA, CH_2Cl_2. (iii) **16**, *n*BuLi, THF.

in the presence of water.[47] Thus, when the crude mixture of sulfoxide **25** and sulfone **19** was treated with diethyl chlorophosphite, it gave the desired sulfide (**23**) in 34% yield from the tin precursor **24**. The overall yield of 4-bromo-thiobicalutamide was low, 1.3%, but this is still acceptable for the preparation of experimental radiopharmaceuticals.

Radiochemistry. Radiochemical Synthesis of [^{18}F]Bicalutamide (^{18}F-1). The synthesis of [^{18}F]bicalutamide (^{18}F-**1**) was attempted with and without a pseudocarrier, as already noted. To produce receptor-targeted imaging agents that are medically useful, very high specific activity is required. Thus, initially a no-carrier-added synthesis of bicalutamide was attempted. This was unsuccessful, however, because it was not possible to titrate precisely the amount of base needed to deprotonate the tracer-level amounts of labeled sulfone (^{18}F-**14**; Scheme 6), and trace amounts of adventitious water readily quenched the low level of the carbanion produced. Pseudocarrier **16** (Scheme 3) was therefore added to raise the amount of total sulfone to a sufficient level so that the required amount of *n*-BuLi could be added accurately. In this case, the increased lipophilic nature of the *t*-butyl group on the final product resulting from reaction with the pseudocarrier (namely, compound **17**) retarded its elution from the reverse-phase HPLC column, compared to that of the labeled product (^{18}F-**1**). Thus, although the chemical reactivity of the *t*-butyl carrier (**16**) is similar to that of the labeled fluorophenyl intermediate (^{18}F-**14**), the product it produces (**17**) can readily be separated from the final product (^{18}F-**1**) and therefore does not increase the mass amount in the final product, as is needed to maintain high effective specific activity (Scheme 6).

Scheme 4. Synthesis of 4-Bromobicalutamide

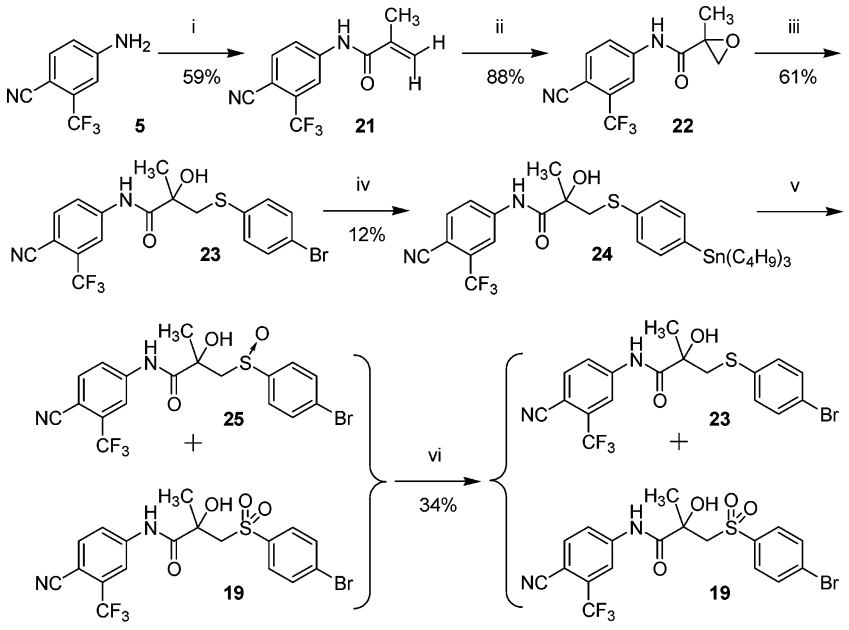


(i) nBuLi, **6**, THF. (ii) Hexabutyl ditin, $Pd(PPh_3)_4$, TEA, tol. (iii) NH_4Br, 10% HOOAc, HOAc.

The synthesis of [^{18}F]bicalutamide (^{18}F-**1**, Scheme 6) was accomplished by the reaction of the ammonium salt precursor **13** with [^{18}F]fluoride ion in the form of tetrabutylammonium [^{18}F]fluoride ([^{18}F]TBAF). The ammonium precursor **13** was treated with [^{18}F]TBAF and subjected to microwave irradiation to produce [^{18}F]fluorophenyl sulfone (^{18}F-**14**). Water was added to the solution, and the resulting mixture was purified by solid-phase extraction on reverse-phase silica gel followed by HPLC to give a radiochemical chemical yield of 61 ± 12% (n = 3, decay corrected), and the radiochemical purity (determined by HPLC with UV and radiometric detection, respectively) was >95%.

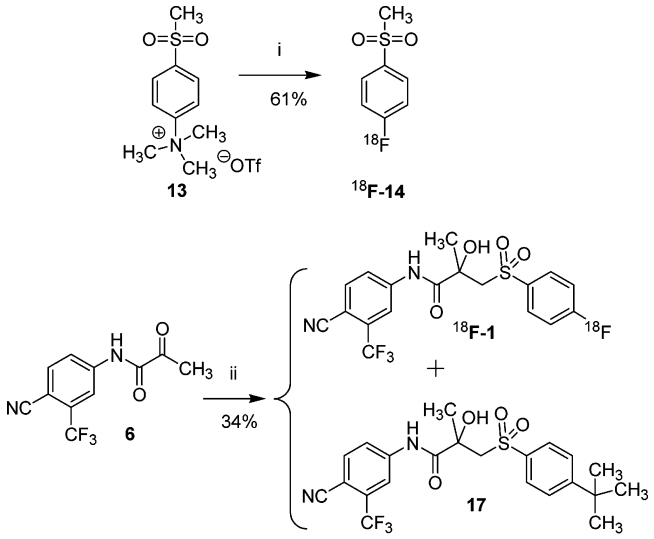
The *t*-butylphenyl pseudocarrier **16** was added to the dry vial containing purified fluorophenyl sulfone (^{18}F-**14**), and the mixture was dissolved in dry THF, cooled to −78 °C, and placed

Scheme 5. Synthesis of 4-Bromo-thiobicalutamide



(i) Methacroyl chloride, TEA, CH_2Cl_2. (ii) H_2O_2, HOCHO.
(iii) 4-bromo-thiophenol, NaH, THF. (iv) Hexabutyl ditin, $Pd(PPh_3)_4$, tol.
(v) 1.6% HOOAc / HOAc, NH_4Br. (vi) Diethyl chlorophosphite, CH_2Cl_2.

Scheme 6. Radiosynthesis of ^{18}F-Bicalutamide



(i) TBA[^{18}F]F, DMSO, 90 °C. (iv) **^{18}F-14**,**16** *n*-BuLi, THF, -78 °C.

under Ar. The resulting solution was treated with *n*-BuLi until a pale-yellow color appeared, indicating formation of the methyl sulfone anion. The vial was stirred for 10 min at −78 °C. At this time, keto amide **6** was added, and the mixture was allowed to warm to room temperature and was stirred for an additional 15 min. The reaction was quenched with saturated ammonium chloride, and the extracted product was purified by reverse-phase HPLC to afford ^{18}F-bicalutamide (^{18}F-**1**). The overall radiochemical chemical yield was 21% decay corrected, and the radiochemical purity (determined by HPLC with UV and radiometric detection, respectively) was >95%. The effective specific activity (determined by analytical HPLC), however, was surprisingly low, only ca. 13 Ci/mmol (480 MBq/μmol).

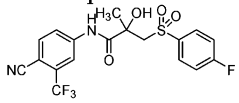
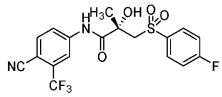
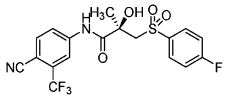
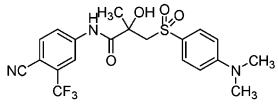
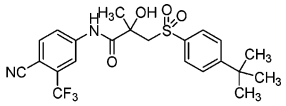
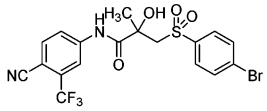
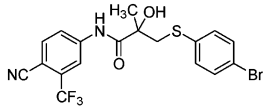
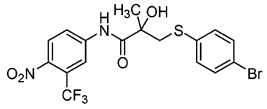
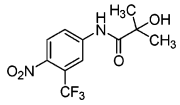
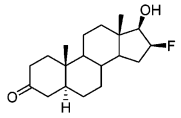
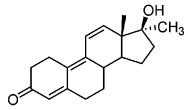
Unfortunately, although the *t*-butyl analog produced from the pseudocarrier (**17**) could be separated effectively, we were unable to isolate the ^{18}F-bicalutamide product (^{18}F-**1**) sufficiently free from other co-eluting material. This resulted in a product with an effective specific activity that was too low for it to be evaluated in vivo. Because of the difficulties in the synthesis and purification of product (^{18}F-**1**), work on this target molecule was discontinued, and we focused on the preparation of the higher affinity ^{76}Br analogs (^{76}Br-**19**).

Radiochemical Synthesis of 4-[^{76}Br]Bromobicalutamide (^{76}Br-19). 4-[^{76}Br]Bromobicalutamide (^{76}Br-**19**) was synthesized by bromination of the tin precursor **20** with bromine-76, according to the sequence shown in Scheme 4. Tributyltin **20** was added to the reaction vial containing dry [^{76}Br]bromide ion along with a 1.6% HOOAc/HOAc solution, and the mixture was stirred at room temperature for 20 min to give the final product, 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**). The overall radiochemical chemical yield was 29 ± 6% (n = 3, decay corrected), the radiochemical purity (determined by HPLC with UV and radiometric detection, respectively) was >95%, and the effective specific activity (determined by analytical HPLC) was approximately 282 Ci/mmol (10.4 GBq/μmol). This radiolabeled compound was used in subsequent tissue distribution and metabolic stability studies (below).

Radiochemical Synthesis of 4-[^{76}Br]Bromo-thiobicalutamide (^{76}Br-23). 4-[^{76}Br]Bromo-thiobicalutamide was synthesized according to the following procedure (cf. Scheme 5): Tin precursor **24** was added to the reaction vial containing dry [^{76}Br]bromide ion along with a 1.6% HOOAc/HOAc solution, and this mixture was stirred at room temperature for 15 min. At this point, H_2O was added, and the crude sulfoxide intermediate (^{76}Br-**25**) and sulfone (^{76}Br-**19**) were isolated by solid-phase extraction on C-18 silica gel. Sulfoxide (^{76}Br-**25**) together with the corresponding sulfone (^{76}Br-**19**) were eluted from the C-18 column, and this mixture was then reduced by treatment with diethyl chlorophosphite (20 μL, 139 μmol) and purified using reverse-phase HPLC.

The overall radiochemical chemical yield of 4-[^{76}Br]Bromo-thiobicalutamide (^{76}Br-**23**) was 4% (decay corrected), and the radiochemical purity (determined by HPLC with UV and

Table 1. Binding Affinities of Bicalutamide and Bromine-Based Analogs

Compound	RBA[a,b]
 **1**	0.044 ± 0.020
 **(R)1**	0.047 ± 0.003
 **(S)1**	0.007 ± 0.002
 **7**	0.055 ± 0.021
 **17**	0.21 ± 0.083
 **19**	0.53 ± 0.061
 **23**	0.61 ± 0.18
 **26**	0.51 ± 0.016
 Hydroxyflutamide	0.045 ± 0.033
 FDHT	43 ± 2.0[4]
 **27** (R1881)	100

[a] Relative binding affinity (RBA) where R1881 (**27**) is 100%. The K_d value of R1881 (**27**) is 0.6 nM.[62] [b] Competitive radiometric binding assays were done with the purified ligand binding domain of rat AR (Panvera/Invitrogen), using [^{3}H]R1881 (^{3}H-**27**) as a tracer, as previously described.[63]

radiometric detection, respectively) was >95%. The specific activity, however, was not calculated as a result of low levels of activity and mass contamination. Because of difficulties encountered in the synthesis and purification of the sulfide (^{76}Br-**23**) and the lack of increased AR binding affinity for this compound compared to that of the sulfone analog **19** (below), further efforts to produce this target molecule were stopped, and it was not brought forward for animal studies in vivo.

Biological Studies. Androgen Receptor Ligand Binding Assays. The androgen receptor binding affinities of the bromo and fluoro analogs of bicalutamide are shown in Table 1, together with those of related compounds for comparison. These binding affinities were determined by a competitive radiometric binding assay using purified AR with the high-affinity steroidal AR ligand [^{3}H]R1881 (^{3}H-**27**, Table 1) used as tracer and unlabeled R1881 (**27**) as a standard. Affinities are expressed as Relative Binding Affinity (RBA) values in which the standard AR ligand **27** has an RBA value of 100.[3,48]

(*R*)-Bicalutamide (*R*)-**1** binds selectively to the AR,[49] and in our hands this compound had an affinity of around 1.3 μM, a value lower than that reported by others.[49] Because the affinities that we measure for DHT and R1881 (**27**) with our binding assay are in accordance with the affinities of these compounds reported by others,[50−53] the origin of the lower affinity we measure for bicalutamide is unclear. Nevertheless, in our modifications of bicalutamide we found that bromine substitution (**19**) for fluorine (**1**) did cause a large increase (12-fold) in the AR affinity so that bromobicalutamide bound with a K_d of 110 nM. The reason for this increased affinity is not known, but it might be due to the lower electronegativity and greater polarizability of bromine versus that of fluorine. Because bromobicalutamide (**19**) was the compound that could be radiolabeled most easily and in highest effective activity and was also the compound having nearly the highest AR binding affinity of the ones investigated in this study, it was the compound selected for further biodistribution and metabolic stability studies.

We also reduced the sulfone linkage to the sulfide on **23** and **26**, but we saw no change in binding affinities for the reduced compounds even though there is reported to be a 10-fold increase in binding affinity when the sulfone in bicalutamide is reduced to the sulfide.[23] We synthesized the nitro arene **26** to see whether there was a change in affinity between the cyano- and nitro-substituted A rings, as reported in some systems, but no change in affinity was noted.[54]

Table 2. 4-[^{76}Br]Bromobicalutamide Tissue Distribution in Adult Rats

	% injected dose/g[a]			
tissue	1 h	1 h block[b]	18 h	18 h block[b]
blood	0.56 ± 0.046	0.62 ± 0.011	0.34 ± 0.010	0.29 ± 0.021
liver	2.1 ± 0.31	2.5 ± 0.18	0.56 ± 0.069	0.36 ± 0.060
kidney	1.0 ± 0.055	1.0 ± 0.076	0.36 ± 0.034	0.26 ± 0.037
muscle	0.34 ± 0.020	0.38 ± 0.024	0.15 ± 0.022	0.11 ± 0.023
bone	0.28 ± 0.015	0.31 ± 0.012	0.13 ± 0.0092	0.12 ± 0.0018
prostate	1.0 ± 0.20	0.68 ± 0.13	0.27 ± 0.049	0.22 ± 0.027

[a] Groups of five animals per data point. [b] Non-castrated, testis-intact animals.

Biodistribution of 4-[^{76}Br]Bromobicalutamide (^{76}Br-19). Purified 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**), the compound selected for further study, was reconstituted in 10% ethanol−saline and injected into mature, male Sprague−Dawley rats that had been castrated to suppress endogenous androgen biosynthesis. Doses of ^{76}Br-**19** employed were 4 or 7 μCi/animal, and animals were sacrificed at 1 and 18 h postinjection, respectively. To ascertain whether tissue accumulation of activity was mediated by a high-affinity, limited-capacity uptake system, one set of animals was left with testes intact. In these animals, high levels of circulating testosterone occupy the AR nearly fully.[55] The results of this experiment are shown in Table 2.

The uptake of 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**) by the prostate appears to be AR mediated. Tissue samples at the 1 h point show prostate/muscle and prostate/blood ratios of 2.9 and 1.8, respectively. At the 1 h time point, the control study (testes intact), in which AR is saturated by endogenous testosterone in the noncastrated animals, shows a significant drop in prostate/blood and prostate/muscle ratios, with the ratios declining to 1.8 and 1.1, respectively. It is important to note that other organs with high levels of activity in the castrated rats (liver, kidney) did not experience a similar drop in bromine-76 incorporation as did the prostate in the testes-intact rats. In fact, their levels increased, whereas the level of prostate incorporation decreased.

Table 3. 4-[^{76}Br]Bromobicalutamide Tissue Distribution in CWR22 Tumor-Bearing Mice

	% injected dose/g[a]		
tissue	30 min	90 min	90 min block[b]
blood	2.7 ± 0.47	3.5 ± 0.47	3.0 ± 0.44
liver	15 ± 1.5	18 ± 1.5	14 ± 0.72
kidney	7.2 ± 1.1	7.8 ± 1.8	7.6 ± 1.3
muscle	2.5 ± 0.54	2.9 ± 0.35	2.8 ± 0.28
prostate	2.2 ± 0.57	2.8 ± 0.90	3.4 ± 1.1
tumor	2.5 ± 0.53	3.8 ± 0.77	4.5 ± 0.56

[a] Groups of five animals per data point. [b] AR-mediated uptake blocked by addition of excess 17α-methyltestosterone.

Analysis of the tissue uptake data using a Student *t* test indicates a >95% confidence that the androgen-depleted prostate has a higher level of incorporation than in the testes-intact rats. In addition, there is >99% confidence that the prostate incorporates more activity than the nontarget tissues of muscle and blood.

At the extended time point of 18 h, there are greatly diminished levels of bromine-76 incorporation in the prostate. In addition, prostate activity levels are nearly the same as in the nontarget tissues, and the testes-intact animals do not show any significant reduction in prostate activity. This indicates that whereas 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**) is taken up by the AR into the prostate at early times, 4-[^{76}Br]bromobicalutamide has a significantly reduced affinity for the AR when compared to that of FDHT (0.53 vs 43%, respectively), a difference that could account for the lower incorporation and poorer retention of ^{76}Br-**19** into the rat prostate compared to that for FDHT.[4] This compound is also metabolized rapidly in blood (below). Thus, although 4-[^{76}Br]bromobicalutamide has an AR affinity higher than that of the parent compound bicalutamide, it is still likely too low to be of clinical importance.

An additional study was undertaken to determine whether 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**) would be taken up into an experimental prostate tumor model. Purified ^{76}Br-**19** was reconstituted in 10% ethanol−saline and injected (iv, tail vein) into mature male mice having a previously implanted tumor prostate (CWR22) in the flank. These animals had also been injected subcutaneously with DES to suppress endogenous androgen biosynthesis.[56] CWR22 is an androgen-dependent human prostate cancer cell line that has a high level of AR expression;[57] however, in 24 h castrated mice CWR22 cells experience a much more significant drop of AR levels than does the prostate.[58]

Doses of ^{76}Br-**19** employed were 6 μCi/animal, and animals were sacrificed at 30 and 90 min postinjection. To ascertain whether tissue accumulation of activity was mediated by a high-affinity, limited-capacity uptake system, one set of animals was co-injected with the radiotracer together with a blocking dose of 17α-methyl testosterone. The results of these experiments are shown in Table 3.

In these tumor-bearing nice, there was little incorporation of 4-[^{76}Br]bromobicalutamide in the prostate tumors or in the target tissues compared to the nontarget tissues. Additionally, there was little difference between the androgen-blocked and the DES-treated mice.

Stability and Metabolism of Bicalutamide, 4-Bromobicalutamide, 4-[^{76}Br]Bromobicalutamide, and 4-Bromo-thiobicalutamide. Following the procedure by Grillo et al.,[59] we incubated bicalutamide, 4-bromobicalutamide, and 4-bromo-thiobicalutamide in a potassium phosphate buffer treated with glutathione to simulate nucleophilic conditions in vivo. Each compound was separately incubated with glutathione and stirred at 37 °C for 24 h. Aliquots at various time points were taken and injected onto an analytical reverse-phase HPLC for analysis of the reaction products. No significant decomposition of the product or nucleophilic displacement of the fluorine or bromine by glutathione was evident, indicating that these compounds are stable under physiological conditions.

To investigate the in vivo stability of 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**), blood samples were taken from each time group of the rats used in the biodistribution study, blocked and unblocked (below), and the amount of intact ^{76}Br-**19** was followed using radiometric normal-phase thin-layer chromatography. Blood analysis showed that at 1 h only circa 20% of the activity was due to intact ^{76}Br-**19** in both sets of animals. The remaining activity was immobile on normal-phase TLC and presumed to be inorganic bromine ion released by metabolism. At 18 h, all of the bromine-76 activity in both sets of animals was found to be immobile, which indicated that no intact ^{76}Br-**19** remained in the blood by this time. No studies were undertaken to examine the activity present in the prostate.

In the tumor-bearing mice, a tumor was taken from each time group, and the resulting activity was analyzed as previously described for rat blood samples. At each time point, there was no evidence of intact 4-[^{76}Br]bromobicalutamide ^{76}Br-**19** in the prostate tumors; consistent with the biodistribution study.

Discussion

To develop nonsteroidal antiandrogens as PET imaging for androgen-independent prostate cancer, we prepared bicalutamide (**1**) and two analogs, bromobicalutamide (**19**) and bromothiobicalutamide (**23**), along with their respective analogs labeled with the positron-emitting radionuclides fluorine-18 (bicalutamide itself) or bromine-76 (the two analogs). We measured the androgen receptor (AR) binding affinity of these and related compounds, and we selected one compound, 4-bromobicalutamide, for further biological study to assess its potential as an in vivo imaging agent for AR-positive prostate tumors. 4-Bromobicalutamide (**19**) was one of the highest-affinity compounds, and of the three, it was the only one that we could prepare in radiolabeled form at high-effective specific activity. We then studied the metabolic stability of 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**) and its tissue distribution in surgically and chemically castrated rats and mice.

We were able to prepare bicalutamide labeled with fluorine-18 by performing an efficient nucleophilic aromatic substitution on the trimethylammonium salt of the phenyl methyl sulfone system followed by the addition of the lithium arylsulfonylmethylide to a pyruvanilide. At the radiotracer level, we were only able to get the second step to work when we added a pseudocarrier sulfone, 4-(*t*-butyl)-phenyl methyl sulfone. Although [^{18}F]bicalutamide, obtained in reasonable yield by this approach, could be separated by HPLC from the more lipophilic product derived from the pseudocarrier sulfone, we were discouraged from working further with this material because the radiolabeled material was still sufficiently contaminated by other coeluting and receptor-binding byproducts..

Radiobromination of tributyltin precurors with [^{76}Br]hypobromite readily gave the two bromobicalutamide analogs. In this manner, 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**) could be obtained in good radiochemical yield (24−29% decay corrected at 65 min) and at high effective specific activity (282 Ci/mmol). By contrast, 4-[^{76}Br]bromo-thiobicalutamide (^{76}Br-**23**), whose production required an additional reduction step, was obtained only in low effective specific activity, insufficient for further studies.

AR binding affinity measurements on these and related compounds showed that 4-bromobicalutamide (**19**) has a

significantly higher affinity for the AR than does the initial lead compound, bicalutamide. Although thio-bicalutamide is reported to bind to AR better than bicalutamide does, we did not find this to be the case with the compounds we prepared in the 4-bromo series, namely, 4-bromo-thiobicalutamide (**23**) versus 4-bromobicalutamide (**19**).[23]

In biodistribution studies, 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**) is the first nonsteroidal AR antagonist to demonstrate AR-mediated uptake into the prostate tissue. Target tissue-selective uptake in rats is limited, however, and further studies in AR-positive prostate tumor-bearing mice did not indicate selective uptake into the tumor or target tissues. The specific activity of our preparation of 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**) was 282 Ci/mmol. Whereas this is reasonably high, we wanted to be sure that the limited uptake of this compound into prostate tissue is not due to saturation of the target tissue AR. At our specific activity, the injected dose of 4 μCi per animal used in the castrated rat model corresponds to a mass amount of 14 pmol. On the basis of uptake studies we have previously done with various radiolabeled androgens in the prostate of adult male rats,[55] we find a maximum of 0.7% ID/g uptake in prostate tissue. In the case of 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**), this would correspond to a maximum exposure of the prostate to 0.10 pmol/g tissue. In earlier studies, we showed that the prostate of surgically castrated adult male rats contains 5.4 pmol/g of AR, all of which are unoccupied.[55] Therefore, the administered dose of 4 μCi of 4-[^{76}Br]bromobicalutamide (^{76}Br-**19**), which gives a prostate exposure of only 0.10 pmol/g, would be sufficient to reach less than a 2% saturation of the AR content of the prostate. Thus, the limited uptake we see for 4-[^{76}Br]-bromobicalutamide (^{76}Br-**19**) in the prostate is not due to the saturation of target tissue AR, but is more likely due to the relatively low affinity of this ligand for the receptor. Low affinity is also the most likely explanation for the lack of AR-mediated target tissue and tumor uptake found in the biodistribution studies done in the CWR22 tumor-bearing mice, although the rapid metabolism of [^{76}Br]bromobicalutamide (^{76}Br-**19**), noted in rat blood, could also limit the extent of target-tissue uptake.

Whereas our studies demonstrate that nonsteroidal androgen receptor ligands can be labeled with positron-emitting radionuclides at high specific activity and that one of these, [^{76}Br]-bromobicalutamide (^{76}Br-**19**), shows AR-mediated uptake in castrated rats, in the principal androgen target tissue, the prostate, this uptake is limited, and this compound is rapidly metabolized. Clearly, the behavior of this radiopharmaceutical is not adequate for imaging of the prostate or prostate tumors in a clinical setting. Thus, there is still a need for the development of more effective nonsteroidal androgens for PET imaging of AR in prostate tumors; future studies should focus on increasing the AR binding affinity of these ligands and should seek to understand and possibly moderate the rate of metabolism of these compounds.

Experimental Section

General Methods. All reagents and solvents were obtained from Aldrich (Milwaukee, WI), except for racemic and enantiomerically pure bicalutamide (**1**) and hydroxyflutamide, which were purchased from Toronto Research Chemicals Inc. (North York, ON, Canada) and tested without further purification. Tetrahydrofuran, methylene chloride, toluene, and diethyl ether were dried by a solvent delivery system (neutral alumina column) designed by J.C. Meyer (Irvine, CA).[60] All reactions were performed under a dry (Drierite) nitrogen atmosphere unless otherwise stated. Reaction progress was monitored using analytical thin-layer chromatography (TLC) on 0.25 mm Merck F-254 silica gel glass plates. Visualization of the TLC was achieved by either UV light (254 nm) or after phosphomolybdic acid indicator spray. Flash chromatography was performed according to a literature method[61] with Woelm silica gel (0.040−0.063 mm) packing. In most cases, product isolation consisted of removing the solvent from the reaction mixture, extracting with an organic solvent, washing with water and brine, drying with anhydrous sodium sulfate, and filtering. The use of such a workup will be indicated by the phrase "product isolation" (which is followed, in parentheses, by the extracting solvent). Purification in most cases was achieved by flash chromatography and is signified by the term "flash chromatography" (which is followed, in parentheses, by the elution solvent used). Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected.

For radiosynthetic purification, a semipreparative reverse-phase HPLC column (Alltech Alltima C18 column, 10 × 250 mm^2) was used. The mobile phase was either THF−water or acetonitrile−water. Analytical purity was determined using a reverse-phase HPLC (Phenomenex Luna C18 column, 4.6 × 150 mm^2). The eluant was monitored with a variable-wavelength detector set at 254 nm and a flow-through sodium iodide scintillation detector, where appropriate. Radioactivity was determined with a dose calibrator. Radiochemical yields are decay corrected to the beginning of synthesis time (BOS).

^{1}H and ^{13}C NMR spectra were recorded on a U500 or U400 Varian FT-NMR spectrometer. Chemical shifts (δ) are reported in ppm downfield by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. Higher-resolution EI mass spectra were obtained on a Finnigan MAT 731 spectrometer. Higher-resolution ESI and FAB mass spectra were obtained on a Micromass Q-Tof Ultima and a Micromass 70-SE-4F, respectively. Combustion analyses were obtained with a CE440 by Exeter Analytical, Inc. and were within 0.4% of calculated values.

Androgen receptor binding affinity (RBA) assays were performed according to literature methods.[62,63] AR preparation used in these experiments was purified from the rat AR ligand binding domain (Panvera/Invitrogen, Madison, WI).

Radiosynthetic isolation and purification of fluorine-18 was obtained from proton bombardment of oxygen-18 enriched water, by an ^{18}O(p, n)^{18}F reaction. Activity in the irradiated water was converted to [^{18}F]TBAF by the addition of tetrabutylammonium hydroxide, followed by careful evaporation of water and azeotropic drying with acetonitrile, as previously described.[64]

Radiosynthetic isolation and purification of bromine-76 was performed according to the following procedure:[65] ^{76}Br$^-$ was obtained from a ^{76}Se(p, n)^{76}Br reaction on an isotopically enriched Cu^{76}Se-coated tungsten incline target. The target was bombarded with a 20 μA−15 MeV proton beam on a Cyclotron Corporation CS15 for 2 h. The activity was dry distilled from the target under argon gas flow in a quartz tube in a 1065 °C oven. The [^{76}Br]-bromide ion and a small amount of target material were deposited outside of the oven in the quartz tube, and the [^{76}Br]bromide ion was washed from the quartz tube using 0.6 N NH_4OH, which was evaporated under a stream of nitrogen with gentle heating. The bromine-76-containing NH_4OH solution was passed over a C-18 separatory column that had been previously treated with H_2O (3 mL). After the NH_4OH was pushed through the column, it was followed with EtOH (300 μL). The resulting solution was placed in a glass reaction vial, and the solvent was removed using heat (90 °C) and a stream of N_2.

***N*-(4-Cyano-3-trifluoromethyl-phenyl)-2-oxo-propionamide (6).** Pyruvic acid (2.683 g, 27.38 mmol) was placed in an oven-dried round-bottomed flask (250 mL), fitted with a magnetic stirring bar, and was dissolved in dry CH_2Cl_2 (200 mL). The flask was capped with a rubber septum. α,α-Dichloro-methyl methyl ether (4.9 mL, 55 mmol) was added dropwise by syringe, and the resulting solution was fitted with a water condenser and refluxed for 1 h. The solution was then removed from heat, and the volatile solvents were removed under reduced pressure. The resulting acid chloride was redissolved in dry CH_2Cl_2 (100 mL), and 4-amino-2-trifluoromethylbenzonitrile (1.273 g, 6.84 mmol) was added. The resulting mixture was capped with a rubber septum, and the mixture was cooled to 0 °C. Pyridine

(2.2 mL, 27 mmol) was added by syringe, and the mixture was slowly warmed to room temperature and stirred for 14 h. Product isolation (CH_2Cl_2, water, Na_2SO_4) followed by flash chromatography (40% EtOAc/60% hexanes) furnished the product (477 mg, 1.86 mmol) in 27% yield as a white solid with mp = 148−149 °C (lit. mp = 147−148 °C).[21] R_f = 0.53 in 40% EtOAc/hex. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.12 (s, 1H), 8.14 (d, J = 2.14 Hz, 1H), 8.00 (dd, J = 2.14, 8.47 Hz, 1H), 7.84 (d, J = 8.47 Hz, 1H), 2.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.92, 157.86, 140.40, 136.03, 134.24 (q,$^3J_{CF}$ = 32.22 Hz), 122.09, 121.93 (q,$^2J_{CF}$ = 274.34 Hz), 117.50 (q,$^4J_{CF}$ = 4.60 Hz), 115.22, 105.57, (q,$^4J_{CF}$ = 1.84 Hz), 23.83; HRMS (EI$^+$) m/z: calcd, 256.0460; found, 256.0460.

***N*-(4-Cyano-3-trifluoromethyl-phenyl)-3-(4-*N*,*N*-dimethylamino-benzenesulfonyl)-2-hydroxy-2-methyl-propionamide (7).** *N*,*N*-Dimethylaniline-4-methyl sulfone (408 mg, 2.05 mmol) was added to a flame-dried pear-shaped flask (65 mL), fitted with a magnetic Teflon stirring vane, and dissolved in dry THF (20 mL). The flask was fitted with a rubber septum and cooled to −78 °C. *n*-Butyl lithium (1.2 M, 1.7 mL, 2.04 mmol) was added dropwise to the chilled solution, and the reaction was stirred for 30 min, at which time a bright-yellow color developed. While the previous vial was stirring, propionamide **6** (547 mg, 2.13 mmol) was added to a flame-dried, round-bottomed flask (100 mL) fitted with a magnetic stirring bar and was dissolved in dry THF (40 mL). The solution was cooled to −78 °C, and the sulfone solution was cannulated into the propionamide solution. The solution was allowed to warm slowly to room temperature and was stirred for 2 h. Product isolation (CH_2Cl_2, water, Na_2SO_4) followed by flash chromatography (15% EtOAc/85% CH_2Cl_2) afforded a pure product as a white solid (281 mg, 0.618 mmol) in 30% yield with mp = 146−151 °C. R_f = 0.16 in 15% EtOAc/85% CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 7.98 (d, J = 2.14 Hz, 1H), 7.73 (d, J = 8.47 Hz, 1H), 7.65 (dd, J = 2.05, 8.58 Hz, 1H), 7.58 (AA'XX', J = 9.22 Hz, 2H), 6.47 (AA'XX', J = 9.22 Hz, 2H), 5.51 (s, 1H), 3.98 (d, J = 14.58 Hz, 1H), 3.37 (d, J = 14.58 Hz, 1H,), 2.93 (s, 6H), 1.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.82, 153.65, 141.41, 135.49, 133.85 (q,$^3J_{CF}$ = 32.22 Hz), 129.87, 125.68, 122.84 (q,$^2J_{CF}$ = 274.36 Hz), 121.70, 117.14 (q,$^4J_{CF}$ = 4.60 Hz), 115.41, 110.63, 104.44 (q,$^4J_{CF}$ = 1.84 Hz), 73.94, 61.15, 39.79, 28.05. HRMS (ESI, Q-TOF) calcd, 456.1205; found, 456.1191. Anal. calcd for ($C_{19}H_{18}F_3N_3O_4S_1$): C, H, N.

Acetic Acid. 1-(4-Cyano-3-trifluoromethyl-phenylcarbamoyl)-2-(4-*N*,*N*-dimethylamino-benzenesulfonyl)-1-methyl-ethyl Ester (8). Amine **7** (280 mg, 0.615 mmol) was added to a flame-dried round-bottomed flask (250 mL), fitted with a stirring bar, and was dissolved in dry THF (50 mL). Acetyl chloride (440 μL, 6.15 mmol), pyridine (430 μL, 6.15 mmol), and DMAP (75 mg, 0.62 mmol) were added to the solution at room temperature, and the mixture was stirred for 3 h. At this time, the volatile solvents were evaporated under reduced pressure, and the mixture was purified with flash chromatography using 15% EtOAc/85% hexanes to produce the purified product (161 mg, 0.324 mmol) as a white solid in 53% yield with mp = 121−123 °C. R_f = 0.19 in 15 EtOAc/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.73 (s, 1H), 8.03 (d, J = 2.04 Hz, 1H), 7.85 (dd, J = 1.93, 8.47 Hz, 1H), 7.73 (d, J = 8.47 Hz, 1H), 7.58 (AA'XX', J = 9.22 Hz, 2H), 6.53 (AA'XX', J = 9.11 Hz, 2H), 4.18 (d, J = 14.36 Hz, 1H), 3.95 (d, J = 14.36 Hz, 1H), 2.94 (s, 6H), 2.22 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.62, 169.13, 153.46, 141.48, 135.49, 133.59 (q,$^3J_{CF}$ = 33.14 Hz), 129.76, 123.87, 122.64, 122.11 (q,$^2J_{CF}$ = 274.34 Hz), 117.92 (q,$^4J_{CF}$ = 5.52 Hz), 115.51, 110.66, 104.39 (q,$^4J_{CF}$ = 1.84 Hz), 80.00, 58.11, 39.78, 24.25, 22.06. HRMS (ESI, Q-TOF) calcd, 498.1311; found, 498.1293.

4-[2-Acetoxy-2-(4-cyano-3-trifluoromethyl-phenylcarbamoyl)-propane-1-sulfonyl]-phenyl-*N*,*N*,*N*-trimethyl-ammonium Trifluoromethanesulfonate (9). Amine **8** (750 mg, 1.50 mmol) was added to a flame-dried round-bottomed flask (100 ml), fitted with a stirring bar, and was dissolved in dry CH_2Cl_2 (40 mL). Methyl trifluoromethanesulfonate (1.8 mL, 15.90 mmol) was added, and the resulting solution was refluxed for 20 h. Product crystallized out from the mother liquor as a white solid (654 mg, 0.990 mmol) in 66% yield. No further purification was necessary. mp = 188−191 °C. ^{1}H NMR (500 MHz, CD_3CN) δ: 9.32 (s, 1H), 8.11 (d, J = 9.22 Hz, 1H), 8.07 (dd, J = 2.14, 8.58 Hz, 1H), 8.06 (AA'XX', J = 9.43 Hz, 2H), 7.89 (AA'XX', J = 8.58 Hz, 2H), 4.22 (d, J = 14.90 Hz, 1H), 4.17 (d, J = 14.90 Hz, 1H), 3.59 (s, 9H), 2.06 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (125 MHz, CD_3CN) δ: 170.96, 170.79, 151.57, 143.26, 143.03, 137.06, 133.46 (q,$^3J_{CF}$ = 32.22 Hz), 131.31, 124.11, 123.47 (q,$^2J_{CF}$ = 273.42 Hz), 122.92, 119.11 (q,$^4J_{CF}$ = 4.60 Hz), 118.38, 116.62, 104.77 (q,$^4J_{CF}$ = 1.84 Hz), 80.17, 58.42, 77.95, 55.24, 23.98, 21.98. HRMS (ESI, Q-TOF) calcd, 512.1449; found, 512.1449.

(4-Methanesulfonyl-phenyl)-*N*,*N*-dimethyl-amine (12). 4-Methylsulfonylaniline hydrochloride (1.050 g, 5.183 mmol) was added to a flame-dried round-bottomed flask (250 mL) and was dissolved in dry THF (150 mL). NaH (1.45 g of a 60% dispersion, 20.7 mmol) was added in portions to the solution. The resulting mixture was capped with a rubber septum, and HMPA (1.8 mL, 10.37 mmol) and CH_3I (3.2 mL, 52 mmol) were added slowly by syringe at room temperature and allowed to stir for 18 h. The reaction was quenched with saturated ammonium chloride (100 mL) and diluted with H_2O (100 mL). Product isolation (CH_2Cl_2, water, Na_2SO_4) followed by flash chromatography (15% EtOAc/85% CH_2Cl_2) yielded a pure product (906 mg, 4.55 mmol) as a white powder in 89% yield with mp = 163−166 °C (lit. mp = 166−167 °C).[25] R_f = 0.50 in 80% EtOAc/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.73 (AA'XX', J = 9.11 Hz, 2H), 6.69 (AA'XX', J = 9.11 Hz, 2H), 3.06 (s, 6H), 3.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.36, 129.04, 125.85, 110.95, 45.07, 40.07. HRMS (EI$^+$) calcd, 199.0667; found, 199.0673.

(4-Methanesulfonyl-phenyl)-*N*,*N*,*N*-trimethyl-ammonium Trifluoromethanesulfonate (13). Methyl sulfone **12** (410 mg, 2.06 mmol) was placed in a flame-dried flask (100 mL), fitted with a magnetic stirring bar, and was dissolved in dry CH_2Cl_2 (40 mL). Methyl trifluoromethanesulfonate (2.3 mL, 21 mmol) was added, and the solution was refluxed for 20 h. Product (233 mg, 0.641 mmol) was found to have precipitated from the mother liquor as a white solid in a 31% yield, and no further purification was necessary. mp = 189−193 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.27 (AA'XX', J = 9.11 Hz, 2H), 8.18 (AA'XX', J = 9.11 Hz, 2H), 3.67 (s, 9H), 3.32 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 150.73, 142.28, 128.98, 122.26, 200.7 (q,$^2J_{CF}$ = 322.22 Hz), 56.52, 43.11. HRMS (FAB) calcd, 214.0902; found, 214.0942.

4-Fluorophenyl Methyl Sulfone (14). The trimethylammonium sulfone precursor **13** (120 mg, 0.331 mmol) was placed in a pear-shaped flask (50 mL), fitted with a magnetic stirring vane, and was dissolved in DMSO (15 mL). TBAF (1 M, 1.7 mL, 1.7 mmol) was added to the solution, and the solution was heated to 90 °C and stirred for 30 min. Product isolation (CH_2Cl_2, $LiCl_{(sat)}$, Na_2SO_4) followed by flash chromatography (30% EtOAc/70% hexanes) afforded a pure product (50 mg, 0.287 mmol) in 87% yield. Product authenticity was verified through coanalysis of NMR with a commercially available compound.

***N*-(4-Cyano-3-trifluoromethyl-phenyl)-3-(4-fluoro-benzenesulfonyl)-2-hydroxy-2-methyl-propionamide (1).** 4-Fluorophenyl methyl sulfone **4** (72 mg, 0.414 mmol) was added to a flame-dried pear-shaped flask (50 mL), fitted with a magnetic stirring vane, and was dissolved in dry THF (20 mL). The resulting solution was cooled to −78 °C. *n*-BuLi (1.2 M, 690 μL, 0.828 mmol) was added drop by drop, and the resulting solution was stirred for 20 min while a bright-yellow color developed. Meanwhile, in a separate flame-dried round-bottomed flask (50 mL), also fitted with a magnetic stirring bar, *N*-(4-cyano-3-trifluoromethyl-phenyl)-2-oxo-propionamide (53 mg, 0.207 mmol) was dissolved in dry THF (10 mL) and cooled to −78 °C. The two solutions were combined through a cannulus, allowed to warm slowly to room temperature, and stirred for 3 h. Product isolation (CH_2Cl_2, water, Na_2SO_4) followed by flash chromatography (5% EtOAc/95% CH_2Cl_2) gave a pure product (85 mg, 0.198 mmol) in 95% yield. Product authenticity was verified through coanalysis of NMR and HPLC with a commercially available compound.

4-*t*-Butylphenyl Methyl Sulfone (16). 4-*t*-Butylbenzene thiol (3.0 mL, 17 mmol) was placed in a round-bottomed flask (50 mL) fitted with a magnetic stirring bar. H_2O (15 mL) and NaOH (680 mg, 17 mmol) were added to the thiol, and the mixture was stirred vigorously. While the solution was stirring, iodomethane (1.1 mL, 17 mmol) was slowly added, and the resulting two-phase system was stirred at room temperature for 2 h. Product isolation (CH_2Cl_2, brine, Na_2SO_4) gave the crude compound that taken to the next step without further purification.

The crude *t*-butylphenyl methyl sulfide was placed in a round-bottomed flask (50 mL), fitted with a magnetic stirring bar, and was dissolved in dry CH_2Cl_2 (30 mL). mCPBA (9.388 g, 51 mmol) was added, and the reaction was stirred overnight at room temperature. The volatile organics were removed under reduced pressure, and the crude product was purified with flash chromatography using 25% EtOAc/75% hexanes to afford a pure product (3.058 g, 13.072 mmol) as a white crystal in 75% yield with mp = 94−96 °C (lit. mp = 90−94 °C).[36] R_f = 0.23 in 25% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (AA'XX', J = 8.67 Hz, 2H), 7.28 (AA'XX', J = 8.67 Hz, 2H), 2.52 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 148.14, 134.77, 126.69, 125.77, 34.27, 31.23, 16.12. HRMS (EI^+) calcd, 212.0871; found, 212.0874.

3-(4-*tert*-Butyl-benzenesulfonyl)-*N*-(4-cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-propionamide (17). 4-*t*-Butylphenyl methyl sulfone (172 mg, 0.811 mmol) was added to a flame-dried pear-shaped flask (65 mL), fitted with a magnetic stirring vane, and was dissolved in dry THF (15 mL). The flask was fitted with a rubber septum and cooled to −78 °C. *n*-Butyl lithium (1.2 M, 0.90 mL) was added dropwise to the chilled solution, and the reaction was stirred for 20 min, at which time a dark-yellow color evolved. While the previous vial was stirring, propionamide **6** (138 mg, 0.541 mmol) was added to a flame-dried round-bottomed flask (100 mL), fitted with a magnetic stirring bar, and was dissolved in dry THF (20 mL). The solution was cooled to −78 °C, and the sulfone solution was cannulated into the propionamide solution. The solution was allowed to warm slowly to room temperature and was stirred for 2 h. Product isolation (CH_2Cl_2, water, Na_2SO_4) followed by flash chromatography (50% EtOAc/50% hexanes) afforded a pure product as a white solid (71 mg, 0.152 mmol) in 28% yield with mp = 89−92 °C. R_f = 0.33 in 10% EtOAc/90% CH_2Cl_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.19 (s, 1H), 8.01 (d, J = 2.04 Hz, 1H), 7.82 (dd, J = 2.14, 8.47 Hz, 1H), 7.78 (AA'XX', J = 8.79 Hz, 2H), 7.75 (d, J = 8.58 Hz, 1H), 7.49 (AA'XX', J = 8.90 Hz, 2H), 5.95 (s, 1H), 3.97 (d, J = 14.47 Hz, 1H), 3.47 (d, J = 14.47 Hz, 1H), 1.59 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.66, 158.85, 141.24, 135.84, 135.76, 134.13, 133.73 (q, $^3J_{CF}$ = 33.14 Hz), 127.73, 126.45, 122.03 (q, $^2J_{CF}$ = 273.34 Hz), 121.89, 117.31 (q, $^4J_{CF}$ = 4.60 Hz), 115.38, 104.76 (q, $^4J_{CF}$ = 1.84 Hz), 74.38, 73.42, 61.40, 35.27, 30.85, 27.74. HRMS (EI^+) calculated 468.1331 found 468.1323. Anal. calcd. ($C_{21}H_{21}F_3N_2O_4S_1$): C, H, N.

3-(4-Bromo-benzenesulfonyl)-*N*-(4-cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-propionamide (19). 4-Bromophenyl methyl sulfone (1.488 mg, 6.33 mmol) was added to a flame-dried pear-shaped flask (65 mL), fitted with a magnetic stirring vane, and was dissolved in dry THF (30 mL). The flask was fitted with a rubber septum and cooled to −78 °C. *n*-Butyl lithium (1.2 M, 5.3 mL) was added dropwise to the chilled solution, and the reaction was stirred for 30 min, at which time a dark-yellow color developed. While the previous vial was stirring, *N*-(4-cyano-3-trifluoromethyl-phenyl)-2-oxo-propionamide (818 mg, 3.20 mmol) was added to a flame-dried round-bottomed flask (100 mL), fitted with a magnetic stirring bar, and was dissolved in dry THF (50 mL). The solution was cooled to −78 °C, and the sulfone solution was cannulated into the propionamide solution. The solution was allowed to warm slowly to room temperature and was stirred for 2 h. Product isolation (CH_2Cl_2, H_2O, Na_2SO_4) followed by flash chromatography (50% EtOAc/50% hexanes) afforded a pure product as a white solid (1.232 g, 2.52 mmol) in 78% yield with mp = 94−96 °C. R_f = 0.24 in 50% EtOAc/hexane. ^{1}H NMR (500 MHz, acetone-d_6) δ: 9.89 (s, 1H), 8.39 (d, J = 1.93 Hz, 1H), 8.19 (dd, J = 2.04, 8.58 Hz, 1H), 8.01 (d, J = 8.58 Hz, 1H), 7.84 (AA'XX', J = 8.47 Hz, 2H), 7.70 (AA'XX', J = 8.47 Hz, 2H), 5.55 (s, 1H), 4.09 (d, J = 14.90 Hz, 1H), 3.69 (d, J = 14.90 Hz, 1H), 1.54 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ: 173.74, 143.69, 140.99, 133.37 (q, $^3J_{CF}$ = 32.22 Hz), 132.90, 131.24, 136.86, 128.94, 123.55 (q, $^2J_{CF}$ = 273.42 Hz), 123.46, 118.27 (q, $^4J_{CF}$ = 4.60 Hz), 116.31, 104.24 (q, $^4J_{CF}$ = 1.84 Hz), 74.45, 63.93, 27.92. HRMS (ESI, Q-TOF) calcd, 490.9888; found, 490.9893. Anal. calcd ($C_{17}H_{12}Br_1F_3N_2O_4S_1$): C, H, N.

***N*-(4-Cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-3-(4-tributylstannanyl-benzenesulfonyl)-propionamide (20).** 4-Bromobicalutamide (1.232 g, 2.60 mmol) was placed in a flame-dried round-bottomed flask I250 mL), fitted with a magnetic stirring bar, and was dissolved in dry toluene (100 mL). Triethylamine (1.9 mL, 26.0 mmol), bis(tributyltin) (6.6 mL, 13.0 mmol), and tetrakis-(triphenylphosphine)palladium(0) (10 mg) were then added, and the mixture was refluxed for 24 h. The volatile solvents were removed under reduced pressure, and the crude mixture was purified with flash chromatograpy using 50% EtOAc/50% hexanes to afford a pure product (512 mg, 0.729 mmol) as an off-white solid in 28% yield with mp = 86−88 °C. R_f = 0.41 in 50% EtOAc/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.29 (s, 1H), 8.05 (d, J = 1.72 Hz, 1H), 7.91 (dd, J = 2.04, 8.58 Hz, 1H), 7.79 (AA'XX', J = 8.25 Hz, 2H), 7.75 (d, J = 8.58 Hz, 1H), 7.64 (AA'XX', J = 8.25 Hz, 2H), 5.16 (s, 1H), 3.96 (d, J = 14.36 Hz, 1H), 3.53 (d, J = 14.36 Hz, 1H), 1.62 (s, 3H), 1.51 (pent, J = 8.15 Hz, 6H), 1.31 (sextet, J = 7.40 Hz, 6H), 1.08 (t, J = 8.04 Hz, 6H), 0.88 (t, J = 7.29 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.07, 153.30, 141.57, 138.72, 137.43, 135.91, 134.02 (q, $^3J_{CF}$ = 33.14 Hz), 126.28, 122.19, 122.05 (q, $^2J_{CF}$ = 274.34 Hz), 117.65 (q, $^4J_{CF}$ = 4.60 Hz), 115.61, 104.79 (q, $^4J_{CF}$ = 1.84 Hz), 74.80, 61.91, 29.06, 27.70, 27.41, 13.76, 9.90. HRMS (ESI, Q-TOF) calcd, 703.1839; found, 703.1831.

3-(4-Bromo-benzenesulfonyl)-*N*-(4-cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-propionamide (19) from *N*-(4-Cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-3-(4-tributylstannanyl-benzenesulfonyl)-propionamide (20). NH_4Br (6 mg, 61 μmol) was placed in a conical vial (5 mL), dissolved in a 10% HOOAc/HOAc solution (500 μL), and stirred for 20 min. During this time, the solution turned a pale-amber color. Propionamide (**20**) (43 mg, 62 μmol) was then added, and the solution was stirred at room temperature open to the atmosphere for 45 min. Product isolation (CH_2Cl_2, bicarbonate, Na_2SO_4) followed by flash chromatography using 50% EtOAc/50% hexanes afforded a pure product as a white solid (26 mg, 52 μmol) in 84% yield.

***N*-(4-Cyano-3-trifluoromethyl-phenyl)-2-methyl-2-oxirane-propionamide (22).** *N*-(4-Cyano-3-trifluoromethyl-phenyl)-2-methyl-acrylamide (513 mg, 2.02 mmol) was dissolved in 96% formic acid (15 mL). H_2O_2 (37%, 8 mL) was slowly added, and the resulting solution was stirred at 40 °C for 2 h. Product isolation (CH_2Cl_2, bicarbonate, Na_2SO_4) followed by flash chromatography (100% CH_2Cl_2) produced a pure product (480 mg, 1.778 mmol) in 88% yield as an off-white powder. (lit. mp = 149−150 °C).[44] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.41 (s, 1H), 8.01 (d, J = 1.93 Hz, 1H), 7.89 (dd, J = 2.64, 8.58 Hz, 1H), 7.78 (d, J = 8.68 Hz, 1H), 2.99 (s, 2H), 1.66 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.28, 141.19, 135.88, 133.78 (q, $^3J_{CF}$ = 33.14 Hz), 122.51 (q, $^2J_{CF}$ = 139.93 Hz), 117.24 (q, $^4J_{CF}$ = 4.60 Hz), 121.78, 115.40, 104.73 (q, $^4J_{CF}$ = 1.84 Hz), 56.65, 54.09, 16.61. HRMS (EI^+) calcd, 290.0514; found, 290.0516.

3-(4-Bromo-phenylsulfanyl)-*N*-(4-cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-propionamide (23). 4-Bromobenzenethiol (832 mg, 3.56 mmol) was added to a flame-dried round-bottomed flask (100 mL), fitted with a magnetic stirring bar, and was dissolved in dry THF (50 mL) and cooled to 0 °C. NaH (60%) (142 mg, 3.56 mmol) was added, and the mixture was allowed to stir for 5 min. While the above reaction was stirring, *N*-(4-cyano-3-trifluoromethyl-phenyl)-2-methyl-2-oxirane-propionamide (480 mg, 1.78 mmol) was added to a flame-dried pear-shaped flask (50 mL) and was dissolved in dry THF (5 mL). The resulting solution was added to the thiol. Product isolation (CH_2Cl_2, ammonium

sulfate, Na_2SO_4) followed by flash chromatography (40% EtOAc/60% hexanes) yielded a pure product as an off-white solid (496 mg, 1.085 mmol) in 61% yield with mp = 62−64 °C. R_f = 0.27 in 40% EtOAc/60% hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.08 (s, 1H), 7.95 (d, J = 1.61 Hz, 1H), 7.76 (dd, J = 2.04, 8.58 Hz, 1H), 7.73 (d, J = 8.58 Hz, 1H), 7.24 (m, 4H), 3.78 (s, 1H), 3.72 (d, J = 14.15 Hz, 1H), 3.12 (d, J = 14.04 Hz, 1H), 1.55 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.39, 141.49, 135.85, 133.90 (q,$^3J_{CF}$ = 33.14 Hz), 133.18, 132.42, 132.14, 122.00 (q,$^2J_{CF}$ = 274.34), 121.88, 121.42, 117.28 (q,$^4J_{CF}$ = 4.60 Hz), 115.75, 104.26 (q,$^4J_{CF}$ = 2.76 Hz), 75.52, 44.71, 26.23. HRMS (EI$^+$) calcd, 457.9915; found, 457.9906. Anal. calcd ($C_{17}H_{12}Br_1F_3N_2O_2S_1$): C, H, N.

***N*-(4-Cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-3-(4-tributylstannanyl-phenylsulfanyl)-propionamide (24).** Propionamide **23** (416 mg, 0.910 mmol) was placed in a flame-dried round-bottomed flask (100 mL), fitted with a magnetic stirring bar, and was dissolved in dry toluene (50 mL). TEA (660 μL, 9.10 mmol), bis(tributyltin) (2.3 mL, 4.55 mmol), and tetrakis(triphenylphosphine)palladium(0) (10 mg) were then added, and the mixture was refluxed for 24 h. The volatile solvents were removed under reduced pressure, and the crude mixture was purified with flash chromatography using 30% EtOAc/70% hexanes to afford a pure product (76 mg, 0.11 mmol) as a clear oil in 12% yield. R_f = 0.26 in 30% EtOAc/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.02 (s, 1H), 7.95 (d, J = 2.04 Hz, 1H), 7.83 (dd, J = 2.14, 8.47 Hz, 1H), 7.73 (d, J = 8.47 Hz, 1H), 7.33 (AA'XX', J = 12.65 Hz, 2H), 7.32 (AA'XX', J = 12.54 Hz, 2H), 3.71 (d, J = 14.15 Hz, 1H), 3.22 (d, J = 14.15 Hz, 1H), 1.48 (m, 6H), 1.30 (sextet, J = 7.40 Hz, 6H), 1.00 (t, J = 8.04 Hz, 6H), 0.87 (t, J = 7.18 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.14, 131.79, 141.32, 137.15, 135.75, 133.94 (q,$^3J_{CF}$ = 33.14 Hz), 133.54, 129.95, 129.82, 122.05 (q,$^2J_{CF}$ = 274.34 Hz), 121.74, 117.19 (q,$^4J_{CF}$ = 4.60 Hz), 115.44, 104.51 (q,$^4J_{CF}$ = 1.84 Hz), 75.67, 44.55, 28.97, 27.28, 13.61, 9.53. HRMS (ESI, Q-TOF) calcd, 671.1941; found, 671.1908.

3-(4-Bromo-phenylsulfanyl)-*N*-(4-cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-propionamide (23) from *N*-(4-Cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-3-(4-tributylstannanyl-phenylsulfanyl)-propionamide (24). NH_4Br (4 mg, 41 μmol) was placed in a conical vial (5 mL), dissolved in 1.5% HOOAc/HOAc (500 μL) solution, and stirred for 10 min, during which time the solution turned a pale-amber color. At this point, propionamide **23** (26 mg, 39 μmol) was added, and the mixture was stirred at room temperature open to the atmosphere for 11 min. The reaction was then diluted with H_2O (300 μL) and passed over a C-18 column. H_2O (3 × 1 mL) was pushed through the column followed by 10 mL of air. This was followed by CH_2Cl_2 (3 × 1 mL) in which the product was eluted. The CH_2Cl_2 fractions were combined, dried with Na_2SO_4, and filtered. The resulting solution, containing a mixture of sulfoxide and sulfone compounds, was treated with a solution of diethyl chlorophosphite (100 μL, 0.916 mmol) in 400 μL of CH_2Cl_2 and stirred at room temperature for 20 min. The volatile solvents were removed under reduced pressure, and the product was purified with flash chromatography using 20% EtOAc/80% hexanes to give the desired product in 34% yield (6 mg, 13 μmol).

3-(4-Bromo-phenylsulfanyl)-2-hydroxy-2-methyl-*N*-(4-nitro-3-trifluoromethyl-phenyl)-propionamide (26). 4-Bromobenzene thiol (188 mg, 0.995 mmol) was added to a flame-dried round-bottomed flask (100 mL), fitted with a stirring bar, and was dissolved in dry THF (30 mL) and cooled to 0 °C. At this point, NaH (60%) (40 mg, 1.0 mmol) was added, and the mixture was allowed to stir for 5 min. While the above reaction was stirring, propionamide **22** (144 mg, 0.497 mmol) was added to a flame-dried pear-shaped flask (50 mL) and dissolved in dry THF (5 mL) and also cooled to 0 °C. The two solutions were combined through a cannula, and the resulting mixture was slowly warmed to room temperature and stirred for 5 h. The reaction was quenched by the addition of a saturated ammonium sulfate solution (10 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined and dried with Na_2SO_4, and the volatile organics were removed using reduced pressure. The crude mixture was purified with flash chromatography using 40% EtOAc/60% hexanes to yield a pure product as an off-white solid (76 mg, 0.159 mmol) in 32% yield with mp = 54−56 °C. R_f = 0.30 in 40% EtOAc/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.03 (s, 1H), 7.94 (d, J = 8.90 Hz, 1H), 7.91 (d, J = 2.25 Hz, 1H), 7.80 (dd, J = 2.36, 8.79 Hz, 1H), 7.26 (m, 4H), 3.78 (d, J = 14.15 Hz, 1H), 3.55 (s, 1H), 3.12 (d, J = 14.26 Hz, 1H), 1.55 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.18, 143.25, 141.41, 132.72, 132.69, 132.32, 127.20, 125.26 (q,$^3J_{CF}$ = 34.98 Hz), 122.08, 121.79, 120.77, 118.23 (q,$^4J_{CF}$ = 5.52 Hz), 75.43, 44.77, 26.38. HRMS (EI$^+$) calcd, 477.9810; found, 477.9803. Anal. calcd ($C_{16}H_{12}Br_1F_3N_2O_4S_1$): C, H, N.

***N*-(4-Cyano-3-trifluoromethyl-phenyl)-3-(4-[^{18}F]fluoro-benzenesulfonyl)-2-hydroxy-2-methyl-propionamide (^{18}F-1).** Resin-treated target [^{18}O]H_2O was subjected to proton bombardment, and an aliquot containing 42.2 mCi (1.56 GBq) of [^{18}F]fluoride was transferred to a Vacutainer that had previously been treated with tetrabutylammonium hydroxide (2 μL). The [^{18}O]H_2O was removed by azeotropic distillation with acetonitrile (3 × 0.75 mL), N_2, and heat.[66] Ammonium precursor **13** (1.1 mg, 3.0 μmol) was added to the vessel and dissolved in DMSO (400 μL). The resulting mixture was heated by microwave irradiation (3 × 20 s). The crude mixture was passed over a silica pipet column (50 mg) with CH_3CN (3 mL), and the volatile organics were then removed using reduced pressure. The vial containing a crude mixture of [^{18}F]fluorophenyl methyl sulfone was dissolved in CH_3CN (500 mL) and injected through a Teflon filter onto a reverse-phase HPLC column (40% CH_3CN/60% H_2O, 3.5 mL/min) to obtain 14.2 mCi (525 MBq) of pure [^{18}F]fluorophenyl methyl sulfone, which eluted at 4.50 min (65% yield, decay corrected, 112 min). Dry [^{18}F]fluorophenyl methyl sulfone was placed in a pear-shaped flask under a stream of argon, and pseudocarrier **16** was added (3 mg, 14 μmol) and dissolved in dry THF (2 mL). The reaction vial was capped and cooled to −78 °C, and *n*-BuLi (70 μL, 110 μmol) was added dropwise by syringe until a yellow color persisted. The reaction was stirred for 10 min, and propionamide **6** was added (30 mg, 120 μmol), at which point the yellow color disappeared. The resulting solution was allowed to warm to room temperature and was stirred for 15 min. The mixture was quenched with saturated ammonium chloride (30 μL) and then injected through a Teflon filter onto a reverse-phase HPLC (50% CH_3CN/50% H_2O, 3.0 mL/min) to obtain 894 μCi of product eluted at 27.02 min (35% yield, decay corrected, 293 min). The total yield was 23% (decay corrected, 405 min). ^{18}F-**1** was identified by co-injection with an authentic sample on HPLC.

3-(4-[^{76}Br]Bromo-benzenesulfonyl)-*N*-(4-cyano-3-trifluoromethyl-phenyl)-2-hydroxy-2-methyl-propionamide (^{76}Br-19). $^{76}Br^-$ was obtained from an isotopically enriched Cu^{76}Se-coated tungsten target that was subjected to proton bombardment, and an aliquot containing 5.8 mCi (215 MBq) was transferred to a small reaction vial in a 0.6 N NH_4OH solution. The bromine-76-containing NH_4-OH solution was passed over a C-18 separatory column that had been previously treated with H_2O (3 mL). After the NH_4OH was pushed through the column, it was followed with EtOH (300 μL). The resulting solution was placed in a glass reaction vial, and the solvent was removed using heat (90 °C) and a stream of N_2. A 1% HOOAc/HOAc (500 μL) solution was placed in the dry vial containing $^{76}Br^-$ along with propionamide **19** (2.3 mg, 3.3 μmol), and this mixture was stirred at room temperature for 20 min. A 400 μL portion of a 50% THF/50% H_2O solution was added to the vial, and the resulting mixture was taken up into a syringe (1 mL) and injected through a Teflon filter onto a reverse-phase HPLC column (40% THF/60% H_2O, 4.0 mL/min) to obtain 1.65 mCi of 4-[^{76}Br]bromobicalutamide, which eluted at 10.08 min (29%, decay corrected, 65 min). [^{76}Br] product was identified by co-injection with an authentic sample on HPLC. An aliquot (194 μCi, 7.18 MBq) was taken and combined with CH_3CN (1 mL), and the solvent was removed under reduced pressure and heat. To the resulting dry flask was added EtOH (500 μL) followed by saline (4.5 mL). The resulting solution was taken up into 26 fractions for biodistribution.

3-(4-Bromo-phenylsulfanyl)-*N*-(4-[^{76}Br]cyano-3-trifluoromethyl-

phenyl)-2-hydroxy-2-methyl-propionamide (^{76}Br-23). ^{76}Br (670 μCi, 24.7 MBq) was delivered in an ammonium hydroxide solution that had been worked up as previously described. The resulting solution was placed in a glass reaction vial, and the solvent was removed using heat (90 °C) and a stream of N_2. Propionamide **24** (6.0 mg, 8.9 μmol) was placed in the ^{76}Br-containing vial along with 1% HOOAc/HOAc (400 μL) and was stirred at room temperature for 15 min. H_2O (500 μL) was added, and the resulting cloudy mixture was taken up into a 1 mL syringe and passed over a C-18 separatory column that had previously been washed with H_2O (2 mL). The column containing the radioactive compound was then flushed with H_2O (2 × 1 mL) and air (2 × 1 mL). The product was eluted from the column using Et_2O (2 × 1 mL), and the organic layers were combined and dried using Na_2SO_4, and the solvent was removed using N_2. CH_2Cl_2 (400 μL) was added to the dry vial containing the crude mixture followed by diethyl chlorophosphite (5 μL, 0.05 μmol). The reaction was stirred for 5 min and then combined with a 50% THF/50% H_2O solution. The resulting mixture was taken up into a 1 mL syringe and injected through a Teflon filter onto a semipreparatory reverse-phase HPLC column (45% THF/65% H_2O, 4.0 mL/min) to obtain 28 μCi of product that eluted at 12.51 min (4%, decay corrected, 125 min). 4-[^{76}Br]-bromo-thiobicalutamide product was identified by co-injection with an authentic sample on HPLC.

Animal Biodistribution Study. In the following experiments, animals were handled in accordance with the Animal Studies Committee at Washington University, School of Medicine. A complete description of the animal handling procedure, including animal care, anesthesia, and monitoring, can be found in ref 67.

In the rat biodistribution study, purified (^{76}Br-**19**) was reconstituted in 10% ethanol−saline and injected (iv, tail vein) into mature male Sprague−Dawley rats (250 g) castrated 7 days prior to the experiment. Doses employed were 4 and 7 μCi/animal, respectively, at the two time points (in 150 and 260 μL volumes, respectively), and animals were sacrificed at 1 and 18 h postinjection. To determine whether uptake was mediated by a high-affinity, limited-capacity system, one set of animals was left with testes intact to provide saturation of the AR by the endogenous androgens. At 1 and 18 h after the injection of the ^{76}Br-tracer, groups of five animals each were killed, tissues of interest were removed, weighed, washed with saline, blotted dry, and the radioactivity was counted. The percent injected dose in each tissue was calculated by comparison to injected dose standards of appropriate count rates.

In the mouse tumor biodistribution study, purified (^{76}Br-**19**) was reconstituted in 10% ethanol−saline and injected (iv, tail vein) into mature male mice (25 g) having a previously implanted tumor prostate (CWR22) in the flank. CWR22 implanted mice had been injected subcutaneously with DES (0.2 mg) in sesame oil (0.1 mL) 24 and 3 h prior to the injection of the tracer to suppress endogenous androgen biosynthesis.[56] Doses of (^{76}Br-**19**) employed were 6 μCi/animal (in 120 μL volume), and animals were sacrificed at 30 and 90 min postinjection. To ascertain whether tissue accumulation of activity was mediated by a high-affinity, limited-capacity uptake system, one set of animals was co-injected with the radiotracer together with a blocking dose (8 μg) of 17α-methyl testosterone.

Glutathione Challenge Test. Bicalutamide, 4-bromobicalutamide, and 4-bromo-thiobicalutamide (10 μmol) were each separately dissolved in THF (400 μL) and then diluted with a 0.05 M potassium phosphate buffer (pH 7.5, 4.6 mL). Glutathione (15 mg, 50 μmol) was added to the solution, and the reaction was stirred at 37 °C for 24 h. Aliquots (100 μL) at various time points were taken (1, 8, and 24 h) and injected through a Teflon filter onto an analytical reverse-phase HPLC column for analysis of the reaction products as described previously. No peaks other than the starting materials and glutathione were present in the HPLC traces.

In Vivo Stability of 4-[^{76}Br]Bromobicalutamide (19). To investigate the in vivo stability of ^{76}Br-**19**, we took blood samples from each time group of animals, and the amount of intact ^{76}Br-**19** was followed using radiometric normal-phase thin-layer chromatography. A sample of heparinized blood (1 mL) was taken from one animal from each data set and analyzed. The sample was centrifuged at 3000 rpm for 4 min to separate the plasma and cellular fractions, and the individual fractions were counted in a well counter. The plasma was then treated with CH_3CN (1 mL) and centrifuged as before, and the supernatant was separated from the precipitated debris. The fractions were again counted, with the bulk of the activity residing the plasma supernatant. The activity in the supernatant was purity analyzed by radiometric thin-layer chromatography. At the 1 h time point, the bulk of the ^{76}Br activity in the blood was found to be immobile with only 20% as intact ^{76}Br-**19**. At the 18 h time point, all ^{76}Br was consistent with the complete debromination of ^{76}Br-**19**.

In the CWR22 tumor implanted mice, a tumor was selected from the DES-treated mice at each time point and ground, extracted with CH_3CN (1 mL), and analyzed as previously described. At each time point, all ^{76}Br was immobile, consistent with the complete debromination of ^{76}Br-**19**.

Acknowledgment. We thank Kathryn E. Carlson for her assistance with RBA analysis. This work was supported in part by DOE grants (FG02 86ER60401 to J.A.K. and FG02 84ER60218 to M.J.W.) and an NIH grant (PHS 1R24 CA86307 to M.J.W.).

Supporting Information Available: Elemental analyses of new derivatives **7**, **17**, **19**, **23**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Jemal, A.; Murray, T.; Samuels, A.; Ghafoor, A.; Ward, E.; Thun Michael, J. Cancer statistics, 2003. *CA. Cancer J. Clin.* **2003**, *53*, 5−26.
(2) Huggins, C. Endocrine-induced regression of cancers. *Cancer Res.* **1967**, *27*, 1925−1930.
(3) Choe, Y. S.; Lidstroem, P. J.; Chi, D. Y.; Bonasera, T. A.; Welch, M. J.; Katzenellenbogen, J. A. Synthesis of 11β-[^{18}F]fluoro-5α-dihydrotestosterone and 11β-[^{18}F]fluoro-19-nor-5α-dihydrotestosterone: Preparation via halofluorination-reduction, receptor binding, and tissue distribution. *J. Med. Chem.* **1995**, *38*, 816−825.
(4) Liu, A.; Dence, C. S.; Welch, M. J.; Katzenellenbogen, J. A. Fluorine-18-labeled androgens: radiochemical synthesis and tissue distribution studies on six fluorine- substituted androgens, potential imaging agents for prostatic cancer. *J. Nucl. Med.* **1992**, *33*, 724−734.
(5) Liu, A.; Katzenellenbogen, J. A.; VanBrocklin, H. F.; Mathias, C. J.; Welch, M. J. 20-[^{18}F]Fluoromibolerone, a positron-emitting radiotracer for androgen receptors: Synthesis and tissue distribution studies. *J. Nucl. Med.* **1991**, *32*, 81−88.
(6) Parent, E. E.; Jenks, C.; Sharp, T.; Welch, M. J.; Katzenellenbogen, J. A. Synthesis and biological evaluation of a nonsteroidal bromine-76-labeled androgen receptor ligand 3-[^{76}Br]bromo-hydroxyflutamide. *Nucl. Med. Biol.* **2006**, *33*, 705−713.
(7) Parent, E. E.; Dence, C. S.; Sharp, T. L.; Welch, M. J.; Katzenellenbogen, J. A. Synthesis and biological evaluation of a fluorine-18-labeled nonsteroidal androgen receptor antagonist, *N*-(3-[^{18}F]-fluoro-4-nitronaphthyl)-cis-5- norbornene-endo-2,3-dicarboxylic imide. *Nucl. Med. Biol.* **2006**, *33*, 615- 624.
(8) Dehdashti, F.; Picus, J.; Michalski, J. M.; Dence, C. S.; Siegel, B. A.; Katzenellenbogen, J. A.; Welch, M. J. Positron tomographic assessment of androgen receptors in prostatic carcinoma. *Eur. J. Nucl. Med. Mol. Imaging* **2005**, *32*, 344−350.
(9) Larson, S. M.; Morris, M.; Gunther, I.; Beattie, B.; Humm, J. L.; Akhurst, T. A.; Finn, R. D.; Erdi, Y.; Pentlow, K.; Dyke, J.; Squire, O.; Bornmann, W.; McCarthy, T.; Welch, M.; Scher, H. Tumor localization of 16β-^{18}F-fluoro-5α-dihydrotestosterone versus ^{18}F-FDG in patients with progressive, metastatic prostate cancer. *J. Nucl. Med.* **2004**, *45*, 366−373.
(10) Small, E. J.; Halabi, S.; Dawson, N. A.; Stadler, W. M.; Rini, B. I.; Picus, J.; Gable, P.; Torti, F. M.; Kaplan, E.; Vogelzang, N. J. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: A phase III trial (CALGB 9583). *J. Clin. Oncol.* **2004**, *22*, 1025−1033.
(11) Scher, H. I.; Liebertz, C.; Kelly, W. K.; Mazumdar, M.; Brett, C.; Schwartz, L.; Kolvenbag, G.; Shapiro, L.; Schwartz, M. Bicalutamide for advanced prostate cancer: The natural versus treated history of disease. *J. Clin. Oncol.* **1997**, *15*, 2928−2938.
(12) Scher, H. I.; Kelly, W. K. Flutamide withdrawal syndrome: Its impact on clinical trials in hormone-refractory prostate cancer. *J. Clin. Oncol.* **1993**, *11*, 1566−1572.

(13) Small, E. J.; Srinivas, S. The antiandrogen withdrawal syndrome. Experience in a large cohort of unselected patients with advanced prostate cancer. *Cancer* **1995**, *76*, 1428−1434.
(14) Figg, W. D.; Sartor, O.; Cooper, M. R.; Thibault, A.; Bergan, R. C.; Dawson, N.; Reed, E.; Myers, C. E. Prostate specific antigen decline following the discontinuation of flutamide in patients with stage D2 prostate cancer. *Am. J. Med.* **1995**, *98*, 412−414.
(15) Taplin, M.-E.; Bubley, G. J.; Shuster, T. D.; Frantz, M. E.; Spooner, A. E.; Ogata, G. K.; Keer, H. N.; Balk, S. P. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N. Engl. J. Med.* **1995**, *332*, 1393−1398.
(16) Jacobson, O.; Bechor, Y.; Icar, A.; Novak, N.; Birman, A.; Marom, H.; Fadeeva, L.; Golan, E.; Leibovitch, I.; Gutman, M.; Even-Sapir, E.; Chisin, R.; Gozin, M.; Mishani, E. Prostate cancer PET bioprobes: Synthesis of [^{18}F]-radiolabeled hydroxyflutamide derivatives. *Bioorg. Med. Chem.* **2005**, *13*, 6195−6205.
(17) Miller, D. D.; Kirkovsky, L. I.; Dalton, J. T.; Mukherjee, A. Nonsteroidal radiolabeled androgen receptor agonist/antagonist compounds, preparation, and use in prostate cancer imaging. 98-US11483 9855153, 19980604. 1998.
(18) Jacobson, O.; Laky, D.; Carlson, K. E.; Elgavish, S.; Gozin, M.; Even-Sapir, E.; Leibovitc, I.; Gutman, M.; Chisin, R.; Katzenellenbogen, J. A.; Mishani, E. Chiral dimethylamine flutamide derivatives modeling, synthesis, androgen receptor affinities and carbon-11 labeling. *Nucl. Med. Biol.* **2006**, *33*, 695−704.
(19) Hallowes, R.; Cox, S.; Hayward, S.; Deshpande, N.; Towler, J. Effects of flutamide and hydroxyflutamide on the growth of human benign prostatic hyperplasia cells in primary culture: A preliminary report. *Anticancer Res.* **1991**, *11*, 1799−1805.
(20) Tucker, H.; Crook, J. W.; Chesterson, G. J. Nonsteroidal antiandrogens. synthesis and structure-activity relationships of 3-substituted derivatives of 2-hydroxypropionanilides. *J. Med. Chem.* **1988**, *31*, 954−959.
(21) James, K. D.; Ekwuribe, N. N. A two-step synthesis of the anticancer drug (*R*,*S*)-bicalutamide. *Synthesis* **2002**, *7*, 850−852.
(22) Mukherjee, A.; Kirkovsky, L.; Yao, X. T.; Yates, R. C.; Miller, D. D.; Dalton, J. T. Enantioselective binding of Casodex, to the androgen receptor. *Xenobiotica* **1996**, *26*, 117−122.
(23) Mukherjee, A.; Kirkovsky, L. I.; Kimura, Y.; Marvel, M. M.; Miller, D. D.; Dalton, J. T. Affinity labeling of the androgen receptor with nonsteroidal chemoaffinity ligands. *Biochem. Pharmacol.* **1999**, *58*, 1259−1267.
(24) Ottenheijm, H. C. J.; De Man, J. H. M. Syntheses of α-keto acid chlorides. *Synthesis* **1975**, *3*, 163−164.
(25) Hoch, H. Dimethylaminobenzene compounds. 74-24544.05 2454405, 19741116, 1976.
(26) Schlessinger, R. H.; Lopes, A. A total synthesis of racemic senepoxide: Formal syntheses of crotepoxide and pipoxide. *J. Org. Chem.* **1981**, *46*, 5252−5253.
(27) Yin, D.; Zhang, L.; Tang, G.; Tang, X.; Wang, Y. Enantioselective synthesis of no-carrier added (NCA) 6-[^{18}F]fluoro-L-Dopa. *J. Radioanal. Nucl. Chem.* **2003**, *257*, 179−185.
(28) Li, Z.; Ding, Y.-S.; Gifford, A.; Fowler, J. S.; Gatley, J. S. Synthesis of structurally identical fluorine-18 and iodine isotope labeling compounds for comparative imaging. *Bioconjugate Chem.* **2003**, *14*, 287−294.
(29) Nicoletti, M.; O'Hagan, D.; Slawin, A. M. Z. *a,b,g*-Trifluoroalkanes: A stereoselective synthesis placing three vicinal fluorines along a hydrocarbon chain. *J. Am. Chem. Soc.* **2005**, *127*, 482−483.
(30) Kim, H. W.; Jeong, J. M.; Lee, Y.-S.; Chi, D. Y.; Chung, K.-H.; Lee, D. S.; Chung, J.-K.; Lee, M. C. Rapid synthesis of [^{18}F]FDG without an evaporation step using an ionic liquid. *Appl. Radiat. Isot.* **2004**, *61*, 1241−1246.
(31) Adams, D. J.; Clark, J. H.; Nightingale, D. J. Tetramethylammonium hydrogen difluoride: A convenient source of nucleophilic fluoride. *Synth. Commun.* **1998**, *28*, 4295−4301.
(32) Clark, J. H.; Wails, D. Fluorodenitration of activated diphenyl sulfones using tetramethylammonium fluoride. *J. Fluorine Chem.* **1995**, *70*, 201−205.
(33) Beaumont, A. J.; Clark, J. H.; Boechat, N. A. Selective fluorodenitration of chloronitroaromatics. *J. Fluorine Chem.* **1993**, *63*, 25−30.
(34) Maertens, F.; Toppet, S.; Hoornaert, G. J.; Compernolle, F. Incorporation of an indole-containing diarylbutylamine pharmacophore into furo[2,3-*a*]carbazole ring systems. *Tetrahedron* **2005**, *61*, 1715−1722.
(35) Cooke, R. S.; Hammond, G. S. Mechanisms of photochemical reactions in solution. LXII. Naphthalene-sensitized photoracemization of sulfoxides. *J. Am. Chem. Soc.* **1970**, *92*, 2739−2745.
(36) Gilbert, E. E. Sulfonation of negatively substituted tert-butylbenzene derivatives. *J. Org. Chem.* **1970**, *35*, 850−852.
(37) Jagoda, E.; Contoreggi, C.; Lee, M.-J.; Kao, C.-H. K.; Szajek, L. P.; Listwak, S.; Gold, P.; Chrousos, G.; Greiner, E.; Kim, B. M.; Jacobson, A. E.; Rice, K. C.; Eckelman, W. Autoradiographic visualization of corticotropin releasing hormone type 1 receptors with a nonpeptide ligand: Synthesis of [^{76}Br]MJL-1−109.−2. *J. Med. Chem.* **2003**, *46*, 3559−3562.
(38) Coleman, R. S.; Seevers, R. H.; Friedman, A. M. Aromatic radiobromination without added carrier. *J. Chem. Soc., Chem. Commun.* **1982**, *21*, 1276−1277.
(39) Emaus, W. J. M.; Henning, H. J. Determination of bromide in sodium chloride matrixes by flow-injection analysis using blank peak elimination and kinetic discrimination. *Anal. Chim. Acta* **1993**, *272*, 245−250.
(40) van Staden, J. F.; Mulaudzi, L. V.; Stefan, R. I. On-line speciation of bromine and bromide using sequential injection analysis with spectrophotometric detection. *Anal. Bioanal. Chem.* **2003**, *375*, 1074−1082.
(41) Kao, C.-H. K.; Sassaman, M. B.; Szajek, L. P.; Ma, Y.; Waki, A.; Eckelman, W. C. The sequential syntheses of [^{76}Br]FBAU 3′,5′-dibenzoate and [^{76}Br]FBAU. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 889−898.
(42) Staelens, L.; Dumont, F.; De Vos, F.; Oltenfreiter, R.; Vandecapelle, M.; Dierckx, R. A.; Slegers, G. Synthesis and radiolabelling of [^{123}I]-4-iodo-*N*-(4-(4-(2- methoxyphenyl)- piperazin-1-yl)butyl)-benzamide, a potential dopamine D3 antagonist for SPECT studies. *J. Labelled Compd. Radiopharm.* **2003**, *46*, 297−305.
(43) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y. L. Iodine(V) reagents in organic synthesis. Part 2. Access to complex molecular architectures via Dess−Martin periodinane-generated *o*-imidoquinones. *J. Am. Chem. Soc.* **2002**, *124*, 2221−2232.
(44) Chen, B.-C.; Zhao, R.; Gove, S.; Wang, B.; Sundeen, J. E.; Salvati, M. E.; Barrish, J. C. Nucleophilic aromatic substitution of methacrylamide anion and its application to the synthesis of the anticancer drug bicalutamide. *J. Org. Chem.* **2003**, *68*, 10 181−10 182.
(45) Wallace, T. J. Reactions of thiols with sulfoxides. I. Scope of the reaction and synthetic applications. *J. Am. Chem. Soc.* **1964**, *86*, 2018−2021.
(46) Madesclaire, M. Reduction of sulfoxides to thioethers. *Tetrahedron* **1988**, *44*, 6537−6580.
(47) Jie, Z.; Rammoorty, V.; Fischer, B. Diethyl chlorophosphite: A versatile reagent. *J. Org. Chem.* **2002**, *67*, 711−719.
(48) Hoyte, R. M.; Borderon, K.; Bryson, K.; Allen, R.; Hochberg, R. B.; Brown, T. J. Synthesis and evaluation of 7α-iodo-5α-dihydrotestosterone as a potential radioligand for androgen receptor. *J. Med. Chem.* **1994**, *37*, 1224−1230.
(49) Dalton, J. T.; Mukherjee, A.; Zhu, Z.; Kirkovsky, L.; Miller, D. D. Discovery of nonsteroidal androgens. *Biochem. Biophys. Res. Commun.* **1998**, *244*, 1−4.
(50) Teutsch, G.; Goubet, F.; Battmann, T.; Bonfils, A.; Bouchoux, F.; Cerede, E.; Gofflo, D.; Gaillardkelly, M.; Philibert, D. Non-steroidal antiandrogens - synthesis and biological profile of high-affinity ligands for the androgen receptor. *J. Steroid Biochem. Mol. Biol.* **1994**, *48*, 111−119.
(51) Asselin, J.; Melancon, R. Characteristics of androgen binding in rat adrenal tissue using [3H]methyltrienolone (R1881) as tracer. *Steroids* **1977**, *30*, 591−604.
(52) Bonne, C.; Raynaud, J. P. Assay of androgen binding sites by exchange with methyltrienolone (R 1881). *Steroids* **1976**, *27*, 497−507.
(53) Ojasoo, T.; Raynaud, J. P. Unique steroid congeners for receptor studies. *Cancer Res.* **1978**, *38*, 4186−4198.
(54) He, Y.; Yin, D.; Perera, M.; Kirkovsky, L.; Stourman, N.; Li, W.; Dalton, J. T.; Miller, D. D. Novel nonsteroidal ligands with high binding affinity and potent functional activity for the androgen receptor. *Eur. J. Med. Chem.* **2002**, *37*, 619−634.
(55) Carlson, K. E.; Katzenellenbogen, J. A. A comparative study of the selectivity and efficiency of target tissue uptake of five tritium-labeled androgens in the rat. *J. Steroid Biochem.* **1990**, *36*, 549−561.
(56) Garg, P. K.; Labaree, D. C.; Hoyte, R. M.; Hochberg, R. B. [7α-^{18}F]Fluoro-17α-methyl-5α-dihydrotestosterone: A ligand for androgen receptor-mediated imaging of prostate cancer. *Nucl. Med. Biol.* **2001**, *28*, 85−90.
(57) Gregory, C. W.; Johnson, R. T.; Mohler, J. L.; French, F. S.; Wilson, E. M. Androgen receptor stabilization in recurrent prostate cancer is associated with hypersensitivity to low androgen. *Cancer Res.* **2001**, *61*, 2892−2898.
(58) Kim, D.; Gregory, C. W.; French, F. S.; Smith, G. J.; Mohler, J. L. Androgen receptor expression and cellular proliferation during transition from androgen-dependent to recurrent growth after castration in the CWR22 prostate cancer xenograft. *Am. J. Pathol.* **2002**, *160*, 219−226.

(59) Grillo, M. P.; Knutson, C. G.; Sanders, P. E.; Waldon, D. J.; Hua, F.; Ware, J. A. Studies on the chemical reactivity of diclofenac acyl glucuronide with glutathione: Identification of diclofenac-*S*-acyl-glutathione in rat bile. *Drug Metab. Dispos.* **2003**, *31*, 1327−1336.
(60) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and convenient procedure for solvent purification. *Organometallics* **1996**, *15*, 1518−1520.
(61) Still, W. C.; Kahn, M.; Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43*, 2923−2925.
(62) Liu, A.; Carlson, K. E.; Katzenellenbogen, J. A. Synthesis of high affinity fluorine-substituted ligands for the androgen receptor. Potential agents for imaging prostatic cancer by positron emission tomography. *J. Med. Chem.* **1992**, *35*, 2113−2129.
(63) Brandes, S. J.; Katzenellenbogen, J. A. Fluorinated androgens and progestins: Molecular probes for androgen and progesterone receptors with potential use in positron emission tomography. *Mol. Pharmacol.* **1987**, *32*, 391−403.
(64) Kilbourn, M. R.; Jerabek, P. A.; Welch, M. J. An improved [^{18}O]-water target for [^{18}F]fluoride production. *Int. J. Appl. Radiat. Isot.* **1985**, *36*, 327−328.
(65) Welch, M. J.; Tang, L. L. W.; Rowland, D. J., Jr. Enhanced separation process for (^{76}Br, ^{77}Br and ^{124}I) preparation and recovery of each. 2004-US25529 (2005014136), 20040807, 2005.
(66) Vijaykumar, D.; Al-Qahtani, M. H.; Welch, M. J.; Katzenellenbogen, J. A. Synthesis and biological evaluation of a fluorine-18 labeled estrogen receptor-α selective ligand: [^{18}F] propyl pyrazole triol. *Nucl. Med. Biol.* **2003**, *30*, 397−404.
(67) Sharp, T. L.; Dence, C. S.; Engelbach, J. A.; Herrero, P.; Gropler, R. J.; Welch, M. J. Techniques necessary for multiple tracer quantitative small-animal imaging studies. *Nucl. Med. Biol.* **2005**, *32*, 875−884.

JM060847R