Journal of Medicinal Chemistry Article

J. Med. Chem. **2010,** *53,* 4917–4926 **4917**
DOI: 10.1021/jm100316f

Design and Synthesis of Androgen Receptor Full Antagonists Bearing a *p*-Carborane Cage: Promising Ligands for Anti-Androgen Withdrawal Syndrome

Tokuhito Goto,[†] Kiminori Ohta,[†] Shinya Fujii,[‡] Shigeru Ohta,[§] and Yasuyuki Endo*,[†]

[†]*Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1, Komatsushima, Aoba-ku, Sendai 981-8558, Japan,* [‡]*School of Medical Science, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10, Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan, and* [§]*Graduate School of Medical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan*

Received March 10, 2010

Pure androgen receptor (AR) full antagonists are candidates to treat anti-androgen refractory prostate cancers. We previously developed a carborane-containing AR antagonist, 3-(12-hydroxymethyl-1,12-dicarba-*closo*-dodecaborane-1-yl)benzonitrile (BA341), which was more potent than hydroxyflutamide (**4**) but acted as an agonist toward LNCaP prostate cancer cells expressing T877A AR mutant. Here, we designed and synthesized novel AR full antagonists structurally based upon the clinically used AR full antagonist (*R*)-bicalutamide (**5**) to test our hypothesis that the carborane cage is suitable as a hydrophobic pharmacophore for AR ligands. Compounds **7b** and **8b** showed good biological profiles in AR binding and transactivation assays and dose-dependently inhibited the testosterone-induced proliferation of LNCaP cells, as well as SC-3 cells. The IC_{50} values of compounds **7b** and **8b** were 3.8×10^{-7} and 4.2×10^{-7} M, respectively [**5**, 8.7×10^{-7} M]. Since compounds **7b** and **8b** did not show any agonistic activity in functional assays, they seem to be pure AR full antagonists and are therefore candidates for treatment of anti-androgen withdrawal syndrome.

Introduction

Androgens play a key role of the development and maintenance of the male reproductive system.[1] A native androgen, testosterone (**1**), or its more potent tissue metabolite dihydrotestosterone (DHT,[a] **2**), binds to androgen receptor (AR), which is a member of the nuclear receptor superfamily, and mediates specific gene transcriptions.[2] Synthetic AR modulators can be structurally classified as either steroidal or nonsteroidal and may have various functional (androgenic, anti-androgenic, or anabolic) activities.[3] A nonsteroidal ligand, flutamide (**3**),[4] which is metabolized to the more potent AR antagonist hydroxyflutamide (**4**),[5] is a well-known AR antagonist used for the treatment of prostate cancer. On the other hand, (*R*)-bicalutamide (**5**) is used for the treatment of D2 stage metastatic prostate cancer.[6] These typical nonsteroidal AR antagonists have high selectivity for AR, in contrast to steroidal ligands (Figure 1).

Ligands containing a nitro or cyano group can form a direct hydrogen bond with R752 of the human AR ligand-binding domain (hAR-LBD)[7] and can also hydrogen-bond to Q711 and M745 via one H_2O molecule.[7] An X-ray cocrystal structure analysis of the complex of hAR-LBD with **2** indicated that the secondary alcohol group of **2** is hydrogen-bonded to T877.[8] The hydrophobic moiety of the ligand should possess sufficient affinity for the hydrophobic surface of the AR in order to increase the binding affinity. The hydrophobic structure also plays a role as a scaffold, fixing the spatial positions of hydrogen-bonding functional groups.

AR antagonists, that is to say anti-androgens, are particularly useful for the treatment of prostate cancer during its early stages.[9] However, prostate cancer often advances to a hormone-refractory state in which the disease progresses despite continued androgen ablation or anti-androgen therapy, owing to the appearance of androgen-independent prostate cancer cells or the ability of adrenal androgens to support tumor growth.[10] Instances of anti-androgen withdrawal syndrome, i.e., where withdrawal of antiandrogen therapy results in clinical improvement, have also been reported after prolonged treatment with anti-androgens.[11] Thus, development of pure AR full antagonists is one of the goals of drug discovery for AR. Although the molecular mechanism is not fully understood, one hypothesis is that mutation of AR occurs.[12] Indeed, such mutation has been found in patients treated with **3**.[13] AR mutations that result in receptor promiscuity and the ability of anti-androgens to exhibit agonist activity might at least partially account for this phenomenon. In particular, T877 point mutation has been found in the AR LBD in anti-androgen withdrawal syndrome patients and has been considered as a hotspot for the critical pathology.[14] Compound **5**, which is the most widely used pure anti-androgen, acts as an anti-androgen for T877A mutant AR but exhibits significant androgenic activity toward W741L or W741C point mutated AR; this is known as bicalutamide withdrawal syndrome.[15] Therefore, it is of interest to develop a new generation of pure anti-androgens that would work with both wild-type and mutant ARs.

Carborane (dicarba-*closo*-dodecaborane, $C_2B_{10}H_{12}$) is an icosahedral boron cluster, has a bulky spherical structure,

*To whom correspondence should be addressed. Phone: +81-22-234-4181. Fax: +81-22-275-2013. E-mail: yendo@tohoku-pharm.ac.jp.

[a] Abbreviations: DHT, dihydrotestosterone; AR, androgen receptor; LBD, ligand binding domain; NaH, sodium hydride; K_2CO_3, potassium carbonate; *m*CPBA, *m*-chloroperbenzoic acid; [^{3}H]DHT, [1,2-^{3}H]-dihydrotestosterone; SO_2, sulfone; SARM, selective androgen receptor modulator.

Published on Web 06/03/2010

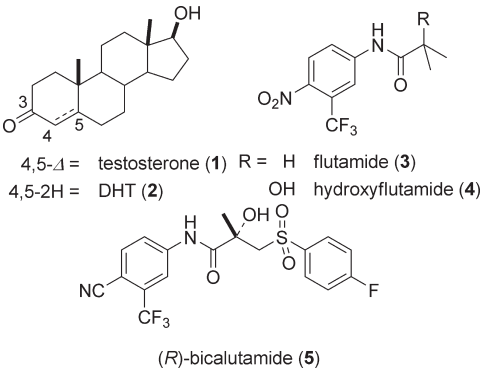


Figure 1. Structures of native and synthetic ligands for AR.

exhibits remarkable thermal stability, and has high hydrophobicity.[16] Carborane-containing ligands are of interest in medicinal chemistry, since they have a different spectrum of ligand responsiveness from other therapeutic agents owing to their unique chemical and structural features.[17] We have reported the development of bioactive molecules, including estrogen receptor modulators,[18] retinoic acid receptor modulators,[19] and retinoid X receptor antagonists,[20] that contain a carborane cage as a hydrophobic pharmacophore, and we have obtained several promising drug candidates. We also developed a carborane-containing AR antagonist, 3-(12-hydroxymethyl-1,12-dicarba-*closo*-dodecaborane-1-yl)benzonitrile (BA341, **6**),[21] which shows more potent AR-binding and AR-antagonistic activity than **4** and its analogues.[22] Our strategy for the development of novel anti-androgens is direct control of helix-12 by using steric repulsion between the bulky carborane cage and several amino acid residues, mainly M895 and F876, in the hydrophobic pocket of the hAR-LBD. In the present work, we first evaluated the biological potential of **6** focusing on its cell proliferation−inhibitory activity toward LNCaP cells, which express the point-mutated receptor, T877A AR. Unfortunately, compound **6** acted as an agonist, showing an EC_{50} value of 6.3×10^{-7} M in a LNCaP cell proliferation assay (Figure 2).

Thus, we next focused upon the development of novel AR full antagonists and designed novel pure anti-androgen candidates **7**−**10** based upon the structure of **5** with a carborane moiety as a hydrophobic pharmacophore (Figure 3). The designed molecules consisted of a linker part X and two aromatic rings A and B, of which ring A is fixed as a 3-cyanophenyl group and ring B contains various substituents at the para position to the linker group. In addition, compound **7g** containing two *p*-carborane cages was also designed to examine whether or not a carborane cage could replace ring B (Figure 3). In this paper, we describe the synthesis of these designed molecules and their biological activities, i.e., AR binding, AR transcriptional activation, and effect on AR-dependent proliferation of SC-3 and LNCaP cells, as well as the structure−activity relationships at the linker X and the B ring for AR full antagonistic activity.

Chemistry

To obtain the designed molecules, we devised an effective synthetic strategy of compounds **7**−**10**. The outline and key intermediate are summarized in Scheme 1. An epoxide **11** is a suitable intermediate for synthesis of the target molecules because the oxirane ring of **11** is availabe for a nucleophilic

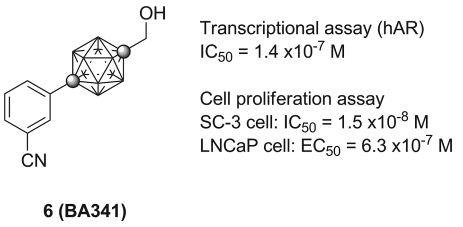
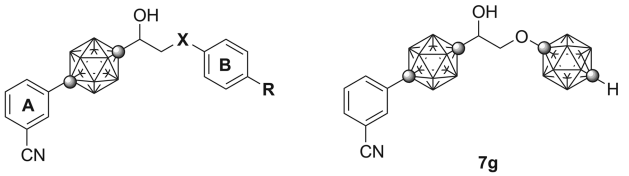


Figure 2. Structure and biological activities of **6**.

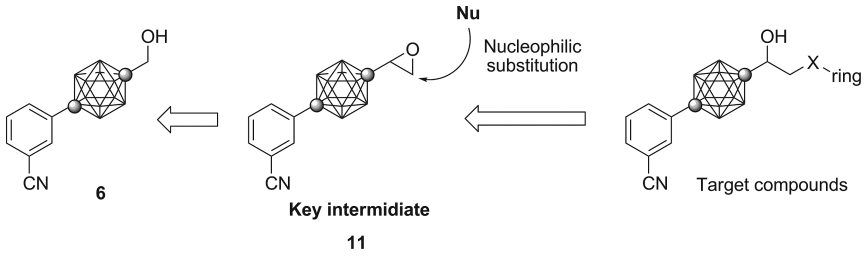


Compound	X	R
7a	O	H
7b		F
7c		OCH_3
7d		$NHCOCH_3$
7e		NO_2
7f		Br
8a	S	H
8b		F
8c		OCH_3
8d		$NHCOCH_3$
8e		CF_3
9a	SO_2	H
9b		F
9c		OCH_3
9d		$NHCOCH_3$
9e		CF_3
10	NH	H

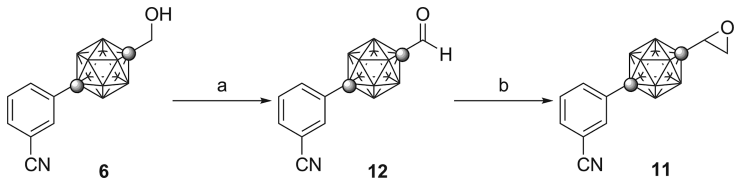
Figure 3. Pure AR antagonist candidates with a *p*-carborane cage as the hydrophobic pharmacophore.

substitution reaction. In addition, compound **11** can be obtained by oxidation reaction of the primary hydroxyl group of **6**, followed by transformation to the epoxide.[21] Therefore, we attempted to synthesize the key intermediate **11** using **6** as a starting material (Scheme 2). The primary hydroxyl group of **6** was oxidized to aldehyde with Dess−Martin periodinate to afford the corresponding compound **12** in 91% yield.[23] We tried to prepare compound **11** by means of Corey−Chaykovsky reaction, which is a good method for the transformation of aldehyde to epoxide.[24] However, the reaction of **12** with trimethylsulfonium iodide in the presence of sodium hydride (NaH) as a base did not give the desired compound **11** but provided the deformylated compound as the main product. Finally, the key intermediate **11** was prepared by the reaction of **12** with zinc carbenoid, which was prepared from diethylzinc and chloroiodomethane in the presence of tetrahydrothiophene, in 71% yield.[25] The general method employed for preparation of the designed compounds **7**−**10** is illustrated in Scheme 3. Nucleophilic attack of several phenols and *p*-carboranol on the oxirane ring of **11** in the presence of potassium carbonate (K_2CO_3) gave the desired molecules **7a**−**g** in 30−90% yields. The key intermediate **11** was reacted with various thiophenols in the presence of NaH to give the corresponding thioether derivatives **8a**−**e** in 67−77% yields, which were easily transformed into the corresponding sulfone derivatives **9a**−**e** by oxidation of the sulfide group with *m*-chloroperbenzoic acid (*m*CPBA) in 75% quantitative yields. The reaction of aniline with **11**

Scheme 1. Synthetic Strategy for Target Compounds

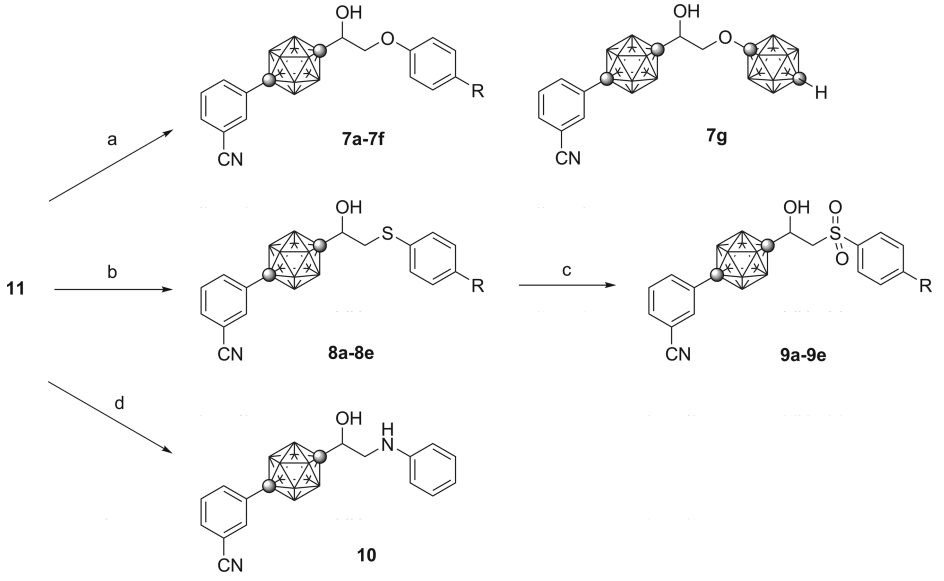


Scheme 2. Synthesis of the Key Intermediate **11**[a]



[a] Reagents and conditions: (a) Dess−Martin periodinate, CH_2Cl_2, 91%; (b) Et_2Zn, $ClCH_2I$, tetrahydrothiophene, CH_2Cl_2, 71%.

Scheme 3. Synthesis of the Designed Compounds **7**−**10**[a]



[a] Reagents and conditions: (a) phenols or *p*-carboranol, K_2CO_3, 2-propanol, 30−90%; (b) thiophenols, NaH, THF, 67−77%; (c) *m*CPBA, CH_2Cl_2, 75% quant; (d) aniline, methanol, 65%.

gave the corresponding derivative **10** in 65% yield. Compounds **7**−**10** all have an asymmetric carbon bearing a secondary alcohol and were used for biological assays in racemic form.

Binding Assay and Biological Studies

The binding affinity of the new carborane-containing compounds for AR was evaluated by means of competitive binding assay using [1,2-^{3}H]dihydrotestosterone ([^{3}H]DHT) and hAR.[26] Table 1 summarizes the binding affinity data of the synthesized compounds. The values indicate the percent displacement of specific [^{3}H]DHT binding to hAR by each compound at 10 μM. The binding of the synthesized compounds to AR is influenced more by the substituents on the B ring than by the linking group X. Compounds bearing phenyl, *p*-fluorophenyl, and *p*-methoxyphenyl rings at the position of the B ring, **7a**−**c**, **8a**−**c**, and **9a**−**c**, showed moderate binding affinity (40−60% displacement of [^{3}H]DHT), regardless of the chemical properties of the linking group. The *p*-bromophenyl derivative, **7f**, also has moderate binding affinity. Compounds **7d** and **8d** containing an acetamide group on the B ring exhibited potent binding affinity for AR (84% and 80% displacement, respectively), although they are less potent than **5** and **6**. On the other hand, another acetamide-containing compound **9d** with a sulfone (SO_2) linker showed very weak binding affinity for AR (12% displacement) despite containing the acetamide group on the B ring. Either the SO_2 linking group or the acetamide group of **9d** seems to work negatively for binding to AR. Compounds **7e**, **8e**, and **9e** bearing a nitro or a trifluoromethyl group on the B ring showed weak binding affinity for AR (around 20% displacement). Introduction of a *p*-carborane cage at the position of the B ring in place of a benzene ring led to a marked decrease of AR-binding affinity, suggesting that the *p*-carborane cage is too bulky to be accommodated at that position in the AR LBD (Table 1, **7g**). Compound **10**, with an amino

Table 1. Binding Affinity of Compounds **7**−**10** versus Specific [1,2-^{3}H]DHT (4 nM) Binding with hAR and Inhibition Percentages of Transactivation Induced by **2**

compd	X	R	binding affinity[a] displacement (%)	transactivation[b] inhibition (%)
7a	O	H	52	37
7b		F	60	51
7c		OCH_3	46	42
7d		$NHCOCH_3$	84	65
7e		NO_2	17	19
7f		Br	46	21
7g			3	nt[c]
8a	S	H	47	27
8b		F	51	38
8c		OCH_3	40	48
8d		$NHCOCH_3$	80	67
8e		CF_3	22	19
9a	SO_2	H	63	54
9b		F	54	23
9c		OCH3	47	19
9d		$NHCOCH_3$	12	44
9e		CF_3	26	21
10	NH	H	32	20
3			12	62
5			90	nt[c]
6			95	88

[a] Values are percentage displacement of [^{3}H]DHT (4 nM) specific binding to hAR by each compound at 10 μM, and the relative binding affinity of **2** is taken as 100. All binding assays were performed in duplicate experiments (n = 2), and the average value is indicated as the binding affinity. [b] NIH3T3 cells were transiently transfected with hAR-expression plasmid, ARE/Luci (firefly luciferase) and pRL/CMV (*Renilla* luciferase) plasmids and were treated with the test compounds at 1 μM in the presence of 0.1 nM **2**. All transactivation assays were performed in triplicate (n = 3). [c] nt indicates not tested.

group as a linker, exhibited a weaker AR-binding affinity than **7a**, **8a**, and **9a** with different linking groups. All the evaluated compounds **7**−**9**, except for the acetamide-containing compounds **7b**, **8b**, and **9b**, exhibited similar structure−activity relationships for the substituents on the B ring, regardless of the chemical and electronic properties of the linking groups. Electronic properties, such as electron-donating or -withdrawing character, of the substituents on the B ring also had no effect on the AR-binding affinity so that a change of electron density on the B ring is not important for the AR-ligand binding. Thus, the main driving forces for the receptor−ligand binding appear to be the formation of hydrogen bonds and van der Waals interactions between the substituents on the B ring, as well as the basic structure of **6**, and amino acid residues of the AR LBD.

The functional activities, agonist or antagonist, of the synthesized compounds were evaluated by means of transient transcriptional assay using NIH3T3 cells co-transfected with hAR expression plasmid, ARE/Luci (firefly luciferase) and pRL/CMV (*Renilla* luciferase) plasmids.[27] All the test compounds dose-dependently inhibited the transcriptional activation in the presence of 0.1 nM **2**. None of the synthesized compounds exhibited androgen agonistic activity. Table 1 summarizes the transactivation data for the synthesized compounds. The values indicate the percent inhibition of 0.1 nM **2**-induced transcriptional activation by each compound at 1 μM. Compounds **7a**−**c**, **8a**−**c**, and **9a** showed moderate AR-antagonistic activity, and the results correlated well with those of binding assay. On the other hand, compounds **7f**, **9b**, and **9c** inhibited **2**-induced AR transactivation by only around 20%, in spite of showing moderate binding to AR. Introductions of a trifluoromethyl group and a nitro group on the B ring and an amino group as a linking group led to a remarkable decrease of the activity, as observed in the results of binding assay (Table 1; **7e**, **8e**, **9e**, and **10**). The high-affinity AR-binding compounds **7d** and **8d** with the acetamide group on the B ring exhibited potent transactivation inhibitory activity (65% and 67%, respectively), being as potent as **3** but less potent than **6**. Unexpectedly, compound **9d**, with weak AR-binding affinity, exhibited moderate AR-antagonistic activity. This kind of biological profile is also observed with the clinically used AR antagonist **3**. These results appear to correlate well with those of binding assay. Among the test compounds, **7a**−**d**, **8a**−**d**, **9a**, and **9d** showed promising biological profiles, and their IC_{50} values were estimated from dose−response curves obtained in this assay (Table 2). The IC_{50} values of **7d**, **8d**, and **9a** were lower than those of the other test compounds (0.80, 0.87, and 0.84 μM, respectively) but are still around 6 times higher than that of the parent AR antagonist **6**.

Table 2. IC_{50} Values of Selected Compounds in AR Transactivation Assay

compd	IC_{50} (M)[a]
7a	2.3×10^{-6}
7b	1.3×10^{-6}
7c	1.0×10^{-6}
7d	8.0×10^{-7}
8a	2.5×10^{-6}
8b	1.3×10^{-6}
8c	1.6×10^{-6}
8d	8.7×10^{-7}
9a	8.4×10^{-7}
9d	1.1×10^{-6}
6	1.4×10^{-7}

[a] NIH3T3 cells were treated with test compounds (1×10^{-8} to 1×10^{-5} M) in the presence of 0.1 nM **2**. All transactivation assays were performed in triplicate (n = 3). IC_{50} values of the test compounds were estimated from the sigmoidal dose−response curves using GraphPad Prism 4 software.

Next, the effects of selected compounds on proliferation of SC-3 and LNCaP cells, which show androgen-dependent growth, were evaluated.[28] Human prostate cancer LNCaP cells express T877A point-mutated AR, toward which compound **4** shows androgenic action, and the evaluation of LNCaP cell proliferation−inhibitory activity is absolutely imperative for the development of pure AR full antagonists and anti-androgen withdrawal syndrome therapeutic agents. The anti-androgenic activity of the selected compounds is summarized in Table 3. In the evaluation using SC-3 cells, none of the test compounds showed growth-promoting activity, suggesting that none was an androgen agonist. All the test compounds, except for **7g**, dose-dependently inhibited SC-3 cell proliferation induced by 1 nM testosterone in the concentration range of 1 nM to 10 μM, although their IC_{50} values are higher than those of **6** and **4**, which showed potent cell growth-inhibitory activity with IC_{50} values of 15 and 24 nM, respectively. Compounds **8d** and **9d** showed similar IC_{50} values, 0.17 and 0.16 μM, to that of **5**, 0.14 μM.

The biological activity of these compounds toward LNCaP cells was examined in terms of the ability to induce cell proliferation alone or to inhibit cell proliferation induced by 1 nM testosterone. As shown in Table 3, compounds **3** and **4** induced cell proliferation alone, as did compound **6**, and did not show antagonistic activity, as expected. In contrast, a clinically used AR full antagonist, **5**, effectively inhibited LNCaP cell proliferation induced by 1 nM testosterone.

Table 3. IC_{50} Values of Selected Compounds for SC-3 and LNCaP Cell Growth

			growth-inhibitory activities IC_{50} (M)[a]	
compd	R	X	SC-3[b]	LNCaP[b]
7a	O	H	2.9×10^{-7}	4.2×10^{-7}
7b		F	2.8×10^{-7}	3.8×10^{-7}
7c		OCH_3	2.5×10^{-7}	7.9×10^{-7}
7d		$NHCOCH_3$	2.6×10^{-7}	$>10^{-5}$
8a	S	H	3.6×10^{-7}	7.5×10^{-7}
8b		F	2.6×10^{-7}	4.2×10^{-7}
8c		OCH_3	3.6×10^{-7}	nt[c]
8d		$NHCOCH_3$	1.7×10^{-7}	1.3×10^{-6}
9a	SO_2	H	7.1×10^{-7}	$>10^{-5}$
9d		$NHCOCH_3$	1.6×10^{-7}	$>10^{-5}$
3			7.2×10^{-7}	agonist
4			2.4×10^{-8}	agonist
5			1.4×10^{-7}	8.7×10^{-7}
6			1.5×10^{-8}	agonist

[a] IC_{50} values of the test compounds were estimated from the sigmoidal dose–response curves using GraphPad Prism 4 software. [b] SC-3 and LNCaP cells were incubated with test compounds (1×10^{-10} to 1×10^{-5} M) in the presence of testosterone (1×10^{-9} M) for 3 and 5 days, respectively. All transactivation assays were performed in triplicate ($n = 3$). [c] nt indicates not tested.

Compounds **7a–c**, **8a**, and **8b** showed more potent cell proliferation–inhibitory activity than **5**. Unfortunately, compounds **7d** and **8d** with an acetamide group on the B ring showed no activity and weak activity as inhibitors of cell proliferation, respectively, although they had shown good biological profiles in AR-binding assay, transactivation assay, and SC-3 cell proliferation assay. Compounds **9a** and **9d** containing a SO_2 linking group were also inactive, and the SO_2 linking group negatively affected LNCaP cell proliferation–inhibitory activity, in contrast to **5**. The negative results obtained with **7d**, **8d**, and **9d** indicate that an acetylamide group is impermissible to interact with the T877A point-mutated AR LBD. Compounds **7b** and **8b** showed the best biological profiles and appear to be candidates for anti-androgen withdrawal syndrome therapeutic agents.

Discussion

Some combination of the structure of **6** and **5** appears to be optimal for the design of AR full antagonists. Our structure–activity relationship study of the designed compounds showed that the linking group and the substituent on the B ring play important roles in AR-binding, Ar transactivation, and cell proliferation–inhibitory activity, at least for SC-3 and LNCaP cells. It is particularly noteworthy that the hybrid compounds **7a–c**, **8a**, and **8b** showed more potent inhibitory activity than **5** in LNCaP cell proliferation assay.

Mutation of AR in prostate cancers has been well-documented, and several mutant ARs, such as T877A, T877S, H874Y, V715M, and L701H/T877A, have a broadened spectrum of ligand responsiveness; compound **4** works as an agonist for these mutants.[29] Compound **5** does not work as an agonist for these mutant ARs in prostate cancer, but it has recently been reported that it does work as an agonist for prostate cancers with W741C and W741L mutated AR.[15] The X-ray crystal structure of the mutant W741L AR LBD bound to **5** has been reported by Bohl et.al.[7] From the viewpoint of bicalutamide withdrawal syndrome and anti-androgen withdrawal syndrome in prostate cancer patients, it seems that T877 and W741 are hot spots of AR mutation selected by treatment with **3** and **5**, respectively.

Generally, carborane-containing ligands are expected to show a different spectrum of ligand responsiveness to known therapeutic agents because a carborane cage has a bulky spherical structure and a highly hydrophobic surface.[17] We previously designed a cyclohexenone–carborane hybrid AR ligand based upon the structure of **1**, a native AR ligand, and reported its AR-antagonistic activity.[22a] The results indicated that the C and D rings of the natural hormone, **1**, play an important role in determining whether a compound's activity is agonistic or antagonistic. The size of the carborane cage seems to be too big to be accommodated in place of the C and D rings of testosterone in the hydrophobic pocket of hAR LBD. These results confirmed the idea that the carborane ring would be a suitable moiety for the expression of AR-antagonistic activity because the bulky carborane structure interacts sterically with M895 and its surrounding amino acid residues in the hydrophobic pocket of wild-type hAR-LBD in such a way that helix-12 is moved away from the location required for expression of agonist activity. Since the hydrophobic structure of these carborane-containing compounds is bulkier than those of **3**, **4**, and **5**, there is greater potential to express AR-antagonistic activity, including a direct repulsion between helix-12 of AR LBD and the carborane cage. Thus, these carborane-containing compounds, especially **7b** and **8b**, might work as AR full antagonists and be candidates for treating anti-androgen withdrawal syndrome.

Miller and co-workers have reported selective androgen receptor modulators (SARMs), which is another goal of the AR ligand discovery, with an ether linking group designed based upon the structure of **5**.[30] It is anticipated that various SARMs could act as antagonists or weak agonists in the prostate, with reduced potential to stimulate nascent prostate cancer, and as agonists in the pituitary and muscle, with potential to treat muscle wasting conditions, hypogonadism, or age-related frailty.[31] The (*R*)-bicalutamide-based SARM candidates reported by Miller and co-workers showed moderate AR-binding affinity and acted as a potent AR agonists.[30] Their compounds exhibited agonistic, weak agonistic, and antagonistic activities in transactivation assay, and there was no correlation between binding affinity and in vitro functional activity. Unlike their SARMs, our carborane-containing compounds exhibited AR-antagonistic activity and showed no agonistic activity in transactivation and cell proliferation assays using SC-3 and LNCaP cells; there was a good correlation between binding affinity and in vitro functional activity. Although the structures of our carborane-containing compounds are similar to those of SARMs, we consider that they can act as pure AR full antagonists owing to the bulkiness of the carborane cage.

In conclusion, we have designed and synthesized novel carboran-containing AR full antagonists based upon the structures of **5** and **6**, examined their structure–activity relationships for AR-antagonistic activity, and found promising candidate AR ligands for the treatment of anti-androgen withdrawal syndrome. Compounds **7d** and **8d** with an acetamide group showed potent AR-biding and AR-transactivation inhibitory activities but were ineffective in LNCaP cells. In contrast, compounds **7b** and **8b** with a fluoro substituent on the B ring showed moderate binding affinities for hAR, better IC_{50} values in AR transactivation assay, and more potent inhibitory activity than **5** for **2**-induced LNCaP cell proliferation. The SO_2 linking group in these compounds seems to be

unfavorable for proliferation of LNCaP cells, regardless of the substituents on the B ring. Since the carborane cage has a bulky spherical structure and a hydrophobic surface, these carborane-containing AR ligands might have a different spectrum of ligand responsiveness from that of **5** and are candidate AR full antagonists for treatment of anti-androgen withdrawal syndromes.

Experimental Section

Chemistry. *p*-Carborane was purchased from Katchem s.r.o. Other chemicals were purchased from Aldrich or Tokyo Kasei Ltd. and used without further purification in the reactions or were prepared according to procedures described in the literature. Reactions were monitored with thin layer chromatography (TLC) conducted on Merck DC-platten Kieselgel $60F_{254}$ with UV detection. The structures of the compounds were confirmed by melting points, NMR spectra (^{1}H and ^{13}C), and MS spectra. The purities of the compounds (≥95%) were determined by elemental analyses. Melting points were determined with a Yanaco micro-melting point apparatus and were not corrected. ^{1}H NMR and ^{13}C NMR were recorded with JEOL JNM-EX-270 and JNM-LA-400 spectrometers. The chemical shifts are reported in parts per million (δ scale), and all coupling constants (J) are in hertz (Hz). The splitting patterns are designed as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Chemical shifts for ^{1}H NMR spectra were referenced to tetramethylsilane (0.0 ppm) as an internal standard. Chemical shifts for ^{13}C NMR spectra were referenced to residual ^{13}C present in deuterated solvent. Mass spectra were recorded on a JEOL JMS-DX-303 spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 CHN spectrometer.

3-(12-Formyl-1,12-dicarba-*closo*-dodecaborane-1-yl)benzonitrile (11). To a solution of **6** (146 mg, 0.53 mmol) in 3 mL of CH_2Cl_2 was added Dess−Martin periodinate (450 mg, 1.06 mmol), and the mixture was stirred at room temperature for 8 h under an argon (Ar) atmosphere. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The crude residue was purified by silica gel column chromatography with 20:1 *n*-hexane/EtOAc to give 129 mg (89%) of the title compound as a colorless solid: colorless cubes (CH_2Cl_2−*n*-hexane); mp 127.5−128.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 7.33 (m, 1H), 7.44 (dd, J = 1.3, 8.2 Hz, 1H), 7.48 (m, 1H), 7.55 (dd, J = 1.3, 7.6 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 81.85, 84.07, 112.63, 117.70, 129.05, 130.38, 131.07, 132.05, 137.19, 185.35. MS (EI) m/z: 273 (M^+, 100). Anal. Calcd for $C_{10}H_{15}B_{10}NO$: C, 43.94; H, 5.53; N, 5.12. Found: C, 44.19; H, 5.61; N, 5.26.

3-(12-Oxiranyl-1,12-dicarba-*closo*-dodecaborane-1-yl)benzonitrile (12). Chloroiodomethane (0.6 mL, 8.24 mmol) was added to a stirred solution of tetrahydrothiophene (727 μL, 8.24 mmol) in 50 mL of CH_2Cl_2 at room temperature under an Ar atmosphere. After 30 min, aldehyde (1.13 g, 4.12 mmol) was added, follwed by 1 M Et_2Zn in hexane (4.12 mL, 4.12 mmol). After 6.5 h, the reaction mixture was poured into water, extracted with CH_2Cl_2, dried over $MgSO_4$, and then concentrated. The crude residue was purified by silica gel column chromatography with 10:1 *n*-hexane/EtOAc to give 843 mg (71%) of the title compound as a colorless solid: colorless cotton (CH_2Cl_2−*n*-hexane); mp 124−125 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.46 (dd, J = 2.3, 4.9 Hz, 1H), 2.64 (dd, J = 3.4, 4.8 Hz, 1H), 2.88 (dd, J = 2.3, 3.8 Hz, 1H), 7.31 (dd, J = 0.7, 7.6 Hz, 1H), 7.43 (ddd, J = 1.2, 2.1, 8.1 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.52 (ddd, J = 1.3, 1.5, 7.6 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 48.11, 52.66, 79.25, 81.29, 112.76, 117.96, 129.37, 130.74, 131.57, 132.19, 137.51. MS (EI) m/z 287 (M^+, 100). Anal. Calcd for $C_{11}H_{17}B_{10}NO$: C, 45.97; H, 5.96; N, 4.87. Found: C, 45.81; H, 5.82; N, 4.80.

General Procedure for Preparation of Ether Derivatives (7). To a solution of compound **11** (100 mg, 0.35 mmol) and the corresponding phenol (0.53 mmol) in 2 mL of 2-propanol was added K_2CO_3 (73 mg, 0.53 mmol), and the mixture was refluxed for 29 h to 6 days under an Ar atmosphere. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with 10% NaOH aqueous solution, water, and brine, dried over $MgSO_4$, and then concentrated. The crude residue was purified by silica gel column chromatography to give the corresponding ether derivative.

3-[12-(1-Hydroxy-2-phenoxyethyl)-1,12-dicarba-*closo*-dodecaborane-1-yl]benzonitrile (7a). Reaction time, 29 h; 90% yield; colorless cubes (methanol); mp 147−149 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.63 (d, J = 4.9 Hz, 1H), 3.65 (dd, J = 8.1, 10.2 Hz, 1H), 3.85−3.92 (m, 2H), 6.85 (d, J = 7.7 Hz, 2H), 6.99 (dd, J = 7.3, 7.4 Hz, 1H), 7.26−7.34 (m, 3H), 7.54 (ddd, J = 1.2, 2.0, 8.2 Hz, 2H), 7.50−7.54 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 70.15, 70.36, 81.91, 82.77, 112.46, 114.46, 117.95, 121.60, 129.02, 129.52, 130.64, 131.41, 131.89, 137.46, 157.59. MS (EI) m/z: 381 (M^+), 94 (100%). Anal. Calcd for $C_{17}H_{23}B_{10}NO_2$: C, 53.52; H, 6.08; N, 3.67. Found: C, 53.32; H, 6.17; N, 3.61.

3-{12-[1-Hydroxy-2-(4-fluorophenoxy)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (7b). Reaction time, 37 h; 89% yield; colorless cubes (*n*-hexane−CH_2Cl_2); mp 130−131 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.85 (brs, 1H), 3.62 (dd, J = 7.1, 9.2 Hz, 1H), 3.82−3.90 (m, 2H), 6.79 (dd, J = 4.3, 9.1 Hz, 2H), 6.96 (dd, J = 8.2, 9.1 Hz, 2H), 7.31 (dd, J = 7.4, 8.2 Hz, 1H), 7.45 (dd, J = 1.3, 8.2 Hz, 1H), 7.49−7.52 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 70.36, 70.91, 81.93, 82.72, 112.45, 115.55, 115.66, 115.74, 116.08, 117.95, 129.05, 130.64, 131.42, 131.90, 137.43, 153.75, 153.77, 155.85, 158.37. MS (EI) m/z: 399 (M^+), 112 (100%). Anal. Calcd for $C_{17}H_{22}B_{10}FNO_2$: C, 51.11; H, 5.55; N, 3.51. Found: C, 51.10; H, 5.74; N, 3.34.

3-{12-[1-Hydroxy-2-(4-methoxyphenoxy)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (7c). Reaction time, 74 h; 30% yield; colorless cubes (*n*-hexane-CH_2Cl_2); mp 111−113 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.60 (d, J = 4.8 Hz, 1H), 3.60 (dd, J = 7.3, 9.6 Hz, 1H), 3.77 (s, 3H), 3.75−3.86 (s, 2H), 6.77−6.85 (m, 4H), 7.30 (dd, J = 7.6, 8.1 Hz, 1H), 7.45 (dd, J = 8.1, 8.3 Hz, 2H), 7.50−7.53 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 55.67, 70.45, 71.05, 81.98, 82.75, 112.53, 114.71, 115.62, 118.01, 129.07, 130.72, 131.60, 131.93, 137.54, 151.75, 154.46. MS (EI) m/z: 411 (M^+), 124 (100%). Anal. Calcd for $C_{18}H_{25}B_{10}NO_3$: C, 52.54; H, 6.12; N, 3.40. Found: C, 52.41; H, 6.22; N, 3.32.

3-{12-[1-Hydroxy-2-(4-acetamidephenoxy)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (7d). Reaction time, 37 h; 71% yield; colorless needles (AcOEt); mp 170−171 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.10 (s, 3H), 3.61 (dd, J = 7.3, 9.4 Hz, 1H), 3.79−3.88 (m, 2H), 6.73 (d, J = 8.9 Hz, 2H), 7.28−7.38 (m, 3H), 7.46 (dd, J = 1.2, 8.1 Hz, 1H), 7.49−7.53 (m, 2H), 8.05 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 24.01, 70.29, 70.62, 81.84, 83.11, 112.35, 114.72, 118.00, 121.99, 129.06, 130.62, 131.48, 131.75, 131.88, 137.49, 154.46, 168.89. MS (EI) m/z: 438 (M^+), 109 (100%). Anal. Calcd for $C_{19}H_{26}B_{10}N_2O_3$: C, 52.04; H, 5.98; N, 6.39. Found: C, 51.92; H, 6.18; N, 6.35.

3-{12-[1-Hydroxy-2-(4-nitrophenoxy)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (7e). Reaction time, 6 days; 61% yield; colorless cubes (*n*-hexane−CH_2Cl_2); mp 191−192 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 3.79 (dd, J = 7.9, 10.2 Hz, 1H), 3.94−4.01 (m, 2H), 6.94 (d, J = 9.2 Hz, 2H), 7.33 (dd, J = 7.6, 9.1 Hz, 1H), 7.44−7.50 (m, 2H), 7.54 (d, J = 7.6 Hz, 1H), 8.20 (d, J = 9.2 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 70.22, 70.82, 82.13, 82.49, 112.49, 114.50, 117.94, 125.88, 129.12, 130.63, 131.43, 131.99, 137.31, 142.01, 162.63. MS (EI) m/z: 426 (M^+), 140 (100%). Anal. Calcd for $C_{19}H_{26}B_{10}N_2O_3$: C, 52.04; H, 5.98; N, 6.39. Found: C, 51.92; H, 6.18; N, 6.35.

3-{12-[1-Hydroxy-2-(4-bromophenoxy)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (7f). Reaction time, 48 h; 82% yield; colorless cotton (AcOEt); mp 178−179 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 3.62 (dd, J = 7.1, 9.2 Hz, 1H), 3.82−3.91 (m, 2H), 6.73 (d, J = 9.1 Hz, 2H), 7.31 (dd, J = 7.6, 8.2 Hz, 1H), 7.37 (d, J = 8.9 Hz, 2H), 7.45 (ddd, J = 1.2, 2.0, 8.2 Hz, 1H), 7.49−7.53 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 70.35, 70.46,

82.01, 82.60, 112.51, 113.88, 116.26, 117.96, 129.07, 130.67, 131.43, 131.94, 132.38, 137.43, 156.76. MS (EI) m/z: 460 (M^+), 172 (100%). Anal. Calcd for $C_{17}H_{22}B_{10}BrNO_2$: C, 44.35; H, 4.82; N, 3.04. Found: C, 44.36; H, 5.12; N, 2.96.

General Procedure for Preparation of Thioether Derivatives (8). A thiophenol (0.7 mmol) was added dropwise to a stirred suspension of NaH (60% in oil, 29 mg, 0.73 mmol) in 5 mL of THF at 0 °C under Ar atmosphere. After 20 min, compound **5** (200 mg, 0.7 mmol) was added to the mixture at 0 °C, and the mixture was stirred at room temperature for 6.5 h to 8 days. The reaction mixture was quenched by addition of water, and the mixture was extracted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, and then concentrated. The crude residue was purified by silica gel column chromatography to give the corresponding thioether.

3-[12-(1-Hydroxy-2-phenylsulfanylethyl)-1,12-dicarba-*closo*-dodecaborane-1-yl]benzonitrile (8a). Reaction time, 75 h; 76% yield; colorless needles (methanol); mp 144−145 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.60 (dd, J = 10.4, 13.8 Hz, 1H), 2.74 (d, J = 3.8 Hz, 1H), 3.07 (dd, J = 2.5, 13.8 Hz, 1H), 3.54 (ddd, J = 2.5, 3.8, 10.4 Hz, 1H), 7.20−7.33 (m, 6H), 7.43 (ddd, J = 1.2, 2.0, 8.1 Hz, 1H), 7.48−7.53 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 41.51, 70.07, 81.72, 84.69, 112.49, 117.95, 127.04, 129.03, 129.19, 129.95, 130.68, 131.43, 131.89, 133.93, 137.46. MS (EI) m/z: 397 (M^+), 124 (100%). Anal. Calcd for $C_{17}H_{23}B_{10}NOS$: C, 51.36; H, 5.83; N, 3.52. Found: C, 51.43; H, 6.11; N, 3.40.

3-{12-[1-Hydroxy-2-(4-fluorophenylsulfanyl)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (8b). Reaction time, 73 h; 77% yield; colorless cubes (methanol); mp 104−105 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.61 (dd, J = 10.4, 13.7 Hz, 1H), 2.97 (dd, J = 2.3, 13.7 Hz, 1H), 3.05 (m, 1H), 3.53 (d, J = 10.1 Hz, 1H), 6.99 (dd, J = 8.6, 8.7 Hz, 2H), 7.27−7.35 (m, 3H), 7.44 (d, J = 8.7 Hz, 1H), 7.49−7.52 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 42.53, 70.19, 81.61, 84.84, 112.37, 116.05, 116.38, 117.85, 128.97, 129.10, 129.15, 130.55, 131.35, 131.82, 132.80, 132.91, 137.34. MS (EI) m/z: 415 (M^+), 141 (100%). Anal. Calcd for $C_{17}H_{22}B_{10}FNOS$: C, 49.14; H, 5.34; N, 3.37. Found: C, 49.15; H, 5.44; N, 3.36.

3-{12-[1-Hydroxy-2-(4-methoxyphenylsulfanyl)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (8c). Reaction time, 6.5 h; 84% yield; colorless cotton (methanol); mp 133−134 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.51 (dd, J = 10.6, 13.7 Hz, 1H), 2.89−2.95 (m, 2H), 3.45 (m, 1H), 3.79 (s, 3H), 7.28−7.32 (m, 3H), 7.43 (dd, J = 1.2, 8.1 Hz, 1H), 7.48−7.52 (m, 2H), 7.84 (d, J = 8.7 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 43.49, 55.26, 69.88, 81.65, 84.64, 112.44, 114.85, 117.96, 123.69, 129.01, 130.65, 131.42, 131.86, 133.69, 137.47, 158.51. MS (EI) m/z: 427 (M^+), 153 (100%). Anal. Calcd for $C_{18}H_{25}B_{10}NO_2S$: C, 50.56; H, 5.89; N, 3.28. Found: C, 50.73; H, 6.10; N, 3.13.

3-{12-[1-Hydroxy-2-(4-acetamidephenylsulfanyl)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (8d). Reaction time, 36 h; 71% yield; colorless leaflets (n-hexane−CH_2Cl_2); mp 142−143 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.19 (s, 3H), 2.55 (dd, J = 10.4, 13.8 Hz, 1H), 3.00 (dd, J = 2.5, 13.8 Hz, 1H), 3.48 (m, 1H), 7.16 (brs, 1H), 7.27−7.33 (m, 3H), 7.42−7.48 (m, 4H), 7.52 (d, J = 7.6 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 24.47, 42.34, 70.09, 81.66, 84.86, 112.41, 118.05, 120.58, 128.73, 129.07, 130.70, 131.52, 131.62, 131.91, 137.35, 137.50, 168.73. MS (EI) m/z: 454 (M^+), 43 (100%). Anal. Calcd for $C_{19}H_{26}B_{10}N_2O_2S$: C, 50.20; H, 5.76; N, 6.16. Found: C, 50.27; H, 5.78; N, 6.04.

3-{12-[1-Hydroxy-2-(4-trifluoromethylphenylsulfanyl)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (8e). Reaction time, 8 days; 67% yield; colorless leaflets (n-hexane−CH_2Cl_2); mp 142−143 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.50 (d, J = 4.3 Hz, 1H), 2.72 (dd, J = 10.2, 14.0 Hz, 1H), 3.13 (dd, J = 2.5, 14.0 Hz, 1H), 3.64 (ddd, J = 2.5, 4.3, 10.2 Hz, 1H), 7.28−7.36 (m, 3H), 7.46 (d, J = 8.2 Hz, 1H), 7.51−7.55 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) 40.01, 70.48, 81.93, 84.66, 112.57, 117.99, 123.89 (J = 272.1 Hz), 125.94 (J = 3.9 Hz), 128.19, 128.70, 129.11, 129.18, 130.72, 131.73 (J = 36.9 Hz), 137.37, 139.98 (J = 1.7 Hz). MS (EI) m/z: 465 (M^+), 192 (100%). Anal. Calcd for $C_{18}H_{22}B_{10}F_3NOS$: C, 46.44; H, 4.76; N, 3.01. Found: C, 46.63; H, 4.98; N, 2.90.

General Procedure for Preparation of Sulfone Derivatives (9). To a stirred solution of the appropriate thioether **8** (1 mmol) in 2 mL of CH_2Cl_2 was added mCPBA (2.6 mmol) in portions. The reaction mixture was stirred at room temperature for 7−45 h. An excess of mCPBA was decomposed with saturated $NaHSO_3$ aqueous solution. The organic layer was separated, washed with saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, and then concentrated. The crude residue was purified by silica gel column chromatography to give the corresponding sulfone derivative.

3-[12-(1-Hydroxy-2-phenylsulfonylethyl)-1,12-dicarba-*closo*-dodecaborane-1-yl]benzonitrile (9a). Reaction time, 7 h; 95% yield; colorless prisms (methanol); mp 182−184 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 3.02 (dd, J = 10.1, 14.0 Hz, 1H), 3.13 (dd, J = 1.8, 14.0 Hz, 1H), 3.33 (d, J = 3.3 Hz, 1H), 4.08−4.12 (m, 1H), 7.30 (m, 1H), 7.41 (ddd, J = 1.2, 2.1, 8.1 Hz, 1H), 7.45 (ddd, J = 1.3, 1.5, 7.4 Hz, 1H), 7.46 (dd, J = 1.4, 1.5 Hz, 2H), 7.71 (tt, J = 2.1, 7.5 Hz, 1H), 7.88 (dd, J = 1.5, 8.4 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 61.50, 67.30, 81.91, 83.83, 112.52, 127.91, 129.11, 129.45, 130.61, 131.38, 131.99, 134.27, 137.22, 138.72. MS (EI) m/z: 429 (M^+), 77 (100%). Anal. Calcd for $C_{17}H_{23}B_{10}NO_3S$: C, 47.53; H, 5.40; N, 3.26. Found: C, 47.65; H, 5.38; N, 3.19.

3-{12-[1-Hydroxy-2-(4-fluorophenylsulfonyl)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (9b). Reaction time, 14 h; 100% yield; colorless cotton (methanol); mp 171.5−172.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 3.01 (dd, J = 10.1, 14.2 Hz, 1H), 3.10−3.15 (m, 2H), 4.11 (m, 1H), 7.23−7.33 (m, 3H), 7.41 (d, J = 8.1 Hz, 1H), 7.46 (s, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.89 (dd, J = 4.9, 8.7 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 61.64, 67.39, 81.83, 84.03, 112.39, 116.45, 116.79, 117.84, 129.09, 130.53, 130.88, 131.03, 131.36, 131.97, 134.99, 135.03, 137.12, 164.01, 167.79. MS (EI) m/z: 447 (M^+), 143 (100%). Anal. Calcd for $C_{17}H_{22}B_{10}FNO_3S$: C, 45.62; H, 4.95; N, 3.13. Found: C, 45.66; H, 4.96; N, 3.11.

3-{12-[1-Hydroxy-2-(4-methoxyphenylsulfonyl)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (9c). Reaction time, 16 h; 94% yield; colorless prisms (methanol); mp 186−187 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 2.97 (dd, J = 10.4, 14.1 Hz, 1H), 3.09 (dd, J = 1.6, 14.1 Hz, 1H), 3.42 (d, J = 3.0 Hz, 1H), 4.04−4.08 (m, 1H), 7.04 (d, J = 9.1 Hz, 2H), 7.26−7.33 (m, 1H), 7.41 (dd, J = 1.3, 8.2 Hz, 1H), 7.46 (s, 1H), 7.52 (dd, J = 1.3, 7.6 Hz, 1H), 7.79 (d, J = 9.1 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 55.77, 61.72, 67.38, 81.96, 83.62, 112.60, 114.72, 117.97, 129.12, 129.90, 130.22, 130.68, 131.41, 132.03, 137.29, 164.24. MS (EI) m/z: 459 (M^+), 108 (100%). Anal. Calcd for $C_{18}H_{25}B_{10}NO_4S$: C, 47.04; H, 5.48; N, 3.05. Found: C, 47.02; H, 5.42; N, 3.00.

3-{12-[1-Hydroxy-2-(4-acetamidephenylsulfonyl)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (9d). Reaction time, 45 h; 75% yield; colorless leaflets (methanol−AcOEt); mp 274−276 °C; ^{1}H NMR (270 MHz, CD_3OD) 1.0−3.5 (brm, 10H), 2.15 (s, 3H), 3.10 (dd, J = 2.8, 14.3 Hz, 1H), 3.19 (dd, J = 9.6, 14.3 Hz, 1H), 4.01 (m, 1H), 7.40 (dd, J = 7.6, 9.1 Hz, 1H), 7.51−7.53 (m, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.78 (s, 4H); ^{13}C NMR (68 MHz, DMSO-d_6) 24.15, 61.12, 67.17, 81.30, 86.76, 111.85, 117.85, 118.34, 129.16, 129.95, 130.05, 131.65, 132.78, 133.23, 136.45, 143.86, 169.11. MS (EI) m/z: 486 (M^+), 135 (100%). Anal. Calcd for $C_{19}H_{26}B_{10}N_2O_4S$: C, 46.90; H, 5.39; N, 5.76. Found: C, 47.06; H, 5.46; N, 5.68.

3-{12-[1-Hydroxy-2-(4-trifluoromethylphenylsulfonyl)ethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (9e). Reaction time, 23 h; 100% yield; colorless cubes (n-hexane−CH_2Cl_2); mp 196−197.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H),

2.92 (d, J = 3.8 Hz, 1H), 3.07 (dd, J = 9.8, 14.4 Hz, 1H), 3.16 (dd, J = 2.3, 14.4 Hz, 1H), 4.19 (ddd, J = 2.3, 3.8, 9.8 Hz, 1H), 7.30 (dd, J = 7.6, 8.2 Hz, 1H), 7.43 (dd, J = 1.3, 8.2 Hz, 1H), 7.46 (s, 1H), 7.52 (dd, J = 1.3, 7.6 Hz, 1H), 7.85 (d, J = 8.7 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 61.56, 67.52, 82.04, 83.88, 112.57, 117.90, 120.96, 124.98, 126.44, 126.50, 128.74, 129.16, 130.64, 131.40, 132.08, 135.50, 135.99, 137.17, 142.76. MS (EI) m/z: 497 (M^+), 193 (100%). Anal. Calcd for $C_{18}H_{22}B_{10}F_3NO_3S$: C, 43.45; H, 4.46; N, 2.82. Found: C, 43.64; H, 4.53; N, 2.78.

3-{12-[1-Hydroxy-2-anilinoethyl]-1,12-dicarba-*closo*-dodecaborane-1-yl}benzonitrile (10). A solution of **11** (97 mg, 0.34 mmol) and aniline (37 μL, 0.41 mmol) in 4 mL of methanol was refluxed for 84 h. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, and then concentrated. The crude residue was purified by silica gel column chromatography with 10:1 to 3:1 *n*-hexane/AcOEt to methanol to give 84 mg (65%) of the title compound as a colorless solid: colorless cubes (AcOEt); mp 171 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 1.0−3.5 (brm, 10H), 3.48 (dd, J = 2.8, 13.4 Hz, 1H), 3.71 (dd, J = 2.8, 9.6 Hz, 1H), 3.79 (dd, J = 9.6, 13.4 Hz, 1H), 6.57 (d, J = 7.6 Hz, 2H), 6.75 (t, J = 7.4 Hz, 2H), 7.18 (dd, J = 7.4 Hz, 2H), 7.31 (dd, J = 7.4, 8.1 Hz, 1H), 7.46 (dd, J = 1.2, 8.1 Hz, 1H), 7.50−7.54 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) 49.20, 70.22, 81.86, 84.48, 112.59, 113.46, 118.06, 118.60, 129.14, 129.42, 130.79, 131.53, 132.01, 137.54, 147.17. MS (EI) m/z: 380 (M^+), 106 (100%). Anal. Calcd for $C_{17}H_{24}B_{10}N_2O$: C, 53.66; H, 6.36; N, 7.36. Found: C, 53.49; H, 6.44; N, 7.22.

Receptor Binding Assay. Binding affinities of test compounds for hAR (human androgen receptor) were measured in competition experiments using [^{3}H]testosterone and cytosolic fraction of hAR-LBD (hAR ligand-binding domain)-transformed *E. coli* as described previously. A hAR-LBD expression plasmid vector that encodes GST-hARLBD (627−919 aa, EF domain) fusion protein under the *lac* promoter (provided by Prof. S. Kato, University of Tokyo) was transfected into *E. coli* strain *HB-101*. An overnight culture (10 mL) of the bacteria was added to 1 L of LB medium and incubated at 27 °C until its optical density reached 0.6−0.7 at 600 nm. Following the addition of IPTG to 1 mM, incubation was continued for an additional 4.5 h. Cells were harvested by centrifugation at 4000*g* at 4 °C for 15 min and stored at −80 °C until use. All subsequent operations were performed at 4 °C. The bacterial pellet obtained from 40 mL of culture was resuspended in 1 mL of ice-cold TEGDM buffer (10 mM Tris-HCl, pH 7.4, 1 mM EDTA, 10% glycerol, 10 mM DTT, 10 mM sodium molybdate). This suspension was subjected to sonication using 10 × 10 s bursts on ice, and crude GST-hARLBD fraction was prepared by centrifugation of the suspension at 12000*g* for 30 min at 4 °C. This crude receptor fraction was diluted with buffer (20 mM Tris-HCl, pH 8.0, 0.3 M KCl, 1 mM EDTA) to a protein concentration of 0.3−0.5 mg/mL and used in binding assays as hAR-LBD fraction. Aliquots of the hAR-LBD fraction were incubated in the dark at 4 °C with [^{3}H]DHT (NEN, 4 nM final concentration), triamcinolone acetonide (1 μM final concentration), and reference or test compounds (dissolved in DMSO). Nonspecific binding was assessed by addition of a 200-fold excess of nonradioactive **2**. After 15 h, a dextran T-70/γ-globulin-coated-charcoal suspension was added to the ligand/protein mixture (1% Norit A, 0.05% γ-globulin, 0.05% dextran T-70 final concentration each) and the whole was incubated at 4 °C for 10 min. The charcoal was removed by centrifugation for 5 min at 1300*g*, and the radioactivity of the supernatant was measured in Atomlight (NEN) by using a liquid scintillation counter.

ARE-Luciferase Reporter Assay. Assay of androgenic activity was performed by means of ARE-luciferase reporter assay using NIH3T3 cells. Culture was conducted in phenol red-free DMEM (Sigma), supplemented with dextran-coated charcoal-stripped FBS (sFBS) to deplete internal stores of steroids, penicillin, and streptomycin for 2−3 days. Transient transfections of NIH3T3 cells were performed using Transfast (Promega) according to the manufacture's protocol. Transfections were done in 48-well plates at 2 × 10^4 cells/well with 50 ng of pSG5-hAR, 300 ng of $p(ARE)_2$-luc, and 10 ng of pRL/CMV (Promega) as an internal standard. Twenty-four hours after addition of the sample (final concentration, 10^{-5}−10^{-7} M) and 1 × 10^{-10} M **2**, cells were harvested with 25 μL of cell lysis buffer (Promega), and the firefly and Renilla luciferase activities were determined with a dual luciferase assay kit (Promega) by measuring luminescence with a Wallac Micro-Beta scintillation counter (PerkinElmer Life Sciences). Firely luciferase reporter activity was normalized to Renilla luciferase activity from pRL/CMV.

SC-3 Cell Proliferation Assay. SC-3 cells were cultured in the presence of MEMα (Wako Co.) supplemented with 2% FBS and 10 nM testosterone at 37 °C under 5% CO_2. All experiments were performed in triplicate or more. Cells were trypsinized and diluted to 2 × 10^{-4} cell/mL with MEMα supplemented with 2% stripped FBS. This cell suspension was seeded in 96-well plates at a volume of 100 μL and incubated at 24 h. After removal of 10 μL of medium from each well, 10 μL of the drug solution, which was supplemented with serial dilutions of the test compounds or DMSO as a dilution control in the presence or absence of 1 nM testosterone, was added. Then the plates were incubated at 37 °C under 5% CO_2 for 3 days, and the cell number was determined using a Cell Counting Kit-8 (DOJINDO). A 10 μL aliquot of WST-8 was added to each well of microcultures, and the cells were incubated for 4 h. The absorbance at 450 nm was measured with a model 680 microplate reader (BIO-RAD). This parameter is related to the number of living cells in the culture.

LNCap Cell Proliferation Assay. The human prostate adenocarcinoma cell line LNCap was cultured in the presence of RPMI-1640 (Wako Co.) supplemented with 10% FBS at 37 °C under 5% CO_2. Cells were trypsinized and diluted to 3 × 10^{-4} cell/mL with RPMI-1640 supplemented with 10% stripped-FBS. This cell suspension was seeded in 96-well plates (100 μL/well) and incubated for 24 h. After removal of 10 μL of medium from each well, 10 μL of drug solution, which was supplemented with serial dilutions of the test compounds or DMSO as a dilution control in the presence or absence of 1 nM testosterone, was added. Then the plates were incubated at 37 °C under 5% CO_2 for 6 days. During this period, half of the medium was removed and medium with the test compounds or DMSO as a dilution control in the presence or absence of 1 nM testosterone was replaced once after 3 days. The cell number was determined using a Cell Counting Kit-8 (CCK-8, DOJINDO). A 10 μL aliquot of CCK-8 was added to each well of microcultures, and the cells were incubated for 4 h. The absorbance at 450 nm was measured with a model 680 microplate reader (BIO-RAD). This parameter is related to the number of living cells in the culture.

Acknowledgment. This research was supported by Grant-in-Aid for High Technology Research Program, Grant-in-Aid for Scientific Research (B) (Grant No. 20390035), and Grant-in-Aid for Young Scientist (B) (Grant No. 21790116) from the Ministry of Education, Culture, Sport, Science and Technology, Japan.

References

(1) (a) Mooradian, A. D.; Morley, J. E.; Korenman, S. G. Biological actions of androgens. *Endocr. Rev.* **1987**, *8*, 1–28. (b) Bagatell, C. J.; Bremner, W. J. Androgens in men—uses and abuses. *N. Engl. J. Med.* **1996**, *334*, 707–714. (c) Kaufman, J. M.; Vermeulen, A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr. Rev.* **2005**, *26*, 833–876.

(2) (a) Evans, R. M. The steroid and thyroid hormone receptor superfamily. *Science* **1988**, *240*, 889–894. (b) MacLean, H. E.; Warne, G. L.; Zajac, J. D. Localization of functional domains in the androgen receptor. *J. Steroid Biochem. Mol. Biol.* **1997**, *62*, 233–242. (c) McEwan, I. J. Gene regulation through chromatin remodeling by members of the nuclear receptor superfamily. *Biochem. Soc. Trans.*

2000, *28*, 369–373. (d) Taplin, M.-E. Androgen receptor: role and novel therapeutic prospects in prostate cancer. *Expert. Rev. Anticancer Ther.* **2008**, *8*, 1495–1508.

(3) (a) Chengalvala, M.; Oh, T.; Roy, A. K. Selective androgen receptor modulators. *Expert Opin. Ther. Pat.* **2003**, *13*, 59–66. (b) Gao, W.; Bohl, C. E.; Dalton, J. T. Chemistry and structural biology of androgen receptor. *Chem. Rev.* **2005**, *105*, 3352–3370. (c) Chen, J.; Kim, J.; Dalton, J. T. Discovery and therapeutic promise selective androgen receptor modulators. *Mol. Invest.* **2005**, *5*, 173–188.

(4) (a) Neri, R. O.; Peets, E. A. Biological aspects of antiandrogens. *J. Steroid Biochem.* **1975**, *6*, 815–819. (b) Koch, H. Flutamide—a new non-steroidal anti-androgen. *Drugs Today* **1984**, *20*, 561–574. (c) Neri, R. Pharmacology and pharmacokinetics of flutamide. *Urology* **1989**, *34*, 19–21.

(5) (a) Wakeling, A. E.; Furr, B. J.; Glen, A. T.; Hughes, L. R. Receptor binding and biological activity of steroidal and nonsteroidal anti-androgens. *J. Steroid Biochem.* **1981**, *15*, 355–359. (b) Yeh, S.; Miyamoto, H.; Chang, C. Hydroxyflutamide may not always be a pure antiandrogen. *Lancet* **1997**, *349*, 852–853. (c) Bohl, C. E.; Miller, D. D.; Chen, J.; Bell, C. E.; Dalton, J. T. Structural basis for accommodation of nonsteroid ligands in the androgen receptor. *J. Biol. Chem.* **2005**, *280*, 37747–37754.

(6) (a) Tucker, H.; Chesterson, G. J. Resolution of the nonsteroidal antiandrogen 4′-cyano-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-3′-(trifluoromethyl)-propionanilide and the determination of the absolute configuration of the active enantiomer. *J. Med. Chem.* **1988**, *31*, 885–887. (b) Fradet, Y. Bicalutamide (Casodex) in the treatment of prostate cancer. *Expert Rev. Anticancer Ther.* **2004**, *4*, 37–48. (c) Kolvenbag, G. J.; Blackledge, G. R.; Gotting-Smith, K. Bicalutamide (Casodex) in the treatment of prostate cancer: history of clinical development. *Prostate* **1998**, *34*, 61–72.

(7) Bohl, C. E.; Gao, W.; Miller, D. D.; Bell, C. E.; Dalton, J. T. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 6201–6206.

(8) (a) Sack, J. S.; Kish, K. F.; Wang, C.; Attar, R. M.; Kiefer, S. E.; An, Y.; Wu, G. Y.; Scheffler, J. E.; Salvati, M. E.; Krystek, S. R., Jr.; Weinmann, R.; Einspahr, H. M. Crystallographic structures of the ligand-binding domains of the androgen receptor and its T877A mutant complexed with the natural agonist dihydrotestosterone. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 4904–4909. (b) De Jésus-Tran, K. P.; Côté, P.-L.; Cantin, L.; Blanchet, J.; Labrie, F.; Breton, R. Comparison of crystal structures of human androgen receptor ligand-binding domain complexed with various agonists reveals molecular determinants responsible for binding affnity. *Protein Sci.* **2006**, *15*, 987–999.

(9) (a) Boccardo, F. Hormone therapy of prostate cancer: Is there a role for antiandrogen monotherapy? *Crit. Rev. Oncol. Hematol.* **2000**, *35*, 121–132. (b) Suzuki, H.; Kamiya, N.; Imamoto, T.; Kawamura, K.; Yano, M.; Takano, M.; Utsumi, T.; Naya, Y.; Ichikawa, T. Current topics and perspectives relating to hormone therapy for prostate cancer. *Int. J. Clin. Oncol.* **2008**, *13*, 401–410.

(10) Scher, H. I.; Steineck, G.; Kelly, W. K. Hormone-refractory (D3) prostate cancer: refining the concept. *Urology* **1995**, *46*, 142–148.

(11) (a) Taplin, M. E.; Rajeshkumar, B.; Halabi, S.; Werner, C. P.; Woda, B. A.; Picus, J.; Stadler, W.; Hayes, D. F.; Kantoff, P. W.; Vogelzang, N. J.; Small, E. J. Androgen receptor mutation in androgen-independent prostate cancer: cancer and leukemia group B study 9663. *J. Clin. Oncol.* **2003**, *21*, 2673–2678. (b) Miyamoto, H.; Rahman, M. M.; Chang, C. Molecular basis for the antiandrogen withdrawal syndrome. *J. Cell. Biochem.* **2003**, *91*, 3–12.

(12) (a) Veldscholte, J.; Berrevoets, C. A.; Brinkmann, A. O.; Grootegoed, J. A.; Mulder, E. Anti-androgens and the mutated androgen receptor LNCaP cells: differential effects on binding affinity, heat-shock protein interaction, and transcription activation. *Biochemistry* **1992**, *31*, 2393–2399. (b) Fenton, M. A.; Shuster, T. D.; Fertig, A. M.; Taplin, M. E.; Kolvenbag, G.; Bubley, G. J.; Balk, S. P. Functional characterization of mutant androgen receptors from androgen-independent prostate cancer. *Clin. Cancer Res.* **1997**, *3*, 1383–1388. (c) Zhao, X. Y.; Malloy, P. J.; Krishnan, A. V.; Swami, S.; Navone, N. M.; Peehl, D. M.; Feldman, D. Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor. *Nat. Med.* **2000**, *6*, 703–706.

(13) Taplin, M. E.; Bubley, G. J.; Ko, Y. J.; Small, E. J.; Upton, M.; Rajeshkumar, B.; Balk, S. P. Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. *Cancer Res.* **1999**, *59*, 2511–2515.

(14) (a) Suzuki, H.; Akakura, K.; Komiya, A.; Aida, S.; Akimoto, S.; Shimazaki, J. Codon 877 mutation in the androgen receptor gene in advanced prostate cancer: relation to antiandrogen withdrawal syndrome. *Prostate* **1996**, *29*, 153–158. (b) Zhou, J.; Liu, B.; Geng, G.; Wu, J. H. Study of the impact of the T877A mutation on ligand induced helix-12 positioning of the androgen receptor resulted in design and synthesis of novel antiandrogens. *Proteins* **2010**, *78*, 623–637.

(15) (a) Hara, T.; Miyazaki, J.; Araki, H.; Yamaoka, M.; Kanzaki, N.; Kusaka, M.; Miyamoto, M. Novel mutations of androgen receptor: a possible mechanism of bicalutamide withdrawal syndrome. *Cancer Res.* **2003**, *63*, 149–153. (b) Yoshida, T.; Kinoshita, H.; Segawa, T.; Nakamura, E.; Inoue, T.; Shimizu, Y.; Kamoto, T.; Ogawa, T. Antiandrogen bicalutamide promotes tumor growth in a novel androgen-dependent prostate cancer xenograft model derived from a bicalutamide-treated patients. *Cancer Res.* **2005**, *65*, 9611–9616.

(16) (a) Bregadze, V. I. Dicarba-*closo*-dodecaboranes $C_2B_{10}H_{12}$ and their derivatives. *Chem. Rev.* **1992**, *92*, 209–223. (b) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. The chemistry of neutron capture therapy. *Chem. Rev.* **1998**, *98*, 1515–1562.

(17) (a) Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. The medicinal chemistry of carboranes. *Coord. Chem. Rev.* **2002**, *232*, 173–230. (b) Armstrong, A. F.; Valliant, J. F. The bioinorganic and medicinal chemistry of carboranes: from new drug discovery to molecular imaging and therapy. *Dalton Trans.* **2007**, 4240–4251.

(18) (a) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Yamaguchi, M.; Fukasawa, H.; Shudo, K. Potent estrogenic agonists bearing dicarba-*closo*-dodecaborane as a hydrophobic pharmacophore. *J. Med. Chem.* **1999**, *42*, 1501–1504. (b) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Fukasawa, H.; Miyaura, C.; Inada, M.; Kubo, A.; Itai, A. Potent agonists based on carborane as a hydrophobic skeletal structure: a new medicinal application of boron clusters. *Chem. Biol.* **2001**, *8*, 341–355. (c) Endo, Y.; Yoshimi, T.; Ohta, K.; Suzuki, T.; Ohta, S. Potent estrogen receptor ligands based on bisphenols with a globular hydrophobic core. *J. Med. Chem.* **2005**, *48*, 3941–3944. (d) Hirata, M.; Inada, M.; Matsumoto, C.; Takita, M.; Ogawa, T.; Endo, Y.; Miyaura, C. A novel carborane analogue, BE360, with a carbon-containing polyhedral boron-cluster is a new selective estrogen receptor modulator for bone. *Biochem. Biophys. Res. Commun.* **2009**, *380*, 218–222. (e) Ohta, K.; Ogawa, T.; Suzuki, T.; Ohta, S.; Endo, Y. Novel estrogen receptor (ER) modulators: carbamate and thiocarbamate derivatives with m-carborane bisphenol structure. *Bioorg. Med. Chem.* **2009**, *17*, 7958–7963.

(19) (a) Iijima, T.; Endo, Y.; Tsuji, M.; Kawachi, E.; Kagechika, H.; Shudo, K. Dicarba-*closo*-dodecaboranes as a pharmacophore. Retinoidal antagonists and potential agonists. *Chem. Pharm. Bull.* **1999**, *47*, 398–404. (b) Endo, Y.; Yaguchi, K.; Kawachi, E.; Kagechika, H. Polymethylcarborane as a novel bioactive moiety: derivatives with potent retinoid antagonistic activity. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1733–1736. (c) Endo, Y.; Iijima, T.; Yaguchi, K.; Kawachi, E.; Inoue, N.; Kagechika, H.; Kubo, K.; Itai, A. Structure−activity study of retinoid agonists bearing substituted dicarba-closo-dodecaborane. Relation between retinoidal activity and conformation of two aromatic nuclei. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1307–1311.

(20) (a) Ohta, K.; Iijima, T.; Kawachi, E.; Kagechika, H.; Endo, Y. Novel retinoid X receptor (RXR) antagonists having a dicarba-*closo*-dodecaborane as a hydrophobic moiety. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5913–5918. (b) Calléja, C.; Messaddeq, N.; Chapellier, B.; Yang, H.; Krezel, W.; Li, M.; Metzger, D.; Mascrez, B.; Ohta, K.; Kagechika, H.; Endo, Y.; Mark, M.; Ghyselinck, N. B.; Chambon, P. Genetic and pharmacological evidence that a retinoic acid cannot be the RXR-activating ligand in mouse epidermis keratinocytes. *Gene Dev.* **2006**, *20*, 1525–1538.

(21) Fujii, S.; Goto, T.; Ohta, K.; Hashimoto, Y.; Suzuki, T.; Ohta, S.; Endo, Y. Potent androgen antagonists based on carborane as a hydrophobic core structure. *J. Med. Chem.* **2005**, *48*, 4654–4662.

(22) (a) Fujii, S.; Hashimoto, Y.; Suzuki, T.; Ohta, S.; Endo, Y. A new class of androgen receptor antagonists bearing carborane in place of a steroidal skeleton. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 227–230. (b) Goto, T.; Ohta, K.; Suzuki, T.; Ohta, S.; Endo, Y. Design and synthesis of novel androgen receptor antagonists with sterically bulky icosahedral carborane. *Bioorg. Med. Chem.* **2005**, *13*, 6414–6424. (c) Ohta, K.; Goto, T.; Fujii, S.; Suzuki, T.; Ohta, S.; Endo, Y. Design and synthesis of carborane-containing androgen receptor (AR) antagonist bearing a pyridine ring. *Bioorg. Med. Chem.* **2008**, *16*, 8022–8028. (d) Fujii, S.; Ohta, K.; Goto, T.; Kagechika, H.; Endo, Y. Acidic heterocycles as novel hydrophilic pharmacophore of androgen receptor ligands with a carborane core structure. *Bioorg. Med. Chem.* **2009**, *17*, 344–350.

(23) (a) Dess, D. B.; Martin, J. C. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. A useful 12-I-5 triacetoxyperiodinane (the Dess−Martin periodinane) for the selective oxidation of primary or secondary alcohols and a variety of related 12-I-5 species. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

(24) (a) Corey, E. J.; Chaykovsky, M. Dimethylsulfonium methylide, a reagent for selective oxirane synthesis from aldehydes and ketones. *J. Am. Chem. Soc.* **1962**, *84*, 3782–3783. (b) Corey, E. J.; Chaykovsky, M.

Dimethyloxosulfonium methylide and dimethylsulfonium methylide. Formation and application to organic synthesis. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.

(25) (a) Aggarwal, V. K.; Ali, A.; Coogan, M. P. A novel procedure for the synthesis of epoxides: Application of Simmons−Smith reagents toward epoxidation. *J. Org. Chem.* **1997**, *62*, 8628–8629. (b) Aggarwal, V. K.; Coogan, M. P.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. Developments in the Simmons−Smith-mediated epoxidation reaction. *Eur. J. Org. Chem.* **2002**, 319–326.

(26) Ishioka, T.; Kubo, A.; Koiso, Y.; Nagasawa, K.; Itai, A.; Hashimoto, Y. Novel non-steroidal/non-anilide type androgen antagonists with an isoxazolone moiety. *Bioorg. Med. Chem.* **2002**, *10*, 1555–1566.

(27) Kitamura, S.; Suzuki, T.; Ohta, S.; Fujimoto, N. Antiandrogenic activity and metabolism of the organophosphorus pesticide fenthion and related compounds. *Environ. Health Perspect.* **2003**, *111*, 503–508.

(28) (a) Hiraoka, D.; Nakamura, N.; Nishizawa, Y.; Uchida, N.; Noguchi, S.; Matsumoto, K.; Sato, B. Inhibitory and stimulatory effects of glucocorticoid on androgen-induced growth of murine Shionogi carcinoma 115 in vivo and in cell culture. *Cancer Res.* **1987**, *47*, 6560–6564. (b) Kasayama, S.; Saito, H.; Kouhara, H.; Sumitani, S.; Sato, B. Suramin interrupts androgen-inducible autocrine loop involving heparin binding growth factor in mouse mammary cancer (Shionogi carcinoma 115) cells. *J. Cell. Physiol.* **1993**, *154*, 254–261.

(29) (a) Culig, Z.; Hobisch, A.; Cronauer, M. V.; Cato, A. C. B.; Hittmair, A.; Radmayr, C.; Eberle, J.; Bartsch, G.; Klocker, H. Mutant androgen receptor detected in an advanced-stage prostatic carcinoma is activated by adrenal androgens and progesterone. *Mol. Endocrinol.* **1993**, *7*, 1541–1550. (b) 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. (c) Marcelli, M.; Ittmann, M.; Mariani, S.; Sutherland, R.; Nigam, R.; Murthy, L.; Zhao, Y.; DiConcini, D.; Puxeddu, E.; Esen, A.; Eastham, J.; Weigel, N. L.; Lamb, D. J. Androgen receptor mutations in prostate cancer. *Cancer Res.* **2000**, *90*, 944–949.

(30) (a) Yin, D.; Gao, W.; Kearbey, J. D.; Xu, H.; Chung, K.; He, Y.; Marhefka, C. A.; Veverka, K. A.; Miller, D. D.; Dalton, J. T. Pharmacodynamics of selective androgen receptor modulators. *J. Pharmacol. Exp. Ther.* **2003**, *304*, 1334–1340. (b) Marhefka, C. A.; Gao, W.; Chung, K.; Kim, J.; He, Y.; Yin, D.; Bohl, C.; Dalton, J. T.; Miller, D. D. Design, synthesis and biological characterization of metabolically stable selective androgen receptor modulators. *J. Med. Chem.* **2004**, *47*, 993–998. (c) Kearbey, J. D.; Gao, W.; Narayanan, R.; Fisher, S. J.; Wu, D.; Miller, D. D.; Dalton, J. T. Selective androgen receptor modulator (SARM) treatment prevents bone loss and reduces body fat in ovariectomized rats. *Pharm. Res.* **2007**, *24*, 328–335.

(31) (a) Zhi, L.; Martinborough, E. *Annu. Rep. Med. Chem.* **2001**, *36*, 169–180. (b) Brown, T. R. Nonsteroidal selective androgen receptor modulators (SARMs): designer androgens with flexible structures provide clinical promise. *Endocrinology* **2004**, *145*, 5417–5419.